CASE REPORT

Missed opportunity for anticoagulation in a patient with AL cardiac amyloidosis and rapidly progressive heart failure

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SUMMARY

A previously healthy 65-year-old woman presented with progressive symptoms of heart failure. Low-voltage ECG and findings on echocardiography were concerning for infiltrative cardiomyopathy. Cardiac MRI showed biventricular late gadolinium enhancement, and endomyocardial biopsy confirmed monoclonal immunoglobulin light-chain (AL) amyloidosis. Bortezomib-based chemotherapy was initiated, but the patient continued to clinically deteriorate. She required hospital readmission after resuscitated out-of-hospital cardiac arrest attributed to progressive conduction disease, and a permanent pacemaker was implanted. Chest CT angiography showed a small subsegmental pulmonary embolism (PE), but anticoagulation was withheld as her lower extremity Doppler was negative. One month later, another pulseless electrical arrest occurred, due to massive PE. Thereafter, she had refractory class IV congestive heart failure with severe right ventricular dysfunction, and was deemed unsuitable for stem-cell or heart transplantation. This case highlights the predilection for thromboembolism in AL cardiac amyloidosis.

BACKGROUND

Patients with light-chain (AL)-type cardiac amyloidosis have a median untreated survival of 6 months and a sobering 1 year mortality of 50% with current treatment.^{1 2} High-dose chemotherapy and stem cell transplantation are disease-modifying treatments for AL amyloid, though not all patients are candidates for stem cell transplant, and chemotherapy carries significant morbidity.³ Our patient requested any possible intervention to prolong life and sought out transplantation referral. The case highlights a missed opportunity to initiate anticoagulation for a subsegmental pulmonary embolism (PE) that heralded a subsequent massive PE. We also discuss the available treatment options for cardiac amyloidosis, reinforcing the limited treatment options once a patient's functional status deteriorates significantly.

CASE PRESENTATION

A 65-year-old Caucasian woman with no medical history presented to our institution with progressive shortness of breath on exertion, accompanied by bilateral lower extremity swelling to her knees. She reported orthopnoea but no paroxysmal

Figure 1 Cardiac MRI, four-chamber view with dilation of the atria (green arrows) and thickened biventricular walls (pink arrows).

nocturnal dyspnoea. On exam, vital signs included a temperature 36.9 Celsius, heart rate 97 bpm, respiratory rate 16 breaths per min and a blood pressure of 92/68 mm Hg with positive orthostatic drop in pressure.

Her ECG showed normal sinus rhythm and a right bundle branch block with low voltage QRS complexes, and her brain natriuretic peptide (BNP) was 380 pg/

Figure 2 Cardiac MRI: two-chamber view with left atrium and LV showing subendocardial late gadolinium enhancement of the entire LV, along with an area of focal transmural enhancement noted in the basal inferior wall (yellow arrow), representing a large deposition of amyloid protein. LV, left ventricle.

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Figure 3 CT angiogram of the chest, with a small subsegmental pulmonary embolism (yellow arrow) on the left.

mL. A two-dimensional transthoracic echocardiogram showed left atrial enlargement, severe diastolic dysfunction with restrictive left ventricular (LV) filling pattern (E/A 2.9, deceleration time 155 ms and lateral mitral E/e' of 33), suggestive of severe diastolic dysfunction, with possible infiltrative cardiomyopathy. Midodrine was started for blood pressure support.

Gadolinium enhanced cardiac MRI revealed normal LV ejection fraction of 59%, biatrial enlargement (figure 1) and diffuse subendocardial late gadolinium uptake in both ventricles (figure 2), suggestive of probable cardiac amyloidosis. An abdominal fat pad biopsy was negative for amyloidosis. Further workup revealed cardiac troponin I (cTnI) level 0.05 ng/mL, elevated creatinine (1.31 mg/dL), haemoglobin 11.5 gm/dL, 2+proteinuria on dipstick, 24 hours urine protein of 3120 mg and albumin level 3.1. Serum free light chains (FLC) had increased lambda FLC (105 mg/dL), normal kappa FLC (1.43 mg/dL) with a decreased kappa/lambda ratio (0.01) and an FLC difference (FLC-diff) of 103.5. Endomyocardial biopsy confirmed AL amyloidosis, and bortezomib-based chemotherapy was initiated.

Five months later, she had an episode of unresponsiveness requiring 5 min of bystander cardiopulmonary resuscitation followed by return of spontaneous circulation with stable

Figure 4 CT angiogram of the chest at the time of second pulseless electrical arrest, with a larger clot on the left (yellow arrow) with an area of pulmonary infarct (green arrow).

Figure 5 Coronal section of CT angiogram of chest showing a segmental pulmonary embolism (red arrow) on the right, with lack of contrast enhancement in the area of clot.

haemodynamics. Her ECG was remarkable for a bifascicular block, and she underwent dual-chamber pacemaker implantation for presumed intermittent complete heart block in the setting of amyloidosis. CT angiography (CTA) chest showed a small subsegmental PE (figure 3), for which observation was elected rather than anticoagulation due to her negative lower extremity Doppler and concurrent anaemia, with a haemoglobin of 8 g/dL.

The patient had a drop in free light chain difference with chemotherapy, but continued to deteriorate functionally. At this point, she and her family were interested in referral for possible orthotopic heart transplantation.

One month later, prior to her scheduled transplantation assessment, she was admitted following a second pulseless electrical arrest (PEA). CTA of the chest showed a new PE with moderate to severe clot burden (figure 4) (figure 5) (figure 6), and her functional

Figure 6 CT angiogram with a right segmental pulmonary embolism (orange arrow).

Figure 7 Graph showing the trend of Dfl (red) and BNP levels (green) during the course of illness with pointers (blue) to major events. BNP, brain natriuretic peptide; Dfl, difference in free light chain levels.

Figure 8 Graph depicting various troponin levels during the course of illness.

class declined to refractory class IV following the event. Echocardiograms were notable for new severe right ventricular dysfunction and systemic anticoagulation with heparin and warfarin was instituted. Yet another PEA arrest occurred a month later, and due to declining functional status, intolerance to chemotherapy and limited functional capacity, she was considered a poor candidate for transplant or LV assist device (refractory multiorgan dysfunction). Given her declining status, she and her family elected conservative measures. She died 2 days later of refractory biventricular failure with recent PE.

DISCUSSION

Cardiac amyloidosis causes rapidly progressive heart failure. The morbidity and mortality depend on the extent of cardiac dysfunction which is a combined effect of extracellular deposition and toxic effects of circulating light chains.³ While ventricular arrhythmias are not infrequent in cardiac amyloidosis and may be treated with the placement of dual chamber implantable cardioverter defibrillators (ICDs), sudden cardiac death from PEA arrest is a major cause of early mortality.⁴ The role

of ICD implantation in the prevention of sudden cardiac death is unclear, as the available data have not shown any definite mortality benefit with ICD implantation.^{4,5}

Although patients with advanced amyloidosis are at an increased risk of bleeding due to increased vessel fragility, they are also at a high risk for thromboembolic disease. In fact, nephrotic syndrome causes a prothrombotic state and is associated with thrombotic events in approximately 25% of cases.⁶ Additionally, atrial dysfunction and mechanical stasis can cause atrial thrombus formation and embolism.^{7,8} Cardiac amyloidosis patients with atrial fibrillation should be considered for anticoagulation irrespective of CHADS2 VASc score. Even among patients in sinus rhythm, finding a diminutive transmitral 'A' wave on Doppler echocardiography or decreased left atrial appendage (LAA) emptying velocity on transoesophageal echocardiography indicates advanced atrial mechanical dysfunction. These findings may be considered in anticoagulation decisions. All patients with an embolic event should have further workup to rule out an atrial thrombus. This is supported by a study done by Da Li Feng *et al* who found that AL cardiac amyloidosis was an independent risk factor for intracardiac thrombus formation including patients in sinus rhythm.^{7,9,10} Whether anticoagulating our patient after her initial PE would have prevented the second massive thromboembolic disease is unknown. While the CHEST guidelines recommend observation for small subsegmental PE in patients who are not at high risk for thromboembolism, with a 2C level of evidence,¹¹ this would not hold true for patients with amyloidosis who are at a high risk of thromboembolic disease.

Diuretics are the mainstay of the treatment of cardiac amyloidosis. Unlike routine management of heart failure with beta blockers, these agents are relatively contraindicated as patients have a relatively fixed cardiac output and are dependent on the tachycardic response to maintain the output.¹²

The patient and family were interested in possible interventions to prolong her survival, particularly cardiac transplantation. Cardiac transplant may be a feasible option in younger patients, who would require high-dose chemotherapy prior to transplant and autologous stem-cell transplant after heart transplant.¹³ Patients who received autologous stem-cell transplant in combination with chemotherapy had mortality benefit compared with patients treated with chemotherapy alone. However, not all patients can tolerate high-dose chemotherapy, and there is a mortality of approximately 50% associated with stem-cell transplant.¹⁴ BNP and troponins are predictors of mortality in AL cardiac amyloidosis,^{15–17} and patients are prognostically staged based on cTnI, (cTnT >0.025 microg/L or cTnI >0.1 microg/L), Pro-BNP (>1800 pg/mL) and the difference in free light chain levels (Dfl ≥18 mg/dL).^{18–21} Based on these criteria, our patient was stage 2 (Dfl) at the start of her chemotherapy, deteriorated to stage 4 (Dfl, BNP level and elevated troponin) after the first PEA arrest and was at stage 2 (elevated troponin) after her second PEA arrest (figure 7) (figure 8). Though different centres employ different exclusion criteria for transplant patients, the Mayo Clinic excludes patients with one or more of the factors, including a N-terminal prohormone BNP >5000, Troponin T>0.06 ng/mL, New York Heart Association (NYHA) class III or IV, BP <90 Hg, diffusion capacity <50% or clinical involvement of >2 organs.^{3,22–24} According to this set of exclusion criteria, the patient was classified as NYHA class IV, which negated her candidacy for stem-cell transplant, even though her Mayo stage was stage II around the time of her second PEA arrest. There is limited data regarding the use of ventricular assist devices in

Learning points

- ▶ The standard risk tools used to determine appropriateness of anticoagulation in patients with atrial fibrillation or in those with deep vein thrombosis (DVT) and pulmonary embolism concerns, may not be accurate in patients with extensive amyloid, as manifested here. Extensive amyloid with nephrotic syndrome and cardiac involvement should be considered embolic high-risk cases.
- ▶ Cardiac transplantation is an option for younger patients, particularly in those with isolated cardiac amyloidosis.
- ▶ High-dose chemotherapy and stem cell therapy are the only available disease-modifying medical treatments but with significant morbidity and mortality. Patients are considered on a case-by-case basis based on their age, troponin, N-terminal prohormone brain natriuretic peptide and New York Heart Association functional class.

patients with cardiac amyloidosis, as they are infrequently used in patients with restrictive cardiomyopathies due to technical difficulties and the presence of associated non-cardiac amyloid.²⁵ Our patient suffered from concomitant renal insufficiency and refractory hypotension.

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REFERENCES

- 1 Kyle RA, Linos A, Beard CM, *et al*. Incidence and Epidemiology of Primary Systemic Amyloidosis (AL) in Olmsted County, Minnesota: 1950 Through 1989. In: *Amyloid and Amyloidosis 1990*, 1991:211–4.
- 2 Kumar SK, Gertz MA, Lacy MQ, *et al*. Recent improvements in survival in primary systemic amyloidosis and the importance of an early mortality risk score. *Mayo Clin Proc* 2011;86:12–18.
- 3 Grogan M, Dispenzieri A. Natural history and therapy of AL cardiac amyloidosis. *Heart Fail Rev* 2015;20:155–62.
- 4 Kristen AV, Dengler TJ, Hegenbart U, *et al*. Prophylactic implantation of cardioverter-defibrillator in patients with severe cardiac amyloidosis and high risk for sudden cardiac death. *Heart Rhythm* 2008;5:235–40.
- 5 Lin G, Dispenzieri A, Kyle R, *et al*. Implantable cardioverter defibrillators in patients with cardiac amyloidosis. *J Cardiovasc Electrophysiol* 2013;24:793–8.
- 6 Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *Clin J Am Soc Nephrol* 2012;7:513–20.
- 7 Dubrey S, Pollak A, Skinner M, *et al*. Atrial thrombi occurring during sinus rhythm in cardiac amyloidosis: evidence for atrial electromechanical dissociation. *Br Heart J* 1995;74:541–4.
- 8 Sucker C, Hetzel GR, Grabensee B, *et al*. Amyloidosis and bleeding: pathophysiology, diagnosis, and therapy. *Am J Kidney Dis* 2006;47:947–55.
- 9 Feng D, Edwards WD, Oh JK, Jk O, *et al*. Intracardiac thrombosis and embolism in patients with cardiac amyloidosis. *Circulation* 2007;116:2420–6.
- 10 Feng D, Syed IS, Martinez M, *et al*. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation* 2009;119:2490–7.
- 11 Kearon C, Akl EA, Ornelas J, *et al*. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016;149:315–52.
- 12 Shah KB, Inoue Y, Mehra MR. Amyloidosis and the heart: a comprehensive review. *Arch Intern Med* 2006;166:1805–13.

- 13 Gillmore JD, Goodman HJ, Lachmann HJ, *et al.* Sequential heart and autologous stem cell transplantation for systemic AL amyloidosis. *Blood* 2006;107:1227–9.
- 14 Saba N, Sutton D, Ross H, *et al.* High treatment-related mortality in cardiac amyloid patients undergoing autologous stem cell transplant. *Bone Marrow Transplant* 1999;24:853–5.
- 15 Gertz MA. Troponin in hematologic oncology. *Leuk Lymphoma* 2008;49:194–203.
- 16 Kato T, Sato Y, Nagao K, *et al.* Serum cardiac troponin T in cardiac amyloidosis: serial observations in five patients. *Tohoku J Exp Med* 2006;208:163–7.
- 17 Palladini G, Foli A, Milani P, *et al.* Best use of cardiac biomarkers in patients with AL amyloidosis and renal failure. *Am J Hematol* 2012;87:465–71.
- 18 Masson S, Vago T, Baldi G, *et al.* Comparative measurement of N-terminal pro-brain natriuretic peptide and brain natriuretic peptide in ambulatory patients with heart failure. *Clin Chem Lab Med* 2002;40:761–3.
- 19 Kumar S, Dispenzieri A, Lacy MQ, *et al.* Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol* 2012;30:989–95.
- 20 Dispenzieri A, Gertz MA, Kyle RA, *et al.* Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol* 2004;22:3751–7.
- 21 Girnius S, Seldin DC, Meier-Ewert HK, *et al.* Safety and efficacy of high-dose melphalan and auto-SCT in patients with AL amyloidosis and cardiac involvement. *Bone Marrow Transplant* 2014;49:434–9.
- 22 Comenzo RL, Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. *Blood* 2002;99:4276–82.
- 23 Gertz MA. How to manage primary amyloidosis. *Leukemia* 2012;26:191–8.
- 24 Gertz MA, Lacy MQ, Dispenzieri A, *et al.* Refinement in patient selection to reduce treatment-related mortality from autologous stem cell transplantation in amyloidosis. *Bone Marrow Transplant* 2013;48:557–61.
- 25 Frazier OH, Cohn WE, Tuzun E, *et al.* Continuous-flow total artificial heart supports long-term survival of a calf. *Tex Heart Inst J* 2009;36:568–74.

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