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CASE REPORT

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Cardiogenic Shock Due to Atrial Arrhythmia as the Initial Presentation of Transthyretin Cardiac Amyloidosis

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ABSTRACT

Atrial arrhythmias are common in transthyretin cardiac amyloidosis (ATTR-CA), with a prevalence of ≤80%. They are often not well tolerated. We describe 3 patients with decompensated heart failure and cardiogenic shock precipitated by atrial arrhythmias who ultimately received diagnoses of ATTR-CA. (**Level of Difficulty: Intermediate.**)
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Transthyretin cardiac amyloidosis (ATTR-CA) is an infiltrative process characterized by the deposition of amyloid fibrils in the myocardium, resulting in a restrictive cardiomyopathy. Historically, ATTR-CA has been under-recognized because of its variable clinical presentation. Atrial fibrillation has a prevalence of 60% to 80% in ATTR-CA.[1-4] Owing to impaired atrial filling, atrial arrhythmias are generally not well tolerated in patients with cardiac amyloidosis. This leads to dependence on heart rate to maintain cardiac output (CO), which can manifest as cardiogenic shock.

LEARNING OBJECTIVES

- To recognize ATTR-CA in acute decompensated heart failure precipitated by atrial arrhythmias with signs of restrictive physiology or lack of expected ventricular dilation on echocardiogram.
- To understand the unique challenges of managing atrial arrhythmias in ATTR-CA.

In this clinical case series, we describe 3 patients who presented with acute decompensation and cardiogenic shock precipitated by atrial arrhythmias in the setting of previously unrecognized ATTR-CA.

CASE PRESENTATIONS

PATIENT 1. An 86-year-old man presented with 1 month of worsening dyspnea and lower extremity edema. An initial electrocardiogram (ECG) revealed new atrial flutter with a ventricular rate of 108 beats/min (**Figure 1A**). On admission, N-terminal pro b-type natriuretic peptide was 8,456 pg/mL, and creatinine was 1.8 mg/dL from 1.3 mg/dL previously.

A transthoracic echocardiogram (TTE) showed a small left ventricular (LV) cavity (LV end-diastolic diameter [LVEDD] 3.8 cm) with severely decreased LV systolic function and global hypokinesis (ejection fraction [EF] 10%) and global longitudinal strain of 5.1% with apical sparing (**Figure 2**). The LV outflow velocity time integral was severely reduced at 7 cm (normal >18 cm) with an estimated stroke volume of

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16 mL and a severely reduced estimated cardiac output of 1.7 L/min (normal 4-6 L/min). LV function had been normal on TTE 1 year prior with an EF of 51%.

Although he improved clinically with intravenous diuresis, he was intolerant of any guideline-directed medical therapy because of hypotension. His heart rate remained stable, under 100 beats/min. Severely reduced systolic function without compensatory LV dilation and intolerance to guideline-directed medical therapy caused concern about the potential for underlying cardiac amyloidosis. A pyrophosphate (PYP) scan confirmed our suspicion, with grade 3 uptake and a heart-to-contralateral ratio of 1.97, consistent with ATTR-CA (**Figure 2**). The result of evaluation for light chain amyloidosis was negative. The result of gene testing for *TTR* gene was negative. He was given tafamidis and apixaban for stroke prevention. The patient declined transesophageal echocardiogram and direct current cardioversion. Despite persistent atrial fibrillation, he was clinically compensated on outpatient follow-up, possibly because of a relatively well-controlled heart rate of 100 beats/min.

PATIENT 2. An 82-year-old woman with a history of paroxysmal atrial fibrillation on apixaban and heart failure with a preserved EF presented with 3 months of worsening dyspnea and weight gain. ECG revealed atrial flutter and ventricular rates up to 150 beats/min (**Figure 1B**). Initial attempts at rate control with β-blockers led to worsening cardiogenic shock with a severely elevated lactate to 7.9 mmol/L, acute kidney injury with creatinine 3.4 mg/dL from a baseline of 1.2 mg/dL, and oliguria requiring initiation of dobutamine. Her symptoms and laboratory results significantly improved with inotropic agents and intravenous diuresis, and she was eventually weaned off the inotropic agent.

TTE revealed a normal-sized LV (LVEDD 4.6 cm) with a reduced systolic function (LVEF 30%). A prior history of carpal tunnel syndrome in addition to her clinical presentation raised a suspicion of cardiac amyloidosis. A PYP scan revealed grade 2 uptake and a heart-to-contralateral ratio of 1.56 consistent with ATTR-CA (**Figure 3**). The results of her work-up for light chain amyloidosis were mildly abnormal, with a faint monoclonal λ light chain on serum immunofixation and mildly elevated κ/λ ratio of 2.44, but analysis of a bone marrow biopsy specimen ruled out plasma cell dyscrasia. Genetic testing confirmed a Val142Ile variant *TTR* gene mutation.

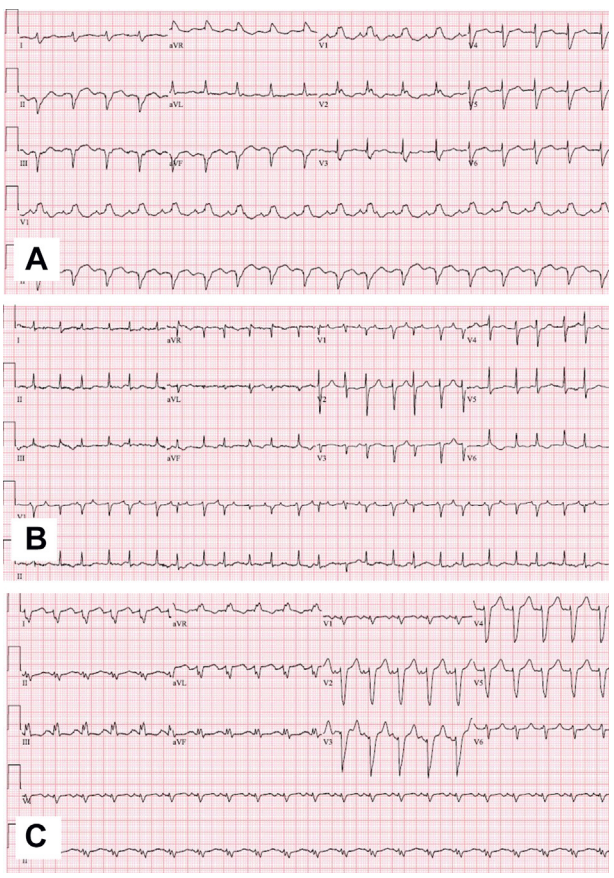
The patient underwent successful transesophageal echocardiogram and direct current cardioversion and was started on tafamidis. She remained in sinus rhythm and clinically compensated on outpatient follow-up 1 month later. Repeated TTE 6 months after hospitalization showed an improvement in LV systolic function with an EF of 69%.

PATIENT 3. A 68-year-old woman with a history of left bundle branch block presented with progressive dyspnea, weakness, and palpitations. Her ECG revealed atrial tachycardia with a ventricular rate of 170 beats/min (**Figure 1C**). Her serum lactate was 3.0 mmol/L, and N-terminal pro b-type natriuretic peptide was 4,304 pg/mL. TTE showed severe biatrial enlargement, severely decreased LV systolic function with global hypokinesis (LVEDD 5.3 cm, LV EF 10%), and global longitudinal strain of 4.7%. Milrinone was initiated, with improvement in end-organ function, and amiodarone was given, with resolution of the atrial tachycardia.

ABBREVIATIONS AND ACRONYMS

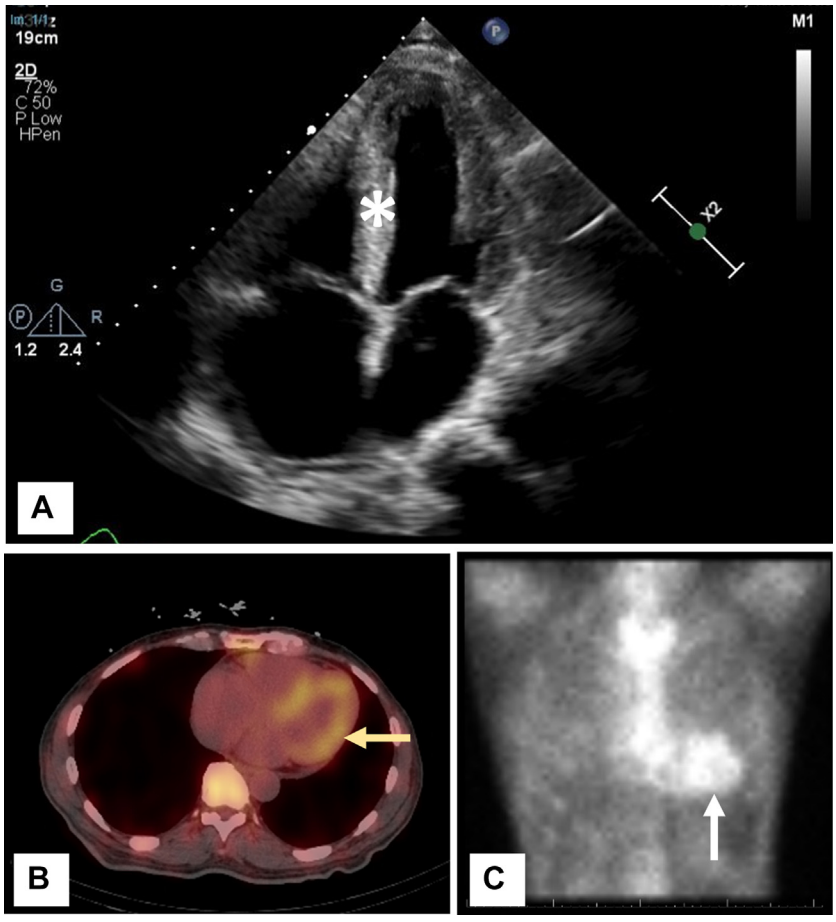
ATTR-CA = transthyretin cardiac amyloidosis
CO = cardiac output
EF = ejection fraction
ECG = electrocardiogram
LV = left ventricle
LVEDD = left ventricular end-diastolic diameter
PYP = pyrophosphate
TTE = transthoracic echocardiogram

FIGURE 1 Electrocardiograms



(A) Atrial flutter in patient 1. **(B)** Atrial fibrillation in patient 2. **(C)** Atrial tachycardia in patient 3.

FIGURE 2 Images of Patient 1



(A) Apical 4-chamber view on echocardiogram with increased LV wall thickness with an interventricular septum thickness of 1.2 cm **(asterisk)** and low normal LV internal diameter at end diastole, measuring 3.8 cm. Pyrophosphate scan with single- photon emission computed tomographic image **(B)** showing increased myocardial uptake **(yellow arrow)** and planar image **(C)** that corresponds to a grade 3 ASNC score and a H/CL of 1.97 **(white arrow)**.

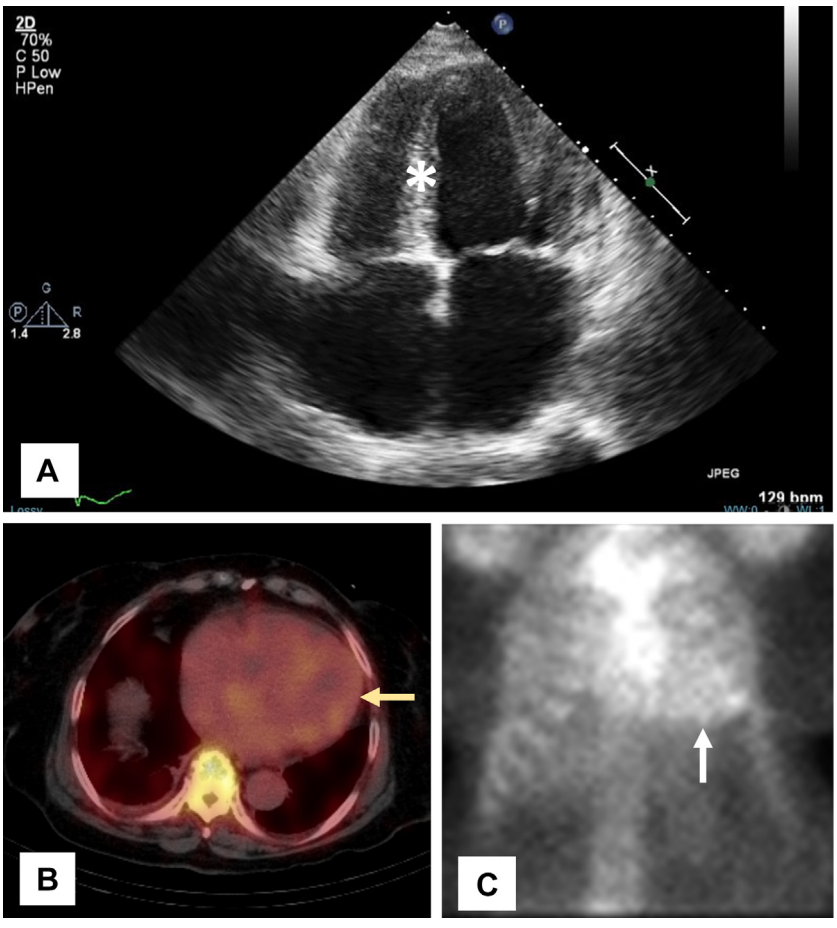
A PYP scan revealed grade 3 uptake and a heart-to-contralateral ratio of 1.72 consistent with ATTR-CA (Figure 4). The result of a work-up for light chain amyloidosis was negative. Analysis of an endomyocardial biopsy specimen showed results that were consistent with amyloidosis, and mass spectrometry revealed ATTR-CA with an Ala140Se variant, confirmed on genetic testing. She was given tafamidis. Unfortunately, she was unable to be weaned from inotropic support, and she ultimately required orthotopic heart transplantation. She continues to do well after transplantation.

DISCUSSION

These 3 cases illustrate how atrial tachyarrhythmias and cardiogenic shock can be the initial presentations of ATTR-CA, and we highlight subtle signs that clinicians may use to unmask unrecognized cardiac amyloidosis. Although tachycardia-induced cardiomyopathy and related shock are not unique to ATTR-CM, there were several clues that raised our clinical suspicion for end-stage ATTR-CA in our patients. They had a newly reduced LV function but without compensatory LV dilation, and the ECGs with relatively low voltage were discordant with increased LV wall thickness on TTE (Figure 5). In these cases, the findings of decreased EF were most consistent with end-stage ATTR-CA, with high degrees of myocardial infiltration.

The restrictive physiology of ATTR-CA leads to reliance on heart rate to maintain CO; bradycardia and tachycardia can lead to a drop in CO. Furthermore, the restrictive physiology of ATTR-CA

FIGURE 3 **Images of Patient 2**



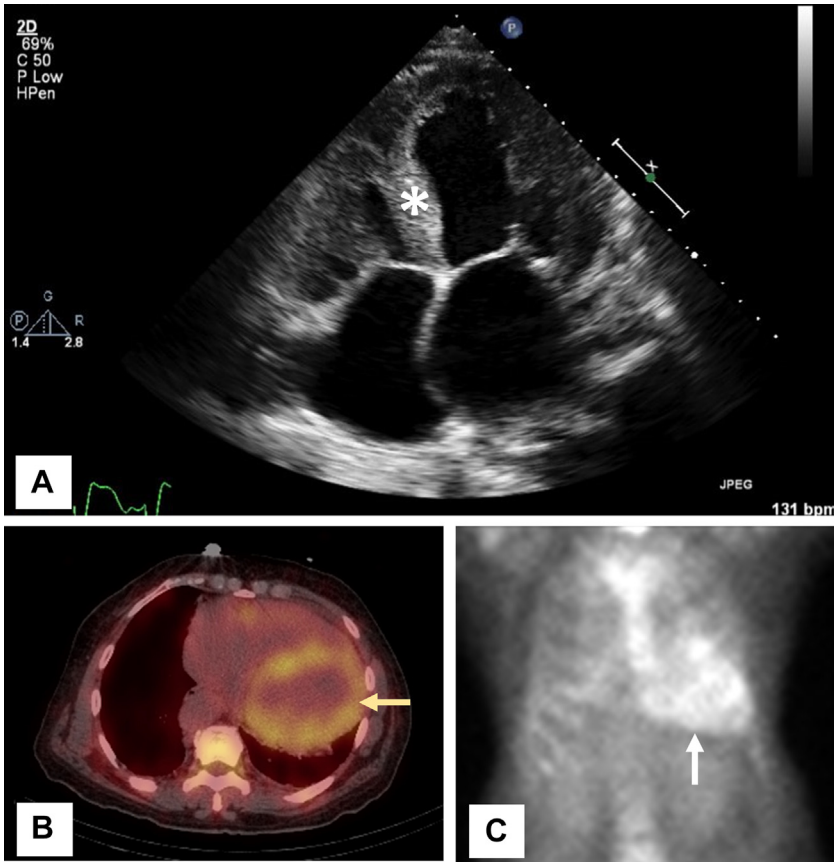
(A) Apical 4-chamber view on echocardiogram with increased an interventricular septum thickness of 1.0 cm **(asterisk)**, normal LV dimension (LVEDD 4.6 cm), and biatrial enlargement. Pyrophosphate scan with single-photon emission computed tomographic image **(B)** showing increased myocardial uptake **(yellow arrow)** and planar image **(C)** that corresponds to a grade 2 ASNC score and H/CL of 1.56 **(white arrow)**.

increases sensitivity to a loss of organized late diastolic atrial contraction,[1] leading to decompensated heart failure and rapid progression to cardiogenic shock. Additionally, 50% to 80% of patients with ATTR can have autonomic dysfunction.[5] This can often manifest as impaired compensatory vasoconstriction and rapid progression to shock, given the impaired ability to increase systemic vascular resistance to compensate for a decrease in CO.[5]

There are 2 possible mechanisms for the predisposition to atrial arrhythmias in ATTR-CA. The first is atrial dilation from ventricular wall thickening and impaired relaxation from amyloid deposition, causing elevated filling pressures.[6] The second is myocardial fibrosis and structural remodeling caused by amyloid deposition.[6] This second mechanism can lead to arrhythmia in the absence of the characteristic left atrial dilation. Given these findings, increased LV wall thickness, nondilated LV, and atrial arrhythmias in patients who present with acute heart failure should prompt suspicion of ATTR-CA.

The management of atrial arrhythmias in ATTR-CA is challenging. There are conflicting data on whether rhythm control is associated with improved survival in patients with ATTR-CA.[2,4] Furthermore, common rate-controlling medications such as β-blockers, calcium channel blockers, and digoxin are linked to worse outcomes in ATTR-CA.[7,8] This supports initial attempts to achieve normal sinus rhythm in these patients. The success of antiarrhythmic agents and direct current cardioversion in ATTR-CA appears to be similar to that in the general population, although more severe ATTR-CA is associated with a higher rate of recurrence of the arrhythmia.[1,9] The choice of

FIGURE 4 Images of Patient 3



(A) Apical 4-chamber view on echocardiogram with increased LV wall thickness with an interventricular septum thickness of 1.3 cm **(asterisk)**, normal LV dimension, and biatrial enlargement. Pyrophosphate scan with single-photon emission computed tomographic image **(B)** showing increased myocardial uptake **(yellow arrow)** and planar image **(C)** that corresponds to a grade 3 ASNC score and H/CL of 1.72 **(white arrow)**.

antiarrhythmic agent is often limited because of comorbid conditions associated with amyloidosis, such as renal impairment and heart failure. Anticoagulation is an important consideration for patients with atrial fibrillation and ATTR-CA because the risk of cardioembolic events is substantial.[4,10]

Two of our patients underwent cardioversion to normal sinus rhythm. However, only 1 patient achieved rapid reversal of cardiogenic shock; the other was dependent on inotropic support and eventually required heart transplantation. This heterogeneity in response speaks to the degree of underlying amyloid infiltration and resulting degree of cardiomyopathy. Our third patient's explanted heart revealed significant infiltration by amyloid fibrils and almost complete loss of normal myocardial architecture.

We hope to highlight atrial arrhythmias as the initial presentation of ATTR-CA and emphasize the need for further research on best management strategies of atrial arrythmias, including rate versus rhythm control, cardioversion, and ablation. These cases underscore the importance of maintaining a high index of suspicion for ATTR-CA in cases of acute heart failure precipitated by arrhythmias, especially when there are signs of restrictive physiology, lack of ventricular dilation on echocardiogram, and discordant low voltage on ECG.

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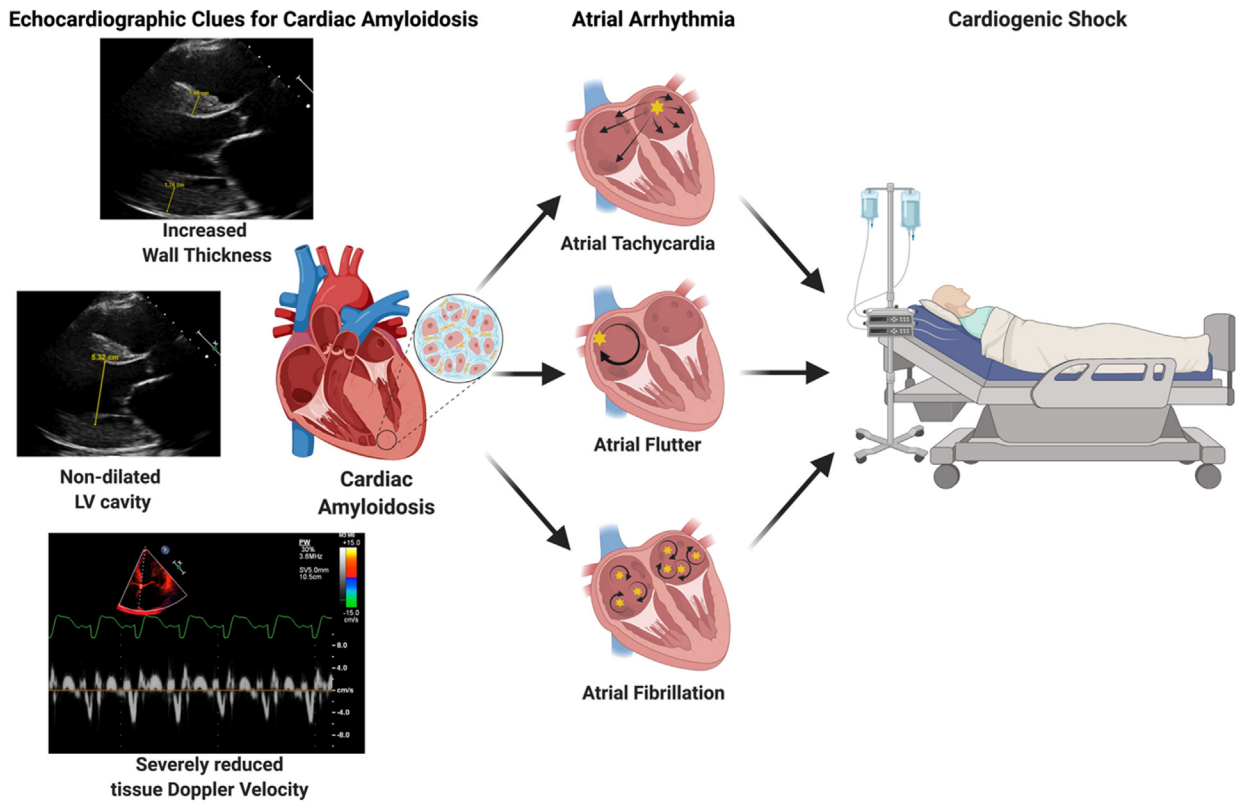
FIGURE 5 Visual Depiction of Echocardiographic Findings in Transthyretin Cardiac Amyloidosis and the Precipitation of Cardiogenic Shock by Atrial Arrhythmias



LV = left ventricular. Figure created using Biorender.

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