Case report

A case of AL amyloidosis presenting with refractory ventricular fibrillation

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\textbf{A B S T R A C T}

A 66-year-old male with recent diagnosis of heart failure with reduced ejection fraction was referred to our institution for management of cardiogenic vasodilatory shock. During his evaluation, he suffered a sudden cardiac arrest from refractory ventricular tachycardia/fibrillation (VT/VF) despite normal electrolytes and no evidence of prior ventricular arrhythmias. He was placed on rescue peripheral veno-arterial extracorporeal membrane oxygenation support (VA-ECMO) for 4 days and was decannulated without end-organ damage. Continued workup revealed Mayo stage IV immunoglobulin light chain (AL) amyloidosis. Unfortunately, he developed acute cerebellar hemorrhage several days later. Autopsy findings were consistent with AL amyloidosis, with extensive cardiac fibrosis and amyloid deposition in the myocardium and vasculature.

While the most common cause of cardiac death in patients with amyloidosis is severe bradycardia and pulseless electrical activity, sustained ventricular arrhythmias have been reported. The use of implantable cardioverter defibrillators (ICD) is highly debated in this population given the lack of survival benefit. Our patient also developed refractory VT/VF arrest, and ICD shocks would not have rescued him while causing significant distress. Emergent VA-ECMO cannulation allowed us to make a diagnosis, yet this intervention cannot be routinely recommended given the limited survival of patients with AL amyloidosis.

1. Introduction

Sustained episodes of ventricular arrhythmias are relatively uncommon in heart failure (HF) occurring in less than 5% of all patients \cite{1}. They are often precipitated by myocardial ischemia, inflammation, underlying structural heart disease, electrolyte abnormalities, excessive neurohormonal activation, or certain medications. Sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) are even rarer in non-ischemic cardiomyopathy, including amyloidosis \cite{2}. Here we present a case of primary immunoglobulin light chain (AL) amyloidosis where patient developed refractory VF ultimately requiring rescue veno-arterial extracorporeal membrane oxygenation (VA-ECMO) cannulation.

2. Case presentation

Our patient is a 66-year-old male with hypertension and heterozygous factor V Leiden mutation who was admitted to an outside facility with new Stage C HF, NYHA Class 3 symptoms in December 2019. He was diagnosed with HF with reduced ejection fraction (LVEF: 30%) in the setting of new-onset atrial fibrillation with rapid ventricular response. Non-invasive invasive evaluation at the time was negative, his volume status was optimized, and heart rate was controlled with oral amiodarone. Guideline-directed medical therapy was initiated and titrated subsequently as outpatient. He was readmitted in June 2020 with 2 weeks of worsening cough, weight gain, and progressive shortness of breath. Treatment was started for community-acquired pneumonia and HF exacerbation; however, the patient became increasingly hypotensive, and renal function continued to worsen. Invasive hemodynamic evaluation revealed significantly elevated filling pressures (pulmonary capillary wedge pressure: 27 mmHg) and reduced cardiac index of 1.8 L/min/m\textsuperscript{2} in the setting of low systemic vascular resistance. Patient was initiated on milrinone and norepinephrine for suspected mixed cardiogenic/septic shock physiology and transferred to our institution for further management. Physical examination on arrival was notable for elevated jugular venous pressure and bilateral lower extremity edema. N-terminal pro-B-type natriuretic peptide was 3194 pg/

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\url{https://doi.org/10.1016/j.rmcr.2021.101349}

Received 3 September 2020; Received in revised form 28 November 2020; Accepted 13 January 2021
Available online 24 January 2021
mL, troponin I was 0.17 µg/L, and blood cultures were repeatedly negative. ECG showed normal sinus rhythm, first-degree atrioventricular (AV) block, and pseudo-infarct pattern in multiple coronary territories (Fig. 1). Transthoracic echocardiography (TTE) revealed an improved left ventricular (LV) ejection fraction at 45%, LV concentric remodeling, grade III diastolic dysfunction, bi-atrial enlargement, and no significant valvular abnormalities (Fig. 2). Patient responded well to aggressive diuresis with medical optimization, and vasoactive medications were titrated off. Cardiac magnetic resonance imaging was planned but delayed due to low glomerular filtration rate. Despite normal electrolytes and no history of ventricular ectopy on telemetry, patient developed cardiac arrest due to VF on day 3. Repeat attempts at defibrillation were unsuccessful, and the decision was made to proceed with peripheral VA-ECMO cannulation for refractory VF. While on full hemodynamic support, patient remained in VF/polymorphic VT for an additional 75 minutes despite defibrillations, amiodarone drip, lidocaine boluses, and deep sedation, before successfully converting to sinus rhythm. Coronary angiogram revealed no obstructive coronary artery disease. He was supported on VA-ECMO for 4 days with no arrhythmia recurrence before uneventful decannulation. Given the constellation of vasoplegia, renal dysfunction, ECG findings, and TTE results, a workup for amyloidosis was initiated. Laboratory evaluation showed significantly elevated serum lambda free light chain at 49.54 mg/dL with free light chain difference of 44.32 mg/dL. While these results were pending, a Technetium 99m Pyrophosphate scan was performed and returned negative, essentially excluding transthyretin (ATTR) cardiac amyloidosis. Endomyocardial biopsy was deemed too high risk in the setting of recent refractory VF arrest. Therefore, abdominal fat pad biopsy was performed, and samples stained with Congo red demonstrated amyloid deposition (Fig. 3). Further typing by liquid chromatography tandem mass spectrometry detected a peptide profile consistent with AL (lambda)-type amyloidosis. Despite our efforts, the patient’s renal function continued to worsen, ultimately requiring continuous renal replacement therapy in the setting of borderline hypotension. His hospital course was further complicated by acute right cerebellar hemorrhage on day 16. Due to his multi-organ failure in the setting of AL amyloidosis, the decision was made with the family to transition to comfort care measures. Despite only mild LV hypertrophy (LVH) on TTE, autopsy revealed marked cardiomegaly at 760g with minimal focal coronary artery disease. Significant myocardial fibrosis was noted on histology with amyloid deposition within the myocardium and the walls of the heart.
of small intramural coronary vessels (Fig. 4). This finding demonstrates that AL cardiomyopathy is both a toxic and infiltrative disease where severe fibrosis may occur despite only mild LVH. While amyloid deposition was present in the heart, lungs, and kidneys, it was not apparent in the brain.

3. Discussion

Amyloidosis refers to a family of diseases characterized by the extracellular deposition of insoluble, misfolded fibrillar proteins. The most commonly affected organs are the heart, kidneys, intestines, nervous system, and the skin [3]. Of the multiple subtypes, AL and ATTR amyloidosis involve the heart most commonly. AL amyloidosis is an overall rare but increasingly recognized cause of HF in developed countries with an estimated incidence of 8–12 per million individuals [4]. It is caused by a clonal plasma cell disorder where misfolded immunoglobulin light chains aggregate into insoluble fibrils and deposit in the extracellular matrix of various organs. The average age at the time of diagnosis is 70 years, and males are affected more frequently [5,6].

The cause of tissue injury and organ dysfunction is usually multifactorial and includes mass effect by the amyloid fibrils and direct cellular toxicity [7]. Amyloid deposition within the myocardium leads to thickening of the atrial and ventricular walls and progressive restrictive cardiomyopathy. Systolic dysfunction typically develops as the disease progresses. This process is due to worsening microvascular ischemia, local myocyte necrosis, and fibrosis [8]. The conduction system involvement often leads to electrophysiological abnormalities [9], such as AV node dysfunction, atrial fibrillation, atrial flutter, premature ventricular contractions, and non-sustained VT [10,11]. On the other hand, sustained and refractory VT and VF are rare, with only a limited number of published case reports in the literature [12]. As for the terminal arrhythmias in patients with AL amyloidosis, pulseless electrical activity and severe bradycardia are recorded most frequently [13–15]. While appropriate shocks delivered by implantable cardioverter defibrillators (ICD) are not uncommon in this population, the intervention yields no significant survival benefit [16–19]. Therefore, the use of ICD remains controversial in patients with amyloidosis, and the ACC/AHA/HRS guidelines emphasize individualized decision making [20].
Our patient initially presented with HF and reduced ejection fraction in the setting of rapid atrial fibrillation. He responded to medical therapy, and tachycardia-induced cardiomyopathy was the working diagnosis. While the possibility of amyloidosis was entertained upon his transfer to our institution, the need for hemodynamic stabilization precluded immediate workup. Ultimately, Mayo stage IV disease was confirmed by fat pad biopsy and serum biomarkers [21]. He developed VT/VF arrest despite normal electrolytes and no prior ventricular arrhythmias that was refractory to repeat external defibrillations. This is consistent with prior reports that ICD therapy would not have rescued our patient or prolonged his survival. Uniquely, we utilized VA-ECMO to stabilize his hemodynamics while a perfusing rhythm was restored. Our case demonstrates that the rapid initiation of mechanical circulatory support may be life-saving, despite an underlying systemic disease. Ultimately, the patient was weaned from VA-ECMO without end-organ damage but developed unexpected right cerebellar hemorrhage several days later. Although special stain with Congo red showed no clear evidence for amyloid deposition within the brain, we suspect that amyloid angiopathy may have contributed to the acute intracranial hemorrhage.

Our case highlights the fact that diagnosing amyloidosis may be challenging, especially at early stages, and a high index of suspicion is needed. It may masquerade as hypertensive heart disease or tachyarrhythmia-induced cardiomyopathy. On the other hand, these “hits” can contribute to worsened systolic function in patients with AL cardiomyopathy. While controlling blood pressure and atrial arrhythmias may lead to a temporary improvement in LV function, these interventions do not change the underlying disease trajectory. Although rare, refractory VT/VF does occur in this population, prompting repeat ICD shocks. This may cause significant distress to patients and families while not necessarily prolonging survival. Although we utilized VA-ECMO successfully to temporarily stabilize our patient, its routine use cannot be recommended given the limited survival with advanced AL amyloidosis.

Declaration of competing interest

The authors have no conflicts of interest or financial ties to disclose with respect to publication of this article.

Sources of funding

The authors received no financial support for the research, authorship, and/or publication of this article.
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