

# Cardiac amyloid presenting as cardiogenic shock: case series

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## Background

Amyloidosis is a systemic infiltrative disease that can affect nearly every organ in the human body. It is characterized by the deposition of misfolded protein within various tissues and organs. Once there is cardiac involvement this portends a worse prognosis.

## Case summary

We describe a case series of two patients with cardiac amyloidosis presenting as a cardiogenic shock. There were several missed opportunities in diagnosing cardiac amyloid prior to their fatal presentations. In the first case, a 65-year-old African-American male patient presented with worsening shortness of breath and signs of heart failure. Echocardiography revealed preserved ejection fraction. He was diagnosed with light chain subtype of cardiac amyloidosis, and rapidly deteriorated during his admission. Patient in the second case is a 75-year-old African-American female who presented with worsening heart failure and hypotension. Echocardiography revealed reduced ejection fraction. She was diagnosed with transthyretin cardiac amyloid. Her clinical status worsened during admission and she went into cardiogenic shock requiring multiple vasopressors.

## Discussion

This case series discusses two incidences of cardiac amyloidosis presenting as cardiogenic shock in African-American patients. This article postulates that cardiac amyloidosis may be misdiagnosed for more common causes of heart failure especially among this demographic group. Once patients with cardiac amyloid present with cardiogenic shock their clinical course is typically rapidly fatal despite aggressive measures. Earlier detection is imperative to prevent poor outcomes.

## Keywords

Case report • Transthyretin amyloidosis • Light chain amyloidosis • Transthoracic echocardiogram • Pyrophosphate scan

## Learning points

- Light chain amyloidosis and transthyretin-associated amyloidosis can cause end-stage heart failure, and earlier diagnosis can lead to improved outcomes.
- Once there is extensive cardiac involvement by amyloidosis, patient's prognosis worsens and treatment options become limited, as the treatment for cardiac amyloid is focused on preventing progression of the disease.
- Treatment for cardiac amyloidosis should be initiated as soon as diagnosis is made, however, in cases of patients presenting with cardiogenic shock, treatment at this stage may be futile.

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## Introduction

Amyloidosis is a systemic infiltrative disease that can affect nearly every organ in the human body. The two most common subtypes of amyloid that present with cardiac involvement are light chain amyloidosis (AL) and transthyretin-associated amyloidosis (ATTR).<sup>1</sup> Both subtypes cause a restrictive cardiomyopathy due to infiltration of amyloid protein into the myocardium.<sup>1</sup> Although amyloidosis with cardiac involvement is considered to have a poor prognosis, treatment has shown to prolong survival time and improve quality of life. AL subtype is typically treated with chemotherapeutic regimens and if possible, autologous stem cell transplant. The development of novel agents for the ATTR subtype has been shown to slow the progression of cardiomyopathy by working as transthyretin silencers and stabilizers.<sup>1</sup> When cardiac amyloidosis presents with cardiogenic shock, mortality rates are high despite aggressive treatment with inotropic support.<sup>2</sup> Once these patients present in shock, their clinical course can be rapidly fatal. With recent advancements, patients can experience better overall prognosis and management of their disease. However, to effectively treat cardiac amyloidosis, it must be diagnosed early and appropriately.

## Timeline

## Case Presentation

### Case 1

A 65-year-old African-American male with a history of hypertension and heart failure with preserved ejection fraction presented with worsening shortness of breath. On arrival, he was febrile, hypotensive (85/60 mm Hg), tachypnoeic (25 breaths/min), and saturating 99% on room air. Cardiac exam revealed elevated jugular venous pressure, regular rate and rhythm, with no murmurs. Bilateral crackles were heard on lung auscultation and there was 3+ pitting oedema of the bilateral lower extremities.

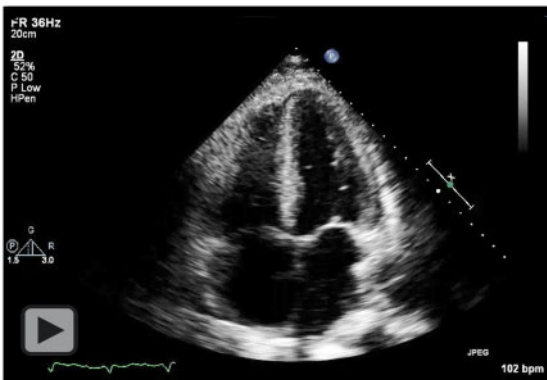
### Investigations

Preliminary lab work revealed elevated pro-brain natriuretic peptide level (2121 pg/mL) and transaminitis (aspartate aminotransferase 44 U/L, alkaline phosphatase 232 U/L). Chest radiograph showed pulmonary vascular congestion with bilateral pleural effusions. Electrocardiogram (ECG) with normal sinus rhythm and low voltage QRS complexes, acute myocardial infarction was ruled out (*Figure 1*). Bedside echocardiography on admission revealed left ventricular (LV) ejection fraction of 60%, without signs of cardiac tamponade or valvular pathology.

Day	Case 1	Day	Case 2
1	A 65-year-old African-American male presents with worsening shortness of breath Vitals: Hypotensive (85/60), tachypnoeic (25 breaths/min), and saturating 99% on room air Labs: Elevated pro-brain natriuretic peptide, transaminitis, and thrombocytopenia ECG: Normal sinus rhythm and low voltage QRS complexes Admitted to internal medicine service for heart failure exacerbation	1	A 75-year-old African-American female presents with worsening shortness of breath and lower extremity oedema Vitals: Hypotensive (87/69), tachycardic (106 beats/min), and saturating 95% on 2L nasal cannula Labs: Elevated pro-brain natriuretic peptide ECG: Sinus tachycardia Admitted to internal medicine service for heart failure exacerbation
2–5	Patient was treated with IV diuretics and supportive care and was haemodynamically stable	2–3	Patient was treated with standard goal-directed medicated therapy and IV diuretics
6	Patient became progressively more obtunded and altered Transferred to cardiac care unit and required intubation for acute hypoxemic respiratory failure and inotropic support with dobutamine Even with use of vasoactive medications, patient remained haemodynamically unstable and went into pulseless electrical activity arrest and was unable to be resuscitated	4	Patient went into atrial fibrillation with rapid ventricular response and was successfully electrically cardioverted Patient's hypotension worsened and transferred to cardiac care unit for vasoactive support
Week later	Autopsy results revealed widespread deposits of light chain amyloid in right and left ventricles, with myocyte hypertrophy Final diagnosis was cardiogenic shock caused by extensive cardiac amyloidosis	5–7	Nuclear medicine pyrophosphate scan ( <sup>99m</sup> Tc-PYP) suggestive of transthyretin cardiac amyloidosis In light of poor prognosis, patient transferred to hospice care and passed shortly after



**Figure 1** Electrocardiogram of patient with light chain amyloidosis revealing sinus tachycardia and low voltage QRS complexes.



**Video 1** Transthoracic echocardiogram patient in Case 1 with light chain amyloidosis with preserved ejection fraction and thickened myocardium.



**Video 2** Transthoracic echocardiogram (parasternal long-axis view) of patient in Case 2 with severe right and left ventricular systolic dysfunction (ejection fraction 20%) with diastolic profile suggestive of restrictive filling pattern, with small left ventricular cavity size, and increased left ventricular wall thickness. Characteristics pathognomonic of cardiac amyloidosis.

## Management

He was admitted for management of heart failure exacerbation. Transaminitis was thought to be secondary to hepatic congestion related to the patient's volume overloaded state. He was treated with intravenous diuretics and supportive care. Despite treatment, he became progressively more obtunded. After 1 week of admission, the patient was transferred to the cardiac critical care unit. He required intubation for acute hypoxemic respiratory failure and inotropic support with dobutamine. Despite the use of vasoactive medications, he remained haemodynamically unstable. He ultimately went into pulseless electrical activity arrest and was unable to be

resuscitated. In the setting of his rapid deterioration, an autopsy was performed. Autopsy revealed widespread deposits of AL amyloid in the right ventricular and LV with myocyte hypertrophy, suggesting long standing cardiac stress. There was diffuse amyloid deposition in the liver which explained the patient's transaminitis. Final diagnosis was cardiogenic shock caused by extensive cardiac amyloidosis.

Notably, this patient had multiple cardiac evaluations for heart failure prior to his presentation of cardiogenic shock. Echocardiography was completed 1 year prior to the patient's admission which demonstrated preserved ejection fraction (60–65%) and thickened



**Video 3** Transthoracic echocardiogram (apical four-chamber view) of patient in Case 2 demonstrating biatrial enlargement, increased left ventricular wall thickness, and speckled left ventricular myocardium.

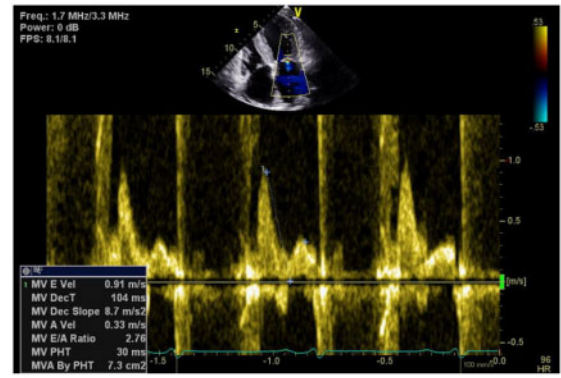


**Figure 2** Transthoracic echocardiogram (parasternal long-axis view) revealing increased left ventricular wall thickness and speckled myocardium suggestive of cardiac amyloidosis.

myocardium (Video 1). Left heart cardiac catheterization completed at that time revealed non-obstructive coronary artery disease. At the time, his heart failure was attributed to long standing hypertension. Per chart review, it was discovered that the patient complained of mild, non-specific symptoms such as shortness of breath and lower extremity oedema during multiple subsequent outpatient clinic appointments. While various medication adjustments were made, there was never further investigation to assess for other aetiologies of his heart failure.

## Case 2

A 75-year-old African-American female with a history of paroxysmal atrial fibrillation, heart failure with reduced ejection fraction, hypertension, and end-stage renal disease presented with worsening shortness of breath, lower extremity oedema, and hypotensive episodes



**Figure 3** Transthoracic echocardiogram demonstrating diastolic dysfunction with restrictive filling pattern which is a characteristic finding in patients with cardiac amyloid. There is an increased E/A ratio of 2.76.

during her haemodialysis session. Vital signs on arrival were notable for hypotension (87/69 mmHg) and tachycardia (106 beats/min). She had a new oxygen requirement of 2 L nasal cannula oxygen to maintain acceptable O<sub>2</sub> saturations.

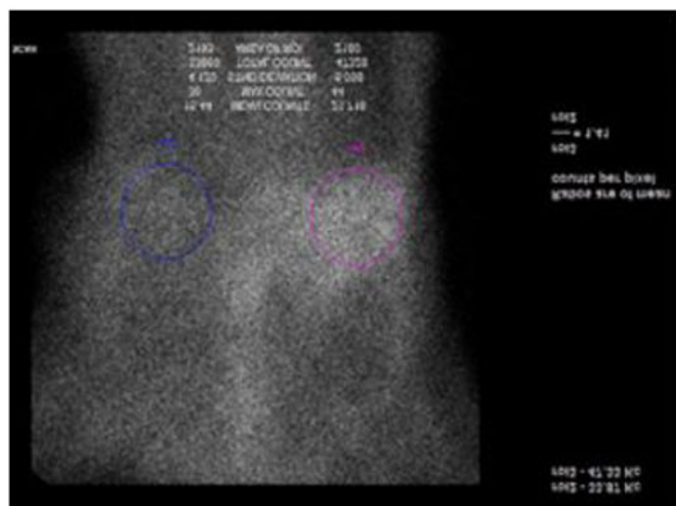
## Investigations

ECG on admission demonstrated low voltage QRS complexes. Troponin T was elevated (0.35 ng/mL), however, when trended, levels remained flat, making the diagnosis of non-ST elevation myocardial infarction unlikely. Pro-brain natriuretic peptide was elevated at 1653 pg/mL. Transthoracic echocardiogram (TTE) showed severe right ventricular and LV systolic dysfunction with ejection fraction of 20% (Videos 2 and 3), with increased LV wall thickness and concerns for restrictive cardiomyopathy based on diastolic profile with impaired filling and increased E/A ratio >2 (Figure 2 and 3).

## Management

She was admitted for heart failure exacerbation and treated with supportive care and IV diuretics. In the setting of her TTE and ECG findings, nuclear medicine pyrophosphate scan (99mTc-PYP) was performed to assess for amyloidosis. There was diffuse radiotracer uptake within the myocardium. The heart to contralateral ratio was 2.3 (Figure 4). Labs were ordered to assess for evidence of a monoclonal protein in the urine and serum which were negative. Findings were strongly suggestive of transthyretin cardiac amyloidosis. Her hospital course was complicated by atrial fibrillation with rapid ventricular response. Her hypotension worsened and she required three vasopressors at maximum doses. Considering her poor prognosis, the palliative care team was consulted for further care guidance and she was eventually transferred to hospice for comfort care, she passed 1 week thereafter.

The patient described in Case 2 was diagnosed with severe systolic dysfunction 1.5 years prior to her presentation of cardiogenic shock. Left heart catheterization conducted at that time demonstrated angiographically normal coronary arteries. Initially, her cardiomyopathy was deemed secondary to hypertension and atrial fibrillation



**Figure 4** Pyrophosphate scan ( $^{99m}\text{Tc}$ -PYP) showing increased cardiac uptake with a heart to contralateral ratio of 2.3, suggestive of transthyretin cardiac amyloidosis.

with therapy primarily based on controlling blood pressure, cardiac rate and rhythm. Once her hypertension and atrial fibrillation were adequately controlled, subsequent therapy focused solely on uptitrating guideline-directed medical therapy for heart failure.

## Discussion

It has been well established that amyloidosis causes cardiac injury and can present with signs of cardiomyopathy. However, the severity of cardiac amyloidosis and its prevalence among historically underserved patients is often overlooked.<sup>3</sup> Our case series highlights two important facets of cardiac amyloid. One is the potential catastrophic impact of a missed cardiac amyloid diagnosis. Second is cardiac amyloid may be misdiagnosed for more common causes of heart failure, especially among African-American patients. Since hypertensive heart disease is far more common than cardiac amyloidosis, it is reasonable to assume many cases of heart failure are due to uncontrolled hypertension. Consequently, this leaves the possibility that some patients with cardiac amyloid are mislabelled leading to underdiagnosis. This is particularly true in transthyretin (TTR)-related cardiac amyloidosis, which closely mimics hypertensive hypertrophic heart disease.<sup>3</sup>

Unfortunately, there were several missed opportunities to diagnose cardiac amyloidosis sooner. Red flags that should raise suspicion for either subtype of cardiac amyloidosis include onset of heart failure at an older age, heart failure with multisystem involvement, non-ischaemic cardiomyopathy, failure to tolerate or improve with guideline-directed medical therapy with beta-blockers and angiotensin-converting enzyme inhibitors, family history of amyloidosis, and unexplained diastolic heart failure with preserved ejection fraction.<sup>3,4</sup> Any of these signs in association with one or more of the following increases speculation for AL amyloidosis: elevated serum free light chains, non-diabetic nephrotic proteinuria, easy bruising and purpura, or hepatomegaly with transaminitis.<sup>5</sup> In the TTR subtype, signs of

neuropathy (i.e. carpal tunnel syndrome) typically precedes cardiomyopathy by years and can be a clinical clue in diagnosis.

Both patients in this case series were African Americans and were diagnosed in the end-stage of their disease. Interestingly, despite being diagnosed with heart failure years prior to developing cardiogenic shock, the aetiology of their heart failure was never thoroughly worked up. As such, neither patient received appropriate disease counselling, prognostic expectations, nor appropriate treatment.

Treatment regarding cardiac amyloidosis varies depending on subtype. The main subtypes of amyloidosis that cause cardiomyopathy are the immunoglobulin light chain (AL) and the ATTR subtypes. With regards to AL amyloidosis, the most common treatment relies upon the proteasome inhibitor, Bortezomib, which is combined with cyclophosphamide and dexamethasone given as a weekly chemotherapeutic regimen. This regimen may be used alone or as a temporizing measure to heart transplant followed by stem cell transplant. Without treatment, patients with AL amyloidosis who present with heart failure have an average survival time of <6 months. However, some studies have shown with an appropriate therapeutic regimen, patients with AL cardiomyopathy have a 65% five-year survival rate.<sup>6,7</sup> Regarding Patient 1, when he first presented a year prior with heart failure symptoms, he may have had a better clinical outcome with prompt initiation of chemotherapy treatment. However, his prognosis was already poor due to his cardiac involvement.

While the treatment for AL cardiomyopathy has been relatively well established, treatment options for ATTR cardiomyopathy have expanded recently with the use of the transthyretin stabilizer Tafamidis to treat ATTR cardiomyopathy. This medication has been shown to reduce all-cause mortality and reduce cardiovascular hospitalizations.<sup>7</sup> There are also off label agents such as TTR gene silencers (Patisiran and Inotersen) typically used for ATTR peripheral neuropathy and the NSAID Diflunisal which have all been shown to have some benefits in treating the cardiac manifestations of ATTR amyloidosis.<sup>8</sup> Regarding Patient 2, prior to developing systolic heart

failure, her prior echocardiograms (ECHOs) did show evidence of heart failure with preserved ejection fraction and diastolic dysfunction with subsequent progression to heart failure with reduced ejection fraction. If diagnosis and treatment of her ATTR cardiac amyloid could have been initiated before the deterioration in her cardiac function, her clinical course may have been improved.

With treatment and diagnostic options rapidly expanding, early diagnosis of cardiac amyloidosis is now extremely important. Current treatment focuses on preventing disease progression rather than disease reversal. In both Case 1 and Case 2, the patients progressed to end-stage heart failure prior to diagnosis. While there is yet to be a consensus on what disease stage that treatment becomes futile, earlier diagnosis does lead to improved outcomes.<sup>7-9</sup>

Characteristic patterns on ECG, ECHO, and cardiac magnetic resonance imaging (cMRI) can assist in earlier recognition of the disease. Signs of ventricular hypertrophy with inappropriately low electrical voltages on ECG are typical, but non-specific, of cardiac amyloid. Some of the classic two-dimensional (2D) ECHO signs of cardiac amyloid are increased LV thickness in end-diastole of  $\geq 12$  mm thickness, speckled LV myocardium appearance from amyloid fibril deposits, a small LV chamber size, left atrial or biatrial enlargement, thickened mitral and tricuspid valves, and diastolic dysfunction with a restrictive filling pattern.<sup>9</sup> New ECHO techniques such as speckle tracking echocardiography (2D-STE) have also shown promising results for the detection of cardiac amyloid in the earlier sub-clinical stages.<sup>9</sup> 2D-STE can detect myocardial dysfunction by assessing impairment of global longitudinal strain (LS). Patients with cardiac amyloid have profoundly altered LV strain parameters, with relative apical sparing of LS typically seen on ECHO.<sup>10</sup> Previous studies have demonstrated that relative sparing of LS in the LV apex using 2D speckle tracking is highly sensitive (93%) and specific (82%) for the diagnosis of cardiac amyloid.<sup>10,11</sup> ECHO findings suggestive of cardiac amyloid in the appropriate clinical setting should prompt consideration for cMRI. If clinical suspicion is high without supportive ECHO findings, cMRI should still be considered; as ECHO findings may not be seen until late stages of the disease when there is already a decrease in the LV ejection fraction. While endomyocardial biopsy is still regarded as the gold standard for the diagnosis of cardiac amyloid, its invasive nature, limited availability, and potential procedural complications have led to the increased use of other diagnostic modalities.<sup>11,12</sup> cMRI is a non-invasive method that provides a detailed assessment of myocardial morphology, functional capacity, and amyloid deposition leading to a safer option to diagnose patients.<sup>12</sup> cMRI will show various patterns of late gadolinium enhancement. Although cMRI can be useful and precise in detecting cardiac amyloid, limitations include the inability to distinguish between the amyloid subtypes.

Nuclear imaging techniques with bone-seeking radiotracers have become a diagnostic method for ATTR-CA and are able to distinguish it from AL-CA with high specificity. This was demonstrated in our Case 2 patient, who had diffuse radiotracer uptake on nuclear medicine pyrophosphate scan with no evidence of monoclonal protein on haematologic workup. This non-invasive imaging scan was able to aid in differentiating between the subtypes of cardiac amyloid, without the need for more invasive testing. The exact mechanism by which these bone-seeking radiotracers accumulate in the myocardium of patients with cardiac amyloidosis remains unclear.

All in all, there is a need for increased awareness of the disparities in diagnosing amyloidosis to both prevent poor outcomes and to provide higher quality of care to these patients.<sup>5</sup> These two cases may suggest that perhaps amyloidosis plays a larger role than previously thought in patients presenting with heart failure.

## Conclusion

Cardiac amyloidosis remains a diagnostic challenge for clinicians. Early and accurate diagnosis of amyloidosis is crucial for the implementation of appropriate patient care and is now more important than ever given the availability of new therapies.

## Lead author biography



Dr Monique Oye is a physician at University of Florida Health Jacksonville. She is completing her Internal Medicine residency, and pursuing cardiology fellowship. Her areas of interest include cardiac amyloid and heart failure.

## Supplementary material

**Supplementary material** is available at *European Heart Journal - Case Reports* online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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## References

1. Rubin J, Maurer M. Cardiac amyloidosis: overlooked, underappreciated, and treatable. *Annu Rev Med* 2020;**71**:203–219.
2. d'Humières T, Fard D, Damy T, Roubille F, Galat A, Doan H-L et al. Outcome of patients with cardiac amyloidosis admitted to an intensive care unit for acute heart failure. *Arch Cardiovasc Dis* 2018;**111**:582–590.
3. Shah KB, Mankad AK, Castano A, Akinboboye OO, Duncan PB, Fergus IV et al. Transthyretin cardiac amyloidosis in black Americans. *Circ Heart Fail* 2016;**9**:e002558.
4. Meier-Ewert HK, Santhorawala V, Berk JL, Ruberg FL. Cardiac amyloidosis: evolving approach to diagnosis and management. *Curr Treat Options Cardiovasc Med* 2011;**13**:528–542.
5. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. *J Am Coll Cardiol* 2016;**68**:1323–1341.

6. Alexander KM, Orav J, Singh A, Jacob SA, Menon A, Padera RF et al. Geographic disparities in reported US amyloidosis mortality from 1979 to 2015: potential underdetection of cardiac amyloidosis. *JAMA Cardiol* 2018;**3**:865–870.
7. Hanna M, Huded C, Rodriguez ER, Phelan D, Kwon D, Jaber W et al. Progress in diagnosing and managing cardiac amyloidosis. *Cleve Clin J Med* 2019;**86**:29–37.
8. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–1016.
9. Tsang W, Lang RM. Echocardiographic evaluation of cardiac amyloid. *Curr Cardiol Rep* 2010;**12**:272–276.
10. Phelan D, Collier P, Thavendirathan P, Popović ZB, Hanna M, Plana JC et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012;**98**:1442–1448.
11. Mohty D, Damy T, Cosnay P, Echahidi N, Casset-Senon D, Viot P et al. Cardiac amyloidosis: updates in diagnosis and management. *Arch Cardiovasc Dis* 2013;**106**:528–540.
12. Zhao L, Tian Z, Fang Q. Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2016;**16**:129.