Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
CORRESPONDENCE FOR AMERICAN COLLEGE OF CARDIOLOGY

All correspondence for the College, other than that related to JACC: Case Reports should be sent to Resource Center, American College of Cardiology, 2400 N Street, NW, Washington, DC 20037

2020-2021 OFFICERS

Athena Poppas, MD, FACC, President
Dipti Itchhaporia, MD, FACC, Vice President
Howard "Bo" T. Walpole, Jr., MD, MBA, FACC, Treasurer
Daniel M. Philbin, Jr., MD, FACC, Secretary and Board of Governors Chair
Cathleen C. Gates, Acting Chief Executive Officer

2020-2021 PUBLICATIONS AND EDITORIAL COORDINATION COMMITTEE

Vivian R. Taqueti, MD, MPH, FACC, Chair
Rhonda M. Cooper-DeHoff, MD, FACC
John U. Doherty, MD, FACC
Islam Y. Elgendy, MD, FACC
Prasad C. Gunasekaran, MD
Fadi G. Hage, MD, FACC
Fred M. Kusumoto, MD, FACC
Renato D. Lopes, MD, PhD, FACC
Sandra M. Oliver-McNeil, DNP, ACNP-BC
Syed Tanveer Rab, MBBS, MACC
Janice Sibley, MS, MA, ACC Executive Vice President, Education and Publishing Divisions
Justine Varieur Turco, MA, ACC Divisional Senior Director, Publishing
CASE REPORT

A Challenging Case of Extensive Spontaneous Coronary Artery Dissection

Nupoor Narula, MD, a Harsimran Singh, MD, MSc, a Udhay Krishnan, MD, a Christopher Sciria, MD, a Adam Vohra, MD, a Jiwon Kim, MD, a Christopher Lau, MD, b Dmitriy Feldman, MD, a Luke Kim, MD, a Julie L. Friedman, MD a

ABSTRACT

The detection of spontaneous coronary artery dissection (SCAD) causing myocardial infarction is integral in pursuing the appropriate management. Our case posed a diagnostic challenge, with Takotsubo cardiomyopathy and coronary embolism among the potential differential diagnoses upon the initial presentation. Extensive propagation of spontaneous coronary artery dissection subsequently resulted in a significant challenge to management requiring surgical revascularization. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1437–42) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 28-year-old female flight attendant without cardiac risk factors or a history of connective tissue disorders presented with substernal chest pain, shortness of breath, bilateral arm numbness, and emesis that started several hours after an international flight. En route to the hospital via ambulance, she was reportedly in atrial fibrillation. She was hemodynamically stable on arrival with a blood pressure of 107/71 mm Hg, a heart rate of 80 beats/min, and an oxygen saturation of 99% on room air. Cardiac, respiratory, and pulse examinations were unremarkable. Although she cited work-related stressors, there were no clear physical or emotional triggers preceding presentation. She additionally denied any antecedent infectious symptoms.

LEARNING OBJECTIVES

- SCAD is a common etiology of ACS in young women and can result in significant morbidity and mortality if not recognized in a timely manner.
- Repeat angiography should be pursued in individuals if clinical suspicion exists for worsening ischemia in the context of myocardial infarction with nonobstructive coronary arteries without clear etiology.
- Although there may be a potential association between SCAD and TTC, SCAD should be carefully excluded when the diagnosis of TTC is entertained because the management strategy may be different. CMR can be very valuable in characterizing the myocardial pathology.

From the aDivision of Cardiology, Weill Cornell Medicine, New York Presbyterian Hospital, New York, New York; and the bDepartment of Cardiothoracic Surgery, Weill Cornell Medical College, New York, New York. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

Manuscript received March 23, 2020; revised manuscript received July 7, 2020, accepted July 7, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.07.005
PAST MEDICAL HISTORY

Before presentation, the patient reported good health with satisfactory employment-mandated routine physical examinations. She denied a history of smoking, alcohol, or illicit drug use. She had never been pregnant and was not on hormone supplementation.

DIFFERENTIAL DIAGNOSES

A wide differential was considered by the admitting team, including pulmonary embolism, acute coronary syndrome (ACS), and pericarditis/myocarditis.

INVESTIGATIONS

The initial laboratory values demonstrated a normal complete blood count, normal metabolic panel, and troponin I. D-dimer was positive (228 ng/ml). A computed tomographic chest scan excluded pulmonary embolism. An electrocardiogram (ECG) revealed anterolateral injury and reciprocal changes in the inferior leads (Figure 1). Troponin I peaked at 48.52 ng/ml. Emergent cardiac catheterization revealed mild luminal irregularity of a small diagonal branch and otherwise angiographically normal coronary arteries (Figure 2). A ventriculogram demonstrated a severely reduced left ventricular ejection fraction (LVEF) of 30% to 35% with akinesis of the anterior, apical, and inferior walls and relative preservation of the basal territories consistent with Takotsubo cardiomyopathy (TTC) or a resolved myocardial infarction (MI) in the proximal wrap-around left anterior descending (LAD) artery distribution. An echocardiogram confirmed reduced LVEF with severe septal and apical hypokinesis.

Given the degree of troponin rise that seemed out of proportion to that typically observed in TTC (1) or expected from the abnormality associated with a small diagonal branch, cardiac magnetic resonance (CMR) was pursued. This demonstrated wall motion abnormalities in the LAD artery territory with late gadolinium enhancement (LGE), strongly suggesting MI of the mid to distal anterior wall, anteroseptum, and apex (Figure 3, Video 1). Her coronary angiogram was re-reviewed by multiple interventional cardiologists without noted evidence of stenosis, dissection, or occlusion involving the LAD (Figure 2).

At this stage, her presentation was suspicious for myocardial infarction with nonobstructive coronary arteries with coronary thrombosis/emboli highest on the differential.
MANAGEMENT

She was started on metoprolol. Her blood pressure did not tolerate further neurohormonal blockade. Unfractionated heparin was started on arrival given the reported atrial fibrillation in the ambulance and was continued because of the concern for potential embolic MI. Ultimately, these ECG strips were obtained, and no atrial fibrillation was noted. A transesophageal echocardiogram did not reveal an embolic source or patent foramen ovale, and unfractionated heparin was promptly discontinued.

Four days into hospitalization, she developed arm numbness, mild chest discomfort, and emesis. An ECG showed more prominent ST-segment depressions in the inferior leads, which had otherwise improved during hospitalization, and <1-mm ST-segment elevations in the anterior leads (Figure 4). Given the recurrent symptoms, ECG findings, and the unclear explanation for her LAD territory MI, a repeat angiogram was cautiously pursued with low-pressure contrast injection not directly engaging the coronary arteries as the presence of coronary artery dissection was considered and the operators wanted to reduce the risk of further coronary artery injury or dissection propagation. The angiogram demonstrated evidence of extensive spontaneous coronary artery dissection (SCAD) involving the left main (LM),
proximal to distal LAD, left circumflex, and first and second diagonal (D1 and D2) coronary arteries (Figure 5, Video 2). An intra-aortic balloon pump was placed because of persistent ischemic symptoms. Although surgical intervention is rarely pursued for SCAD given the technical difficulty in differentiating true and false lumens, cardiothoracic surgery consultation was obtained because of the ongoing ischemic symptoms, hypotension, and extent of dissection with LM involvement. After multidisciplinary discussion, the decision was made to pursue surgical intervention, and a 4-vessel coronary artery bypass graft surgery (CABG) was performed with good graft anastomoses in the unaffected portions of the target vessels.

**DISCUSSION**

**HOW COMMON IS SCAD?** SCAD is an under-recognized cause of ACS in young women, despite accounting for over 25% of ACS in those ≈50 years, and can result in significant morbidity and mortality (2).

**HOW IS THE DIAGNOSIS OF SCAD SUSPECTED AND CONFIRMED?** A high index of suspicion should exist in young individuals, primarily of female sex, with a paucity of coronary artery disease risk factors presenting with MI. In these cases, coronary angiography should be pursued expeditiously for definitive diagnosis with the use of supplemental intracoronary imaging such as intravascular ultrasonography and optical coherence tomography if the diagnosis remains unclear (3).

**WHY WAS THE DIAGNOSIS OF SCAD IN THE CURRENT CASE CHALLENGING?** The case was challenging in light of her fairly unremarkable coronary angiogram relative to her dramatic presentation. After her initial angiogram, which did not demonstrate an obstructive coronary lesion, concern remained high for TTC or missed SCAD. Given the small caliber of the abnormal diagonal branch, intravascular imaging was not feasible for further investigation of the abnormal coronary segment. Repeat angiography, although initially considered, has associated risk if SCAD is on the differential diagnosis, given the possibility of propagating dissection with coronary instrumentation. Cardiac imaging in this case, namely with CMR, helped to narrow the differential diagnosis (see later), and recurrence of ischemia drove the decision for repeat angiography, which ultimately confirmed the diagnosis.

**DO SCAD AND TTC COEXIST, AND, IF SO, HOW DO WE DIFFERENTIATE BETWEEN THE 2 ETIOLOGIES? HOW DOES CMR HELP?** The potential concurrency of

---

**FIGURE 4 Evolving Electrocardiographic Changes**

Evolving electrocardiogram changes revealed anteroseptal myocardial infarction and repolarization abnormalities consistent with anteroseptal injury or ventricular aneurysm.

---

Narula et al. JACC: CASE REPORTS, VOL. 2, NO. 10, 2020 Extensive Spontaneous Coronary Artery Dissection

AUGUST 2020:1437–42
SCAD and TTC has been previously described (4). It is hypothesized that an acute adrenergic rise in TTC may potentiate coronary artery shear stress and SCAD or that stress associated with SCAD may theoretically manifest as TTC (3,5). Interestingly, in 2 series of patients originally diagnosed with TTC, re-review of angiograms revealed the presence of previously unrecognized SCAD in up to 9% (6,7). The persistent clinical syndrome, discordantly elevated troponin peak, ECG evolution, and presence of LGE in a single coronary territory played a critical role in differentiating our case from TTC and prompting the team to evaluate for alternative diagnoses. Furthermore, in TTC, the wall motion abnormalities typically extend beyond territories supplied directly by the LAD, including the inferior, posterior, and lateral territories, which were not noted in this case. Although routine follow-up angiography is not often pursued, there is a role for repeat testing in cases with diagnostic uncertainty or ongoing ischemia. Therefore, this case underscores the importance of avoiding committing to a single diagnosis when discordant clinical and investigative findings develop. Our case additionally highlights the utility of CMR in delineating myocardial pathology and the various etiologies of myocardial infarction with nonobstructive coronary arteries (MINOCA) through the identification of LGE, myocardial edema, and wall motion abnormalities (8).

HOW COMMONLY DOES SCAD INVOLVE MULTIPLE TERRITORIES? The LAD is the most commonly affected coronary artery, with multivessel involvement in less than one-fourth of cases (3,9).

WHAT IS THE MAINSTAY OF THERAPY IN SCAD, AND WHY IS REVASCULARIZATION UNCOMMONLY PURSUED? The mainstay of management for most SCAD is medical therapy due to spontaneous healing over time in the majority of cases, the risk of propagating dissection with repeat invasive evaluation, and poor long-term patency of grafts; however, revascularization with CABG is considered in very select situations after comprehensive clinical decision making, including in cases with LM or proximal coronary involvement, ongoing ischemia despite conservative measures, or cardiogenic shock (9,10). In these scenarios, it is critical for the surgeon to differentiate a false versus a true lumen to provide the highest likelihood of graft patency.

FOLLOW-UP

The patient recovered well post-CABG and will be returning to her hometown (internationally) where she will undergo evaluation for fibromuscular dysplasia and connective tissue disorders.

CONCLUSIONS

SCAD can have a challenging clinical and angiographic presentation. As such, clinical familiarity with this entity is integral to prevent associated morbidity and mortality. Although there may be an association or overlap between SCAD and TTC, careful consideration with various imaging modalities, including intravascular or magnetic resonance imaging as well as a detailed review of coronary angiography, may be integral in delineating etiology and guiding further management.

ADDRESS FOR CORRESPONDENCE: Dr. Julie L. Friedman, Division of Cardiology, Department of Medicine, Weill Cornell Medicine, 520 East 70th Street, Starr Pavilion, 4th Floor, New York, New York 10021. E-mail: jlf4001@med.cornell.edu.
REFERENCES

1. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. N Engl J Med 2015;373:929-38.

2. Nakashima T, Noguchi T, Haruta S, et al. Prognostic impact of spontaneous coronary artery dissection in young female patients with acute myocardial infarction: a report from the Angina Pectoris-Myocardial Infarction Multicenter Investigators in Japan. Int J Cardiol 2016;207:341-8.

3. Hayes SN, Kim ESH, Saw J, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. Circulation 2018;137:e523-57.

4. Duran JM, Naderi S, Vidula M, et al. Spontaneous coronary artery dissection and its association with takotsubo syndrome: novel insights from a tertiary center registry. Catheter Cardiovasc Interv 2020;95:485-91.

5. Buccheri D, Zambelli G. The link between spontaneous coronary artery dissection and takotsubo cardiomyopathy: analysis of the published cases. J Thorac Dis 2017;9:5489-92.

6. Chou AY, Sedlak T, Aymong E, et al. Spontaneous coronary artery dissection misdiagnosed as Takotsubo cardiomyopathy: a case series. Can J Cardiol 2015;31:1073.e5-8.

7. Hausvater A, Smilowitz NR, Saw J, et al. Spontaneous coronary artery dissection in patients with a provisional diagnosis of Takotsubo syndrome. J Am Heart Assoc 2019;8:e013581.

8. Dastidar AG, Baritussio A, De Garate E, et al. Prognostic role of cardiac MRI and conventional risk factors in myocardial infarction with non-obstructed coronary arteries. J Am Coll Cardiol Img 2019;12:1973-83.

9. Tweet MS, Eleid MF, Best PJ, et al. Spontaneous coronary artery dissection: revascularization versus conservative therapy. Circ Cardiovasc Interv 2014;7:777-86.

10. Hassan S, Prakash R, Starovoytov A, et al. Natural history of spontaneous coronary artery dissection with spontaneous angiographic healing. J Am Coll Cardiol Img 2019;12:518-27.

KEY WORDS spontaneous coronary artery dissection, Takotsubo cardiomyopathy, women’s health

APPENDIX For supplemental videos, please see the online version of this paper.

Go to http://www.acc.org/jacc-journals-cme to take the CME/MOC/ECME quiz for this article.
Simultaneous Transcatheter Double Valve Treatment of Mediastinal Radiation-Induced Severe Calcific Aortic and Mitral Stenosis

Christopher J. Allen, MBChB(Hons), BSc(Hons),a,b Tiffany Patterson, MBBS, PhD,a,b Bernard Prendergast, BM, BS, MD,b Ross L. Roberts-Thompson, MBBS, BMEdSc(Hons),a Ronak Rajani, MBBS, MD,b Simon R. Redwood, MBBS, MDa,b

ABSTRACT

Mediastinal radiation-induced severe calcific valve disease carries increased operative mortality. Transcatheter therapies are also challenging and potentially hazardous. We used a unique constellation of imaging and planning technologies to successfully plan, simulate, and perform novel combined transcatheter aortic valve replacement and valve in mitral annular calcification in a high-risk patient. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1443–7) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

We present a 61-year-old woman with New York Heart Association functional class II to III dyspnea after undergoing lifesaving mantle field radiotherapy and chemotherapy for Hodgkin lymphoma 20 years ago. Notable past medical history included paroxysmal atrial fibrillation. Heart rate was 90 beats/min, blood pressure was 121/60 mm Hg, respiratory rate was 17 breaths/min, and oxygen saturations was 99% on room air. Echocardiography demonstrated good left ventricular function, critical aortic stenosis (mean gradient = 50 mm Hg, valve area = 0.5 cm²), and severe mitral stenosis (mean gradient = 18 mm Hg, valve area = 0.9 cm²). Dedicated multiphase cardiac computed tomography angiography (CTA) highlighted extensive calcification throughout the aortomitral continuity.

LEARNING OBJECTIVES

• To discuss the potential long-term cardiopulmonary sequelae of mediastinal radiation.
• To understand the technical challenges to valve intervention imposed by extensive calcific valve disease, particularly involving the aortomitral continuity.
• To understand the potential role of preprocedural modeling informed by multimodality imaging to mitigate these hazards and plan transcatheter interventions.
aortomitral continuity with severely calcified aortic valve leaflets and circumferential mitral annular calcification (Figures 1A to 1C). Coronary angiography indicated eccentric, angiographically mild, biostial left main stem and right coronary artery disease, likely reflecting the underlying radiation-induced pathology.

Despite relatively low perioperative risk scores (European System for Cardiac Operative Risk Evaluation II = 1.8% and Society of Thoracic Surgeons score = 3.6%), the extensively calcified anatomy posed high surgical risk. The consensus across heart teams in multiple international centers was that conventional dual-valve replacement was not technically feasible, and they proposed the “Commando” procedure to reconstruct the aortomitral continuity after mitral annular decalcification in conjunction with mitral and aortic valve replacement (1). The patient declined, citing unacceptable operative risk, thereby prompting consideration of transcatheter options.

DIFFERENTIAL DIAGNOSIS

- Radiation-induced, severe calcific valve disease;
- Degenerative valve disease;
- Noncardiac dyspnea (e.g., pulmonary fibrosis).

INVESTIGATIONS

Extensive planning was performed to predict the procedural outcome. CTA indicated borderline narrow sinuses of Valsalva (27 × 30 × 30 mm) but sufficient coronary heights (left main stem = 16 mm, right coronary artery = 17 mm) to suggest a low risk of coronary obstruction. From the CTA, we performed computer-simulated finite element modeling (FEM) (FEops, Ghent, Belgium) to simulate mitral transcatheter heart valve (THV) implantation to derive a neo-left ventricular outflow tract (LVOT) area and predict the likelihood of paravalvular regurgitation (Figure 1D, Video 1) (2). Subsequent computational fluid dynamics modeled the pressure gradient within the neo-LVOT and predicted an acceptable, unobstructed outcome (Figures 1E and 1F, Videos 2A and 2B) (3). Finally, a 3-dimensional-printed bespoke heart model aided pre-procedural implant simulation (Mimics Innovation Suite and HeartPrint Flex, Materialise, Leuven, Belgium) (Figure 1G).

MANAGEMENT

After placement of a cerebral embolic protection (CEP) device (Sentinel, Boston Scientific, Quincy, Massachusetts) via the right radial artery and systemic heparinization guided by the activated clotting time, a 23-mm Sapien 3 (Edwards Lifesciences, Irvine, California) transcatheter aortic valve replacement was performed via the left femoral artery without complication (Figure 2A, Video 3). Atrial transseptal puncture was performed with an electrified Brockenbrough needle via an SLO sheath (Swart, Abbott Vascular, Santa Clara, California) from the right femoral vein using computed tomography-simulated fluoroscopic guidance (Figure 2B) (4). After 18-mm atrial balloon septostomy (Figure 2C) (VACS-II, Osypka, Longmont, California), a Safari wire (Boston Scientific, Quincy, Massachusetts) was positioned in the left ventricle via an Agilis steerable sheath (Abbott Vascular). Correct positioning of the 29-mm Sapien 3 valve within the mitral annulus required snaring of the Safari wire into the aorta via the left femoral artery to provide additional support (Figures 2D and 2E, Videos 4A and 4B). After successful deployment under rapid left ventricular pacing (120 beats/min), completion of the left ventriculogram demonstrated a well-functioning mitral prosthesis (Figure 2F, Video 5) confirmed on Doppler, 4-dimensional imaging, and blood speckle imaging echocardiography (Figures 2G to 2I, Video 6). Hemodynamics improved dramatically, and the patient has remained well.

DISCUSSION

Depending on the precise definition used, clinically significant calcific valve disease may develop in up to 37% of patients after mediastinal radiation (5,6). The incidence is dose dependent, and, as in this case, extensive field radiation (e.g., Mantle) and co-administration of chemotherapeutic agents are recognized risk factors (7). Moreover, as survival from malignancies such as Hodgkin lymphoma continues to improve (20-year survival now >80%), the incidence of remote cardiac complications is expected to increase (8).

Patients with radiation-induced valve disease undergoing conventional cardiac surgery are at increased risk of perioperative complications in a manner not reflected in traditional risk stratification models. The potential sequelae of radiation exposure including mediastinal fibrosis/adhesions; pulmonary fibrosis; pericardial constriction; and coronary, cardiac, and aortic calcification confer an increased risk of perioperative bleeding, cardiorespiratory failure, rhythm disturbance, embolic stroke, and death (9,10).

As present in this case, extensive calcification of the aortomitral continuity presents a particularly formidable surgical challenge, with the attendant risks of intractable hemorrhage, atrioventricular
disruption, coronary artery injury, and ventricular rupture. Decalcification followed by reconstruction of the intervalvular fibrous body with either glutaraldehyde-fixed bovine pericardium or Dacron polyester fabric during aortic and mitral valve replacement was first described in this setting over 20 years ago (1), although it remains restricted to a few expert centers worldwide, with technical failures, complications, and operative mortality (>10%) still relatively high, even in experienced hands (11).

In the face of prohibitive or unacceptable surgical risk, transcatheter techniques may offer an alternative, although the treatment of dual radiation-induced valve pathology demonstrated here has not previously been systematically described (12–14). In particular, complex, calcified mitral valve anatomy poses numerous challenges to treatment with a round THV without an anchoring mechanism, with potential complications including paravalvular regurgitation, valve migration, and principally LVOT obstruction through distortion of the subvalvular apparatus. Thus, despite technical advancements, 30-day mortality for transcatheter valve in mitral annular calcification remains unacceptably high (25% to 30%) (15,16). Appropriate patient selection is key to minimizing risk, with cardiac computed tomography to measure the expected neo-LVOT area considered mandatory. However, this approach does not permit modeling of the dynamic interaction of the valve with the host and vice versa (e.g., mitral annulus calcification deformation under conditions of radial stress). As such, the evaluation based on geometric measurements alone is likely insufficient to accurately predict outcome.

The patient-specific computer simulation used here enabled virtual implantation of a THV using FEM in which the geometric and mechanical properties of the valve and host are integrated. Simulating deformation of the device after deployment and other interactions of the device with neighboring anatomy improved the predictive power of geometric measurement to permit comprehensive assessment of the likelihood of LVOT obstruction and paravalvular regurgitation. To our knowledge, the only system that is available for performing FEM in this fashion is the platform used here. Computational fluid dynamics further enabled patient-specific modeling of a physiological response to mitral THV implantation to

**FIGURE 1** Pre-Operative Planning: Fusion Imaging, Finite Element Modeling and Computational Fluid Dynamics

(A to C) Dedicated multiphase cardiac CTA with echocardiographic fusion imaging indicating severe calcific valve disease, with calcification extending throughout the aortomitral continuity (asterisk). (D) Mitral THV implant simulation via finite element modeling predicting a safe neo-LVOT area with a 60:40 implant position. (E and F) Computational fluid dynamic modeling after virtual mitral THV implant predicting a safe neo-LVOT pressure gradient (maximum = 3 mm Hg). (G) Three-dimensional–printed bespoke heart model for implantation rehearsal and planning. CTA = computed tomographic angiography; LVOT = left ventricular outflow tract; THV = transcatheter heart valve.
predict the pressure gradient within the neo-LVOT after deployment (17). As a final safety assurance, a 3-dimensional–printed bespoke heart model was manufactured to aid the operator in procedural planning. Further integration of these detailed imaging analyses into periprocedural computed tomography–fluoroscopic and computed tomography–transoesophageal echocardiogram fusion imaging guidance with blood speckle imaging flow characterization enhanced the safety and technical success of the procedure.

The dual-filter CEP system (Sentinel) deployed in this case is licensed by the Food and Drug Administration for embolic protection during transcatheter procedures. The aggregate data support a positive effect on clinical stroke reduction, although an appropriately powered randomized efficacy trial is awaited (18). Our institutional practice is to evaluate the requirement for cerebral protection on an individual case basis. The consensus of the heart team discussion was that this young, high-functioning patient had a number of risk factors to increase embolic potential, including known atrial fibrillation, extreme valvular/LVOT calcification, and procedural complexity/time, which supported the use of CEP in this case.

We selected a balloon-expandable prosthesis for the mitral position, reflecting the majority of experience worldwide in this setting (15). We also opted for a balloon-expandable prosthesis in the aortic position because, although there is a degree of clinical equipoise in the setting of LVOT calcification, in our experience a carefully sized balloon prosthesis can achieve excellent results at low risk. Moreover, in the presence of high procedural complexity and increased risk, we have found that selecting the device with which we have the greatest experience has, as in this case, enhanced procedural safety. The low-profile, intra-annular nature of the device could also have the added benefit of permitting more routine coronary reaccess. The durability of THVs remains an area of active research in need of further long-term data. Accepting the patient’s young age, the potential requirement for subsequent reintervention was considered. Based on the patient’s anatomy and size and position of the prostheses, we were able to first

(A) Successful deployment of a 23-mm balloon-expandable valve in the aortic position under rapid LV pacing. (B) Transseptal puncture assisted by both simulation and landmark computed tomography–fluoroscopic fusion imaging, indicating left atrial and mitral anatomy, and puncture position target, respectively. (C) An 18-mm balloon septostomy. (D and E) The stiff Safari wire was snared (arrowheads) to increase delivery support, aiding correct positioning and deployment of the 29-mm balloon-expandable mitral THV between the preplanned landmarks indicated on computed tomographic–fluoroscopic fusion imaging. (F) Completion imaging demonstrating a well-functioning valve with (G) appropriate reduction in transvalvular gradient on continuous wave Doppler. (H and I) Corresponding pre- and post-intervention blood speckle imaging echocardiography demonstrating improved flow characteristics. LV = left ventricular; THV = transcatheter heart valve.
simulate and then implant; we were satisfied that a redo transcatheter procedure(s) would be technically feasible in the future.

FOLLOW-UP

The patient underwent an uneventful postprocedure recovery and was discharged after 24 h. She was re-established on long-term warfarin anticoagulation and has progressed remarkably well through the 30-day and 6-month follow-ups, enjoying an excellent symptomatic improvement.

CONCLUSIONS

Transcatheter heart interventions continue to provide new treatment options for patients unsuitable/high risk for conventional surgery. The unique constellation of imaging and planning technologies used to orchestrate a successful outcome in this case illustrate a potential framework to enhance safety and provide greater certainty for procedures that otherwise may be deemed unfeasible.

ACKNOWLEDGMENTS  The authors are most grateful for the support of the specialist teams at GE Medical Systems Ltd. (UK and Ireland), FEpS HEARTguideTM (Ghent, Belgium), and Materialise (Leuven, Belgium) for their support in this case and the preparation of this manuscript.

ADDRESS FOR CORRESPONDENCE: Dr. Christopher J. Allen, Cardiovascular Division, The Rayne Institute, British Heart Foundation Centre of Research Excellence, St. Thomas’ Hospital, King’s College London, Westminster Bridge Road, London SE1 7EP, United Kingdom. E-mail: christopher.allen@kcl.ac.uk.

REFERENCES

1. David TE, Kuo J, Armstrong S. Aortic and mitral valve replacement with reconstruction of the intervalvular fibrous body. J Thorac Cardiovasc Surg 1997;114:766-72.
2. Kárdy J, Ntalas I, Prendergast B, et al. Transcatheter mitral valve replacement in mitral annulus calcification: The art of computer simulation. J Cardiovasc Comput Tomogr 2018;12:153-7.
3. De Vecchi A, Niederer S, Rajani R, Redwood S, Prendergast B. Individual patient-specific planning of minimally invasive transcatheter intervention for heart valve disease. EClinicalMedicine 2018;6:9-10.
4. Serban R, Redwood S, Prendergast B, Rajani R. Real-time image integration for transcatheter mitral valve replacement in mitral annular calcification. J Thorac Cardiovasc Surg 2019;157:e135-9.
5. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schmittger I. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol 2003;42:743-9.
6. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin’s disease treated with chest radiotherapy. J Clin Oncol 2004;22:3139-48.
7. Cuffer DJ, Schaevpeld M, Darby SC, et al. Risk for valvarul heart disease after treatment for hodgkin lymphoma. Natl Cancer Inst 2015;107:dv008.
8. Gujral OM, Lloyd G, Bhattacharyya S. Radiation-induced valvular heart disease. Heart 2016;102:269 LP-76 LP.
9. Chang ASY, Smedira NG, Chang CL, et al. Cardiac surgery after mediastinal radiation: Extent of exposure influences outcome. J Thorac Cardiovasc Surg 2007;133:404-13.e3.
10. Wiliis W, Ahmad M, B PZ, et al. Long-term survival of patients with radiation heart disease undergoing cardiac surgery. Circulation 2013;127:1476-84.
11. Feindel CM, Tufail Z, David TE, Ivanov J, Armstrong S. Mitral valve surgery in patients with extensive calcification of the mitral annulus. J Thorac Cardiovasc Surg 2003;126:777-81.
12. Paven E, Cimadevilla C, Urena M, et al. Management of radiation-induced valvular heart disease due to Hodgkin’s Lymphoma in the modern era. EuroIntervention 2008;13:e1771-3.
13. Bashir M, Sigurdsson G, Horwitz PA, Zahr F. Simultaneous transfemoral aortic and transseptal mitral valve replacement utilising SAPIEN 3 valves in native aortic and mitral valves. EuroIntervention 2017;12:1649-52.
14. Fanari Z, Mahmalji H, Nandish S, Goswami NJ. Simultaneous transcatheter transfemoral aortic and transseptal mitral valve replacement using Edward SAPIEN S3. Catheter Cardiovasc Interv 2018;92:988-92.
15. Yoon S-H, Whisenant BK, Bleiziffer S, et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. Eur Heart J 2019;40:441-51.
16. Guerrero M, Vemulapalli S, Xiang Q, et al. Thirty-day outcomes of transcatheter mitral valve replacement for degenerated mitral bioprostheses (valve-in-valve), failed surgical rings (valve-in-ring), and native valve with severe mitral annular calcification (valve-in-mitral annular calcification). Circ Cardiovasc Interv 2020;13:e008425.
17. De Vecchi A, Marlevi D, Nordsletten DA, et al. Left ventricular outflow obstruction predicts increase in systolic pressure gradients and blood residence time after transcatheter mitral valve replacement. Sci Rep 2018;8:15540.
18. Seeger J, Kapadia SR, Kodali S, et al. Rate of peri-procedural stroke observed with cerebral embolic protection during transcatheter aortic valve replacement: a patient-level propensity-matched analysis. Eur Heart J 2018;40:1334-40.
Look, Simulate, Treat
Multimodality Imaging Guiding Bivalve Complex Transcatheter Replacement*

Agustín Fernández Cisnal, MD,a Alfredo Redondo Diéguez, MD,b Adbel Hakim Moustafa, MDc

Since the 1960s, high-dose, extended-field radiotherapy (RT) has played a key role in the treatment of Hodgkin lymphoma (1) and has usually been applied in an anteroposterior/posteroanterior technique irradiating all chest tissues, including the heart, leading to several cardiac complications including cardiomyopathy, arrhythmia, conduction disorders, and pericardial and valvular diseases.

The prevalence of valvulopathies after RT ranges from 2% to 37% (2), of which approximately 17% develop moderate to severe stenosis or regurgitation (3). Although the physiopathology is not widely known, it seems that radiation activates fibrogenic growth factors (4) and induces valve interstitial cell differentiation to an osteogenic phenotype (5). These facts could explain the severe valve thickening and calcification present in these patients. Multivalvular heart disease is a growing condition against which we must make decisions based on expert opinions or previous clinical experiences (6). RT-induced valvulopathies are associated with cardiopulmonary disorders such as mediastinal and pulmonary fibrosis, constrictive pericarditis, coronary disease, porcelain aorta, and extensive valve calcification which incurs an elevated surgical risk that is not predicted by standard surgical risk scoring systems (7). Likewise, the effects of RT on valves are usually extensive, and adjacent structures, such as subvalvular apparatus, annulus, and especially the aortomitral curtain (7), are commonly involved, and higher thickening is a robust predictor of mortality (8). Mitral and aortic valves are usually affected simultaneously, and even if there is only moderate disease in one of them, it is recommended that both valves be replaced because there is a rapid progression and the very high risk of a potential reoperation. There are 2 special issues concerning valve replacement in radiation induced valve disease, the first is severe continuous calcification involvement from the aortic annulus to the aortomitral curtain and the anterior leaflet of the mitral valve (9), which requires extensive debridement and decalcification to expose healthy tissue for suture placement. The second issue is a small aortic and mitral annulus which can result in a mismatch between prosthesis and patient, resulting in inadequate hemodynamics. Both problems tend to be solved by using the Commando operation, in which the mitral annulus, aortomitral curtain, aortic annulus, and aortic valve are repaired with a pericardium or polyethylene terephthalate (Dacron, DuPont, Wilmington, Delaware) patch allowing for better fixation of the prosthesis and an adequate valve sizing. Unfortunately, this surgery presents a high rate of in-hospital mortality (10) and should be reserved for a patient in whom there are no other suitable alternative procedures (11).

Preprocedural planning using multimodality imaging is crucial for the success of this complex procedure, where cardiac computed tomography (CT) with coverage of the entire cardiac cycle provides important static and dynamic information to...
determine procedure feasibility and device sizing and enhances understanding of the interaction between the patient-specific anatomy and the device by using 3D computational modeling and 3D printing.

Patient-specific 3D computational modeling is increasingly applied in structural heart interventions (transcatheter aortic valve replacement [TAVR] and transcatheter mitral valve replacement [TMVR]), using commercially available software that provides a complete virtual simulation environment for device implantation, to predict the anatomical and physiological consequences of device deformation, paravalvular leakage, obtaining gradients and velocities and flow streamlining within the neo-left ventricular outflow tract (LVOT) using computational fluid dynamics (12).

The application of 3D printing technology in cardiology has grown in the last decade, and it has emerged as a planning tool for complex structural heart disease (13). 3D printing allows creating patient-specific biomodels that replicate accurately the real anatomy. Multimaterial printing techniques allow simulating the physical properties of different tissues. This is of special interest in cases where calcium of fibrous tissue determines the indication for prosthetic devices such as TAVR or valve-in-mitral annular calcification (MAC) procedures. Recently the use of metamaterials has been reported; this is a special multimaterial printing technique that takes into account spatial orientation of reinforcements, allowing to best mimic the strain and stress behavior of certain tissues.

These models allow for not only better understanding of the anatomy but also simulation of the procedures and implantation of the device and even evaluation of the physiologic response to the implant. Several cases have been reported using 3D print for TAVR and TMVR (14), mostly used for preoperative planning.

In this issue of JACC: Case Reports, Allen et al. (15) present a case of a 61-year-old female who had been treated 20 years previously with mantle field RT for Hodgkin lymphoma and presented with severe and symptomatic mitral and aortic stenosis (Video 1). After multiple heart teams at different centers evaluated her case, all of them proposed a surgical solution using the Commando procedure. The patient was informed about the high operative risk and considered it was unacceptable and declined the surgical choice.

This is a challenging case for many reasons. First, there is a lack of evidence-based recommendations for multivalvular heart disease (6); second, transcatheter mitral valve therapies are one of the most challenge procedures due the complex mitral valve anatomic relationship and potential complications; and third, there is little or no experience with transcatheter simultaneous aortic mitral valve replacement, so planning the procedure should be done carefully in order to avoid potential, predictable complications and take into account similar diseases, anatomies, and techniques.

Allen et al. (15) performed an extensive multimodality analysis, anticipating predicted and potential complications. CT scanning is crucial for preplanning TMVR and other advanced image techniques (3D printing, finite element analysis).

The main concerns of TMVR in a severely calcified annulus (also known as valve-in-MAC) are, first, valve sizing and device stability. The mitral annulus is a noncircular structure that offers limited prosthetic anchorage with a considerable risk for paravalvular leakage and even embolization. Those concerns cannot be predicted based only on morphological data acquired from CT scans or ultrasound images, on which the device-patient interplay depends, including not only anatomy but also properties of the physical tissues. The authors faced this situation by reproducing the implantation of aortic and mitral valves using finite element modeling that combined anatomy, physical properties of the tissues, and virtual valve prosthetic models to predict the interactions between all elements, simulating deformations and achieving a reliable model for the procedure which would be able to predict paravalvular leakage and measure the neo-LVOT area.

The second concern is neo-LVOT obstruction. During mitral prosthesis implantation, the anterior mitral leaflet is shifted anteriorly toward the basal septum creating a so-called neo-LVOT (16) that is likely to be obstructive depending on valve sizing, basal septum anatomy, and mitroaortic angle. Guerrero et al. (17) reported an incidence of neo-LVOT obstruction of 9.3% with poor outcomes. A neo-LVOT cross-sectional minimal area cutoff of 1.7 cm² has been described to rule out a significant neo-LVOT obstruction (18). Nevertheless, this has theoretical limitation because in the neo-LVOT 3D configuration, neither flow is taken into account. Interestingly authors have used the 3D biomodel to evaluate the physiological response in terms of gradients and pressures especially within the neo-LVOT, using computational fluid dynamic systems. Finally,
a biomodel of both valves was 3D printed by using a multimaterial technology with elastic and rigid materials mimicking the real patient’s anatomy and allowing the operator to have a touchable and out-of-screen assessment.

This case illustrates how innovative and diverse imaging modalities are essential tools for selecting candidate patients and guiding complex transcatheter procedures and how they can be used in combination to successfully carry out such complex interventions.

**ADDRESS FOR CORRESPONDENCE:** Dr. Agustín Fernández Cisnal, Hospital Clinic i Universitari de València, Avenida Blasco Ibáñez, 17, 46010 Valencia, Spain. E-mail: fecia82@gmail.com. Twitter: @afcisnal.

**REFERENCES**

1. Eichenerauer DA, Aleman BMP, Andre M, et al. Hodgkin lymphoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29 Suppl 4:v19-29.

2. Gujral DM, Lloyd G, Bhattacharyya S. Radiation-induced valvular heart disease. Heart 2016;102: 269-76.

3. van Nimwegen FA, Schaapveld M, Janus CP, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med 2015;175:1007-17.

4. Yarnold J, Brotons MC. Pathogenetic mechanisms in radiation fibrosis. Radiother Oncol 2010; 97:149-61.

5. Nadlonek NA, Weyant MJ, Yu JA, et al. Radiation induces osteogenesis in human aortic valve interstitial cells. J Thorac Cardiovasc Surg 2012; 144:1466-70.

6. Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC focused update of the 2014 aha/acc guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159-95.

7. Kamdar AR, Meadows TA, Roselli EE, et al. Multidetector computed tomographic angiography in planning of reoperative cardiothoracic surgery. Ann Thorac Surg 2008;85:1239-45.

8. Dolmaci OB, Farag ES, Boekholt SM, van Boven WJP, Kaya A. Outcomes of cardiac surgery after mediastinal radiation therapy: a single-center experience. J Card Surg 2020;35:612-9.

9. Desai MY, Wu W, Masri A, et al. Increased aorto-mitral curtain thickness independently predicts mortality in patients with radiation-associated cardiac disease undergoing cardiac surgery. Ann Thorac Surg 2014;97:1348-55.

10. Forteza A, Centeno J, Osipina V, et al. Outcomes in aortic and mitral valve replacement with intervalvular fibrous body reconstruction. Ann Thorac Surg 2015;99:838-45.

11. De Oliveira NC, David TE, Armstrong S, Ivanov J. Aortic and mitral valve replacement with reconstruction of the intervalvular fibrous body: an analysis of clinical outcomes. J Thorac Cardiovasc Surg 2005;129:286-90.

12. Vukicevic M, Mosadegh B, Min JK, Little SH. Cardiac 3D printing and its future directions. J Am Coll Cardiol Img 2017;10:182-93.

13. De Oliveira-Santos M, Oliveira-Santos E, Gondalves L, Silva Marques J. Cardiovascular three-dimensional printing in non-congenital percutaneous interventions. Heart Lung Circ 2019;28:1525-34.

14. Tuncay V, van Doijen PMA. 3D printing for heart valve disease: a systematic review. Eur Radiol Exp 2019;3:9.

15. Allen CH, Patterson T, Prendergast B, et al. Simultaneous transcatheter double valve treatment of mediastinal radiation-induced severe calcific aortic and mitral stenosis. J Am Coll Cardiol Case Rep 2020;2:1443-7.

16. Blank P, Naoum C, Dvir D, et al. Predicting LVOT obstruction in transcatheter mitral valve implantation: concept of the neo-LVOT. J Am Coll Cardiol Img 2017;10:482-5.

17. Guerrero M, Dvir D, Himbert D, et al. Transcatheter mitral valve replacement in native mitral valve disease with severe mitral annular calcification: results from the first multicenter global registry. J Am Coll Cardiol Intv 2016;9: 1361-71.

18. Yoon S-H, Bleiziffer S, Latib A, et al. Predictors of left ventricular outflow tract obstruction after transcatheter mitral valve replacement. J Am Coll Cardiol Intv 2019;12:182-93.

**KEY WORDS** 3D print, finite elements analysis, multimodality imaging, transcatheter aortic valve replacement, transcatheter mitral valve replacement

**APPENDIX** For a supplemental video, please see the online version of this paper.
A woman in her 50s developed acute coronary syndrome with de Winter pattern electrocardiogram (ECG). A coronary angiography revealed diagonal branch lesion caused by spontaneous coronary artery dissection, whereas the left-anterior descending artery was intact. The ECG change was transient and returned to normal without treatment 2 h later. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1451–3) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A woman in her 50s presented to the emergency room because of chest pain lasting for 90 min. Twenty years before this presentation, she had myocardial infarction (MI) with atrioventricular (AV) branch lesion of the right coronary artery (RCA), which was treated medically, and renal artery stenosis, which was treated with angioplasty.

Initial blood pressure was 138/80 mm Hg, heart rate was 70 beats/min, and respiratory rate was 30/min. Electrocardiogram (ECG) revealed marked down sloping ST-segment depression in V2 to V4 and mild ST-segment elevation in lead I and aVL (Figure 1A). Her next ECG, taken 39 min later during coronary angiography (CAG), revealed typical de Winter pattern with ST-segment depression in V2 to V5 and peaked T-wave in V3 to V5 (Figure 1B). Emergency CAG revealed high-grade abrupt tapering at the diagonal branch, which distributed parallel to the normal left anterior descending (LAD) artery (Figures 1D and 1E, Videos 1 and 2). There was no significant stenosis at the RCA (Figure 1F, Video 3). Because there was a Thrombolysis In Myocardial Infarction (TIMI) flow grade 3, and the morphology of the stenosis was consistent with type 2 spontaneous coronary artery dissection (SCAD), coronary intervention was deferred (1). Moreover, the history of renal artery stenosis (fibromuscular dysplasia) and complete resolution of AV branch lesion were also consistent with SCAD. The ECG change resolved in 2 h (Figure 1C), and her clinical course was stable. Repeat CAG 9 months later showed normalized diagonal lesion (Video 4).
The de Winter ECG pattern is usually caused by occlusion of the proximal LAD artery (2). de Winter ECG patterns caused by non-LAD artery lesion have been seldom reported. Montero Cabezas reported a case in which occlusion of the diagonal branch was the cause (3). The diagonal branch was large and distributed parallel to the LAD artery, as in the current case. Another important point learned from this case is that de Winter ECG pattern may reflect 1 frame of a dynamic ECG change, as shown in Figures 1A to 1C.

Recognition of de Winter ECG pattern is important, as it must be regarded as an ST-segment elevation MI (STEMI) equivalent requiring urgent CAG.

ACKNOWLEDGMENTS The authors thank Editage for their English-language editing.

ADDRESS FOR CORRESPONDENCE: Dr. Kazuhito Hirata, Division of Cardiology, Okinawa Chubu Hospital, 281 Miyazato, Uruma, Okinawa 904-2293, Japan. E-mail: kheart911@yahoo.co.jp.

**FIGURE 1** Electrocardiogram

(A) Initial electrocardiogram (ECG) showing down-sloping ST-segment depression without T peaking. (B) ECG taken at the time of coronary angiography (CAG), showing the classic de Winter pattern. (C) ECG taken 2 h post-CAG with resolution of ST-segment changes. (D) Left anterior oblique and (E) right anterior oblique: the middle of diagonal branch shows high grade tapering (white arrow), whereas left-anterior descending artery is normal. (F) Right coronary artery is normal.
REFERENCES

1. Hayes SN, Kim ESH, Saw J, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. Circulation 2018; 137:e523–57.

2. Verouden NJ, Koch KT, Peters RJ, et al. Persistent precordial “hyperacute” T-waves signify proximal left anterior descending artery occlusion. Heart 2009;95:1701–6.

3. Montero Cabezas JM, Karalis I, Schalij MJ. de Winter electrocardiographic pattern related with a non-left anterior descending coronary artery occlusion. Ann Noninvasive Electrocardiol 2016;26:526–8.

KEY WORDS acute myocardial infarction, de Winter pattern, spontaneous coronary artery dissection

APPENDIX For supplemental videos, please see the online version of this paper.
Left Ventricular Assist Device Outflow Cannula Obstruction

Importance of Multimodality Imaging

Majid Asawaeer, MD,a Sajid Kadir, MD,a Arif Albulushi, MD,a Anthony W. Castleberry, MD,b Yiannis S. Chatzizisis, MD, PhD

ABSTRACT

One of the dreaded complications of left ventricular assist device implantation is mechanical obstruction of the device secondary to pump thrombosis or mechanical outflow cannula obstruction. We describe a case of outflow cannula obstruction caused by kinking and twisting of the outflow graft after surgical manipulation of the pump. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1454–6) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Our patient was a 66-year-old man with ischemic cardiomyopathy. He had a HeartMate II (Abbott, Abbott Park, Illinois) left ventricular (LV) assist device (LVAD) implanted in 2013, and he presented with dyspnea on exertion and low-flow, high-power LVAD alarms. He denied chest pain or dizziness. On physical examination, he appeared in no distress, his mean arterial pressure was 76 mm Hg, his heart rate was 80 beats/min, and his oxygen saturation on room air was 97%. No elevated jugular venous pressure or peripheral edema was noted. A 12-lead electrocardiogram showed no acute ischemic changes. His blood work-up was significant for a subtherapeutic international normalized ratio with an elevated lactic acid dehydrogenase level. The differential diagnosis included pump thrombosis, anticoagulation noncompliance, and hemolysis secondary to cannula malpositioning, kinking, or pannus formation on the inflow or outflow cannula. He was started on a bivalirudin infusion. Despite adequate anticoagulation, the lactic acid dehydrogenase levels continued to rise (from 787 U/l on admission to 1,505 U/l). A pre-pump exchange echocardiogram showed normal LV size with severely depressed LV function (LV ejection fraction 5% to 10%), with an inflow cannula velocity of 150 to 200 cm/s and an outflow cannula velocity of 180 to 220 cm/s. Given his prohibitive surgical risk for redo thoracotomy, he underwent pump exchange with a HeartMate II LVAD through a left subcostal incision. The outflow cannula velocity went up to 347 cm/s (peak gradient 48 mm Hg) intraoperatively and post-exchange on transesophageal echocardiogram (Figure 1A). Chest computed tomography angiography revealed outflow cannula obstruction secondary to kinking and twisting of the outflow graft (Figures 1B and 1C). Given the prohibitive risk for further surgical procedures and the patient’s wishes, conservative management was pursued.
LVAD outflow obstruction is usually caused by external compression from mediastinal tissue, twisting or kinking of the outflow graft, or accumulation of gelatinous protein matrix or biodebris (1,2). The outflow graft may be subject to twisting and kinking, resulting in decreased flow and hemodynamic instability, especially during surgical manipulation, as noted in our case. Multimodality imaging should be considered, including chest radiography and echocardiogram to assess biventricular function and size and cannula flow velocities, and, if results are equivocal, computed tomography angiography to delineate possible mechanical complications of LVAD (Figure 1D) (3). In our case, pathological examination of the explanted pump revealed fragments of thrombus on the inflow stator region, indicating that our patient had both pump thrombosis and outflow cannula obstruction as causes of the low-flow, high-power alarms. Extra attention during cardiac surgical interventions is needed to avoid outflow cannula mechanical obstruction.

**FIGURE 1** LVAD Outflow Cannula Obstruction

(A) Transesophageal (TEE) echocardiogram with continuous wave (CW) Doppler imaging demonstrating a high gradient across the outflow cannula, (B) computed tomography (CT) angiography, and (C) 3-dimensional rendering images showing left ventricular assist device (LVAD) outflow graft narrowing (arrows) consistent with kinking and twisting of the graft proximal to the anastomosis site at the ascending aorta. (D) Algorithmic approach to low-flow LVAD alarms. LV = left ventricular; RV = right ventricular.
ADDRESS FOR CORRESPONDENCE: Dr. Yiannis S. Chatzizisis, Cardiovascular Division, University of Nebraska Medical Center, 982265 Nebraska Medical Center, Omaha, Nebraska 68198. E-mail: ychatzizisis@icloud.com.

REFERENCES

1. Barac YD, Nevo A, Schroder JN, Milano CA, Daneshmand MA. LVAD outflow graft role in pump thrombosis. ASAIO J 2017;63:14–23.

2. Trankle CR, Grizzard JD, Shah KB, et al. Left ventricular assist device outflow graft compression: incidence, clinical associations and potential etiologies. J Card Fail 2019;25:545–52.

3. Estep JD, Stainback RF, Little SH, Torre G, Zoghbi WA. The role of echocardiography and other imaging modalities in patients with left ventricular assist devices. J Am Coll Cardiol Img 2010;3:1049–64.

KEY WORDS cardiac assist devices, cardiomyopathy, computed tomography
Integrated Imaging to Investigate Low-Flow Alarms of Left Ventricular Assist Devices*

Alberto Aimo, MD,a Giacomo Bianchi, MD, PHD,b Giuseppe Vergaro, MD, PhD,a,c

With the ongoing shortage of available organs for heart transplantation, mechanical circulatory support devices have been increasingly used to manage acute and chronic heart failure that is refractory to medical therapy (1). In particular, the introduction of left ventricular (LV) assist devices (LVADs) has revolutionized this field, by extending life as either a bridge to transplantation or a destination therapy (1). Although first-generation devices provided pulsatile flow, current LVAD devices produce continuous flow and are further classified according to their impeller technology (i.e., axial or centrifugal). Normal components include the pump, inflow and outflow cannulas, a driveline, and an external controller. Clinical trials and real-world experience have revealed the possibility of many potentially life-threatening complications (2). These complications can be categorized as LVAD-specific and LVAD-associated complications, and many of them can result in severe patient morbidity and mortality (2). LVAD-specific complications include device malfunctioning or failure, pump thrombosis, and suction events, whereas LVAD-associated complications include bleeding, cerebrovascular events, infection, right ventricular failure, arrhythmias, and aortic regurgitation (2).

The evaluation and management of patients with LVAD require a team-based approach, and consultation with an LVAD specialist is recommended (3). LVAD dysfunction may be indicated by device alarm systems sensing a low pump flow with high power, possibly associated with LVAD power spikes, ventricular arrhythmias, or clinical evidence of pulmonary congestion or tissue hypoperfusion. The first step in evaluating the patient with alarms reported by the LVAD controller is the assessment of clinical status, to determine the treatment priority and the setting where the patient should be treated (i.e., medical department or intensive care unit).

One of the complications that can generate a low-flow and high-energy consumption alarm is pump thrombosis. Thrombosis of the device can occur in any of its parts (inflow cannula, rotor, outflow cannula, and distal anastomosis zone) and recognizes different causes depending on the zone. At the inflow level, thrombosis can be determined by inadequate myectomy at the time of device implantation or by positioning against the interventricular septum. At the impeller level, it is influenced by the design of the pump itself (axial vs. centrifugal, fully magnetic levitation vs. magnetic rotation with blood displacement) and by operational rotations per minute. At the outflow graft level, thrombosis can occur by twisting, kinking, or ab extrinseco compression, as well as by fibrin platelet thrombosis.

In suspected pump thrombosis, laboratory examination is crucial because it can predict pump thrombosis at an early stage, before machine alarms sound or imaging is obtained (4). Combining an elevated lactate dehydrogenase (LDH) and plasma-free

*Editorials published in JACC: Case Reports reflect the views of the authors and do not necessarily represent the views of JACC: Case Reports or the American College of Cardiology.

From the aInstitute of Life Sciences, Scuola Superiore Sant’Anna, Pisa, Italy; bDivision of Adult Cardiac Surgery, Fondazione Toscana Gabriele Monasterio, Massa, Italy; and the cDivision of Cardiology and Cardiovascular Medicine, Fondazione Toscana Gabriele Monasterio, Pisa, Italy. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

ISSN 2666-0849

https://doi.org/10.1016/j.jaccas.2020.07.006
hemoglobin reading with other common markers for hemolysis, such as reduced levels of hemoglobin, hematocrit, and haptoglobin and increased indirect bilirubin levels, is strongly suggestive of ongoing hemolysis from pump thrombosis.

Multimodality imaging is then crucial to refine or rule out the pump thrombosis and its location. Chest radiography allows assessment of the position of the inflow cannula and the presence of pulmonary congestion secondary to insufficient unloading (from outflow obstruction). Transthoracic echocardiography (TTE) is the primary imaging modality to facilitate pre-LVAD management and for post-implantation monitoring because it is noninvasive, is widely available, and can be performed at the bedside (5). A comprehensive LVAD evaluation consists of standard TTE with a focus on biventricular size and function, valvular function, velocities in the inflow and outflow conduits, contribution of the native left ventricle and LVAD to systemic flow, pulmonary pressures, and evidence of LV recovery (5). Investigators have proposed performing baseline TTE 2 weeks after implantation and then routinely every 3 to 6 months and as clinically indicated (5). If echocardiographic evaluation is technically difficult despite the use of a contrast agent, transesophageal echocardiography is usually performed when LVAD dysfunction or other complications are suspected (5).

Cardiac computed tomography (CT) angiography can be used if there is persistent clinical concern for inflow-outflow graft thrombosis or malposition in the setting of a nondiagnostic echocardiogram (6). CT angiography allows an accurate evaluation of LVAD cannulas. Unlike echocardiography, CT angiography is not limited by acoustic windows and lacks acoustic shadowing. Furthermore, LVAD cannulas can be
interrogated from multiple views, thus permitting direct visualization (6). The sensitivity and specificity of CT angiography to detect cannula thrombosis or inflow cannula malposition by using intraoperative findings as the gold standard are as high as 85% and 100%, respectively (7). Possible limitations of CT angiography are the need for radiation exposure and the risk of nephrotoxicity from iodinated contrast agents (8). Additionally, when there is evidence of outflow graft lumen narrowing in the portion covered by the bend relief, CT angiography does not allow the clinician to discriminate between intraluminal thrombosis and extrinsic compression by biodebris between the bend relief and the outflow graft, although treatment of these 2 conditions is radically different (e.g., anticoagulation vs. percutaneous stenting within the graft) (8). Narrowing of the outflow graft lumen is not a rare occurrence; it was found in 14% of patients in a recent case series (8). Apart from direct surgical revision of the device, luminal thrombosis and extrinsic compression can be differentiated by invasive graft examination with intravascular ultrasound (8).

In this issue of JACC: Case Reports, Asawaeer et al. (9) reappraised the topics of LVAD complications and the choice of imaging techniques for identification of these complications. They reported the case of a 66-year-old man who underwent HeartMate II (Abbott Laboratories, Abbott Park, Illinois) LVAD implantation in 2013 for end-stage ischemic heart failure and who recently presented with exertional dyspnea and high-power LVAD alarms. Laboratory examinations showed an international normalized ratio lower than the therapeutic range and elevated LDH levels, 2 findings that were compatible with (but by no means specific for) thrombotic events. This prompted the treating physicians to start anticoagulation therapy with bivalirudin, which did not prevent further LDH elevation. Echocardiography revealed inflow and outflow velocities ranging around the upper reference limit (2 m/s) (10). The patient underwent pump exchange through a left subcostal incision, but outflow cannula velocity rose to 3.5 m/s immediately after the exchange. At this point, CT angiography revealed an obstruction of the outflow cannula secondary to kinking and twisting, which were apparently attributed to device replacement. Interestingly, evaluation of the explanted pump showed thrombosis of the inflow stator region, which was considered the original cause of the low-flow alarm (9).

Asawaeer et al. (9) should be commended for presenting this interesting case and also for providing a simple diagnostic flowchart for the use of imaging techniques to assess patients with low-flow alarms. A schematic depiction of the main causes of low-flow, high-power LVAD alarms is provided in the Central Illustration. The first-line imaging examination is TTE, which may be augmented by the use of ultrasound contrast agents or transesophageal echocardiographic evaluation. Echocardiography should allow the clinician to evaluate cannula position, flow velocities, and biventricular size and function. The Central Illustration shows the following possibilities: malposition of the inflow or outflow cannula, right ventricular dysfunction, indirect evidence of pump malfunctioning (increased LV size with reduced flow velocities), pericardial tamponade, or inconclusive findings (particularly increased flow velocities with an unclear mechanism). In the last case, problems with the inflow or outflow cannulas (thrombosis, malpositioning, or kinking) can be readily detected by CT angiography. As stated earlier, CT angiography does not allow discrimination between intraluminal thrombosis and extrinsic compression of the outflow graft. Therefore, intravascular ultrasound evaluation or direct surgical revision of the device is warranted.

ADDRESS FOR CORRESPONDENCE: Dr. Giuseppe Vergaro, Division of Cardiology and Cardiovascular Medicine, Fondazione Toscana Gabriele Monasterio, Via Moruzzi, 1, 56124 Pisa, Italy. E-mail: vergaro@ftgm.it.
8. Trankle CR, Grizzard JD, Shah KB, et al. Left ventricular assist device outflow graft compression: incidence, clinical associations and potential etiologies. J Card Fail 2019;25:545–52.

9. Asawaer M, Kadir S, Albulushi A, Castleberry AW, Chatzizisis YS. Left ventricular assist device outflow cannula obstruction: importance of multimodality imaging. J Am Coll Cardiol Case Rep 2020;2:1454–6.

10. Stainback RF, Estep JD, Agler DA, et al. Echocardiography in the management of patients with left ventricular assist devices: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2015;28:853–909.

**KEY WORDS** cardiac assist devices, cardiomyopathy, computed tomography
A Novel Treatment for a Rare Cause of Cardiogenic Shock
Mohsin Chowdhury, MD,a Bani M. Azari, MD, PhDb Nihar R. Desai, MD, MPH,c Tariq Ahmad, MD, MPHE

ABSTRACT
Drug rash with eosinophilia and systemic symptoms (DRESS)–associated myocarditis is a rare but life-threatening adverse drug reaction with a very high mortality rate and no effective therapies. We report a case of DRESS-associated myocarditis complicated by cardiogenic shock successfully treated with a novel targeted therapy.

HISTORY OF PRESENTATION
A 37-year-old Hispanic woman with no cardiac history presented with facial swelling, chills, night sweats, and diffuse morbilliform rash approximately 3 weeks after being started on a course of minocycline for acne vulgaris. She was found to have eosinophilia, transaminitis, and atypical lymphocytes on peripheral smear. At that time, her cardiovascular examination was unremarkable, electrocardiogram did not show any significant abnormalities, and troponin T concentration was within normal limits. A transthoracic echocardiogram demonstrated a normal left ventricular function with left ventricular ejection fraction (LVEF) of 68%.

LEARNING OBJECTIVES
- To understand the pathophysiology and clinical manifestation of DRESS-associated eosinophilic myocarditis.
- To review the mechanism of tofacitinib and understand its potential role in treatment of DRESS myocarditis.

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, severe, and potentially life-threatening adverse drug reaction. Visceral organ involvement typically manifests as hepatic dysfunction, but may include lymphadenopathy, nephritis, interstitial pneumonitis, and myocarditis. Eosinophilic myocarditis is a fatal and underrecognized manifestation of DRESS with a mortality rate of more than 80% (1). Currently, there are no effective therapies for this syndrome. Here, we report a case of DRESS-associated myocarditis complicated by cardiogenic shock successfully treated with a novel targeted therapy, Janus kinase (JAK) 1/3 inhibitor tofacitinib (Xeljanz, Pfizer, New York, New York).
PAST MEDICAL HISTORY

The patient has a history of acne vulgaris. She does not have any known cardiac history.

DIFFERENTIAL DIAGNOSIS

Cutaneous drug eruptions, viral or bacterial infections, hypereosinophilic syndrome, lymphoma, autoimmune connective tissue disease, and DRESS syndrome were on the differential diagnosis for our patient’s presentation. She was diagnosed with definite minocycline-induced DRESS syndrome based on RegiSCAR scoring criteria (2,3).

INVESTIGATIONS

She was initially treated with high doses of methylprednisolone followed by prednison, with resolution of her rash. She was discharged home. Following 2 weeks of therapy with high-dose prednisone, she was readmitted with chest tightness and dyspnea, and was found to be in cardiogenic shock requiring vasopressors and intra-aortic balloon pump (IABP). TTE demonstrated severe global hypokinesis of the left ventricle, LVEF of <20%, N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of 21,300 pg/ml, and cardiac troponin T (cTnT) of 2.53 ng/ml (Figure 1).

Cardiovascular magnetic resonance imaging demonstrated a nonischemic pattern of delayed enhancement suggestive of myocarditis (Figure 2). An endomyocardial biopsy was not performed due to ensuing clinical instability.

MANAGEMENT AND CLINICAL COURSE

Despite initiation of high-dose methylprednisolone and cyclosporine, the patient continued to rapidly decline, and therapeutic options were limited to urgent mechanical circulatory support. With limited treatment options available, we elected for a targeted treatment strategy using tofacitinib (10 mg twice daily), a JAK 1/3 inhibitor, due to its mechanism aimed at suppression of interleukin (IL)-5, a potent eosinophil cytokine. Within days of tofacitinib initiation, she was able to be weaned off of inotropes and the IABP. A repeat TTE revealed an LVEF of 45%, natriuretic peptide levels decreased dramatically (1,860 pg/ml), and cTnT levels were undetectable.

As an outpatient, over the next 6 months, the patient remained free of heart failure symptoms and tolerated up-titration of neurohormonal agents. Of note, during this time she developed near-complete paraplegia with loss of spinal reflexes. Magnetic resonance imaging of the brain and total spine demonstrated leptomeningeal disease involving the lumbar levels and cauda equina as well as the skull base—no clear cause was found, but it was presumed...
to have the same pathophysiological basis as her cardiac dysfunction.

Due to her continued off-label use, the patient had insurance denial for tofacitinib. She was unable to afford the out-of-pocket cost of therapy, was forced to self-discontinue tofacitinib for 2 weeks, and was readmitted with profound cardiogenic shock requiring inotropes and IABP. A repeat TTE showed

Cardiovascular magnetic resonance imaging with contrast and velocity flow (vertical long-axis view [left] and short-axis view [right]) demonstrated nonischemic patterns of delayed enhancement suggestive of myocarditis (arrows).

18F-fluorodeoxyglucose positron emission tomography demonstrated active inflammation in the mid to apical inferior left ventricle, right ventricle, right atrium, and liver.
severe left ventricular dysfunction with an LVEF of 30%, her NT-proBNP level was 28,300 pg/ml, and troponin T was 9.44 ng/ml. 18F-fluorodeoxyglucose positron emission tomography performed at the time demonstrated focal uptake in the mid to apical inferior wall, mild diffuse update in the right atrium and right ventricle, and diffuse uptake in the liver (Figure 3). This was consistent with active cardiac and hepatic inflammation in a pattern consistent with eosinophilic myocarditis and hepatitis. Tofacitinib (10 mg twice daily) was promptly reintroduced. She rapidly recovered; she was weaned off of cardiac support, she tolerated neurohormonal blockade, and TTE performed 2 days after tofacitinib reintroduction demonstrated an EF of 45% with NT-proBNP levels that had decreased to 4,750 pg/ml and undetectable cTnT.

The patient was started on higher-dose steroids for her neurological symptoms. In this setting, the decision was made to decrease tofacitinib dosing by one-half (from 10 mg twice daily to 5 mg twice daily). With this, she developed symptomatic heart failure and needed hospitalization. Her LVEF was noted to be 15% and NT-proBNP level was 28,000 pg/ml; cTnT was not checked. Tofacitinib at the higher dosing (10 mg twice daily) was initiated and symptoms of heart failure improved rapidly over the course of days.

**DISCUSSION**

Eosinophilic myocarditis is an uncommon but often fatal late complication of DRESS that can occur up to several months after the original diagnosis. It is due to delayed hypersensitivity reaction rather than direct toxicity of the drug. The mechanism of eosinophilic myocarditis is due to eosinophilic tissue infiltration followed by eosinophilic degranulation leading to cardiomyocyte necrosis (4). Inflammatory cytokines are responsible for multiple steps in the pathways of eosinophilic infiltration, migration, and granular release. These cytokines transmit intracellular signaling for downstream gene expression through JAK signal transducer and activator of transcription proteins pathways. Cytokines bind to an
extracellular receptor, which dimerizes and phosphorylates signal transducer and activator of transcription protein that translocates to the nucleus, binds DNA, and initiates gene transcription. Currently, there are no effective therapies for eosinophilic myocarditis, and global immunosuppression is utilized as the mainstay of therapy. However, with the previously mentioned understanding of the pathophysiology, it is reasonable to hypothesize that inflammatory cascade leading to cardiomyocyte necrosis can be blunted or reversed by implementing a therapy that causes direct inhibition of eosinophilic migration, maturation, and degranulation.

Tofacitinib (Xeljanz) is an oral JAK1/JAK3 inhibitor that is approved for the treatment of rheumatoid arthritis and is undergoing trials for other autoimmune diseases. Tofacitinib has structural similarity to adenosine triphosphate, which enables it to act as a reversible, competitive inhibitor of adenosine triphosphate binding site in the catalytic cleft of the kinase domain of JAK proteins. By inhibition of the phosphorylation and activation of JAK1/JAK3 proteins, tofacitinib blocks signaling through the common chain-containing receptors for cytokines, including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, which leads to its antieosinophilic effects (Figure 4). The use and practice of targeted therapy precision medicine has become common practice in the field of oncology, and rheumatology and is now emerging in cardiovascular medicine. The effectiveness of a targeted therapy, which proved to be life-saving in this case, underscores the importance of investigating the utility of tofacitinib for the treatment of eosinophilic myocarditis.

FOLLOW-UP

Within 6 months, the patient’s LVEF had improved to 35% and NT-proBNP had decreased to 1,573 pg/ml. The last set of cardiovascular parameters (1.5 years post-initial hospitalization) revealed an LVEF of 45% and NT-proBNP of 406 pg/ml. She remains on tofacitinib through the manufacturer compassionate use program. She has not experienced any adverse events related to the drug.

CONCLUSIONS

To our knowledge, this is the first reported case of using a targeted JAK inhibitor to treat DRESS-associated myocarditis. Our case highlights the novel mechanism and potential for targeted therapy for the treatment of eosinophilic myocarditis, a rare but fatal illness.

ADDRESS FOR CORRESPONDENCE: Dr. Mohsin Chowdhury, Beth Israel Deaconess Medical Center, Harvard Medical School, 185 Pilgrim Road, Baker 4, Boston, Massachusetts 02215. E-mail: mchowdhu@bidmc.harvard.edu.

REFERENCES

1. Bourgeois GP, Cafardi JA, Groyzman V, Hughey LC. A review of DRESS-associated myocarditis. J Am Acad Dermatol 2012;66:e229–36.
2. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. Am J Med 2011;124:588–97.
3. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2007;156:609-11.
4. Brambatti M, Matassini MV, Adler ED, Klingel K, Camici PG, Ammirati E. Eosinophilic myocarditis: characteristics, treatment, and outcomes. J Am Coll Cardiol 2017;70:2363-75.

KEY WORDS cardiomypathy, DRESS, eosinophilia, myocarditis, shock, tofacitinib
Prior Authorization
Overwhelming Burden and Critical Need for Reform*

Eugene Yang, MD, MS, Sushan Yang, MD

High health care expenditures in the United States have prompted health insurance carriers to increasingly rely on utilization management strategies such as prior authorization (PA) to lower costs. This process is plagued by inefficiency and overwhelming administrative burden at the expense of patient safety. Patients wait for decisions regarding coverage approval for days or weeks, only to find that their coverage is denied. Unfortunately, the patients who most require these services can least afford care delays.

In this issue of JACC: Case Reports, Chowdhury et al. (1) describe a case of a patient who developed drug rash with eosinophilia and systemic symptoms syndrome leading to eosinophilic myocarditis and cardiogenic shock. The patient did not respond to high-dose steroids and immunosuppression but quickly improved with tofacitinib, a JAK1/3 (Janus kinase 1/3) inhibitor. Following discharge, the insurance carrier denied further coverage of this medication. The patient could not afford its cost, stopped taking it, and then needed to be rehospitalized for recurrent cardiogenic shock. Tofacitinib was reinitiated with rapid clinical improvement.

Reports of adverse patient outcomes resulting from PA requirements are not uncommon. In a recent American Medical Association survey on PA (2), 91% of physicians reported that patients requiring necessary care experienced care delays, and 75% of patients abandoned their treatments because of obstacles associated with the PA process. Overall, 91% of physicians believed that PA negatively impacted patient outcomes. Recent studies have demonstrated how PA directly results in patient harm. When PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitors were first introduced, over 45,000 patients received prescriptions within the first year of Food and Drug Administration approval. Only half received coverage approval and one-third of those approved abandoned treatment because of high copays (3). Patients who were denied coverage or discontinued treatment had significantly higher rates of acute coronary syndrome, coronary intervention, stroke, and cardiac arrest compared with those who took the medication (4).

To prevent these adverse outcomes, clinicians invest significant resources to ensure that appropriate care is accessible to patients. Physicians and staff spend over 20 h/week interacting with health plans. That translates to an annual opportunity cost of approximately $70,000 per practice and $31 billion nationally (5). The amount of time wasted on these nonclinical activities is a leading cause of physician burnout (6,7).

In response to the heavy load PA places on clinicians, the American College of Cardiology (ACC) has been actively working to find solutions. The ACC Prior Authorization Reporting Tool (PARTool) was developed to collect PA denial information. Preliminary data establish that many PA requests are denied even though such services are deemed “appropriate” based on appropriate use criteria. Over 50% of denied services either do not lead to further peer-to-peer discussion or are denied despite appeals (8). In response, the ACC established guiding...
principles for PA reform (9) and has set a foundation for advocacy efforts at the state and national levels.

In 2016, the first bill (Senate Bill [SB] 129) addressing PA reform was passed in Ohio (10). SB 129 improved transparency and streamlined the PA process. Insurance carriers are mandated to disclose requirements for PA approval and provide 30-day notice of any new requirements before implementation. Insurers must provide approval decisions within specified deadlines, and once PA requests are approved, they cannot be retroactively denied. Converting PA to an electronic format also streamlined the appeals process. By engaging key

| Year | State | Bill | Status | Disclose PA Services and Requirements | Specify Notification Time of PA Changes | Specify Duration of PA Validity | Prohibit Retrospective Denial of Previously Approved PA | Prohibit PA for Emergency Services | Deadline for PA Decision |
|------|-------|------|--------|--------------------------------------|----------------------------------------|----------------------------------|-------------------------------------------------|----------------------------|-------------------------|
| 2016 | Ohio  | SB 129 | Signed | X                                   | X                                      | X                               | X                                               | X                                         |
| 2016 | Delaware | HB 381 | Signed | X                                   | X                                      | X                               | X                                               | X                                         |
| 2018 | New Jersey | A3845 | Introduced | X                                      | X                                      | X                               | X                                               | X                                         |
| 2019 | Colorado  | HB 19-1221 | Signed | X                                   | X                                      | X                               | X                                               | X                                         |
| 2019 | Kentucky | SB 54 | Signed | X                                   | X                                      | X                               | X                                               | X                                         |
| 2019 | Montana | HB 555 | Signed | X                                   | X                                      | X                               | X                                               | X                                         |
| 2019 | Virginia | SB 1607 | Signed | X                                   | X                                      | X                               | X                                               | X                                         |
| 2019 | West Virginia | HB 2351 | Signed | X                                   | X                                      | X                               | X                                               | X                                         |
| 2019 | New York | AO4521 | Introduced | X                                      | X                                      | X                               | X                                               | X                                         |
| 2019 | Pennsylvania | SB 920 | Introduced | X                                      | X                                      | X                               | X                                               | X                                         |
| 2019 | National | HR 3107 | Introduced | X                                      | X                                      | X                               | X                                               | X                                         |
| 2020 | Washington | SB 6404 | Signed | X                                   | X                                      | X                               | X                                               | X                                         |
| 2020 | Illinois | HB 510 | Introduced | X                                      | X                                      | X                               | X                                               | X                                         |
| 2020 | Minnesota | SF 3204 | Introduced | X                                      | X                                      | X                               | X                                               | X                                         |
| 2020 | Oregon | HB 4102 A | Introduced | X                                      | X                                      | X                               | X                                               | X                                         |
| 2020 | Florida | SB 820 | Died | X                                   | X                                      | X                               | X                                               | X                                         |

**TABLE 1 Continued**

| Year | State | Honor Previously Approved PA | Review by Same Specialty Physician | Electronic PA Process | Report Statistics Regarding PA Requests | Other |
|------|-------|-------------------------------|-------------------------------------|-----------------------|-------------------------------------------|-------|
| 2016 | Ohio  | X                             | X                                   |                       | Standardize appeals process               |       |
| 2016 | Delaware | X                             | X                                   |                       | Limit use of PAs only to providers whose practice patterns differ significantly from those of peers |       |
| 2018 | New Jersey | X                             |                                      |                       |                                           |       |
| 2019 | Colorado  | X                             |                                      |                       |                                           |       |
| 2019 | Kentucky | X                             |                                      |                       |                                           |       |
| 2019 | Montana | X                             |                                      |                       |                                           |       |
| 2019 | Virginia | X                             |                                      |                       | Prohibit PA for certain services associated with substance abuse treatment |       |
| 2019 | West Virginia | X                             | X                                   |                       | Practitioners meeting specified requirements may be exempted from PA process for 6 months |       |
| 2019 | New York | X                             |                                      |                       | Duration of PA validity only applies to medications |       |
| 2019 | Pennsylvania | X                             | X                                   |                       | Provides framework for exempting patients from step therapy |       |
| 2019 | National | X                             | X                                   |                       | Automatic PA decisions may be applied for routinely approved services |       |
| 2020 | Washington | X                             |                                      |                       |                                           |       |
| 2020 | Illinois | X                             | X                                   | X                     | PA is automatically authorized if carrier fails to comply with any provisions prohibit denial of services associated with approved procedure or for certain services associated with substance abuse treatment |       |
| 2020 | Minnesota | X                             | X                                   | X                     | Standardize appeals process               |       |
| 2020 | Oregon | X                             |                                      |                       |                                           |       |
| 2020 | Florida | X                             |                                      |                       | Provides framework for exempting patients from step therapy and prohibits denial of services associated with approved procedure |       |

HB — house bill; PA — prior authorization; SB — senate bill.
stakeholders including state medical societies, the Ohio bill passed without significant opposition.

Delaware also enacted PA reform (House Bill [HB] 381) following a 2011 case that garnered national attention when a patient was denied nuclear stress testing despite 2 physician appeals (11). Thirty-five days later, the patient presented to the emergency department and underwent urgent coronary artery bypass surgery. HB 381 carries many similar provisions to SB 129, but one key difference is that it specifies the duration of validity for approved PAs: medications for 1 year and services for 60 days (12).

In recent years, PA reform has gained traction in many states, with bills progressing through various stages of the legislative process (Table 1) (1). Most states have not achieved the same success as Ohio and Delaware because the bills are undermined by insurance lobbyists. Washington SB 6404 only requires carriers to provide data regarding approved, denied, and appealed requests (13). Other states have passed bills that are limited in scope but introduce new elements. Colorado HB 19-1211 urges carriers to limit the use of PA to providers whose practice patterns differ significantly from their peers (14). Virginia SB 1607 maintains continuity of care when patients transition between plans by mandating that previously approved PAs must be honored for a specified period (15), while West Virginia HB 2351 stipulates that PA appeals must be performed by a practitioner in a similar specialty (16). Additional states have introduced new legislation in the past 2 years (17–26).

At the national level, H.R. 3107 was introduced in 2019 (27). It strives to improve efficiency of the PA process for Medicare Advantage program participants. Under this bill, health plans would be mandated to standardize PA requirements, make the process electronic, automate decisions for routinely approved services, and increase transparency by reporting PA request statistics.

As this case report highlights, prior authorization can cause harm to patients and places overwhelming burdens on clinicians. To ensure patient access to timely, evidence-based care, PA must be regulated and standardized. Although several states have made progress in improving this process, many others still face considerable obstacles. Bringing key stakeholders together, including state medical societies, patient advocacy groups, and insurance plans, is critical to implementing meaningful PA reform. Now is the time.

ADDRESS FOR CORRESPONDENCE: Dr. Eugene Yang, University of Washington School of Medicine, Department of Medicine, Division of Cardiology, 1959 NE Pacific Street, Box 356005, Seattle, Washington 98195. E-mail: eyang01@uw.edu.
20. Minnesota Legislature. SF 3204. Available at: https://www.revisor.mn.gov/bills/bill.php?b=Senate&f=SF%203204&ssn=0&y=2019. Accessed May 15, 2020.

21. Montana Legislature. HB 555. Available at: http://laws.leg.mt.gov/legprd/LAW0210W%24BSIV.ActionQuery?P_BILL_NO1=555&P_BLTP_BILL_TYP_CD=HB&Z_ACTION=Find&P_SESS=20191. Accessed May 15, 2020.

22. New Jersey Legislature. Assembly, No. 3845. Available at: https://www.njleg.state.nj.us/2018/Bills/A4000/3845_I1.PDF. Accessed May 15, 2020.

23. New York State Assembly. A04521. Available at: https://assembly.state.ny.us/leg/?default_fld=&bn=A04521&term=2019&summary=Y&Actions=Y&Text=Y&Committee%26nbsp;Votes=Y&Floor%26nbsp;Votes=Y. Accessed May 15, 2020.

24. Oregon State Legislature. HB 4102 A. Available at: https://olis.leg.state.or.us/liz/2020R1/Masures/Overview/HB4102. Accessed May 15, 2020.

25. Pennsylvania General Assembly. Senate Bill 920. Available at: https://www.legis.state.pa.us/cfdocs/billInfo/billInfo.cfm?sYear=2019&sInd=0&body=S&type=B&bn=920. Accessed May 15, 2020.

26. Pennsylvania General Assembly. House Bill 1194. Available at: https://www.legis.state.pa.us/cfdocs/billInfo/billInfo.cfm?sYear=2019&sInd=0&body=H&type=B&bn=1194. Accessed May 15, 2020.

27. Library of Congress. H.R.3107 – Improving Seniors’ Timely Access to Care Act of 2019. Available at: https://www.congress.gov/bill/116th-congress/house-bill/3107. Accessed May 15, 2020.

**KEY WORDS** cardiogenic shock, myocarditis, prior authorization
Left Ventricular Thrombus Formation in the Setting of Normal Systolic Function

Christopher Svendsen, BA, a Eric Pauley, MD, b George A. Stouffer, MD b,c

ABSTRACT

We describe the case of a 42-year-old female with recurrent left ventricular (LV) thrombus and multiple embolic events despite having normal LV systolic function. The clinical presentation, associated conditions, diagnostic evaluation and treatment of patients with LV thrombus in the setting of normal LV systolic function are discussed.

(Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1470-4) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY

A 42-year-old female presented to another hospital after she was found unconscious at home. Vital signs on arrival at the hospital were a pulse of 72 beats/min, respiratory rate of 18 breaths/min, blood pressure of 131/70 mm Hg, and oxygen saturation of 94% on room air. Physical examination was remarkable for normal breath sounds and normal heart sounds without murmurs, rubs, or gallops. She was awake and oriented with slurred speech. Her strength was 5/5 in the left upper and lower extremities and 4/5 in the right upper and lower extremities. Cranial nerves II through XII, and sensation throughout her extremities and reflexes were intact. She was in rhabdomyolysis with acute kidney injury and had altered mental status. Cardiac magnetic resonance showed regions of acute and subacute extension of a chronic right frontal lobe infarct, with a distribution concerning for a proximal embolic source.

LEARNING OBJECTIVES

- To review the clinical presentation of patients with LV thrombus in the setting of normal LV systolic function.
- To understand underlying conditions that have been associated with the development of LV thrombus in the setting of normal LV systolic function.
- To review the evaluation and management of patients with LV thrombus in the setting of normal LV systolic function.

MEDICAL HISTORY

The patient had hypertension, hyperlipidemia, type 2 diabetes, chronic kidney disease, and a 4-year history of multiple cerebrovascular accidents (CVA) and used tobacco. A left ventricular (LV) mass had been identified 2 years previously, and the patient was treated with aspirin and rivaroxaban for an unknown period of time. She had stopped taking rivaroxaban due to financial concerns.
DIFFERENTIAL DIAGNOSIS

Given her history of LV thrombus and multiple CVAs, the most likely cause was recurrent LV thrombus with embolization. Other potential causes of CVA in a 42-year-old female would include paroxysmal atrial fibrillation, deep vein thrombosis with a patent foramen ovale or atrial septal defect, vasculitis, and intracerebral pathology.

INVESTIGATIONS

An echocardiogram showed no valvular abnormalities, normal LV systolic function with an ejection fraction of 55% to 60%, and a pedunculated mobile 2.5- x 0.9-cm mass at the apex of the LV (Figure 1, Video 1). Electrocardiography showed sinus tachycardia without ischemic changes (Figure 2). Cardiac magnetic resonance confirmed the presence of an LV...
mass and normal LV systolic function (Figures 3A and 3B, Video 2). Perfusion sequence imaging showed no perfusion in the mass (Figure 3C), and late gadolinium imaging with inversion time (TI) of 270 (Figure 3D) or TI of 700 (image not shown) showed no enhancement and a low signal. These findings are highly suggestive of thrombus as most cardiac tumors will take up gadolinium (1). Angiography showed a mild narrowing in the proximal left circumflex artery but no evidence of significant coronary artery disease (Figures 3E and 3F). Bilateral popliteal artery thrombi were identified and suspected to be an embolic complication from the LV thrombus. 

Hematology evaluation found no evidence of a hypercoagulable state. Protein S and protein C activity levels were in the normal range (reference range, 83% to 123%). Factor V Leiden and factor II gene mutations were not present. Levels of β-2
glycoprotein immunoglobulin G (IgG) and IgM antibodies and anti-cardiolipin IgG and IgM antibodies were within normal limits. There was no evidence of a lupus anticoagulant. The patient denied any family history of clotting disorders. Age-appropriate screening for malignancy was unremarkable, including a mammogram, a Papanicolaou smear, and stool testing for occult blood.

**MANAGEMENT**

The patient underwent a thoracotomy with removal of a 2.5×1 cm mass lodged between the posterior medial papillary muscle, the crossing bands, and the septal wall. Pathological examination was consistent with an organizing thrombus. The patient’s rhabdomyolysis-induced acute kidney injury resolved. The patient was discharged to a long-term care facility on rivaroxaban.

**DISCUSSION**

LV thrombus with normal LV systolic function is rare, with only 31 cases reported in the medical literature. For these cases, the median age was 43 years (range: 39 to 60 years), with a slight male predominance (58%). The majority of patients presented with embolic complications (27 of 31 [87%]). Unlike the situation with the present patient, most cases occurred in the setting of an identifiable medical condition that carries an increased risk of thrombosis including connective tissue disease, ulcerative colitis, rheumatoid arthritis, Crohn’s disease, vasculitis, acute febrile neutrophilic dermatosis, or a malignancy (Table 1). No discernable predisposing factors were identified in the current patient.

The apex appears to be uniquely susceptible to LV thrombus formation. Most LV thrombi in patients with normal LV systolic function occur at the apex, with other locations in the septum and the mitral valve apparatus. The apex is also the most common site of thrombus in patients with myocardial infarction (2).

Treatment generally includes anticoagulation with or without surgical removal or systemic thrombolysis. There are no studies or guidelines to guide treatment of LV thrombus in patients with normal LV systolic function, but some insight can be gained from examining recommendations for treatment of LV thrombus in patients with compromised LV function. The 2013 American College of Cardiology Foundation/ American Heart Association ST-segment elevation myocardial infarction (STEMI) guidelines advise treatment with a vitamin K antagonist for 3 months with goal INR values of 2 to 2.5 or >2.5, respectively (3). The 2017 European Society of Cardiology STEMI guidelines advise treatment with a vitamin K antagonist for up to 6 months. The American Heart Association/American Stroke Association guidelines noted that dabigatran, rivaroxaban, or apixaban could be considered alternatives to vitamin K antagonists. Recurrence of LV thrombus and/or recurrent embolic events, as seen in the current case, have been previously reported in patients with LV thrombus and normal LV systolic function, suggesting that long-term anticoagulation may be needed (4–6).

**FOLLOW-UP**

At 12 months follow-up, the patient had not experienced any more thrombotic or embolic complications, and repeated echocardiography showed no recurrence of the LV mass and normal ventricular function. She continued to take rivaroxaban on a daily basis.

**CONCLUSIONS**

LV thrombus rarely occurs in patients with normal LV systolic function but is associated with a high rate of embolic complications. The cause is not clear, although most patients have an underlying malignancy, inflammatory condition, blood dyscrasia, or prothrombotic state. Recurrent thrombi have been reported in several patients suggesting that prolonged anticoagulation may be necessary.

**ADDRESS FOR CORRESPONDENCE:** Dr. George A. Stouffer, UNC Medical Center, CB 7075, Division of Cardiology, University of North Carolina Chapel Hill, North Carolina 27599-7075. E-mail: rstouff@med.unc.edu.

**TABLE 1** Disease States Reported in Patients with Left Ventricular Thrombus in the Setting of Normal Left Ventricular Systolic Function

| Inflammatory conditions                                      | Connective tissue disease | Ulcerative colitis | Rheumatoid arthritis | Crohn’s disease | Takayasu arteritis | Acute febrile neutrophilic dermatosis (Sweet syndrome) |
|--------------------------------------------------------------|----------------------------|--------------------|----------------------|-----------------|-------------------|-------------------------------------------------------|
| Malignancies                                                 | Breast cancer              | Myelogenous leukemia | Metastatic oat cell carcinoma of the lung | T-cell lymphoma |
| Blood dyscrasias                                             | Hypereosinophilia          | Essential thrombocythemia | Myelofibrosis |
| Hypercoagulable states                                       | Lupus anticoagulant        |                     |                      |                 |
| Medications                                                  | Tamoxifen                  | Erythropoietin      | Cocaine use         |                 |
| Miscellaneous                                                | Pheochromocytoma           | Congenital hepatic fibrosis |               |
REFERENCES

1. Motwani M, Kidambi A, Herzog BA, Uddin A, Greenwood JP, Plein S. MR imaging of cardiac tumors and masses: a review of methods and clinical applications. Radiology 2013;268:26–43.

2. Jugdutt BI, Sivaram CA, Wortman C, Trudell C, Penner P. Prospective two-dimensional echocardiographic evaluation of left ventricular thrombus and embolism after acute myocardial infarction. J Am Coll Cardiol 1989;13:554–64.

3. McCarthy CP, Vaduganathan M, McCarthy KJ, Januzzi JL, Bhatt DL, McEvoy JW. Left ventricular thrombus after acute myocardial infarction: screening, prevention, and treatment. JAMA Cardiol 2018;3:642–9.

4. Schmaier AH, Denenberg B. Left ventricular thrombus with normal left ventricular function and hyperaggregable platelets in a patient with polycystic disease of multiple organs. Am J Med Sci 1984;288:223–7.

5. Bose Reddy SC, Ziady GM, Zerbe T, Matesic C, Griffith B. Recurrence of a left ventricular thrombus after surgical excision in a young patient with normal left ventricular systolic function—a case report. Angiology 1993;44:923–8.

6. Iyer A, Marney L, Ipp S, Bough G, McCoombes D, Tam R. Recurrent left ventricular thrombus in Crohn’s disease: a rare presentation. Asian Cardiovasc Thorac Ann 2014;22:86–8.

KEY WORDS cardiac magnetic resonance, echocardiography, thrombus

APPENDIX For supplemental videos, please see the online version of this paper.
**MINI-FOCUS ISSUE: HEART FAILURE**

**CASE REPORT: CLINICAL CASE**

**Percutaneous Biventricular Hemodynamic Support Using Biatral Extracorporeal Membrane Oxygenation**

Iyad N. Isseh, MD, Mir B. Basir, DO, Khaldoon Alaswad, MD

**ABSTRACT**

We describe the use of a fully percutaneous, biatrial extracorporeal membrane oxygenation circuit, to provide biventricular support with left heart unloading by using a single TandemHeart (LivaNova, London, United Kingdom) circuit during high-risk percutaneous coronary intervention. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1475–9) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In this report, we present the use of fully percutaneous biatrial extracorporeal membrane oxygenation (BA-ECMO) for high-risk percutaneous coronary intervention (HRPCI) in a patient with severe biventricular failure and pulmonary hypertension.

**PAST MEDICAL HISTORY**

A 62-year-old man had a history of multivessel coronary artery disease that was diagnosed 6 months before admission, ischemic cardiomyopathy, pulmonary hypertension, insulin-dependent diabetes, chronic kidney disease, post-traumatic stress disorder, and severe traumatic kyphotic posture.

**HISTORY OF PRESENTATION**

Our patient presented to our emergency department (Henry Ford Hospital, Detroit, Michigan) for decompensated heart failure. His prior coronary angiography films were obtained and reviewed. He was evaluated by a cardiac surgeon, who deemed him a high risk for coronary artery bypass. The patient underwent Swan-Ganz catheter-guided diuresis and medical optimization and was subsequently discharged on guideline-directed medical therapy.

During his outpatient follow-up appointment in the advanced heart failure clinic, he continued to have Canadian Cardiovascular Society class II angina and New York Heart Association functional class III symptoms. He had a heart team discussion with specialists in advanced heart failure, cardiac surgery, and interventional cardiology. The plan was to undergo HRPCI with the goal of providing complete...
revascularization and subsequent reassessment of cardiac function before consideration of advanced heart failure therapies. In January 2018, our patient was admitted for elective HRPCI.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses included complex coronary artery disease, congestive heart failure in the setting of severe biventricular failure, and pulmonary hypertension. Our patient was planned to undergo elective HRPCI with mechanical circulatory support (MCS) to provide biventricular support with left-sided unloading.

INVESTIGATIONS

Coronary angiography (Videos 1 and 2) revealed the following: no left main coronary artery lesion; ostial chronic total occlusion of the left anterior descending coronary artery; an ostial to proximal critical lesion of the left circumflex artery; and mid-total occlusion of the dominant right coronary artery.

Echocardiography (Videos 3, 4, and 5) detected the following: severe left ventricular (LV) dysfunction with an estimated ejection fraction of 15% to 20%; moderate increase in LV cavity size; moderate decrease in right ventricular systolic function; and severe pulmonary hypertension.

Right-sided cardiac catheterization findings were as follows: mean right atrial (RA) pressure, 9 mm Hg; pulmonary artery systolic, diastolic, and mean pressure: 85 mm Hg, 35 mm Hg, and 52 mm Hg, respectively; mean pulmonary capillary wedge pressure, 30 mm Hg; along with reduced cardiac output and index by thermodilution: 3.2 l/min and 1.58 l/min/m²; and Fick: 3.47 l/min and 1.71 l/min/m², respectively. Pulmonary vascular resistance using Fick cardiac output was 6.9 WU.

MANAGEMENT

Given the underlying biventricular failure and invasive hemodynamics, BA-ECMO support was used (Figures 1A and 1B). A 24-F left femoral vein cannula was delivered to the inferior vena cava and right atrium; a 21-F right femoral vein cannula was delivered to the left atrium through transseptal puncture; both venous inflow cannulas were connected in a “Y” fashion through the inlet cannula to the TandemHeart and oxygenator (LivaNova, London, United Kingdom) providing 4 to 5 l/min of flow through a 19-F left femoral arterial outflow cannula; antegrade 6-F access was placed in the left femoral artery to assist with perfusion of the left lower extremity.

The patient underwent successful percutaneous coronary intervention (PCI) of the proximal to middle left circumflex artery and the proximal second obtuse marginal artery with bifurcation stenting;

**ABBREVIATIONS AND ACRONYMS**

BA-ECMO = biatrial extracorporeal membrane oxygenation
ECMO = extracorporeal membrane oxygenation
HRPCI = high-risk percutaneous coronary intervention
LA = left atrial
LV = left ventricular
MCS = mechanical circulatory support
PCI = percutaneous coronary intervention
RA = right atrial

**FIGURE 1** Biatrial Extracorporeal Membrane Oxygenation

(A) Still fluoroscopy of biatrial cannulas. (B) “Y” connector and circuit. CAUD = caudal; LA = left atrium; LAO = left anterior oblique; RA = right atrium.
successful chronic total occlusion PCI of the right coronary artery with 3 overlapping drug-eluting stents, the RCA CTO was crossed retrograde via left circumflex epicardial collateral vessels using reverse controlled antegrade and retrograde tracking (rCART). The procedure was performed over an externalized wire. Intravascular ultrasound was used for stent sizing and optimization. Angiographic results are seen in Videos 6 and 7. The left anterior descending artery was scheduled to undergo intervention at a later date.

The patient tolerated the procedure without complications. Results of invasive hemodynamic monitoring remained stable (Table 1). Flow probes attached to the RA and left atrial (LA) drainage cannulas revealed flow to be 2.8 l/min and 2.2 l/min, respectively. On completion of the procedure, the patient was admitted to the cardiac intensive care unit with BA-ECMO support.

Weaning from BA-ECMO occurred the following day. Hemodynamics remained stable, and he was successfully decannulated in the cardiac catheterization laboratory 24 h after the index procedure. He was subsequently discharged home in 72 h in good condition.

**FOLLOW-UP**

At 6-month follow-up with advanced heart failure and interventional cardiology specialists, he is alive and well. He reported Canadian Cardiovascular Society class I angina and New York Heart Association functional class II symptoms. He has been maintained on appropriate guideline-directed medical therapy and has not required advanced heart failure therapies.

**D I S C U S S I O N**

Hemodynamic instability during HRPCI can result from repeated transient interruptions of coronary blood flow, leading to myocardial ischemia and negative inotropic effects. Percutaneous MCS may prevent hemodynamic compromise during HRPCI, which may allow for a more complete revascularization (1). Venoarterial extracorporeal membrane oxygenation (ECMO) has increasingly been used in providing biventricular support. However, retrograde aortic flow through the arterial outflow cannula and a supraphysiologic afterload against which an impaired left ventricle is pumping can potentially lead to left ventricular distention. This phenomenon can lead to increased pulmonary capillary wedge pressure, pulmonary artery pressures, myocardial oxygen demand, and pulmonary edema. LV unloading has been proposed to counteract this through multiple strategies.

---

**TABLE 1** Right-Sided Heart Catheterization Hemodynamic Parameters Pre- and Post-BA-ECMO

| BA-ECMO       | Pre (Prior Admission for CHF) | Post (CICU) | Weaning (2-l Flow) |
|---------------|-------------------------------|-------------|-------------------|
| Mean RA (mm Hg) | 9                             | 10          | 12                |
| PA systolic/diastolic/mean (mm Hg) | 85/35/52                     | 28/15/19    | 34/22/26          |
| Mean PCWP (mm Hg) | 30                            | NA          | NA                |
| CO/cardiac index (Fick) (l/min) | 3.47/1.7                      | 6.2/3.1     | 5.1/2.5           |
| MAP (mm Hg) | 110                           | 100         | 100               |
| SVR (dynes/s/cm$^2$) | 2,328                         | 1,161       | 1,349             |

BA-ECMO = biventricular extracorporeal membrane oxygenation; CHF = congestive heart failure; CICU = cardiac intensive care unit; CO = cardiac output; MAP = mean arterial pressure; NA = not applicable; PA = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RA = right atrium pressure; SVR = systemic vascular resistance.

---

**TABLE 2** Characteristics of Different Forms of Percutaneous VA-ECMO

| "Conventional" VA-ECMO | TandemHeart and Oxygenator | BA-ECMO |
|-------------------------|---------------------------|---------|
| **Pump mechanism**      | Centrifugal               | Centrifugal | Centrifugal |
| **Flow**                | >4 l/min                  | >4 l/min | >4 l/min |
| **Cannula size**        | 21-F to 25-F inflow; 15-F to 19-F outflow | 21-F inflow; 15-F to 19-F outflow | 21-F to 25-F inflow (RA); 21-F inflow (LA); 15-F to 19-F (outflow) |
| **Cannula location**    | Inflow cannula into the RA through the femoral vein | Inflow cannula into LA through femoral vein and transseptal puncture | Inflow cannula into LA through femoral vein and transseptal puncture |
|                         | Outflow cannula into the femoral artery | Outflow cannula into the femoral artery | Second inflow cannula into RA through the femoral vein |
|                         |                           |                           | Outflow cannula into femoral artery |
| **Hemodynamics**        |                           |                           |                                 |
| RV support              | Yes ✓                     | No ✗                    | Yes ✓                           |
| Afterload               | ↑ ✓                       | ↑ ✓                     | ↑ ✓                             |
| LVEDP                   | ↑/−/++                    | ↓ ✓                     | ↓ ✓                             |
| PCWP                    | ↑/−/++                    | ↓ ✓                     | ↓ ✓                             |

BA-ECMO = biventricular extracorporeal membrane oxygenation; LA = left atrium; LVEDP = left ventricular end diastolic pressure; PCWP = pulmonary capillary wedge pressure; RA = right atrium; RV = right ventricle; VA-ECMO = venoarterial extracorporeal membrane oxygenation; ↑ = increased; − = no significant change; ↓ = decreased.
Percutaneous options for left-sided heart unloading include the use of an Impella device (Abiomed, Danvers, Massachusetts); however, this requires a second large-bore arterial access. Risk of bleeding and other vascular complications can potentially be mitigated when percutaneous left-sided heart unloading occurs without the need for separate arterial access, such as in BA-ECMO. We searched published articles for prior reports of fully percutaneous BA-ECMO (2–5). All prior reports and series describe BA-ECMO in the setting of acute cardiogenic shock. Our patient had BA-ECMO in place for HRPCI and was not in shock at the time of BA-ECMO placement. We have used BA-ECMO in a similar fashion in 2 other patients with severe biventricular failure who were undergoing elective HRPCI. Both patients survived their index procedure and were hemodynamically stable throughout.

There are multiple possible configurations of MCS, each with their own set of advantages and disadvantages. Understanding the hemodynamic effects of common ECMO circuits allows clinicians to use each device in the appropriate clinical context (Table 2, Figures 2A to 2C). An important hemodynamic concept in BA-ECMO that has not been described previously is the preferential drainage of the right atrium compared with the left atrium. Our first patient had flow measurement of approximately 2.8 l/min and 2.2 l/min from RA and LA drainage cannulas, respectively. Using flow probes intra-procedurally is essential to ensure adequate biventricular unloading. Additionally, our patient had biventricular support with left-sided heart unloading by using a single TandemHeart circuit. The potential advantages of using only 1 pump include resource use and cost reduction. Another common clinical scenario encountered in severe LV dysfunction is the presence of LV thrombus. There are limited, if any, percutaneous options when the need for biventricular support with left-sided heart unloading arises in a patient with LV thrombus. The unique configuration of BA-ECMO can be used in this clinical scenario (3,6). The ability to de-escalate support in a stepwise fashion from biventricular support to LV support only by first removing the RA cannula and leaving the transseptal LA cannula can be helpful when weaning MCS (5,7). Similarly, escalation can occur in a stepwise fashion as well.

**CONCLUSIONS**

We report a case of fully percutaneous BA-ECMO used for HRPCI in a patient with severe biventricular dysfunction and pulmonary hypertension by using simultaneous drainage of both atria to provide biventricular support with left-sided heart unloading.

**ADDRESS FOR CORRESPONDENCE:** Dr. Khaldoon Alaswad, Division of Cardiovascular Medicine, Department of Internal Medicine, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, Michigan 48202. E-mail: kalaswa1@hfhs.org.
REFERENCES

1. Kovacic JC, Kini A, Banerjee S, et al. Patients with 3-vessel CAD and impaired ventricular function undergoing PCI with Impella 2.5 hemodynamic support have improved 90-day outcomes compared to IABP: a sub-study of the PROTECT II trial. J Interv Cardiol 2015;28:32-40.

2. Alkhouli M, Narins CR, Lehoux J, et al. Percutaneous decompression of the left ventricle in cardiogenic shock patients on venoarterial extracorporeal membrane oxygenation. J Card Surg 2016;31:177-82.

3. Marwan Jumean M, Pham DT, Kapur NK. Percutaneous bi-atrial extracorporeal membrane oxygenation for acute circulatory support in advanced heart failure. Catheter Cardiovasc Interv 2015;85:1097-9.

4. Dulnau T, Guglin M, Zwischenberger J, et al. Left atrial veno-arterial extracorporeal membrane oxygenation: percutaneous bi-atrial drainage to avoid pulmonary edema in patients with left ventricular systolic dysfunction. Ann Cardiothorac Surg 2019;8:9-18.

5. Bernhardt AM, Hillebrandb M, Yildrima Y, et al. Percutaneous left atrial unloading to prevent pulmonary oedema and to facilitate ventricular recovery under extracorporeal membrane oxygenation therapy. Interact Cardiovasc Thorac Surg 2018;26:4-7.

6. Mohamedali B, Tatooles A, Bhat G. Use of a single circuit to provide temporary mechanical respiratory and circulatory support in patients with LV apical thrombus and cardiogenic shock. Perfusion 2014;29:483-7.

7. Aggarwal A, Modi S, Kumar S, et al. Use of a single-circuit CentriMag® for biventricular support in postpartum cardiomyopathy. Perfusion 2013;28:156-9.

KEY WORDS cardiomyopathy, chronic heart failure, hemodynamics, percutaneous coronary intervention

APPENDIX For supplemental videos, please see the online version of this paper.
Endothelial Function and Oxidative Stress in X-Linked, gp91phox Deficiency, Chronic Granulomatous Disease

Yukihiro Higashi, MD, PhD, Shinji Kishimoto, MD, PhD, Tatsuya Maruhashi, MD, PhD

ABSTRACT

Two patients with X-linked chronic granulomatous disease without NAPDH oxidase activity and with high responses of flow-mediated vasodilation are reported. Bone marrow transplantation restored oxidative stress to the levels of those in healthy subjects and decreased flow-mediated vasodilation to the levels of those in healthy subjects in both of the patients. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1480–3) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Chronic granulomatous disease (CGD) is a rare, heterogeneous, and inherited phagocyte disorder that affects approximately 1 in 250,000 births (1). X-linked CGD accounts for approximately 70% of cases of CGD and is due to mutation of the CYBB gene encoding gp91phox, which is located in the region Xp21.1 of the short arm of the X chromosome (1). NAPDH oxidase activity is diminished in activated polymorphonuclear leukocytes in these patients, leading to a reduction in reactive oxygen species (ROS), which results in severe and recurrent bacterial and fungal infections.

A balance between ambient levels of superoxide and nitric oxide release plays a critical role in the maintenance of normal endothelial function (2). We have shown that 1 mechanism of endothelial dysfunction is an increase in oxidative stress in patients with renovascular hypertension, who are ideal models of excess angiotensin II and angiotensin II–related increase in oxidative stress through the activation of NADPH oxidase (3). By contrast, patients with X-linked CGD are ideal models for determining how endothelium-dependent vasodilation is affected by gp91phox-deficiency-related decrease in oxidative stress. Indeed, Violi et al. (4) showed an increase in endothelium-dependent vasodilation and a decrease in the oxidative stress marker isoprostan. We hypothesized that the restoration of ROS by bone marrow transplantation (BMT) would decrease...
endothelium-dependent vasodilation in patients with X-linked CGD by increasing oxidative stress.

We present flow-mediated vasodilation (FMD) and oxidative stress markers before and after BMT in 2 patients with X-linked CGD who had gp91phox deficiency phenotype X910.

**HISTORY OF PRESENTATION**

**CASE 1.** Case 1 was a 26-year-old man who presented with recurrent upper and lower respiratory infections and hepatic abscesses. His first episode of pneumonia was at the age of 11 years, but he had been well until that time. Since then, he had recurrent pneumonia at the ages of 13, 15, 16, 18, 21, and 24 years, and had an episode of liver abscess at the age of 24 years. The number of episodes of infection (e.g., lung, liver, and skin) that required hospitalization was 11 before BMT. Cytochrome b558 protein, gp91phox, NADPH oxidase activity, and superoxide generation in activated leukocytes were totally absent (Figure 1A). The mutation in Case 1 was identified as a single-base substitution of adenosine to thymine in base 1309 in exon 10, resulting in the formation of a stop codon (TAA) (Figure 1B). This nonsense mutation was located in the putative NADPH oxidase-binding motif (Figure 1B). The phenotype of X-linked CGD was X910.

**CASE 2.** Case 2 was a 9-year-old boy who presented with recurrent upper and lower respiratory infections and a fistulized infection by a fungus. He had pneumonia and encephalitis at the age of 2 months and had 2 episodes of liver abscesses at the ages of 1 and 3 years. Since then, he had some infections every year. In the following 2 years from the age of 7 years, he had fistulized infections by a fungus in the skin. The number of episodes of infection (e.g., lung, liver, brain, skin, and bone) that required hospitalization was 8 before BMT. Cytochrome b558 protein, gp91phox, NADPH oxidase activity, and superoxide generation in activated leukocytes were totally absent (Figure 1A). The mutation in Case 2 was identified as a deletion of the nucleotides TTTGATACACATCATCT in base 614 in exon 6, resulting in a frameshift and formation of a stop codon (Figure 1B). We confirmed that the mutation in Case 2 was de novo in accordance with previous studies (5) and the CYBB gene database. This de novo mutation was localized in the transmembrane region (Figure 1B). The phenotype of X-linked CGD was X910.

**MANAGEMENT AND INTERVENTIONS**

**CASES 1 AND 2.** The presence of cytochrome b558 on the surface of intact cells was determined by fluorescence-activated cell sorter analysis after binding on monoclonal antibody 7D5 with fluorescein isothiocyanate–conjugated mouse anti-mouse immunoglobulin. Oligonucleotide primers used in this study for the polymerase chain reaction and sequencing for the CYBB (gp91phox) gene are presented in Supplemental Table 1. BMT was performed in Cases 1 and 2 as previously described (6). FMD was measured before and after BMT as described previously (7).

Mean FMD was 8.6 ± 3.7% (range 1.8% to 18.7%) in 128 healthy young men (22 ± 2 years of age; range, 17 to 28 years of age). Before BMT, FMD was 27.4% in Case 1 and 26.0% in Case 2. FMD in Cases 1 and 2 before BMT was higher than the maximum FMD in healthy young men (Figure 2). Serum malondialdehyde-modified low-density lipoprotein (MDA-LDL) concentration, plasma nitrite/nitrate concentration, urinary excretion of 8-OHdG, and urinary excretion of nitrite/nitrate in 51 healthy young men (22 ± 3 years of age; range, 18 to 28 years of age) and 2 patients with CGD are shown in Supplemental Table 2. Oxidative stress marker levels, serum MDA-LDL concentration, and urinary excretion of 8-OHdG in the 2 cases before BMT were smaller than the minimum values in healthy young men. Plasma nitrite/nitrate concentration was in the range of the mean ± SD values in healthy subjects (Supplemental Table 2).

Cases 1 and 2 had no clinical symptoms and were well after BMT. After BMT, levels of 7D5 staining were restored to the levels of those in normal control subjects in both cases (Figure 1A). BMT attenuated FMD from 27.4% to 10.2% in Case 1 and from 26.0% to 9.6% in Case 2 (Figure 2). After BMT, serum MDA-LDL concentration and urinary excretion of 8-OHdG increased in both cases, and plasma concentration or urinary excretion of nitrite/nitrate was not altered in either case (Supplemental Table 2).

**DISCUSSION**

Endothelial dysfunction is the initial step in the pathogenesis of atherosclerosis. Oxidative stress plays an important role in the pathogenesis and development of cardiovascular diseases (2). Enhanced nitric oxide inactivation caused by excess production of ROS under the condition of NADPH oxidase activation plays an important role in endothelial dysfunction. In the present study, FMD was markedly enhanced in 2 patients with X-linked CGD. In addition, after BMT for treatment of X-linked CGD, FMD decreased to the levels of those in healthy
subjects by increasing oxidative stress. These findings suggest that even a normal condition of oxidative stress in healthy subjects may induce endothelial dysfunction, leading to atherosclerosis by long-term exposure to a normal range of oxidative stress.

**CONCLUSIONS**

Oxidative stress in healthy subjects attenuates endothelium-dependent vasodilation by about two-thirds compared with that under the condition in...
which oxidative stress is absent. These findings also indicate that oxidative stress is a dual-edged sword for the maintenance of a healthy condition. It is likely that superoxide generated by leukocyte NADPH oxidase plays an important role in endothelial function even under normal conditions without cardiovascular risk factors.

ADDRESS FOR CORRESPONDENCE: Prof. Yukihito Higashi, Department of Cardiovascular Regeneration and Medicine, Research Institute for Radiation Biology and Medicine, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. E-mail: yhigashi@hiroshima-u.ac.jp.

REFERENCES

1. Winkelstein JA, Marino MC, Johnston RB Jr., et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) 2000;79:155-69.
2. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000;87:840-4.
3. Higashi Y, Sasaki S, Nakagawa K, et al. Endothelial function and oxidative stress in renovascular hypertension. N Engl J Med 2002;346:1954-62.
4. Violi F, Sangiulini V, Carnevale R, et al. Hereditary deficiency of gp91(phox) is associated with enhanced arterial dilatation: results of a multi-center study. Circulation 2009;120:1616-22.
5. Rae J, Newburger PE, Dinauer MC, et al. X-linked chronic granulomatous disease: mutations in the CYBB gene encoding the gp91-phox component of respiratory-burst oxidase. Am J Hum Genet 1998;62:1320-31.
6. Horwitz ME, Barrett AJ, Brown MR, et al. Treatment of chronic granulomatous disease with nonmyeloablative conditioning and a T-cell-depleted hematopoietic allograft. N Engl J Med 2001;344:881-8.
7. Soga J, Nakamura S, Nishioka K, et al. Relationship between augmentation index and flow-mediated vasodilation in the brachial artery. Hypertens Res 2008;31:1293-8.

KEY WORDS chronic granulomatous disease, endothelial function, gp91phox, NADPH oxidase, nitric oxide, oxidative stress

APPENDIX For supplemental tables, please see the online version of this paper.
We report a case of giant cell myocarditis in a 76-year-old patient managed with combined immunosuppression and biventricular intravascular microaxial blood pumps. This case highlights a feasible approach for managing such patients who are not candidates for transplantation or durable ventricular assist devices. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1484–8) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

PRESENTATION

A 76-year-old man presented to his local emergency department with weakness and presyncope. He recently developed upper respiratory symptoms after a vacation in Vietnam. Upon admission, he was afebrile with heart rate of 126 beats/min, blood pressure of 80/50 mm Hg, and normal oxygen saturation. The physical examination was notable for findings of cool extremities, elevated jugular venous pressure, and weak pulse.

MEDICAL HISTORY

The patient had a medical history of pituitary adenoma status post-resection with subsequent panhypopituitarism. His personal and family history were negative for cardiovascular, autoimmune, or rheumatologic disease.

LEARNING OBJECTIVES

- To maintain a high clinical suspicion for GCM and perform EMB at an early stage of presentation in patients of any age.
- To consider prolonged temporary MCS for GCM patients who are not candidates for transplantation or durable MCS.

DIFFERENTIAL DIAGNOSIS

The initial differential diagnosis included cardiogenic shock (acute coronary syndrome, cardiac tamponade, acute decompensated heart failure [HF], fulminant myocarditis), pneumonia with septic shock, or distributive shock due to adrenal insufficiency, pulmonary embolism, and acute aortic syndromes.
INVESTIGATIONS

Troponin I concentration was 26.9 ng/ml, rising to 144.4 ng/ml (normal values are 0.00 to 0.09 ng/ml). B-type natriuretic peptide (BNP) was 2,092 pg/ml (normal values are 0 to 99 pg/ml). Initial transthoracic echocardiogram (TTE) showed left ventricular ejection fraction (LVEF) of 30%. Coronary angiography showed no obstructive disease.

MANAGEMENT

The following day, he had multiple ventricular tachycardia arrests requiring shocks and intubation. He also developed third-degree atrioventricular block prompting temporary pacer wire placement. An intravascular microaxial blood pump (Impella 5.0, Abiomed, Danvers, Massachusetts) was placed in the left ventricle, and he was transferred to the authors' hospital for evaluation of heart transplantation. His vital signs upon transfer showed a heart rate of 110 beats/min and a blood pressure of 75/60 mm Hg, despite multiple inotropic and vasopressor agents (Table 1). On physical examination, he was intubated and sedated with mildly elevated jugular venous pressure and no lower extremity edema. He was noted to have ventricular tachycardia requiring lidocaine and mexiletine. A second TTE showed biventricular failure with LVEF dropping to 10% to 15%, prompting placement of a right ventricular intravascular microaxial blood pump (Impella RP, Abiomed) (Figure 1A). He was also urgently placed on continuous venovenous hemofiltration for anuria. An endomyocardial biopsy (EMB) was performed and histology confirmed giant cell myocarditis (GCM) (Figure 1B). Given his age and severe biventricular HF, he was not a candidate for heart transplantation. He was not a candidate for a durable left ventricular assist device due to his right ventricular dysfunction and renal failure. He was treated with 1 dose of rabbit anti-thymocyte globulin (1 mg/kg), pulse-dose intravenous methylprednisolone (1 g/day) for 3 days with rapid tapering in the following days to stress dosages given the presence of panhypopituitarism; cyclosporine, 50 mg twice daily (with a blood concentration goal of 200 to 300 ng/ml); and azathioprine, 50 mg daily. Tracheostomy was performed on hospital day 6. The transvenous pacer was removed on hospital day 12 with complete resolution of ventricular tachycardia (Figure 1C) and heart block and recovery of sinus rhythm (Figure 1D). Right-sided mechanical circulatory support (MCS) was removed on hospital day 14, with complete recovery of right ventricular function on repeated TTEs. Due to reactivation of a cytomegalovirus (CMV) infection (7 million copies/ml) with tracheitis, colitis, and worsening transaminitis, his immunosuppressive steroids and azathioprine were discontinued. Despite lowering immunosuppression, cardiac function slowly stabilized throughout the patient’s hospital course. Left-sided MCS was removed on hospital day 28. LVEF improved to 25% off all circulatory support prior to discharge. High-sensitivity troponin T and CK-MB concentrations improved from the time of transfer to 41,143 ng/ml (normal values are 0 to 22 ng/ml) and 94 ng/ml (normal values 0.0 to 4.8 ng/ml), respectively, to 1,148 ng/ml and 4 ng/ml at 1 week after MCS was removed (Figure 2). Mycophenolate mofetil therapy was initiated after CMV titers decreased (990 copies/ml; white blood count: 9.8 1,000/mm³). The patient was weaned from all circulatory support and discharged to a long-term acute care facility with cyclosporine, 75 mg twice daily, and mycophenolate mofetil, 500 mg twice daily. He was discharged on intermittent hemodialysis due to end-stage persistent anuric renal failure.

DISCUSSION

GCM is a rare cause of myocarditis, typically presenting as fulminant HF and/or episodes of ventricular arrhythmia (1,2). GCM primarily affects middle-aged adults of both sexes at a median age of 43 to 53 years at onset (1,3). The diagnosis requires histopathological evidence of giant cells on EMB, and treatment consists of hemodynamic support with vasopressors, inotropes, MCS, combined immunosuppression, and ultimately transplantation (3). The prognosis is extremely poor, with an international registry demonstrating that GCM carries a significantly worse prognosis than other forms of fulminant myocarditis (4). A French multicenter registry reported 100% mortality or transplantation in patients with GCM requiring MCS (5).

The present case is unique because the patient was much older than the average age of GCM patients (1).

| TABLE 1 Clinical Variables upon Hospital Transfer After Left Ventricular Microaxial Blood Pump Placement on Dobutamine, Dopamine, and Norepinephrine |
|---------------------------------------------------------------|
| High-sensitivity troponin T (reference: 0 to 22 ng/ml), ng/ml | 41,143 |
| C-reactive protein (reference 0.0 to 0.5 mg/dl), mg/dl | 7.9 |
| Lactate (reference: 0.5 to 2.0 mmol/l), mmol/l | 4.7 |
| White blood cell count (reference: 4.0 to 10.0,000/mm³), 1,000/mm³ | 20.0 |
| Eosinophils (0.0% to 6.0%), % | 0 |
| Cardiac output (Fick), l/min/m² | 3.39 |
| Cardiac index (Fick), l/min/m² | 1.82 |
| Ejection fraction (by transthoracic echocardiogram), % | 12 |

ABBREVIATIONS AND ACRONYMS

- BNP = B-type natriuretic peptide
- CMV = cytomegalovirus
- EMB = endomyocardial biopsy
- GCM = giant cell myocarditis
- HF = heart failure
- LVEF = left ventricular ejection fraction
- TTE = transthoracic echocardiogram
Although GCM is widely reported to affect middle-aged adults, the medical literature suggests that this is due to an underdiagnosis, with many patients being diagnosed at autopsy.

The patient’s age and comorbidities provided a formidable challenge to his management, as they precluded both transplantation and durable MCS. Although a variety of temporary MCS devices are available, including intra-aortic balloon pump, temporary axial flow devices, and venous arterial-extracorporeal membrane oxygenation (VA-ECMO), this patient needed significant biventricular temporary support which limited his treatment options to axial flow devices or VA-ECMO. We chose biventricular temporary microaxial pumps for 2 reasons. First, they avoid the issue of increased afterload in VA-ECMO while providing percutaneous biventricular unloading (6). Second, the patient was already receiving left-sided intravascular microaxial blood pump, so it was easier to add right ventricular support instead of placing VA-ECMO. Although there was a favorable short-term outcome for this patient, it is worth noting that prolonged microaxial pump support may also be associated with a risk of complications. Other approaches to MCS in such settings would be reasonable to consider when accounting for patient- and center-specific factors.

Additionally, this patient also followed the suggested multiple-drug immunosuppressive regimen including antithymocyte globulins. Published case series have used different protocols. One study used rabbit antithymocyte globulin and pulse-dose steroids alone, whereas other studies recommended azathioprine, prednisone, and cyclosporine or alternatives such as mycophenolate mofetil or methotrexate (3,7). Given that this patient was not a candidate for transplantation due to his age, rabbit antithymocyte globulin, pulse-dose steroids, and cyclosporine were used as were a maintenance immunosuppressive regimen of cyclosporine, prednisone, and azathioprine. That regimen required a few weeks before a tangible improvement was obtained (12 days for the recovery of sinus rhythm).
the atrioventricular block and 28 days for the weaning from the MCS), which is consistent with previously described cases of GCM and other causes of myocarditis (2,6,8). One complication of this patient’s high-dose immunosuppression, however, was the reactivation of CMV infection, requiring modification of his immunosuppressive regimen. In retrospect, the patient might have benefited from consideration of prophylactic antimicrobial therapy in conjunction with aggressive immunosuppression.

**FOLLOW-UP**

Two weeks later, the patient was readmitted to another hospital with septic shock. Vital signs upon admission showed a low-grade fever of 100.6°F, heart rate of 92 beats/min, and blood pressure of 92/64 mm Hg. Physical examination revealed dry mucous membranes and cold extremities without clinical signs of heart failure. His troponin-I concentration of 0.93 ng/ml (normal values are 0.0 to 0.03 ng/ml) suggested acute decompensated HF; however, bacteremia due to high-grade methicillin-resistant *Staphylococcus aureus* infection, likely from his dialysis catheter, and colitis from *Clostridium difficile* infection made overwhelming infection much more likely as the cause of decompensation. Despite broad-spectrum antibiotics and maximal vasopressor support, he died 93 days after his initial presentation.

This patient’s sepsis was likely due to multiple factors, including his recent prolonged hospitalization, ongoing hemodialysis, and immunosuppression. However, his survival from discharge from the authors’ hospital to 3 months illustrates the necessity of immunosuppression for a disease state for which the rate of mortality or heart transplantation has been shown to be 63% at 60 days from onset and 81% at 3 years of follow-up (3).

**CONCLUSIONS**

This paper describes a case of GCM in an elderly patient with partial recovery following combined immunosuppression and prolonged biventricular microaxial blood pump support. In conclusion, this report illustrates a feasible approach to treating elderly patients who otherwise could not undergo transplantation or receive durable MCS.

**ADDRESS FOR CORRESPONDENCE:** Dr. Eric Adler, Division of Cardiovascular Medicine, University of California San Diego, Sulpizio Cardiovascular Center, 9434 Medical Center Drive, La Jolla, California 92037. E-mail: eradler@health.ucsd.edu.
REFERENCES

1. Cooper L, Berry G, Shabetai R. Idiopathic giant-cell myocarditis—natural history and treatment. N Engl J Med 1997;336:1860-6.

2. Ammirati E, Oliva F, Belli O, et al. Giant cell myocarditis successfully treated with antithymocyte globulin and extracorporeal membrane oxygenation for 21 days. J Cardiovasc Med 2016;17 Suppl 2:e151-3.

3. Kandolin R, Lehtonen J, Salmenkivi K, et al. Diagnosis, treatment, and outcome of giant-cell myocarditis in the era of combined immunosuppression. Circ Heart Fail 2013;6:15-22.

4. Ammirati E, Veronese G, Brambatti M, et al. Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2019;73:299-311.

5. Montero S, Aissaoui N, Tadie J, et al. Fulminant giant-cell myocarditis on mechanical circulatory support: management and outcomes of a French multicentre cohort. Int J Cardiol 2018;253:105-12.

6. Tschöppe C, Van Lithout S, Klein O, et al. Mechanical unloading by fulminant myocarditis: Lv-Impella, Ecmella, Bi-Pella, and Propella concepts. J Cardiovasc Transl Res 2019;12:116-23.

7. Suarez-Barrientos A, Wong J, Bell A, et al. Usefulness of rabbit anti-thymocyte globulin in patients with giant cell myocarditis. Am J Cardiol 2015;116:447-51.

8. Ammirati E, Cipriani M, Lilliu M, et al. Survival and left ventricular function changes in fulminant versus nonfulminant acute myocarditis. Circulation 2017;136:529-45.

KEY WORDS acute heart failure, cardiac assist devices, hemodynamics, inotropes
EDITORIAL COMMENT

Giant Cell Myocarditis
Still the Deadly Giant*

Nowell M. Fine, MD, SM

Giant cell myocarditis (GCM) remains a feared diagnosis among health care providers. This disease has remained somewhat of an enigma over the years, partly because of its low incidence, often fulminant clinical presentation with similarities to other forms of myocarditis (both clinically and histopathologically), variable treatment approaches, frequently rapid clinical progression, and overall poor prognosis. GCM presents significant challenges at all stages of its disease course, from its initial presentation through to its long-term management for those patients who survive the acute stage. As a result, there has been much written about GCM; however, our knowledge about the disease has actually advanced relatively slowly, and much remains uncertain and still to be determined. As an example, the pathophysiology of GCM is not well understood beyond its recognition as an autoimmune disorder attributable to T-lymphocyte-mediated myocardial inflammation (1). There is a known association with other autoimmune disorders such as inflammatory bowel disease, fibromyalgia, and Hashimoto thyroiditis (2). However, the true nature of this relationship, including which patients may be most at risk for GCM, remains unclear.

The clinical presentation is typically marked by rapidly progressive myocarditis deteriorating to a fulminant state accompanied by cardiogenic shock. However, other clinical presentations may occur, including those characterized predominantly by arrhythmia such as atrioventricular block or ventricular arrhythmias (3). Such features are shared with other causes of myocarditis, such as lymphocytic or cardiac sarcoidosis, and clinical features, in addition to laboratory and imaging findings, are typically unhelpful for differentiating among them. Furthermore, in some series, more indolent presentations of GCM have been described (1,4,5). Therefore, diagnostic confirmation requires demonstration of characteristic features by endomyocardial biopsy (EMB). These features include diffuse myocardial inflammatory infiltrate and the presence of multinucleated giant cells with associated myocyte necrosis in the absence of a viral origin. However, pathologic characteristics may resemble those of other forms of myocarditis, in particular cardiac sarcoidosis, whose primary distinguishing feature is the predominance of noncaseating granulomas, as well as more extensive fibrosis (6). In addition, EMB may also be subject to sampling error, leading to a possible false negative result, and therefore the need for repeat EMB in the setting of high clinical suspicion in a patient with a negative or equivocal pathologic result has been advocated (1,4,7). Some reports have also recommended targeted biopsy of involved myocardial regions on the basis of cardiovascular magnetic resonance findings (7). Early diagnosis and differentiation from other forms myocarditis are critical to facilitate prompt initiation of immunosuppression therapy because GCM remains one of the few causes of fulminant myocarditis where immunosuppression has been proven to improve outcomes when therapy is administered in the acute stage (1). However,
reliance on EMB may present a barrier to early diagnosis depending on availability, awareness, and clinical course, given that physicians may be less likely to pursue EMB for patients with less severe presentations or a high burden of comorbid illness. The spread of the coronavirus disease-2019 (COVID-19) pandemic and the risk of associated cardiomyopathy may contribute to such barriers (8) because clinicians may wish to exclude a diagnosis of COVID-19 before considering an invasive work-up. A high index of clinical suspicion remains vital for appropriate diagnostic work-up and early recognition.

Once the diagnosis is confirmed, early institution of combined (multiple-agent) immunosuppression is considered the standard of care because treatment with corticosteroids alone is generally recognized as inadequate to achieve disease stabilization and remission. The importance of this approach is now well established, and some series have demonstrated improved outcomes with immunosuppression regimens that combine both corticosteroid and non-corticosteroid agents (1,2). Despite this improvement, multiple regimens may be used at different centers, usually on the basis of experience, and no consensus approach exists, nor have clinical trials been conducted to guide decision making. Perhaps even more challenging are decisions about long-term therapy, including approach to weaning immunosuppression and total duration of therapy, because clinicians rely on a constellation of clinical, imaging, and serum markers to determine the optimal approach for each patient. The role of serial EMB to guide treatment decisions beyond the acute phase remains an area of uncertainty. Again, the low incidence translates into limited experience for many clinicians, thus adding further to the degree of difficulty. Long-term immunosuppression is often required given the known risk of recurrence, even after heart transplantation (1,2,4,5,9).

The proliferation of mechanical circulatory support (MCS) devices has expanded the armamentarium of treatment options available to patients presenting with fulminant myocarditis. MCS therapies may allow for stabilization of patients to facilitate further investigations such as EMB, and they may also bridge patients toward recovery as immunosuppression is instituted. Patients remaining on long-term MCS support even after cessation of immunosuppression have also been described (10). Although MCS provides opportunities to improve survival, its use in patients with GCM also presents unique challenges. Important among these is the heightened risk of infection in patients receiving concurrent immunosuppression therapy.

In this issue of JACC: Case Reports, we are again reminded of the numerous management challenges this diagnosis presents. Ma et al. (11) describe a case of 1 of the older patients (76 years of age) reported to have this disease, which typically manifests in the fourth or fifth decade of life. Previous reports have also highlighted the importance of maintaining a high index of clinical suspicion among patients presenting with fulminant myocarditis at both extremes of the age spectrum because GCM has been reported in patients as young as the second decade of life and as old as the eighth decade (4,12,13). Older patients are naturally at higher risk of poor outcomes, in part because of their more limited eligibility for heart transplantation, regarded as the definitive therapy for patients with GCM who do not achieve remission with immunosuppression. In this case, percutaneous microaxial biventricular assist devices were used to stabilize the patient and facilitate initiation of immunosuppression therapy, thereby allowing for a degree of recovery and eventual discontinuation of MCS. The use of multiple types of MCS devices has been described to manage GCM, including percutaneous MCS, extracorporeal membrane oxygenation, paracorporeal ventricular assist devices, and durable (ambulatory) ventricular assist devices (14). This case further illustrates how MCS device selection depends on several patient- and facility-related factors, including availability and experience. Despite this patient’s survival beyond the acute stage and eventual discharge from the hospital, this case also illustrates how susceptible patients with GCM are to complications of both the disease and its therapy. This patient ultimately died only 3 months after diagnosis as a result of sepsis related to a catheter infection, after he became dependent on hemodialysis during the index hospitalization with GCM.

More recent series have demonstrated that patient survival and outcomes are better than the abysmal mortality rates described in earlier reports. Much has been learned about GCM, in particular the spectrum of clinical presentations and the disease course. Our understanding of its management has also evolved, with regard to both immunosuppression and the value of MCS in the acute phase and in the longer term for some patients. However, advances and
The dissemination of knowledge can move slowly for rare diseases, and there remains much to learn. Important areas of ongoing research include disease-specific markers of prognosis and response to therapy toward developing consensus criteria to guide clinical decision making. In addition, the need for more multicenter data remains high. Despite the important advances that have improved our understanding and management of GCM, it still remains a very deadly giant among cardiovascular diseases.

**ADDRESS FOR CORRESPONDENCE:** Dr. Nowell M. Fine, University of Calgary, Libin Cardiovascular Institute, South Health Campus, 4448 Front Street Southeast, Calgary, Alberta T3M 1M4, Canada. E-mail: nmfine@ucalgary.ca.

**REFERENCES**

1. Kandolin R, Lehtonen J, Salmenkivi K, Raisanen-Sokolowski A, Lommi J, Kupari M. Diagnosis, treatment, and outcome of giant-cell myocarditis in the era of combined immunosuppression. Circ Heart Fail 2013;6:15-22.
2. Cooper LT Jr., Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis-natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. N Engl J Med 1997;336:1860-6.
3. Ekstrom K, Lehtonen J, Kandolin R, Raisanen-Sokolowski A, Salmenkivi K, Kupari M. Incidence, risk factors, and outcome of life-threatening ventricular arrhythmias in giant cell myocarditis. Circ Arhythm Electrophysiol 2016;9:e004559.
4. Maleszewski JJ, Orellana VM, Hodge DO, Kuhl U, Schultheiss HP, Cooper LT. Long-term risk of recurrence, morbidity and mortality in giant cell myocarditis. Am J Cardiol 2015;115:1733-8.
5. Ekstrom K, Lehtonen J, Kandolin R, Raisanen-Sokolowski A, Salmenkivi K, Kupari M. Long-term outcome and its predictors in giant cell myocarditis. Eur J Heart Fail 2016;18:1452-8.
6. Blauset LA, Cooper LT. Idiopathic giant cell myocarditis and cardiac sarcoidosis. Heart Fail Rev 2013;18:733-46.
7. Kalra A, Kneeland R, Samara MA, Cooper LT Jr. The changing role for endomyocardial biopsy in the diagnosis of giant-cell myocarditis. Cardiol Ther 2014;3:53-9.
8. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminating myocarditis saved with glucocorticoid and human immunoglobulin. Eur Heart J 2020 Mar 16 [E-pub ahead of print].
9. Toscano G, Tartaro P, Fedrigo M, Angelini A, Marcolongo R. Rituximab in recurrent idiopathic giant cell myocarditis after heart transplantation: a potential therapeutic approach. Transpl Int 2014;27:e38-42.
10. Bireta C, Tirilomis T, Grossmann M, et al. Long term biventricular support with Berlin Heart Excor in a septuagenarian with giant-cell myocarditis. J Cardiothorac Surg 2015;10:14.
11. Ma J, Ammirati E, Brambatti M, Adler E. Biventricular intravascular microaxial blood pumps and immunosuppression as bridge to recovery in giant cell myocarditis. J Am Coll Cardiol Case Rep 2020;2:1484-8.
12. Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. Circ Arhythm Electrophysiol 2011;4:303-9.
13. Kasouridis I, Majo J, MacGowan G, Clark AL. Giant cell myocarditis presenting with acute heart failure. BMJ Case Rep 2017;2017:br2017219574.
14. Nakajima-Doi S, Mochizuki H, Iwasaki K, et al. Mechanical circulatory support combined with immunosuppression for the treatment of giant cell myocarditis- a single-center experience in Japan. Circ J 2020;84:815-9.
A Long-Term Survivor With Alveolar Capillary Dysplasia

Chandler E. Yost, BS,a Angelica R. Putnam, MD,a Megan K. Dishop, MD,b Lynda O. Jorgensen, RN,a Paul E. Wirkus, MD,c Ronald W. Day, MDa

ABSTRACT

A patient with alveolar capillary dysplasia has survived more than 56 months with medical therapy. Intrauterine exposure to metformin potentially modified the severity of disease. In combination with other agents, endothelin receptor antagonists and amlodipine have been key medications in lowering pulmonary arterial pressure and managing right heart failure. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1492–5) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

T

he majority of patients with alveolar capillary dysplasia (ACD) die in early infancy from respiratory failure with hypoxemia and pulmonary hypertension (1). However, a recent report has reviewed several patients with an atypical phenotype and relatively long survival (2). The role of medical therapy in ACD is unknown because atypical patients may be overlooked if genetic testing or a histological evaluation is not performed. Here, we report a patient who has survived for more than 56 months with medical therapy including key agents that potentially modified the severity of pulmonary vascular disease or lowered pulmonary artery pressure.

LEARNING OBJECTIVES

- To demonstrate that rare patients with alveolar capillary dysplasia can be treated long term with medical therapy.
- To highlight key elements of medical care that potentially modified the severity of pulmonary vascular disease or improved cardiovascular function.

HISTORY OF PRESENTATION

A 43-year-old woman developed gestational diabetes and started treatment with metformin 1,000 mg/day at 14 weeks’ gestation. The dose was increased to 2,000 mg/day at 17 weeks’ gestation. A fetal right pleural effusion, noted during the third trimester, resolved before birth. A male neonate was born at a gestational age of 37 weeks. He developed acute respiratory failure and pulmonary hypertension (PH) during the first day of life. Hypoxemia and PH persisted despite treatment with high-frequency oscillatory ventilation, surfactant, and inhaled nitric oxide (iNO). He was transported and supported with venous/venous extracorporeal membrane oxygenation from 17 h of age to 6 days of age. In addition to iNO, inpatient therapy included epoprostenol, sildenafil, and bosentan. His end-systolic eccentricity index, a measure of ventricular septal flattening or increased systolic pulmonary arterial pressure, normalized after the onset of treatment with bosentan, allowing iNO and epoprostenol to be stopped.

From the aUniversity of Utah, Salt Lake City, Utah; bPhoenix Children’s Hospital, Phoenix, Arizona; and cWasatch Pediatrics, Salt Lake City, Utah. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

Manuscript received April 22, 2020; accepted May 13, 2020.

ISSN 2666-0849

https://doi.org/10.1016/j.jaccas.2020.05.055
MANAGEMENT

Figure 1 shows his clinical course over time with noteworthy events, end-systolic eccentricity indices, B-type natriuretic peptide levels, and medications. He was initially treated as an outpatient with sildenafil, bosentan, furosemide, and full-time supplemental oxygen. His clinical course was consistent with resolving pulmonary hypertension. Bosentan was discontinued, and he was transitioned from full-time oxygen to nighttime oxygen. He was

**ABBREVIATIONS AND ACRONYMS**

ACD = alveolar capillary dysplasia
iNO = inhaled nitric oxide
PH = pulmonary hypertension
admitted to the hospital at 10 months of life with evidence of severe PH and right heart failure. Airway secretions tested positive for rhinovirus and beta-lactamase-negative Hemophilus influenza. A high-resolution computed tomography scan of the chest showed bilateral ground glass opacities and septal thickening. A lung biopsy showed evidence of “a mild form of alveolar capillary dysplasia with misalignment of the pulmonary veins,” as shown in Figure 2.

Genetic testing revealed a c.246C>G (p. F82L) heterozygous, novel, and de novo variant in the FOXF1 gene. He was again treated as an outpatient with sildenafil, full-time oxygen, and furosemide, with the addition of bosentan, digoxin, chlorothiazide, spironolactone, beclomethasone, albuterol, and aspirin.

During the subsequent year, he again developed findings consistent with a mild increase in the severity of PH and right heart failure. A hemodynamic evaluation was performed at 25 months of life to explore options for treatment with additional medications. The results of heart catheterization and acute vasodilator testing are shown in Table 1. His response to supplemental oxygen with iNO suggested that he may benefit from treatment with a calcium-channel blocker. His acute response to intravenous nicardipine confirmed that this may be an appropriate option for precision care. Over time, his end-systolic eccentricity indices and B-type natriuretic peptide levels have improved while he is being treated with amlodipine. He is able to perform at the same level of physical activity as his healthy siblings. He has not developed evidence of right heart failure despite occasional respiratory infections. He is currently being treated with sildenafil, ambrisentan, amlodipine, digoxin, furosemide, aspirin, fluticasone, and blow-by oxygen at night.

**DISCUSSION**

This case describes a patient with a variant in the FOXF1 gene and histological findings consistent with a mild form of ACD who has survived for more than 56 months. It is possible that intrauterine exposure to metformin modified the severity of disease. We do not know whether medical therapy modified the severity of disease following birth. However, a combination of medications has provided enough cardiovascular support for him to participate in

![Histology Samples Demonstrating a Mild Variant of Alveolar Capillary Dysplasia](image_url)

(A) There is medial muscularization of the intralobular arterioles (a) with adjacent dilated venules (b). (B) A thickened pulmonary arteriole (c) is surrounded by an adjacent bronchial venule (d, misaligned pulmonary vein) and bronchiolo (e). In both images, the capillary bed is diminished, and there is heterogeneous alveolar septal thickening. The lack of homogenous septal thickening demonstrates a milder pattern in this disease process.

**TABLE 1** Arterial Blood Gases, Pressure Measurements, and Hemodynamic Calculations

|                         | 35% Oxygen | 100% Oxygen | 100% Oxygen Nitric Oxide 20 ppm | 100% Oxygen | 100% Oxygen Nicardipine 3 μg/kg/min |
|-------------------------|------------|-------------|---------------------------------|-------------|-------------------------------------|
| pH                      | 7.39       | 7.41        | 7.40                            | 7.41        | 7.39                                |
| PaO2, mm Hg             | 101        | 308         | 349                             | 356         | 309                                 |
| mPAP, mm Hg             | 51         | 49          | 39                              | 47          | 43                                  |
| mLAP, mm Hg             | 7          | –           | –                               | –           | –                                   |
| mSAP, mm Hg             | –          | –           | –                               | –           | –                                   |
| mRAP, mm Hg             | 47         | 49          | 44                              | 52          | 47                                  |
| CI, l/min/m²            | 3.09       | 2.72        | 2.81                            | 2.65        | 2.72                                |
| Rₚ, U·m²                | 14.2       | 15.4        | 11.4                            | 15.1        | 13.2                                |
| Rₛ, U·m²                | 12.9       | 15.4        | 14.4                            | 17.0        | 14.7                                |

Cl = cardiac index; mLAP = mean left atrial pressure; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; mSAP = mean systemic arterial pressure; PaO2 = systemic arterial oxygen tension; Rp = pulmonary vascular resistance index; Rs = systemic vascular resistance index.
age-appropriate activities. Only 2 other reported children with ACD have lived longer than 2 years without lung transplantation (2). A favorable outcome potentially depends on the extent of arteriolar obstruction and intrapulmonary shunting through bronchial veins and venules (3,4). Furthermore, some patients may respond favorably to specific medications.

Variants in FOXF1 may inhibit STAT3, a critical transcriptional regulator of angiogenesis, and cause ACD in the mouse (5). Metformin may also inhibit STAT3 signaling, raising concern that intrauterine exposure might further exacerbate the disease process. However, metformin might modify the severity of disease when STAT3 signaling is suppressed with a genetic variant by facilitating angiogenesis through other pathways during vascular development, including an increase in adenosine monophosphate–activated protein kinase signaling (6). If so, additional studies are needed to determine whether there is a critical period before or after birth when metformin could favorably modify the severity of ACD. None of the previous reports of atypical ACD included a maternal medication history (2).

Additional potential key elements of care are medications that decrease pulmonary vascular resistance. We do not know whether iNO, epoprostenol and sildenafil independently influenced early survival. However, eccentricity indices improved with these agents and normalized after treatment with bosentan. Clinical worsening occurred after stopping bosentan, suggesting that endothelin receptor antagonists have been key medications for long-term care. However, we acknowledge that clinical worsening could have occurred with a respiratory infection even if bosentan was continued. iNO decreased pulmonary arterial pressure during heart catheterization at 2 years of age. If available in the future, iNO may be a key option for the long-term precision care of our patient. Intravenous nicardipine acutely improved pulmonary arterial pressure to a lesser extent than iNO. Accordingly, amlodipine has provided long-term precision care.

**CONCLUSIONS**

A small subset of patients with ACD may survive with medical therapy. Additional studies are needed to determine whether metformin or other agents may modify the severity of disease during pulmonary vascular development. For this patient, key agents were identified when clinical worsening occurred following withdrawal of a medication and when pulmonary arterial pressure decreased during acute vasodilator testing. Precision care may prevent right heart failure and improve functional capacity by maintaining the lowest attainable pulmonary vascular resistance.

**ACKNOWLEDGMENTS** The institutional review board of the University of Utah approved this study (IRB_00033414) and waived the need for informed consent.

**ADDRESS FOR CORRESPONDENCE:** Ms. Chandler E. Yost, University of Utah School of Medicine, 131 South 1000 E #26, Salt Lake City, Utah 84102. E-mail: Chandler.yost@hsc.utah.edu.

**REFERENCES**

1. Bishop NB, Stankiewicz P, Steinhorn RH. Alveolar capillary dysplasia. Am J Respir Crit Care Med 2011;184:172-9.
2. Edwards JJ, Murali C, Pogoriler J, et al. Histopathological and genetic features of alveolar capillary dysplasia with atypical late presentation and prolonged survival. J Pediatr 2019;210:214–9.
3. Galambos C, Sims-Lucas S, Ali N, Gien J, Dishop MK, Abman SH. Intrapulmonary vascular shunt pathways in alveolar capillary dysplasia with misalignment of pulmonary veins. Thorax 2015;70:84–5.
4. Norvik CC, Westöö CK, Peruzzi N, et al. Synchrotron-based phase contrast micro-CT as a tool for understanding pulmonary vascular pathobiology and the 3-D microanatomy of alveolar capillary dysplasia. Am J Physiol Lung Cell Mol Physiol 2020;318:L65-75.
5. Pradhan A, Dunn A, Ustiyan V, et al. The SSZ2 FOXF1 mutation inhibits STAT3 signaling and causes alveolar capillary dysplasia. Am J Respir Crit Care Med 2019;200:1045-56.
6. Teng RJ, Du J, Afolayan AJ, Eis A, Shi Y, Konduri GG. AMP kinase activation improves angiogenesis in pulmonary artery endothelial cells with in utero pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol 2013;304:L29-42.

**KEY WORDS** echocardiography, pulmonary hypertension, right-sided heart catheterization.
A Rare Case of Lead-Induced Cardiomyopathy

Shruti Hegde, MD,a Michael Maysky,a Abbas Zaidi, MDb

ABSTRACT

A 39-year-old man, painter by profession, presented with symptoms of heart failure. His work up was unrevealing except for elevated blood lead levels (BLL). He was started on guideline-directed medical therapy and was referred to occupational therapy. No improvement in his ejection fraction was noted until his BLL decreased. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1496–500) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

PRESENTATION

A 39-year-old male presented to the emergency room with complaints of shortness of breath on exertion and pedal edema for 1 month. His vital signs were significant for a heart rate of 105 beats/min, blood pressure of 150/95 mm Hg; he was afebrile, and his oxygen saturation was 94% on room air. Physical examination was notable for elevated jugular venous pressure, 2+ pitting pedal edema, and bibasilar crackles on respiratory examination, and S3 was heard on cardiac auscultation.

MEDICAL HISTORY

His medical history was significant for resistant hypertension, which was diagnosed at 35 years of age. He initially required 4 different antihypertensive agents for optimal control of his blood pressure. With lifestyle changes and weight loss, his therapy was reduced to hydrochlorothiazide and metoprolol succinate. He had undergone complete workup for secondary hypertension at the time of diagnosis and was negative. The patient was a painter by profession, was never a smoker, and used alcohol occasionally but not illicit drugs. His family history was significant for diabetes in his mother. A transthoracic echocardiogram performed at the time of diagnosis of his hypertension showed normal left ventricular ejection fraction (LVEF).

LEARNING OBJECTIVES

- To recognize chronic lead exposure as one of the causes of cardiomyopathy and myocarditis.
- To understand that, with early diagnosis and management, there can be a potential improvement in ejection fraction.
- To understand the spectrum of cardiovascular effects of chronic lead exposure.

MEDICAL HISTORY

Electrocardiography revealed sinus tachycardia with left ventricular hypertrophy and secondary ST-T changes. A chest radiograph revealed an enlarged cardiac silhouette and pulmonary vascular congestion.

From the aDivision of Cardiology, St. Elizabeth’s Medical Center, Tufts School of Medicine, Brighton, Massachusetts; and the bDepartment of Internal Medicine, St. Elizabeth’s Medical Center, Tufts School of Medicine, Brighton, Massachusetts. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Ashwin Ravichandran, MD, served as Guest Editor for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

Manuscript received March 3, 2020; revised manuscript received April 29, 2020, accepted May 26, 2020.

ISSN 2666-0849

https://doi.org/10.1016/j.jaccas.2020.05.047
Complete blood count and basic metabolic profile were within normal limits, as was his N-terminal pro-B-type natriuretic peptide concentration, and his troponin T peaked at 0.2 ng/ml (normal is <0.03 ng/ml). A transthoracic echocardiogram showed an LVEF of 23%, a mild LV dilation, a severe left ventricular hypertrophy (LVH) (139 g/m²; normal 50 to 102 g/m²), a markedly reduced right ventricular (RV) function, a mild to moderate central mitral regurgitation, and global hypokinesis.

**DIFFERENTIAL DIAGNOSIS AND WORK-UP**

He underwent cardiac catheterization, which showed no angiographically apparent epicardial coronary artery disease and elevated filling pressures with normal cardiac output and index. He had had no viral syndromes in the preceding 6 months, and he tested negative for Trypanosoma cruzi infection, HIV, and Lyme disease. His serum and urine protein electrophoreses were normal, as were his serum iron and ferritin levels. He had no history of cocaine or other illicit drug use. He drank 2 to 4 beers/week. He underwent cardiac magnetic resonance (CMR), which revealed diffuse enlargement of all cardiac chambers, with focal areas of subepicardial abnormal delayed enhancement consistent with myocarditis. Diffuse moderate hypokinesis of the left ventricle without the focal area of dyskinesis. Small pericardial effusion and depressed left and right ventricular functions were observed.

**TREATMENT AND FOLLOW-UP**

He continued to do well for the next 2 years. He remained compliant with his medications and outpatient follow-up examinations. Thereafter, he presented with congestive heart failure symptoms to his primary care physician again. During his visit, he admitted to going back to his painting profession but has not been wearing masks. Repeat TTE showed a decline in LVEF to 31% and an increase in LV mass (141 g/m²), and his BLLs had increased to 38.7 µg/dl. He refused to switch jobs, hence, he was extensively counseled on wearing protective gear during work. His BLLs decreased slowly but steadily. TTE was repeated 6 months later, which showed improvement in EF to 46% and regression of LV mass index to 124 g/m² (Videos 1 and 2).

**DISCUSSION**

Lead is a common environmental toxin absorbed into the human body through the respiratory system, gastrointestinal tract, and skin. Chronic lead exposure is well known to affect a variety of organ systems. However, little is known about its effect on the cardiovascular system. More recently, the effect of chronic lead exposure has been implicated in resistant hypertension. The exact mechanism is still unclear, but it is believed to be related to oxidative stress, nitric oxide dysregulation, and alteration in the renin-angiotensin-aldosterone system (1). Population studies in the United States conducted by National Health and Nutrition Survey has found a direct relationship between lead exposure and elevated blood pressure (2). This patient initially came to medical attention years before the diagnosis of lead toxicity with resistant hypertension, which was likely secondary to his chronic lead exposure. Lead intoxication has also been associated with an increased incidence of coronary artery disease, stroke, peripheral arterial disease, and an increase in non-high-density lipoprotein cholesterol. Potential mechanisms of these agents remains to be studied (3).

The effect of lead exposure on myocardial structure and function has yet to be determined. Small case-controlled and observational studies have reported a decline in LVEF and global longitudinal strain in people chronically exposed to lead (4,5). A similar observation was made in this patient, as well (Figures 1 and 2). He had no other causes for his LV dysfunction other than elevated BLLs. His LVEF was at the lowest when his BLLs were at their peaks. As the BLL decreased, his LVEF, and his LV mass...
regressed. When he started painting again, his BLLs increased, LVEF dropped, and LV mass increased. This temporal association strongly suggested the possibility of direct lead toxicity as the cause of a drop in his cardiac contractility. The exact association between LVEF and lead is unknown. Animal experiments have indicated that the cardiotoxic effects of lead are likely related to its interference with calcium-dependent cellular processes (6). There is also a suggestion that depressed myocardial contractility may be due to impaired phosphorylation of the myocardial contractile proteins (7). These findings have yet to be confirmed.

Finally, BLL is reported to significantly affect LV mass, LV end-diastolic dimension, and relative wall thickness. In a study conducted in Poland, Kasperczyk et al. (4) compared a group of individuals exposed to lead in lead factories with a control group of administrative workers, who were not exposed to lead and found that the LV end-diastolic dimension was 6% higher and there was an 11% increase in LV mass index in the group with lead exposure (4). That study did not eliminate the confounding factor of blood pressure. A study by Schwartz (8) in 1991 showed a similar finding after controlling for blood pressure. The present patient had evidence of concentric LVH with LV mass index of 140 g/m², an LV end-diastolic dimension of 59 cm, and a relative wall thickness of 0.44. Because hypertension is an independent risk factor for LVH, it became a confounder in interpreting these data in the present patient.

His initial presentation was consistent with myocarditis with elevated troponin levels, depressed RV and LVEF, and CMR results suggestive of myocarditis with marked thinning of the myocardium. This
The patient had a complete workup for myocarditis, short of endomyocardial biopsy (EMB). CMR is the imaging mode of choice for the workup of myocarditis. Fluorodeoxyglucose-labeled positron emission tomography is a good alternative when cardiac CMR cannot be performed. Despite its limited sensitivity and specificity, EMB remains the gold standard for the diagnosis of myocarditis. However, given the rarity of lead cardiomyopathy, there are no defined guidelines or findings to diagnose myocarditis caused by lead by EMB definitively. Histopathological examinations of heart specimens of rats intoxicated with lead showed degenerative changes in myocardial fibers, loss of muscle structure, and focal fibrosis (9). However, the exact mechanism of myocardial damage by lead is largely unknown. Some of the postulated mechanisms include a direct irritant effect on the myocardium, inhibition of cardiometabolic enzymes, and selective disturbance of coronary circulation. None of the above-mentioned hypotheses has been proven (10,11).

Myocarditis due to lead toxicity is a rare condition. It is a very challenging to diagnose because the possibility of coincidental viral myocarditis cannot be ruled out. Nevertheless, the diagnosis of lead cardiomyopathy was more likely in this patient with no viral prodromes in preceding months, and the temporal association of his BLL with his LV function and LV mass. In a review of the medical literature, 3 other cases of myocarditis due to chronic lead exposure in adults (9,12,13) were found. To the best of these authors’ knowledge, this case is the fourth reported case of lead myocarditis and second reported case in an adult male.

CONCLUSIONS

The development of cardiomyopathy due to chronic lead exposure is most likely secondary to its direct toxic effect on the myocardium. More experimental
studies are required to establish the cardiotoxic mechanisms of lead. Meanwhile, cardiovascular ill effects of chronic lead exposure should be brought to the awareness of our health care providers for early diagnosis and management of these patients.

**REFERENCES**

1. Vaziri ND. Mechanisms of lead-induced hypertension and cardiovascular disease. Am J Physiol Heart Circ Physiol 2008;295:454–65.
2. Harlan WR, Landis JR, Schmouder RL, Goldstein NG, Harlan L CJ. Blood lead and blood pressure. Relationship in the adolescent and adult US population. JAMA 1985;253:530–4.
3. Navas-Acien A, Guallar E, Silbergeld EK, Rotenberg SJ. Lead exposure and cardiovascular disease—a systematic review. Environ Health Perspect 2007;115:3–11.
4. Kasperczyk S, Przywara-Chowaniec B, Kasperczyk A, et al. Function of heart muscle in people chronically exposed to lead. Ann Agric Environ Med 2005;12:207–10.
5. Yang W-Y, Zhang Z-Y, Thijs L, et al. Left ventricular structure and function in relation to environmental exposure to lead and cadmium. J Am Heart Assoc 2017;6:1-5.
6. Kopp SJ, Barany M, Erlanger M, Perry EF, Perry HM. The influence of chronic low-level cadmium and/or lead feeding on myocardial contractility related to phosphorylation of cardiac myofibrillar proteins. Toxicol Appl Pharmacol 1980;54:48–56.
7. Prentice RC, Kopp SJ. Cardiotoxicity of lead at various perfusate calcium concentrations: functional and metabolic responses of the perfused rat heart. Toxicol Appl Pharmacol 1985;81:491–501.
8. Schwartz J. Lead, blood pressure, and cardiovascular disease in men and women. Environ Health Perspect 1991;91:71–5.
9. Beintker E. On the work of Richard Haubrich: Communication of a case of cardiac wall aneurysm after acute lead poisoning. Klin Wochenschr 1948;26:473–4.
10. Kosmider S, Petelenz T. Zmiany elektrokardiograficzne u starszych osób z przewlekim zawodowym zatruciem olowiem. Pol Arch Med 1962;32:347–40.
11. Sroczyński J. Zmiany elektrokardiograficzne w przewleklej doswiadczonej olowicy u królików. Postepy Hig Med 1961;15:353–9.
12. Freeman R. Reversible myocarditis due to chronic lead poisoning in childhood. Arch Dis Child 1965;40:389–93.
13. Read JL, Williams JP. Lead myocarditis: report of a case. Am Heart J 1952;44:797–802.

**KEY WORDS** cardiomypathy, global longitudinal strain, lead toxicity, myocarditis

**APPENDIX** For supplemental videos, please see the online version of this paper.

**ADDRESS FOR CORRESPONDENCE:** Dr. Shruti Hegde, Cardiovascular Division, Saint Elizabeth’s Medical Center, 736 Cambridge Street, Brighton, Massachusetts 02135. E-mail: Shruti.Hegde15@gmail.com.
Recurrent Left Ventricular Thrombus Formation on Rivaroxaban Therapy in Cardiomyopathy and Liver Cirrhosis

Usman Ghani, MD, a Karlo A. Wiley, BS, b Raman Singhal, MD, a Cristina Sanina, MD c

ABSTRACT

Left ventricular (LV) thrombus in patients with reduced LV systolic function carries significant thromboembolic risk. Direct oral anticoagulants are an attractive alternative to warfarin for LV thrombus management. However, there are not enough data regarding the safety and efficacy of direct oral anticoagulants for the treatment of LV thrombus.

(Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1501–4) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 50-year-old man with a history of nonischemic dilated cardiomyopathy with left ventricular (LV) ejection fraction of 15% initially complicated by LV thrombus formation was treated with warfarin. Two repeat echocardiograms showed successful thrombus resolution. Furthermore, warfarin was switched to rivaroxaban because of difficulties in achieving a steady therapeutic international normalized ratio level. Two months later, the patient presented to the hospital with sudden onset of right-sided weakness and altered mental status. Physical exam revealed lethargy, aphasia, spatial neglect to the right side, gaze preference to the left, and right hemiplegia, and Glasgow coma scale 10 to 15 (eye subscore: 5, verbal subscore: 1, motor subscore: 5). Eye examination showed equal and round pupils reactive to light. A cardiovascular exam revealed normal rate, regular rhythm, and normal heart sounds. Vital signs were normal: blood pressure 113/83 mm Hg, pulse 78 beats/min, temperature 97.8°F (36.6°C), respiratory rate 20/min, and 98% oxygen saturation at room air.

LEARNING OBJECTIVES

- Patients with severe LV systolic dysfunction and history of LV thrombus should be continued on anticoagulation for life to prevent recurrent LV thrombus formation and systemic thromboembolism.
- Rivaroxaban should not be used in liver cirrhosis patients, as drug metabolism, thrombin, von Willebrand factor, and albumin levels are altered in liver disease.
- To date, warfarin and low-molecular-weight heparins should be used in patients with liver cirrhosis to treat and prevent LV thrombus.
PAST MEDICAL HISTORY

The patient had well-controlled diabetes mellitus, arterial hypertension, compensated heart failure, history of implantable cardioverter-defibrillator, compensated alcoholic liver cirrhosis, hyperlipidemia, and chronic punctuated infarcts of the right occipital lobe, left superior cerebellum, and left superior frontal gyrus.

DIFFERENTIAL DIAGNOSIS

Based on patient presentation, the differential diagnosis included thromboembolic stroke from de novo LV thrombus versus intracranial bleeding versus thromboembolic stroke because of paroxysmal atrial fibrillation.

INVESTIGATIONS

Initial head computed tomography and angiography revealed acute left occipital and left middle cerebral artery territory infarcts and left M1 occlusion (Figures 1A and 1B); echocardiography showed large apical LV thrombus (Figure 2, Videos 1 and 2).

MANAGEMENT

The patient was not a candidate for tissue plasminogen activator treatment (owing to rivaroxaban use) or thrombectomy (ASPECTS [Alberta Stroke Program Early CT Score] of 4; endovascular therapy is recommended in patients with baseline ASPECTS $\geq 6$) (1). Given LV thrombus and high risk for recurrent stroke, neurology recommended intravenous heparin infusion. Six hours after heparin was started, the patient’s status deteriorated; he developed acute respiratory failure and was intubated. Absences of gag, pupillary, and corneal reflexes were noted. Repeat computed tomography of the head revealed massive parenchymal hemorrhage and vasogenic edema with a left-to-right 2-cm midline shift. Hemorrhage extended into the bilateral lateral ventricles, with enlargement of the occipital and temporal horns of the lateral ventricles (Figure 3).

DISCUSSION

Severe LV systolic dysfunction often leads to LV thrombus formation. Thromboembolic events occur in 10% to 40% of patients with LV thrombus and no anticoagulation. Currently, the American Heart Association and the European Society of Cardiology recommend warfarin for patients with LV thrombus formation.

Abbreviations and Acronyms

DOAC = direct oral anticoagulant
LV = left ventricular

Figure 1

Acute Strokes of Left Frontal and Occipital Lobes and Left M1 Cerebral Artery Occlusion

(A) Computed tomography angiography of cerebral arteries. The blue arrow depicts left M1 occlusion. (B) Computed tomography of the head, axial view. The blue arrow indicates M1 territory acute infarct (loss of gray-white matter differentiation), and the yellow arrow depicts chronic left occipital infarct (encephalomalacia).
based on observational studies. The 2014 American Heart Association stroke guidelines recommended direct oral anticoagulants (DOACs) in patients with LV mural thrombus as an alternative to warfarin (Class IIb, Level of Evidence: C) (2). Multiple cases of LV thrombus resolution with rivaroxaban have been reported (3). Additionally, a recent meta-analysis of case reports of DOACs for the treatment of LV thrombus reported LV thrombus resolution in 45 patients and failure to resolve in 4 patients (4). Degheime et al. (2) reported LV thrombus formation on rivaroxaban in patients with nonischemic cardiomyopathy. Our case raises concern over the efficacy of DOACs in the management of LV thrombus in patients with liver cirrhosis who are thought to be in a procoagulant state and thus prone to thrombus formation. The liver synthesized anticoagulant, such as protein C and S, antithrombin III, as well as fibrinolytic factors that are not measured in routine blood assays. Moreover, the cirrhotic liver cannot clear von Willebrand factor, leading to an abnormally high level of von Willebrand factor, which further adds to the prothrombotic effects of cirrhosis (5). Rivaroxaban is 65% metabolized by the liver, and in cirrhosis P450-mediated DOAC metabolism is altered leading to a change in pharmacokinetics to various degrees. Previous studies have shown that rivaroxaban resulted in a reduced anticoagulant effect in deep venous thrombosis treatment in Child-Turcotte-Pugh class C cirrhosis patients, suggesting the limitations of DOACs use (6). Potze et al. (7) did not recommend rivaroxaban use in patients with Child-Turcotte-Pugh class B and C cirrhosis as well, owing to reduced anticoagulant effect in vitro with standard DOAC dosage, and suggested factor X plasma level monitoring in cirrhotic patients (5). For portal vein thrombosis, Basili et al. (8) recommended low-molecular-weight heparins instead of DOACs. Hence, current evidence does not support the routine use of DOACs in these patients (8). Respectively, in patients with liver cirrhosis and atrial fibrillation, the use of DOACs was associated with fewer bleeding events compared with warfarin (9). Despite the practical advantages of rivaroxaban (predictable dosing, no requirement for a regular blood draw for international normalized ratio monitoring, no dietary restrictions, and minimal drug interactions), the use of rivaroxaban in standard dose cannot be recommended in cirrhotic patients because of lack of evidence that any DOAC prevents systemic thromboembolism. Currently, there is 1 ongoing clinical trial aimed to investigate the efficacy of apixaban versus warfarin in patients with LV thrombus who have suffered a recent myocardial infarction (NCT03232398) and 2
trials (NCT02643212, NCT03193502) that will study the effects of rivaroxaban in patients with liver cirrhosis. Perhaps these studies will help to establish the patient population with liver cirrhosis and LV thrombus that will benefit from DOACs and the correct drug dosage.

CONCLUSIONS

Patients with a history of LV thrombus and liver cirrhosis should be treated with warfarin or low-molecular-weight heparins. Further studies are necessary to confirm or refute the safety and efficacy of LV thrombus treatment with DOACs in cirrhotic patients.

ADDRESS FOR CORRESPONDENCE: Dr. Cristina Sanina, Division of Cardiology, Montefiore Medical Center, Albert Einstein College of Medicine, 111 East 210th Street, 2nd floor, Bronx, New York 10467. E-mail: csanina@montefiore.org.

REFERENCES

1. Mokin M, Primiani CT, Siddiqui AH, Turk AS. ASPECTS (Alberta Stroke Program Early CT Score) measurement using Hounsfield unit values when selecting patients for stroke thrombectomy. Stroke 2017;48:1574–9.
2. Degheem G, Berry A, Zughib M. Off label use of direct oral anticoagulants for left ventricular thrombus. Is it appropriate? Am J Cardiovasc Dis 2017;7:98-101.
3. Abdelnaby M, Almaghraby A, Abdelkarim O, Saleh Y, Hammad B, Badran H. The role of rivaroxaban in left ventricular thrombi. Anatol J Cardiol 2019;21:47–50.
4. Tomasoni D, Sciatti E, Bonelli A, Vizzardi E, Metra M. Direct oral anticoagulants for the treatment of left ventricular thrombus - a new indication? A meta-summary of case reports DOACs in left ventricular thrombosis. J Cardiovasc Pharmacol 2020;75:530-4.
5. Verbeek TA, Stone JG, Saner FH, Beziniow D. Hypercoagulability in end-stage liver disease: review of epidemiology, etiology, and management. Transplant Direct 2018;4:e403.
6. Al Moussawi H, Chalhoub JM, Lafferty J, Deeb L. Direct oral anticoagulants in cirrhotic patients: current evidence and clinical observations. Can J Gastroenterol Hepatol 2019;2019:4383269.
7. Potze W, Arshad F, Adelmenejer J, et al. Differential in vitro inhibition of thrombin generation by anticoagulant drugs in plasma from patients with cirrhosis. PLoS One 2014;9:e88390.
8. Basili S, Pastori D, Raparelli V, Vieri F. Anticoagulant therapy in patients with liver cirrhosis and portal vein thrombosis: insights for the clinician. Therap Adv Gastroenterol 2018;11:1756284818793561.
9. Pastori D, Lip GYH, Farcomeni A, et al., ATHERO-AF Study Group. Incidence of bleeding in patients with atrial fibrillation and advanced liver fibrosis on treatment with vitamin K or non-vitamin K antagonist oral anticoagulants. Int J Cardiol 2018;264:58-63.

KEY WORDS cirrhosis, LV thrombus, oral anticoagulation, rivaroxaban

APPENDIX For supplemental videos, please see the online version of this paper.
**ABSTRACT**

Immunoglobulin G4 (IgG4)-related pericarditis, an immune-mediated fibro-inflammatory condition, is a rare yet life-threatening disease presenting with constrictive pericarditis. We describe a case of IgG4-related pericarditis presenting with epicardial nodules successfully treated with corticosteroids. This case highlights the clinical significance of assessing IgG4-related pericarditis in the diagnostic workup of pericardial masses. *(Level of Difficulty: Advanced.)*

*(J Am Coll Cardiol Case Rep 2020;2:1505-9) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

**HISTORY OF PRESENTATION**

A 75-year-old man with a 20-year history of diabetes underwent percutaneous coronary intervention for angina. Cardiac enzyme levels were elevated, and minor electrocardiographic abnormalities were observed although the patient was asymptomatic during follow-up. We suspected myocardial ischemia and performed coronary computed tomography angiography (CCTA) because the patient was unable to exercise. His vital signs were: blood pressure, 130/80 mm Hg; heart rate, 66 beats/min; respiratory rate, 12 breaths/min; and temperature, 36.0°C. Physical examination results were unremarkable. CCTA revealed no significant coronary artery stenosis, but pericardial masses were detected incidentally. We also noted multiple visceral pericardial nodules adjacent to epicardial fat, concurrent with localized pericardial thickening and pericardial and paraphrenic lymph node enlargement *(Figures 1A and 1B).*

**MEDICAL HISTORY**

The patient had a history of diabetes mellitus, dementia, and angina.

**DIFFERENTIAL DIAGNOSIS**

Differential diagnoses based on cardiac magnetic resonance (CMR) findings include metastatic...
neoplasm (lung or breast carcinoma and lymphoma), primary neoplasm (malignant lymphoma and mesothelioma), tuberculous pericarditis, or cardiac sarcoidosis.

INVESTIGATIONS

Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) revealed weak metabolic activity in the same nodular lesions, suggesting malignancy or infection (e.g., tuberculosis) (Figures 1C and 1D). CMR screening revealed epicardial thickening with inhomogeneous gadolinium enhancement and pericardial effusion (PE) (Figure 2). Results of cardiac catheterization and hemodynamic study were unremarkable, with no evidence of constrictive physiology. Laboratory tests revealed elevated serum immunoglobulin G4 (IgG4) (212 mg/dl, normal range: 4 to 108 mg/dl), high-sensitivity cardiac troponin T (0.058 ng/ml, normal range: 0 to 0.010 ng/ml), IgE (69,303 IU/ml, normal range: 0 to 170 IU/ml), and soluble interleukin-2 receptor (1,574 U/ml, normal range: 122 to 496 U/ml) levels. An open surgical biopsy was performed for diagnosis. The pericardium was diffusely reddish. The resected

**ABBREVIATIONS AND ACRONYMS**

CCTA = coronary computed tomography angiography
CMR = cardiac magnetic resonance
CP = constrictive pericarditis
FDG PET/CT = fluorodeoxyglucose positron-emission tomography/computed tomography
IgG4 = immunoglobulin G4
IgG4-RD = immunoglobulin G4-related disease
PE = pericardial effusion

**FIGURE 1 Pericardial Masses**

(A, B) Coronary computed tomography angiography reveals multiple epicardial nodules (A, arrowheads), a localized thickened pericardium, enlarged pericardial lymph nodes (A, dashed arrows), and an enlarged paraphrenic lymph node (B, arrow). (C, D) Fluorodeoxyglucose (FDG) positron-emission tomography/computed tomography reveals mildly increased FDG uptake in epicardial nodules, suggesting increased metabolic activity (arrowheads).
thickened pericardium was stiff (Figure 3A). PE analysis revealed lymphocyte-predominant exudates and elevated IgG4 levels (395 mg/dl). The adenosine deaminase activity in PE was 45 U/l, suggesting tuberculous pericarditis; polymerase chain reaction test for Mycobacterium tuberculosis was negative. PE cytology as well as bacterial and fungal cultures were unremarkable. Pathologic examination of the specimen revealed fibrous thickening, patchy lymphoplasmacytic infiltration with eosinophils, and hemorrhage (Figure 3B). Immunostaining revealed increased numbers of IgG4-positive plasma cells (mean 29/high-power field counted from 3 active spots) and an IgG4/IgG-positive plasma cell ratio of 51% (Figure 3C). These findings met the comprehensive criteria for IgG4-related disease (IgG4-RD) following exclusion of IgG4-RD mimics (malignancies, infectious diseases, autoimmune diseases, Churg–Strauss syndrome, or Castleman disease). Moreover, fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT) ruled out involvement of other organs in IgG4-RD.

**MANAGEMENT**

A subsequent high-dose corticosteroid treatment (prednisolone 30 mg daily) exhibited a dramatic beneficial response on the pericardial lesion (Figure 4). CCTA following a 6-month course of treatment showed significant reduction in the number and size of epicardial nodules and the enlarged paraphrenic lymph node. Moreover, the enlarged pericardial lymph nodes and PE disappeared. The prednisolone dose was gradually tapered to 2.5 mg daily.

**DISCUSSION**

IgG4-RD is a systemic fibro-inflammatory disorder characterized by an elevated serum IgG4 level and histologic findings of IgG4-positive lymphoplasmacytic infiltration (1). Although pericardial involvement is rare, IgG4-related pericarditis manifests as chronic pericarditis associated with PE. Etiologies of PE are diverse and poorly understood despite exhaustive examination. Therefore, IgG4-related pericarditis may remain undiagnosed or misdiagnosed as idiopathic pericarditis, and patients might receive inappropriate treatment. If left untreated, serious complications such as cardiac tamponade and constrictive pericarditis (CP) may occur at an advanced stage (2,3). However, early diagnosis is extremely challenging because of the lack of specific signs or symptoms in early disease stages. Herein, we describe a patient with IgG4-related pericarditis presenting with epicardial nodules.

This case may offer several valuable clinical lessons. IgG4-related pericarditis can present as epicardial nodules and not CP, which is recognized as its more typical presentation (4). Although most patients present with symptoms and signs of right-sided heart failure, our patient exhibited pericardial masses; this has been reported for the first time per our knowledge.

The pericardial biopsy was useful for the definitive diagnosis. Histologic analysis of the pericardium is available in a limited number of cases (2–5). IgG4 immunoprofile showed that cases with CP tended to show more IgG4-positive cells and higher IgG4/IgG ratios than our case. Because the number of IgG4-positive cells can decrease as fibrosis formation progresses to an advanced stage, differences in immunoprofile might not reflect accurate IgG4-pericarditis activity.

Generally, patients with IgG4-RD respond well to corticosteroid treatment. However, a corticosteroid trial for diagnostic purposes should be strictly avoided because it may mask or exacerbate the clinical picture of IgG4-RD mimics, leading to delayed or incorrect diagnosis (6). The pericardial biopsy enabled us in timely diagnosis of IgG4-related pericarditis, resulting in complete recovery with corticosteroid treatment. The pericardial biopsy suggested that the parietal pericardial lesion initiated concurrently with epicardial nodule formation. Although the precise mode of action remains unknown, epicardial
nODULES MIGHT BE THE FIRST STEP IN THE PATHOGENESIS OF IgG4-RELATED PERICARDITIS. FURTHER REPORTS SHOULD BE ASSESSED TO VERIFY THE EARLY DIAGNOSTIC VALUE AND PROVE THE VALIDITY OF THIS MANIFESTATION.

CMR WAS ALSO HELPFUL FOR THE DIAGNOSIS OF EARLY-STAGE IgG4-RELATED PERICARDITIS. CMR ENABLES ANATOMICAL AND DYNAMIC EVALUATION OF THE PERICARDIUM, PROVIDING DETAILED INFORMATION ON PE LOCATION AND CHARACTERIZATION AND PERICARDIAL THICKENING (7). THUS, CMR SCREENING SHOULD BE CONSIDERED FOR ALL PATIENTS WITH PERICARDIAL MASSES BECAUSE EARLY-STAGE IgG4-RELATED PERICARDITIS MAY BE UNDIAGNOSED.

PATIENTS WITH IgG4-RELATED PERICARDITIS RESPOND WELL TO CORTICOSTEROIDS (2,3). HOWEVER, HIGH RELAPSE RATES DURING AND AFTER CORTICOSTEROID TAPERING ARE MAJOR CONCERNS. MOREOVER, THERE IS A RISK OF SERIOUS ADVERSE EFFECTS OF PROLONGED TREATMENT, SUCH AS DIABETES, CUSHING SYNDROME, AND INFECTIONS. RITUXIMAB CAN BE USED AS MAINTENANCE THERAPY FOLLOWING STEROID TAPERING OR AS A POTENTIAL PROMISING THERAPY IN HIGH-RISK PATIENTS WITH STEROID INTOLERANCE (8). OTHER IMMUNOMODULATORS SUCH AS CYCLOPHOSPHAMIDE ARE ALSO EFFECTIVE IN COMBINATION WITH STEROIDS (9). CONVERSELY, NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

(A) Resected pericardium. (B) Photomicrograph with hematoxylin and eosin stain (Bar: 200 μm). (C) Photomicrograph with immunostaining against immunoglobulin G4 (Bar: 400 μm).

(A, B) Coronary computed tomography angiography following a 6 months course of corticosteroid treatment reveals a marked reduction in the number and size of epicardial nodules (arrowheads) and the enlarged paraphrenic lymph node (arrow). Note the disappearance of enlarged pericardial lymph nodes and pericardial effusion.
plus colchicine is the first-line therapy for chronic pericarditis of idiopathic or viral origin (10). Whether these drugs show similar beneficial effects on IgG4-related pericarditis remains unclear; however, these were not useful in IgG4-related pericarditis according to a case report (5). The future challenge is to establish site-specific diagnostic and therapeutic methods for IgG4-related pericarditis.

**FOLLOW-UP**

The patient remains symptom-free during the follow-up examinations.

**CONCLUSIONS**

Herein, we describe a case of biopsy-proven early-stage IgG4-related pericarditis successfully treated with corticosteroids. IgG4-related pericarditis can present as epicardial nodules; CMR is helpful for the diagnosis of this clinical entity. Although IgG4-related pericarditis is rare, it can cause a potentially lethal cardiac disease which can be cured if treated properly at an early stage. Tissue diagnosis is essential for early diagnostic testing and appropriate treatment. Therefore, all clinicians should recognize the clinical significance of IgG4-RD in the diagnostic workup of pericardial mass and should not hesitate to perform a pericardial biopsy.

**ADDRESS FOR CORRESPONDENCE:** Dr. Hiroyuki Yamamoto, Department of Cardiovascular Medicine, Narita-Tomisato Tokushukai Hospital, 1-1-1 Hiyoshi-dai, Tomisato, Chiba 286-0201, Japan. E-mail: hyamamoto19700908@gmail.com.

**REFERENCES**

1. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet 2015;385:1460-71.
2. Morita T, Izawa A, Hamano H, et al. Significant pericardial involvement of immunoglobulin G4-related disease. Ann Thorac Surg 2014;98:e47-9.
3. Sekiguchi H, Horie R, Suri RM, Yi ES, Ryu JH. Constrictive pericarditis caused by immunoglobulins G4-related disease. Circ Heart Fail 2012;5:e30-1.
4. Ibe T, Nakamura T, Taniguchi Y, Momomura S. IgG4-related effusive constrictive pericarditis. Eur Heart J Cardiovasc Imaging 2016;17:707.
5. Yassi U, Iqbal F, Stevenson HL. IgG4-related sclerosing pericarditis in a young man with recurrent chest pain. Ann Thorac Surg 2019 Oct;108:e261-3.
6. Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-1) 2011. Mod Rheumatol 2012;22:21-30.
7. Bogaert J, Francone M. Cardiovascular magnetic resonance in pericardial diseases. J Cardiovasc Magn Reson 2009;11:14.
8. Perugini CA, Wallace ZS, Meyersohn N, Oliveira G, Stone JR, Stone JH. Large vessel involvement by IgG4-related disease. Medicine (Baltimore) 2016;95:e3344.
9. Yunyun F, Yu C, Panpan Z, et al. Efficacy of cyclophosphamide treatment for immunoglobulin G4-related disease with addition of glucocorticoids. Sci Rep 2017;7:6195.
10. Imazio M, Gaita F, LeWinter M. Evaluation and treatment of pericarditis: a systematic review. JAMA 2015;314:1498-506.

**KEY WORDS** cardiac magnetic resonance, computed tomography, immunoglobulin G4-related disease, immunoglobulin G4-related pericarditis, pericardial effusion
MINI-FOCUS ISSUE: HEART FAILURE

CASE REPORT: CLINICAL CASE

Hypersecretory Paraganglioma Presenting as Acute Aortic Dissection

Christian J. Lorenzo, MD,a Qassem K. Abdelal, MD,a Jorge I. Conte, MD,a Ricardo J. Villasmil, MD,a Wilhelmine Wiese-Rometsch, MD,a Jeffrey E. Sell, MDb

ABSTRACT

Abrupt, transient, and severe hypertension evoked by catecholamine-secreting tumors has the potential to manifest as acute aortic dissection. We report the successful, multidisciplinary management of an insidious, extra-adrenal, functional paraganglioma, suddenly presenting as acute aortic dissection. (Level of Difficulty: Beginner.)

(J Am Coll Cardiol Case Rep 2020;2:1510–4) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 32-year-old man presented with acute substernal chest pain that radiated into the neck and had persisted over 48 h. He described severe, pressure-like pain slightly mitigated by ibuprofen. Ensuing dyspnea and diaphoresis prompted presentation to the emergency department. He reported associated intermittent headaches and generalized weakness. He disclosed smoking tobacco and drinking alcohol socially but denied illicit drug use. Family history identified early-onset hypertension in both parents. On arrival, blood pressure (BP) was 197/121 mm Hg with a heart rate (HR) of 86 beats/min. Physical examination demonstrated acute distress secondary to chest pain. Cardiopulmonary examination revealed a regular rate and rhythm without murmurs, rubs, or gallops and clear lungs. Abdominal examination exhibited no palpable masses. Distal pulses were 2+ throughout.

PAST MEDICAL HISTORY

Past medical history includes only hypertension. An unknown antihypertensive medication was initiated 2 years prior but had elapsed several months ago.

DIFFERENTIAL DIAGNOSIS

Acute-onset, severe chest pain with associated dyspnea is especially concerning for life-threatening conditions including acute coronary syndrome, acute aortic dissection (AoD), pulmonary embolism, tension pneumothorax, esophageal rupture, and cardiac tamponade. Markedly elevated BP at his age raised concern for secondary hypertension. Severe

From the aDepartment of Medicine, Sarasota Memorial Hospital, Florida State University College of Medicine, Sarasota, Florida; and the bDivision of Cardiothoracic Surgery, Department of Surgery, Sarasota Memorial Hospital, Sarasota, Florida. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

Manuscript received May 6, 2020; accepted May 20, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.05.097
pain alone could have elevated BP, but this should not have been the only suspected cause. Major causes of secondary hypertension include medications (nonsteroidal anti-inflammatory drugs and so on), illicit drug use, chronic kidney disease, primary aldosteronism, hypercortisolism, pheochromocytoma, and functional paraganglioma.

INVESTIGATIONS

Blood chemistry revealed a creatinine level of 1.55 mg/dl (reference range, 0.55 to 1.02 mg/dl) without a baseline value for comparison. Electrocardiogram demonstrated left ventricular hypertrophy with diffusely inverted T-waves (Figure 1). Serial troponin draws had negative results. Urine toxicology detected tetrahydrocannabinol but not methamphetamine or cocaine. Chest x-ray displayed no effusions, pneumothorax, or mediastinal widening (Figure 2).

Computed tomography (CT) angiogram revealed a Stanford type A AoD involving the ascending thoracic aorta and aortic arch (Figure 3) with patency of the major aortic branch vessels. Due to surgical urgency, secondary hypertension work-up occurred after AoD repair and demonstrated normal serum aldosterone and renin activity. However, urine metanephrines and normetanephrines were elevated at 1,919 μg/24 h (reference range, 36 to 190 μg/24 h) and 12,352 μg/24 h (reference range, 35 to 482 μg/24 h), respectively. Free plasma metanephrines and normetanephrines were elevated at 494 pg/ml (reference range, <57 pg/ml) and 4,279 pg/ml (reference range, <148 pg/ml), respectively. Renal ultrasound revealed a hypoechoic mass adjacent to the left kidney. CT of the abdomen and pelvis confirmed a 5.8-cm left pararenal mass exhibiting an effect on the renal pelvis (Figure 4) with secondary left hydronephrosis.

MANAGEMENT

Clonidine and labetalol had mild success in controlling BP. Subsequent esmolol infusion was modestly effective. Because he showed no additional evidence of end-organ compromise, the patient was taken urgently for replacement of ascending aorta and underside of the transverse arch via cardiopulmonary bypass with deep hypothermic arrest and antegrade cerebral perfusion. Because intraoperative transthoracic echocardiogram showed no aortic insufficiency and only mild left ventricular hypertrophy, the procedure was limited to replacement of the ascending aorta, which included the site of intimal disruption. Hypertension persisted postoperative day 2, requiring high-dose clevidipine and nitroglycerin infusion. Eventually, BP was controlled, and secondary surgical
intervention was planned to address the suspected hypersecretory tumor. In addition to strategic adrenergic blockade with labetalol and doxazosin, the patient was discharged with amlodipine and lisinopril prescriptions on postoperative day 5.

The patient returned in 6 weeks for tumor extraction. Mild BP elevation occurred during meticulous tumor resection. Post-resection hypotension did not occur. Open excision yielded a 72-g, grossly intact, tan, rubbery mass measuring 7.5 × 4.7 × 4.5 cm (Figure 5) immediately opposed to the renal vasculature. Repair of the renal vessels was required. Histological staining with hematoxylin and eosin revealed nests of bland spindle cells separated by thin trabeculae (Figure 6). Immunohistochemical stains yielded synaptophysin (neuroendocrine marker) with scattered cells displaying S100 proteins (embryonically derived from the neural crest) consistent with
paraganglioma (PGL). Post-operative BP improvement was dramatic.

**DISCUSSION**

Stanford classification has established 2 categories for AoD: those involving the ascending aorta (type A) and those not (type B). Urgent and definitive imaging using transesophageal echocardiogram (preferred if hemodynamically unstable), CT, or magnetic resonance imaging is recommended. Initial management should decrease aortic wall stress by controlling HR and BP, limiting the extension of dissection. Intravenous beta-blockade is recommended and should be titrated to a HR ≤60 beats/min and systolic BP of 100 to 120 mm Hg. If systolic BP remains suboptimal, intravenous vasodilators (e.g., clevidine and nitroglycerin) should be administered. Emergent surgical evaluation should be sought given the associated risk of life-threatening complications. Surgery, typically indicated for type A AoD, involves intimal tear excision, obliteration of the false lumen entry, reconstitution of the aorta with placement of a synthetic vascular graft, and repair or replacement of the aortic valve (1).

PGLs, present in about 0.1% to 0.6% of the hypertensive population, are neuroendocrine tumors arising from extra-adrenal autonomic paraganglia (2). They consist of neural crest-derived neuroendocrine cells with the potential to secrete catecholamines in abundance. PGLs are categorized as sympathetic or parasympathetic depending on parangangia origination. Sympathetic PGLs, commonly located in sympathetic paravertebral ganglia of the thorax, abdomen, and pelvis, frequently are functional (catecholamine-secreting). Norepinephrine-secreting tumors usually cause sustained hypertension directly proportional to norepinephrine levels, whereas tumors that produce epinephrine co-secreted with norepinephrine typically produce paroxysmal hypertension. Symptoms can include headaches, sweating, palpitations, anxiety, tremors, pallor, and nausea. Histologically and functionally similar, a PGL that forms in the adrenal medulla is a pheochromocytoma (PCC) (2,3). Although rare, abrupt, transient, and severe hypertension evoked by intra-adrenal PCCs has manifested as AoD, but PGL-induced reports are extremely scarce (4). The current literature reveals annual incidence of both PCC/PGL (2 to 10 cases/million) and AoD (2 to 3.5 cases per 100,000 person-years) to be particularly rare (1,3). These 2 entities occurring together has only been reported a handful of times, typically in the form of PCC-induced AoD, however, to our knowledge, there has only been one other reported PGL-induced AoD (5). Surgical treatment of functional PGLs presents several challenges requiring multidisciplinary expertise and pre-operative planning. Secondary PGL extraction can produce intractable hypertensive crisis secondary to tumor manipulation (4). Pre-operative adrenergic blockade is essential prophylaxis for catecholamine release. In our case, PGL extraction was planned 6 weeks later to establish ample adrenergic blockade. Nevertheless, at least 10 to 14 days of blockade are recommended (4). Traditionally, PGLs are resected by means of open surgical procedures due to their multicentricity and close relationship with major vascular structures. PGLs can be highly vascular, especially in the head and neck, which should be considered during surgical excision. Once a functional PGL is removed, BP medications should be reassessed accordingly.

**FOLLOW-UP**

The patient tolerated both procedures very well. Once the PGL was removed, improvement in BP was significant, and he was eventually weaned off all antihypertensive medications. Plasma free metanephrines, drawn 8 weeks post-extraction normalized to 48 pg/ml (reference range, <57 pg/ml). His
acute kidney injury resolved, and he is able to work and exercises 3 days per week without limitation.

**CONCLUSIONS**

In summary, this case demonstrates a multifaceted diagnostic dilemma of important clinical significance. AoD risk posed by hypertensive emergencies is real, but occurrence is especially rare in the setting of a hypersecretory PGL. To our knowledge, this is the second reported case of this entity. Of critical importance is the allowance of ample duration between initial AoD repair and secondary PGL extraction for sufficient adrenergic prophylaxis prior to PGL manipulation. Moreover, this case describes a safe, strategic, and multidisciplinary approach to address 2 uniquely challenging cardiovascular events.

**ADDRESS FOR CORRESPONDENCE:** Dr. Christian J. Lorenzo, Sarasota Memorial Hospital, 1700 S. Tamiami Trail, Sarasota, Florida 34239. E-mail: Christian-lorenzo@smh.com.

**REFERENCES**

1. Hiratzka L, Bakris G, Beckman J, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. J Am Coll Cardiol 2010;55:e27–129.

2. Costa MH, Ortiga-Carvalho TM, Violante AD, Vaisman M. Pheochromocytomas and paragangliomas: clinical and genetic approaches. Front Endocrinol (Lausanne) 2015;6:126.

3. Welander J, Söderkvist P, Gimm O. Genetics and clinical characteristics of hereditary pheochromocytomas and paragangliomas. Endocr Relat Cancer 2011;18:R253–76.

4. Runyan B, Hanak CR, Mahendiran S, Allamaneni S, Vester S. Type A aortic dissection complicated by pheochromocytoma. Ann Thorac Surg 2019;107:e13–4.

5. Borrego AD, Ferreira PC, Pinto FJ. Acute type A aortic dissection in a patient with paraganglioma. Rev Port Cardiol 2017;36:777.e1–6.

**KEY WORDS** aorta, chest pain, dissection, hypertension, post-operative, thoracic
ABSTRACT

A 77-year-old woman with critical limb ischemia, venous insufficiency, and progressive pulmonary hypertension presented for evaluation. Lower extremity angiography showed a common iliac arteriovenous fistula. Closure was achieved with a covered stent placed in the artery. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1515–9) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 77-year-old woman with peripheral artery disease (PAD) and venous insufficiency presented for evaluation of critical limb ischemia. She recently developed a left foot ulcer with Rutherford 5 symptoms in the left leg, and a lower extremity (LE) arterial ultrasound revealed no detectable waveform in the left great toe. She also had developed severe, persistent bilateral LE edema in the preceding months, requiring hospitalization for treatment with intravenous diuretics. In addition, the patient had mild chronic obstructive pulmonary disease (COPD), and over the prior 2 months, she had reported severe worsening from her baseline dyspnea. She was diagnosed with pulmonary hypertension (PH) and given a poor prognosis, based on her severely limiting symptoms and poor functional status.

On examination, the patient was afebrile with blood pressure of 131/54 mm Hg, heart rate of 92 beats/min, respiratory rate of 20 breaths/min, and an oxygen saturation of 90% on 2 l of oxygen. She appeared thin and frail. There was a 3/6 systolic murmur that worsened with inspiration. Respirations were unlabored with clear breath sounds. She had significant bilateral LE edema to the mid-thigh with ulceration on the second digit on the left foot.

LEARNING OBJECTIVES

- To present a patient with critical limb ischemia, venous insufficiency, and PH.
- To discuss the pathophysiology and differential diagnosis in a patient with cor pulmonale.
- To review the complications of venous stent placement.
- To discuss management for a high-flow AV fistula.

MEDICAL HISTORY

The patient’s medical history included PAD, venous insufficiency with prior venous stent placement, tobacco use (60 pack-year history), COPD, rheumatoid arthritis, and type 2 diabetes.

DIFFERENTIAL DIAGNOSIS

It is unclear if the patient’s development of a foot ulcer, worsening LE edema, and progressive dyspnea...
resulted from a single or multiple pathological processes. Limb ischemia may result from progression of PAD; however, the patient should be considered for sources of nonatherosclerotic PAD. Rheumatoid arthritis does result in a hypercoagulable state, placing her at risk for arterial disease, deep vein thrombosis, and chronic thromboembolic pulmonary hypertension, which could explain her symptoms. Complications of venous stent placement include stent stenosis, thrombosis, and erosion of stent struts into an adjacent artery, resulting in aneurysm or arteriovenous (AV) fistula formation. Although rare, fistula formation may lead to arterial insufficiency, venous insufficiency, and PH, thus explaining the patient’s symptoms (1,2).

Progressive COPD could explain the patient’s worsening LE edema and dyspnea. Left heart disease may result in similar symptoms. Although multiple disease processes may play a role, the timely development of her symptoms in the preceding 2 months is suspicious for a culprit process.

INVESTIGATIONS

The patient’s complete blood cell count and chemistry panels were normal. Renal function was normal, and rheumatologic evaluation was unremarkable. Computed tomographic pulmonary angiography revealed emphysematous changes and no pulmonary embolus. Results of pulmonary function testing were consistent with mild COPD. Echocardiography showed normal left ventricular systolic function, an enlarged right atrium and ventricle, and reduced right ventricular (RV) systolic function. Estimated RV systolic pressure was 105 mm Hg with severe tricuspid regurgitation. There was mitral annular calcification with no other significant valvular abnormalities (Figure 1).

RV failure from pulmonary disease (commonly termed cor pulmonale) is a sign of advanced PH and indicates a poor prognosis. Cor pulmonale can occur from diseases that cause hypoxia and hypercapnia or from diseases that result in high transpulmonary flow (3) (Figure 2). We suspected a disease of high transpulmonary flow, and with critical limb ischemia and

**Figure 1** Transthoracic Echocardiogram Images

(A) Four-chamber view shows a dilated right atrium (RA) and right ventricle (RV). (B) A plethoric inferior vena cava (IVC) is seen, suggestive of elevated right atrial pressures. (C) Color Doppler shows severe tricuspid regurgitation. (D) Continuous-wave Doppler shows a dense regurgitant jet (highlighted in red). LA = left atrium; LV = left ventricle.
prior venous stents, LE arterial angiography was pursued. Angiography revealed substantial, brisk flow into the venous system from an AV fistula measuring 15 mm in length. The fistula was located at the site of a previously placed venous stent, connecting the left common iliac artery and vein. Sampling from the vein showed venous oxygen saturation of 94%. A drop in arterial pressure of 40 mm Hg was shown across the fistula. There was significant atherosclerotic disease in the left posterior tibial artery and left peroneal artery, with mild diffuse disease in the left anterior tibial artery.

**MANAGEMENT**

A percutaneous approach with endovascular therapy was pursued. Given the critical severity of PAD, we first performed directional atherectomy and drug-coated balloon angioplasty to the left posterior tibial artery. This no-stent approach was technically successful with excellent angiographic results (Figure 3).

The fistula was addressed 1 week later. Access was achieved with both retrograde left femoral arterial and retrograde right femoral arterial access (anterograde to the left femoral artery). Intravascular ultrasound was used to confirm lumen size of the iliac and femoral arteries, along with ensuring that there was no encroachment of the venous stents into the common iliac artery. Occlusive pressure at the fistula was tested with serial balloon inflations, and fistula location was confirmed with hand injections of contrast. An 8 mm × 59 mm covered stent was deployed in the artery, across the fistula. This was followed by postdilation of the stent with a 12 mm × 40 mm balloon proximally and a 10 mm × 40 mm balloon distally. This approach resulted in complete resolution of the AV fistula with brisk flow restored to the left LE (Figure 4).

**DISCUSSION**

High-flow fistulas often present with a high-output state, and previous case reports have described fistulas between the common iliac artery and ipsilateral vein with similar but varying presentations (2,4). More frequently seen and well-described phenomena are the high-output state and distal hypoperfusion.
ischemic syndrome in dialysis patients with a large AV fistula (5,6).

Endovascular therapy is a proven and safe treatment for AV fistulas with high success rates and low rates of complications (7). AV fistulas are a rare finding; however, fistulas of this size may present with the temporal development of limb ischemia, venous insufficiency, and PH.
FOLLOW-UP

Within 2 weeks of fistula closure, the patient no longer required oxygen and had near-resolution of dyspnea. LE edema substantially improved. Right heart catheterization performed 3 months after fistula closure revealed a RV systolic pressure of 46 mm Hg.

CONCLUSIONS

AV fistula formation with subsequent cor pulmonale is a rare but devastating complication of venous stent placement. This case highlights the importance of clinical suspicion and appropriate management when such an AV fistula is found. Identification of limb ischemia, venous insufficiency, and PH may aid in diagnosis.

ADDRESS FOR CORRESPONDENCE: Dr. John G. Winscott, University of Mississippi Medical Center, 2500 N. State Street, Jackson, Mississippi 39216. E-mail: jwinscott@umc.edu.

REFERENCES

1. Coelho A, Brandao P, Lobo M, Lojo I, Carredo A. Ilio-iliac arteriovenous fistulae—an unusual diagnosis with an even more unusual clinical presentation. Ann Vasc Surg 2018;50:298.e1-5.

2. Dewane MP, Fares WH, Ochoa Chaar CI. Endovascular treatment of a large iliac vein aneurysm and high-flow arteriovenous fistula. Ann Vasc Surg 2018;53:266.e5-7.

3. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension. A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573-619.

4. Konstantinou N, Kolbel T, Rohloff F, Heidemann F, Debus SE, Tsilimparis N. Endovascular repair of a large ilioliac fistula using a reversed ilioliac limb endograft. Ann Vasc Surg 2019;56:354.e11-5.

5. Reddy YNV, Melenovsky V, Redfield MM, Nishimura RA, Borlaug BA. High-output heart failure: a 15-year experience. J Am Coll Cardiol 2016;68:473-82.

6. Malik J, Tuka V, Kasalova Z, et al. Understanding the dialysis access steal syndrome. A review of the etiologies, diagnosis, prevention and treatment strategies. J Vasc Access 2008;9:155-66.

7. Sarac TP, Vargas L, Kashyap V, Cardella J, Chaar CO. Covered stent grafts for acquired arterial venous fistulas: a case series. Ann Vasc Surg 2018;46:369.e1-5.

KEY WORDS arteriovenous fistula, cor pulmonale, critical limb ischemia, pulmonary hypertension, venous stent
Fat-Finding Mission
Primary Pleomorphic Liposarcoma of the Heart and Pericardium

Jeremy R. Burt, MD,a Joseph Limback, MD,b Melanie Molina, BS,c Jorge Suarez, MD,d Tarek Mekhail, MD,d Naim Fanaian, MD,d Gilberto Aquino, MD,a Ismail Kabakus, MD, PHD,a Austin Weyant, DO,a Kurt Scherer, MDd

ABSTRACT
Primary cardiac liposarcomas are rare tumors with a poor prognosis and no well-defined imaging characteristics or treatment guidelines. Here, we present a case of primary pleomorphic liposarcoma of the heart and pericardium with multimodality imaging findings and our institution’s treatment approach. *(Level of Difficulty: Intermediate.)*

(J Am Coll Cardiol Case Rep 2020;2:1520–6) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 72-year-old woman presented to her primary care physician with symptoms of coughing and shortness of breath for the past 2 weeks. Heart rate, blood pressure, and respiratory rate were 58 beats/min, 128/75 mm Hg, and 26 breaths/min, respectively. Pulse oximetry done in the office showed 90% oxygen saturation on room air.

MEDICAL HISTORY
The patient had a history of hypertension, hyperlipidemia, and alcohol consumption.

DIFFERENTIAL DIAGNOSIS
The patient’s presenting symptoms were nonspecific and suggestive of either primary cardiac or pulmonary disease.

INVESTIGATIONS
Initial chest radiograph was performed *(Figure 1)* and she was admitted to the hospital for further work-up. Transthoracic echocardiogram revealed a partially mobile echogenic mass in the pericardium, septal, and inferior cardiac walls. Because of poor visualization of the mass within the right ventricular outflow tract, transesophageal echocardiogram was...
performed (Figure 2). A small pericardial effusion was noted with no tamponade physiology. Once again the mass was seen in the right ventricular outflow tract but visualization of the pulmonic valve on transesophageal echocardiogram was limited.

A computed tomography angiogram of the chest was performed to further characterize the relationship of the mass with the pericardium and left hemidiaphragm and for prebiopsy planning. The mass appeared to extend from the pericardium into the left basilar pleural space. No fat was visualized within the mass on computed tomography angiogram (Figure 3).

A subxiphoid pericardial window was performed, and the pericardial and epicardial portions of the mass were biopsied. Subsequent analysis demonstrated a pleomorphic malignant neoplasm likely originating from the pericardium (Figure 4). Using immunohistochemistry, S100 highlighted lipoblasts, and the tumor cells were strongly positive for p53, focally positive for myoD1, and negative for PD-L1, AE1/AE3, calretinin, WT1, myogenin, CAM5.2, desmin, BerEp4, CD31, CD68, S100, and CD15. Based on biopsy and pathology results, the expert histopathology opinion was that this was a primary pleomorphic liposarcoma.

Further staging work-up with positron emission tomography/computed tomography (CT) was performed (Figure 5A). Lack of involvement beyond the pericardium was confirmed.

Limited cardiac magnetic resonance imaging without contrast was performed to clarify the anatomical relationship of the mass with the pulmonic valve and any functional consequence because this remained unclear from echocardiography and CT (Figure 6). However, further tissue characterization assessment with contrast was not performed as the study was stopped early due to shortness of breath and tissue diagnosis had already been confirmed based on biopsy.

MANAGEMENT

After presentation at an interdisciplinary tumor board, review of the literature, and discussion with the patient, the patient was started on eribulin mesylate (Halaven, Eisai Incorporated, Woodcliff Lake, New Jersey). Surgical resection was considered undesirable by both the surgical team and the patient due to the large size of the tumor, extensive cardiac and pericardial involvement, and multiple comorbidities.
pericardium. The differential diagnosis of circumferential encasement of the heart should include primary pericardial sarcomas, non-Hodgkin lymphoma (usually diffuse, large B-cell lymphoma), pericardial primitive neuroectodermal tumor, and primary pericardial mesothelioma (6).

Just as there are no imaging criteria for this disease, there are also no established treatment regimens. Complications of these tumors are potentially severe and include valvular dysfunction, intracavity obstruction, peripheral embolization, arrhythmias, and tamponade (7). Surgical resection is the preferred treatment if possible. In our case, eribulin mesylate proved to be effective. Initial studies for this medication have shown promise in overall survival by targeting microtubules in soft tissues and pausing and inhibiting their growth (8).

**FOLLOW-UP**

Post-treatment positron emission tomography/CT 1 month after initiation of treatment showed a decrease in the size of the intraseptal component from 4.9 cm to 4 cm and decreased metabolic activity (Figure 5B). At her 3-month follow-up, the patient had improved performance status compared with initial presentation, and improvement of her presenting symptoms.

**CONCLUSIONS**

Primary liposarcomas of the heart and pericardium are rare tumors without established diagnostic imaging criteria or treatment regimens. In our case, the tumor followed imaging characteristics of pleomorphic liposarcomas found elsewhere in the body. Useful and distinctive imaging findings include circumferential encasement of the heart within the pericardium and, in some cases, subtle foci of fat. Multimodal cardiac imaging is essential to define tumor characteristics and staging, guide surgical appropriateness and approach, and identify potential complications.

**ACKNOWLEDGMENT** The authors thank Shaun Hinen, MD, for editorial assistance.

**ADDRESS FOR CORRESPONDENCE:** Dr. Jeremy Burt, Medical University of South Carolina, 96 Jonathan Lucas Street, MSC 323, Clinical Science Bldg, Rm 210, Charleston, South Carolina 29425. E-mail: burtje@musc.edu.
Reformatted, Contrast-Enhanced Computed Tomography Images of the Chest

(A) Vertical long axis, (B) horizontal long axis, (C) right ventricular (RV) inflow-outflow, and (D) short-axis projections showing a mass (m) centered in the interventricular septum and throughout much of the pericardial space 87 Hounsfield units. Ao = aorta; PA = pulmonary artery; other abbreviations as in Figure 2.
FIGURE 4 Biopsy Results

(A) 4×, (B) 10×, and (C) 40× microscopy slides of biopsy of mass from the pericardial space after hematoxylin and eosin stain, showing lipoblasts (arrowhead) with pleomorphic, atypical nuclei, over a background of myxoid stroma admixed with numerous lipoblasts and interspersed “chicken wire” capillaries (arrows).

FIGURE 5 FDG-PET CT Before and After Treatment

(A) Before treatment: sagittal positron emission tomography (PET)-computed tomography CT (a), whole body planar PET (b), coronal PET-CT (c), and axial PET-CT (d) images from initial fluorodeoxyglucose (FDG)-PET CT imaging showing a metabolically active mass. SUVmax: 12.8. (B) After treatment: FDG-PET CT (a to d) demonstrating significantly decreased metabolic activity. SUVmax: 4.6.
Balanced steady-state free precession cardiac magnetic resonance images in (A) short axis, (B) vertical long axis, (C) axial planes of imaging showing the large mass (m) prior to treatment. The portion of the mass in the RVOT was mobile throughout the cardiac cycle and abutted the inferior surface of the pulmonic valve, with normal pulmonic valve function using phase contrast imaging (not shown). (D) Axial triple inversion recovery sequence of the mass within the pericardium. The mass has a mildly heterogenous increased signal with a few subtle foci of fat (arrows). Abbreviations as in Figure 2 and 3.
REFERENCES

1. Wang JG, Wang B, Hu Y, et al. Clinicopathologic features and outcomes of primary cardiac tumors: a 16-year-experience with 212 patients at a Chinese medical center. Cardiovasc Pathol 2018;33:45-54.

2. Lee ATJ, Thway K, Huang PH, Jones RL. Clinical and molecular spectrum of liposarcoma. J Clin Oncol 2018;362:151-9.

3. Levy AD, Manning MA, Miettinen MM. Soft-Tissue sarcomas of the abdomen and pelvis: radiologic-pathologic features, part 2-uncommon sarcomas. Radiographics 2017;37:797-812.

4. Murphey MD, Arcara LA, Fanburg-Smith J. From the archives of the AFIP: imaging of musculoskeletal liposarcoma with radiologic-pathologic correlation. Radiographics 2005;25:1371-95.

5. Jelinek JS, Kransdorf MJ, Shmookler BM, Abouafla AJ, Malawer MM. Liposarcoma of the extremities: MR and CT findings in the histologic subtypes. Radiology 1993;186:455-9.

6. Restrepo CS, Vargas D, Ocazionez D, Martinez-Jimenez S, Betancourt Cuellar SL, Gutierrez FR. Primary pericardial tumors. Radiographics 2013;33:1613-30.

7. Uemura S, Watanabe M, lwama H, Saito Y. Extensive primary cardiac liposarcoma with multiple functional complications. Heart 2004;90:e48.

8. Schoffski P, Chavla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet 2016;387:1629-37.

KEY WORDS cardiac imaging, cardiac pleomorphic liposarcoma, neoplasm of the pericardium
Relapsing Polychondritis Requiring Orthotopic Heart Transplant Despite Coronary Artery Bypass and Surgical Aortic Valve Replacement

David Bae, MD, Corey Lum, DO, Robin Chand, MD, Eugene DePasquale, MD, Ali Nsair, MD, Reza Ardehali, MD, PhD

ABSTRACT

A 32-year-old man with a history of relapsing polychondritis presented with acute coronary syndrome due to aortitis with ostial coronary artery involvement from his underlying autoimmune condition. Concomitant aortic insufficiency with ostial coronary lesions is a rare complication of relapsing polychondritis, requiring a multidisciplinary team approach for management. (Level of Difficulty: Advanced) (J Am Coll Cardiol Case Rep 2020;2:1527-31) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 32-year-old man with relapsing polychondritis (RP) presented to our emergency department for worsening chest pain of 10 days’ duration. The pain was substernal and pressure-like, radiating to the left shoulder and arm. Examination findings at the time were as follows: blood pressure, 159/94 mm Hg; heart rate, 87 beats/min; respiratory rate, 16 breaths/min; temperature, 36.3°C; 99% oxygen saturation on room air; and grade 4 of 6 decrescendo diastolic murmur in the right upper sternal edge. His troponin I level was 0.21 ng/ml.

MEDICAL HISTORY

The patient had an 11-year history of RP and coarctation of the descending thoracic aorta requiring percutaneous stenting 1 year before presentation. He initially presented with nasal and auricular chondritis, inflammatory arthritis, and aortitis. He was started on azathioprine, but it was discontinued due to pancreatitis. He was transitioned to prednisone and methotrexate, which was tapered 3 weeks before presentation.
Abbreviations and Acronyms

ECG = electrocardiography
ECMO = extracorporeal membrane oxygenation
LAD = left anterior descending
MMF = mycophenolate mofetil
OHT = orthotopic heart transplant
RCA = right coronary artery
RP = relapsing polychondritis

Differential Diagnosis

Fulminant aortitis with involvement of the coronary arteries was our initial concern, as the patient’s symptoms coincided with recent taper of immunosuppression, and diagnostic testing (electrocardiography [ECG] and troponin levels) was concerning for coronary ischemia. Aortic dissection, a severe complication of aortitis, was also considered. Vasculitis of the coronary arteries, plaque rupture, spontaneous coronary artery dissection, and coronary artery embolism are in the differential diagnosis for a patient with vasculitis and hypercoagulability.

Investigations

The first 12-lead ECG revealed no significant ST-segment changes (Figure 1A). One hour later, the patient’s chest pain acutely worsened. A repeat ECG revealed diffuse ST-segment depressions (Figure 1B). Subsequent computed tomography angiography of the aorta showed thickening of the aortic root to the proximal descending thoracic aorta and left subclavian artery consistent with large vessel vasculitis, with no evidence of superimposed dissection (Figure 2). Another ECG immediately after aortic imaging showed ST-segment elevation in V1 to V3 (Figure 1C). The patient was emergently taken to the cardiac catheterization laboratory, and coronary angiography was performed (Figure 3). This showed 95% ostial stenosis of the left main coronary artery. The left anterior descending (LAD) and left circumflex arteries were patent (Video 1). The right coronary artery (RCA) was unable to be engaged, with no vessel noted on aortography. The aortogram demonstrated severe aortic regurgitation (Video 2).

Management

Given the severe aortic regurgitation with critical left main coronary artery stenosis, cardiothoracic surgery was consulted for emergent surgical aortic valve replacement and coronary artery bypass graft surgery. During anesthesia induction, the patient developed pulseless electrical activity. Cardiopulmonary resuscitation was initiated while the surgeon performed a median sternotomy. Internal cardiac massage was continued as the patient was centrally cannulated for extracorporeal membrane oxygenation (ECMO). The patient had return of spontaneous circulation in 21 min. Given the patient’s history of vasculitis, the left internal mammary artery was not harvested. The patient underwent saphenous vein graft bypass of the LAD and RCA with mechanical aortic valve replacement (Regent 21 mm, Abbott, Abbott Park, Illinois). An intra-operative transesophageal echocardiogram revealed severely reduced biventricular function. Despite surgical intervention, the patient was unable to be weaned from the ECMO apparatus, with a cardiac index <1.2 l/min/m². Six days after cannulation for ECMO, the patient was transitioned to a biventricular CentriMag assist device via central cannulation (Abbott, Abbott Park, Illinois). The patient was started on methylprednisolone and mycophenolate mofetil (MMF) with subsequent positron emission tomography-computed tomography imaging showing resolution of active inflammation. Ultimately, he was accepted for listing for an orthotopic heart transplant (OHT) with the United Network for Organ Sharing as status 1. Six weeks after a biventricular assist device was placed, the patient successfully underwent transplant. The patient was maintained on prednisone, MMF, and tacrolimus.

Discussion

RP is a rare autoimmune condition that involves cartilaginous tissues, with an incidence of 3.5 cases per million (1). Cardiovascular manifestations have been reported in 11% to 56% of these patients and include vasculitis of both large- and medium-sized arteries, aortic regurgitation, and pericarditis (2). Although aortic insufficiency is the most common cardiovascular complication observed in 4% to 9% of these patients (3), the combination of aortic insufficiency from aortitis with ostial coronary lesion is exceptionally rare: 7 cases have previously been described in the literature. Of those cases, only 1 patient successfully underwent coronary artery bypass grafting with aortic valve replacement.

A combination of coronary artery bypass graft with aortic valve replacement for RP has been reported by Kisamori et al. (4), in which the RCA was involved. However, in the current case, both the left and right coronary arteries had critical ostial lesions. Given the left subclavian artery involvement with vasculitis in this case, there was concern that the left internal mammary artery was compromised. As such, saphenous venous grafts were opted to bypass the LAD and RCA. Despite revascularization and resolution of aortic insufficiency, the patient remained in cardiogenic shock requiring biventricular mechanical support. OHT was subsequently offered as rescue therapy.

The mortality rate for RP with cardiovascular involvement is abysmal, with estimates as high as...
FIGURE 1  Progression of Ischemia on 12-Lead ECGs During Hospitalization Course

(A) 12-lead electrocardiography (ECG) showing sinus bradycardia with left ventricular hypertrophy. (B) 12-lead ECG showing ST-segment elevation in aVR and ST-segment depressions in V2 to V6, III, aVF, and I. (C) 12-lead ECG showing ST-segment elevation in the precordial leads, V1 to V3.
52.6% (5); this is a departure from the overall prognosis of RP, which has been reported as 91% in 10 years (6). Although many of these patients with RP will require surgical intervention for cardiac manifestations, outcomes have been poor in this cohort. Post-operative complications from valve and aortic root replacements include paravalvular leakage and prosthesis dehiscence related to the friable tissue from the inflammatory process, with up to 24% of patients requiring re-operation (5). Some authors have suggested a prophylactic Bentall operation for RP involving the ascending aorta (2).

The known post-operative complications were applicable in our patient undergoing OHT, requiring surgical anastomosis to an inflamed aortic root. As such, the patient’s RP was first stabilized by using a combination of immunosuppressive therapies (glucocorticoids and MMF). Sharma et al. (7) describe a RP case series with successful use of second-line agents, including azathioprine, methotrexate, cyclosporine, and MMF. Considering our patient’s tenuous renal function and pancreatitis with azathioprine use, MMF was selected as an adjunctive therapy, leading to resolution of the RP flare. At the time of OHT, the prophylactic Bentall procedure was deferred given that the sutures held well on the thickened aorta, the aortic root was of normal size (2.2 cm × 2.8 cm), and an aortic root replacement would significantly add to the complexity of the surgery.

This case still represents the second case of OHT for RP. Immunosuppressive treatment, the same for OHT and RP, led to successful resolution of the RP.

FOLLOW-UP

The patient is 1 year out of his OHT, with no relapse of RP. Subsequent coronary angiography revealed patent transplant coronary arteries, most recently 3 months from OHT. The patient is continued on prednisone indefinitely in addition to tacrolimus and MMF.

CONCLUSIONS

Concomitant aortic insufficiency from aortitis with ostial coronary lesions is a rare complication of RP. This case highlights the critical importance of a multidisciplinary team approach to managing a patient with this rare condition.

ADDRESS FOR CORRESPONDENCE: Dr. David Bae, UCLA Division of Cardiology, David Geffen School of Medicine at UCLA, 650 Charles E. Young Drive South, A2-237 CHS, Los Angeles, California 90095-1679. E-mail: dbae@mednet.ucla.edu.
REFERENCES

1. Sugrue G, Durcan L, Bell L, et al. Unsuspected cardiovascular involvement in relapsing polychondritis. Circ Cardiovasc Imaging 2014;7:409–41.

2. Stein JD, Lee P, Kuriya B, et al. Critical coronary artery stenosis and aortitis in a patient with relapsing polychondritis. J Rheumatol 2008;35:1898–901.

3. Vaidyanathan RK, Byalal JR, Sundaramoorthi T, et al. Rapidly progressive coronary ostial stenosis after aortic valve replacement in relapsing polychondritis. J Thorac Cardiovasc Surg 2006;131:1395–6.

4. Kisamori E, Otani S, Yamamoto T, et al. Concomitant aortic valve replacement, mitral valve replacement, and coronary artery bypass grafting for aortic stenosis and mitral regurgitation in a patient with relapsing polychondritis. Gen Thorac Cardiovasc Surg 2020;68:185–9.

5. Dormoy L, Berlin A, Labombarda F. Heart transplantation as last resort treatment for relapsing polychondritis with severe cardiac involvement. Prog Transplant 2017;27:321–3.

6. Pulchal X, Terrier B, Mouthon L, et al. Relapsing polychondritis. Joint Bone Spine 2014;81:118–24.

7. Sharma A, Law A, Bambery P, et al. Relapsing polychondritis: clinical presentations, disease activity and outcomes. Orphanet J Rare Dis 2014;9:198.

KEY WORDS aortic insufficiency, cardiogenic shock, heart transplant, myocardial infarction, ostial coronary lesion

APPENDIX For supplemental videos, please see the online version of this paper.

FIGURE 3 Coronary Angiogram Demonstrating Ostial Left Main Coronary Artery Stenosis and Right Coronary Artery Stenosis

(A) Right anterior oblique caudal angiographic image showing 95% lesion in the ostial left main coronary artery. (B) Left anterior oblique cranial angiographic image showing significant ostial left main coronary artery stenosis. The left circumflex and left anterior descending arteries are patent. (C) The right coronary artery is unable to be engaged.
A 79-year-old woman presented with dyspnea and cough. Workup revealed a pulmonary artery mass. After undergoing surgery, she was treated with adjuvant immunotherapy for an undifferentiated pulmonary artery sarcoma. Fifteen months after surgery, there was no evidence of recurrence. The case is discussed, imaging presented, and the published reports reviewed. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1532–5) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 79-year-old retired nurse presented with 5 days of progressive dyspnea and dry cough. Outside hospital computed tomography angiography (Video 1) demonstrated a lobulated low-attenuation intraluminal mass in the right ventricular (RV) outflow tract (RVOT), extending into the right pulmonary artery (PA), and small filling defects in the distal segmental PA branches. She was started on heparin and transferred to our hospital. On presentation, she was afebrile with a heart rate of 81 beats/min, blood pressure 113/73 mm Hg, respiratory rate of 20 breaths/min, and oxygen saturation of 96% on room air. On exam, she appeared well and in no acute distress, and had clear bilateral breath sounds with no increased work of breathing. On cardiac exam, she had a regular rate and rhythm, normal S1 and S2, and an III/VI crescendo systolic murmur at the left upper sternal border. The abdomen was soft and nontender, and extremities were warm and well perfused, without edema.

PAST MEDICAL HISTORY

Past medical history was significant for hypertension, hyperlipidemia, glaucoma, and stage III chronic kidney disease. She had a surgical history of cholecystectomy and hysterectomy.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis at this point included pulmonary artery thromboembolism and pulmonary artery tumor.
INVESTIGATIONS

Transthoracic echocardiogram (Video 2) showed an ejection fraction of 55% to 60%, moderately enlarged RV, and moderately reduced RV function with flattening of the interventricular septum throughout the cardiac cycle consistent with RV pressure and volume overload. There was moderate tricuspid regurgitation. A large heterogenous mass was seen attached to the RV measuring approximately 5.3 by 3.2 cm and prolapsing across the pulmonic valve, partially obstructing the RVOT. The peak gradient across the pulmonic valve was 74 mm Hg with peak velocity 4.3 m/s. Only trace pulmonic insufficiency was noted. Estimated RV systolic pressure was 89 mm Hg. Cardiac magnetic resonance imaging (MRI) (Video 3) revealed an enhancing RVOT mass consistent with PA sarcoma causing RVOT and pulmonic valve obstruction with increased pressure and size of the right-sided chambers, as well as filling defects in the segmental PAs. Fluorodeoxyglucose (FDG)-positron emission tomography scan showed this mass to be hypermetabolic, along with several hypermetabolic lung nodules, increasing the concern for malignancy. Pre-operative coronary angiography revealed no significant coronary disease.

MANAGEMENT

The patient was taken to the operating room for surgical excision of the mass. In the operating room, we observed a very large, broad-based mass filling a large part of the RVOT near the atrioventricular groove, extending from the tricuspid annulus to pulmonic valve annulus and protruding through the pulmonic valve (Videos 4 and 5, Figure 1). Upon opening the right PA, another large mass was seen occupying most of the lumen with extension into the lobar branches of the right PA. Frozen sections were sent that identified thrombus. There was no obvious infiltration of the tumors into the epicardial surface; however, given the intraluminal extension and involvement of intracardiac structures, it was judged that complete resection would result in an irreparable RV defect and possible injury to the left and right coronary arteries. As a result, we performed a palliative debulking procedure, pulmonic valve replacement, and pulmonary thromboendarterectomy.

Pathology identified an undifferentiated pleomorphic sarcoma with distribution typical for an intimal sarcoma. It was noted to be arising from the subendocardium and intima of the PA. Programmed death-ligand 1 (PD-L1) testing with partial membranous staining demonstrated nearly 90% of tumor infiltrating immune cells strongly positive for PD-L1. Mouse double minute 2 homolog (mdm2) staining was negative.

Post-operatively, the patient initially required support for mixed cardiogenic and vasoplastic shock with inotropes, vasopressors, and inhaled pulmonary vasodilators. She had a mild acute chronic kidney injury, from which she ultimately recovered. After about a month in the hospital, she was discharged to acute in-patient rehab, where she was started on immunotherapy with pembrolizumab for this strongly PD-L1 tumor.

DISCUSSION

Primary PA sarcoma (PPAS) is rare, with only several hundred cases reported in the published reports. A retrospective report covering 20 years from the Cleveland Clinic identified just 10 cases (1). One reason for its rarity may be that PPAS is frequently misdiagnosed as pulmonary embolism (PE), with one study showing nearly one-half of patients initially treated for PE and early studies reporting around 60% of PPAS first recognized at autopsy (1,2). Patients typically present between 45 and 55 years of age, with a female-to-male predominance of 2:1 (3).

PPAS usually arise from the dorsal surface of the main pulmonary trunk (85%) with frequent involvement of the right PA (71%) and left PA (65%) (4). In about one-third of patients the pulmonic valve is involved (4). Commonly, there is a significant amount of intraluminal extension before growth outside the vessel is seen (5).

Histopathologically, 13 types of PPAS have been recognized, with leiomyosarcoma (20%) being most common, followed by spindle cell sarcoma (15%), fibrous histiocytoma (12%), and undifferentiated sarcoma (12%) (1). Bandyopadhyay et al. (1) report that the median age of presentation is lowest for myofibroblastic sarcoma (43 years) and undifferentiated sarcoma (48 years), and highest for rhabdomyosarcoma (66 years) and liposarcoma (67 years). Huo et al. (6) report longer survival associated with leiomyosarcoma and worse prognosis with rhabdomyosarcoma. Routine immunohistochemical staining includes desmin, cytokeratin, vimentin, and actin (5,7). These tumors frequently overexpress mdm2 (5,7).

On clinical presentation, PPAS often resembles PE, with the commonest symptoms being dyspnea (74%), chest pain (31%), cough (23%), and hemoptysis (15%).
Initial misdiagnosis and treatment of PE delays proper management of these tumors, which increases mortality (8).

Given the ease with which PPAS may be mistaken for PE, multimodality imaging is critical for accurate diagnosis. Transthoracic echocardiogram typically shows a mobile mass with globular rather than filamentous morphology with attachment to the PA wall or pulmonic valve (8). Invasion of the vessel wall may be seen on transesophageal echocardiography (8). Gadolinium-enhanced MRI can differentiate PE from tumor because PPAS tends to enhance more than thrombus (5). FDG-positron emission tomography may demonstrate increased uptake within the tumor, helping distinguish it from thrombus, and also may reveal metastases, aiding in post-operative medical management and prognosis (5).

Optimal management for PPAS includes complete surgical resection and neoadjuvant chemotherapy. Neoadjuvant chemotherapy is advised to shrink the tumor size and improve the likelihood of curative resection as well as identify chemoresponders who are likely to benefit from surgery (8). In practice, as a result of misdiagnosis or clinical circumstances, few patients receive pre-operative chemotherapy (8). Likewise, curative resection is not always feasible, and resectability is usually impossible to determine before surgical exploration (5). Treatment with either chemotherapy or surgery alone is associated with poorer outcomes. Blackmon et al. (5) report that median and 5-year survival was 24.7 ± 8.5 months and 33.4%, respectively, for patients undergoing multimodality treatment compared with 8 ± 1.7 months and 30.6%, respectively, for patients who had only 1 modality of therapy.

Palliative surgical options include debulking, pneumonectomy, endarterectomy, and PA stenting. Patients who are not candidates for curative resection may still benefit from palliative procedures, although prognosis is poorer (5). Comparing curative resection with palliative surgery, Blackmon et al. (5) found that median and 5-year survival was 36.5 ± 20.2 months and 49.2%, respectively, for patients undergoing complete resection compared with 11 ± 3 months and 0%, respectively, for patients undergoing tumor debulking, palliative pneumonectomy, exploration, or thromboendarterectomy. In patients undergoing palliative procedures, recurrence is generally expected.

There is no consensus on the benefit of adjuvant chemotherapy, and there are no standard guidelines available on which agents to use. Doxorubicin and ifosfamide are frequently used as first-line neoadjuvant therapy with platinum-vinorelbine regimens reserved for those who fail doxorubicin-based treatment (8).

**FOLLOW-UP**

The patient was most recently seen in outpatient clinic by her oncologist 15 months after surgery, at which time surveillance computed tomography scan of the chest showed an overall decrease in size of the lung nodules, and transthoracic echocardiogram was stable, with normal ejection fraction and no evidence of recurrent mass.

**CONCLUSIONS**

PPAS are rare tumors with a poor prognosis. Their clinical presentation is often confused for PE, which delays appropriate treatment and worsens outcomes. Thorough workup and imaging with correct early diagnosis, aggressive curative surgical resection, and multimodality therapy offer patients the best chance of survival. We report here a patient with a large, metastatic tumor who was unable to receive neoadjuvant chemotherapy and underwent incomplete surgical resection but nevertheless has had a good clinical outcome at 15 months with targeted adjuvant immunotherapy.

**ADDRESS FOR CORRESPONDENCE:** Dr. Koji Takeda, Columbia University Irving Medical Center, 177 Fort Washington Avenue, 7GN-735, New York, New York 10032. E-mail: Kt2485@cumc.columbia.edu.
REFERENCES

1. Bandyopadhyay D, Panchabhai TS, Bajaj NS, Patil PD, Bunte MC. Primary pulmonary artery sarcoma: a close associate of pulmonary embolism—20-year observational analysis. J Thorac Dis 2016;8:2592-601.

2. Krüger I, Borowski A, Horst M, de Vivie ER, Theissen P, Gross-Fengels W. Symptoms, diagnosis, and therapy of primary sarcomas of the pulmonary artery. Thorac Cardiovasc Surg 1990;38:91-5.

3. Gan HL, Zhang JQ, Huang XY, Yu W. The wall eclipsing sign on pulmonary artery computed tomography angiography is pathognomonic for pulmonary artery sarcoma. PLoS One 2013;8:e83200.

4. Restrepo CS, Betancourt SL, Martinez-Jimenez S, Gutierrez FR. Tumors of the pulmonary artery and veins. Semin Ultrasound CT MR 2012;33:580-90.

5. Blackmon SH, Rice DC, Correa AM. Management of primary pulmonary artery sarcomas. Ann Thorac Surg 2009;87:977-84.

6. Huo L, Moran CA, Fuller GN, Gladish G, Suster S. Pulmonary artery sarcoma: a clinicopathologic and immunohistochemical study of 12 cases. Am J Clin Pathol 2006;125:419-24.

7. Moguillansky N, Verma N, Shah P, Knapik J, Mohammed TL. Pulmonary artery sarcoma: Case report and review of the literature. Respir Med Case Rep 2019;27:100857.

8. Al-Mehisen R, Al-Halees Z, Alnemri K, Al-Hemayed W, Al-Mohaissen M. Primary pulmonary artery sarcoma: A rare and overlooked differential diagnosis of pulmonary embolism. Clues to diagnosis. Int J Surg Case Rep 2019;65:15-9.

KEY WORDS imaging, pulmonic valve, right ventricle

APPENDIX For supplemental videos, please see the online version of this paper.
Incessant Pericarditis With Recurrent Cardiac Tamponade as the Manifestation of Autoimmune Polyglandular Syndrome Type II

Ana V. Marinho, MD,a Rui Baptista, PHD,a,b,c,d Luís Cardoso, MD,e Patrícia M. Alves, MD,a Sílvia Monteiro, MD,a Francisco Gonçalves, MD,a Lino Gonçalves, PHDa,b,c,d

ABSTRACT

A 23-year-old man was admitted for acute pericarditis that evolved to cardiac tamponade and shock with need of emergent pericardiocentesis and inotropic support. Corticosteroid therapy was successful, but despite a gradual tapering, the patient relapsed. Incidentally, the patient developed hyperkalemia with hyponatremia. Subsequent hormonal measurements confirmed autoimmune polyglandular syndrome type-2. (Level of Difficulty: Intermediate.)(J Am Coll Cardiol Case Rep 2020;2:1536–41) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 23-year-old man presented with retrosternal pleuritic chest pain and low-grade fever for 3 days. On presentation, he was apyretic, normotensive, and a pericardial rub was present. The electrocardiogram showed sinus tachycardia and widespread ST elevation associated with PR segment depression (Figure 1) and echocardiography showed a mild, circumferential pericardial effusion. The laboratory workup demonstrated normal high sensitivity troponin I (<3.2 ng/l; 99th <34 ng/l), mild leukocytosis (11.9 × 109/l), and very elevated C-reactive protein (27.6 mg/dl, normal: <0.5 mg/dl). The next day, the patient developed cardiac tamponade and an emergent pericardiocentesis was performed. However, after the immediate evacuation of 350 ml of serous fluid, he progressed to profound shock, dependent on high noradrenaline doses. In extreme, a 1-g bolus of methylprednisolone was administered and an immediate, excellent clinical response was verified, allowing the weaning of

LEARNING OBJECTIVES

- To recognize the large spectrum of clinical presentations of Addisonian crisis and prompt diagnosis of this rare but life-threatening situation.
- To emphasize the need of a broader etiological study in incessant pericarditis with cardiac tamponade, particularly in younger age.
- To highlight the role of multidisciplinary and multimodality imaging in management of pericardial diseases.

From the aCardiology Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; bCoimbra Institute for Clinical and Biomedical Research (ICB), Faculty of Medicine, University of Coimbra, Coimbra, Portugal; cCenter for Innovative Biomedicine and Biotechnology (CIBB), University of Coimbra, Coimbra, Portugal; dClinical Academic Centre of Coimbra (CACC), Coimbra, Portugal; and the eEndocrinology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

Manuscript received May 20, 2020; accepted May 29, 2020.

ISSN 2666-0849

https://doi.org/10.1016/j.jaccas.2020.05.083
noradrenaline the next day and progressive resolution of the effusion.

**PAST MEDICAL HISTORY**

He had childhood asthma, nonallergic rhinitis, and an idiopathic episcleritis, controlled with topical corticosteroids. One month earlier, he had been admitted to an intensive care unit due to septic shock complicating tonsillitis.

**DIFFERENTIAL DIAGNOSIS**

A pericardial friction rub in the presence of retrosternal pleuritic chest pain in a young man is highly suggestive of acute pericarditis. However, other diagnoses as myocarditis, pulmonary embolism, pneumonias, asthma exacerbation, and pneumothorax also should be considered.

**INVESTIGATIONS**

*Streptococcus mitis* was isolated in the pericardial fluid and ceftriaxone was initiated. At this point, the echocardiogram showed constrictive-effusive physiology (*Figures 2 to 4, Videos 1 and 2*). Although the autoimmunity workup was pendent, the patient was discharged on colchicine 0.5 mg every day (q.d.),

---

**FIGURE 1 Patient Electrocardiogram**

Patient electrocardiogram showing widespread ST-segment elevation and PR depression of in inferior and V2 to V6 leads.
ibuprofen 600 mg 3 times a day, and prednisolone 5 mg q.d., with a working diagnosis of idiopathic acute pericarditis. However, he was readmitted 4 weeks later due to incessant pericarditis with cardiac tamponade, needing immediate pericardiocentesis. A pleuro-pericardial window was then performed, and a pericardial biopsy obtained (Figure 5). Cardiac magnetic resonance showed the presence of diastolic paradoxical septal movement, and diffuse pericardial late gadolinium enhancement (Figure 6, Videos 3 and 4).

**MANAGEMENT**

The etiologic study performed so far (Table 1) was inconclusive and the patient was discharged with a higher dose of methylprednisolone (32 mg q.d.). Despite the gradual corticosteroid tapering, symptoms recurred whenever the dose was lowered to <10 mg, leading to several readmissions. Incidentally, during the third rehospitalization, with normal kidney function, a combination of hyperkalemia (5.9 mmol/l) with hyponatremia (129 mmol/l) was found, leading to the suspicion of adrenal insufficiency (AI). Adrenal axis measurements were performed, showing very high levels of adrenocorticotropic (172 pg/ml, normal: 9 to 52 pg/ml) and cortisol under the limit of detection (<1 μg/dl), leading to the diagnosis of Addison’s disease. Hormonal replacement therapy with fludrocortisone 0.1 mg q.d. and prednisolone 15 mg q.d. was initiated. Further evaluation for autoimmune diseases showed the presence of anti-intrinsic factor autoantibodies and primary hypogonadism was further found.
Ultimately, a diagnosis of autoimmune polyglandular syndrome type 2 (APS-2) was established.

**DISCUSSION**

We report the case of a young man admitted for acute pericarditis progressing to recurrent cardiac tamponade and shock. Serendipitously, a high-dose bolus of corticosteroid reverted the shock and its maintenance contributed to a progressive and robust clinical response. A few weeks before, he had been admitted for tonsillitis complicated by a septic shock. Retrospectively, both clinical scenarios have in common an impaired response to a stressful event and were probably manifestations of a previously unrecognized adrenal crisis, a life-threatening emergency associated with high mortality unless appropriately recognized and treated (1,2). In our case, it was unknowingly reverted by a bolus of methylprednisolone.

AI is characterized by impaired production or action of glucocorticoids, with or without deficiency in mineralocorticoids and/or adrenal androgens. It can result from disease intrinsic to the adrenal cortex (primary AI or Addison’s disease), from pituitary diseases that hamper the release of corticotropin (secondary AI) or from hypothalamic disorders that impair the secretion of the corticotropin-releasing hormone (tertiary AI). The manifestations of primary AI result from deficiency of all adrenocortical hormones, but they can also include signs of other concurrent autoimmune conditions (3). In our patient, the use of methylprednisolone for pericarditis corrected the deficiency of cortisol but not of mineralocorticoids, due to the weak methylprednisolone mineralocorticoid effect. This resulted in hyponatremia and hyperkalemia, manifestations of mineralocorticoid insufficiency.

Addison’s disease can be associated with other autoimmune conditions. The APS comprise a group of entities characterized by autoimmune activity against more than 1 endocrine organ, can occur in patients of any age, and new components of a given syndrome can appear throughout life. There are rare monogenic forms, as APS-1, and a more common polygenic varieties, APS-2; both have Addison’s disease as a prominent component. There are very few reported cases of cardiac tamponade as the first manifestation of APS-2, and most have a prior history of an autoimmune disease. To our knowledge, only 1 case was described (4).
Currently, there are no specific tests to detect APS-2, but measurement of organ-specific antibodies (Abs) are helpful in assessing disease risk, because these “silent Abs” precede clinical disease and are detectable years before disease onset (5,6). There is no specific treatment for APS-2, only hormonal replacement of associated endocrine disorders (7).

Nonsteroidal anti-inflammatory drugs and colchicine are the mainstay of therapy for recurrent pericarditis, and when a specific cause is identified, treatment should be etiological (8). Corticosteroids provide rapid control of symptoms, but they also favor chronicity and more recurrences. When used, tapering should be particularly slow and if recurrence occurs, every effort should be made to not increase the dose or to reinstate. In cases of corticosteroid dependence, agents such as intravenous immunoglobulin, Anakinra, or azathioprine may be considered (9). If these agents are effective in APS-associated pericarditis is unknown.

FOLLOW-UP

During the past months, prednisolone was successfully tapered to 5 mg q.d., but unfortunately, he suffered a new recurrence with the for higher doses (currently, 15 mg q.d.).

CONCLUSIONS

The Addisonian crisis is life-threatening situation, because it is rare and has multiple clinical presentations, the diagnosis is very challenging. Pericardial tamponade as the first clinical presentation of pericarditis in a young patient without an evident cause should motivate a broader etiological study.

ADDRESS FOR CORRESPONDENCE: Dr. Ana Vera Marinho, Cardiology Unit, Centro Hospitalar e Universitário de Coimbra, Praceta Professor Mota Pinto, 3000-075 Coimbra, Portugal. E-mail: ana.vera.marinho@gmail.com.
REFERENCES

1. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2016;101:364-89.

2. Puar THK, Stikkelbroeck NMML, Smans LCCJ, et al. Adrenal crisis: still a deadly event in the 21st century. Am J Med 2016;129:339.e1-9.

3. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. Ann Intern Med 2003;139:194-204.

4. Alkaabi JM, Chik CL, Lewanczuk RZ. Pericarditis with cardiac tamponade and Addisonian crisis as the presenting features of autoimmune polyglandular syndrome type II: a case series. Endocr Pract 2008;14:474-8.

5. Kahaly GJ. Polyglandular autoimmune syndromes. Eur J Endocrinol 2009;161:11-20.

6. Husebye ES, Anderson MS, Kampe O. Autoimmune polyendocrine syndromes. N Engl J Med 2018;378:1132-41.

7. Arlt W. Emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. Endocr Connect 2016;5:G1-3.

8. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. Eur Heart J 2015;36:2921-64.

9. Chiabrando JG, Bonaventura A, Vecchié A, et al. Management of acute and recurrent pericarditis. JACC state-of-the-art review. J Am Coll Cardiol 2020;75:76-92.

KEY WORDS acute pericarditis, Addison crisis, autoimmune polyangular syndrome type 2, cardiac tamponade

APPENDIX For supplemental videos, please see the online version of this paper.
Idiopathic Constrictive Pericarditis and Eggshell Calcification of the Heart

Rajesh Vijayvergiya, MD, a Navjyot Kaur, MD, a Ramesh Patel, MD, a Anupam Lal, MD, b Ganesh Kasinadhuni, MD a

ABSTRACT

Extensive pericardial calcification is rare in patients with chronic constrictive pericarditis (CCP). We report the case of a young man who had CCP with “eggshell” calcification of the pericardium and the classic features of CCP on echocardiography and cardiac catheterization. The patient had an uneventful recovery following surgical pericardiectomy.

(Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1542–4) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 30-year-old man presented with gradually increasing pedal edema, abdominal distention, and dyspnea on exertion of 5 months’ duration. He had distended jugular veins with a positive Kussmaul sign and prominent x and y venous descent. He also had tender hepatomegaly, ascites, and grade II pedal edema. Cardiac auscultation revealed a diastolic pericardial knock.

Echocardiography revealed the following: calcified pericardium that was approximately 11 mm thick; septal bounce; medial and lateral mitral e’ velocity of 12 and 7 cm/s, respectively; more than 25% variation in mitral inflow velocity with respiratory movements (Figure 1A); a dilated inferior vena cava; and expiratory diastolic flow reversal in hepatic veins (Figure 1B). Fluoroscopy revealed dense circumferential pericardial calcification (Figure 1C, Video 1), and computed tomography demonstrated classic “eggshell” calcification encircling the heart (Figures 1D and 1E). Constrictive physiology was further confirmed on cardiac catheterization, which revealed elevated and equalization of all pressures including mean right atrial pressure, pulmonary capillary wedge pressure, right ventricular pressure, and left ventricular end-diastolic pressure (i.e., 30 mm Hg). Biventricular pressure tracings showed a typical “dip-and-plateau” configuration, as well as ventricular discordance (Figure 1F, white arrow) suggestive of CCP. The initial tracing (Figure 1F) also showed ventricular concordance suggestive of underlying myocardial involvement (restrictive physiology) associated with extensive pericardial calcification.

Surgical pericardiectomy was performed through a median thoracotomy. The calcified, firmly adherent pericardium was resected from the anterior and left lateral aspect of the heart. The patient had uneventful recovery. Histopathologic examination of resected pericardial tissue revealed extensive fibrosis, hyalinization, and calcification, without any granulomatous or giant cell inflammation.

CCP manifests as right-sided heart failure. The dyspnea on exertion results from raised filling pressures, whereas easy fatigability is caused by decreased cardiac output. The most common type of CCP is idiopathic (1), as in the index case, followed by CCP caused by infections, post-cardiac surgery status, radiation therapy.
Although mild calcification is common in pericarditis, extensive calcification as seen in the index case is extremely rare in CCP (2).

The diagnosis of CCP is made on the basis of echocardiographic findings of increased ventricular interdependence in the form of septal bounce and respiratory variation in atrioventricular valve inflow velocities, annulus reversus with medial e’ velocity more than lateral, and late diastolic expiratory flow reversal in hepatic veins (3). Pericardial calcification and thickening can be clearly seen on computed tomography, and cardiac catheterization confirms the diagnosis.

Typically, all chambers have raised and equalization of diastolic pressures, as in the index case (3). Ventricular discordance is a specific hemodynamic finding in CCP (3). Because of cessation of negative intrathoracic pressure transmission to the heart in CCP, there are decreases in left ventricle filling and systolic pressure during inspiration, whereas right ventricular filling and systolic pressure are relatively maintained, thus resulting in exaggerated interdependence and ventricular discordance (3). Surgical pericardiectomy is associated with increased morbidity and mortality in such cases because of incomplete resection of the adherent calcified pericardium and poor hemodynamic recovery (2). Nonetheless, our patient had an uneventful postoperative recovery and remained asymptomatic for the next 5 years of follow-up.

**FIGURE 1** Idiopathic Constrictive Pericarditis and Eggshell Calcification of the Heart

(A) Transmural pulse-wave Doppler showing respiratory variation in inflow velocities. (B) Echocardiography showing a distended inferior vena cava and expiratory diastolic flow reversal of the hepatic veins. (C) Fluoroscopy image in the lateral view showing thickened calcified pericardium around the heart. (D) Computed tomography reconstructed image in the coronal plane showing thick, calcified pericardium around the heart. (E) Volume rendered reconstructed computed tomography image showing “eggshell” calcification of the heart. (F) Biventricular pressure tracing showing raised and equal end-diastolic ventricular pressure, a “dip-and-plateau” configuration, and ventricular discordance suggestive of chronic constrictive pericarditis.
ADDRESS FOR CORRESPONDENCE: Dr. Rajesh Vijayvergiya, Department of Cardiology, Advanced Cardiac Centre, Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh 160 012, India. E-mail: rajeshvijay999@hotmail.com. Twitter: @DrRajeshVijay.

REFERENCES

1. LeWinter MM, Hopkins WE. Pericardial diseases. In: Libby P, Bonow RO, Mann DL, Zipes DP, editors. Braunwald’s Heart Disease. 10th edition. Philadelphia, PA: Elsevier, 2015:1636-57.

2. Ling LH, Oh JK, Breen JF, et al. Calcific constrictive pericarditis: is it still with us? Ann Intern Med 2000;132:444-50.

3. Welch TD. Constrictive pericarditis: diagnosis, management and clinical outcomes. Heart 2018;104:725-31.

KEY WORDS calcification, constrictive pericarditis, pericardiectomy, right-sided heart failure

APPENDIX For a supplemental video, please see the online version of this paper.
“Asymptomatic” Flash Pulmonary Edema by Point-of-Care Ultrasound
A Novel Bedside Finding of Transient Global Ischemia

Bruce J. Kimura, MD, Keshav R. Nayak, MD

ABSTRACT
A 65-year-old man with remitted chest pain and no tachypnea was taken urgently to catheterization because of diffuse lung ultrasound B-lines on bedside examination. He was found to have severe left-main disease. This case emphasizes the value of ultrasound to recognize acute cardiogenic interstitial pulmonary edema despite minimal symptoms. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1545–9) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 65-year-old man reported substernal chest pressure while carrying boxes at work. Although he had been told in the past that this discomfort was gastroesophageal reflux, he called 911 because of its persistence for 45 min. Paramedics upon arrival suspected ST-segment changes and administered sublingual nitroglycerin. The discomfort completely resolved.

LEARNING OBJECTIVES
- B-lines can be detected by a brief POCUS lung examination, are a finding of interstitial pulmonary edema, and have been associated with a worse prognosis in acute coronary syndromes.
- Detectable by POCUS, “flash” interstitial pulmonary edema can be an early presentation of life-threatening global LV ischemia and occur with minimal or no symptoms.

PHYSICAL EXAMINATION
Upon arrival to the emergency department, his blood pressure was 117/84 mm Hg, heart rate was 80 beats/min, respiratory rate was 16/min, and oxygen saturation was 97% on 2 l via nasal cannula. The patient denied chest discomfort or dyspnea, was in no distress, and was lying flat for examination. Neither the ED physician nor cardiologist reported jugular venous distension, murmurs, gallops, or rales.

PAST MEDICAL HISTORY
The patient reported gastroesophageal reflux disease, hypertension, diabetes, and hypercholesterolemia. He was taking esomeprazole, ranitidine, metoprolol, metformin, and simvastatin. He had never smoked.

DIFFERENTIAL DIAGNOSIS
Besides transient cardiac ischemia, the differential diagnosis included esophageal disease,
musculoskeletal discomfort, and—unlikely—aortic dissection, pericarditis, or pulmonary embolism.

**INVESTIGATIONS**

Initial troponin I level was normal, the electrocardiogram (ECG) showed no significant ST-segment changes (Figure 1), and portable chest radiograph (Figure 2) was without infilrates or effusions.

Using a cardiac ultrasound transducer (Lumify, S4-1 MHz, Philips Healthcare, Andover, Massachusetts), a 4-view point of care ultrasound (POCUS) lung examination (1) demonstrated multiple B-lines in all zones (Figure 3). An evidence-based POCUS cardiac examination (2) showed preserved left-ventricular (LV) function and a small left atrium and inferior vena cava. The patient was suspected of having flash pulmonary edema, based upon the diffuse B-lines.

**MANAGEMENT**

He was given nitrates and intravenous heparin and underwent a stat limited echo en route to urgent coronary angiography. Echo data demonstrated LV ejection fraction of 55%, mild anteroseptal and inferolateral wall motion abnormalities, no significant valve disease, and normal dynamics of the right heart and inferior vena cava. Coronary angiography demonstrated critical left main coronary stenosis, occluded proximal circumflex and mid-left anterior descending arteries, a 90% posterior descending artery stenosis, and collateralization from the right coronary artery (Figure 4). Left ventricular end-diastolic pressure measured 25 mm Hg. The patient received an intra-aortic balloon pump and surgical consultation. Preoperative computed tomography (CT) scanning showed no underlying pulmonary interstitial disease or ground-glass infiltrates. He underwent successful 3-vessel bypass surgery.

**DISCUSSION**

Acute pulmonary edema is a medical emergency in which immediate recognition can be life saving (3). Global LV ischemia can result in the rapid accumulation of fluid within the pulmonary interstitium and alveoli in so-called flash pulmonary edema. Alveolar flooding typically results in severe hypoxemia, dyspnea, cardiac crackles, and wheezing, with chest radiography noting central “batwing” infiltrates and CT demonstrating ground-glass infiltrates. Lung ultrasound has shown increased sensitivity for edema (4). With the cardiac transducer placed in the intercostal spaces in a patient with lung edema or fibrosis,
abnormal vertical lines, so-called B-lines, can be seen originating from the bright horizontal pleural line in the near field and extending to the bottom of the screen. B-lines, formerly referred to as “comets” or “comet-tail artifacts,” represent a ring-down artifact caused by reverberation of the ultrasound beam within water-filled or fibrotic regions near the pleural surface, have prognostic value in hospitalized patients undergoing echocardiography (1,5,6), and have been formalized in evidence-based recommendations (7). POCUS techniques for B-lines are easy to learn and have been applied using a variety of echo platforms. Although studies have related the number of B-lines with congestive heart failure decompensation (8), few have described B-lines in flash pulmonary edema with clinical symptomatology.

We report an unusual case of acute LV ischemia resulting in B-lines without dyspnea. Presenting with <1 h of chest discomfort that the patient attributed to reflux disease and no significant findings in troponin level, ST-segment, and chest radiograph, the patient demonstrated bilateral, diffuse B-lines, quickly recognized during initial examination. At the time, the patient denied dyspnea and was in no respiratory distress. Our case shows that the enhanced sensitivity of ultrasound B-lines to detect an asymptomatic stage of interstitial edema can be life saving, perhaps allowing a novel care pathway to pre-empt the development of flash alveolar edema and its dramatic, life-threatening presentation. In addition, the lung ultrasound findings helped to narrow the differential diagnosis, as B-lines would have been atypical for gastroesophageal reflux disease, musculoskeletal pain, aortic dissection, or pulmonary embolism: diagnostic considerations that would have been erroneous and would have resulted in delays.

**ASSOCIATION WITH CURRENT GUIDELINES, POSITION PAPERS, AND CURRENT PRACTICE.** Adding to previous studies that have consistently shown the prognostic value of B-line detection in clinical
presentations of dyspnea, chest pain, congestive heart failure, or acute coronary syndromes during inpatient echocardiography (1,5,6), the case presented uniquely demonstrates a “working method” of using a pocket-sized device to detect evanescent B-lines during initial physical examination. Furthermore, the ultrasound findings illustrate the physiological possibility that an early phase of pulmonary edema can exist involving primarily the interstitium that perhaps occurs before alveolar edema and pleural effusions and without severe LV systolic dysfunction or elevation of central venous pressures. The case demonstrates that a patient with a benign clinical assessment at the point of initial contact can have a malignant sign of interstitial pulmonary edema demonstrated by ultrasound.

Pocket-sized devices promote convenient ultrasound application as ultrasound stethoscopes,
leveraging short boot-up times and maneuverability in the limited time and space of a patient's bedside evaluation. Despite the undisputed value of traditional cardiopulmonary physical examination, learning to detect the simple, more accurate POCUS equivalents of those signs (9) has had only lukewarm adoption by practicing cardiologists, despite diagnostic value in acute cardiac presentations (5–7,10).

**FOLLOW-UP**

In postoperative office follow-up, the patient had recovered uneventfully and demonstrated a normal lung ultrasound examination, with resolution of his B-lines.

**CONCLUSIONS**

When applied even in the absence of symptoms, a simple 4-view lung ultrasound examination may have had life-saving implications in risk stratification of acute ischemia. Emergency department physicians, cardiologists, and hospitalists should be aware of ultrasound lung B-lines in the commonplace evaluation of apparently stable patients with transient chest pain.

**ADDRESS FOR CORRESPONDENCE:** Dr. Bruce J. Kimura, University of California—San Diego, 4077 Fifth Avenue, MER74, San Diego, California 92113. E-mail: kimura.bruce@scrippshealth.org.

**REFERENCES**

1. Garibyan VN, Amundson SA, Shaw DJ, et al. Lung ultrasound findings detected during inpatient echocardiography are common and associated with short- and long-term mortality. J Ultrasound Med 2018;37:1641–8.

2. Kimura BJ, Shaw DJ, Amundson SA, Phan JN, Blanchard DG, DeMaria AN. Cardiac limited ultrasound exam techniques to augment the bedside cardiac physical. J Ultrasound Med 2015;34:1683–90.

3. Ware LB, Matthay MD. Acute pulmonary edema. N Engl J Med 2005;353:2788–96.

4. Picano E, Scali MC, Ciampi Q, Lichtenstein DA. Lung ultrasound for the cardiologist. J Am Coll Cardiol Img 2018;11:1692–705.

5. Frassi F, Gargani L, Tesorio P, et al. Prognostic value of extravascular lung water assessed with ultrasound lung comets by chest sonography with dyspnea and/or chest pain. J Cardiac Fail 2007;13:830–5.

6. Bedetti G, Gargani L, Sicari R, et al. Comparison of prognostic value of echographic (corrected) risk score with the Thrombolysis in Myocardial Infarction (TIMI) and Global Registry in Acute Coronary Events (GRACE) risk scores in acute coronary syndrome. Am J Cardiol 2010;106:1709–16.

7. Volpicelli G, Elbarbary M, Blaivas M, et al. International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med 2012;38:577–91.

8. Picano E, Frassi F, Agricola E, et al. Ultrasound lung comets: a clinically useful sign of extravascular lung water. J Am Soc Echocardiogr 2006;19:356–63.

9. Kimura BJ. Point-of-care cardiac ultrasound techniques in the physical examination: better at the bedside. Heart 2017;103:987–94.

10. Al Deeb M, Barbic S, Featherstone R, et al. Point-of-care ultrasonography for the diagnosis of acute cardiogenic pulmonary edema in patients presenting with acute dyspnea: a systematic review and meta-analysis. Acad Emerg Med 2014;21:843–52.

**KEY WORDS** acute coronary syndrome, coronary artery disease, point-of-care ultrasound, pulmonary edema, risk stratification.
EDITORIAL COMMENT

The Sound of Silence
The Power of Lung Ultrasound in the Interstitial-Alveolar Syndrome*

Hatem Soliman-Aboumarie, MBBS, MS,a Marcelo Haertel Miglioranza, MD, PhDb,c

“Listen to the silence; it has so much to say.” – Rumi (1)

The conventional clinical evaluation alone is not always accurate enough to assess patients in the critical care environment. In this context, point-of-care ultrasound (POCUS) has been increasingly incorporated into daily clinical practice. At the bedside, POCUS may help to differentiate a variety of acute cardiorespiratory disorders. Lung ultrasound (LUS) has shown a high added value when used for the bedside diagnosis of alveolar-interstitial syndrome because it is more accurate than chest radiography and clinical examination alone (2,3). There is evidence that POCUS could have a positive impact on patient outcomes and could potentially reduce the length of hospital stay (4).

The case highlighted by Kimura et al. (5) in this issue of JACC: Case Reports is an excellent example of the role of LUS as a diagnostic tool in acute care. They report the case of a patient who had only a mild, atypical presentation with substernal chest discomfort on effort with no other symptoms and whose LUS examination showed a picture of flash pulmonary edema demonstrated by a diffuse B-lines pattern. This asymptomatic flash pulmonary edema was caused by critical coronary artery disease and was a reflection of elevated left ventricular filling pressures induced by myocardial ischemia. This clinical case illustrates the role of LUS in detecting the dynamic elevation of extravascular lung water in the context of unstable ischemic heart disease, as hypothesized by Picano et al. (6) (Figure 1).

From this case reported by Kimura et al. (5), we can see the vital role of LUS as a bedside screening tool in critically ill patients in emergency settings. It also demonstrates the high sensitivity of LUS in detecting alveolar-interstitial edema even in the absence of dyspnea. This sensitivity broadens our view of the role of LUS, and POCUS in general, in acute care settings. Moreover, we can see the value of handheld ultrasound devices in assisting in the diagnosis of life-threatening cardiorespiratory disorders, a practice that could prove very useful in limited-resource settings.

POCUS is increasingly recognized as an essential bedside diagnostic tool, and we may see it as an extension of the daily clinical examination. Although we do not foresee POCUS replacing our current diagnostic tools (e.g., chest radiography, stethoscope), we think that a comprehensive, integrated multimodality diagnostic approach will be the future of bedside clinical diagnosis and examination.

The presence of B-lines is the sonographic sign of interstitial-alveolar syndrome. These lines are vertical artifacts that start from the pleural line and extend to the far field of the ultrasound sector, typically moving with the pleural sliding with every breath. The number of B-lines correlates well with the degree

*Editorials published in JACC: Case Reports reflect the views of the authors and do not necessarily represent the views of JACC: Case Reports or the American College of Cardiology.

From the aDepartment of Anaesthetics and Critical Care, Harefield Hospital, Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom; bInstitute of Cardiology, University Foundation of Cardiology, Porto Alegre, Brazil; and the cPrevencor, Mãe de Deus Hospital, Porto Alegre, Brazil. Dr. Miglioranza has received a post-graduate grant from CAPES, the Brazilian governmental agency for post-graduate support; has received a research grant from CNPq, the Brazilian governmental agency for research support and has received a grant from FAPERGS, the Rio Grande do Sul State governmental agency for research support. Dr. Soliman-Aboumarie has reported that he has no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

ISSN 2666-0849

https://doi.org/10.1016/j.jaccas.2020.07.009
of extravascular lung water (7). B-lines have also been found to have a 95% specificity and 97% sensitivity for the diagnosis of pulmonary edema (8).

Therefore, the number and pattern of B-lines (B-profile) can be used to track dynamic changes in pulmonary congestion and to monitor the response to therapy (9). This evolving body of evidence has led to incorporating B-lines assessment by LUS in international heart failure guidelines.

However, challenges exist regarding the future use of POCUS in acute cardiac care. POCUS data should be interpreted with caution and in the appropriate clinical context. It should be used as part of an integrated approach that includes clinical, laboratory, and other imaging tools. Supervised training and accreditation are essential to ensure quality control while maintaining patient safety. Focused ultrasound examinations performed by
clinicians who only had a basic level of training may not be appropriate in the assessment of complex cardiothoracic patients who are critically ill and whose ultrasound studies often require more advanced skills. POCUS in these patients should be performed with a thorough understanding of the pathophysiology and hemodynamics of each case.

**REFERENCES**

1. al-Din Rumi J. The Masnavi, Book One-Oxford World’s Classics (Paperback). Dr. Jawid Mojaddedi (translator). 2014.
2. Maw AM, Hassanin A, Ho MP, et al. Diagnostic accuracy of point-of-care lung ultrasonography and chest radiography in adults with symptoms suggestive of acute decompensated heart failure: a systematic review and meta-analysis. JAMA Netw Open 2019;2:e190703.
3. Mohammad Al, Deeb MA, Barbara S, Featherstone R, Dankoff J, Barbara D. Point-of-care ultrasonography for the diagnosis of acute cardiogenic pulmonary edema in patients presenting with acute dyspnea: a systematic review and meta-analysis. Acad Emerg Med 2014;21:843-52.
4. Mozzi C, Di Dio PM, Pesce G, et al. Lung ultrasound in internal medicine efficiently drives the management of patients with heart failure and speeds up the discharge time. Intern Emerg Med 2018;13:27-33.
5. Kimura BJ, Nayak KR. “Asymptomatic” flash pulmonary edema by point-of-care ultrasound: a novel bedside finding of transient global ischemia. J Am Coll Cardiol Case Rep 2020;2:3545-9.
6. Picano E, Scali MC, Campi Q, Lichtenstein D. Lung ultrasound for the cardiologist. J Am Coll Cardiol Img 2018;11:1692-705.
7. Volpicelli G, Caramello V, Cardinale L, Mussa A, Bar F, Frascisco MF. Bedside ultrasound of the lung for the monitoring of acute decompensated heart failure. Am J Emerg Med 2008;26:585-91.
8. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. Chest 2008;134:117-25.
9. Platz E, Mez AA, Jhund PS, Vazir A, Campbell R, McMurray JJ. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: a systematic review. Eur J Heart Fail 2017;19:1154-63.

**KEY WORDS** acute coronary syndrome, interstitial-alveolar syndrome, lung ultrasound, POCUS, point-of-care ultrasound, pulmonary congestion, pulmonary edema, unstable ischemic heart disease

**ADDRESS FOR CORRESPONDENCE:** Dr. Marcelo Haertel Miglioranza, Cardiovascular Imaging Research Group, Institute of Cardiology, University Foundation of Cardiology, Av. Princesa Isabel, 370, Porto Alegre / RS, CEP 90620-000, Brazil. E-mail: marcelohaertel@gmail.com.
Infliximab Treatment of Refractory Cardiac Sarcoidosis

Majid Asawaeer, MD, a Benjamin Widener, MD, b Varda Singhal, MBBS, a Matthew J. DeVries, MD, c Debra J. Romberger, MD, d Alan R. Erickson, MD, b Yiannis S. Chatzizisis, MD, PhD a

ABSTRACT

Treatment of cardiac sarcoidosis is challenging, as the disease can be refractory to traditional treatment with steroids. Infliximab, a tumor necrosis factor-α inhibitor, has been reportedly used in cardiac sarcoidosis, but published evidence is limited. The potential cardiotoxicity of infliximab and the Food and Drug Administration black-box warning for patients with heart failure have hindered the use of this agent in cardiac sarcoidosis. Here, we report a case of refractory cardiac sarcoidosis successfully treated with infliximab and discuss the important role of fluorine-18-fluorodeoxyglucose positron emission tomography in prognostication and guidance of therapy. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1553–7) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 63-year-old male patient with biopsy-proven pulmonary sarcoidosis and clinical suspicion of cardiac involvement was referred to our cardiac sarcoidosis (CS) clinic at the University of Nebraska Medical Center, Omaha, Nebraska. He had episodic atypical chest pain and palpitations. His cardiac examination was normal. An electrocardiogram showed normal sinus rhythm with no conduction abnormalities. A transthoracic echocardiogram showed normal left ventricular systolic function without major valvular abnormalities and normal global longitudinal strain (~20%).

PAST MEDICAL HISTORY

The patient had history of hypertension, hypothyroidism, and pulmonary sarcoidosis. He never smoked and had no family history of cardiac disease or sarcoidosis.

DIFFERENTIAL DIAGNOSIS

Our patient presented with atypical chest pain and occasional palpitations. These otherwise atypical symptoms could occur in a broad spectrum of diseases, including myopericarditis, myocardial...
ischemia, pleurisy, and musculoskeletal involvement. The biopsy-proven lung sarcoidosis raised the suspicion of symptomatic cardiac involvement, which occurs in approximately 5% of patients with pulmonary sarcoidosis (1). Myopericarditis and myocardial ischemia were ruled out with echocardiography and exercise stress echocardiography, respectively. Musculoskeletal causes of chest pain were ruled out by history and physical examination.

**INVESTIGATIONS**

We obtained a cardiac magnetic resonance (CMR) scan that showed evidence of mid-myocardial late gadolinium enhancement at the basal septal wall, suggestive of CS (Figure 1A). To investigate the CMR findings further and stage CS, we obtained a fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET) scan (Figure 1B), which showed basal septal FDG uptake co-localizing with the late gadolinium enhancement on CMR (Figure 1C), a finding highly suggestive of the early active stage of CS.

**MANAGEMENT**

The patient was already receiving steroid therapy for pulmonary sarcoidosis. Given the presence of late gadolinium enhancement on CMR and the history of palpitations, the patient underwent an electrophysiology study, which had negative results. Implantable cardioverter-defibrillator insertion was not pursued (2). A repeat $^{18}$F-FDG PET scan at 3 months after the diagnosis of CS showed unchanged FDG uptake extending to the lateral wall and apex of the heart (Figure 2). At that point we added mycophenolate mofetil and continued the steroid therapy. Repeat $^{18}$F-FDG PET at 6 months from the diagnosis of CS showed worsening FDG uptake (Figure 2). Given the refractory status of CS and the patient’s worsening chest pain, the decision was made to initiate therapy with infliximab, a tumor necrosis factor (TNF)-α inhibitor. The risks and benefits of the drug were discussed with the patient in our joint CS and rheumatology clinic. Serial $^{18}$F-FDG PET scans at 9, 21, and 33 months from the diagnosis of CS showed gradual improvement and finally complete resolution of cardiac inflammation (Figures 2 and 3). Clinical improvement was also noted. Notably, pulmonary sarcoidosis showed total resolution by chest radiography (Figure 4). The patient’s left ventricular systolic function remained within the normal range on serial transthoracic echocardiograms throughout the course of therapy. After complete resolution of cardiac inflammation, the patient entered the maintenance stage with mycophenolate mofetil therapy only (Figure 2).

**FIGURE 1** Cardiac Magnetic Resonance and $^{18}$F-FDG PET in CS

(A) Cardiac magnetic resonance and (B) fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET) imaging and (C) their superimposition at baseline showing co-localization of late gadolinium enhancement with fluorine-18-fluorodeoxyglucose in the basal or midseptal and lateral walls. CS = cardiac sarcoidosis; MRI = magnetic resonance imaging.
FIGURE 2  Serial Cardiac $^{18}$F-FDG PET in CS

The scans show the qualitative and quantitative response of cardiac sarcoidosis (CS) to escalating anti-inflammatory therapies. Max SUV liver values show standardization of the background glucose uptake. Max — maximum; SUV — standardized uptake value; other abbreviations as in Figure 1.

FIGURE 3  Whole body $^{18}$F-FDG PET (Coronal Plane) at Baseline and at 21 and 33 Months After CS Diagnosis

The images show gradual improvement and finally complete resolution of cardiac inflammation. Abbreviations as in Figure 1.
FOLLOW-UP

We plan to follow up with a final $^{18}$F-FDG PET scan at 40 months post-diagnosis of CS.

DISCUSSION

This case highlights 2 important aspects of the diagnosis and therapy of CS. CMR and $^{18}$F-FDG PET are complementary to each other in the investigation of suspected CS. Sometimes, 1 test can have positive results and the other negative, so both tests should be performed for the initial CS diagnosis (3). Studies showed that $^{18}$F-FDG PET has good sensitivity (89%), but low specificity (33.3%) for the diagnosis of CS (4). After the diagnosis of CS is established, serial $^{18}$F-FDG PET is the best approach to assess disease activity and response to therapy (3). Although CMR has a potentially superior negative predictive value in the initial evaluation of suspected CS compared with $^{18}$F-FDG PET, it cannot provide reliable longitudinal monitoring of disease activity (5). The ability to quantify FDG uptake in CS is the foundation for the most important advantage of $^{18}$F-FDG PET over CMR in CS imaging (2,3). The reproducibility of FDG PET without clinical or therapeutic changes between studies has been reported in publications. Adherence to a strict high fat, low carbohydrate diet preparation protocol (Supplemental Appendix) and extension of FDG incubation time to 120 min improve cardiac FDG reproducibility (6).

CS is sometimes difficult to control with steroid treatment, the first-line therapy (refractory CS). Treatment of refractory CS is not well established because of a lack of randomized controlled trials. In refractory CS, biological agents, including TNF-$\alpha$ inhibitors, can be considered for second- or third-line therapy. Case series and observational studies have demonstrated an encouraging response of CS to TNF-$\alpha$ inhibitors. However, the potential for worsening heart failure with any of the TNF-$\alpha$ inhibitors remains a considerable concern. In the ATTACH (Anti-TNF Therapy Against Congestive Heart Failure) trial, where patients with congestive heart failure were treated with infliximab, infliximab increased all-cause mortality and hospitalizations (7). The RENEWAL (Randomized Etanercept Worldwide Evaluation) trial failed to show any clinically-relevant benefit in congestive heart failure with targeted anticytokine therapy with etanercept, a soluble TNF antagonist (8). However, the results of the ATTACH and RENEWAL trials cannot be generalized to patients with normal left ventricular function or cardiomyopathy secondary to sarcoidosis. A recent cohort analysis showed significant improvement of CS with infliximab without worsening systolic function (9). In line with the findings of this cohort, our case report suggests that infliximab may be a promising second- or third-line therapy for patients with refractory CS.

CONCLUSIONS

CMR and $^{18}$F-FDG PET are indispensable tools in the initial diagnosis of CS. $^{18}$F-FDG PET offers quantifiable monitoring of disease activity and response to therapy, thereby enabling prompt identification of patients with steroid-refractory CS who could benefit from escalation of anti-inflammatory therapy.
Infliximab may be a promising second- or third-line therapy for patients with refractory CS. Future randomized clinical trials are warranted to determine the safety and efficacy of infliximab and other TNF-α inhibitors in CS.

**REFERENCES**

1. Hulten E, Aslam S, Osborne M, Abbasi S, Bittencourt MS, Blankstein R. Cardiac sarcoidosis—state of the art review. Cardiovasc Diagn Ther 2016;6:50-63.

2. Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm 2014;11:1305-23.

3. Bravo PE, Singh A, Di Carlo MF, Blankstein R. Advanced cardiovascular imaging for the evaluation of cardiac sarcoidosis. J Nucl Cardiol 2019;26:188-99.

4. Divakaran S, Stewart GC, Lakdawala NK, et al. Diagnostic accuracy of advanced imaging in cardiac sarcoidosis. Circ Cardiovasc Imaging 2019;12: e008975.

5. Wicks EC, Menezes LJ, Barnes A, et al. Diagnostic accuracy and prognostic value of simultaneous hybrid 18F-fluorodeoxyglucose positron emission tomography/magnetic resonance imaging in cardiac sarcoidosis. Eur Heart J Cardiovasc Imaging 2018;19:757-67.

6. Alvi RM, Young BD, Shahab Z, et al. Repeatability and optimization of FDG positron emission tomography for evaluation of cardiac sarcoidosis. J Am Coll Cardiol Img 2019;12:1284–7.

7. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Anti-TNF Therapy Against Congestive Heart Failure investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133-404.

8. Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594-602.

9. Harper LJ, McCarthy M, Ribeiro Neto ML, et al. Infliximab for refractory cardiac sarcoidosis. Am J Cardiol 2019;124:1630-5.

**KEY WORDS**

Cardiac sarcoidosis, infliximab, magnetic resonance imaging, positron emission tomography

**APPENDIX** For a supplemental imaging protocol, please see the online version of this paper.

**ADDRESS FOR CORRESPONDENCE:** Dr. Yiannis S. Chatzizisis, Cardiovascular Division, University of Nebraska Medical Center, Omaha, Nebraska 68198. E-mail: ychatzizisis@icloud.com.
ABSTRACT

Immunoglobulin G4–related disease is a systemic fibroinflammatory disease; pericardial involvement has occasionally been reported in publications. A 79-year-old man with biopsy-proven immunoglobulin G4–related disease with pleural involvement was admitted in acute heart failure, with imaging and hemodynamic studies consistent with constrictive pericarditis. He was treated with corticosteroids for 2 months with partial response manifest by decreases in pericardial thickening and immunoglobulin G4 levels. However, persistent constriction required pericardiectomy, leading to significant symptomatic improvement. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1558–63) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 79-year-old man with a history of recurrent right-sided loculated pleural effusion presented with progressive dyspnea and was found to be in acute heart failure. Two months before admission he underwent video-assisted thoracoscopic surgery with pleural biopsy and mediastinoscopy with lymph node biopsy. Lymph node biopsy revealed a collagenized granuloma, and the pleural biopsy demonstrated moderate to marked lymphoplasmacytic inflammation and fibrosis with a focal storiform pattern. Most of the plasma cells tested positive for immunoglobulin G4 (IgG4) by immunohistochemical staining. On the basis of the presence of focal storiform fibrosis and numerous IgG4-positive plasma cells, the pleural disease was believed to be consistent with IgG4–related disease (Figures 1A and 1B).

On this current presentation to the emergency department, he was afebrile, his heart rate was 96 beats/min, blood pressure was 117/76 mm Hg, and oxygen saturation was 94% on 3 l of oxygen through a
nasal cannula. Examination was significant for jugular venous distention, decreased breath sounds in the right lung field, abdominal distention, and 3+ edema bilaterally. Laboratory data were significant for a creatinine concentration of 1.46 mg/dl similar to baseline, white blood cell count of 7.5 × 10^3/μl, hemoglobin of 13.2 g/dl, and platelet count of 189 × 10^3/μl. The electrocardiogram demonstrated sinus rhythm with an incomplete right bundle branch block and a left anterior fascicular block. Chest computed tomography was obtained and showed a large right-sided pleural effusion, a pericardial effusion with some degree of pericardial thickening (up to 6 mm), and a few subcentimeter mediastinal lymph nodes (Figure 2A). Pericardial calcifications were absent. A transthoracic echocardiogram (TTE) revealed a left ventricular ejection fraction of 55%, normal right ventricular function, and a prominent septal bounce without pericardial effusion (Figures 3A and 3B, Video 1). The study was of limited quality to evaluate tissue velocities or hepatic vein Doppler imaging adequately.

**PAST MEDICAL HISTORY**

The patient had a pleural effusion that was thought to be related to IgG4-RD, as well as chronic diastolic heart failure.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis included constrictive pericarditis (CP) related to IgG4-RD, CP related to alternative causes (viral, idiopathic), chronic diastolic heart failure, and pulmonary hypertension.

---

**ABBREVIATIONS AND ACRONYMS**

CP = constrictive pericarditis
IgG4-RD = immunoglobulin G4-related disease
TTE = transthoracic echocardiogram

---

(A) Section of the pleural biopsy shows dense lymphoplasmacytic inflammation with focal storiform fibrosis (arrow). (B) Immunohistochemical stain for immunoglobulin G4 antibody shows numerous immunoglobulin G4-positive plasma cells. The patient subsequently presented with constrictive pericarditis. Pericardectomy was performed after only partial clinical response to steroids. The pericardium shows (C) dense fibrosis with focal storiform pattern (arrow) and only mild lymphoplasmacytic inflammation with (D) few immunoglobulin G4-positive cells.
INVESTIGATIONS

A diagnosis of IgG4-RD CP was suspected. Immunoglobulin levels were obtained, with a total IgG level of 2,854 mg/dl (normal range 768 to 1,632 mg/dl) and an IgG subclass 4 level of 306 mg/dl (normal range 1 to 123 mg/dl). Additional laboratory data were significant for an antinuclear antibody value of 1:320 (normal <1:80), a complement C3 level of 126 mg/dl (normal 80 to 180 mg/dl), and a C4 level of 18 mg/dl (normal 10 to 45 mg/dl). The patient underwent cardiac magnetic resonance, which demonstrated septal shudder and septal bounce (Figures 4A and 4B, Video2). Simultaneous left- and right-sided heart catheterization demonstrated enhanced ventricular interdependence with inspiratory increase in right ventricular pressure and a simultaneous decrease in left ventricular pressures (Figure 5). At the time of catheterization, the mean pulmonary artery pressure was 17 mm Hg, with pulmonary vascular resistance of 1 WU. Additionally, the right and left ventricular end-diastolic pressures were equal at 18 to 20 mm Hg, and a dip-and-plateau pattern was noted. The patient was started on a regimen of prednisone, 60 mg orally daily, and he underwent diuresis over the course of 10 days with a plan to re-evaluate his clinical status over the next few months and to determine the need for pericardiectomy.

MANAGEMENT

Two months later he was readmitted with progressive dyspnea and weight gain. Repeat chest computed tomography demonstrated a large, right-sided pleural effusion with pericardial thickening slightly decreased from the previous study (3 mm from 6 mm) (Figure 2B), and his IgG 4 level had decreased to 117 mg/dl. Repeat TTE was significant for septal bounce unchanged from his initial study. He was therefore referred to cardiac surgery for pericardiectomy. The patient underwent phrenic-to-phrenic pericardial excision. Intraoperatively, the pericardium was thickened, with patches of calcification. Microscopically, the pericardium showed predominantly fibrosis, with focal suggestion of storiform fibrosis and only mild lymphoplasmacytic inflammation with very few IgG4-positive plasma cells (Figures 1C and 1D). Although the number of IgG4 plasma cells did not meet the published criteria for diagnosing IgG4-related disease, given the patient’s history of previous pleural involvement and the presence of elevated serum IgG and IgG4 levels before steroid treatment, a diagnosis of IgG4-related disease involving the pericardium was favored. Working with our rheumatology colleagues, we were unable to identify additional manifestations of the disease or other autoimmune conditions.

DISCUSSION

Initially described as a disease of the pancreas, IgG4-RD is an immune-mediated fibroinflammatory condition that can affect virtually every organ system. Pathological findings include lymphoplasmacytic infiltration with a high ratio of IgG4-positive plasma cells to IgG-positive plasma cells (1-4). Cardiovascular
The manifestations include aortitis, pericarditis, and coronary arteritis or periarteritis. The main therapy for IgG4-RD consists of corticosteroids, with prednisone at a dose of 30 mg/day to 1 mg/kg/day (2). Approximately one-half to two-thirds of patients respond within weeks of treatment (2,4).

There are scant published data to inform the management of CP caused by IgG4-RD, and the response to corticosteroid therapy in CP is unknown. Sekiguchi et al. (5) described a 29-year-old woman with biopsy-proven IgG4-RD manifest by pleural effusions requiring video-assisted thoracoscopic surgery and decortication who had evidence of CP by echocardiography, as well as pericardial thickening on computed tomography. After 3 months of corticosteroid treatment, imaging no longer showed constrictive physiology, and she was free of symptoms (5). Several case reports have noted resolution of constrictive and improvement in symptoms following pericardiectomy. However, in those instances, IgG4-RD was usually diagnosed after pericardiectomy, patients were sicker and at times in shock, and steroid therapy was not attempted before surgery (2).

By contrast, our patient had biopsy-proven IgG4-RD of the pleura with CP demonstrated by TTE findings of septal shudder and bounce, cardiac magnetic resonance demonstration of the same, and invasive hemodynamics demonstrating ventricular discordance. An initial trial of corticosteroid therapy was attempted with partial response manifest by decrease in pericardial thickening and IgG4 levels. Similarly, Kondo et al. (6) described a case of a 78-year-old man with IgG4-RD leading to fibroinflammatory lesions of the pericardium, pleura, and bile ducts. After 1 month of steroid therapy, this patient had resolution of pleural effusions and improved liver function test results; however, CP persisted and required pericardiectomy (6). Although it is possible that more significant improvement would have been noted with a longer treatment course in our case, ongoing CP with recurrent limiting symptoms prompted surgery.

**FOLLOW-UP**

After pericardiectomy, the patient’s central venous pressure dropped from 18 mm Hg to 10 mm Hg. He had an uncomplicated post-operative course and underwent steroid tapering. On 2-month follow-up, his anasarca had resolved, and his exercise tolerance had greatly improved.

**CONCLUSIONS**

We described a case of CP in a patient with biopsy-proven IgG4-RD of the pleura who demonstrated an incomplete response to corticosteroid therapy with resolution of CP following pericardiectomy. Our case highlights the need to consider IgG4-RD in cases of idiopathic CP. Although there are insufficient published data to inform the response to steroids in cases...
FIGURE 4  Cardiac Magnetic Resonance

(A and B) Cardiac magnetic resonance during normal breathing demonstrating septal bounce, or motion of the interventricular septum (arrows) toward the left ventricle in early diastole.

FIGURE 5  Simultaneous Right and Left Ventricular Pressure Tracings

Ventricular discordance is demonstrated as an inspiratory increase in right ventricular (RV) pressure with a simultaneous decrease in left ventricular (LV) pressure (arrows). The opposite phenomenon occurs on expiration. The RV and LV end-diastolic pressures were equalized at 18 to 20 mm Hg. The mean pulmonary artery pressure is 17 mm Hg, with a pulmonary vascular resistance of 1 WU. A dip-and-plateau pattern is noted.
of CP secondary to IgG4-RD, a trial of corticosteroid treatment in stable patients with close monitoring of symptoms may be reasonable. The finding that a significant fibrotic component may limit steroid response emphasizes the importance of early diagnosis.

ADDRESS FOR CORRESPONDENCE: Dr. Eugene Yuriditsky, Leon H. Charney Division of Cardiology, Department of Medicine, NYU Langone Health, 530 First Avenue, Skirball 9R, New York, New York 10016. E-mail: eugene.yuriditsky@nyulangone.org.

REFERENCES
1. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med 2012;336:539–51.
2. Mavrogeni S, Markousis-Mavrogenis G, Kolovou G. IgG4-related cardiovascular disease. The emerging role of cardiovascular imaging. Eur J Radiol 2017;86:169–75.
3. Sekiguchi H, Horie R, Suri RM, Yi ES, Ryu HJ. Constrictive pericarditis caused by immunoglobulin G4-related disease. Circ Heart Fail 2012;5:e30–1.
4. Matsumiya R, Hosono O, Yoshikawa N, et al. Elevated serum IgG4 complicated by pericardial involvement with a patchy 18F-FDG uptake in PET/CT: atypical presentation of IgG4-related disease. Intern Med 2015;54:2337–41.
5. Sekiguchi H, Horie R, Utz JP, Ryu HJ. IgG4-related systemic disease presenting with lung entrapment and constrictive pericarditis. Chest 2012;142:781–3.
6. Kondo T, Uehara T. Immunoglobulin G4-related disease with fibroinflammatory lesions in the pleura, bile ducts and pericardium. CMAJ 2016;188:972.

KEY WORDS constrictive pericarditis, IgG4-related disease

APPENDIX For supplemental videos, please see the online version of this paper.
A 66-year-old man developed sudden-onset severe central chest and epigastric pain at rest. The electrocardiogram (ECG) performed by the paramedics showed ST-segment elevation in V1 to V5 and II, III, and aVF (Figure 1). His observations revealed hypertension (180/100 mm Hg) and a heart rate of 60 beats/min. On arrival, he had ongoing chest pain, was diaphoretic and clammy, and appeared acutely unwell. The rest of the cardiorespiratory examination was unremarkable. There was no history of a recent viral illness.

PAST MEDICAL HISTORY

The patient had a history of Miller Fisher syndrome, hypertension, and dyslipidemia.

DIFFERENTIAL DIAGNOSIS

Given the findings of severe central chest pain and ST-segment elevation, the most likely differential diagnosis is acute myocardial infarction via coronary artery occlusion. However, our patient had no prior history of coronary artery disease, and diagnostic coronary angiography revealed no angiographic abnormalities.
diagnosis was ST-segment elevation myocardial infarction (STEMI). Other important differentials considered were myocarditis, pericarditis, pulmonary embolus, and bowel ischemia.

**INVESTIGATIONS**

Initial high-sensitivity troponin T level was 50 ng/l, which peaked at 1,229 ng/l (normal range <14 ng/l). C-reactive protein (CRP) was <5 mg/l (normal range <6.0 mg/l). The only other abnormality on blood tests was a metabolic acidosis, with a venous lactate of 6.0 mmol/l (normal range 0.5 to 2.2 mmol/l).

**MANAGEMENT**

Immediate coronary angiography showed an unobstructed left main stem with mild to moderate plaque disease in the left anterior descending (LAD) artery, first diagonal, and left circumflex arteries. The right coronary artery only demonstrated mild plaque disease (Figure 2, Videos 1, 2, 3, 4, 5, and 6). Given the high index of clinical suspicion of a myocardial infarction (MI), detailed review of the angiographic images was performed, which did not suggest an ostial occlusion of a branch coronary artery. In addition, based on the predominantly anterolateral ECG changes at presentation, optical coherence tomography (OCT) was performed in the LAD, circumflex, or first obtuse marginal arteries, and this confirmed that there was no intravascular evidence of a ruptured plaque or coronary dissection. Left ventricular (LV) ventriculogram was normal.

The patient was returned to the coronary care unit with a working diagnosis of MI with nonobstructive coronary arteries (MINOCA). Dual antiplatelet therapy and standard secondary prevention was started pending further investigations.

Bedside echocardiography showed mildly impaired right ventricular (RV) systolic function with severe hypokinesia of the RV free wall and mild right atrial enlargement. LV function was normal, with no regional wall motion abnormality and no significant valvular abnormality. Computed tomography (CT) pulmonary angiography (CTPA) results were normal.

Cardiac magnetic resonance (CMR) was performed 1 day following the presentation (Figure 3). This revealed normal LV systolic function with no regional wall abnormalities. However, there was marked systolic flattening of the interventricular septum, and the RV was mildly dilated with impaired ejection fraction (EF) (49%) and severe hypokinesia/akinesia of the mid to apical RV free wall. T2-short tau inversion recovery (STIR) imaging was normal, and there was no late gadolinium enhancement (LGE) to suggest any acute edema or acute MI. In addition, the

---

**FIGURE 1** 12-Lead Electrocardiogram on Admission

---

**ABBREVIATIONS AND ACRONYMS**

- **CMR** = cardiac magnetic resonance
- **CTPA** = computed tomography pulmonary angiogram
- **CRP** = C-reactive protein
- **ECG** = electrocardiogram
- **LAD** = left anterior descending
- **LGE** = late gadolinium enhancement
- **MINOCA** = myocardial infarction with nonobstructive coronary arteries
- **MVO** = microvascular obstruction
- **OCT** = optical coherence tomography
- **RV** = right ventricle
pericardium appeared normal, and there was no evidence of pericardial effusion.

A working diagnosis of RV predominant myopericarditis was made, and the patient was started on anti-inflammatory medication, analgesia, and was advised to abstain from strenuous exercise for 6 months.

Repeat CMR was performed at 6 weeks as part of a local research study (Figure 4). The RV remained impaired with the previously described regional wall motion abnormalities. However, the LGE images now clearly showed transmural late enhancement of the basal to mid-right ventricular free wall and part of the diaphragmatic wall, consistent with RV infarction.

Review of the initial CMR (Figure 3) demonstrated very low signal throughout the RV free wall on the early post-contrast images, consistent with extensive microvascular obstruction (MVO) (Figure 5). This had been incorrectly interpreted as normal myocardium, given the signal characteristics and the challenge of the thin-walled RV free wall, the absence of normal reference myocardium within the same segment, and the rarity of RV MVO.

**DISCUSSION**

Myocardial infarction with nonobstructive coronary arteries is relatively common, affecting up to 6% of patients with acute MI (1). A 2019 AHA scientific statement (2) sought to clarify some of the confusion around the diagnostic term “MINOCA.” It is made clear that MINOCA is a descriptive working diagnosis in patients with presumed ischemic etiology to their presentation. Diagnosis requires a rise or fall in cardiac troponin (usually defined as a 20% change) with a value >99th centile; corroborative evidence of infarction: for example, symptoms consistent with myocardial ischemia; the absence of obstructive coronary artery disease on angiography (no stenosis ≥50% in any major epicardial vessel); and the absence of any alternate diagnosis for the clinical presentation (such as sepsis, pulmonary embolism, or myocarditis). They advocate a traffic-light approach to comprehensively assess these patients. Suggested steps include detailed review of the angiogram in light of further clinical information, imaging with echo and/or CMR, intravascular coronary imaging,
FIGURE 3  Cardiac Magnetic Resonance at Presentation

Four-chamber (4ch) cine image (A) demonstrating a mildly dilated right ventricle (RV). Short axis view in end systole (B) demonstrating flattened septum consistent with RV pressure overload; 4ch and mid ventricular short axis (SA) T2-short tau inversion recovery (STIR) images (C and D) showing no myocardial edema. Early gadolinium 4ch long axis (E) and mid-SA (F) images. Late gadolinium 4ch long axis (G) and SA (H) images.

FIGURE 4  Cardiac Magnetic Resonance at 6-Week Follow-Up

Four-chamber (4ch) cine image (A) and mid-ventricular SA view in end systole (B) demonstrating ongoing mildly dilated right ventricle (RV) but now reduced septal flattening; 4ch and mid-SA T2-STIR images (C, D) showing no myocardial edema. Early gadolinium 4ch long axis (E) and mid-SA (F) showing relatively increased signal in the RV free wall, compared with the previous scan, in keeping with resolution of acute microvascular obstruction and some perfusion of contrast into the RV free wall. Late gadolinium 4ch long axis (G) and SA (H) now showing very high signal in the RV free wall in keeping with established RV myocardial infarction (white arrows).
and coronary functional assessment. Furthermore, a recent consensus statement advocates comprehensive intracoronary imaging in cases of suspected MINOCA, and this case strengthens this recommendation, as imaging of the RCA was overlooked but may have provided an acute diagnosis (3).

CMR is recommended as a key investigation in the diagnostic work-up of patients with MINOCA and can make a diagnosis in approximately 3 of 4 patients (4). CMR is a noninvasive imaging modality used to investigate cardiac anatomy, function, and tissue characterization. CMR can facilitate identification of cardiomyopathies—such as myocarditis, pericarditis, acute MI, and Takotsubo—in patients presenting with MINOCA. CMR performed within 2 weeks of presentation can increase the diagnostic yield from ~70% to ~84% (5). LGE can detect as little as 1g of infarcted myocardium (6).

We report a rare case of isolated RV MI with MVO. Despite following established recommendations, the diagnosis still took 6 weeks to be confirmed, highlighting the unique intellectual challenges in this cohort of patients.

Although there are sparse reports of RV MVO in the literature (7,8) there is not a published case report to our knowledge of isolated RV MVO.
MVO is seen following coronary reperfusion in patients who have had significant periods of ischemia. Its appearances on CMR are caused by the inability of gadolinium contrast material to pass through the myocardial microvasculature, as reperfused myocytes become edematous because of osmotic overload and occlude the capillaries (9). This leads to a focal, well-defined area of absent signal within an area of high-signal infarction or acute ischemia (8). Myocardium with microvascular obstruction is less likely to regain function and leads to ventricular wall scarring and remodeling when compared with patients who have no microvascular obstruction (10). The presence of microvascular obstruction is associated with higher rates of cardiovascular events in the first 2 years following an MI and a poorer prognosis.

**FOLLOW-UP**

Our final diagnosis was a transmural, nonviable, RV MI. The patient was contacted to explain the diagnosis and was restarted on aspirin 75 mg, clopidogrel 75 mg, and appropriate secondary prevention.

The presumed culprit lesion was an ostial RV branch occlusion, which could not be identified on angiography. Subsequent ECGs (Supplemental Figures 1 and 2) demonstrated findings consistent with a transmural infarction.

The role of antiplatelet therapy in MINOCA is controversial. In our case, we thought that the most likely underlying pathophysiology was an ostial plaque rupture event, and so we decided to treat the patient as a nonreperfused STEMI, as per the 2017 ESC guidelines (11).

**CONCLUSIONS**

This is the first reported case of isolated RV infarction with MVO and highlights the value of CMR in patients with MINOCA.

**ADDRESS FOR CORRESPONDENCE:** Dr. Chiara Bucciarelli-Ducci, Cardiac MRI Department (C503), Bristol Heart Institute, BRI, Upper Maudlin Street, Bristol BS2 8HW, United Kingdom. E-mail: c.bucciarelli-ducci@bristol.ac.uk.

---

**REFERENCES**

1. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation 2015;131:861-70.

2. Tamis-Holland JE, Jneid H, Reynolds HR, et al. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: a scientific statement from the American Heart Association. Circulation 2019;139:e891.

3. Johnson TW, Raber L, di Mario C, et al. Clinical use of intracoronary imaging. Part 2: acute coronary syndromes, ambiguous coronary angiography findings, and guiding interventional decision-making: an expert consensus document of the European Association of Percutaneous Cardivascular Interventions. Eur Heart J 2019;40:2566-84.

4. Dastidar AG, Baritussio A, De Garate E, et al. Prognostic role of CMR and conventional risk factors in myocardial infarction with nonobstructed coronary arteries. J Am Coll Cardiol Img 2019;12:1973-82.

5. Dastidar AG, Rodrigues JCL, Johnson TW, et al. Myocardial infarction with nonobstructed coronary arteries: impact of CMR early after presentation. J Am Coll Cardiol Img 2017;10:1204-6.

6. Agewall S, Beltrame JF, Reynolds HR, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J 2017;38:143-53.

7. Andreini D, Pontone G, Mushtaq S, Pepi M, Bogaert J, Masci PG. Microvascular obstruction complicating acute right ventricular myocardial infarction. J Cardiovasc Med (Hagerstown) 2015;16 Suppl 1:S12-4.

8. Abbas A, Matthews GH, Brown IW, Shambrook JS, Peebles CR, Harden SP. Cardiac MR assessment of microvascular obstruction. Br J Radiol 2015;88:20140470.

9. Bekkers SC, Yazdani SK, Virmani R, Waltenberger J. Microvascular obstruction: underlying pathophysiology and clinical diagnosis. J Am Coll Cardiol 2010;55:1649-60.

10. Wu KC, Zerhouni EA, Judd RM, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation 1998;97:765-72.

11. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2018;39:119-77.

**KEY WORDS** cardiac magnetic resonance, coronary angiography, myocardial infarction, right ventricle

**APPENDIX** For supplemental videos and figures, please see the online version of this paper.
Invasive Cardiac Lipoma Complicating Visceral Inversion

Takahide Kadosaka, MD,a Shingo Tsujinaga, MD, PHD,a Hiroyuki Iwano, MD, PHD,a Noriko Oyama-Manabe, MD, PHD,b Toshihisa Anzai, MD, PHDa

ABSTRACT

We report a case of cardiac lipoma with intramyocardial invasion complicated by visceral inversion, which, to the best of our knowledge, has not been reported before. Multimodality imaging played an important role in differential diagnosis and determination of the management strategy. (Level of Difficulty: Advanced.) (J Am Coll Cardiol Case Rep 2020;2:1570–1)

© 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 63-year-old asymptomatic woman with visceral inversion, rheumatoid arthritis, and scleroderma treated with prednisolone 9 mg/day and methotrexate 16 mg/week was admitted for management of an intracardiac mass incidentally found on computed tomography (CT). Although visceral inversion was detected on CT when the patient was in her thirties, the intracardiac mass was not identified at the time. On admission, her blood pressure was 124/75 mm Hg and pulse rate 88 beats/min. Clinical examination revealed no heart murmur. CT revealed a 3-cm low-density mass with mean CT value of -40 HU in the apical anterior wall of the left ventricle; it infiltrated the muscle layer and showed no contrast enhancement (Figure 1A). Echocardiography revealed protrusion of a slightly mobile mass into the left ventricular (LV) cavity (Video 1). Although thrombosis after myocardial infarction must be considered for a mass in the LV apex, LV wall motion did not suggest myocardial infarction. 18F-fluoro-deoxyglucose positron emission tomography-CT showed no significant focal uptake in the mass (Figure 1B), suggesting low probability of malignancy. Cardiac magnetic resonance imaging (MRI) showed a high intensity on T1- and T2-weighted images with fat suppression without contrast enhancement (Figure 1C to 1F, Videos 2 and 3). Based on these findings, benign cardiac lipoma was suspected. Owing to the high surgical risk for histological diagnosis and absence of tumor-related symptoms, careful follow-up was planned. Follow-up CT after 6 months showed no change in the size of the mass and no tumor-associated symptoms on follow-up for 9 months.

Cardiac lipomas represent 8.4% of primary cardiac tumors (1), most commonly originating in the subendocardium (50%), followed by the myocardium (25%) and subepicardium (25%); typical locations include the right atrium and the left ventricle (1). The degree of symptoms depends on the location and size of the tumors. Notably, cardiac lipoma complicating visceral inversion has never been reported. Visceral inversion is associated with genetic mechanisms but not with the development of cardiac tumors (2). Despite reports of concurrent development of visceral inversion and digestive system neoplasms, the presence of cardiac lipoma and visceral inversion could be incidental. Accordingly, the clinical manifestation of this case is rare.

From the aDepartment of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan; and the bDepartment of Radiology, Saitama Medical Center, Ichi Medical University, Omiya, Japan. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

Manuscript received March 18, 2020; revised manuscript received May 13, 2020, accepted May 26, 2020.
Recent advances in cardiac imaging have enabled accurate diagnosis of cardiac tumors (3) although it must be confirmed based on pathological findings. Surgical resection is the standard management of benign cardiac tumors to relieve tumor-associated symptoms or reduce the risk of embolic events. However, management of asymptomatic patients as in this case remains unstandardized and is based on the risk of invasive strategy. In LV lipomas with invasion into the myocardium, surgical resection is unsafe owing to surgical complications such as intraoperative cardiac rupture, coronary artery injury, and postoperative lethal arrhythmias (3). Our case was complicated with connective tissue disease requiring immunosuppressive therapy, which also increased the perioperative risk of complications, resulting in careful follow-up without surgical resection.

In conclusion, we report the first case of cardiac lipoma with intramyocardial invasion complicating visceral inversion. Multiple imaging enabled noninvasive differential diagnosis and management of the cardiac tumor.

**ADDRESS FOR CORRESPONDENCE:** Dr. Shingo Tsujinaga, Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan. E-mail: shingo-t.0207@med.hokudai.ac.jp.

**REFERENCES**

1. D’Souza J, Shah R, Abbass A, Burt JR, Goud A, Dahagam C. Invasive cardiac lipoma: a case report and review of literature. BMC Cardiovasc Disord 2017;17:28.
2. Peeters H, Devriendt K. Human laterality disorders. Eur J Med Genet 2006;49:349–62.
3. Sun X, Liu G, Kim H, Sun W. Left ventricular lipoma resected using thoracoscope-assisted limited sternotomy: a case report and literature review. Medicine (Baltimore) 2018;97:e11436.

**ABBREVIATIONS AND ACRONYMS**

CT = computed tomography
LV = left ventricular
MRI = magnetic resonance imaging

**FIGURE 1 Multimodality Imaging of Invasive Cardiac Lipoma Complicating Visceral Inversion**

The red star shows the left ventricle, whereas the yellow star shows the right ventricle. (A) Contrast-enhanced CT demonstrates a 29 × 27 mm low-density mass (mean CT value of -40 HU) in the anterior wall of the apical left ventricle (A, light blue arrow), which shows no contrast enhancement. The anatomy indicates visceral inversion. (B) 18F-fluoro-deoxyglucose positron emission tomography–CT shows no focal uptake in the intracardiac mass (B, light blue arrow). (C and D) Cardiac MRI shows a high intensity in the mass on both of T1WI (C, light blue arrow) and T2WI (D, light blue arrow). (E) The high intensity of the mass was suppressed in the fat-suppressed T1WI (E, light blue arrow). (F) Gadolinium-enhanced TIWI shows no contrast effect in the mass (F, light blue arrow). CT = computed tomography; MRI = magnetic resonance imaging; TIWI = T1-weighted image.

**KEY WORDS** cardiac lipoma, intramyocardial left ventricular lipoma, visceral inversion

**APPENDIX** For supplemental videos, please see the online version of this paper.
An Unusual Case of Bioprosthetic Mitral Valve Failure

Shiro Miura, MD, MSC,a Takehiro Yamashita, MD, PhD,a Masaki Murata, MD, PhD,b Hiroyuki Iwano, MD, PhD,c Youhei Ohkawa, MD, PhDd

ABSTRACT

We report a case of sudden-onset pulmonary edema due to failure of a bioprosthetic mitral valve. Gross inspection revealed a leaflet tear at a stent post without calcification or pannus formation and no evidence of sutures. This case highlights the mechanical failure of a bioprosthetic mitral valve associated with missing sutures. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1572–4) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

An 86-year-old man with a medical history of surgical mitral replacement 10 years prior with a 27-mm Carpentier-Edwards Perimount plus pericardial mitral valve (Model 6900P, Edwards Lifesciences, Irvine, California) due to post-inflammatory mitral stenosis presented with acute onset of fever and dyspnea. On admission, his blood pressure, pulse rate, body temperature, and oxygen saturation were 171/106 mm Hg, 170 beats/min, 37.2°C, and 84% (room), respectively. Physical examination revealed that bibasilar crackles were heard with no obvious heart murmur or jugular vein distention. Initial transthoracic echocardiogram (TTE) was notable for a left ventricular ejection fraction of 82% and mild transvalvular mitral regurgitation (MR) with an effective regurgitant orifice area of 16 mm². Subsequent chest computed tomography examination revealed extensive bilateral infiltrates and pleural effusion. Despite elevated white blood cell count (14,600/µl) and serum C-reactive protein (7.9 mg/dl), 3 sets of blood cultures were all negative. He was initially diagnosed with community-acquired pneumonia, which responded well to intravenous ceftriaxone. On hospital day 19, he developed sudden-onset dyspnea; chest radiography revealed bilateral pulmonary congestion (Figure 1A). Vital sign measurements showed a blood pressure of 140/81 mm Hg, heart rate of 98 beats/min, and oxygen saturation of 88% (room). Chest auscultation was remarkable for bilateral coarse crackles and a holosystolic murmur (4/6 intensity), maximal at the apex radiating to the axilla. TTE showed an eccentric, severe MR jet with a prolapsed posteromedial leaflet towards the lateral wall of the left atrium associated with an effective regurgitant orifice area of 41 mm² and left ventricular ejection fraction of 79%. Right-sided cardiac catheterization revealed prominent v waves (30 mm Hg) on pulmonary capillary wedge pressure (PCWP) tracing with a mean PCWP of 24 mm Hg. Serum levels of N-terminal pro-B-type natriuretic peptide increased from 501 to 10,887 pg/ml. These findings are consistent with a
diagnosis of acute MR associated with cardiogenic pulmonary edema. Intravenous diuretics were initiated immediately, resulting in insufficient hemodynamic improvement. A transesophageal echocardiogram performed on hospital day 23 revealed a torn mitral valve leaflet undergoing prolapse into the left atrium (Figures 1B to 1D, Videos 1 and 2). Although percutaneous valve-in-valve implantation was considered a promising option (1), this procedure is not fully reimbursed for clinical use in Japan. On hospital day 23, after multidisciplinary discussion between the cardiology and cardiothoracic surgery departments, the failed valve was surgically replaced with a 29-mm St. Jude Medical mechanical valve (St. Jude Medical, Inc., St. Paul, Minnesota), which was selected based on several factors: valve durability, re-intervention risks, the need for

**FIGURE 1** Imaging and Pathologic Findings

(A) Chest radiograph from hospital day 19 revealed bilateral pulmonary congestion. (B) Transesophageal echocardiogram (TEE) (left) with color Doppler (right) documented a leaflet tear prolapsing into the left atrium during systole in association with significant mitral regurgitation (MR) (Video 1). (C) Three-dimensional (3D) TEE image, viewed from the left atrium confirmed prolapse (red arrow) in the posteromedial leaflet where (D) an eccentric transvalvular MR jet (red arrowhead) was directed at the lateral wall of the left atrium; and 3D color Doppler image (Video 2). (E) Flow and (F) non-flow surfaced of the excised bioprosthetic mitral valve revealed a slit-like tear (red arrowhead) along the stent post on the affected side; no significant leaflet calcification, pannus formation, or valve thrombosis was observed. (G) Histologic findings (hematoxylin and eosin staining) highlight the area within the square, as shown in E. Sutures were partially absent along the stent post on the affected side (red arrowhead); sutures supporting the stent post were present on the opposite side (asterisk).
long-term anticoagulation, and patient preference as per international guidelines (2). The patient was uneventfully discharged on postoperative day 33.

Pathologic examination revealed a slit-like leaflet tear along one side of the stent post with no significant calcification, pannus formation, or valve thrombosis (Figures 1E and 1F). Histologically, no sutures were detected at the affected side of the stent post, although they were clearly present along the opposite side of the valve (Figure 1G). Microscopic examination revealed no significant inflammation, fibrosis, calcification, or myxomatous degeneration that may contribute to a leaflet tear of this nature (3). Accordingly, we concluded that the missing sutures most likely played a pivotal role in promoting acute prosthetic valve dysfunction, although we do not know whether the sutures were absent initially or became unfastened over the years of use. There is reportedly an intense concentration of tensile stress at the top of the stent post (i.e., the commissure), roughly 5 times greater than the maximum detected at the center of the leaflet (4). Moreover, the hemodynamic changes and systemic inflammation related to community-acquired pneumonia may have had an indirect negative impact on valve function.

ADDRESS FOR CORRESPONDENCE: Dr. Shiro Miura, Department of Cardiology, Hokkaido Ohno Memorial Hospital, 2-1-16-1 Miyanosawa, Nishi-ku, Sapporo 063-0052, Japan. E-mail: s.miura@ohno-kinen.or.jp.

REFERENCES
1. Wilbring M, Alexiou K, Tugtekin SM, et al. Transapical transcatheter valve-in-valve implantation for deteriorated mitral valve bioprostheses. Ann Thorac Surg 2013;95:111-7.
2. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521-643.
3. Siddiqui RF, Abraham JR, Butany J. Bioprosthetic heart valves: modes of failure. Histopathology 2009;55:135-44.
4. Haziza F, Papouin G, Barratt-Boyes B, et al. Tears in bioprosthetic heart valve leaflets without calcific degeneration. J Heart Valve Dis 1996;5:35-9.

KEY WORDS echocardiography, imaging, mitral valve, valve replacement

APPENDIX For supplemental videos, please see the online version of this paper.
Using 3-dimensional speckle-tracking echocardiography-derived activation imaging system, we visualized interventricular dyssynchrony in a repaired tetralogy of Fallot case with pacing-induced left ventricular dysfunction. The activation imaging system visualized interventricular dyssynchrony and resynchronization after cardiac resynchronization therapy and may be useful to assess electromechanical disturbance in complicated congenital heart diseases. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1575–7) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Cardiac resynchronization therapy (CRT) has been performed in adult congenital heart diseases (ACHD) with electrophysiological disturbances. However, the evaluations of mechanical dyssynchrony are often challenging because of complicated anatomical and electrophysiological matters. Three-dimensional speckle-tracking echocardiography (3D-STE) is available as the activation imaging, which can image the propagation of regional myocardial contraction in both ventricles (1,2). Recently, the authors developed an activation imaging system that can visualize images integrating both ventricular contractions. Then, they used the modality in assessing the effect of CRT in a patient with ACHD.

A 24-year-old man with tetralogy of Fallot had a history of intracardiac repair that was performed when he was 3 years of age and elimination of remaining right ventricular (RV) outflow obstruction that was performed when he was 8 years of age. During the second operation with a monocusp transannular patch, the complete atrioventricular block was caused, and epicardial DDD pacemaker implantation was performed, and the RV lead was located at RV outflow (Supplemental Figure 1). When he was 21 years old, he presented with left ventricular (LV) systolic dysfunction with 28% LV ejection fraction (EF) and was treated with enalapril and carvedilol, which could not improve LV systolic function. Also, severe pulmonary regurgitation PR was concomitant. Because magnetic resonance imaging was not available due to the magnetic resonance imaging nonconditional pacemaker, 3D-STE was used in assessing both ventricular functions and revealed that LVEF was 30% and RVEF was 42%. Besides, the activation imaging system allowed us to visualize the
intraventricular and interventricular dyssynchrony (Figure 1, Videos 1, 2, 3, and 4). Despite the presence of severe pulmonary regurgitation, it was apparent that his critical issue was LV dysfunction caused by pacemaker-induced LV dyssynchrony. Then, CRT was performed when he was 22 years old, and intraventricular and interventricular dyssynchrony was dramatically resynchronized (Figure 1). At 1 year after CRT, LV reverse remodeling was obtained (LV end-systolic volume, 113 to 90 ml, 20% reduction, LVEF 30% to 42%). In contrast, despite RV resynchronization, RVEF was reduced from 42% to 38%. The residual significant pulmonary insufficiency may be related to the nonresponded RV function after CRT.

**DISCUSSION**

Because of the large variability of electromechanical sequences with very different structures, patients with ACHD require tailor-made therapy for each case. The integrated activation imaging of both ventricles may be helpful in assessing the pathophysiology and be a guide for a strategy using cardiac implantable electronic devices in patients with ACHD. In the present case, we used the 3D-STE, which is derived from the cubic pattern-matching technology using the cube-shaped template in a 3D echocardiography volume dataset (3). 3D-STE is better than 2-dimensional (2D)-STE in the following points. First, 3D-STE is not affected by the 3D movement of the heart. In the setting of 2D echocardiography, the heart moves through the 2D plane of interest, and, in fact, different myocardium appear in the 2D image frame by frame (4). This is called “through plane or out of the plane phenomenon.” Second, for RV, 2D assessment has drawbacks related to the intrinsic complexity in its anatomy and deformation pattern. As a result, this may cause no negligible effects on the accuracy of tissue tracking in 2D images. In contrast, 3D full-volume LV and RV data overcome the limitation of the plane-dependency of the 2D image (5).

We presented this case with the development of pacemaker-induced dyssynchrony in congenital heart disease, which is a critical sequela in ACHD care with the previous implantation of a pacemaker at childhood. The initial pacemaker ventricular lead was on the RV outflow region, which is an uncommon site for epicardial pacing. According to the multicenter study by Janousek et al. (6), epicardial pacing lead site is rarely at RV outflow tract (n = 8 of 178; 5%), and they concluded that the pacing from the RV outflow tract/lateral RV was related to significantly decreased LV function.

**FIGURE 1** The Activation Imaging System Allowed Visualization of the Intraventricular and Interventricular Dysynchrony

(A) ECG at baseline showing RVOT pacing. (B) Front view of AI at baseline. The color bar shows each color corresponding time from QRS complex to the contraction onset. The RVOT showed early contraction coded in blue by AI, and LV free wall showed delayed contraction in red by AI. (C) En face view of AI at baseline. (D) ECG after CRT. (E) Front view of AI after CRT. (F) En face view of AI after CRT. AI = activation imaging; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; LV = left ventricle; MV = mitral valve; PV = pulmonary valve; RV = right ventricular; RVOT = right ventricular outflow tract.

**ADDRESS FOR CORRESPONDENCE:** Dr. Yoshihiro Seo, Department of Cardiology, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-Cho, Mizuho-Ku, Nagoya 467-8601, Japan. E-mail: yo-seo@med.nagoya-cu.ac.jp.
REFERENCES

1. Seo Y, Ishizu T, Kawamura R, et al. Three-dimensional propagation imaging of left ventricular activation by speckle-tracking echocardiography to predict responses to cardiac resynchronization therapy. J Am Soc Echocardiogr 2015;28:606-14.

2. Ishizu T, Seo Y, Atsumi A, et al. Global and regional right ventricular function assessed by novel three-dimensional speckle-tracking echocardiography. J Am Soc Echocardiogr 2017;30:1203-13.

3. Takeguchi T, Nishiura M, Abe Y, Ohuchi H, Kawagishi T. Practical considerations for a method of rapid cardiac function analysis based on three-dimensional speckle tracking in a three-dimensional diagnostic ultrasound system. J Med Ultrasond 2010;37:41-9.

4. Mann DL, Gillam LD, Weyman AE. Cross-sectional echocardiographic assessment of regional left ventricular performance and myocardial perfusion. Prog Cardiovasc Dis 1986;29:1-52.

5. Seo Y, Ishizu T, Atsumi A, Kawamura R, Aonuma K. Three-dimensional speckle tracking echocardiography. Circ J 2014;78:1290-301.

6. Janoušek J, van Geldorp IE, Krupišková S, et al. Permanent cardiac pacing in children: choosing the optimal pacing site: a multicenter study. Circulation 2013;127:613-23.

KEY WORDS activation imaging system, tetralogy of Fallot, 3-dimensional speckle-tracking echocardiography

APPENDIX For a supplemental figure and videos, please see the online version of this paper.
A 69-year-old male presented to the emergency room with progressive dyspnea on exertion associated with an intermittent cough lasting more than 2 weeks. He had no prior symptoms and denied weight gain, orthopnea, or paroxysmal nocturnal dyspnea. Although he had no history of a murmur, physical examination revealed a 3/6 systolic ejection murmur best heard at the right upper sternal border with no carotid radiation. He had bibasilar crackles with no extremity edema. His blood pressure was 130/72 mm Hg, heart rate was 58 beats/min, and his oxygen saturation was 91% on room air. The findings from the rest of his physical examination were normal. Electrocardiogram showed an old left bundle branch block and first-degree atrioventricular block with frequent premature ventricular complexes. For further evaluation of his murmur, transthoracic echocardiography (TTE) was ordered. TTE showed a depressed left ventricular ejection fraction of 35% to 40%, mild aortic regurgitation, and a mobile ill-defined subaortic structure prolapsing into the left ventricular outflow tract (LVOT) causing LVOT obstruction. LVOT peak velocity was 2.85 m/s with a gradient of 32.5 mm Hg, a post-premature ventricular complex LVOT gradient increased to 37.5 mm Hg with a peak velocity of 4.4 m/s (Figure 1). Parenthetically there was no change in

**LEARNING OBJECTIVES**

- AMTV is a rare congenital anomaly consisting of an endocardial cushion that typically arises from the anterior mitral leaflet and often a cause of LVOT obstruction.
- Patients with AMVT may have an asymptomatic murmur or present with chest pain, palpitations related to arrhythmia, congestive heart failure, cerebrovascular events, fatigue, or syncope.
- Echocardiography is pivotal for diagnosis and follow-up. Surgical resection is recommended in symptomatic patients and patients with significant LVOT obstruction.
the gradient with a Valsalva maneuver. There was no prior TTE for comparison.

**MEDICAL HISTORY**

He had a history of hypertension and left bundle branch block that was seen on prior electrocardiograms. He had no prior workup for his left bundle branch block.

**DIFFERENTIAL DIAGNOSIS**

Identification of a mobile structure in the LVOT raises concerns for vegetation, subaortic membrane, redundant mitral valve chordae, primary or secondary cardiac tumors, and accessory mitral valve tissue (AcMVT).

**INVESTIGATIONS**

Because his TTE was nondiagnostic, transesophageal echocardiography (TEE) was pursued to better define the ill-defined structure in the LVOT. On the standard mid-esophageal 4-chamber TEE view there was a parachute-like subaortic structure prolapsing into the LVOT, consistent with an AcMVT (Videos 1 and 2). As the aortic valve opened, the parachute-like structure was noted to prolapse in a “peek-a-boo” manner toward the aortic valve (Video 3). Color comparison imaging showed flow acceleration around but not through this structure (Video 4). Associated mild aortic insufficiency was noted (Video 5). Given the high suspicion for AcVMT on TEE, no further diagnostic imaging was pursued.

**MANAGEMENT**

Because the patient was symptomatic with echocardiographic findings of significant LVOT obstruction, surgical intervention was recommended. Preoperative cardiac catheterization showed non-obstructive coronary artery disease. Intraoperative inspection of the LVOT showed a completely formed mitral valve reminiscent of an anterior mitral leaflet affixed to the basal interventricular septum with chordal attachments to the papillary muscle. The complete structure was excised, and histopathology confirmed the diagnosis of accessory mitral valve tissue with degenerative changes (Figures 2 to 5). His perioperative period was uncomplicated, and he was discharged to cardiac rehabilitation on goal-directed heart failure therapy for his depressed left ventricular ejection fraction.

**DISCUSSION**

AcMVT is a rare congenital anomaly of the endocardial cushion that typically arises from the anterior mitral
leaflet or less commonly both leaflets simultaneously. It is usually diagnosed in childhood because it is often associated with other congenital intracardiac or vascular anomalies. AcMVT as an isolated finding, as described in the present patient, is rare. The incidence of AcVMT in adulthood is 1 in 26,000 persons (1). AcMVT can be obstructive or nonobstructive, with the patient having an asymptomatic murmur (2). Symptoms of LVOT obstruction include exertional dyspnea, chest pain, syncope, stroke, thromboembolism, low cardiac output due to subaortic obstruction, and decompensated heart failure, as in this patient. The pathophysiology of LVOT obstruction is thought to be related to the mass effect of the AcMVT in the LVOT. As the AcMVT expands, there is progressive narrowing of the LVOT. Also, continuous turbulent flow in the LVOT leads to deposition of fibrous tissue and scarring, which contributes to LVOT obstruction (3,4). As with a fixed subaortic membrane, flow acceleration across the valve may lead to aortic insufficiency as seen in the present patient. Echocardiography is pivotal in the diagnosis of AcMVT, evaluation of associated congenital anomalies, LVOT obstruction, and other valvular abnormalities. In 2003, Prifti et al. (5) reviewed 90 published cases of patients with AcMVT. Severe LVOT obstruction with a trans-LVOT gradient more than 50 mm Hg was present in most cases, and mild LVOT obstruction was found in 15 patients, 11 of whom had a LVOT mean gradient <31 mm Hg and 3 other patients who presented with no LVOT obstruction (5). Although echocardiography remains the gold standard for the diagnosis of AcMVT, cardiac computer tomography and magnetic resonance imaging are useful modalities in its assessment and may better evaluate cardiac tumors and other cardiac anomalies. Surgical resection is recommended for patients with a significant LVOT obstruction mean gradient of >25 mm Hg and for those undergoing cardiac surgery for other cardiac pathology (6). There are no clear guidelines for management of asymptomatic patients (7).

**FOLLOW-UP**

At his 2 weeks follow-up, this patient was completely asymptomatic. Repeated TTE 1 month after surgery showed resolution of LVOT obstruction but
unfortunately did not show any improvement in his left ventricular systolic function. It is hoped that further from his surgery his left ventricular systolic function may improve.

CONCLUSIONS

AcMVT is a rare congenital cardiac anomaly that can cause LVOT obstruction. The present case describes an adult male who presented with heart failure symptoms and was found to have LVOT obstruction in the setting of an isolated AcMVT. Echocardiography played an important role in this diagnosis, surgical resection was required as he was symptomatic and had significant LVOT obstruction.

ADDRESS FOR CORRESPONDENCE: Dr. Deborah Tosin Akanya, Yale New Haven Health-Bridgeport Hospital, Department of Cardiology, 267 Grant Street, 10th Floor, Bridgeport, Connecticut 06610. E-mail: akanyadeborah@gmail.com.

REFERENCES

1. Rovner A, Thangiraj S, Perez JE. Accessory mitral valve in an adult population: the role of echocardiography in diagnosis and management. J Am Soc Echocardiogr 2005;18:494-8.
2. Yuan S-M, Shinfeld A, Mishaly D, Haider R, Ghosh P, Raanani E. Accessory mitral valve tissue: a case report and an updated review of literature. J Card Surg 2008;23:769-72.
3. Hartyánszky IL, Kádár K, Bojeldein S, Bodor G. Mitral valve anomalies obstructing left ventricular outflow. Eur J Cardiothorac Surg 1997;12:504-6.
4. Panduranga P, Eappen T, Al-Maskari S, Al-Farqani A. Accessory mitral valve tissue causing severe left ventricular outflow tract obstruction in a post-Senning patient with transposition of the great arteries. Heart Int 2011;6: e6-e.
5. Prifti E, Bonacchi M, Bartolozzi F, Frati G, Leacche M, Vanini V. Postoperative outcome in patients with accessory mitral valve tissue. Med Sci Monit 2003;9:RA126-33.
6. Manganaro R, Zito C, Khanderia BK, et al. Accessory mitral valve tissue: an updated review of the literature. Eur Heart J Cardiovasc Imaging 2014;15:489-97.
7. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e81-192.

KEY WORDS acute heart failure, chordae, mitral valve, murmur

APPENDIX For supplemental videos, please see the online version of this paper.
SAM and Severe Mitral Regurgitation Post–Acute Type A Aortic Dissection Surgery Treated With MitraClip

Ana Paula Tagliari, MD,a b Mara Gavazzoni, MD,c Mizuki Miura, MD,d Maurizio Taramasso, MD,a Francesco Maisano, MDa

ABSTRACT

Post-operative systolic anterior motion associated with mitral regurgitation can be a challenging combination. We present the case of a 64-year-old male patient managed by MitraClip (Abbott Laboratories, Abbott Park, Illinois) implantation for systolic anterior motion and severe mitral regurgitation in the early post-operative period after aortic dissection surgery. This is the first description of MitraClip use post-aortic dissection. (Level of Difficulty: Intermediate.)

LEARNING OBJECTIVES

- Precise and prompt recognition of this potentially lethal association is vital to provide adequate clinical and interventional management.
- MitraClip can be an effective and lifesaving alternative to manage SAM associated with severe MR in patients with high surgical risk or a contraindication to conventional cardiac surgery.

Although mitral valve (MV) systolic anterior motion (SAM) was initially described in patients with hypertrophic obstructive cardiomyopathy, it can also be present in patients with complex dynamic left ventricular anatomy. This “dynamic SAM” can potentially occur after cardiac surgery and significantly affect perioperative management and the patient’s prognosis.

The MitraClip system (Abbott Laboratories, Abbott Park, Illinois) has been used to manage new onset SAM after MV repair or aortic valve (AV) interventions. Clinical hemodynamic outcomes suggest that it could be a feasible and safe alternative in these settings. We describe a rare case of SAM associated with severe mitral regurgitation (MR) complicating the early post-operative period after treatment of type A aortic dissection.
acute aortic dissection (AAD), which was successfully managed with a MitraClip intervention.

**HISTORY OF PRESENTATION**

A 64-year-old man was admitted to the emergency department with a sudden onset of retrosternal discomfort radiating to the back and superior abdomen associated with weakness in the right arm. On emergency department arrival, vital signs were as follows: noninvasive blood pressure 134/100 mm Hg, heart rate 86 beats/min, oxygen saturation level 98%, Glasgow Coma Scale score 15. The right lower limb was colder than the left, and he had no palpable pulse.

**PAST MEDICAL HISTORY**

His previous medical history included hypertension, ascending aorta ectasia (46-mm diameter, 2-mm progression in the last 2 years), persistent atrial fibrillation treated with oral anticoagulant therapy (rivaroxaban 20 mg/day); active smoking (70 pack-years), and alcohol abuse. A previous transthoracic echocardiogram (performed 10 months earlier) showed mild to moderate AV regurgitation, mild MR, and posterior leaflet prolapse.

**INVESTIGATIONS**

The chest radiograph showed mediastinal widening, the electrocardiogram was normal, and chest computed tomography revealed a Stanford type A AAD involving the entire ascending, descending, and abdominal aorta, with no pericardial or pleural effusion. A transesophageal echocardiogram (TEE) showed a tricuspid AV with moderate regurgitation, moderate MR, and nonsignificant SAM (Figures 1A and 1B, Video 1). Left ventricular ejection fraction was 60%.

**MANAGEMENT**

Emergency aortic surgery was indicated. Cardiopulmonary bypass was established through the right subclavian artery and right atrium. Under antegrade cerebral perfusion and moderate hypothermia, the ascending aorta was inspected. An AV resuspension, with ascending aorta and hemiarch replacement, was performed using a 28-mm Dacron (Abbott Vascular, Santa Clara, California) graft and a Teflon (Chemours, Wilmington, Delaware) felt sandwich technique. Cardiopulmonary bypass and aortic cross-clamping times were 216 and 117 min, respectively. Because of a significant coagulation disturbance and excessive bleeding, a strategy of delayed sternal closure was adopted. At the end of the procedure, the SAM was classified as moderate (5) (no left ventricular outflow tract [LVOT] obstruction, moderate MR) and easily reversible (reversible with intravascular volume expansion).

**FIGURE 1** Pre-Operative TEE During Surgery for Acute Type A AAD

(A) Moderate aortic valve regurgitation. (B) Moderate mitral regurgitation and nonsignificant systolic anterior motion. AAD = acute aortic dissection; TEE = transesophageal echocardiogram.

**ABBREVIATIONS AND ACRONYMS**

AAD = acute aortic dissection  
AV = aortic valve  
LVOT = left ventricular outflow tract  
MR = mitral regurgitation  
MV = mitral valve  
SAM = systolic anterior motion  
TEE = transesophageal echocardiogram
During the first post-operative days, hemodynamic stabilization was not obtained, and high doses of inotropic and vasopressor agents were required. TEE was repeated and revealed severe MR, an anteriorly directed eccentric jet, P1 to P2 leaflet prolapse, and severe and persistent SAM (no LVOT obstruction, severe MR, not reversible with intravascular volume expansion and increase in the afterload) (Figures 2A and 2B, Videos 2 and 3).

The case was discussed among colleagues, and the patient was judged to be at too high risk for immediate surgical reintervention. Hence a percutaneous MV approach was planned.

On the seventh post-operative day, MitraClip implantation was performed using 2 XTR clips. Under TEE guidance, the first clip was oriented to the A2-P2 segment. Grasping was achieved using X-plane visualization, and the TEE confirmed a broad tissue bridge between A2 and P2. The second clip was implanted in a slightly more lateral position. By the end of the procedure, there was a mild central residual MR, 2 mm Hg mean gradient, and no residual SAM (Figures 3A and 3B, Videos 4A and 4B). Because of the patient's baseline hemodynamic condition and right ventricular dysfunction, an 8-mm Amplatzer atrial septal defect closure device (Abbott Laboratories) was used to occlude the iatrogenic atrial septal defect. Hemodynamic parameters, such as invasive blood pressure (before, 94/52 mm Hg; after, 117/55 mm Hg) and mean left atrial pressure (before, 20 mm Hg; after, 10 mm Hg) improved immediately.

Following MitraClip implantation, the patient showed clinical improvement. He changed from a status of complete hemodynamic instability, under ventilatory and inotropic support, to a stable condition. He was weaned from mechanical ventilation and inotropic support, and his chest was definitively closed 2 days after the MitraClip was implanted.

**DISCUSSION**

SAM of the MV, combined with significant MR, with or without significant LVOT obstruction, can be a life-threatening condition requiring precise and prompt diagnosis and management, especially if it complicates the early post-operative setting.

Following aortic stenosis interventions, SAM is an often unrecognized cause of hemodynamic instability (3). One of the proposed pathophysiological explanations is that, by relieving the LVOT obstruction imposed by the aortic stenosis, the LVOT pressure drops, thereby reducing the LVOT cross-sectional area resulting from high-velocity flow (Bernoulli theorem). This “low-pressure zone” would affect the MV apparatus directly by “pulling” the anterior leaflet toward the LVOT (3). After aortic regurgitation interventions, although possible, SAM is rarer once the dilated left ventricle tends to widen during systole, thus preventing anterior leaflet-LVOT apposition (6).

We report the case of a rare and potentially lethal combination of SAM and severe MR in the early post-operative phase of a surgical procedure for AAD. Post-

---

**FIGURE 2 TEE Performed After AAD Surgery**

Images show (A) severe mitral regurgitation with an eccentric regurgitant jet directed anteriorly to the atrial roof, combined with (B) systolic anterior motion. Abbreviations as in **Figure 1**.
operative hypovolemia and hypotension, combined with reduced systemic vascular resistance and persistent atrial fibrillation, may have led to left ventricular underfilling. This condition, aggravated by the presence of a hyperdynamic state resulting from inotropic agent and excessive sympathetic activation, has been identified as a potential SAM-aggravating mechanism (6,7).

Regarding the MR mechanism, it is noteworthy that, although MR mediated by SAM is traditionally characterized by a posteriorly directed jet on Doppler echocardiography, our patient had a predominantly anteriorly directed eccentric jet, which suggests the presence of an intrinsic MV disease. This statement is strengthened by the observation that, in patients with SAM and central or anterior MR jets, a significantly elongated posterior leaftet is usually present (8). A posterior leaftet basal portion bulging beyond the anterior leaftet may reduce the amount of posterior leaftet area effectively available to follow and coapt with the anterior leaftet toward the septum, thus explaining why MR is usually more significant when prolapse is present (9). Nonetheless, a more careful analysis of the available echocardiographic images could suggest the presence of chordal SAM associated with MV prolapse and increased left ventricular contractility, rather than true SAM involving the anterior leaftet body.

When MR worsens following aorta surgery, investigators have proposed that because of the proximity between the MV and the AV, surgical intervention in the latter can damage the former or alter the normal dynamics of the aortomitral curtain (10). In our patient, the AV resuspension technique could have displaced the MV leaftets towards the aorta, thereby reducing the coaptation length and increasing the posterior leaftet prolapse. This surgically provoked MV anterior translocation may have aggravated the pre-existing MR and impaired clinical recovery.

In the present case, transcatheter MV repair was considered the best option because of the patient’s hemodynamic instability and absolute refractoriness to medical management, both of which created a condition of “too high risk” for open cardiac surgery reintervention. Despite the successful outcome obtained in this patient, it is important to keep in mind that conservative medical therapy is usually enough to stabilize patients with post-operative SAM. A 2-step approach, consisting of intravascular volume expansion simultaneously with any inotropic drug discontinuation (first step), followed by maneuvers to increase the afterload simultaneously and in the short term with a bolus administration of esmolol (1 mg/kg) (second step, applied when the first step fails to elicit a response), has been proposed. Following these steps, invasive management is indicated when the SAM does not disappear after conservative management (persistent SAM) (5).

This case shows that, in selected patients, MitraClip use can be a feasible alternative to address refractory MR and SAM, with excellent safety profile and hemodynamic outcomes.
FOLLOW-UP

After chest closure, the patient had no major complications related to the MitraClip procedure. At 1- and 3-month follow-up, he had no cardiovascular symptoms. The 1-month echocardiographic image revealed mild AV regurgitation, mild MR, and 3 mm Hg mean MV gradient.

CONCLUSIONS

To the best of our knowledge, this is the first description of MitraClip implantation in the immediate post-operative period in a patient with type A AAD surgery performed to address SAM and severe MR. In this setting, less invasive percutaneous management can be considered as a first-line option instead of higher-risk redo surgery.

ADDRESS FOR CORRESPONDENCE: Dr. Francesco Maisano, Cardiovascular Surgery Department, University Hospital of Zurich, Rämistrasse 100, 8091 Zurich, Switzerland. E-mail: francesco.maisano@usz.ch.

REFERENCES

1. Raut M, Maheshwari A, Swain B. Awareness of ‘systolic anterior motion’ in different conditions. Clin Med Insights Cardiol 2018;12:1179546817751921.
2. Agricola E, Taramasso M, Marini C, et al. First-in-man MitraClip implantation to treat late post-operative systolic anterior motion: rare cause of tardive mitral repair failure. Circ Cardiovasc Interv 2014;7:860–2.
3. Grasso C, Scandura S, Buccheri S, et al. MitraClip implantation for the treatment of new-onset systolic anterior motion of the mitral valve after transcatheter aortic valve replacement. Ann Thorac Surg 2016;102:e517–9.
4. Thomas F, Rader F, Siegel RJ. The use of MitraClip for symptomatic patients with hypertrophic obstructive cardiomyopathy. Cardiology 2017;137:58–61.
5. Crescenti G, Landoni G, Zangrillo A, et al. Management and decision-making strategy for systolic anterior motion after mitral valve repair. J Thorac Cardiovasc Surg 2009;137:320–5.
6. Sukernik MR, Sumner AD, Pae WE. Systolic anterior motion of the mitral valve after aortic valve replacement for aortic insufficiency. J Cardiothorac Vasc Anesth 2007;21:574–6.
7. Xu J, Wen J, Shu L, Liu C, Zhang J, Zhao W. Mechanism and correlated factors of SAM phenomenon after aortic valve replacement. Huazhong Univ Sci Technolog Med Sci 2007;27:72–4.
8. Hang D, Schaff HV, Nishimura RA, et al. Accuracy of jet direction on Doppler echocardiography in identifying the etiology of mitral regurgitation in obstructive hypertrophic cardiomyopathy. J Am Soc Echocardiogr 2019;32:333–40.
9. Petrone RK, Klues HG, Panza JA, Peterson EE, Maron BJ. Coexistence of mitral valve prolapse in a consecutive group of 528 patients with hypertrophic cardiomyopathy assessed with echocardiography. J Am Coll Cardiol 1992;20:55–61.
10. Weiner MM, Rodriguez-Diaz CA. A case of severe SAM following a David procedure. Middle East J Anaesthesiol 2012;21:875–7.

KEY WORDS aorta, dissection, mitral valve, post-operative

APPENDIX For supplemental videos, please see the online version of this paper.
MINI-FOCUS ISSUE: IMAGING

IMAGING VIGNETTE: CLINICAL VIGNETTE

Valvular Disease Begets Valvular Disease

Diana DeCampos, MD,a Rogério Teixeira, MD, PhD,a, b João Lopes, MD,a Carolina Saleiro, MD,a Lino Gonçalves, MD, PhD,a,b

ABSTRACT

In acute severe aortic regurgitation, an inversion of pressure gradient from the left ventricle to the left atrium causes the classical sign of end-diastolic mitral regurgitation. Here we present a case of mid-diastolic mitral regurgitation in a 51-year-old man with severe aortic regurgitation secondary to infective endocarditis. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1587–8) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 51-year-old man with a past history of drug addiction and chronic hepatitis C was admitted to the hospital with fever and acute prostration. Cardiac examination demonstrated a high-pitched grade III/VI systolic murmur that radiated throughout the precordium and no diastolic murmur. The lungs were clear. Janeway lesions and Osler nodules were evident, as well as brain, liver, kidney, and spleen embolization noted on a computed tomography scan. The electrocardiogram showed sinus rhythm at 98 beats/min with no other significant abnormalities. Transthoracic echocardiography revealed nondilated cardiac chambers and normal wall motion and left ventricular (LV) function. A vegetation attached to the aortic valve was evident (Figures 1A and 1B). Severe diastolic aortic regurgitation (AR) (Figures 1C and 1D) was demonstrated by color flow Doppler imaging, fast deceleration (pressure half-time of 180 ms) on continuous wave Doppler, and an increased LV outflow tract velocity time integral (36 cm). No diastolic mitral flow reversal was evident. Transesophageal echocardiography was performed to rule out local complications and confirmed a vegetative of approximately 18-mm attached to the noncoronary cusp with severe AR. After initial antibiotic therapy and before surgery, transesophageal echocardiography was repeated and showed not only systolic but also diastolic mitral flow (Videos 1, 2, 3, and 4). Diastolic mitral regurgitation (DMR) was documented by color flow Doppler imaging (Figure 1E). Pulsed wave Doppler imaging of mitral inflow revealed a short E-wave deceleration time and DMR after the E-wave (Figure 1F).

DMR is not a common phenomenon. For it to occur, 1 of 2 conditions must be present. First, DMR occurs whenever there is a reversal of the atrioventricular pressure gradient, as in severe AR (1) or dilated cardiomyopathy (2). Second, DMR results from the absence or delay of effective LV contraction essential to mitral valve closure, as in atrioventricular block (3) and atrial tachyarrhythmias (2). Acute AR is classically associated with end-DMR (1). In our patient, DMR was observed in mid-diastole, immediately after the E-wave. This finding suggests that DMR was generated directly by overshoot backward aortic flow to the left atrium, instead of the very typical high diastolic LV pressure. Mid-DMR in atrioventricular block is reported (2). It is believed
that DMR is not hemodynamically significant. In addition, because of its relatively low velocity, DMR may be difficult to diagnose noninvasively (2).

**ADDRESS FOR CORRESPONDENCE:** Dr. Diana DeCampos, Centro Hospitalar e Universitário de Coimbra, Quinta dos Vales, 3041-801 São Martinho do Bispo, Coimbra, Portugal. E-mail: dianadecampos@icloud.com.

**REFERENCES**

1. Konka M, Kusmierczyk-Droszcz B, Wozniak O, Hoffman P. Aortic regurgitation and unusual diastolic mitral regurgitation. Eur J Echocardiogr 2008;9:709–11.

2. Sisu RC, Vinereanu D. Different mechanisms for diastolic mitral regurgitation illustrated by three comparative cases. Echocardiography 2011;28:476–9.

3. Agmon Y, Freeman WK, Oh JK, Seward JB. Diastolic mitral regurgitation. Circulation 1999;99:e13.

**ABBREVIATIONS AND ACRONYMS**

**AR** = aortic regurgitation

**DMR** = diastolic mitral regurgitation

**LV** = left ventricular

**KEY WORDS** aortic valve, echocardiography, endocarditis, insufficiency, mitral valve

**FIGURE 1** Transesophageal Echocardiography

(A and B) Vegetation attached to the noncoronary cusp (arrows). (C and D) Severe aortic regurgitation. (E) Color Doppler showing diastolic mitral regurgitation (arrow). (F) Pulsed waved Doppler of the mitral valve: 1, E-wave; 2, A-wave; 3, systolic mitral regurgitation; 4, diastolic mitral regurgitation.

**APPENDIX** For supplemental videos,
ABSTRACT

The purpose of this series was to improve assessment of the aortic valve by echocardiography and to encourage echocardiographers to assess the cause of aortic regurgitation. The study illustrates the use of the Carpentier classification system for classifying the causes of regurgitation with a case series. (Level of Difficulty: Intermediate.)

PRESENTATION

CASE 1. A 38-year-old man with a history of poorly controlled hypertension, end-stage renal disease on dialysis, and pulmonary embolism taking warfarin therapy was admitted with congestive heart failure. Transthoracic echocardiography (TTE) performed on hospitalization day 3 showed moderate concentric left ventricular (LV) hypertrophy with an LV ejection fraction (LVEF) of 35%. There was moderate to severe AR as they do MR by using the Carpentier classification system (Table 1).
ventriculooaortic junction (VAJ) were normal in size (Figures 1A and 1B, Video 1). The sinotubular junction (SJ) was enlarged and effaced with dilation of the ascending aorta (AAo) (Figures 1A and 1B) and central AR (Figures 1C and 1D). Given the normal aortic cusp motion and the presence of SJ and AAo dilation, this patient’s AR was classified as Type Ia.

**CASE 2.** A 70-year-old man with a history of renal cell carcinoma status post-nephrectomy, hypertension, cerebrovascular accident, and remote myocardial infarction was referred to the cardiology clinic for aortic root dilation and AR. His only symptom was fatigue. A TTE followed by transesophageal echocardiography (TEE) revealed Type Ib AR (Figure 2, far left panel) with normal AV leaflets and dilation of the SoV and SJ (Figure 2A, Video 2). There was moderate AR by vena contracta (58 mm) (Figure 2B). The VAJ was within normal limits (Figure 2C), whereas the AAo measured 45 mm, 65 mm from the VAJ. His LVEF was 55% to 60%.

**CASE 3.** A 67-year-old man with a history of hypertension was being evaluated in the electrophysiology clinic for recent onset palpitations. A TTE showed Type Ic AR (Figure 3, far left panel) with normal AV leaflets and dilation of the VAJ (Figure 3A). The SoV size was borderline normal, and the SJ and AAo sizes were also normal (Figure 3B). There was severe AR (Figure 3C)

**CASE 4.** A 31-year-old male construction worker with a history of chronic severe AR was seen in the cardiology clinic for worsening shortness of breath. A TEE was performed as part of his work-up for possible AV repair. This patient’s condition was an example of Type Id AR (Figure 4, far left panel). The SoV, SJ, and VAJ were within normal limits (Figures 4A and 4B), but there was clear perforation of the noncoronary cusp (Figures 4C and 4D, blue arrows, Video 3). This was seen on the 2-dimensional (2D) mid-esophageal short-axis view of the AV (Figures 4E and 4F, blue arrow), on the 3D narrow-angle imaging captured in end-systole (Figure 4G, blue arrow), and on 3D color Doppler imaging, also captured in end-systole (Figure 4H, blue arrow).

**CASE 5.** A 49-year-old man with a history of hypertension, diabetes, and hyperlipidemia with asymptomatic chronic AR (until the current admission when he presented with congestive heart failure). The patient’s TEE was obtained to determine the mechanism of AR. This patient’s condition is an example of Type II AR (Figure 5, far left panel), associated with excess leaflet motion. The SoV, SJ, and VAJ were dilated (Figure 5A). There was prolapse of the right coronary cusp (Figures 5B and 5C, yellow R, Video 4). The resultant AR was eccentric and directed toward the anterior mitral valve leaflet (Figure 5D). The predominant cause of AR was right coronary cusp prolapse (Type II) with associated Type I disease.

**CASE 6.** A 67-year-old healthy man with asymptomatic chronic moderate AR was being followed on a regular basis until he developed a drop in LVEF on TTE. A TEE was ordered to better assess AR severity. The TEE revealed Type III severe AR (Figure 6, far left). The SoV was mildly dilated. The SJ and VAJ were normal in size (Figure 6A). The AAo was 42 mm (mildly dilated). The AV leaflets were thickened and restricted on 2D imaging (Figure 6B), resulting in malcoaptation and AR (Figure 6C). The leaflet thickening and restriction was clearly observed on the 3D narrow-angle image taken in end-diastole (Figure 6D).

### Table 1: Carpenter Classification of Aortic Regurgitation

| AR Type | Aortic Annulus | Sinus of Valsalva | Sinotubular Junction | Ascending Aorta | Other |
|---------|----------------|-------------------|----------------------|----------------|-------|
| Normal Leaflets | | | | | |
| Type Ia | -- | -- | ↑↑ | ↑↑ | -- |
| Type Ib | -- | ↑↑ | ↑↑ | -- | -- |
| Type Ic | ↑↑ | -- | -- | -- | -- |
| Type Id | -- | -- | -- | -- | Perforation |
| Type II | -- | -- | -- | -- | Cusp prolapse |
| Type III | -- | -- | -- | -- | Cusp restriction |

-- Denotes that the measurement could be increased/decreased or normal.
AR = aortic regurgitation.
Figures 6E to 6G show systolic frames of the AV from the aortic perspective (Figure 6E), the LV outflow tract perspective (Figure 6F), and with 3D color Doppler from the aortic perspective (Figure 6G).

All 3D narrow-angle datasets (Figures 6D to 6F, Video 5) confirmed thickening of the free margin on the leaflets. Normally, aortic leaflets are thin and difficult to image on 3D. Here the leaflets were not
translucent and were seen in their entirety on 3D imaging due to the abnormal thickening. A 3D color Doppler confirmed the fact that the origin of the AR was the area of malcoaptation (Figure 6G), which seems to be in the middle of all 3 leaflets.

DISCUSSION

The AV is part of the aortic root (Figure 7). The VAJ forms the basal attachment of the AV cusps and denotes the aortic annulus. The SJ forms the proximal
The valve leaflets extend from the aortic annulus to the SJ within the SoV in a “crown-like” formation. Type Ia AR is characterized by dilation of the SJ, Type Ib AR by dilation of the SoV and SJ, whereas dilation of the VAJ is noted in Type Ic AR. Note that dilation of the AAo alone will not cause AR unless it is coupled with dilation of the SJ. Type Id AR is associated with leaflet perforation. Type II is due to excessive leaflet motion (e.g., prolapse) or loss of commissural integrity and type III AR to leaflet restriction and sometimes commissural fusion (e.g., bicuspid aortic valve disease, rheumatic aortic valve disease).

Application of the Carpentier classification system to the dysfunctional MV has improved interdisciplinary communication and decision making regarding options for managing MR. Recent surgical studies have supported the use of the Carpentier
classification system for AR, suggesting that it could help the surgeon optimize the selection of repair techniques and predict the durability of these techniques (1,3). Both Types I and II AR have been shown to have better post-repair outcomes than Type III AR, suggesting that leaflet restriction causing AR is the most challenging type to repair.

**CONCLUSIONS**

As imagers, we spend less time characterizing AR lesions than we do MR lesions. The Carpentier classification illustrated with cases here was pioneered by surgeons in the operating theater to help guide AV repair. Adopting this schema in echocardiography laboratories for AR could help unify the way we report classifications of AR and advance the way we think about this lesion.

**ADDRESS FOR CORRESPONDENCE:** Dr. Karima Addetia, Section of Cardiology, University of Chicago Medical Center, 5842 South Maryland Avenue, MC 9067, Chicago, Illinois 60637. E-mail: kaddetia@medicine.bsd.uchicago.edu.

---

**REFERENCES**

1. Boodhwani M, de Kerchove L, Glineur D, et al. Repair-oriented classification of aortic insufficiency: impact on surgical techniques and clinical outcomes. J Thorac Cardiovasc Surg 2009;137:286–94.

2. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303–71.

3. le Polain de Waroux JB, Pouleur AC, et al. Functional anatomy of aortic regurgitation: accuracy, prediction of surgical repairability, and outcome implications of transesophageal echocardiography. Circulation 2007;116 Suppl: I264–9.

**KEY WORDS** aortic regurgitation, Carpentier classification, echocardiography, mechanisms of aortic regurgitation

**APPENDIX** For supplemental videos, please see the online version of this paper.
Ventricular Septal Rupture Complicating Delayed Acute Myocardial Infarction Presentation During the COVID-19 Pandemic

Said Alsidawi, MD, Alex Campbell, MD, Ashenafi Tamene, MD, Santiago Garcia, MD

ABSTRACT

The rate of mechanical complications of acute myocardial infarction has declined. Recent publications raised concerns over the reduction in cardiac catheterization laboratory activation for ST-segment myocardial infarction (STEMI) during the coronavirus disease-2019 (COVID-19) pandemic. We present 2 recent cases of ventricular septal rupture in patients who presented to our institution with delayed STEMI. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1595–8) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Primary percutaneous coronary intervention remains the gold standard for the management of patients presenting with ST-segment elevation myocardial infarction (STEMI) (1). Timely intervention reduces mechanical complications such as ventricular septal rupture, free wall rupture, papillary muscle rupture, or systolic cardiomyopathy.

The rate of mechanical complications of acute myocardial infarction has declined significantly with timely percutaneous coronary intervention (2).

Recent publications raised concerns over the reduction in cardiac catheterization laboratory activation for STEMI in the United States (3) and Spain (4) during the coronavirus disease-2019 (COVID-19) pandemic. Many factors were suggested to play a role in this, mainly patients’ hesitance to present to the emergency department (ED) under the concern of contracting COVID-19, as well as, health care workers’ fear of contracting the disease from direct patient care.

With the delay in presentation of patients with STEMI, the rate of mechanical complications is expected to increase. We present 2 recent cases of...
ventricular septal rupture in patients who presented to our institution with delayed STEMI.

**PATIENT #1**

A 67-year-old woman with prior left circumflex stenting developed chest pain at rest, which was not improved with nitroglycerine. She delayed seeking medical attention because of concern of contracting COVID-19 in the ED. After 14 h of pain, she presented to the ED where she was found to have inferior ST-segment elevation with Q waves (Figure 1). She was taken to the catheterization laboratory where her dominant right coronary artery was totally occluded (100% occlusion of the mid-segment with Thrombolysis In Myocardial Infarction [TIMI] flow grade 0) (Figure 2). Despite crossing the occlusion with the wire and aggressive aspiration thrombectomy, there was no return of flow (TIMI flow grade 0) and a stent was not implanted due to resolution of chest pain and late presentation. Troponin I peaked at 44 (μg/l). Echocardiogram suggested an ejection fraction of 50% with hypokinesis of the inferior and infero-septal myocardium. She was discharged home 3 days later.

Five days later, she re-presented to the ED with recurrent chest pain, shortness of breath, and hypotension with a blood pressure of 85/40 mm Hg and a heart rate of 105 beats/min. Her physical examination was consistent with a holo-systolic murmur heard across the precordium. Her electrocardiogram was unchanged and repeat echocardiogram showed an ejection fraction of 50% with an apical ventricular septal rupture with left-right shunting and pulmonic/systemic flow for shunt calculation (QP/QS): 1.6/1 (Video 1). Echo with Definity (Lantheus Medical Imaging) showed a complex interventricular septal rupture (Video 2).

Given persistent hypotension and shortness of breath, she was taken to the operating room and underwent complex ventricular septal repair (large part of the septum was necrotic). Postoperatively she developed severe right ventricular dysfunction and required implantation of a right ventricular assist device. She remains critically ill in the intensive cardiac care unit.

**PATIENT #2**

A 62-year-old woman with hypertension and advanced multiple sclerosis developed substernal chest pain 4 days before her presentation, associated
with dyspnea and a low-grade fever. Given the concern of contracting COVID-19, she did not present for medical care. The day of her presentation, she developed acute worsening of dyspnea and weakness. In the ED she was found to be hypotensive with a blood pressure of 87/55 mm Hg and a heart rate of 115 beats/min. She had a systolic thrill on cardiac examination and cool extremities. Electrocardiogram showed anterior ST-segment elevation with Q waves consistent with subacute infarct in the left anterior descending (LAD) artery territory (Figure 3). Echocardiogram (Videos 3 and 4) showed large LAD wall motion abnormality with an ejection fraction of 35% along with an apical ventricular septal rupture and a QP/QS of 1.5/1. The patient elected for noninvasive management due to severe debilitation from her multiple sclerosis and transitioned to hospice care. Her COVID-19 test done in the ED returned negative.

CONCLUSIONS

The cardiovascular community has made significant progress toward reducing cardiovascular morbidity and mortality in the past decades (5). The fear of contracting COVID-19 infection, although justified, will likely result in an increase in non-COVID morbidity and mortality caused by avoidance of the medical system. A significant increase in 911 calls and cardiac arrest at home was noted in areas highly

FIGURE 2 Patient #1 Angiogram

Right coronary artery selective angiography showing completely occluded vessel in the mid-segment.

FIGURE 3 Patient #2 Electrocardiogram

Electrocardiogram from the second patient consistent with ST-segment elevation in the anterior leads with Q waves present.
affected by COVID-19 (6). We suspect many of these deaths are related to untreated cardiovascular emergencies, as illustrated by our 2 cases. The total effect will be difficult to measure until after the pandemic, but in the meantime, it is imperative to educate the public and develop systems of care that minimize delays and maintain high quality. Rapid testing and wider availability of personal protective equipment may facilitate achievement of these goals.

**ADDRESS FOR CORRESPONDENCE:** Dr. Said Alsidawi, Minneapolis Heart Institute at Abbott Northwestern Hospital, 800 East 28th Street, Minneapolis, Minnesota 55407. E-mail: Saidalsidawi@hotmail.com.

**REFERENCES**

1. O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.

2. Elbadawi A, Elgendy IV, Mahmoud K, et al. Temporal trends and outcomes of mechanical complications in patients with acute myocardial infarction. J Am Coll Cardiol Intv 2019;12:1825.

3. Garcia S, Albaghdadi MS, Meraj PM, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am Coll Cardiol 2020;75:2871–2.

4. Rodríguez-Leor O, Cid-Alvarez B, Ojeda S, et al. Impacto de la pandemia de COVID-19 sobre la actividad asistencial en cardiología intervencionista en España. REC Interv Cardiol 2020;2:82–9.

5. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. Deaths from coronary disease, 1980-2000. N Engl J Med 2007;356:2388–98.

6. Deaths from cardiac arrest have surged in New York City. Available at: https://www.economist.com/graphic-detail/2020/04/13/deaths-from-cardiac-arrests-have-surged-in-new-york-city. Accessed April 26, 2020.

**KEY WORDS** mechanical complications, septal rupture, STEMI

**APPENDIX** For supplemental videos, please see the online version of this paper.
Delayed Presentation of STEMI Complicated by Ventricular Septal Rupture in the Era of COVID-19 Pandemic

Taha Ahmed, MD, Ashoka Nautiyal, MD, Samir Kapadia, MD, Steven E. Nissen, MD

ABSTRACT

A significant concern in current coronavirus disease-2019 (COVID-19) pandemic era is delay in first medical contact in patients with ST-segment elevation myocardial infarction (STEMI), due to reluctance to visit the hospital. We report a case of delayed presentation of STEMI as ventricular septal rupture during the COVID-19 pandemic, a rare presentation in the current age of primary percutaneous coronary intervention. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1599–602) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

On March 14, 2020, a 65-year-old man presented to the emergency department with shortness of breath. The current symptoms started gradually 3 days before and worsened, prompting him to call the emergency medical squad. On presentation, the patient had tachycardia (heart rate of 115 beats/min), normal blood pressure of 117/90 mm Hg, tachypnea (respiratory rate of 24 breaths/min), and a temperature of 98.2°F. Physical examination revealed the patient to be in respiratory distress, and a grade 3/6 holosystolic murmur was heard over the left sternal border on chest auscultation. The electrocardiogram (ECG) revealed ST-segment elevation in leads II, III, and aVF with small Q waves (Figure 1). High-sensitivity troponin was elevated to 1,506 ng/l (normal <12 ng/l), and the patient was immediately transferred to the cardiac catheterization laboratory.

PAST MEDICAL HISTORY

Past medical history was significant for a 60-pack-year history of cigarette smoking. He had not seen a physician for many years and had no prior cardiac evaluation. The patient recalled an episode of severe left-sided chest pain while performing push-ups...
7 days before admission, which resolved after he stopped. He was reluctant to visit the hospital and getting exposed to the ongoing viral pandemic, hence stayed at home, and the pain abated on its own. Family history was also remarkable for heart disease in both parents in their 50s.

**DIFFERENTIAL DIAGNOSIS**

Differential diagnosis incudes ST-segment elevation myocardial infarction (STEMI), takotsubo cardiomyopathy, acute pericarditis/myocarditis, hyperkalemia, pulmonary embolism, and Prinzmetal’s angina.

**INVESTIGATIONS**

Repeat ECG revealed persistence of ST-segment elevation with Q waves in leads II, III, and aVF. Complete blood count and basic metabolic panel were unremarkable. N-terminal pro-B-type natriuretic peptide was elevated to 3,231 pg/ml (normal <125 pg/ml). Creatine kinase and creatine kinase-myocardial band fractions were within normal limits, and troponin T was elevated to 1.2 ng/ml (normal 0 to 0.029 ng/ml) and trended downward on repeat testing. Coronavirus testing via nasopharyngeal swab was negative.

Left heart catheterization revealed a completely occluded right coronary artery (RCA) at the mid-segment (Video 1). Because no antiplatelet agents were administered before the catheterization, the patient was maintained on a bivalirudin drip.

**MANAGEMENT**

The RCA lesion was difficult to cross because the lesion appeared hard and fibrotic, but eventually, the lesion was successfully crossed, and a wire placed in the distal RCA. Owing to the difficulties encountered while crossing, it was elected to perform balloon angioplasty with the smallest balloon available. Three inflations were performed using a 1.5 × 10-mm balloon with no change in the intraprocedural ECG. Dye injection with balloon pullback revealed extravasation of contrast involving what appeared to be the trabeculae of the right ventricle, with delayed washout (Video 2). Bivalirudin was discontinued, and 50 mg of intravenous protamine administered. Repeated injections were administered, and eventually after 10 min, no further extravasation was noted. The patient was hemodynamically stable with no hypotension, chest pain, arrhythmias, or heart block.
A transthoracic echocardiogram (TTE) was performed, which did not show a pericardial effusion, but instead, revealed a large ventricular septal defect involving the distal interventricular septum with moderate tricuspid regurgitation (Figure 2). A pulmonary artery (PA) catheter was placed in the right heart with measurements of hemodynamics and cardiac chamber pressures. Cardiac output was measured using the Fick’s principle. Right heart catheterization showed an elevated PA pressure, a PA oxygen saturation level of 77.9%, and a Qp/Qs ratio of 4.6 (Table 1).

The case was concluded, the PA catheter was removed, and via the pigtail catheter, a ventriculogram obtained in the left anterior oblique projection confirming large left-to-right shunt (Video 3). The patient subsequently underwent a computed tomography scan of his chest revealing large 2.5-cm ventricular septal rupture (VSR) in the mid-inferoseptum with thinning of the basal and mid-inferior wall and inferoseptum (Figure 3).

DISCUSSION

There has been a decrease in admissions for STEMI during the coronavirus disease-2019 (COVID-19) pandemic. The Interventional Cardiology Association of the Spanish Society of Cardiology reported a 40% reduction in cases of interventions with STEMI across Spain (1). Recently, Garcia et al. (2) quantified and analyzed STEMI activations for 9 high-volume cardiac catheterization laboratories in the United States from January 1, 2019, to March 31, 2020, with the time period after March 1, 2020, classified as “after COVID” for comparative analysis. This analysis during the early phase of the COVID-19 pandemic showed an estimated 38% reduction in the cardiac catheterization laboratory STEMI activations. An avoidance of medical care due to social distancing, concerns of contracting COVID-19 in the hospital, STEMI misdiagnosis, and increased use of pharmacological reperfusion due to COVID-19 has been the commonly attributed etiologies for a decrease in STEMI primary interventions (2). We presume our patient likely had the index myocardial infarction (MI) 7 days before presentation with a delayed presentation with a post-infarction VSR.

VSR is a devastating complication following acute MI, and its incidence has decreased from 1% to 3% following STEMI in the pre-reperfusion era to 0.17% to 0.31% following primary percutaneous coronary intervention (3). The Becker and van Mantgem classification is the most commonly accepted, and our patient exhibited a Becker type 3 rupture, which results from perforation of thinned aneurysmal myocardium in the late-phase post-MI and frequently in the absence of reperfusion injury (4). VSR in such cases occurs subacutely, typically 3 to 5 days after an index MI. The RCA is the most common infarct-related artery, accounting for 46% of total cases of VSR (5). VSRs are known to cause left-to-right shunting, and right ventricular volume and pressure overload. TTE is essential to diagnose the presence, size, and impact of the VSR and exclude other etiologies in cases of hemodynamic

TABLE 1 Right Heart Catheterization

| Parameter                                         | Value         |
|---------------------------------------------------|---------------|
| Aortic pressure, systolic/diastolic (mean), mm Hg | 87/62 (74)    |
| Right ventricle pressure, systolic/diastolic (mean), mm Hg | 50/18 (22) |
| Pulmonary artery pressure, systolic/diastolic (mean), mm Hg | 48/21 (34) |
| Right atrium pressure, mean, mm Hg                | 16            |
| Pulmonary capillary wedge pressure, mean, mm Hg   | 22            |
| Pulmonary blood flow, Qp, l/min                   | 14.34         |
| Systemic blood flow, Qs, l/min                    | 3.07          |
| Qp/Qs ratio                                       | 4.6           |
compromise. In occasions with unexplained hemodynamic compromise in the cardiac catheterization laboratory, left ventriculography can help confirm the presence of VSR, as exhibited by our case. Pulmonary artery catheterization reveals a step-up in oxygen saturation in the right ventricle and can be used to calculate the Qp/Qs, as was performed in our case. Surgical repair is the definitive treatment of choice and was adapted for our patient with good post-surgical recovery (6).

**FOLLOW-UP**

The patient was transferred to the cardiac intensive care unit, and an intra-aortic balloon pump was inserted to reduce shunting and improve forward flow. Cardiothoracic surgery was consulted, and the patient underwent coronary artery bypass grafting of the posterior descending coronary artery, and a patch repair of the VSD with a tricuspid annulus repair. The patient tolerated the procedure well and was weaned off the balloon pump support within 48 h. Post-operative TTE showed a left ventricular ejection fraction of 40% with a residual VSR; however, a subsequent right heart catheterization ruled out any residual shunt. The patient was discharged home on post-operative day 10 with cardiology follow-up as an outpatient.

**CONCLUSIONS**

In the current scenario of the COVID-19 pandemic, there has been a considerable decrease in STEMI volume. Physicians should be prepared to encounter late complications of STEMI such as VSR, which is a rare presenting encounter in the era of primary percutaneous intervention.

**ADDRESS FOR CORRESPONDENCE:** Dr. Taha Ahmed, Department of Internal Medicine, Cleveland Clinic Foundation (Fairview), 18101 Lorain Avenue, Cleveland, Ohio 44111. E-mail: tahaahmedfairview@gmail.com.

**REFERENCES**

1. Rodríguez-Leor O, Alvarez-Álvarez B, Ojeda S, et al. Impacto de la pandemia de COVID-19 sobre la actividad asistencial en cardiología intervencionista en España. REC Interv Cardiol 2020;2:82-9.

2. García S, Albaghadi MS, Menaj PM, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am Coll Cardiol 2020;75:2871-2.

3. Jones BM, Kapadia SR, Smedira NG, et al. Ventricular septal rupture complicating acute myocardial infarction: a contemporary review. Eur Heart J 2014;35:2060-8.

4. Honda S, Asaumi Y, Yamane T, et al. Trends in the clinical and pathological characteristics of cardiac rupture in patients with acute myocardial infarction over 35 years. J Am Heart Assoc 2014;3:e000984.

5. Menon V, Webb JG, Hillis LD, et al. Outcome and profile of ventricular septal rupture with cardiogenic shock after myocardial infarction: a report from the SHOCK Trial Registry. J Am Coll Cardiol 2000;36 Suppl 1:1110-6.

6. Arnaoutakis GJ, Zhao Y, George TJ, Sciortino CM, McCarthy PM, Conte JV. Surgical repair of ventricular septal defect after myocardial infarction: outcomes from the Society of Thoracic Surgeons National Database. Ann Thorac Surg 2012;94:436-43.

**KEY WORDS** coronavirus disease-2019, COVID-19, pandemic, ST-segment elevation myocardial infarction, ventricular septal rupture

**APPENDIX** For supplemental videos, please see the online version of this paper.
MINI-FOCUS ISSUE: SCAI

CASE REPORT: CLINICAL CASE

Subacute Left Ventricular Free Wall Rupture after Delayed STEMI Presentation During the COVID-19 Pandemic

Remo Albiero, MD, Giuseppe Seresini, MD

ABSTRACT

The coronavirus disease-2019 (COVID-19) pandemic is causing delayed ST-segment elevation myocardial infarction (STEMI) presentations associated with now unusual postinfarction complications. We describe a delayed (5-day) STEMI presentation because the patient feared contracting COVID-19 in the hospital. The patient experienced an extensive anterolateral STEMI complicated by subacute left ventricular free wall rupture that required a rapid surgical repair. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1603–9) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 72-year-old man came to emergency services on April 2020 after an episode of severe chest pain. He reported a similar episode 5 days before, and recurrent short similar episodes over the next 4 days. He never called emergency services for fear of contracting coronavirus disease-2019 (COVID-19). At first contact, his blood pressure was 85/50 mm Hg, and his heart rate 100 beats/min. Examinations of his heart and lungs were unremarkable.

LEARNING OBJECTIVES

- COVID-19 may contribute to delayed presentations of acute myocardial infarction.
- Delayed presentation with late reperfusion is associated with an increased risk of LVFWR.
- When a high suspicion arises for an impending LVFWR in a patient recovering from extensive anterolateral transmural myocardial infarction, an early diagnosis and surgical repair initiated promptly can make a substantial difference in the outcome of this sometimes fatal complication.

MEDICAL HISTORY

The patient had no cardiovascular risk factors, no individual history, and no family history of cardiovascular disease, and was not taking any medications or drugs.

DIFFERENTIAL DIAGNOSIS

No other diagnosis was possible, as the presentation was clearly an ST-segment elevation myocardial infarction (STEMI).
INVESTIGATIONS

The first contact electrocardiogram (ECG) was indicative of an extensive anterolateral STEMI (Figure 1A), therefore the patient was brought to the hospital to perform a primary percutaneous coronary intervention (PCI). Pertinent laboratory findings on admission and in the next 4 days are shown on Table 1. The transthoracic echocardiogram (TTE) on admission (Figure 2A, Video 1) demonstrated akinesia of the left ventricle (LV) anterolateral-apical wall, a large apical mural thrombus, severe LV dysfunction with an ejection fraction of 25%, mild-to-moderate circumferential pericardial effusion, diastolic right ventricle (RV) (Figure 2B) and systolic right atrium (RA) collapse (Figure 2A, Video 1). Coronary angiography showed proximal left anterior descending (LAD) artery occlusion (Figure 3A) and the remaining coronary arteries were normal.

MANAGEMENT

Primary PCI was performed. After manual thrombectomy, a stent was implanted at the LAD ostium with good final result (Figure 3B, Video 2). After PCI, the patient became asymptomatic. He remained asymptomatic, hemodynamically stable, with normal blood pressure and regular heart rate for the next 4 days,
receiving medical therapy with aspirin, ticagrelor, intravenous (IV) heparin, diuretics, and a beta-blocker. As shown in Figure 1B, ECGs recorded after PCI from day 1 until day 5 demonstrated persistent ST-segment elevation, indicative of an aneurysmatic evolution. The TTE performed on day 4 (Figure 2C, Video 3) confirmed the presence of an aneurysmatic expansion of the anterolateral and apical LV walls. In addition, TTE showed mild worsening (ejection fraction ~20%) of the already severely depressed LV function, mild reduction of both LV apical thrombosis and pericardial effusion, and the presence of an intramyocardial dissecting hematoma (Figure 3A to 3F, Video 4). Cardiac CT scanning with IV contrast revealed the presence of an aneurysmatic expansion of the anterolateral and apical LV walls (Figure 4, Videos 5 and 6). At that point, it was evident that the patient had an impending LVFWR. On day 5, the patient was transferred to the cardiac surgery department for rapid surgical repair (3). However, because the patient was asymptomatic and was receiving dual antiplatelet therapy and had minimal pericardial effusion and was a high surgical risk, the cardiac surgeons opted for initial short conservative management. In the meantime, a sudden cardiac arrest occurred on day 8 that required an emergency open-heart surgery repair. In the operating room, an “oozing-type” LVFWR was detected in the aneurysmatic anterolateral wall, which was very thin. It was repaired with a polyethylene terephthalate patch (Dacron, Dupont, Wilmington, Delaware) fixed onto the myocardial surface with surgical adhesive (BioGlue, CryoLife, Kennesaw, Georgia). Intra-aortic balloon pump (IABP) counterpulsation was started immediately after operation.

**DISCUSSION**

The coronavirus disease-2019 (COVID-19) pandemic may contribute to patients’ delayed presentations of STEMI for fear of contracting the infection in the hospital. A delayed presentation is associated with extensive myocardial necrosis and worse outcomes (4). In addition, a delayed presentation increases the probability of mechanical ventricular complications including LVFWR, ventricular septal defect, and acute papillary muscle rupture. These severe mechanical complications carry a high mortality. LVFWR occurs up to 10 times more frequently than septal or papillary muscle rupture. It usually occurs unexpectedly before the fifth day after STEMI (5) and is almost always fatal. Relatively few cases of LVFWR are diagnosed before death. In a multinational Global Registry of Acute Coronary Events registry, one of the largest studies, the incidence of LVFWR was 0.2% with an in-hospital mortality of 80% (6). Late patients with STEMI who present late face a worse risk profile and prognosis than patients who arrive <12 h from onset of symptoms. A 20-fold higher increase of myocardial rupture (4.1% vs. 0.2%, respectively; p < 0.001) has been reported in late-presenting STEMI patients by Cerrato et al. (4). The clinical suspicion of an impending LVFWR should be considered in patients recovering from a transmural myocardial infarction (MI) presenting with persistent ST-segment elevation, pericardial effusion, and an expanding LV aneurysm. LVFWR is an extreme form of infarct expansion during the early phase of STEMI. Defective infarct healing, as well as left ventricular wall stress, plays a major role in infarct expansion and may play an important role in the development of LVFWR. The myocardium is vulnerable to wall stress in the first week after infarction. In the present patient (Table 1), suspicion of LVFWR was supported by the disproportionate elevation of C-reactive protein levels, >20 mg/dl, and by the neutrophil-to-lymphocyte (N/L) ratio >3.7. Regarding the relationship between post-MI mechanical complications and inflammation,

| TABLE 1 Patient Laboratory Values on Admission and During Hospitalization |
|---------------------------------|--------|--------|--------|--------|--------|
| Normal Value                   | Range  | Day 1  | Day 2  | Day 3  | Day 4  |
| AST, U/l                        | 3-40   | 840    | 522    | 208    | 125    | 66 |
| ALT, U/l                        | 3-37   | 1129   | 979    | 700    | 628    | 425 |
| LDH, U/l                        | 120-240| 1549   | NR     | 644    | NR     | NR |
| ALT/LDH ratio                   | >1.50  | 0.73   | NR     | 1.09   | NR     | NR |
| TB, mg/dl                       | 0.30-1.00| 1.60 | 1.03   | 1.01   | NR     | NR |
| CK, U/l                         | 30-200 | 340    | NR     | 131    | 97     | 97 |
| Troponin I HS, ng/l             | 0.0-34.2| 32,906.0| 26,710.8| 20,079.3| NR     | NR |
| CRP, mg/l                       | 0.0-5.0| 177.1  | 156.0  | 129.9  | 113.3  | 114.2 |
| WBC, 10^3/μl                    | 4.0-10.0| 15.63  | 14.78  | 15.57  | 16.77  | 20.03 |
| Neutrophil number, 10^3/μl      | 1.90-8.00| 13.27 | 11.85  | 13.59  | 13.15  | 17.01 |
| Lymphocyte number, 10^3/μl      | 1.00-4.00| 1.11  | 1.92   | 1.88   | 2.25   | 1.28 |
| N/L ratio                       | <3.7   | 11.95  | 6.17   | 7.23   | 5.84   | 13.28 |
| aPTT ratio                      | 0.80-1.20| 1.28  | 1.56   | 1.93   | 1.92   | 1.97 |
| Hemoglobin, g/dl                | 13.0-17.0| 13.5  | 11.4   | 12.3   | 13.4   | 14.1 |
| Creatinine, mg/dl               | 0.73-1.18| 1.07  | 0.99   | 0.91   | NR     | NR |
Anzai et al. (7) found C-reactive protein levels >20 mg/dl to be an independent predictor of cardiac rupture after the first STEMI (7). Pieck et al. (8) evaluated the levels of neutrophil and lymphocyte, 2 independent markers of inflammation, and showed that STEMI patients with LVFWR had increased N/L ratios. The use of these inflammatory markers has been proposed for predicting postinfarction LVFWR (8). Thus, STEMI patients with a disproportionate elevation of C-reactive protein levels >20 mg/dl and/or an elevated N/L ratio >3.7 should be followed more closely in terms of mechanical complications. In the present patient, the suspicion of impending LVFWR was reinforced by the angiographic presence of a

Admission echocardiogram in 4-chamber (A) and parasternal long-axis views (B) showing left ventricular (LV) apical mural thrombus, mild circumferential pericardial effusion, systolic right atrial (RA) (A, arrow) and diastolic right ventricular (RV) (B, arrow) collapse. Echocardiogram performed on day 4 shows (C) mild reduction in LV apical thrombus and pericardial effusion with expansion (arrowheads) of the anterolateral apical LV wall, and (D) a ruptured LV false tendon (dashed arrow).
diffuse dynamic systolic severe compression of the mid-distal LAD which was described as the first clue of a postinfarction mechanical complication and pseudoaneurysm formation by Kadavath et al. (1). The suspicion of LVFWR was finally confirmed by cardiac CT that detected an intramyocardial dissecting hematoma (2). In a percentage of STEMI patients, LVFWR does not occur as a sudden, explosive, and fatal episode but as an insidious, progressive entity. This “subacute” rupture, classified as an “oozing” type, is characterized by a small rupture or leakage through a friable aneurysm that may leak blood into the LV wall creating a subepicardial hematoma before massive rupture ensues (3). In this particular subgroup of patients, when diagnosis is suspected, surgical treatment is possible and must be initiated promptly to be lifesaving (3). In this patient, in whom the impending LVFWR was diagnosed on day 5 but
surgery was delayed until day 8, an earlier surgery would have possibly decreased his risk of death.

Up to now, few data are available about the risk of LVFWR after revascularization by PCI in patients with late STEMI presentation. The indication to perform primary PCI in this patient was based on European guidelines (9) indicating that, in patients presenting days after the acute event with a completed MI, those with recurrent angina may be considered for revascularization when the infarct artery is occluded. The authors observed the presence of baseline Q waves in the admission ECG (Figure 1A), which is associated with adverse outcomes in patients with STEMI (10). Primary PCI of the occluded infarct-related artery may be less beneficial or even detrimental in STEMI patients with baseline Q waves or when performed 3 to 28 days after myocardial infarction, as demonstrated in the OAT (Occluded Artery Trial) (11). It is important to note, however that, even in the presence of Q waves, most patients have successful reperfusion as measured by ST-segment resolution after primary PCI (12). Moreover, the final myocardial salvage index in STEMI patients with Q waves was been reported as substantial (13). Our patient experienced recurrent episodes of chest pain after the initial episode, suggesting that the obstructed artery might have been spontaneously recanalized and that the obstruction might have been dynamic before the final episode and therefore the “full ischemic time” and the estimation of Q wave onset were indeterminable.

**FIGURE 4** Cardiac Computed Tomography Images

Cardiac computed tomography images in long-axis (A) and short-axis (B) views show the intramyocardial dissecting hematoma into the aneurysmatic and thinner left ventricular anterolateral wall (arrows). Three-dimensional reconstruction (C) shows, in detail (D), its position (arrows).
FOLLOW-UP

After undergoing surgical repair, the patient remained critically ill and died on day 9.

CONCLUSIONS

STEMI patients with a delayed presentation during COVID-19 pandemic due to fear of contracting the infection in the hospital will experience unnecessary morbidity and mortality. Delayed presentation with late reperfusion is often associated with an increased risk of LVFWR. Early diagnosis of an impending LVFWR and the surgical repair initiated promptly are crucial, even though mortality rates are still high.

ADDRESS FOR CORRESPONDENCE:  Dr. Remo Albiero, Interventional Cardiology Unit, Cardiology Department, Sondrio Hospital, Via Stelvio, 25, 23100 Sondrio, Italy. E-mail: albiero@panvascular.com. Twitter: @RemoAlbiero.

REFERENCES

1. Kadavath S, Ayan M, Al-Hawwas M. Dynamic systolic compression of the left anterior descending coronary artery as the first clue of postinfarction left ventricular pseudaneurysm. Can J Cardiol 2019;35:e9-1419e11.
2. Bekkers BC, Prenger K, Waltenberger J. Images in cardiology: intramyocardial dissection after subacute anterior wall myocardial infarction. Heart 2005;91:e54.
3. Matteucci M, Fina D, Jiritano F, et al. Treatment strategies for post-infarction left ventricular free-wall rupture. Eur Heart J Acute Cardiovasc Care 2019;8:379-87.
4. Cerrato E, Forno D, Ferro S, Chinaglia A. Characteristics, in-hospital management and outcome of late acute ST-elevation myocardial infarction presenters. J Cardiovasc Med (Hagerstown) 2017;18:567-71.
5. Figueras J, Cortadellas J, Soler-Soler J. Left ventricular free wall rupture: clinical presentation and management. Heart 2000;83:499-504.
6. Lopez-Sendon J, Gurfinkel EP, Lopez de Sa E, et al. Factors related to heart rupture in acute coronary syndromes in the Global Registry of Acute Coronary Events. Eur Heart J 2010;31:1449-56.
7. Arzai T, Yoshikawa T, Shiraki H, et al. C-reactive protein as a predictor of infarct expansion and cardiac rupture after a first Q-wave acute myocardial infarction. Circulation 1997;96:778-84.
8. Ipek G, Onuk T, Karatas MB, et al. Relationship between neutrophil-to-lymphocyte ratio and left ventricular free wall rupture in acute myocardial infarction. Cardiology 2015;132:105-10.
9. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019;40:87-165.
10. Zheng Y, Bainey KR, Tyrell BD, Brass N, Armstrong PW, Welch RC. Relationships between baseline Q Waves, time from symptom onset, and clinical outcomes in ST-segment-elevation myocardial infarction: insights from the vital heart response registry. Circ Cardiovasc Interv 2017;10.
11. Hochman JS, Lamas GA, Buller CE, et al. Coronary intervention for persistent occlusion after myocardial infarction. N Engl J Med 2006;355:2395-407.
12. Kochar A, Granger CB. Q waves at presentation in patients with ST-segment-elevation myocardial infarction: an underappreciated marker of risk. Circ Cardiovasc Interv 2017;10.
13. Topal DG, Lonborg J, Ahtarovski KA, et al. Association between early Q waves and reperfusion success in patients with ST-segment-elevation myocardial infarction treated with primary percutaneous coronary intervention: a cardiac magnetic resonance imaging study. Circ Cardiovasc Interv 2017;10.

KEY WORDS coronary angiography, coronavirus disease-2019, left ventricular aneurysm, LVFWR, myocardial infarction, percutaneous coronary intervention, pericardial effusion

APPENDIX For supplemental videos, please see the online version of this paper.
Complication of Late Presenting STEMI Due to Avoidance of Medical Care During the COVID-19 Pandemic

Diana Otero, MD, Narayana Sarma V. Singam, MD, Neil Barry, DO, Prafull Raheja, MD, Alisya Solankhi, BS, Naresh Solankhi, MD

ABSTRACT

Patients are avoiding hospitals for fear of contracting severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). We are witnessing a re-emergence of rare complications of myocardial infarctions (MI) due to delayed revascularization. Herein, we describe a case of hemorrhagic pericarditis from thrombolytics administered to a patient with late presenting MI. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1610–3) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

PRESENTATION

A 69-year-old male presented to an outside hospital with exertional chest pain of unknown duration. His vital signs on admission were: blood pressure 99/71 mm Hg; heart rate was 66 beats/min; his oxygen saturation was 97% on room air.

Physical examination of his general appearance revealed he was in distress due to pain; his jugular vein distention was 2 cm above the clavicle; his chest was clear bilaterally; he had regular heart sounds of S1/S2, audible with no murmurs, and his extremities were warm with trace edema bilaterally.

MEDICAL HISTORY

His history included hypertension, hyperlipidemia, abdominal aortic aneurysm of 2.7 cm, uncontrolled diabetes, and tobacco use of 1 pack-year.

INVESTIGATION

Electrocardiography revealed a posterior ST-segment elevation myocardial infarction (STEMI) (Figure 1) for which he received tenecteplase, clopidogrel, and aspirin. He was airlifted to the authors’ hospital for coronary angiography due to ongoing chest pain and persistent ST-segment elevation. Angiography revealed a left-dominant system with a culprit 100% thrombotic occlusion of the left circumflex coronary artery and a nonculprit 90% proximally diseased left anterior descending artery (Figures 2 and 3, Videos 1...
and 2). Although the present authors were able to wire past the lesion, balloon angioplasty was unsuccessful due to extensive thrombus burden.

**MANAGEMENT**

An intra-aortic balloon pump was inserted, and he was transferred to the coronary care unit for medical management of a STEMI. Transthoracic echocardiography revealed a left ventricular ejection fraction of 25% (Video 3) and a small circumferential pericardial effusion with visible thrombus (Figure 4, Video 4). On further inquiry about the duration of symptoms, he admitted having chest pain for the last 6 days but had been avoiding seeking medical care due to the ongoing pandemic. Hemorrhagic pericarditis was diagnosed after treatment of the myocardial infarction (MI) with tenecteplase. His STEMI was managed with aspirin, 81 mg daily, and ticagrelor, 90 mg twice daily. Anticoagulation was avoided, and the intra-aortic balloon pump was removed the next day. He tested negative for coronavirus disease-2019 (COVID-19).

**DISCUSSION**

The COVID-19 syndrome triggered a global pandemic with more than 3 million confirmed cases to date. Hospital systems worldwide have instituted emergency protocols to limit the spread of this pandemic, and some have transitioned to fibrinolytic agents for initial management of MI, including STEMI (1). Although STEMI presentations are on the decline because patients are afraid of hospital contact (2-4), delayed revascularization poses a challenge due to re-emergence of rare MI-related complications.

A study conducted in China reported that patients with STEMI delayed seeking help out of fear of COVID-19 infection (2). Italy also revealed a decrease in MI admissions for the last several months compared to the same time frame in the previous year (3). Moroni et al. (5) described complications of STEMI in 3 Italian patients who avoided the hospital because of COVID-19 infection. One U.S. study observed a 38% reduction of STEMI activations during the early phase of the pandemic (4). Multiple studies corroborate the fact that public fear of contracting severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is leading to a decline in timely presentation of MI patients (2-4). This phenomenon has been reported before in the SARS-CoV-1, and H1N1 pandemics of 2003 and 2009, respectively (6). The present patient reported avoiding early medical care due to a fear of acquiring COVID-19 infection in the hospital. One

```latex
\textbf{FIGURE 1} 12-Lead Electrocardiography
```

A 12-lead electrocardiogram shows 4-mm horizontal ST-segment depression in leads V1 to V3, a tall broad R-wave (>30 ms) in leads V1 to V6, and an upright T-wave in lead V3. A 2-mm ST-segment elevation is observable in II, aVF, and V6. This is compatible with inferior-lateral-posterior ST-segment elevation myocardial infarction.
study suggested a significant increase in mortality during ongoing pandemic that is not fully explained by COVID-19 deaths alone (3). This raise the question of whether some patients died from undiagnosed MI.

The incidence of MI-related complications increases with delayed presentation and management (7). In addition to the common sequelae of MI (i.e., arrhythmia and heart failure), rare complications such as papillary muscle rupture, ventricular septal rupture, and pericarditis can develop from delayed management (8). Streptokinase trials from the early 1990s revealed that the incidence of early post-infarction pericarditis (first 2 to 5 days after the MI) was 20%, with a decline to 6% after thrombolytic therapy, and 4% after primary PCI. Generally, a pericardial effusion is not present in this group of patients (8). Late pericarditis (i.e., Dressler’s syndrome) develops 1 week after MI and has an incidence of 3% in the pre-revascularization era that has currently decreased to 0.1% (8). Diagnosis can be made from symptoms, diffuse ST elevations on electrocardiography, and a pericardial effusion on echocardiography (8). The risk of Dressler’s syndrome is increased after early post-MI pericarditis (8). Risk factors include late presentation (>6 h) and primary PCI failure (odds ratio: 2.8), both of which are expressions of reduced myocardial salvage or failed revascularization (8). This patient’s course was complicated by hemorrhagic pericardial effusion, likely from thrombolytic treatments and an
underlying inflamed pericardium. Hemorrhagic pericarditis has been described in case reports in patients with large transmural MI receiving thrombolytic therapy as early as 2 h after the institution of therapy (5). This complication usually evolves into tamponade with hemodynamic instability requiring pericardiocentesis (9). Fortunately, this patient’s small pericardial effusion did not require invasive therapy and was managed with avoidance of anticoagulation during his stay in the coronary care unit.

Prompt coronary vascular reperfusion has decreased the incidence of rare MI complications and has reduced mortality (7). Before the COVID-19 pandemic, approximately 13% of STEMs in the United States were managed with fibrinolytic-focused reperfusion strategies, mostly in geographically isolated areas (1). In the COVID-19 era, the American College of Cardiology still recommends PCI as the standard of care for STEMI (10). However, emergency departments are facing delays in patient triage, and similarly, cardiac catheterization laboratory activations are slowed due to extra steps required to ensure safety of the staff (2). In centers capable of performing PCI, immediate fibrinolytic administration in the emergency department may mitigate system-based delays. However, hemorrhagic pericarditis could represent a caveat to this eminent and necessary strategy, especially in cases of delayed MI.

FOLLOW-UP

Echocardiography after 6 days showed resolution of hemorrhagic pericardial effusion. The present patient successfully underwent a staged PCI of the left anterior descending artery lesion on the 10th day and was transferred to the cardiology ward before discharge on hospital day 19.

CONCLUSIONS

With the progression of this pandemic, management of MI with thrombolytics or delayed reperfusion strategies may show a re-emergence of rare complications such as post-MI pericarditis. This will be further exacerbated by patients who avoid medical care due to fear of contracting SARS-CoV-2 infection. Hemorrhagic pericarditis is a rare entity precipitated by thrombolytic drugs in late-presenting MI, which may lead to deleterious outcomes. Health care providers should continue educating patients to recognize life-threatening cardiovascular symptoms and seek timely care to avoid serious complications.

ADDRESS FOR CORRESPONDENCE: Dr. Diana Otero, University of Louisville, 201 Abraham Flexner Way, Suite 600, Louisville, Kentucky 40202. E-mail: diaaom24@gmail.com.

REFERENCES

1. Daniels MJ, Cohen MG, Bavry AA, Kumbhani DJ. Reperfusion of STEMI in the COVID-19 Era—business as usual? Circulation 2020;141:1948-50.
2. Tam CCF, Cheung KS, Lam S, et al. Impact of coronavirus disease 2019 (COVID-19) outbreak on ST-segment-elevation myocardial infarction care in Hong Kong, China. Circ Cardiovasc Qual Outcomes 2020;13:e006631.
3. De Filippo O, D’Ascenzo F, Angelini F, et al. Reduced rate of hospital admissions for ACS during covid-19 outbreak in Northern Italy. N Engl J Med 2020;383:88-99.
4. Garcia S, Albaghadi MS, Meraj PM, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am Coll Cardiol 2020;75:2871-2.
5. Morini F, Gramena M, Ajello S, Baldetti L, Vilca LM. Collateral damage: medical care avoidance behavior among patients with acute coronary syndrome during the COVID-19 pandemic. J Am Coll Cardiol Case Rep 2020;2:1620-4.
6. Yeung NY, Lau JTF, Choi KC, Griffiths S. Population responses during the pandemic phase of the influenza A(H1N1)pdm09 epidemic, Hong Kong, China. Emerg Infect Dis 2017;23:813-5.
7. Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/ACR/ASE/ASNC/SCAI/SCCT/STS 2016 appropriate use criteria for coronary revascularization in patients with acute coronary syndromes: a report of the American College of Cardiology appropriate use criteria task force. American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. J Am Coll Cardiol 2017;69:570-91.
8. Imazio M, Negro A, Belli R, et al. Frequency and prognostic significance of pericarditis following acute myocardial infarction treated by primary percutaneous coronary intervention. Am J Cardiol 2009;103:1525-9.
9. Renkin J, De Bruyne B, Benit E, Joris JM, Carlier M, Col J. Cardiac tamponade early after thrombolysis for acute myocardial infarction: a rare but not reported hemorrhagic complication. J Am Coll Cardiol 1991;17:280-5.
10. Mahmoud E, Dauerman HL, Welt FG, et al. Management of acute myocardial infarction during the COVID-19 pandemic. Catheter Cardiovasc Interv 2020 Apr 20 [E-pub ahead of print]

KEY WORDS complication, COVID-19, myocardial infarction, STEMI

APPENDIX For supplemental videos, please see the online version of this paper.
MINI-FOCUS ISSUE: SCAI

CASE REPORT: CLINICAL CASE

Misdiagnosis in the COVID-19 Era
When Zebras Are Everywhere, Don’t Forget the Horses

Rayan Yousefzai, MD, Arvind Bhimaraj, MD

ABSTRACT

We describe a patient who presented with respiratory failure, chest pain, and fever. In the COVID-19 pandemic era, the focus was diverted to the coronavirus infection, and ST-segment elevation myocardial infarction was missed. Although we need to be vigilant in the diagnosis of COVID-19, we should not forget about the common disorders. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1614–9) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 56-year-old male patient presented with shortness of breath. His symptoms started 10 days before the admission. He had a virtual visit with his primary care doctor. At that visit, he described his symptoms as shortness of breath and cough associated with dull chest pain. He also reported fatigue, myalgia, and a recorded temperature of 102°F. On further questioning, he also mentioned similar episodes of chest pain in the past, with exertion. He was started on bronchodilators and antibiotics. Three days after the virtual visit with his primary care doctor, his symptoms continued to worsen, and he decided to call 911. On presentation to the hospital, he was found to be in respiratory distress.

PAST MEDICAL HISTORY

The patient had a history of hypertension and was taking lisinopril, 20 mg daily, and hydrochlorothiazide, 12.5 mg daily. He had a 40-pack-year smoking history. He worked in different restaurants and had exposure to a large number of people.

LEARNING OBJECTIVES

- In the COVID-19 era, vigilance for timely diagnosis, isolation, and treatment of COVID-19 patients is imperative.
- However, fear should not deter us from recognizing common disorders.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included the following: acute coronary syndrome; an infectious or inflammatory process, including coronavirus disease-2019 (COVID-19); acute respiratory distress syndrome; and pulmonary embolism.
INVESTIGATIONS

The chest radiograph showed diffuse patchy airspace opacities throughout the lungs (Figure 1). Arterial blood gas measurements on presentation showed the following: pH, 7.11; arterial partial pressure of carbon dioxide (PaCO₂), 66 mm Hg; arterial partial pressure of oxygen (PaO₂), 50 mm Hg; and bicarbonate, 20.1 mmol/l. The patient was intubated. On 100% fraction of inspired oxygen (FiO₂), arterial blood gas measurements were as follows: pH, 7.02; PaCO₂, 84 mm Hg; PaO₂, 97 mm Hg; and bicarbonate, 21 mmol/l; with a PaO₂/FiO₂ ratio of 97 g. A COVID-19 polymerase chain reaction test was ordered. An electrocardiogram was done, which showed a new left bundle branch block (Figure 2), which was not present on an electrocardiogram from 2 months earlier (Figure 3). The troponin level was 56.82 ng/ml (normal range 0.00 to 0.04 ng/ml), and the B-type natriuretic peptide level was 2493 pg/ml (normal range 0 to 100 pg/ml). Echocardiography was performed, which showed severe left ventricular (LV) dysfunction with wall motion abnormalities (Figure 4, Video 1).

MANAGEMENT

On the basis of the patient’s symptoms on presentation and his history COVID-19 was suspected. The patient was intubated, but venovenous extracorporeal membrane oxygenation (ECMO) was soon considered on an emergency basis. The troponin elevation was considered a manifestation of myocarditis. Norepinephrine and vasopressin were started for hypotension. Venovenous ECMO placement was complicated by right ventricular rupture with worsening hypotension. Consequently, the patient underwent emergency placement of peripheral venoarterial ECMO followed by repair of the right ventricle and placement of a central LV vent to decompress the left ventricle. The patient was then transferred to our institution for a higher level of care. The COVID-19 polymerase chain reaction result was negative twice by this time. After arrival at our institution, he was taken to the cardiac catheterization laboratory. A coronary angiogram showed severe 99% stenosis of the mid–left anterior descending (LAD) artery with Thrombolysis In Myocardial Infarction (TIMI) flow grade 2, 60% long-segment stenosis in the proximal left circumflex artery, and a moderately diffusely diseased right coronary artery (Figures 5 to 7, Videos 2, 3, and 4).

DISCUSSION

In December 2019, an outbreak of pneumonia caused by a novel coronavirus occurred in Wuhan, China (1). The virus was identified as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which leads to COVID-19 (2). Even though the primary manifestation of COVID-19 consists of respiratory symptoms, some patients have severe cardiovascular damage (3). Patients with cardiovascular disease have an increased risk of death. Cardiovascular manifestations of patients with COVID-19 include heart failure, myocarditis, arrhythmia, and elevated troponin, which can mimic STEMI or non-ST-segment elevation myocardial infarction. In Wuhan, out of 72,312 patients, 81% had mild symptoms, 13.9% had severe symptoms requiring oxygen, and 4.7% were critically ill needing care in the intensive care unit (4). In a case series from Zhongnan Hospital of Wuhan University, the manifestation of myocardial injury included 8.7% shock, 16.7% arrhythmia, and 7.2% acute cardiac injury (5). In another series (6), 6% of the COVID-19–positive patients presented with ventricular tachycardia or ventricular fibrillation, and 27.8% had myocardial injury ascertained by elevated troponin levels.

ABBREVIATIONS AND ACRONYMS

COVID-19 = coronavirus disease-2019
ECMO = extracorporeal membrane oxygenation
LAD = left anterior descending
LV = left ventricular
STEMI = ST-elevation myocardial infarction

FIGURE 1 Chest Radiograph at Presentation

Chest radiograph shows diffuse patchy airspace opacities throughout the lungs, suggested as an infectious/inflammatory process such as multifocal pneumonia versus pulmonary edema or acute respiratory distress syndrome.
The electrocardiogram at presentation shows sinus tachycardia and a left bundle branch block.

The previous electrocardiogram shows normal sinus rhythm and an incomplete right bundle branch block.
The COVID-19 pandemic has undoubtedly alerted the cardiology community to the cardiovascular manifestations of COVID (5). The vigilance and precautions needed for patients suspected of having COVID-19 in no way should be relaxed, but fear should not preclude us from delivering appropriate care. For example, in the case of the patient we presented, before the COVID-19 era, he most likely would have been referred for a further evaluation immediately. The patient has significant risk factors for coronary artery disease, with a history suggestive of chronic angina; therefore, further investigations were warranted. In the COVID-19 era, the hesitation of patients to go to the hospital to avoid exposure, the reservation of providers to send their patients to health care facilities, and the limitation of resources have created significant barriers for evaluation. Even in the case of patients who are already admitted to the hospital, when the suspicion of COVID-19 is raised, it can affect care either by distracting providers from other diagnoses or by delaying procedures to avoid exposure. For example, in this case, while the patient was being considered for ECMO, an angiogram should have been performed, with proper protection.

Recently, the neurology community released a plea to the public not to ignore symptoms of a stroke. We also send out a plea to the cardiology community to do the same and to be vigilant about the common cardiac-related diagnosis that we may mislabel in the COVID-19 era.

**FOLLOW-UP**

Because the patient had completed the LAD artery infarct (Figure 8), the decision was made against LAD artery revascularization. The patient was taken to the operating room, an Impella 5.5 device (Abiomed, Danvers, Massachusetts) was placed through the axillary artery, and the patient was weaned from ECMO successfully. Currently, he remains in the intensive care unit and is recuperating from an arduous journey to be able to be considered for options of potential revascularization (after proven viability) or LV assist device placement (if he cannot be weaned from the Impella device) versus cardiac recovery (if he is able to be weaned from the Impella device successfully).

**CONCLUSIONS**

We have presented the case of a 56-year-old man with risk factors for coronary artery disease who presented with STEMI. In the COVID-19 era, the diagnosis was diverted toward COVID-19, and STEMI was missed. COVID-19 patients can present with cardiovascular
**FIGURE 6** Angiography: LAD and LCX

Coronary angiogram left anterior oblique (LAO) 36, cranial (CRAN) 20 view, shows 99% stenosis of the mid-left anterior descending artery (LAD), 60% long segment stenosis in the proximal left circumflex artery (LCX) with the severe diffuse disease in the distal artery.

**FIGURE 7** Angiography: RCA

Coronary angiogram left anterior oblique (LAO) 48, caudal (CAUD) 2 view shows moderately diffusely diseased right coronary artery (RCA).
manifestations. We have to be vigilant in diagnosing COVID-19 patients; however, we should not forget about the common diagnosis. The appropriate diagnostic tests and care should be delivered to patients who are suspected of having COVID-19, with the proper precautions taken.

ADDRESS FOR CORRESPONDENCE: Dr. Rayan Yousefzai, Houston Methodist DeBakey Heart and Vascular Center, 6550 Fannin Street, Suite 1801, Houston, Texas 77030. E-mail: ryousefzai@houstonmethodist.org.

REFERENCES

1. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.

2. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3.

3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.

4. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. J Am Coll Cardiol 2020;75:2352-71.

5. CCA-ACC: Communication Conference of COVID-19-American College of Cardiology COVID 19 Conference, March 18, 2020, Part 2. Available at: https://www.acc.org/~/media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/Latest%20in%20Cardiology/COVID19-Hub/acc-cca-covid19-webinar-transcript-march-18-epidemiology-cvd-treatment-and-management.pdf. Accessed May 2020.

6. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcome of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:1-8.

KEY WORDS acute coronary syndrome, cardiomyopathy, myocardial infarction

APPENDIX For supplemental videos, please see the online version of this paper.
Collateral Damage
Medical Care Avoidance Behavior Among Patients With Myocardial Infarction During the COVID-19 Pandemic

Francesco Moroni, MD,a Mario Gramegna, MD,b Silvia Ajello, MD,c Alessandro Beneduce, MD,a Luca Baidetti, MD,b Luz Maria Vilca, MD, PhD, MPH,d Alberto Cappelletti, MD,b Anna Mara Scandroglio, MD,c Lorenzo Azzalini, MD, PhD, MSc e

ABSTRACT
The coronavirus disease-2019 (COVID-19) pandemic has caused an enormous strain on healthcare systems and society on a global scale. We report a new phenomenon of medical care avoidance among patients with acute coronary syndrome, which is due to concerns about contracting severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection during hospital stay, ultimately leading to dire clinical outcomes. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1620–4) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The following patients came to our attention in March 2020, in the midst of the coronavirus disease-2019 (COVID-19) pandemic in the Lombardy region of Italy. None of them presented symptoms of COVID-19, and all tested negative for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection.

CASE PRESENTATION
A 64-year-old man presented to the emergency department due to a 3-day history of worsening left lower limb pain, which was accompanied by cyanosis and paresthesia. Concomitantly, he also endorsed chest pressure and shortness of breath at rest for 10 days, for which he had been self-medicating with homemade natural remedies. Upon admission, critical left lower limb ischemia with skin mottling and cyanosis was noted. Fine crackles were audible throughout both lung fields, and jugular venous distension was noted. Electrocardiography (ECG) showed Q waves and ST-segment elevation on the anterior leads (Figure 1). Severe left ventricular (LV) dilation and systolic dysfunction with apical thrombosis were observed on transthoracic echocardiography (Video 1) and computed...
tomography angiography (Figure 1), which also revealed left anterior descending artery (LAD) occlusion, consistent with subacute anterior ST-segment elevation myocardial infarction (STEMI). Thromboembolic material was identified in both femoral arteries. Emergent amputation of the left lower limb was performed, which was complicated by cardiogenic shock necessitating inotropic and intra-aortic balloon pump. The patient slowly recovered and was discharged from the cardiac intensive care unit (ICU).

A 65-year-old woman presented to the emergency department with a 5-day history of progressive dyspnea and orthopnea, and was found to be hypotensive and in respiratory distress. A few days earlier, she had experienced a prolonged episode of epigastric tightness, which she had treated at home with antacids. Physical examination revealed bilateral crackles up to the apical regions, with abolished breath sounds at the bases bilaterally. Jugular venous distension was present, as well as bilateral pitting edema. Chest x-ray film was consistent with acute pulmonary edema. The ECG showed anterior lead ST-segment elevation and Q waves (Figure 2). Echocardiogram showed severe LV dysfunction with apical aneurysm and extensive anteroseptal and anteroapical dyskinesia (Video 2). Computed tomography angiography (Figure 2) confirmed the echocardiographic findings and demonstrated a critical stenosis of the LAD. The clinical picture was consistent with a late presentation of anterior myocardial infarction (MI). The patient was admitted to the cardiac ICU and required treatment with intravenous diuretics, inotropic support, and noninvasive ventilation, before being transferred to the cardiology ward.

A 60-year-old man presented to the emergency department with hypotension, diaphoresis, and respiratory distress. He had experienced a 4-day history of crushing chest pain. The ECG showed ST-segment elevation and Q waves on the anterior leads (Figure 3), consistent with subacute anterior STEMI. Owing to ongoing pain and hypotension, he was transferred to the

---

**FIGURE 1** Late-Presentation Anterior Myocardial Infarction Complicated by Apical Thrombosis With Systemic Embolization

Patient #1: electrocardiography computed tomography angiography, and echocardiography images showing late-presentation anterior myocardial infarction due to (sub)acute occlusion of the left anterior descending artery (LAD), with subsequent formation of an apical left ventricular (LV) thrombus, which induced thromboembolic showers into both femoral arteries, ultimately leading to critical limb ischemia in the left leg.
catheterization laboratory. Emergent coronary angiography (Figure 3) showed chronic total occlusion of the proximal right coronary artery and a left posterolateral branch, as well as acute thrombotic occlusion of the proximal LAD. He therefore underwent percutaneous coronary intervention (PCI) on the LAD. Upon stent implantation, the no-reflow phenomenon was observed (Video 3). The patient then suffered ventricular fibrillation and was defibrillated and intubated. After recovery of spontaneous circulation, he was in deep cardiogenic shock necessitating inotropes as well as mechanical circulatory support with Impella CP (Abiomed, Danvers, Massachusetts). Transesophageal echocardiography showed severe LV dysfunction, with anteroseptal, anteroapical, and lateral akinesia (Video 4). The patient subsequently presented multiorgan failure and died after few days.

DISCUSSION

The dramatic presentation of acute MI in these patients, as well as the permanent sequelae they will carry along, might have been reduced by an earlier referral to emergency medical services (EMS). Indeed, the impact of timing from symptoms onset to coronary reperfusion has been well established. Strategies to reduce ischemic time decrease mortality and the incidence of MI-related complications and, ultimately, heart failure (1). The creation of networks to provide around-the-clock fast access to primary PCI has improved STEMI outcomes (2). Furthermore, patient education programs can critically reduce total ischemic time by rising the awareness of ischemic symptoms and prompting rapid EMS contact (2).

However, in the cases presented previously, it was neither the absence of primary PCI programs nor the lack of patient education that led to delayed referral. In fact, all 3 subjects lived close to Milan, a province of Northern Italy heavily hit by the ongoing COVID-19 epidemic. When directly asked, the patients admitted having avoided seeking medical attention due to fear of acquiring SARS-CoV-2 infection in the hospitals, which were overwhelmed with COVID-19 patients. Fear is a well-known determinant of medical care avoidance, which, in turn, has been associated with a high toll in terms of health outcomes as well as financial costs (3). Fear of having a serious illness or undergoing medical tests and procedures (mainly owing to pain) has traditionally been identified as a barrier to pursue treatment (3). During epidemics, hospital avoidance behaviors have been reported, and were traditionally associated with misconceptions regarding disease severity and modes of
The ongoing COVID-19 pandemic has received immense news coverage, and particular emphasis has been devoted to the description of the most common forms of contagion and places where SARS-CoV-2 spreads more easily. The 3 patients described previously lived in communities in which the magnitude of the COVID-19 outbreak was well over the national average, and they were very reluctant to seek medical attention. Specifically, on March 24, 2020 (the week when these 3 patients presented to our attention), 30,703 COVID-19 cases were present in Lombardy, which represented 44% of the 69,176 cases in Italy.

The burden associated with the treatment of subjects infected with SARS-CoV-2 may reduce the overall efficacy of a health care system facing multiple emergencies at once. EMS in Lombardy handled on average ~2,500 missions/day before the pandemic, with time to first medical contact below 12 min for high-priority events. In contrast, in the third week of March 2020, EMS had to handle ~3,200 missions/day (E. Ammirati, personal communication, March 2020). On the one hand, although data on time from call to first medical contact are not yet available, it is highly likely that ambulance wait times could have been prolonged due to the sudden increase in demand. Furthermore, given the overwhelming number of patients with critical SARS-CoV-2 infection, ICU bed shortage might prevent optimal care delivery to acute cardiovascular patients (6). On the other hand, ICU-sparing strategies are advocated to optimize resources when caring for cardiac patients (6). In this context, local government-led initiatives to concentrate all cardiovascular emergencies in few hub centers might be beneficial to keep emergency facilities rapidly available for cardiac patients while allowing most of other hospitals to focus on COVID-19 care. For confirmed or suspected SARS-CoV-2 patients, Chinese institutions have developed alternative protocols for acute MI, which favor fibrinolysis for STEMI and a delayed invasive or conservative strategy for non-STEMI (7), to decrease the risk of in-hospital spread of the virus. However, in Italy, health care authorities have preferred still guaranteeing the

**FIGURE 3** Late-Presentation Anterior Myocardial Infarction Complicated by Cardiogenic Shock

Patient #3: electrocardiography, coronary angiogram, and echocardiography images showing late-presentation anterior myocardial infarction in a patient with chronic total occlusion (CTO) of the left posterolateral branch (LPL) and proximal right coronary artery (RCA), as well as thrombotic occlusion of the mid LAD, which was treated with emergent percutaneous intervention and complicated with the no-reflow phenomenon and cardiac arrest. Transesophageal echocardiography showed extensive akinesia of the anteroseptal, anteroapical, and lateral wall and severe LV dysfunction. Abbreviations as in Figure 1.
gold-standard primary PCI for all STEMI cases, following the strictest standards in terms of prevention of SARS-CoV-2 in-hospital spread.

CONCLUSIONS

Although utmost effort should be made to limit the propagation of the COVID-19 pandemic, attention should also be dedicated to not compromise acute cardiovascular care. In this difficult scenario, cardiologists can play a unique role in the (re-)education of patients to recognize symptoms of life-threatening cardiac conditions and seek appropriate care in a timely fashion. Late presenters may in fact pose a 2-fold problem: patients may experience worse prognosis and complications related to their underlying cardiac condition and, in turn, may require longer ICU and overall hospital stay. Priority should be given to less resource-consuming therapeutic options whenever possible, and novel organizational models are warranted to optimize cardiovascular care and outcomes during the COVID-19 emergency.

ADDRESS FOR CORRESPONDENCE: Dr. Lorenzo Azzalini, Klingenstein Clinical Center, 7th Floor North, The Mount Sinai Hospital, 1450 Madison Avenue, New York, New York 10029. E-mail: lorenzo.azzalini@mountsinai.org.

REFERENCES

1. Vogel B, Claessen BE, Arnold SV, et al. ST-segment elevation myocardial infarction. Nat Rev Dis Prim 2019;5:39.
2. Antman EM. Time is muscle: translation into practice. J Am Coll Cardiol 2008;52:1216–21.
3. Kannan VD, Vezzie PJ. Predictors of avoiding medical care and reasons for avoidance behavior. Med Care 2014;52:336–45.
4. Lau JTF, Griffiths S, Choi KC, Tsui HY. Avoidance behaviors and negative psychological responses in the general population in the initial stage of the H1N1 pandemic in Hong Kong. BMC Infect Dis 2010;10:139.
5. PCM-DPC dati forniti dal Ministero della Salute. Available at: http://www.salute.gov.it/imgs/C_17_paginaAree_5351_32_file.pdf. Accessed May 2020.
6. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. J Am Coll Cardiol 2020;75:2352–71.
7. Zeng J, Huang J, Pan L. How to balance acute myocardial infarction and COVID-19: the protocols from Sichuan Provincial People’s Hospital. Intensive Care Med 2020;46:1111–3.

KEY WORDS acute coronary syndrome, complication, myocardial infarction

APPENDIX For supplemental videos, please see the online version of this paper.
ST-Segment Elevation Myocardial Infarction Care During COVID-19

Losing Sight of the Forest for the Trees*

Oriol Rodriguez-Leor, MD, PhD,a,b Belen Cid-Alvarez, MDc

By the end of December 2019, a new coronavirus, severe acute respiratory syndrome-coronavirus-2, was identified as the cause of a disease outbreak that originated in the city of Wuhan, China. The disease it causes was named coronavirus disease-2019 (COVID-19). The infection spread rapidly, and the World Health Organization, on March 11, characterized COVID-19 as a pandemic. On April 11, 2020, more than 1.6 million cases had been diagnosed in 179 countries on 5 continents, with nearly 100,000 confirmed deaths (1). Since the start of the outbreak, as the weeks have passed, unexpected side effects that directly affect medical attention to other pathologies have been witnessed.

In this issue of *JACC: Case Reports*, Moroni et al. (2) report 3 cases of ST-segment elevation myocardial infarction (STEMI) that were attended in the midst of the COVID-19 pandemic in the Lombardy region of Italy, which at that time had the highest incidence of cases worldwide. In all 3 cases, despite presenting clear symptoms and having a hospital nearby, patients decided not to go to the emergency room because of fear of acquiring the virus in the hospital, which was overwhelmed with COVID-19 patients. After a few days, they ended up going to the hospital after suffering serious complications related to STEMI, which caused serious sequelae or even death. Risk perception is irrational, and fear of infection opens a new scenario in which patients with serious pathologies avoid going to hospitals, despite the fact that the risk of untreated STEMI exceeds by far the risk of COVID-19 itself.

Preliminary analyses have shown an important and disturbing decrease in the number of STEMI patients attending hospitals in Europe and in North America during the COVID-19 outbreak. A nationwide analysis in 73 Spanish centers involved in STEMI care networks revealed a 40% decrease in patients treated for STEMI when comparing activity before and during the current outbreak (3). In the same direction, an American study revealed an estimated 38% reduction in catheterization laboratories STEMI activations in 9 high-volume centers during the early phase of the COVID-19 pandemic (4). In both cases, STEMI care networks were working normally, so potential etiologies for this decrease should be a combination of avoidance of medical care due to social distancing, concerns of contracting COVID-19 in the hospital, STEMI misdiagnosis, or increased use of pharmacological reperfusion (Table 1).

Regarding reperfusion therapy, primary angioplasty has consistently proven to reduce mortality, reinfarction, stroke, and mechanical complications and avoid bleeding events when compared with thrombolysis as reperfusion treatment in STEMI patients, if delay to treatment between both options is similar (5), and should probably be kept as the first treatment option. Different scientific societies have developed protocols with recommendations on choice of reperfusion treatment during the COVID-19 outbreak, with advice that may be opposed, depending on the conditions in each country. For...
example, in China, Peking Union Medical College Hospital recommended thrombolysis as first-choice treatment, and only recommended coronary intervention after ruling out COVID-19, even in case of thrombolytic contraindication (6). Conversely, in Spain, the Interventional Cardiology Association recommended primary angioplasty as first-choice treatment, considering thrombolysis only in the case that the patient was in a center without primary angioplasty capability and required a transfer that would delay treatment for more than 120 min, or in patients who have tested positive for COVID-19 with poor clinical state that makes transfer difficult, or in patients who have tested positive for COVID-19 with low hemorrhagic risk and symptoms of <3 h duration (7). Primary angioplasty also allows early discharge without further invasive examinations in a significant percentage of patients, which simplifies the management of these patients, limits patients’ exposition to the hospital environment, and reduces hospital occupation.

In addition to the decrease in the number of patients who consult in hospitals, those who consult will do so with a longer delay. A recent study by Tam et al. (8) during the actual COVID-19 outbreak in Hong Kong, China, showed an almost 4-fold increase in median time from symptoms onset to first medical contact (from 82.5 to 318 min), and a more than 2-fold increase in median time from door to device (from 84.5 to 110 min). Ischemic time duration is the major determinant of infarct size and is directly related to short- and long-term survival (9). The increase in ischemic time may be due to patient’s delay in consulting, or due to delay in diagnosis, because of the work overload of the emergency services or due to the difficulty of organizing and performing the procedure with appropriate personal protective equipment (10).

In the current situation, in which patients avoid going to the emergency services (or if they go, they do it with long delays), a disturbing increase in out-of-hospital sudden cardiac arrest (OHSCA) mortality should also be expected. Although it is difficult to know the real incidence of OHSCA in the setting of STEMI, it is estimated that up to 75% of mortality occurs before contact with the health system (11), and the main way to prevent OHSCA is to seek hospital treatment as soon as symptoms of STEMI occur (12). Furthermore, very controversially, it has been suggested not to start chest compressions or ventilation in patients who are in cardiac arrest if they have suspected or diagnosed COVID-19, unless they are in the emergency department and staff are wearing full personal protective equipment (13).

As described by Moroni et al. (2), lack of or delayed access to reperfusion treatment will lead to an increase in short-term STEMI complications, such as left ventricular systolic disfunction, cardiogenic shock, intraventricular thrombus formation, and peripheral embolism or mechanical complications (14). Short-term complications, in addition to increasing mortality, require prolonged admission in critical care units, which could be a serious problem in these times of scarce resources.

In the long term, suboptimal revascularization and larger infarct size will lead to an increase in complications related to worse ventricular remodeling, such as chronic heart failure or ventricular arrhythmias (15).

Last, but not least, the current moment requires special care by health care organizations to prevent nosocomial infection in patients with cardiovascular disease, who are especially vulnerable if affected by COVID-19 (16). Health care personnel caring for patients must be equipped with appropriate personal protective equipment. It is absolutely inadmissible that the lack of these equipment causes situations such as those experienced these days in Spain, the United States, or Italy, where up to 20% of responding health care workers have been infected, and some have died (17).

**ADDRESS FOR CORRESPONDENCE:** Dr. Oriol Rodriguez Leor, Unitat Cardiologia Intervencionista, Hospital Germans Trias i Pujol, Carretera de Canyet SN, 08916 Badalona, Spain. E-mail: oriolrodriguez5@gmail.com. Twitter: @oriolrodriguez.

---

**TABLE 1 Main Concerns Regarding STEMI Care During the COVID-19 Outbreak**

| STEMI Treatment | COVID-19 Management |
|-----------------|---------------------|
| 1. Decrease in number of patients attending emergency systems | 1. Revascularization strategies in STEMI patients with COVID-19 |
| 2. Increase in out-of-hospital sudden cardiac arrest | 2. Infection prevention in patients admitted for STEMI |
| 3. Increase in delays from symptoms onset to reperfusion | 3. Infection prevention in health care personnel |
| 4. Increased use of thrombolysis as reperfusion therapy | |
| 5. Increased short- and long-term complications | |
| 6. Increased short- and long-term mortality | |

COVID-19 – coronavirus disease-2019; STEMI – ST-segment elevation myocardial infarction.
REFERENCES

1. World Health Organization. Coronavirus disease 2019 situation report. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Accessed April 13, 2020.

2. Moroni F, Gramegna M, Ajello S, et al. Collateral damage: medical care avoidance behavior among patients with myocardial infarction during the COVID-19 pandemic. J Am Coll Cardiol Case Rep 2020;2:1620-4.

3. Rodriguez-Leor O, Cid-Alvarez B, Ojeda S, et al. Impact of the COVID-19 pandemic on interventional cardiology activity in Spain. REC Interv Cardiol 2020;2:82-9.

4. Garcia S, Albaghdadi MS, Mejran PM, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am Coll Cardiol 2020;75:2871-2.

5. Ibañez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2018;39:119-77.

6. Junq ZC, Zhu HD, Yan XW, Chai WZ, Zhang S. Recommendations from the Peking Union Medical College Hospital for the management of acute myocardial infarction during the COVID-19 outbreak. Eur Heart J 2020;41:1791-4.

7. Romaguera R, Cruz-Gonzalez I, Jurado-Roman A, et al. Considerations on the invasive management of ischemic and structural heart disease during the COVID-19 coronavirus outbreak. Consensus statement of the Interventional Cardiology Association and the Ischemic Heart Disease and Acute Cardiac Care Association of the Spanish Society of Cardiology. REC Interv Cardiol 2020 Apr 3 [E-pub ahead of print].

8. Tam CF, Cheung KS, Lam S, et al. Impact of coronavirus disease 2019 (COVID-19) outbreak on ST-segment-elevation myocardial infarction care in Hong Kong, China. Circ Cardiovasc Qual Outcomes 2020;13:e006631.

9. Scholz KH, Maier SKG, Maier LS, et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction patients presenting with and without haemodynamic instability: results from the German prospective, multicenter FITT-STEMI trial. Eur Heart J 2018;39:1065-74.

10. Romaguera R, Cruz-Gonzalez I, Ojeda S, et al. Consensus document of the Interventional Cardiology and Heart Rhythm Associations of the Spanish Society of Cardiology on the management of invasive cardiac procedure rooms during the COVID-19 coronavirus outbreak. REC Interv Cardiol 2020 Mar 20 [E-pub ahead of print].

11. Dudas K, Lappas G, Stewart S, Rosengren A. Trends in out-of-hospital deaths due to coronary heart disease in Sweden (1991 to 2006). Circulation 2011;123:46-52.

12. Karam N, Batalie S, Marjion E, et al. Incidence, mortality, and outcome-predictors of sudden cardiac arrest complicating myocardial infarction prior to hospital admission. Circ Cardiovasc Interv 2019;12:e007081.

13. Mahase E, Kmi etowicz Z. Covid-19: doctors are told not to perform CPR on patients in cardiac arrest. BMJ 2020;368:m1282.

14. Puerto E, Viana-Tejedor A, Martinez-Selles M, et al. Temporal trends in mechanical complications of acute myocardial infarction in the elderly. J Am Coll Cardiol 2018;72:959-66.

15. Sutton M, Lee D, Rouleau JL, et al. Left ventricular remodeling and ventricular arrhythmias after myocardial infarction. Circulation 2003;107:2577-82.

16. Ardati AK, Mena Lora AJ. Be prepared. Circ Cardiovasc Qual Outcomes 2020;13:e006661.

17. The Lancet. COVID-19: protecting health-care workers. Lancet 2020;395:922.

KEY WORDS COVID-19, STEMI
Post-MI Ventricular Septal Defect During the COVID-19 Pandemic

Saurabh Joshi, MD, Faraz Nasim Kazmi, MD, Immad Sadiq, MD, Talhat Azemi, MD

ABSTRACT

With the COVID-19 pandemic, the fear among patients of contracting it has made them reluctant to seek medical attention on a timely basis even for emergent conditions. We present a case of post infarction ventricular septal rupture due to delayed presentation as a consequence of the fear of COVID-19. (Level of Difficulty: Intermediate.) (J Am Coll Cardiol Case Rep 2020;2:1628–32) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 72-year-old woman presented with substernal chest heaviness radiating to her back and bilateral upper extremities with associated lightheadedness. At the onset of symptoms, the chest discomfort was severe but she did not come to the hospital for the fear of contracting COVID-19. After 14 h of persistent symptoms, she finally presented to an outside hospital that did not have primary percutaneous coronary intervention (PCI) capability. Vitals were notable for normal temperature, hypotensive with blood pressure of 70/50 mm Hg, pulse of 50 beats/min, and O₂ saturations of 95% on room air. Jugular venous distension was not appreciated. Cardiac auscultation revealed no obvious murmur and the initial pulmonary examination revealed scattered crackles. Lower extremities were cool to touch without any pitting edema.

The patient developed a bradycardic cardiac arrest necessitating brief cardiopulmonary resuscitation with return of spontaneous circulation. During the cardiac arrest, she was intubated for airway protection and was started on multiple vasopressors/inotropes for persistent hypotension. Ultimately, the patient was transferred to our facility for further consideration of emergent cardiac catheterization.

LEARNING OBJECTIVES

- Mechanical complications such as VSR, papillary muscle rupture, or free ventricular wall rupture should be high on the differential in patients who present late with acute MI and are hemodynamically unstable.
- The COVID-19 pandemic and fear among patients of contracting the infection within the hospital is playing a detrimental role in delayed presentation of acute MI, and leading to resurgence of post MI mechanical complications.
- Classic presentation and catheterization findings of post MI VSR include late MI presentation, cardiogenic shock, evidence of contrast filling of the RV on left ventriculogram, prominent "v" waves, and step-up in O₂ saturation at the level of RV resulting in increased Qp:Qs ratio.
PAST MEDICAL HISTORY

The patient had hypertension, dyslipidemia, and coronary artery disease (CAD) with prior PCI with stents to the right coronary artery (RCA) in 2002.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes inferior myocardial infarction (MI) with right ventricle (RV) failure, inferior MI with ventricular septal rupture (VSR), inferior MI with posteromedial papillary muscle rupture with resultant mitral regurgitation, and aortic dissection with involvement of RCA.

INVESTIGATIONS

Initial electrocardiogram at the outside hospital revealed ST-segment elevation in the inferior leads with associated Q waves and reciprocal ST-segment depressions in high lateral leads (Figure 1). The computed tomography angiogram showed no evidence of aortic dissection or pulmonary embolism. Initial troponin I was elevated (>25 ng/ml). On arterial blood gas, pH was noted to be 6.9 with a PCO₂ of 52.5 mm Hg and a bicarbonate of 10 mmol/l.

Coronary angiography demonstrated acute thrombotic occlusion of the mid RCA stent (Figure 2) and no obstructive CAD in the left main, left anterior descending (LAD), and left circumflex arteries. The left ventriculogram in right anterior oblique and left anterior oblique projection demonstrated contrast filling of the RV and main pulmonary artery consistent with a VSR and no evidence of mitral regurgitation (Figures 3 and 4, Videos 1 and 2).

Right heart catheterization demonstrated a mean pulmonary capillary wedge pressure of 28 mm Hg associated with significant “v” waves (Figure 5), pulmonary artery pressure of 54/26 mm Hg, and mean right atrial pressure of 23 mm Hg. O₂ saturation shunt run revealed a step-up in the RV (O₂ saturations: right atrium 55.6%, RV 85.4%, pulmonary artery 75.2%, and systemic arterial 91%). The calculated shunt fraction (Qp:Qs) was 2.2:1 with a cardiac index of 2.2 l/min/m².

MANAGEMENT

The patient received aspirin and intravenous unfractionated heparin bolus per acute coronary syndrome protocol before cardiac catheterization. The patient underwent percutaneous coronary intervention of the mid RCA with 1 drug-eluting stent. After discussion with cardiac surgery, emergent surgical intervention for the VSR was deemed to be futile. Given the grim prognosis and the patient’s documented wish of not continuing futile life-saving measures, she was made “comfort measures only,” and soon after she died.

DISCUSSION

VSR following acute MI occurs due to ischemic necrosis of the interventricular septum after a...
transmural infarct. The LAD supplies the anterior portion of the interventricular septum while a dominant RCA usually supplies the inferior portion of the IVS (1). Thus, infarction in the LAD territory may result in an apical VSR, whereas an infarction involving the RCA can result in a basal inferoposterior VSR (1), similar to what was seen in our patient. Before the advent of early reperfusion therapies, VSR occurred at a rate of 1% to 2% after acute MI (2). With contemporary reperfusion therapy, the rate of VSR has decreased significantly to approximately 0.17% to 0.31% (2,3). Despite advancement in percutaneous and surgical techniques, survival in patients with VSR remains poor. Even with early surgical repair, 30-day survival is approximately 60%, with a 5-year survival of only 38% (4), whereas, conservative management resulted in a grim prognosis and a 30-day mortality of 100% (5). Because of this, it is important to minimize the risk of VSR with prompt symptom recognition and presentation for early revascularization.

With the current COVID-19 pandemic, there has been a reorganization of health care and community resources to combat the pandemic. The effects of previously successful awareness campaigns regarding the need for early assessment of acute chest pain have waned in the light of the new campaigns for social distancing and self-isolation (6). There is also hesitancy among the patients about coming to the hospital for the fear of being exposed to COVID-19. As a result of this, there has been a decrease in cardiac catheterization laboratory (cath lab) activations for ST-segment elevation MI by approximately 38% in the United States (7). Furthermore, the likelihood of delayed
presentations, such as the one seen in our patient, has increased. Tam et al. (8) showed that the time from symptom onset to first medical contact has increased by approximately 300% during the current COVID-19 pandemic in Asia. In addition to this, extensive donning and doffing protocols in the cath lab have increased cath lab arrival-to-first device time (8). Rescheduling of the “nonemergent” coronary angiograms has resulted in delay in definitive diagnosis and treatment of patients with undefined coronary anatomies. With these factors, we are likely to see an increase in the post MI mechanical complications as well as chronic total occlusions in the coming months.

Although the extremely important campaigns for awareness for COVID-19 and social distancing are ongoing, it is equally important for health care professionals to highlight symptoms and situations for which the patients should urgently seek medical attention without delay. Such awareness should be created both at the individual patient level (through physician offices) as well as at the community level through public health forums and professional medical societies (9).

CONCLUSIONS

Our case illustrates the classic presentation and cardiac catheterization findings of post MI VSR associated with a late presentation inferior ST-segment elevation myocardial infarction. More importantly, it also highlights the detrimental role of the COVID-19 pandemic as the cause for delayed presentations, which could result in the resurgence of mechanical complications of acute MI.

ADDRESS FOR CORRESPONDENCE: Dr. Saurabh Joshi, Cardiac Catheterization Laboratory, Hartford Hospital, 80 Seymour Street, Hartford, Connecticut 06102. E-mail: sjoshi24@gmail.com.

REFERENCES
1. Mubarik A, Iqbal AM. Ventricular Septal Rupture. Treasure Island, FL: StatPearls, 2020.
2. Singh V, Rodriguez AP, Bhatt P, et al. Ventricular septal defect complicating ST-elevation myocardial infarctions: a call for action. Am J Med 2017;130:863.e12.
3. Moreyra AE, Huang MS, Wilson AC, et al. Trends in incidence and mortality rates of ventricular septal rupture during acute myocardial infarction. Am J Cardiol 2010;106:1095–100.
4. Jeppsson A, Liden H, Johnsson P, Hartford M, Rådegran K. Surgical repair of post
infarction ventricular septal defects: a national experience. Eur J Cardiothorac Surg 2005;27:216–21.

5. Poulsen SH, Praestholm M, Munk K, Wierup P, Egeblad H, Nielsen-Kudsk JE. Ventricular septal rupture complicating acute myocardial infarction: clinical characteristics and contemporary outcome. Ann Thorac Surg 2008;85:1591–6.

6. Gori T, Lelieveld J, Münzel T. Perspective: cardiovascular disease and the Covid-19 pandemic. Basic Res Cardiol 2020;115:32.

7. Garcia S, Albaghdadi M, Meraj PM, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am Coll Cardiol 2020;75:2871–2.

8. Tam CF, Cheung KS, Lam S, et al. Impact of Coronavirus Disease 2019 (COVID-19) outbreak on ST-segment-elevation myocardial infarction care in Hong Kong, China. Circ Cardiovasc Qual Outcomes 2020;13:e006631.

9. Mahmud E, Dauerman HL, Welt FG, et al. Management of acute myocardial infarction during the COVID-19 pandemic. J Am Coll Cardiol 2020 Apr 21 [E-pub ahead of print].

**KEY WORDS** chest pain, complication, left-sided catheterization, myocardial infarction, right-sided catheterization, ventricular septal defect

**APPENDIX** For supplemental videos, please see the online version of this paper.
Papillary Muscle Rupture Due to Delayed STEMI Presentation in a Patient Self-Isolating for Presumed COVID-19

Katherine J. Kunkel, MD, Saif Anwaruddin, MD

ABSTRACT

A 57-year-old man acutely developed chest tightness and dyspnea. Given concern that his symptoms were consistent with COVID-19, the patient self-isolated. After 1 week of worsening symptoms, the patient presented with hypoxia and hypotension. He was found to have an occluded right coronary artery and ruptured posteromedial papillary muscle. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1633–6) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

On April 3, 2020, a 57-year old man with a family history notable for premature coronary artery disease presented to the emergency department with 7 days of worsening chest tightness and shortness of breath. One week before presentation, the patient woke from sleep with chest tightness, diaphoresis, and shortness of breath. Given concern for coronavirus disease-2019 (COVID-19), the patient self-isolated at home, during which time he had intermittent fevers to 101°F and cough, worsening exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. On presentation, he was afebrile (99.3°F), hypotensive (86/68 mm Hg), tachycardic (103 beats/min), tachypneic (24 breaths/min), and hypoxic (86% on room air).

PAST MEDICAL HISTORY

His past medical history included hypertension, hyperlipidemia, former tobacco use, family history of premature coronary artery disease, stage II chronic kidney disease, and intermittent asthma.

INVESTIGATIONS

Laboratory investigations were notable for elevated creatinine (3.08 mg/dl), transaminits (alanine aminotransferase 82 U/l, aspartate aminotransferase 44 U/l), leukocytosis (16.1 K/µl), and elevated troponin-T (1.29 ng/ml). The results of a respiratory pathogen
profile, including influenza and Xpert Xpress severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) assay (Cepheid, Sunnyvale, California), were negative. Portable chest radiograph revealed right upper lung patchy opacity consistent with focal pneumonia. Computed tomography of the chest was notable for bilateral patchy, rounded, ground-glass opacities predominantly located centrally and in the upper lobes (Figure 1). The patient’s electrocardiogram was notable for inferior Q waves and T-wave inversions with no ST-segment changes (Figure 2).

Given concern for hypoxia, fevers, and cough, the patient was admitted to the COVID-19 unit as a person under investigation. The result of a repeat SARS-CoV-2 test was negative. Bedside transthoracic echocardiogram demonstrated an ejection fraction of 65% with inferior hypokinesis and at least mild to moderate mitral regurgitation. Diagnostic coronary angiography was notable for an occluded right coronary artery with non-obstructive disease in the left system (Figures 3 and 4). Transesophageal echocardiography demonstrated severe mitral regurgitation with a ruptured postero medial papillary muscle with flail P2 and P3 segments of the posterior mitral leaflet (Figure 5, Video 1).

**MANAGEMENT**

Despite placement of an intra-aortic balloon pump, the patient became increasingly hypoxic and hypotensive, and he required escalating doses of vasopressors. The patient was ultimately intubated and peripherally cannulated for venoarterial extracorporeal membrane oxygenation (ECMO). Two days later, following clinical improvement in oxygenation and renal function, the patient underwent mitral valve replacement with a No. 31 St Jude mechanical mitral valve prosthesis (Abbott, Abbott Park, Illinois) and ECMO decannulation.

**DISCUSSION**

The incidence of papillary muscle rupture has decreased dramatically following the widespread
adoption of primary percutaneous coronary intervention in patients with STEMI. In modern series, the incidence of ischemic papillary muscle rupture in patients presenting with STEMI is 0.25% (1). Although this complication is rare, it carries a poor prognosis, with an in-hospital mortality exceeding 50% (2).

In the setting of acute myocardial infarction, the rupture of the posteromedial papillary muscle is much more common than anterolateral papillary muscle rupture given the single blood supply of the posteromedial papillary muscle from either the dominant right coronary artery or the dominant left circumflex coronary artery. The anterolateral papillary muscle has a dual blood supply and is thus considerably less susceptible to ischemic injury. Papillary muscle rupture generally occurs between 2 and 7 days following an inferior myocardial infarction and is responsible for 7% of patients presenting in cardiogenic shock following myocardial infarction (3).

The hemodynamic consequences of acute mitral regurgitation result from the rapid delivery of a large volume load on the left atrium and ventricle leading to right-sided dysfunction. As a result of acute volume loading of an un-remodeled left atrium, there is a marked rise in left atrial pressure leading to elevated pulmonary pressure and pulmonary edema. This can result in refractory hypoxemia and cardiogenic shock (4).

Medical management of acute mitral regurgitation consists primarily of afterload reduction with vasodilators and inodilators such as sodium nitroprusside and milrinone. These patients may also benefit from mechanical unloading with an intra-aortic balloon pump or venoarterial ECMO for circulatory and respiratory support (3). Despite a high perioperative mortality (24%), surgical replacement of the mitral valve remains the cornerstone of treatment (5). The timing of surgery is generally recommended to be as early in the patient’s course as is feasible (6).

FOLLOW-UP

The patient was successfully extubated on post-operative day 1. His post-operative course was uncomplicated. He was discharged on post-operative day 9 with a therapeutic international normalized ratio. At a telemedicine visit with the patient 1 week after discharge, the patient reported no chest discomfort, shortness of breath, or activity limitations.

CONCLUSIONS

This case demonstrates the potential dangers of public messaging that encourages patients with respiratory symptoms to avoid medical care during the SARS-CoV-2/COVID-19 global pandemic. Additionally, potential anchoring bias in a patient reporting cough and fevers who presented with hypoxia led to delays in the diagnosis and management of severe
mitral regurgitation secondary to a ruptured posteromedial papillary muscle and a completed inferior STEMI. Prompt recognition and surgical management of this mechanical complication of myocardial infarction are critical to ensure a satisfactory outcome.

REFERENCES

1. French JK, Hellkamp AS, Armstrong PW, et al. Mechanical complications after percutaneous coronary intervention in ST-elevation myocardial infarction (from APEX-AMI). Am J Cardiol 2010; 105:59–63.

2. French JK, Armstrong PW, Cohen E, et al. Cardiogenic shock and heart failure post-percutaneous intervention in ST-elevation myocardial infarction: observations from "Assessment of Pexelizumab on Acute Myocardial Infarction." Am Heart J 2011;162:89–97.

3. Kutty RS, Hones N, Moorjani N. Mechanical complications of acute myocardial infarction Cardiol. Clin 2013;31:519–31.

4. Harari R, Bansal P, Yatskar I, et al. Papillary muscle rupture following acute myocardial infarction: anatomic, echocardiographic, and surgical insights Echocardiography 2017;34:1702–7.

5. Chevalier PE, Burri H, Fahrat F, et al. Perioperative outcome and long-term survival of surgery for acute post-infarction mitral regurgitation. Eur J Cardiothorac Surg 2004;26:330-5.

6. Nishimura RA, Schaff HV, Gersh BJ, et al. Early repair of mechanical complications after acute myocardial infarction. JAMA 1986;256:47-50.

KEY WORDS COVID-19, papillary muscle rupture, ST-segment elevation myocardial infarction (STEMI)

ADDRESS FOR CORRESPONDENCE: Dr. Katherine J. Kunkel, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, Pennsylvania 19103. E-mail: katherine.kunkel@pennmedicine.upenn.edu. Twitter: @kjkunkelmd.

APPENDIX For a supplemental video, please see the online version of this paper.
Acute Myocardial Infarction and Papillary Muscle Rupture in the COVID-19 Era

Auras R. Atreya, MD, MPH, Kris Kawamoto, MD, Prasanthi Yelavarthy, MD, Mansoor A. Arain, MD, David G. Cohen, MD, Brett L. Wanamaker, MD, Ashraf Abou El Ela, MD, Matthew A. Romano, MD, Paul M. Grossman, MD

ABSTRACT

Mechanical complications of acute myocardial infarction are infrequent in the modern era of primary percutaneous coronary intervention, but they are associated with high mortality rates. Papillary muscle rupture with acute severe mitral regurgitation is one such life-threatening complication that requires early detection and urgent surgical intervention. (Level of Difficulty: Beginner.) (J Am Coll Cardiol Case Rep 2020;2:1637–41) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 52-year-old firefighter presented with shortness of breath, chest pressure, and altered mental status. The patient was unaccompanied and, because of his altered mental status, was unable to provide a history of symptom duration. Initial evaluation revealed normal body temperature, severe respiratory distress (respiratory rate of 30 breaths/min, peripheral oxygen saturation of 93% on 15 l/min O2), blood pressure of 87/41 mm Hg, heart rate of 89 beats/min, and rales at the lung bases bilaterally. A murmur could not be auscultated. An electrocardiogram showed sinus rhythm with ST-segment depression in the precordial leads suggestive of posterior myocardial injury (Figure 1).

PAST MEDICAL HISTORY

The patient had a history of hyperlipidemia, prediabetes, gout, and well-controlled hypertension.

DIFFERENTIAL DIAGNOSIS

Given the patient’s severe respiratory distress, electrocardiographic abnormalities, and his occupation, there was moderate suspicion of coronavirus disease-2019 (COVID-19). The differential diagnosis also included posterior ST-segment elevation myocardial infarction (STEMI) with pulmonary edema.

LEARNING OBJECTIVES

- To diagnose ruptured papillary muscle in the cardiac catheterization laboratory.
- To understand the pathophysiology of acute MR and understand noninvasive and invasive therapies for stabilization of hemodynamics.
INVESTIGATIONS

The chest radiogram showed a diffuse interstitial abnormality suggestive of pulmonary edema (Figure 2). The patient was brought on an emergency basis to a negative pressure cardiac catheterization laboratory, and a decision was made to intubate the patient because of his worsening respiratory distress. While he was being intubated, copious pink, frothy fluid emanated into the oropharynx and made endotracheal tube placement extremely difficult; intubation took 10 min. During this time, he progressed to pulseless electrical activity arrest, and cardiopulmonary resuscitation was initiated. As cardiopulmonary resuscitation was being performed, left femoral arterial and venous access was obtained for venoarterial extra corporeal membrane oxygenation (VA ECMO), and mechanical circulatory support was initiated. Shortly thereafter, his heart rhythm transitioned to ventricular fibrillation. Sinus rhythm was restored following 200-J external defibrillation.

Once he was stabilized on VA ECMO, diagnostic coronary angiography revealed right-dominant circulation with thrombotic occlusion of the middle left circumflex artery (Figure 3). Out of concern for acute severe ischemic mitral regurgitation (MR), a biplane left ventriculogram was performed that showed a normal ejection fraction with inferolateral hypokinesis (Video 1). Severe MR was noted, with concern for a ruptured papillary muscle. Transesophageal echocardiogram (TEE) confirmed the diagnosis of severe MR with flail medial anterior and posterior mitral leaflets, consistent with a posterior medial papillary muscle rupture (Video 2). TEE also revealed insignificant left ventricular forward flow into the aorta with only intermittent aortic valve opening. A high-sensitivity troponin assay obtained in the emergency department was 386 pg/ml (reference 0 to 19 pg/ml), and his creatine phosphokinase level was 181 IU/l (reference 38 to 240 IU/l). The peak high-sensitivity troponin level was 2,151 pg/ml, and the creatine phosphokinase level was 4,122 IU/l on day 5 after presentation. A reverse transcription polymerase chain reaction assay for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) had a negative result.

MANAGEMENT

Right-sided heart catheterization revealed pulmonary capillary wedge pressure of 29 mm Hg and mean pulmonary artery pressure of 30 mm Hg on VA ECMO. Intra-aortic balloon pump (IABP) counterpulsation was initiated to help reduce afterload and improve forward flow in the setting of severe MR and VA ECMO. There was significant augmentation of diastolic blood pressure after IABP implantation. In the intensive care unit, therapeutic hypothermia was
achieved through the ECMO circuit. He underwent mitral valve replacement with a No. 29 Edwards Magna mitral tissue valve (Edwards Lifesciences, Irvine, California) 2 days after his initial presentation (Figure 4, Video 3).

DISCUSSION

Mechanical complications of acute myocardial infarction (AMI) include left ventricular free wall rupture, interventricular septal rupture, and acute MR secondary to papillary muscle dysfunction or rupture. The incidence of mechanical complications in the pre-fibrinolytic era was as high as 6% and has significantly decreased to <1% in the reperfusion era (1). A recent analysis of nearly 4 million patients hospitalized with STEMI between 2003 and 2015 reported an incidence of 0.27% for all mechanical complications: 0.21% had interventricular septal rupture, 0.05% had papillary muscle rupture, and 0.01% had free wall rupture (2).

Papillary muscle rupture usually occurs 2 to 7 days after AMI and typically is a complication of inferior STEMI (3). The posteromedial papillary muscle is more likely to be supplied by a single coronary artery (either branches of the right posterior descending or right posterolateral artery or the left coronary obtuse marginal arteries) compared with the anterolateral papillary muscle, which receives a dual blood supply from the left anterior descending artery and the left circumflex artery (4). It is hypothesized that papillary muscle rupture usually occurs in the setting of small infarcts related to single-vessel coronary disease because limited myocardial injury allows for preserved left ventricular function and greater shearing force at the site of potential rupture (3).

Acute severe MR secondary to papillary muscle rupture and flail mitral valve leaflet manifests with rapid pulmonary edema and often is complicated by cardiogenic shock. Because the healthy left atrium is noncompliant, these patients rapidly experience elevated left atrial pressures with predominant backward flow of blood into the pulmonary veins with pulmonary edema and hypoxemia (5). Simultaneously, decreased forward flow into the systemic circulation results in cardiogenic shock and a vasoconstrictor response. Given the rapid equalization of left ventricular and left atrial pressures in patients with acute severe MR, a systolic murmur on auscultation is classically absent. The diagnosis requires a high degree of suspicion and prompt evaluation with echocardiography or contrast left ventriculography.

Emergency medical and surgical treatment is required when papillary muscle rupture occurs. Mechanical ventilation for management of pulmonary edema and afterload reduction with vasodilator therapy and IABP counterpulsation are used for temporary hemodynamic stabilization until surgical intervention is performed. Afterload reduction with an IABP improves forward flow and has been shown to increase blood pressure and cardiac output and reduce pulmonary capillary wedge pressure (5). Another option for hemodynamic support is the TandemHeart (LivaNova, London, United Kingdom) left ventricular assist device that serves to decompress the left atrium and left ventricle and improve
cardiac output by returning blood to the systemic circulation (6). The Impella left ventricular assist device (Abiomed, Danvers, Massachusetts) is contraindicated in patients with a ruptured papillary muscle because of hyperdynamic left ventricular contraction and catheter interaction with the ruptured chordal apparatus. In our patient, the TEE obtained during VA ECMO and before IABP catheter insertion revealed nearly absent forward flow through the aortic valve, with the entire stroke volume directed toward the left atrium and pulmonary veins. These findings are consistent with increased afterload conditions created by the VA ECMO circuit in addition to severe MR. Following IABP implantation, there was considerable augmentation of blood pressure, a finding indicating adequate flow from the left ventricle into the aorta.

AMI complicated by acute severe MR portends a very poor prognosis with in-hospital mortality approaching 70% when surgery is not performed (7). The timing of surgery remains controversial. Studies have shown lower operative mortality when surgery is delayed for more than 3 months after AMI (3). However, this finding reflects survival bias. Earlier surgical intervention increases operative mortality, but it improves long-term mortality. Patients who survive the perioperative period after mitral valve surgery have a good prognosis, with heart failure-free survival rates nearly identical to those in patients presenting with AMI who do not have a mechanical complication (8).

With the ongoing COVID-19 pandemic, there have been reported delays in access to care (9). Delays and lack of prompt pharmacologic or invasive reperfusion therapies are bound to increase mechanical complications of AMI, so emergency department physicians and cardiologists need to be aware of atypical presentations of AMI and possible mechanical complications. As demonstrated in this case, although the differential diagnosis of COVID-19 infection could have delayed his cardiovascular diagnosis, a decision to transport the patient to the cardiac catheterization laboratory was critical to achieve resuscitation from cardiac arrest and facilitate investigations to diagnose papillary muscle rupture rapidly. Additionally, hospitals need to be ready to respond to such emergencies with adequate personnel, personal protective equipment, and appropriate facilities (10).

FOLLOW-UP

Although an initial computed tomographic scan of the head following cardiac catheterization laboratory resuscitation did not reveal ischemic brain injury, myoclonic seizures developed in this patient, and subsequent computed tomographic scans revealed loss of gray-white differentiation consistent with severe global hypoxic injury. Given the lack of improvement in clinical status, care was withdrawn by the patient’s family, and the patient died on hospital day 9.

CONCLUSIONS

This case highlights the importance of early recognition of mechanical complications associated with STEMI and prompt initiation of resuscitative and therapeutic measures, within the confines of modern-day COVID-19–driven institutional protocols.

ADDRESS FOR CORRESPONDENCE: Dr. Auras R. Atreya, Frankel Cardiovascular Center, University of Michigan, 1500 East Medical Center Drive Ann Arbor, Michigan 48109. E-mail: auras@med.umich.edu. Twitter: @AurasAtreya.
REFERENCES

1. Figueras J, Alcalde O, Barrabes JA, et al. Changes in hospital mortality rates in 425 patients with acute ST-elevation myocardial infarction and cardiac rupture over a 30-year period. Circulation 2008;118:2783–9.

2. Elbadawi A, Elgendy IY, Mahmoud K, et al. Temporal trends and outcomes of mechanical complications in patients with acute myocardial infarction. J Am Coll Cardiol Intv 2019;12:1825–36.

3. Nishimura RA, Schaff HV, Shub C, et al. Papillary muscle rupture complicating acute myocardial infarction: analysis of 17 patients. Am J Cardiol 1983;51:373–7.

4. James TN. Anatomy of the coronary arteries in health and disease. Circulation 1965;32:1020–33.

5. Stout KK, Verrier ED. Acute valvular regurgitation. Circulation 2009;119:3232–41.

6. DiVita M, Visveswaran GK, Makam K, et al. Emergent TandemHeart-ECMO for acute severe mitral regurgitation with cardiogenic shock and hypoxaemia: a case series. Eur Heart J Case Rep 2020;4:1–6.

7. Lavie CJ, Gersh BJ. Mechanical and electrical complications of acute myocardial infarction. Mayo Clin Proc 1990;65:709–30.

8. Russo A, Suri RM, Grigioni F, et al. Clinical outcome after surgical correction of mitral regurgitation due to papillary muscle rupture. Circulation 2008;118:1528–34.

9. Rodriguez-Leor O, Cid-Alvarez B. STEMI care during COVID-19: losing sight of the forest for the trees. J Am Coll Cardiol Case Rep 2020;2:1625–7.

10. Truesdell M, Guttman P, Clarke B, et al. Conversion of positive pressure cardiac catheterization and electrophysiology laboratories to a novel 2-zone negative pressure system during COVID-19 pandemic. J Cardiovasc Electrophysiol 2020 May 23 [E-pub ahead of print].

KEY WORDS acute coronary syndrome, COVID-19, mitral regurgitation, papillary muscle rupture, percutaneous coronary intervention, ST-segment elevation myocardial infarction, transesophageal echocardiography

APPENDIX For supplemental videos, please see the online version of this paper.
Surge in Delayed Myocardial Infarction Presentations
An Inadvertent Consequence of Social Distancing During the COVID-19 Pandemic

Kulin Shah, MD, Delphine Tang, MD, Fady Ibrahim, MD, Bobby Ghosh, MD, Sabha Bhatti, MD, Ehimare Akhabue, MD, Tudor Vagaonescu, MD, Ramzan Zakir, MD, Abdul Hakeem, MD

ABSTRACT
This case series summarizes our experience of delayed acute myocardial infarction presentations during the coronavirus disease-2019 pandemic predominantly driven by patient fear of contracting the virus in the hospital. Many presented with complications rarely seen in the primary percutaneous coronary intervention era including ventricular septal rupture, left ventricular pseudoaneurysm, and right ventricular infarction. (Level of Difficulty: Beginner.)

Several reports have emerged highlighting a drastic drop in the number of acute myocardial infarctions (MIs), particularly ST-segment elevation myocardial infarctions (STEMI), since the coronavirus disease-2019 (COVID-19) pandemic began late last year. This seemingly has been an unintended yet not unexpected consequence of “social distancing,” which has “flattened” the curve of COVID-19 cases on the one hand while also dramatically decreasing STEMI presentations to the hospital. Is this phenomenon an added blessing of social distancing whereby elimination of the many population-attributable triggers of MI such as traffic exposure, air pollution, moderate to intense physical exertion, and stress have actually decreased the incidence of MI? (1). The concerning antithesis to this assumption is the following: Are patients with MIs too afraid to seek prompt medical attention out of fear of potential health care exposure to the virus with consequent morbidity and mortality? Although it may be too late to wait for the real answer until population-based studies with sound scientific methods are conducted, the recently reported 400% increase in at-home cardiac arrests in New York City being solely attributed to COVID-19 is alarming. Could a large proportion of these patients represent MI?

LEARNING OBJECTIVES
• To understand the potential scope and adverse outcomes of late MI presentations during the pandemic due to fear of contracting infection.
• To institute public awareness and education regarding the potential hazards of delayed presentation with concerning symptoms of MI.
cases who are too petrified to come to the emergency department?

New Jersey is the second most affected state in the United States by the COVID-19 pandemic with over 134,000 confirmed cases and nearly 9,000 deaths as of May 8, 2020 (2). We have seen a dramatic drop in all spectra of acute coronary syndrome (ACS) cases over the past 6 weeks. Among those who have presented with acute MI to our hospital, we present a case series of 10 patients from our cardiac catheterization laboratory in central New Jersey highlighting a concerning pattern.

This case series provides a troubling snapshot of acute MI presentations in non-COVID patients at one of the busiest cardiac care hospitals in New Jersey during the peak of the COVID-19 pandemic. From March 1, 2020, to April 25, 2020, our cardiac catheterization laboratory saw a significant drop in the number of STEMI cases. Ten patients presenting with acute MI, all of whom had delayed presentation, are summarized in Table 1. Details of their clinical presentations, electrocardiograms, procedures, and outcomes are summarized in the Supplemental Appendix and Supplemental Figures 1 to 20.

A unifying theme among all cases was delayed presentation with extremely prolonged ischemic times defined as symptom onset to arrival to the emergency room. This delay was mainly driven by fear of seeking medical attention because of the risk of health care exposure and contracting the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus. However, all patients eventually tested negative for SARS-CoV-2 by polymerase chain reaction assays. Patients often presented critically ill with high-risk features such as significant left ventricular dysfunction, atrioventricular block, ventricular arrhythmias, and cardiac arrest. The majority required complex coronary interventions with some requiring mechanical circulatory support for cardiogenic shock. For example, Case 7 illustrates a patient who presented with a total ischemic time over 18 h and was found to be in complete heart block.

| Case # | Age (yrs)/Sex | Time to Presentation (Onset of Symptoms to Presentation to ER) | ECG Findings | Anatomic Findings | Complications | LVEF (%) |
|--------|---------------|---------------------------------------------------------------|--------------|-------------------|---------------|----------|
| 1      | 77/male       | 48 h                                                          | Inferior STE and Q waves (II, III, aVF) | 100% RCA occlusion, TIMI flow grade 0 | CHF           | 45       |
| 2      | 76/male       | 48 h                                                          | Anteroseptal STE and Q waves (V1–V3) | 100% ostial LAD occlusion, TIMI flow grade 0 | LVEDP 36 mm Hg CHF | 35-40    |
| 3      | 86/female     | 72 h                                                          | Anteroseptal STE and Q waves (V1–V3) | 95% mid-LAD stenosis, TIMI flow grade 2 | LVEDP 29 mm Hg CHF | 40-45    |
| 4      | 77/female     | 48 h                                                          | T-wave inversion V1, V2 | 99% mid-LAD, TIMI flow grade 1 | None          | 50-55    |
| 5      | 75/female     | 7 days                                                        | Inferolateral STE Inferior Q waves Broad R waves V1-V2 | Tortuous 100% mid-RCA occlusion with TIMI flow grade 0 80% distal left main 80% proximal LAD | Post-MI VSD Basal inferolateral wall pseudoaneurysm IABP | 50-55    |
| 6      | 47/male       | 5 days                                                        | Inferior STE ST-segment depressions V1-V2 | 100% LCX, TIMI flow grade 0 | Cardiac arrest on presentation CHF | 35-40    |
| 7      | 79/male       | 24 h                                                          | Inferior STE Anterolateral STE | 100% ostial RCA occlusion, TIMI flow grade 0 Cardiac standstill | Cardiogenic shock RV failure Ventricular fibrillation Impella CP | 20-25    |
| 8      | 64/male       | 7 days                                                        | Inferior STE Posterior infarct | Multiple lesions in sequential saphenous venous graft to posterior descending artery with 100% occluded posterolateral branch | None          | 50       |
| 9      | 61/female     | 14 days                                                       | Sinus arrhythmia Nonspecific T-wave abnormalities | 100% proximal RCA occlusion with TIMI flow grade 0 | None          | 50       |
| 10     | 84/male       | 48 h                                                          | Biventricular pacing PVC | 100% proximal LAD, TIMI flow grade 0, occluded LIMA to LAD 99% ramus intermedius stenosis Subtotally occluded left circumflex | Prolonged hospital course, CHF, hemodialysis due to contrast-induced nephropathy | 20       |

CHF = congestive heart failure; LVEDP = left ventricular end-diastolic pressure; MI = myocardial infarction; STE = ST-segment elevation; VSD = ventricular septal defect; other abbreviations as in Figures 1 and 2.
On arrival to the catheterization laboratory, the patient developed cardiac arrest and underwent complex coronary intervention of a totally occluded ostial right coronary artery (RCA) during active cardiopulmonary resuscitation and repeated defibrillation therapy, ultimately requiring mechanical circulatory support (Figure 1B, Videos 1, 2, 3, and 4).

Case 5 demonstrates a patient who presented with an inferolateral STEMI after having chest discomfort for 1 week (Figure 2A). She was found to have an occluded mid-RCA with severe left main disease and a totally occluded left circumflex artery. Thrombolysis In Myocardial Infarction flow grade 3 was established during percutaneous intervention, and an intra-aortic balloon pump was placed (Figure 2B, Videos 5 and 6). The patient developed a ventricular septal rupture and
FIGURE 2  Delayed Presentation Inferolateral Wall MI

(A) A 12-lead electrocardiogram showing inferoposterior ST-segment elevation myocardial infarction with posterolateral infarct pattern. (B) (a) RCA occlusion; (b) severe distal left main disease, proximal LAD disease, and occluded LCX; and (c and d) post wiring improved TIMI flow grade 3, revealing a severely calcified mid-RCA lesion. (C) Basal inferolateral pseudoaneurysm and ventricular septal rupture. LCX = left circumflex artery; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Figure 1.
a posterior wall pseudoaneurysm and was taken urgently to surgery (Figure 2C, Videos 7, 8, 9, and 10).

Multiple reports from areas deeply impacted by COVID-19 have shown a similar drop in acute MI presentations to their hospitals. A recent study from 9 hospital systems in the United States demonstrated a 38% drop in acute MI cases (3). Another large study from Northern California demonstrated weekly rates of hospitalization for acute MI decreased by 48% during the COVID-19 period (4). Other countries have shown similar data with up to 40% declines in STEMIs in Spain and parts of Italy (5). One may expect an increase in the number of acute MIs during a pandemic because of heightened environmental and psychosocial stressors such as job and financial insecurity. However, while the exact reasons for the observed decline are not clearly understood, it is hypothesized that fear of contracting SARS-CoV-2 by presenting to health care facilities is a major determinant. Our experience demonstrates an alarming pattern of delayed MI presentations associated with higher rates of adverse outcomes such as left ventricular dysfunction, cardiogenic shock, mechanical complications, and death. Another very concerning aspect of our experience was that these cases were not due to patients being unable to recognize their symptoms but rather, that they were often ignoring their symptoms in the hope they would resolve, thereby avoiding any potential health care exposure risk.

Although the concern of contracting SARS-CoV-2 is real for both patients and health care workers, it is important that it not be a deterrent in providing optimal treatments known to improve outcomes. In response to the COVID-19 pandemic at our hospital, where we have treated over 1,200 COVID patients thus far, we have developed algorithms to help streamline patients who would benefit from immediate percutaneous coronary intervention while maintaining patient and health care worker safety. One major challenge is that patients with COVID-19 may present with a STEMI syndrome but often have other conditions such as myocarditis, stress cardiomyopathy, or supply-demand mismatch that differs from an acutely occluded coronary artery. Therefore, a high index of clinical suspicion and a low threshold for testing are critical in identifying patients with known or suspected SARS-CoV-2 infection. Once the decision has been made to take the patient urgently to the cardiac catheterization laboratory, the patient...
should be tested and treated as a COVID-19 person under investigation until the test has resulted. Staff must use proper personal protective equipment including N95 masks, face shields or fully protective eye goggles, a bouffant cap, standard sterile gloves and gown, and a powered air-purifying respirator when performing endotracheal intubations.

Our experience demonstrates the consequences of delaying seeking medical care for patients with acute coronary syndrome. As we start to experience a second surge of the COVID-19 pandemic in the United States, it is crucial to educate the public that even during this pandemic, we continue to use the necessary measures needed to minimize exposure to SARS-CoV-2 and to therefore not disregard symptoms out of fear but rather seek prompt medical attention.

ADDRESS FOR CORRESPONDENCE: Dr. Abdul Hakeem, Division of Cardiovascular Diseases and Hypertension, Robert Wood Johnson Medical School, Rutgers University, 51 French Street, MEB 5th Floor, #578B, New Brunswick, New Jersey 08903. E-mail: ahakeem@gmail.com.

REFERENCES

1. Nawrot TS, Perez L, Künzli N, Munters E, Nemery B. Public health importance of triggers of myocardial infarction: a comparative risk assessment. Lancet 2011;377:732–40.

2. State of New Jersey Department of Health. Communicable Disease Service. COVID-19. Available at: https://www.state.nj.us/health/cd/topics/ncov.shtml. Accessed May 8, 2020.

3. Garcia S, Albadghdadi M, Perwaiz M, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am Coll Cardiol 2020;75:2871–2.

4. Solomon MD, McNulty EJ, Rana JS, et al. The Covid-19 pandemic and the incidence of acute myocardial infarction. N Engl J Med 2020 May 19 [E-pub ahead of print].

5. De Filippo O, D’Ascenzo F, Angelini F, et al. Reduced rate of hospital admissions for ACS during Covid-19 outbreak in northern Italy. N Engl J Med 2020;383:88–9.

KEY WORDS coronary angiography, myocardial infarction, percutaneous coronary intervention

APPENDIX For supplemental material, figures, and videos, please see the online version of this paper.
This is the story of my start as a consultant (British for attending physician) during the coronavirus disease-2019 (COVID-19) pandemic. I am a British interventional cardiologist, and in February 2020 I was working as a fellow on Vancouver Island, British Columbia, Canada. I had just returned from a week skiing in Whistler and was looking forward to the final 4 months of my fellowship, getting to grips with more transcatheter aortic valve replacements, and pushing on with the most complex aspects of coronary intervention. Like most doctors, I had not grasped what was coming and the life-changing impact the disease would have.

Some clarification is perhaps necessary before I start because the British training system is somewhat different from that in North America. British interventional cardiologists complete a combined general and interventional fellowship (after 4 years of internal medicine) lasting 5 years and known as registrar training. However, it is very common for interventional cardiologists to do an extra year or 2 of training overseas before taking a consultant (attending) position. With most British interventional cardiologists also taking time out for a PhD or similar degree, our postgraduate training is often much longer than in the United States. Do not feel too sorry for us—we graduate with much less debt, work shorter hours in training, and can go to medical school directly after high school. Regardless, I had completed my UK training and was taking my extra year doing a fellowship in Canada, with a consultant position sewn up in Liverpool, United Kingdom, on my planned return in August of this year.

Suddenly in late February there was a new disease on the horizon. Of course, we had all seen small pieces on the bottom half of news websites, but in the case of British news it was far less prominent than discussion of Brexit or President Trump. We had also been through these scares before, and ultimately they had little impact on our lives or clinical practice (severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS], Ebola, H1N1 influenza). No one I interacted with in "real life" believed that this coronavirus would be different—I guess it is a matter for debate whether Twitter provided better insight. However, over the course of a couple of weeks in February and March we started to see something different happening in Italy. Colleagues were tweeting about the chaos in Lombardy—health services were overwhelmed, and hospitals were shutting down for almost all but COVID care. Things started to escalate rapidly. In British Columbia as well, services were quickly curtailed, and before long the number of patients through the laboratory was falling. My attendings were retriaging referrals to select urgent cases only. The office where I undertook research closed down and laid off some of its staff. The province itself quickly went into lockdown with the border with the United States closed, and supermarket shelves emptied of some essential goods as panic buying ensued. My young daughters’ preschool shut down, as did gym, ballet, and swimming classes. They could not even interact with friends at the playground and were shut up for most of the day in our small home. Friends and colleagues on fellowships started to talk about returning home. Back in the United Kingdom, my father-in-law received a letter asking him to “shield”—to stay in the house without leaving even to shop or exercise (not even going into the yard). We were more
than 4,000 miles from home, but that felt much more distant than a few weeks earlier. As the hospital prepared for the coming storm, the catheterization laboratory hours were reduced, and we had less work than fellows to do it. It seemed that there was little further clinical experience to gain from staying; other fellows needed the laboratory time more than I did. As it turned out, the good planning in British Columbia meant that hospital services returned to normal much more quickly than elsewhere. Not having the benefit of this hindsight, as a family we made a decision to return home.

My decision was graciously accepted by the program director, but that was the easy part. I spoke with the team in Liverpool, but an early start during the pandemic was not what that department needed. However, we had left Cambridge a year earlier, and an email conversation with the medical director at Royal Papworth Hospital quickly led to the offer of a short-term position as an interventional cardiology consultant. This would see me through until I started in Liverpool later in the year. From enquiry to consultant appointment in <24 h—surely a record. The real downside was a lack of time to prepare for this new role. We were to fly back to the United Kingdom on the 16th of April, and I was to start work on the 20th. Within days we had multiple offers of subsidized accommodation, and flights home were organized. We packed our bags, said socially distant goodbyes, and with no little sadness headed home.

Starting as a consultant in the middle of the COVID pandemic was not easy. To begin with, each week I was rostered for some days providing back-up care on the COVID intensive care unit (ICU) rather than doing the cardiology I had trained for. The ICU had expanded to take over a good portion of the hospital. The ICU capacity of our 300-bed hospital was now at 90 beds when I arrived, and at peak the hospital had 19 patients treated with extracorporeal membrane oxygen, a record for our institution. Fortunately, my involvement in the direct management of COVID was very limited. The intensivists (and our brilliant nursing staff) took much of the strain. Others will write articles in detail on the challenges of 12-h ICU shifts in full personal protective equipment in the ICU—I was not one of these heroes. But undertaking your first percutaneous coronary interventions (PCIs) as a consultant, in full personal protective equipment, was an experience I was unprepared for. In the year since I had left Royal Papworth, many of the catheterization laboratory staff had changed. Masks and visors are uncomfortable and a real hassle to clean properly between cases, but the breakdown in communication they cause was the hardest thing to deal with. I am fairly softly spoken in the laboratory. In fact, the nursing staff in Canada described me as a “mumbler,” even before N95 masks. I felt that I needed to shout in the laboratory to be heard, and this was much worse when I was just getting to know most of the team. The usual telepathic bond in the catheterization laboratory had not yet cemented. To cap it all, the cases were different from routine catheterization laboratory fare. PCI was more complex than usual because surgery was ruled out for all but the neediest patients. In fact, my very first case as a consultant was a left main stem bifurcation in a COVID-positive patient. Although I had plenty of complex PCI experience as a fellow, starting out as a consultant or attending physician, you want a bit of time to get your feet under the table. It has not all been difficult, however. I have found colleagues to be supportive and understanding. They have always been willing to chat through tough cases and, despite my abbreviated tenure, have included me in all aspects of the department.

So that is the story of my move back to the United Kingdom and my start as a consultant interventional cardiologist in the difficult time of COVID-19. It is not done yet, as in a few weeks I move again, to Liverpool Heart and Chest Hospital.

What lessons can I draw from this experience for myself and others? Well, first, I have been surprised and delighted with the kindness of both friends and strangers, particularly while traveling back from abroad. Fees were waived for excess baggage on the flights home, rental car companies went out of their way to help, and friends and complete strangers offered to shop for us, give us a place to stay, and help in a hundred other small ways. I have seen the way that staff in the UK National Health Service have been treated with applause every week. People have shown that they value the work of physicians and other health care staff for society. I hope this recognition (not for me—for others who deserve it more) continues once the crisis is past. I also hope that I can be as kind and generous as others have been when they have tough times.

Second, in these difficult days I have been reminded of the immense privilege I have been given. COVID-19 has not been the only issue in the past few months to agonize over. We have seen the resurgence of the Black Lives Matter movement on both sides of the Atlantic in the wake of the brutal murder of George Floyd. I am reminded that I personally have been given so much in my life—a medical education funded in large proportion by the state, a stable job in
which I have no concern about where my next pay check or meal is coming from, the opportunity to travel the world, and good health. More than this, I have never been systematically discriminated against, either as a doctor or in my private life. However difficult my life has become during COVID-19, it pales in comparison to the struggle others go through each and every day. I must remind myself of this each morning. I must examine my own prejudice in this time. It is a privilege for me to get up and go to work without fear.

Third, the lack of time to prepare for this role was arguably the hardest thing I found. In the circumstances there was little choice, and in the end it has been okay, but I wonder about the long-term ramifications. Perhaps there is an increased risk of burnout. I am actively considering ways to prevent this (the focus of a different essay, perhaps) but to others who do not find themselves starting work in a pandemic, I would suggest taking a breath before you begin. Some cardiologists will be starting this summer, particularly in North America, where cases of COVID-19 seem to be ticking up again as I write this. I hope my experience provides some help or insight.

Finally, I have spent some time reflecting on what we can learn from the wider uncertainty in our world today. I am reminded of the words of James in the New Testament, which speak to those of any faith or none. He writes:

Now listen, you who say, “Today or tomorrow we will go to this or that city, spend a year there, carry on business and make money.” Why, you do not even know what will happen tomorrow. What is your life? You are a mist that appears for a little while and then vanishes. Instead, you ought to say, “If it is the Lord’s will, we will live and do this or that” (1).

We do not know what the future holds. I left the United Kingdom for fellowship with a clear plan for the future, yet within a short period of time it was rewritten. Many others have had the same experience. As cardiologists, and physicians in general, we can be so focused on deadlines, projects, and the day-to-day bustle of our practice that we lose sight of the important aspects of our lives. The COVID crisis has provided an opportunity to pause for reflection. I have learned to be more grateful for the time with family, for our health, and for my work. I would like to finish this essay by inviting you as the reader to pause and take a moment to consider whether despite all the difficulties there are things that you, too, can be grateful during the crisis.

ADDRESS FOR CORRESPONDENCE: Dr. Joel Giblett, Department of Cardiology, Royal Papworth Hospital, Papworth Road, Cambridge CB2 0QQ, United Kingdom. E-mail: joel.giblett@doctors.org.uk.

REFERENCE
1. James 4:13-15. In: Holy Bible. New International Version. Grand Rapids, MI: Zondervan, 2011.

KEY WORDS COVID-19, early career, reflections
The current severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic has resulted in a unique global challenge for health care delivery, both in terms of the clinical sequelae of viral infection (coronavirus disease-2019 [COVID-19]) and the unintended consequences related to over-taxed health care systems. The virus enters cells by binding to the angiotensin-converting enzyme-2 receptor, which is abundantly present in the lung, heart, and vascular endothelial cells (1). This entry mechanism likely contributes to the clinical presentation of COVID-19 that includes pneumonia, hypoxemia, myocardial cell damage, cardiac dysfunction, and thrombosis, among others. The specific mechanism(s) of cardiac injury may include viral myocarditis, microthrombosis of small arterioles, cytokine-mediated plaque erosion or rupture, right-heart failure from acute respiratory distress syndrome, and oxygen supply-demand mismatch related to fever, tachycardia, and hypotension (1,2). Elevation in serum troponin reflects cardiomyocyte injury (direct or indirect), which occurs in 12% to 28% of hospitalized COVID-19 patients and predicts a 5- to 10-fold increased risk of in-hospital death (3). Thus, cardiac involvement in COVID-19 is both common and predictive of worse outcomes in affected patients.

In an effort to preserve resources, including personal protective equipment, hospital beds, and respiratory ventilators, the Centers for Disease Control and Prevention recommended deferral of elective cardiac procedures including coronary angiography and revascularization using either percutaneous coronary intervention (PCI) or coronary artery bypass grafting at the onset of the COVID-19 pandemic (4). As hospitals filled with COVID-19 patients, fear grew among both care providers and the public regarding potential exposure to COVID-19, and many patients avoided going to hospitals or clinics (5). Additionally, hospitals adopted extremely limited visitation policies, often excluding family members of patients who were undergoing urgent or emergency procedures or who were in critical condition, which worsened public perception of health care facilities as COVID-19 “hotspots.” However, coincident with the rise in COVID-19 hospital admissions was an abrupt 30% to 40% decline in hospital visits for cardiovascular emergencies including STEMI, stroke, heart failure, and aortic dissection, in both Europe and the United States, despite the fact that patients with cardiovascular disease were at higher risk of complications related to COVID-19, including thrombotic events (6,7). At a time when pandemic-related environmental and psychosocial stressors might have prompted an increased incidence of STEMI, this paradoxical decrease in STEMI presentation was associated with significant increases in out-of-hospital cardiac arrest and of death at home, compared to a similar time period in 2019, prior to the COVID-19 pandemic (8,9). Furthermore, door-to-balloon and transfer in (door-to-door-to-balloon) STEMI times for primary PCI were also prolonged due to extensive safety precautions required to protect physicians and hospital staff and limit infectious exposure (10,11).

Concern over COVID-19 cardiac involvement...
“masquerading” as STEMI with ST-segment elevation in the absence of obstructive coronary disease in up to 50% of cases caused additional ambiguity in diagnosis for patients presenting with STEMI and created impediments to timely care delivery (12–15). Even for those STEMI patients who presented for medical attention, the lack of accurate diagnostic COVID-19 testing coupled with concern by clinicians for infectious exposure prompted calls for thrombolytic therapy (“no touch approach”) even in PCI-capable centers, despite established data that primary PCI reduced mortality associated with STEMI compared to thrombolytic therapy and current societal guidelines supporting primary PCI as the standard of care for STEMI (10,16). Thus, both the delayed and the diminished presentations of STEMI have been associated with an increased incidence of out-of-hospital cardiac arrest and death at home, many of which were likely STEMIs occurring at home. Additionally, there appears to have been an increase in mechanical complications of late-presenting STEMI (ventricular septal defect, free wall rupture, papillary muscle rupture, left ventricular thrombus, congestive heart failure, and cardiogenic shock), as shown in the Central Illustration (7,12-13).

This issue of JACC: Case Reports focuses on the impact of delayed presentation of STEMI during the COVID era and the ensuing mechanical complications. Alsidawi et al. (17) present cases of delayed STEMI presentation due to patient reluctance to seek medical attention that manifested as subacute coronary occlusions and concurrent ventricular septal defects. Albiero and Seresini et al. (18) present a case of delayed anterolateral STEMI resulting in a ventricular free-wall rupture that required emergent surgical repair. Moroni et al. (19) present a series of patients with delayed presentation for STEMI associated with cardiogenic shock on presentation. Kunkel and Anwaruddin (20) describe a patient with delayed presentation of inferior STEMI that resulted...
in papillary muscle rupture and severe mitral regurgitation which required emergency surgical intervention. Yousefzai and Bhimaraj (21) present a patient who was misdiagnosed with presumed COVID-19 infection but who actually had an acute coronary syndrome. Unfortunately, the delay in diagnosis had significant consequences.

Thus, COVID-19 has directly and indirectly impacted the care of patients with cardiovascular emergencies. Ambiguity in diagnosis, delay or lack of myocardial reperfusion, and regression from primary PCI as the treatment of choice for STEMI to thrombolysis despite current clinical practice guideline recommendations have taken STEMI care backward in time by decades (10). Therefore, the Society for Cardiovascular Angiography and Interventions recently launched “The Seconds Still Count: Cardiovascular Disease Doesn’t Stop for COVID-19” campaign (22). We need strong support from current professional societal guidelines and a concerted public education campaign to bring the care of STEMI patients “Back to the Future.”

**ADDRESS FOR CORRESPONDENCE:** Dr. Robert F. Riley, Christ Hospital Health Network, 2123 Auburn Avenue, Suite 136, Cincinnati, Ohio 45219. E-mail: robert.riley@thechristhospital.com.

**REFERENCES**

1. Atri D, Siddiqi HK, Lang J, Nauffal V, Morrow D, Bohula E. COVID-19 for the cardiologist: a current review of the virology, clinical epidemiology, cardiac and other clinical manifestations and potential therapeutic strategies. J Am Coll Cardiol Basic Trans Science 2020;5:518-36.
2. Fried JA, Ramasubbu K, Bhatt R, et al. The variety of cardiovascular presentations of COVID-19. Circulation 2020;141:1930-6.
3. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 2020;5:1-8.
4. American College of Surgeons. Joint Statement: Roadmap for Resuming Elective Surgery after COVID-19 Pandemic. Available at: https://www.facs.org/covid-19/clinical-guidance/roadmap-elective-surgery. Accessed June 30, 2020.
5. De Filippo I, D’Ascenzo F, Angelini F, et al. Reduced rate of hospital admissions for ACS during COVID-19 outbreak in Northern Italy. N Eng J Med 2020;383:88-9.
6. Metzler B, Siostrzonek P, Binder RK, et al. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. Eur Heart J 2020;41:1852-3.
7. Garcia S, Albaghdadi MS, Meraj PM, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am Coll Cardiol 2020;75:2871-2.
8. Baldi E, Sechi OM, Mare C, et al. Out-of-hospital cardiac arrest during the COVID-19 outbreak in Italy. N Eng J Med 2020;383:496-8.
9. Wong LE, Hawkins JE, Langness S, Murrell KD, Iris P, Sannmann A. Where are all the patients? Addressing covid-19 fear to encourage sick patients to seek emergency care. N Engl J Med 2020 Apr 21 [E-pub ahead of print].
10. Mahmud E, Dauerman HL, Welt FGP, et al. Management of acute myocardial infarction during the COVID-19 pandemic. J Am Coll Cardiol 2020 Apr 21 [E-pub ahead of print].
11. Welt FGP, Shah PB, Aronow HD, et al. Catheterization laboratory considerations during the coronavirus (COVID-19) pandemic: from ACC’s Interventional Council and SCAI. J Am Coll Cardiol 2020;75:2372-5.
12. Solomon MD, McNulty EJ, Rana JS, et al. The covid-19 pandemic and the incidence of acute myocardial infarction. N Engl J Med 2020 May 19 [E-pub ahead of print].
13. Bhatt AS, Moscone A, McElrath EE, et al. Fewer hospitalizations for acute cardiovascular conditions during the COVID-19 pandemic. J Am Coll Cardiol 2020;76:280-8.
14. Bangalore S, Sharma A, Slotwiner A, et al. ST-segment elevation in patients with covid-19-A case series. N Engl J Med 2020;382:2478-80.
15. Stefani GG, Montorfano M, Trabattoni D, et al. ST-elevation myocardial infarction in patients with COVID-19: clinical and angiographic outcomes. Circulation 2020;141:2113-6.
16. Baimen KR, Bates EH, Armstrong PW. ST-segment-elevation myocardial infarction care and COVID-19. The value proposition of fibrinolytic therapy and the pharmacoinvasive strategy. Circ Cardiovasc Qual Outcomes 2020;13:e006834.
17. Alsidawi S, Campbell A, Tamene A, Garcia S. Ventricular septal rupture complicating delayed acute myocardial infarction presentation during the COVID-19 pandemic. J Am Coll Cardiol Case Rep 2020;2:1595-8.
18. Albiero R, Sersi G. Subacute left ventricular free wall rupture after delayed STEMI presentation during COVID-19 pandemic: a case report. J Am Coll Cardiol Case Rep 2020;2:1603-9.
19. Moroni F, Gramegna M, Ajello S, Baldetti L, Vlicca LM. Collateral damage: medical care avoidance behavior among patients with acute coronary syndrome during the COVID-19 pandemic. J Am Coll Cardiol Case Rep 2020;2:1620-4.
20. Kunkei KJ, Anwaruddin S. Papillary muscle rupture due to delayed STEMI presentation in a patient self-isolating for presumed COVID-19. J Am Coll Cardiol Case Rep 2020;2:1633-6.
21. Yousefzai R, Bhimaraj A. Misdiagnosis in the COVID era: when zebras are everywhere, don’t forget the horses. J Am Coll Cardiol Case Rep 2020;2:1614-9.
22. Society for Cardiovascular Angiography and Interventions. Cardiovascular Disease Doesn’t Stop for COVID-19. SCAI, Washington, DC. Available at: http://secondscount.org/heart-resources/covid-19-facts#.XwTN9iKq2w. Accessed July 15, 2020.

**KEY WORDS** acute coronary syndrome, complication, public health, STEMI
Letters

Persistently Elevated Troponin Level Caused by Heterophile Antibodies

Challenge in Everyday Clinical Practice

We read with great interest the case report by Santos et al. (1), published in a recent issue of JACC: Case Reports, that showed how the presence of heterophile antibodies is a rare possible cause of false positive troponin levels.

Moreover, according to our experience, an additional challenge in determining the optimal course of treatment in such patients is borderline stenosis of 1 or more coronary arteries. In the context of elevated troponin levels, accompanied by a clinical presentation understood and treated as acute coronary syndrome without ST-segment elevation, borderline 70% stenosis of the circumflex coronary artery found on a coronary angiogram of our patient was considered a "culprit" lesion, and percutaneous coronary intervention with stent implantation was performed. Repeated chest pain and elevated troponin led to another coronary angiogram, which showed no in-stent stenosis or thrombosis. Persistently elevated troponin was then suspected to be false positive resulting from the existence of heterophile antibodies in the patient's serum; and this was proven by measuring both concentration of troponin I (false positive) and troponin T (normal). The patient did not have acute coronary syndrome without ST-segment elevation, and the borderline stenosis of the circumflex artery found in the coronary angiogram was only a coincidence within her moderate cardiovascular risk profile, rather than a culprit lesion.

In this context of chronic basal elevation of troponin inconsistent with other performed diagnostic methods (repeatedly normal echocardiography and electrocardiography findings), even when borderline coronary artery stenosis is found on a coronary angiogram, it is important for clinicians to consider the possibility of heterophile antibody presence as a cause of persistently elevated troponin and avoid misdiagnosis and overtreatment. Furthermore, additional functional tests such as instantaneous wave-free ratio or fractional flow reserve should be performed to estimate the significance of a borderline coronary artery lesion, and imaging methods (single-photon emission computed tomography, cardiac magnetic resonance) should be used for detection of ischemia (2,3). Visually based conclusions regarding the hemodynamic severity of borderline coronary artery stenosis are subjective and possibly inaccurate, and they alter treatment decisions that can be of prognostic significance and cause overtreatment, especially in patients with heterophile antibodies.

*Ivana Sopek Merka, MD
Nenad Lakusić, MD, PhD
*Department of Cardiology
Special Hospital for Medical Rehabilitation Krapinske Toplice
Gajeva 2
HR-49217 Krapinske Toplice
Croatia
E-mail: ivana.sopek92@gmail.com

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

REFERENCES
1. Santos LG, Carvalho RR, Sa FM, et al. Circulating heterophile antibodies causing cardiac troponin elevation: an unusual differential diagnosis of myocardial disease. J Am Coll Cardiol Case Rep 2020;2:456-60.
2. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407-77.
3. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019;40:87-165.

REPLY: Persistently Elevated Troponin Level Caused by Heterophile Antibodies

Challenge in Everyday Clinical Practice

We thank Drs. Merka and Lakusić for their interest in our case report (1) and congratulate them for sharing their experience regarding the issue of
persistent cardiac troponin (cTn) elevation secondary to heterophile antibody (hAb) interference.

In their letter, a case-based experience is used to raise an even more challenging scenario: the presence of obstructive coronary artery disease (70% stenosis of the left circumflex artery [LCX]) in a patient with a clinical presentation similar to that of our patient (chest pain, elevated cTn-I, and no ST-segment elevation). Given the assumption of non-ST-segment elevation myocardial infarction (NSTEMI), the LCX stenosis was considered a “culprit” lesion and was successfully treated with percutaneous coronary intervention (PCI). The presence of false positive results justifying persistent cTn-I elevation was suspected following a repeat coronary angiogram that was performed to evaluate new onset of chest pain associated with cTn-I elevation and that was unremarkable. It was proven when a different troponin assay was used. As a consequence, Drs. Merkaš and Lakusič hypothesize that the patient did not experience an NSTEMI and that the intermediate LCX stenosis was probably an incidental finding.

Overall, we find that this challenging case was well managed by our colleagues and congratulate them for suspecting false positive cTn results before proceeding to additional investigation or interventions. Although we agree that the patient did not have an NSTEMI, hAb interference can only be considered likely. As proposed by Mair et al. (2), the patient’s blood sample should be treated with interference blocking proteins to confirm such a phenomenon because other analytical constraints may also cause false positive results of a given cTn assay. Regarding the appropriateness of PCI, we agree that functional tests such as fractional flow reserve may be performed to estimate the functional significance of noncritical coronary stenosis, although further studies are needed to assess the validity of culprit vessel identification in patients who have had an NSTEMI (3). Similarly, cardiac magnetic resonance would be helpful for the assessment of ischemia within the LCX territory if PCI was deferred for some reason (e.g., suspicion of false positive results) or if doubts remained following PCI (4), as well as to assess alternative causes of myocardial injury (e.g., myocarditis) (1,2).

In conclusion, the consequences of hAb interference resulting in falsely elevated cTn values may be more pronounced in patients presenting with acute chest pain and noncritical coronary artery stenosis. A high level of suspicion and appropriate complementary evaluation may reduce misdiagnosis and overtreatment, thus avoiding unnecessary prognostic implications.

*Luís Graça Santos, MD
João Morais, MD, PhD
*Department of Cardiology
Leiria Hospital Centre
Rua de Santo André
2410-197 Leiria
Portugal
E-mail: luismscp1@gmail.com
Twitter: @LuisMGSantos
https://doi.org/10.1016/j.jaccas.2020.07.008

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Case Reports author instructions page.

REFERENCES
1. Santos LG, Carvalho RR, Sa FM, et al. Circulating heterophile antibodies causing cardiac troponin elevation: an unusual differential diagnosis of myocardial disease. J Am Coll Cardiol Case Rep 2020;2:456-60.
2. Mair J, Lindahl B, Muller C, et al. What to do when you question cardiac troponin values. Eur Heart J Acute Cardiovasc Care 2018;7:577-86.
3. Idhayid AR, Koh JS, Ramzy J, et al. The role of fractional flow reserve and instantaneous wave-free ratio measurements in patients with acute coronary syndrome. Curr Cardiol Rep 2019;21:159.
4. Knuzi J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407-77.
CORRECTION

Indolfi C, Spaccarotella C

The Outbreak of COVID-19 in Italy: Fighting the Pandemic

J Am Coll Cardiol Case Rep 2020;2:1414-8

The following sentence:

On February 21, 2019, the first Italian patient with COVID-19 was diagnosed, a 38-year-old man hospitalized at Codogno Hospital, Lodi, in northern Italy.

should have been:

On February 21, 2020, the first Italian patient with COVID-19 was diagnosed, a 38-year-old man hospitalized at Codogno Hospital, Lodi, in northern Italy.

The authors apologize for this error.
The current online version has been corrected to reflect this change.

https://doi.org/10.1016/j.jaccas.2020.07.027