CASE REPORT

Cardiac amyloidosis masquerading as biventricular hypertrophy in a patient with multiple myeloma

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SUMMARY

Cardiac amyloidosis or amyloid cardiomyopathy is a rare disorder characterised by extracellular deposition of insoluble polymers composed of low-molecular-weight subunit proteins within the myocardium. This often results in an infiltrative cardiomyopathy with restrictive pathophysiology, leading to progressive heart failure. In this report, we present an interesting case of cardiac amyloidosis that eventually led to the diagnosis of underlying multiple myeloma in a patient with no previous cardiac history. Cardiac amyloidosis should be suspected in patients with unexplained congestive heart-failure symptoms accompanied by low-voltage complexes on ECG, preserved ejection fraction with asymmetric ventricular hypertrophy and abnormal myocardial texture, described as 'granular sparkling' on echocardiogram. Patients with cardiac amyloidosis should be closely monitored as mortality remains high, despite advances in treatment.

BACKGROUND

Amyloidoses constitute a group of heterogeneous disorders caused by deposition of amyloid fibrils, which are composed of misfolded proteins in one or more organs.¹ Amyloid fibrils are composed of insoluble, low-molecular-weight subunits ranging from 5 to 25 kDa, which are usually derived from the partial folding or unfolding of the precursor protein. To date, 27 amyloid precursor proteins have been identified in humans.² The most commonly encountered systemic amyloidoses in clinical practice are AL (primary) amyloidosis and AA (secondary) amyloidosis. Other clinical types include dialysis-associated amyloidosis, senile amyloidosis, heritable amyloidosis and organ-specific amyloidosis. Cardiac involvement could be the initial presentation of amyloidosis. Cardiac involvement occurs in up to 50% of patients with AL amyloidosis and up to 5% in patients with AA amyloidosis.^{3 4} Isolated cardiac amyloidosis as the sole manifestation of the disease is rare, reportedly around 4%.⁴ Here, we present an interesting case of cardiac AL amyloidosis in a postmenopausal woman, who initially presented with symptoms of heart failure. Subsequent workup, however, led to the diagnosis of multiple myeloma (MM) as the underlying cause of AL amyloidosis in our patient.

CASE PRESENTATION

A 60-year-old Caucasian woman with no significant medical history developed exercise intolerance, fatigue and shortness of breath on exertion over the several months prior to her presentation to our

outpatient clinic. At the time of presentation, she also reported of dry cough, orthopnea, paroxysmal nocturnal dyspnoea, generalised weakness and intermittent numbness of her hands and feet. Social history was negative for smoking, alcohol or illicit drugs. Physical examination was unremarkable, except for jugular venous distension, audible S1 and S2 sounds, bilateral crackles on lung auscultation and bilateral pitting oedema.

INVESTIGATIONS

Chest X-ray showed cardiomegaly, pulmonary oedema and small-sized bilateral pleural effusions. A 12-lead ECG demonstrated normal sinus rhythm, low-voltage complexes and extreme right-axis deviation (figure 1). Transthoracic echocardiogram (TTE) demonstrated asymmetric biventricular hypertrophy with preserved ejection fraction of 60%, elevated right-ventricular systolic pressure of 36 mm Hg and abnormal myocardial texture, described as 'granular sparkling' (figure 2). Coronary CT angiogram demonstrated normal coronary arteries. Subsequently, cardiac MRI demonstrated early and diffuse subendocardial delayed enhancement, concerning for infiltrative myocardial disease and for diffuse biventricular hypertrophy, with normal ejection fraction (figure 3). The patient underwent right heart catheterisation with endomyocardial biopsy, revealing diffuse amyloidosis with amorphous proteinaceous material around cardiac myocytes and within blood vessels, which was positive for Congo red stain (figure 4). Subsequent laboratory evaluation registered elevated, free λ light chains (86.3 mg/L (normal: 5.7–26.3 mg/L)) and positive Bence-Jones protein (0.37 g/24 h) in the urine. Bone marrow biopsy revealed greater than 10% infiltration of CD19⁺ CD56⁺ CD138⁺ plasma cells with reversal of marrow κ/λ ratio (<1:2, normal: 2:1), consistent with MM. The patient was eventually diagnosed with systemic AL amyloidosis with advanced, stage III, cardiac amyloidosis due to underlying MM.

OUTCOME AND FOLLOW-UP

Given her advanced cardiac amyloidosis, the patient was deemed a poor candidate for autologous stem-cell transplantation. The patient was started on systemic chemotherapy with melphalan and dexamethasone. Despite receiving standard therapy for heart failure—including diuretics, β -blockers and ACE inhibitors—the patient's condition continued to worsen and she succumbed to sudden cardiac death.

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Figure 1 A 12-lead ECG demonstrating low-voltage complexes and extreme right-axis deviation in a patient with cardiac amyloidosis.

DISCUSSION

Cardiac amyloidosis is an infiltrative cardiomyopathy with predominant involvement of the ventricular myocardium and conduction system. However, amyloid deposits of clinical significance have also been found in the coronary arteries, atrial myocardium, pericardium and valves.⁵ Advanced age and African-American ethnicity are potential risk factors for developing amyloidosis. One study identified the presence of an amyloidogenic allele, TTR Val122Ile, as the contributing factor for increased prevalence of cardiac amyloidosis in African-American patients. The prevalence of this allele is reported to be 23% in African-American patients with cardiac amyloidosis, compared with 3.9% in the general Africa-American population and 0% in Caucasian patients with cardiac amyloidosis.⁶ Different types of amyloid proteins contribute to the heterogeneity of cardiac

Figure 2 Transthoracic echocardiogram demonstrating biventricular hypertrophy, asymmetric septal hypertrophy and abnormal myocardial texture, described as 'granular sparkling'.

involvement and clinical presentation in patients with amyloidosis. Amyloid deposits in AL amyloidosis, the most common form of cardiac amyloidosis, are usually composed of monoclonal light chains. AL amyloidosis is characterised by deposition of protein derived from immunoglobulin light-chain fragments and can occur in association with monoclonal gammopathy of undetermined significance (MGUS) and MM. AL amyloidosis shares common chromosomal abnormalities with MGUS and MM, involving the immunoglobulin heavy-chain gene at 14q32 and deletions of the long arm of chromosome 13, [del (13q)].⁷ The mean age of diagnosis of patients with AL amyloidosis is 64 years.⁸ In a long-term follow-up of patients at Mayo Clinic, about 3% of patients presented with a MGUS as the cause for an AL amyloidosis.⁹ Clinical symptoms in cardiac amyloidosis are mostly related to exercise intolerance, fatigue, breathlessness and occasionally, syncope or presyncope. Further cardiac findings include those of right-sided heart failure. Amyloid deposition in coronary arteries can contribute to typical angina.¹⁰ However, since amyloid deposition shows a predilection for intramyocardial vessels and spares epicardial vessels, coronary angiography can be falsely normal. Exertional syncope could indicate advanced disease and is associated with high mortality. Cardioembolic stroke due to an intracardiac thrombus, which is more common in AL amyloidosis than other types, could be the initial presentation. Physical examination in patients with cardiac amyloidosis usually reveals signs of right heart failure, including elevated jugular pulses, hepatomegaly and pitting pedal oedema. Involvement of heart valves in amyloidosis resulting in audible murmur is a rare finding, so is cardiac tamponade secondary to amyloid deposition involving the pericardium. Orthostatic hypotension in patients with AL amyloidosis usually indicates underlying autonomic neuropathy. The most common ECG abnormalities in patients with AL amyloidosis are low-voltage complexes (46%) and pseudo-infarct pattern (47%).¹¹ Furthermore, electrophysiological studies suggest that the His-Purkinje system is the most affected part of the

Figure 3 Cardiac MRI showing early and diffuse subendocardial delayed enhancement, concerning for infiltrative myocardial disease and for diffuse biventricular hypertrophy (A and B).

conduction system in patients with cardiac amyloidosis. In fact, prolongation of the His–ventricular interval has been identified to be a predictor of sudden death in these patients. Similarly, late potentials on signal-averaged ECG have been shown to independently predict sudden cardiac death in patients with AL amyloidosis.¹²

Typical echocardiographic findings are an inappropriate, concentric, left-ventricular hypertrophy (LVH); right-ventricular thickening; prominent valves and infiltration of the atrial septum. Left ventricular-wall thickening and diastolic dysfunction are the earliest echocardiographic features of cardiac amyloidosis. Restrictive cardiomyopathy—resulting in a small, left-ventricular cavity—is

Figure 4 Congo red staining of endomyocardial biopsy demonstrating pinkish amorphous material interspersed between cardiac muscle fibres, consistent with cardiac amyloidosis (×10, inset ×40 magnification).

usually seen in advanced disease. Increased echogenicity of the myocardium, described as 'granular sparkling', is also consistent with an infiltrative process, typical of amyloidosis. Intracardiac thrombus can be identified in up to 27% of patient with AL amyloidosis.¹³ LVH is often diagnosed in AL amyloidosis on TTE but, unlike true LVH, AL amyloidosis is associated with low-voltage complexes on an ECG. The reduced-voltage-to-mass ratio is highly sensitive than ECG, echocardiography and nuclear studies for the diagnosis of cardiac amyloidosis. Cardiac MRI in patients with cardiac amyloidosis usually demonstrates global and subendocardial late gadolinium enhancement of the myocardium. However, gadolinium-based MRI should be used with extreme caution and preferably avoided in patients with moderate to severe renal disease, due to the risk of nephrogenic systemic fibrosis. The gold standard for the diagnosis of cardiac amyloidosis is tissue biopsy demonstrating amyloid deposits on endomyocardial biopsy, which typically bind Congo red, leading to green birefringence under polarised light.^{14 15} In our patient, cardiac amyloidosis was initially suspected based on diffuse biventricular enlargement with abnormal myocardial texture on TTE. Subsequent work-up included cardiac MRI and endomyocardial biopsy and confirmed the diagnosis of an infiltrative process consistent with cardiac amyloidosis.

For patients who are not candidates for haematopoietic stem cell (HSC) transplantation, the preferred regimen is: (1) melphalan plus dexamethasone or (2) cyclophosphamide, thalidomide and dexamethasone.^{16–19} One study reported that the administration of up to nine courses of melphalan and dexamethasone resulted in a ≥ 2 mm reduction in interventricular septum thickness and marked improvement in New York Heart Association (NYHA) class.¹⁹ HSC usually is indicated for patients with cardiac amyloidosis who do not have decompensated heart failure and have a left-ventricular ejection fraction (LVEF) $< 40\%$ and a systolic pressure < 90 mm Hg.²⁰ Since a majority of patients with cardiac amyloidosis have extracardiac involvement with other comorbidities, they are deemed poor candidates for cardiac transplantation. Cardiac transplantation is usually reserved for patients with isolated cardiac disease who can withstand high-dose chemotherapy and HSC within 12 months following a transplantation.²¹ The role of prophylactic implantable cardiac devices to prevent sudden cardiac death in patients with cardiac amyloidosis is unclear and currently there is no strong evidence to support its widespread use.²²

In summary, the clinician should look for amyloidosis when presented with the clinical constellation of an aggressive and progressive heart-failure syndrome, low blood pressure, low-voltage ECG complexes and typical echocardiographic findings of a non-dilated ventricle, inappropriate ventricular hypertrophy and relatively preserved LVEF.

Learning points

- Cardiac amyloidosis is an infiltrative cardiomyopathy that can occasionally be the initial manifestation of an underlying systemic disorder such as multiple myeloma, as seen in our patient.
- The diagnosis of cardiac amyloidosis should be considered with a high index of suspicion, especially in patients with low-voltage ECG complexes and inappropriate ventricular hypertrophy, along with other clinical symptoms and signs of amyloidosis.
- Despite advances in treatment, the mortality in patients with cardiac amyloidosis is still high.

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