



LETTER TO THE EDITOR

Senile cardiac amyloidosis: Clinical manifestations and non-invasive diagnostic approach



KEYWORDS

Restrictive
cardiomyopathy;
Amyloid types;
Cardiac involvement;
Echocardiography

1. Introduction

Cardiac amyloidosis (CA) refers to a rare metabolic storage disease with poor prognosis that relies on identification of the amyloid type.¹ In our aging population, wild-type transthyretin amyloidosis (ATTRwt), also known as senile cardiac amyloidosis (SCA), is more common and must be differentiated from other amyloid types.¹ We present a case of SCA diagnosed in a patient with signs and symptoms of congestive heart failure and discuss the clinical features, imaging study findings and the key “red flags” a clinician should evaluate to avoid underdiagnosis of SCA.

2. Case Presentation

A 76-year-old white Caucasian man was referred to our hospital due to progressive shortness of breath. The patient denied having had any chest pain or syncope in the past. He had a past medical history negative for arterial hypertension, diabetes mellitus, dyslipidemia, and smoking or alcohol abuse. Nevertheless, he had a prior hospitalization one year ago for the same reason, and a diagnosis of ‘restrictive cardiomyopathy’ was made without any further investigation; he was administered 20 mg/day furosemide. He also underwent coronary angiography, revealing patent

epicardial coronary arteries without fixed critical stenosis. The patient also had a history of carpal tunnel syndrome 7 years ago that was treated surgically.

Physical examination revealed mild lower extremity edema. Vital signs included blood pressure of 116/81 mmHg without orthostatic hypotension, 82 beats per minute (bpm), temperature of 36.3°C and respiratory rate of 12 breaths/min with peripheral oxygen saturation (SpO₂) 95%. Electrocardiogram (ECG) indicated a sinus rhythm, 74 bpm, 1st-degree atrioventricular block, right bundle branch block (RBBB), left anterior hemiblock (LAH) and Q waves in inferior leads (Figure 1). A chest X-ray revealed mild right pleural effusion without cardiomegaly. Blood count was within normal range. Serum biochemistry was unremarkable except for elevated high sensitive cardiac troponin (0.092 ng/ml, normal range <0.010). Pro-B-type natriuretic peptide (pro-BNP) was increased (1279 pg/ml). Transthoracic echocardiographic study revealed a non-dilated left ventricle (LV) with severe symmetric hypertrophy and a granular “sparkling” texture (Figure 2A, B). Thickened papillary muscles, atrial septum, mitral valve leaflets and biatrial enlargement were also notable findings. Left ventricular ejection fraction (LVEF) was preserved, and pulsed-wave Doppler revealed diastolic dysfunction with a pseudonormal LV filling pattern. Tissue Doppler imaging revealed reduced diastolic annular velocities and high LV filling pressures (E/E' = 19) (Figure 2C). Mild to moderate mitral, tricuspid and pulmonary valve regurgitation was noted, and the estimated pulmonary arterial systolic pressure was 31 mmHg. An acute coronary event was excluded by serial ECG testing and cardiac biochemistry. Speckle-tracking echocardiography was performed, which revealed reduced LV global longitudinal strain (Figure 3).

We strongly suggested the diagnosis of cardiac amyloidosis, and cardiac magnetic resonance imaging (CMR) was performed, which supported our diagnosis by demonstrating diffuse subendocardial delayed myocardial signal enhancement after gadolinium injection and lack of signal suppression of the LV myocardium with several different inversion times and at several time points (Figure 4A, B). Pleural

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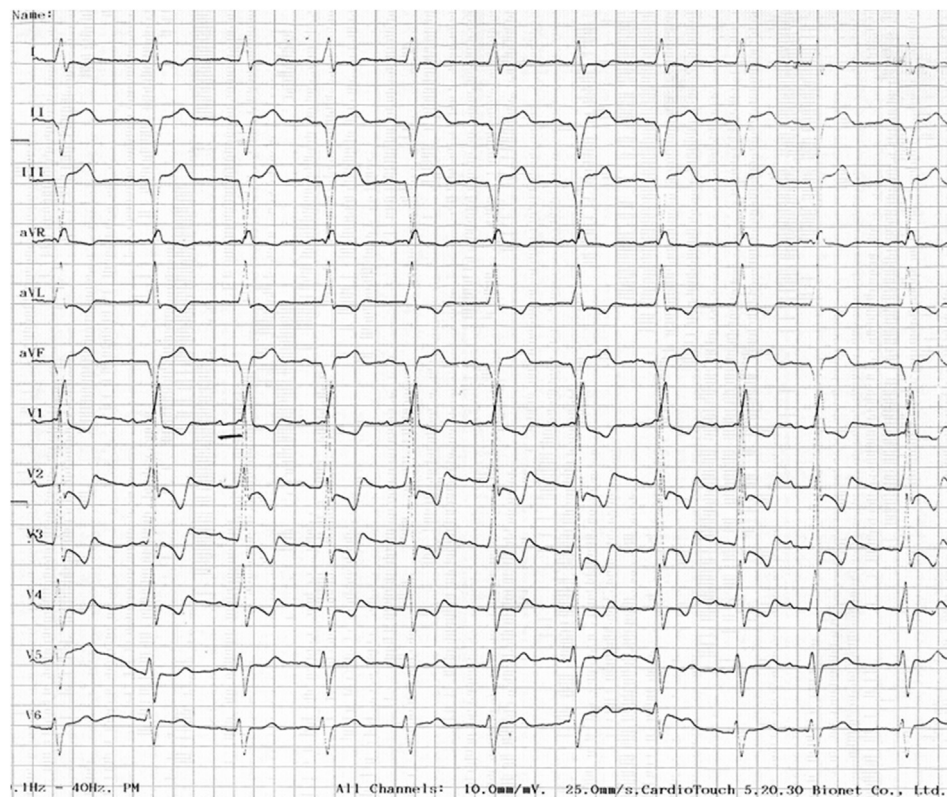


Figure 1 Resting 12-lead ECG on admission exhibiting a pseudo-infarct pattern in inferior leads.

effusion was present. LVEF was 63%, and moderate mitral, tricuspid and pulmonary valve regurgitation was also observed. The findings were characteristic of infiltrative heart disease, particularly cardiac amyloidosis. The patient was referred to a hematologist, and plasma cell dyscrasia was excluded by serum and urine protein electrophoresis, immunofixation and normal serum range of κ , λ free light chains and κ/λ ratio. An abdominal fat biopsy was negative for amyloid. He was administered 40 mg/day furosemide, 2.5 mg of ramipril and 25 mg of metoprolol bid with prompt improvement of his clinical status. Forty days later, the patient was admitted to our department due to syncope on the basis of complete atrioventricular block and treated with temporary pacing. The patient underwent permanent dual chamber pacemaker implantation. He is currently stable and asymptomatic 5 months after our diagnosis and 18 months after initial presentation.

3. Discussion

Cardiac amyloidosis is characterized by extracellular amyloid infiltration throughout the heart, which leads to restrictive cardiomyopathy and conduction abnormalities.² There are various amyloid types, such as primary (AL) amyloidosis, hereditary or variant amyloidosis, systemic AA amyloidosis, complicating chronic inflammatory diseases, and ATTRwt (SCA), each of which are associated with different clinical features, prognosis and treatment.²

We believe this is an interesting case given the patient's typical disease course with signs/symptoms of restrictive cardiomyopathy and conduction abnormalities. Moreover,

this case highlights the focus that should be paid not only in diagnosing cardiac involvement but also in identifying the correct amyloid type to avoid errors in management and the information conveyed to the patient.

Our patient initially presented with signs and symptoms of right heart failure with echocardiographic findings of restrictive cardiomyopathy with severe ventricular hypertrophy and preserved LV systolic function. A non-invasive diagnostic approach of CA in routine clinical practice includes chest X-ray, biomarkers, ECG, echocardiography and CMR. Low-voltage waves in the limb and precordial leads is a common ECG finding in CA and present in 46%.³ Moreover, approximately 40% of patients with SCA have typical low QRS voltages versus 60% of AL amyloidosis patients.³ Our patient did not have low voltages but a pseudo-infarct pattern, which is estimated to be present in approximately 47% of patients with amyloidosis and cardiac involvement.³ The granular "sparkling" appearance of the myocardium in echocardiography is characteristic, especially in combination with biatrial enlargement.⁴ Furthermore, in strain and strain rate imaging derived by speckle-tracking, greater restriction is noted for basal compared with apical movement.⁵ Regarding cardiac biomarkers, increased cardiac troponin concentrations have been characterized as a marker of poor prognosis among patients with CA, especially in combination with BNP/pro-BNP measurements. However, the condition has been mostly studied in patients with AL amyloidosis.³ CMR contributes to the diagnosis by offering the advantage of noninvasive myocardial tissue characterization with paramagnetic contrast enhancement.³

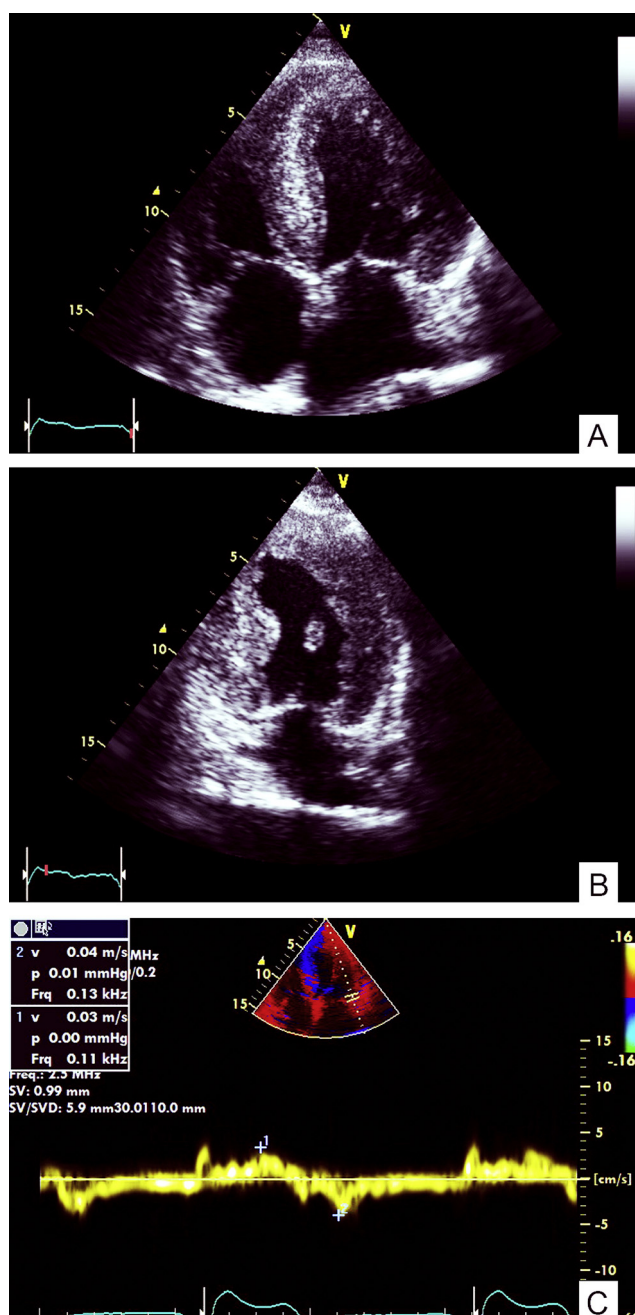


Figure 2 Transthoracic echocardiographic study demonstrating severe symmetric hypertrophy of the left ventricle with a granular 'sparkling' texture and thickened papillary muscles on the apical four- and two-chamber view (A, B). Tissue Doppler imaging at the lateral mitral annulus revealing reduced annular velocities (C).

While asymptomatic, our patient developed conduction abnormalities treated with permanent pacemaker implantation. The sinus and atrioventricular node are most often infiltrated by amyloid, which causes dysfunction.² Bifascicular block on the ECG is common, and progression to complete atrioventricular block occurs frequently in patients with SCA, necessitating pacemaker implantation.² Patients with CA might also develop ventricular

arrhythmias due to the widespread myocardial fibrosis, and risk stratification is needed when considering implantation of an implantable cardioverter defibrillator for primary prevention of sudden cardiac death.

Senile cardiac amyloidosis is a disease of the >60-year age group. It almost exclusively affects men and is often misdiagnosed as hypertensive heart disease.⁶ The symptoms are slowly progressive. According to the literature, the median survival is approximately 7.5 years from presentation, which is significantly superior to AL cardiac amyloidosis for which median survival ranges between 8 and 15 months.⁶ Disease progression manifested in our patient 12 months after initial presentation, requiring hospitalization and making a diagnosis of AL amyloidosis less likely. Moreover, supporting the diagnosis of SCA over AL amyloidosis, no extracardiac involvement was present in our case, such as plasma cell dyscrasia, nephrotic syndrome, autonomic neuropathy (e.g., orthostatic hypotension), respiratory disease, dermatological manifestations, easy bruising or makroglossia, referring to possible systemic amyloidosis. The only exception was the history of carpal tunnel syndrome, which is reported to precede heart failure by 3 to 5 years in 34-48% of patients with SCA.⁷

Regarding treatment, there is no specific licensed treatment for SCA. Patients often tolerate angiotensin converting enzyme inhibitors opposed to AL amyloidosis; however, the cautious use of diuretics remains the cornerstone of the therapy.² In contrast, patients with systemic amyloidosis typically require additional therapies and specific strategies that suppress production of the amyloid, e.g., chemotherapy for AL amyloidosis or targeted drug therapy for hereditary amyloidosis.³

Senile cardiac amyloidosis is underdiagnosed.⁶ The 'gold standard' for safe diagnosis of SCA remains myocardial biopsy followed by Congo Red staining and immunochemistry, but possible sampling errors and procedural risks limit its clinical use, especially in the elderly patients given that some of them are not keen to undergo such an invasive investigation. Two-dimensional echocardiography, tissue Doppler imaging, speckle-tracking echocardiography and CMR provide valuable information that along with the patient's clinical characteristics can be of assistance in establishing the diagnosis of SCA. Pinney et al sought to design a diagnostic algorithm for the approach of a patient with CA, in which patients are likely to have SCA over AL amyloidosis if they are over 70 years of age and do not have extracardiac involvement, plasma cell dyscrasia and elevated serum BNP/pro-BNP levels (cut-off value of 1420 pmol/L or 387 pg/ml).¹ They also demonstrated that patients with SCA exhibit more arrhythmias and are more likely to require permanent pacing therapy.¹

In summary, diagnosing CA when evaluating patients with restrictive cardiomyopathy is only the first step and requires a high index of suspicion. Accurately diagnosing the amyloid type in patients with cardiac involvement is crucial. Cardiac AL amyloidosis and SCA are separate diseases with different prognoses and treatments. When histological confirmation is impossible, clinicians must rely on a combination of clinical history, physical examination, imaging studies and laboratory parameters to establish diagnosis. They also should be more alert and closely

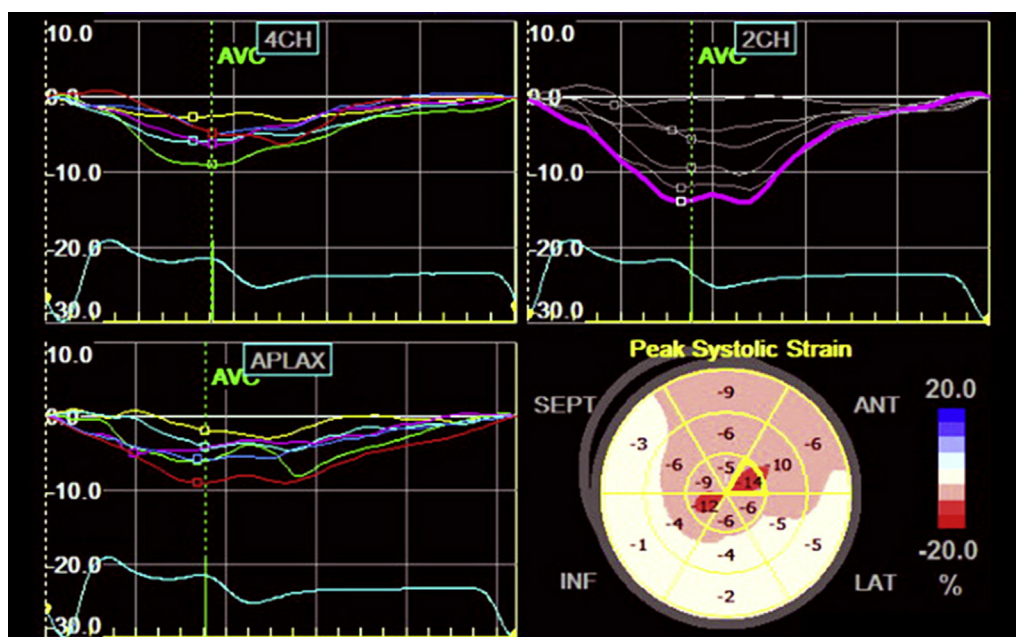


Figure 3 Speckle-tracking echocardiography exhibiting a reduced average value with a global longitudinal peak strain of -6.1% (normal reference value $>-18\%$).⁵

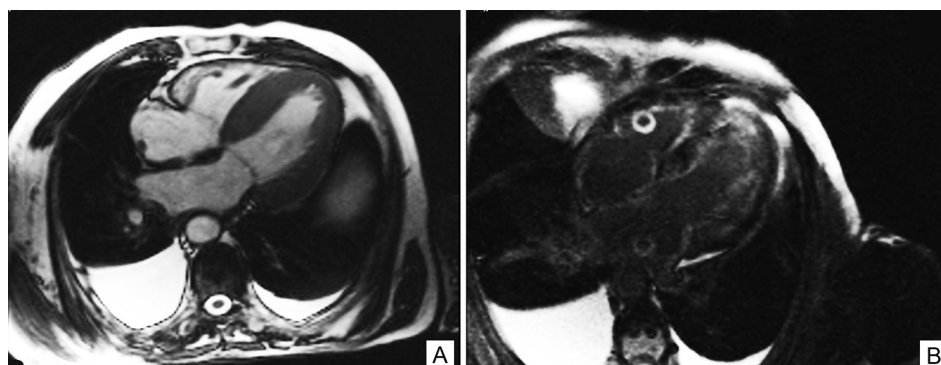


Figure 4 Diastolic image from the cardiac magnetic resonance study in the four-chamber orientation, demonstrating increased thickness of the myocardial walls with normal systolic function and bilateral pleural effusion (A). Delayed gadolinium-enhanced image demonstrating diffuse myocardial signal enhancement (B).

monitor these patients for possible symptom deterioration or occurrence of conduction abnormalities.

Conflict of interest

None to declare.

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