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Cardiac involvement in light chain amyloidosis: a case report

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Amyloidosis refers to a group of heterogeneous diseases in which amyloid fibers deposited in organ and extracellular tissue comprise misfolded precursor proteins.[1] According to the variety of misfolded proteins, the site of production and the type of tissue infiltrated, amyloidosis of the myocardium is divided into five subtypes: immunoglobulin light chain (AL), secondary amyloidosis (or reactive amyloidosis), familial amyloidosis [transthyretin (ATTR) amyloidosis or hereditary amyloidosis], dialysis-related amyloidosis, and senile systemic amyloidosis. AL amyloidosis is the most common type of amyloidosis in developed countries, derived from the immunoglobulin light chain, produced by monoclonal plasma cell dyscrasia.[2] Cardiac involvement is commonly associated with adverse prognosis due to severe heart failure (HF), thromboembolic events, and sudden cardiac arrest. Here, we describe a cardiac amyloidosis (CA) patient with HF, conduction defects, and atrial arrhythmias.

A 72-year-old Chinese man who presented to the Sixth Medical Center of Chinese PLA General Hospital suffered from exertional dyspnea in the last six months. On admission, the patient had heart rate of 90 beats per minute, blood pressure of 102/62 mmHg, and clear lungs and mild edema in both legs. Laboratory tests showed elevated plasma troponin I levels (0.226 μg/L; normal range: < 0.04 μg/L) and N-terminal pro B-type natriuretic peptide (NT-pro BNP: 18299 pg/mL; normal range: 300–1800 pg/mL). Twelve-lead electrocardiogram (ECG) revealed a sinus rhythm of 75 beats/min, abnormal Q waves, and elevated ST-segment in V1 to V3 (Figure 1). Echocardiography revealed dilated bi-atria, symmetrically thickened left ventricular septum (14 mm),

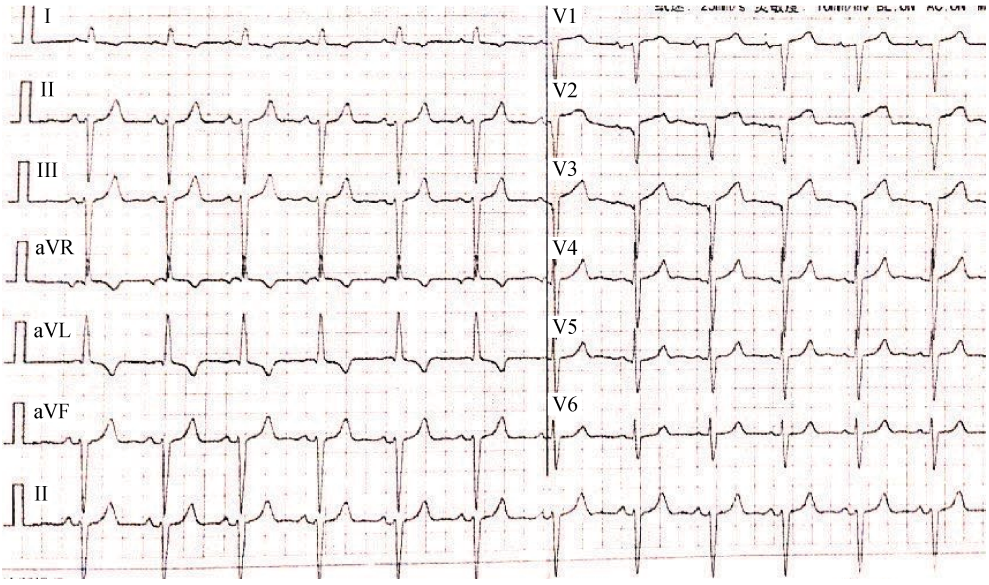

Figure 1. Electrocardiogram shows sinus rhythm of 75 beats/min, abnormal Q waves, elevated ST-segment in V1 to V3, and left anterior branch block.

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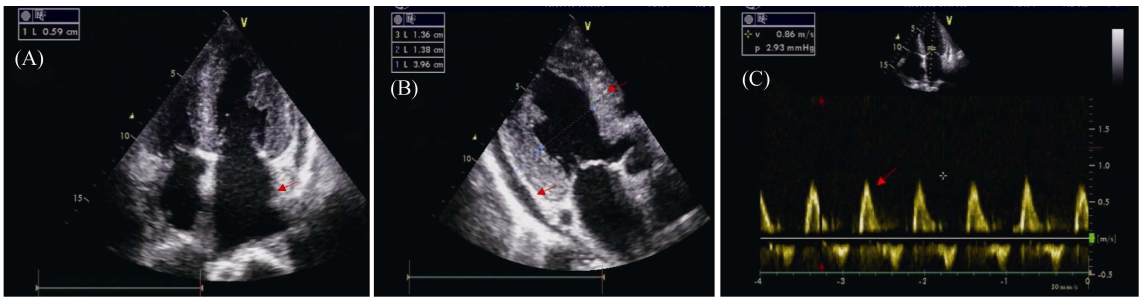

Figure 2. Echocardiography of the cardiac amyloidosis patient. (A): Echocardiography revealed dilated bi-atria (arrow); (B): symmetrically thickened left ventricular septum (14 mm), granular high echoic spots at the ventricular septum (arrow) and mild pericardial effusion (arrow); and (C): diastolic dysfunction with E/A (arrow), 74/31.

restrictive filling pattern (mitral valve E/A, 74/31), granular high echoic spots at the ventricular septum, and decreased left ventricular ejection fraction to 42% (Figure 2). Cardiac magnetic resonance imaging showed a delayed enhancement signal diffused in the subendocardium of the myocardium with postinjection of gadolinium (Figure 3).

These typical observations were all characteristics of amyloid cardiomyopathy. Subsequently, plasmacytosis was observed in bone marrow biopsy, and abnormal proliferation of monoclonal plasma cells was confirmed by immunophenotyping of the hematologic tumor (Figure 4). The concentration of free lambda light chain was higher in the serum assay (69.6; normal range: 5.7–26.3). Nevertheless, serum immunofixation electrophoresis was negative. The patient was finally diagnosed with monoclonal AL amyloidosis. Thereafter, the patient was referred for hematological treatment with bortezomib-dexamethasone-cyclophosphamide, melphalan-dexamethasone, and ixazomib-dexamethasone consecutively. Unfortunately, the patient suddenly became unconscious, with the longest sinus arrest at 6.28 s and alternating with atrial fibrillation (AF) as shown in Figure 5.

A single chamber permanent pacemaker was placed to prevent cardiac arrest. However, persistent atrial tachycardia

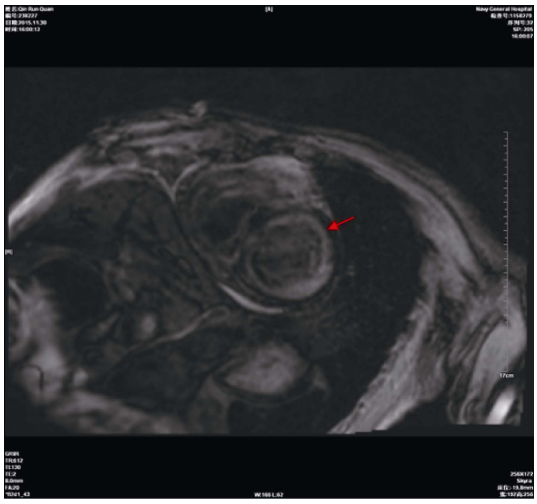

Figure 3. Cardiac magnetic resonance imaging presented delayed enhancement signal diffused in subendocardial of myocardial with post-injection the gadolinium (arrow).

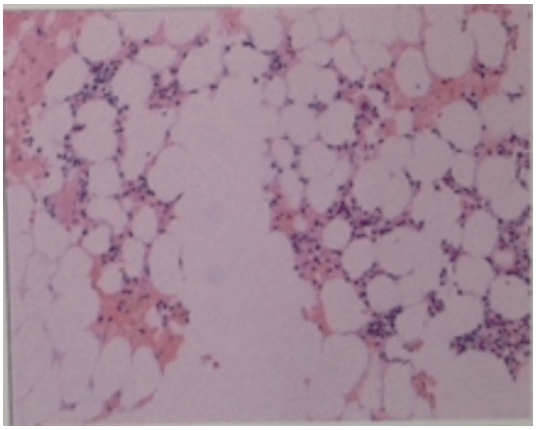

Figure 4. Bone marrow biopsy shows plasmacytosis.

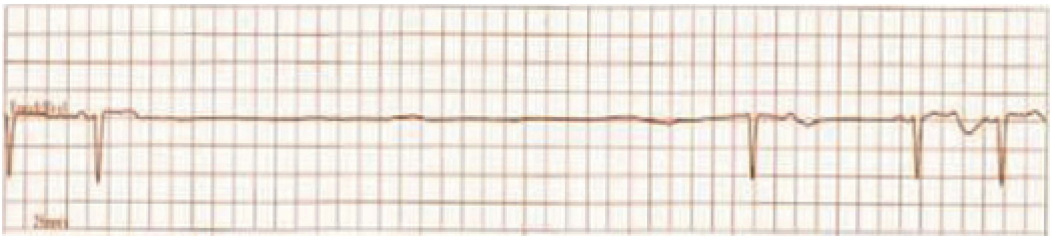

Figure 5. Electrocardiogram monitoring shows sinus arrest for 6.28 s.

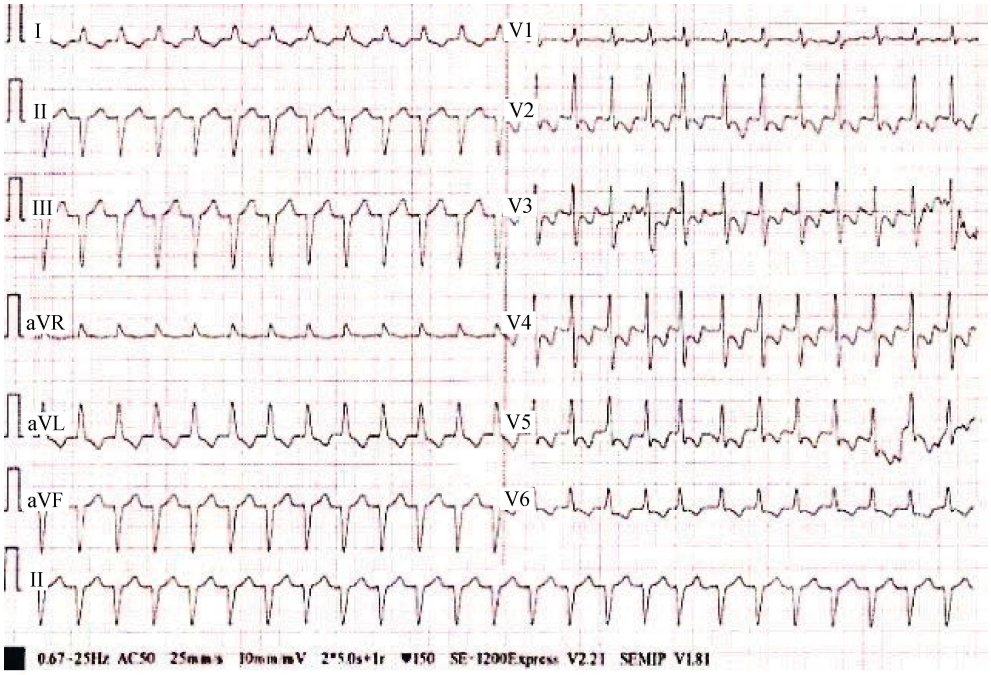

Figure 6. Electrocardiogram shows atrial tachycardia of 150 beats/min, depressed ST-segment, inverted T wave in V2 to V6, and left anterior branch block.

(AT) also worsened HF and hypotension, occasionally alternating with AF (Figure 6).

In addition, thromboembolisms of the lower extremity artery occurred, which were initially surgically treated with anticoagulation. Antiarrhythmic drugs were ineffective in converting to sinus arrhythmias. Therefore, catheter ablation is the feasible and effective therapeutic strategy. A three-dimensional electroanatomic model (ECM) was constructed involving the right atrium, superior and inferior vena cava, and tricuspid valve under the Carto system, which maps the best target located in the junction of the right atrial appendage and superior vena cava, to receive ablation for 300 s at 35 watts. Then, the AT with low frequency (120 beats/min) could still be induced. Concerning amyloid fibrils that infiltrated the myocardium and the mapped atrial low voltage, atria are supposedly electrically silent. Therefore, atrioventricular node (AVN) ablation was performed, with careful consideration of the possibility of AT recurrence. The pacing frequency of the pacemaker was adjusted to 80 beats/min to avoid any relevant adverse problems for the sudden reduction in heart rate. The patient was noted to be pacemaker-dependent post-ablation and has been free from any type of atrial arrythmias recurrence so far (Figure 7). Currently, the patient showed improvement of NYHA class symptoms and is in a stable condition. The patient remains alive at the five- year follow-up since the initial diagnosis.

The CA is caused by misfolded proteins deposited in the extracellular matrix of the heart, which is independent of cardiomyocyte disease.[3] Most CA patients have AL amyloidosis or ATTR amyloidosis. The AL refers to systemic immunoglobulin light chain-derived amyloidosis that occurs in plasma cell dyscrasias and other B-cell disorders.[4] It remains underdiagnosed, and its clinical manifestations are diverse, lacking specificity. Initially, this patient was fallaciously considered to have acute myocardial infarction due to the pseudoinfarction pattern on ECG and troponin I elevated in serum. It is similar to commonly misdiagnosing CA as hypertrophic cardiomyopathy or any restrictive cardiomyopathy owing to thickening of the left ventricular wall and diastolic dysfunction on echocardiography. With the presentation of unexplained or refractory HF in patients, especially with restrictive cardiomyopathy, it is reasonable to suspect CA after standard investigations for HF. At this time, the correlation of a variety of examinations should be rechecked and comprehensively analyzed, especially left ventricular wall thickening on echocardiography with paradoxical appearance of low voltage on ECG. The magnetic resonance imaging pattern of late gadolinium enhancement (LGE) appears to be a characteristic delayed and enhanced signal.[5] The gold standard for diagnosis is endomyocardial biopsy. It is regrettable that this patient refused to undergo this procedure because of the risk since the result of prior abdominal fat biopsy was negative. The prognosis of CA is dependent on subtype and the extent of cardiac and other organ involvement. The treatment includes HF and arrhythmias, along with specific chemotherapy for amyloidosis.

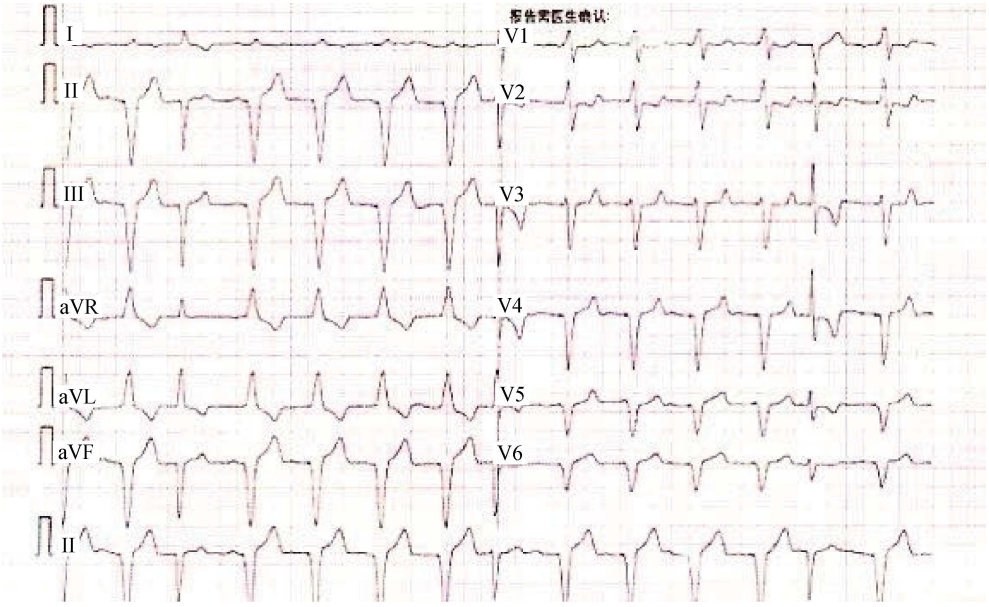

Figure 7. Electrocardiogram shows pacemaker rhythm of 80 beats/min, and pacing and perceptive functions were normal.

This patient has obvious conduction defects with sinus arrest and refractory atrial tachyarrhythmias that deteriorated HF. These problems may result from amyloid fibril infiltration and side effects of chemotherapeutic drugs for the underlying disease. However, various types of arrhythmias, as well as distinct degrees of conduction disruption and bundle branch block, are also common manifestations of ECG in the CA patients. These are due to amyloid infiltration and direct light chain toxicity, which impair the conduction system and left ventricular systolic function by immediately depositing or gradually promoting adjacent myocardial tissue fibrosis.[6] Additionally, left ventricular filling pressure increased, which resulted in atrial wall dilation and potentially myocardial fibrosis.[7] Regarding the electrophysiologic assessment of the conduction system in CA, the data are limited. The three-dimensional model of the atrium can be constructed using an ECM, and the degree of atrial substrate lesions can be evaluated using the magnitude of voltage amplitude. This method can effectively detect atrial fibrosis or surgical scar areas. At present, the atrial voltage is less than 0.5 mV is considered low voltage, and less than 0.1 mV is considered the scar area.[8] In a study conducted by Barbhaiya CR, *et al*.[9], the mean voltage of the atrial myocardium was lower in the CA patients (279 ± 351 *vs.* 499 ± 202, P = 0.08), and the proportion of low-voltage area was largely greater in the CA group than that in the non-CA persistent AF group overall (63% ± 22% *vs.* 34% ± 22%, P = 0.009). We consider that fibrillatory activation by amyloid infiltration potentially induces electrical and tissue structural remodeling, leading to a reduction in myocardial voltage, which is why antiarrhythmic drugs are always failures at higher frequencies and more refractory of atrial arrythmias in the CA patients. Catheter ablation is often required to resolve this complex situation. The CA patients show the improvement symptoms after atrial arrhythmia ablation, but the recurrence of arrhythmias remains high. The main cause is that the pathophysiological matrix of the atria has not been reversed or even continues to develop during the underlying disease process. Therefore, AVN ablation (AVNA) is typically performed after all other therapeutic options and safely after previous pacemaker or defibrillator implantation. The main benefits of this strategy can obviously prolong left ventricular filling time by controlling the rate and regulating the R-R interval. Tan NY, *et al*.[10] affirmed AVNA had effectively improved symptoms with refractory atrial arrhythmias in the CA patients, and most surviving CA patients had free recurrence years after the ablation procedure. Although survival was poor in the AVNA group, malignant ventricular arrhythmias did not appear among patients who died. For this case, we observed that the function of HF is obviously improved for two years after the AVNA procedure, elevating the left ventricular ejection fraction to 60%, and is free of any arrhythmias from the atria and ventricle. To date, the study of the CA patients utilizing catheter ablation therapy for various atrial arrythmias is limited, and the sample size is still small. Catheter ablation may help the CA patients be free from refractory atrial arrhythmias, but further studies need to verify the reliability of this strategy.

The CA patients have also been reported to have com-

mon complications such as ischemic stroke, even in the sinus rhythm or those treated with anticoagulation agents, a significant contributor to mortality in the CA patients.[11] A study from the Mayo clinic showed that 42 of 156 CA patients had intracardiac thrombi utilizing transthoracic and transesophageal echocardiograms, among which AL amyloid had a higher frequency than other types (35% *vs.* 18%, $P = 0.02$), despite younger patients and a lower prevalence of AF.[12] They confirmed that left ventricular diastolic dysfunction, lower left atrial appendage emptying velocity, and AF were independent risk factors for intracardiac thrombosis, while anticoagulation was protectively correlated.[12] Oxidative stress and free radical activation, secondary to amyloid infiltration, lead to cardiomyocyte and endothelial cell dysfunction, electromechanical dissociation and hypercoagulability.[13] This may explain why intracardiac thrombi are usually identified in the CA patients with sinus rhythm. Another important conclusion of the study is that the risk for thrombosis increased if systolic blood pressure was lower and AF was present, whereas the conventional risk factors only have a modest effect.[12] Therefore, the CHA_2DS_2-VASC score alone may not be suitable for the assessment of such complex patients. We speculate that the HAS-BLED score alone assessing the risk of bleeding may also not be sufficient, because blood vessel walls were destroyed by amyloid deposition. It is worth noting that the frequency of thrombosis and embolism could have been underestimated, because microthrombi may be clinically silent and may have been overlooked, especially in the right atrial appendage. Consequently, screening for thrombi by more widespread use of transesophageal echocardiography as early as possible would be required when atrial systolic failure is present, regardless of rhythm.

The AL amyloidosis is a rare life-threatening disease. The survival outcome is significantly affected by the extent and severity of organs involved, particularly those with cardiac involvement. In the Mayo clinic study, risk stratification was carried out by elevated levels of biomarkers, including NT-pro BNP (332 pg/mL), cardiac troponin T (0.035 ng/mL) or troponin I (0.1 ng/mL). These CA patients were categorized into Mayo stage I (both values below cutoff), II (either one above), and III (both above), the median survival times of which were 26.4, 10.5, and 3.5 months, respectively.[14,15] In the AL, chemotherapy is effective against plasma cell-derived amyloid-forming immunoglobulin light chains, which remains the cornerstone of treatment.[16] Apart from the above specific treatment, symptomatic management and supportive treatment to prevent the exacerbation of organ function should be performed simultaneously. However, the overall prognosis remains poor. Thus, it is necessary to identify complex patients by using available diagnostic techniques for echocardiography, cardiac magnetic resonance (CMR) with LGE and nuclear imaging. Among them, echocardiography and CMR with LGE have potential use in early diagnosis and serve as predictors for prognosis to some extent.[16] It is paramount to individually correlate the findings based on the clinical presentation and case suspicion. Generally, specific chemotherapy, supportive therapy for organ failure, and symptomatic improvement are the main options. The more effective techniques for early identification of amyloidosis and aggressive treatment for the underlying plasma dyscrasia and various serious complications are on the horizon owing to the high mortality.[1]

All in all, the CA patient had severe HF, a variety of atrial arrhythmias and multiple thromboembolisms, any of which is a fatal complication. The patients in this case report has been alive for five years since initially diagnosed with AL amyloidosis, far longer than the 3.5-month mean survival mentioned in the Mayo study.[15] Currently, the patient has been free from cardiac hospitalization for two years since the AVNA procedure. This case confirms that symptomatic therapies related to arrhythmias are reasonable and effective. Whether the strategies could assist in improving the prognosis in the AL amyloidosis group still needs prospective and large-scale clinical trials to be studied further.

Acknowledgments

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References

1 Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. *Lancet* 2016; 387: 2641–2654.
2 Barrett CD, Alexander KM, Zhao H, *et al*. Outcomes in patients with cardiac amyloidosis undergoing heart transplantation. *JACC Heart Fail* 2020; 8: 461–468.
3 Fontana M, Ćorović A, Scully P, *et al*. Myocardial amyloidosis: the exemplar interstitial disease. *JACC Cardiovasc Imaging* 2019; 12: 2345–2356.
4 Joseph NS, Kaufman JL. Novel approaches for the management of AL amyloidosis. *Curr Hematol Malig Rep* 2018; 13: 212–219.
5 Knight DS, Zumbo G, Barcella W, *et al*. Cardiac structural and functional consequences of amyloid deposition by cardiac magnetic resonance and echocardiography and their prognostic roles. *JACC Cardiovasc Imaging* 2019; 12: 823–833.
6 Loungani RS, Rehorn MR, Geurink KR, *et al*. Outcomes

following cardioversion for patients with cardiac amyloidosis and atrial fibrillation or atrial flutter. *Am Heart J* 2020; 222: 26–29.
7 Sanchis K, Cariou E, Colombat M, *et al*. Atrial fibrillation and subtype of atrial fibrillation in cardiac amyloidosis: clinical and echocardiographic features, impact on mortality. *Amyloid* 2019; 26: 128–138.
8 Teh AW, Kistler PM, Lee G, *et al*. Long-term effects of catheter ablation for lone atrial fibrillation: progressive atrial electroanatomic substrate remodeling despite successful ablation. *Heart Rhythm* 2012; 9: 473–480.
9 Barbhaiya CR, Kumar S, Baldinger SH, *et al*. Electrophysiologic assessment of conduction abnormalities and atrial arrhythmias associated with amyloid cardiomyopathy. *Heart Rhythm* 2016; 13: 383–390.
10 Tan NY, Mohsin Y, Hodge DO, *et al*. Catheter ablation for atrial arrhythmias in patients with cardiac amyloidosis. *J Cardiovasc Electrophysiol* 2016; 27: 1167–1173.
11 Ballantyne B, Manian U, Sheyin O, *et al*. Stroke risk and atrial mechanical dysfunction in cardiac amyloidosis. *ESC Heart Fail* 2020; 7: 705–707.
12 Feng D, Syed IS, Martinez M, *et al*. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation* 2009; 119: 2490–2497.
13 Berghoff M, Kathpal M, Khan F. Endothelial dysfunction precedes C-fiber abnormalities in primary (AL) amyloidosis. *Ann Neurol* 2003; 53: 725–730.
14 Venner CP. AL amyloidosis cardiac staging updated using BNP. *Blood* 2019; 133: 184–185.
15 Palladini G, Campana C, Klersy C, *et al*. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. *Circulation* 2003; 107: 2440–2445.
16 Bhogal S, Ladia V, Sitwala P, *et al*. Cardiac amyloidosis: an updated review with emphasis on diagnosis and future directions. *Curr Probl Cardiol* 2018; 43: 10–34.