Delayed Presentation of Carcinoid Heart Disease and Subsequent Modified Healthcare Delivery in the COVID-19 Era

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INTRODUCTION

Primary causes of tricuspid regurgitation (TR) account for 8%-10% of cases, whereas secondary causes account for the vast majority. Carcinoid heart disease (CHD) is an important etiology of primary valvular disease for which early detection dramatically improves morbidity and mortality. However, establishing the diagnosis and creating an individualized treatment plan remains complex when utilizing several subspecialties and determining candidacy for surgical intervention. In the COVID-19 era, many patients experience delays in the evaluation and management of new and preexisting medical conditions that are both self-imposed due to fear of infection and secondary to an ever-strained healthcare delivery system. We describe the case of a 55-year-old man presenting with advanced CHD for which initial presentation was delayed due to fear of COVID-19.

CASE PRESENTATION

A 55-year-old man with a medical history of hypertension sought care delivery system. We describe the case of a 55-year-old man due to fear of infection and secondary to an ever-strained health-care delivery system. We describe the case of a 55-year-old man presenting with advanced CHD for which initial presentation was delayed due to fear of COVID-19.

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Conflicts of Interest: None.

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demonstrated elevated right-sided filling pressure (mean right atrial pressure, 15 mm Hg), normal pulmonary artery pressures, normal pulmonary capillary wedge pressure, and a low cardiac index (1.9 L/minute/m² by the Fick method). Due to rapid equalization of RV and RA pressure in the setting of severe TR, pulmonary artery systolic pressure can be underestimated by Doppler echocardiography. Thus, invasive hemodynamic assessment was performed and excluded pulmonary hypertension in this patient.

The patient was initiated on octreotide therapy and remained on oral diuretics for symptomatic management. After consultation with a cardiac surgeon, surgical tricuspid valve replacement was deferred until the patient demonstrated a satisfactory response to chemotherapy. The patient was also referred to surgical oncology for consideration of tumor debulking but deemed not to be a candidate due to his metastatic disease burden. The patient was subsequently transitioned to lutetium-177 DOTA-TATE radiopharmaceutical therapy by endocrinology, and he has since been evaluated for minimally invasive endoscopic tricuspid valve replacement.

**DISCUSSION**

Carcinoid tumors are rare neuroendocrine tumors that most commonly arise from the gastrointestinal tract. Carcinoid tumors arising from the midgut may secrete vasoactive substances, including 5-hydroxytryptamine (5-HT), tachykinins, and prostaglandins. Monoamine oxidase enzymes in the liver, lung, and brain convert 5-HT into the inactive metabolite 5-hydroxyindoleacetic acid, which is then excreted in the urine. Disease confined to the gastrointestinal tract does not produce overt carcinoid syndrome as the vasoactive substances are largely removed from the portal venous system. Metastatic disease, however, releases vasoactive substances into the systemic circulation, resulting in the clinical carcinoid syndrome. Carcinoid syndrome is characterized by symptoms of flushing, diarrhea, and bronchospasm. Carcinoid heart disease is attributed to 5-HT-induced valvulopathies and classically affects the right side of the heart. Stimulation of 5-HT receptors on cardiac valve results in plaque-like, fibrous endothelial deposits on the valve leaflets, subvalvular apparatus, atria, and ventricles. These changes are classically seen in the tricuspid and pulmonic valves; left-sided lesions are less common given the presence of monoamine oxidase enzymes in the lung parenchyma. Although CHD is rare, this diagnosis should be considered in a patient presenting with symptoms of either TR or right heart failure and symptoms of CHD. Carcinoid heart disease typically presents late in the disease course, as premetastatic disease is often clinically silent. Still more, our patient cited his fear of the COVID-19 pandemic as the reason for his delayed presentation.

Comprehensive echocardiographic findings in CHD are well described. Typically, the right-sided valves are affected, presenting most commonly with TR followed by pulmonic regurgitation and/or stenosis. In mild cases, the valve leaflets become diffusely thickened, causing them to appear straightened and stiff with minimal dysfunction. With progressive disease, there is continued thickening of the leaflets and subvalvular apparatus. As the chordae and papillary muscles of the subvalvular apparatus thicken, the chordae may become fused and shortened, resulting in varying degrees of reduced mobility with valvular retraction and tethering. In severe cases, the valve leaflets become retracted and fixed in a semiopen position, resulting in a combination of regurgitation and stenosis. Echocardiographic criteria used to grade severe TR include a dilated annulus with no valve coaptation or flail leaflet, large central jet encompassing >50% of the RA, vena contracta showing reflux of iodinated contrast into the inferior vena cava (red arrow).
Figure 2  Two-dimensional TTE oriented in an apical four-chamber view showing fixed, semiopen tricuspid valve leaflets during systole (A). Continuous-wave Doppler echocardiogram showing dense, triangular envelope of TR (B).

Figure 3  Magnified, color Doppler TTE oriented in an apical four-chamber view showing turbulent tricuspid inflow with trivial stenotic physiology (A) and severe TR (B).

Figure 4  Two-dimensional TTE oriented in a right ventricular inflow view showing a thickened and fixed, semiopen tricuspid valve with minimal change between end systole (A) and end diastole (B). Color Doppler revealed severe TR due to the leaflets being fixed in a semiopen position (C).
width > 0.7 cm, proximal isovelocity surface area radius > 0.9 cm at the Nyquist limit of 30-40 cm/sec, dense/triangular continuous-wave Doppler jet or sine wave pattern, and systolic reversal of hepatic vein flow. In the case of severe TR in CHD, echocardiographic findings are commonly described as a “dagger-shaped” form on continuous-wave Doppler with early peak pressures and rapid decline (Figure 2B).

Two-dimensional TTE is the reference standard for the diagnosis of CHD and is recommended for follow-up every 3-6 months in patients with established CHD. However, a multimodality imaging approach should be considered in these patients as part of a comprehensive evaluation and is often useful in perioperative planning. Additional imaging techniques, such as transesophageal echocardiography, three-dimensional echocardiography, and cardiovascular magnetic resonance imaging can better evaluate the pulmonic valve and more accurately quantify the right ventricular size and function. The presence of severe TR limits the accuracy of estimating RV systolic function by TTE (e.g., RV ejection fraction, fractional area change, tricuspid annular planar systolic excursion, and peak systolic annular velocity [S’]) as these parameters overestimate RV performance with severe TR. As with severe mitral regurgitation, hyperdynamic ventricular function is required to maintain a normal forward stroke volume, and care should be taken to identify “inappropriately normal” RV functional measurements.

Three-dimensional transesophageal echocardiography and cardiovascular magnetic resonance imaging are useful alternatives to TTE in assessing RV performance as they provide volumetric stroke volume assessment. Additional imaging is also important in CHD patients with left-sided valvular lesions, which are present in up to 15% of patients with CHD and generally less severe than right-sided

Figure 5 Two-dimensional TTE oriented in a subcostal view with pulsed-wave Doppler (A) and color flow Doppler (B) demonstrating hepatic vein systolic flow reversal consistent with severe TR.

Figure 6 M-mode echocardiography oriented in a parasternal short-axis view showing diastolic septal flattening (white arrows) from volume overload of the RV.
valvular involvement. When left-sided valvular lesions are present, an agitated saline contrast echocardiography should be performed to evaluate for a patent foramen ovale, which allows for direct transport of 5-HT to the left side of the heart, bypassing the inactivation that occurs in the pulmonary vascular bed.

As our patient continues systemic therapy for advanced CHD, he is planned to undergo a minimally invasive, endoscopic tricuspid valve replacement. Surgical management of CHD is indicated in patients with severe valvular regurgitation and well-controlled systemic disease. Generally, patients with CHD are referred for valve replacement surgery based on the severity of their right heart failure symptoms (e.g., fatigue, dyspnea, edema, ascites) and/or evidence of right ventricular dysfunction on echocardiography. The native valve is usually not repairable in CHD. For any patient with severe and complex valvular disease, evaluation by a multidisciplinary heart valve team is a class I recommendation. However, there is a paucity of data on the optimal timing of valve replacement surgery in patients with CHD because the decision for surgical intervention is often individualized and guided by a multidisciplinary team. Patients with successful valvular replacements have been found to have an improvement in symptoms and a decrease in early mortality. Current literature supports that early surgical intervention may lead to improved outcomes; further investigation in this area is needed.

The COVID-19 pandemic has transformed and reorganized many aspects of healthcare delivery. Regarding cancer care, experts have suggested potential modifications while preserving standards of care for patients with neuroendocrine neoplasia (NEN) during the COVID-19 era. An example of such modification includes the utilization of teledicine to facilitate continued multidisciplinary care and social distancing. Another example is the consideration of deescalation of care, when appropriate, to minimize the risk of exposure and reduce the impact on the healthcare system. Although these modifications may have little impact on slow-growing NENs and may be reasonable, these experts also strongly urge providers to make individual determinations based on the potential harms of modifying and delaying care. Furthermore, care for patients with highly functional NENs (e.g., uncontrolled carcinoid syndrome and/or CHD) should be prioritized. In our patient’s case, he was stabilized in the hospital and nonemergent testing and imaging were deferred until after the recommended quarantine period. He then had outpatient follow-up with multidisciplinary specialists to comanage his care. As the COVID-19 pandemic continues, the healthcare community is learning together how to best care and advocate for patients during these unprecedented times.

**CONCLUSION**

Herein we describe the case of a middle-aged man presenting with severe TR and resultant right heart failure secondary to CHD. Although rare, CHD represents an important etiology of primary valvular dysfunction. Despite carcinoid syndrome being a well-recognized clinical entity, establishing a diagnosis and making an individualized treatment plan remain a significant challenge and require utilization of several subspecialties. Despite this patient’s modified evaluation due to COVID-19, our case highlights the use of medical therapy to curb the progression of disease in addition to chemotherapy before attempting surgical intervention. While valvular replacement offers definitive therapy, the optimal timing for the intervention remains complex.
SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.case.2022.01.006.

REFERENCES

1. Fender EA, Zack CJ, Nishimura RA. Isolated tricuspid regurgitation: outcomes and therapeutic interventions. Heart 2018;104:798-806.
2. Prihadi E. Tricuspid valve regurgitation: no longer the “forgotten valve.” Eur Soc Cardiol 2018;16.
3. Bhattacharyya S, Davar J, Dreyfus G, Caplin ME. Carcinoid heart disease. Circulation 2007;116:2860-5.
4. Davar J, Connolly HM, Caplin ME, Pavel M, Zacks J, Bhattacharyya S, et al. Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumors: an expert statement. J Am Coll Cardiol 2017;69:1288-304.
5. Pellikka PA, Tajik AJ, Khandheria BK, Seward JB, Callahan JA, Pitot HC, et al. Carcinoid heart disease: clinical and echocardiographic spectrum in 74 patients. Circulation 1993;87:1188-96.
6. Bhattacharyya S, Toumpanakis C, Burke M, Taylor AM, Caplin ME, Davar J. Features of carcinoid heart disease identified by 2-and 3-dimensional echocardiography and cardiac MRI. Circ Cardiovasc Imaging 2010;3:103-11.
7. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, 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.
8. Muraru D, Tuveri MF, Marra LP, Badano LP, Iliceto S. Carcinoid tricuspid valve disease: incremental value of three-dimensional echocardiography. Eur J Echocardiogr 2012;13:329.
9. Oleinikov K, Korach A, Planer D, Gilon D, Grozinsky-Glasberg S. Update in carcinoid heart disease—the heart of the matter. Rev Endocr Metab Disord 2021;22:553-61.
10. Nguyen A, Schaff HV, Abel MD, Luis SA, Lahr BD, Halfdanarson TR, et al. Improving outcome of valve replacement for carcinoid heart disease. J Thorac Cardiovasc Surg 2019;158:99-1072.
11. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation February 2021;143:E72-227.
12. Connolly HM, Schaff HV, Abel MD, Rubin J, Askew JW, Li Z, et al. Early and late outcomes of surgical treatment in carcinoid heart disease. J Am Coll Cardiol 2015;66:2189-96.
13. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. Gastroenterology 2011;140:1807-1801.61.
14. Møller JE, Pellikka PA, Bernheim AM, Schaff HV, Rubin J, Connolly HM. Prognosis of carcinoid heart disease: analysis of 200 cases over two decades. Circulation 2005;112:3320-7.
15. Rodríguez-Freixinos V, Capdevila J, Pavel M, Thawer A, Baudin E, O’Toole D, et al. Practical recommendations for the management of patients with gastroenteropancreatic and thoracic (carcinoid) neuroendocrine neoplasms in the COVID-19 era. Eur J Cancer 2021;144:200-14.