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CASE REPORT

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Chest pain in a patient with transthyretin cardiac amyloidosis: A case report

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Key Clinical Message

Patients with transthyretin cardiac amyloidosis (ATTR-CM) commonly present with dyspnea, fatigue, and edema. In our case, the main presentation was exertional angina, which was atypical in patients with ATTR-CM and should be paid more attention to.

Abstract

A 54-year-old woman was admitted with a complaint of exertional chest pain, and she had a history of hypertension. The results of the electrocardiogram and echocardiography revealed the clues of cardiac amyloidosis, and the patient was finally diagnosed with transthyretin cardiac amyloidosis, then she received tafamidis, and the symptoms improved significantly.

KEYWORDS

chest pain, Tafamidis, Technetium-99m pyrophosphate, transthyretin cardiac amyloidosis

1 | INTRODUCTION

Transthyretin cardiac amyloidosis (ATTR-CM) is a rare restrictive cardiomyopathy caused by extracellular deposition of insoluble transthyretin amyloid fibrils in the myocardium.[1] Patients with ATTR-CM commonly present with symptoms of heart failure including dyspnea, fatigue, and edema,[1] however, some rare atypical symptoms are not well recognized. Here we report a case that presented with exertional chest pain and was finally diagnosed with hereditary ATTR-CM.

2 | CASE HISTORY

A 54-year-old woman presented to the cardiology department complaining of 6 months of exertional chest pain. Her chest pain was squeezing-like, and she was relieved after rest. She had no obvious activity tolerance limitations and denied nocturnal paroxysmal dyspnea or lower limb edema. Recently, her symptom worsened and a brisk walking or climbing 1 floor could induce chest pain, accompanied by palpitation and tachypnea. She suffered from hypertension for 8 years, for which she had been taking irbesartan and amlodipine and her blood pressure was stable around 110/70 mmHg. She denied histories of coronary artery disease, diabetes, and hyperlipidemia. Also, she reported no medical family history. Recently, the echocardiogram indicated a thickened ventricular septum (13 mm). Besides, she had a history of chronic nephritis but the creatinine level was normal. On examination, she was relaxed with the following vital signs: blood pressure 106/66 mmHg, heart rate of 80 bmp, respiratory rate of 20 breaths/min. The physical examination was unremarkable.

3 | METHODS

After being hospitalized, the patient received an electrocardiogram (ECG), which showed a sinus rhythm with a premature ventricular beat, pathological Q-wave and poor R-wave progression (PRWP) in the precordial leads, first degree atrioventricular block, and left anterior fascicular block (Figure 1). Based on the patient's medical history, coronary artery disease with an old myocardial infarction was suspected, however, the treadmill exercise test and next coronary angiography were negative.

Then, the patient's history and examinations were reviewed again, and more examinations were obtained. Apart from a higher level of N-terminal pro-B-type natriuretic peptide (834 pg/mL), other blood tests, including the cardiac enzymes, were within normal limits. Ambulatory blood pressure monitoring showed a mean blood pressure of 104/60 mmHg. Echocardiography showed a thickened ventricular septum (13 mm) with a normal left ventricular ejection fraction (67%) the heart valve and pericardium were normal (Figure 2) and reduced longitudinal strain with apical sparing (Figure 3). Furthermore, cardiac magnetic resonance (CMR) imaging revealed the left ventricular hypertrophy (LVH), late gadolinium enhancement in left ventricular, endocardium, and artium (Figure 4). Therefore, a rare disease, cardiac amyloidosis (CM) was suspected. After ruling out light-chain CM, the technetium-99 m pyrophosphate (^{99m}Tc-PYP) imaging showed that the patient had a cardiac scintigraphy with a visual score of 3 (Figure 5). Next, gene testing with a panel of whole exome sequencing (Illumina NovaSeq 6000, Illumina, US) revealed a mutation of TTR gene at chromosome 18:291 with 128G > A. The patient was finally diagnosed with hereditary ATTR-CM. Initially, the patients refused to receive tafamidis for the treatment of ATTR-CM, and other medications like nitrates to help with her anginal symptoms were also not taken for the reason that nitrates could reduce preload and result in hypotension. Fortunately, at 7 months after being diagnosed with ATTR-CM, she received tafamidis with a dose of 61 mg per day.

4 | CONCLUSION AND RESULTS

Up to now, she has taken tafamidis for 9 months. After taking tafamidies, the patient gradually felt better, and now she feels free of exertional chest pain. At 16 months after discharge, echocardiography still showed a thickened ventricular septum (14 mm) with a normal left ventricular ejection fraction (67%) and the heart valve and pericardium were normal. Besides, NT-proBNP was 942 pg/mL during follow-up period. Figure 6 summarized the process from symptom onset to treatment with tafamidis and the conditions during the follow-up period.

5 | DISCUSSION

ATTR-CM is an infiltrative cardiomyopathy caused by extracellular deposition of insoluble transthyretin amyloid fibrils in the myocardium.[1] Although ATTR-CM is usually regarded as a rare disease, its incidence is not so low. For example, ATTR deposition is seen in up to 16% of patients with degenerative aortic stenosis[2] and 13% to 17% of patients with heart failure with preserved ejection fraction (HFpEF).[3,4] ATTR-CM is progressive and life-threatening, so early diagnosis is critical; however, ATTR-CM is often misdiagnosed due to a lack of knowledge of ATTR-CM. Additionally, patients with LVH are often misdiagnosed as hypertensive cardiomyopathy for a high prevalence of hypertension in general patients. Actually, besides hypertensive cardiomyopathy, LVH is associated with a broader clinical setting, such as CM, hypertrophic cardiomyopathy, aortic stenosis, and rare genetic disorders such as Fabry disease.[5] However, finding out the clues to these diseases is sometimes very challenging.

The common symptoms of ATTR-CM are dyspnea, fatigue, and edema, but these symptoms are nonspecific and often misdiagnosed as HFpEF. There are several clues helping clinicians increase the vigilance for CM. First, myocardial wall thickness exists on echocardiogram while the ECG shows no LVH. Actually, most patients present with low voltage on the ECG. This contradictory phenomenon is enough to render clinicians to further exclude CM. In our case, the patient had a history of hypertension and the LVH seemed reasonable, but contradicted to a well-controlled blood pressure and normal voltage on the ECG. Second, pseudo-myocardial infarction on the ECG is an important clue. Pathological Q-wave on the ECG is commonly seen in myocardial infarction; however, many other diseases such as ATTR-CM could also cause pathological Q-wave. The mechanism may be the amyloid deposits in the microcirculation and smaller intramyocardial arteries. A study demonstrated that obstructive intramural coronary amyloidosis was present in 66% CM patients and microscopic changes of myocardial ischemia were more common in patients with obstructive intramural coronary amyloidosis.[6] Thirdly, PRWP on the ECG is also an important clue for CM. Cyrille et al.[7] reported that PRWP was observed in 60%–70% CM, and was one of the most frequent ECG changes. The occurrence of PRWP may be related to the amyloid deposits in the cardiac muscle and conduction tissue, causing conduction abnormality. The initial anterior electrical forces may be reduced in magnitude or be directed posteriorly, the anterior leads on the ECG are therefore, presented with PRWP.[8]

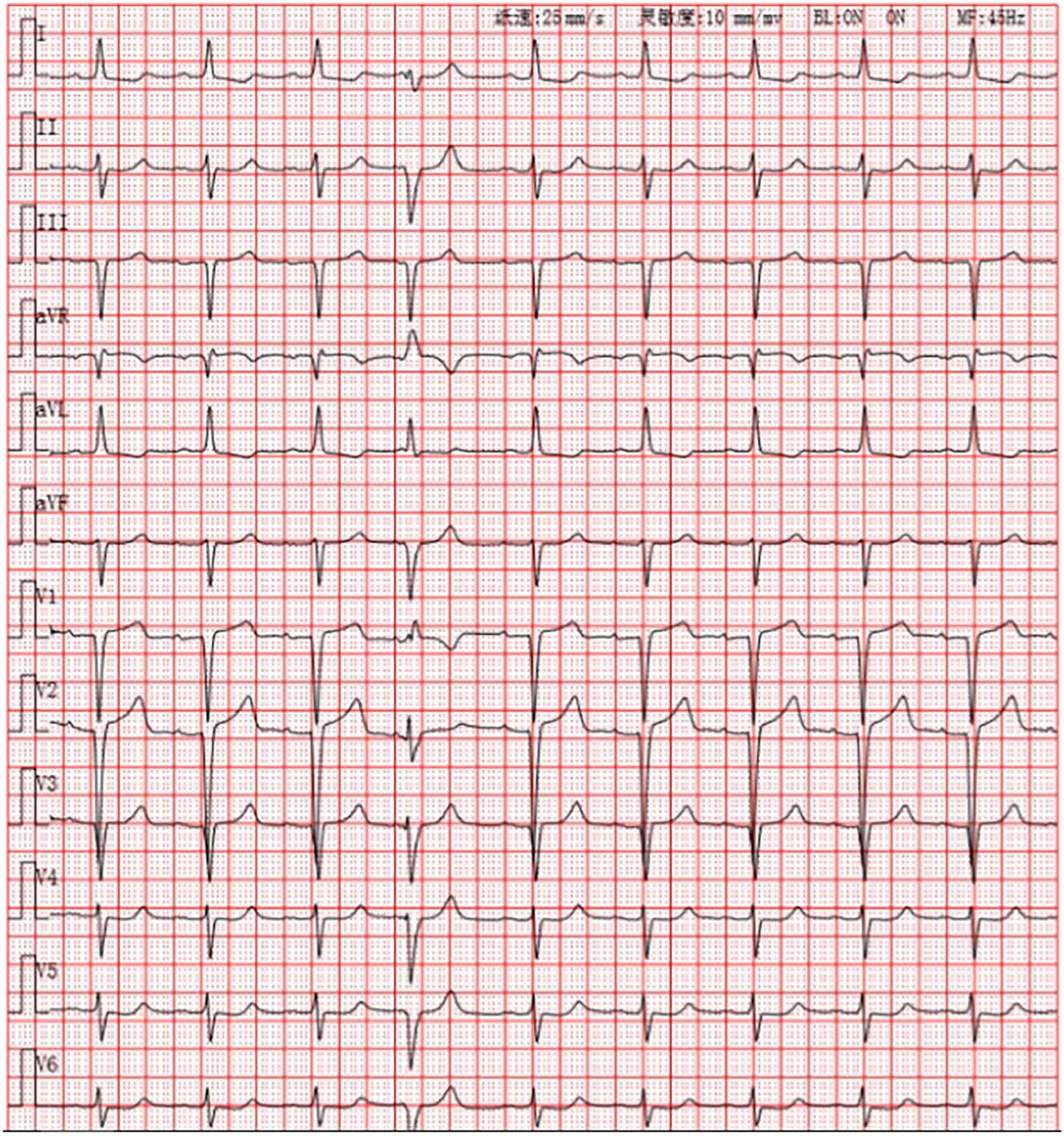

FIGURE 1 The ECG revealed a sinus rhythm of 78 bpm, and there was a premature ventricular beat. Pathological Q-wave could be observed in leads III, aVF, and V1-V3. There was a poor R-wave progression in the precordial leads. The P-R interval was 216 ms, indicating a first degree atrioventricular block. Moreover, II, III and aVF leads presented with the rS-wave, while I and aVL leads presented with the qR-wave, indicating a left anterior fascicular block.

Besides LVH, there are some other echocardiogramic features for CM, such as right ventricular hypertrophy, atrial septum thickening, thickened atrioventricular valves, atria dilation, pericardial effusion, "granular sparkling" appearance, etc.[9] Reduced longitudinal strain with apical sparing has a relatively high specificity for CM.[10] Moreover, as a multisystemic disease, patients often accompanied other symptoms such as carpal tunnel syndrome, lumbar spinal stenosis, and autonomic or sensory polyneuropathy,[11] which are all called "red flag signs" for CM.

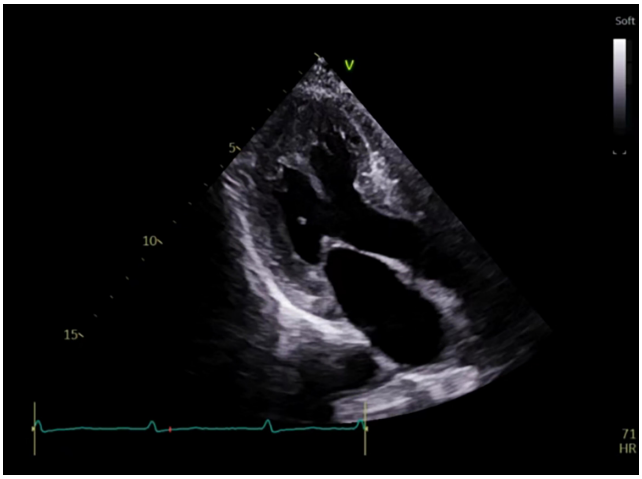

FIGURE 2 The echocardiography revealed a thickened ventricular septum (13 mm) with preserved ejection fraction (67%).

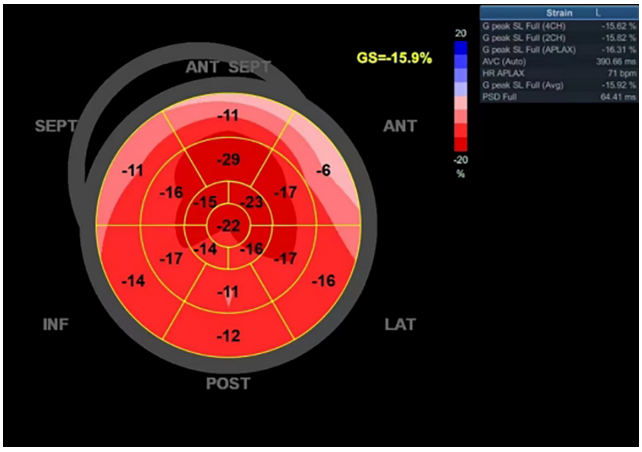

FIGURE 3 The speckle tracking echocardiography showed a reduction in longitudinal strain with apical sparing.

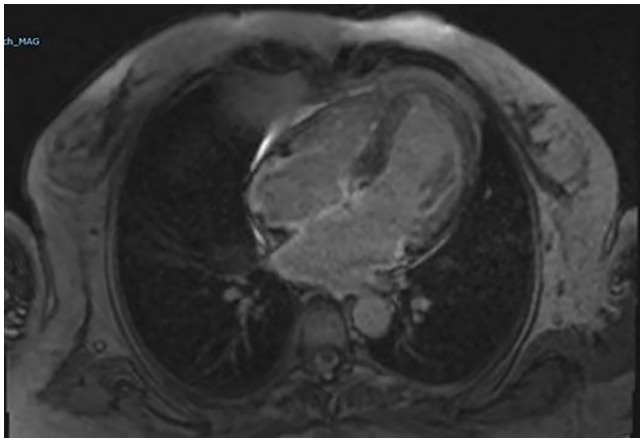

FIGURE 4 Cardiac magnetic resonance revealed left ventricular hypertrophy, especially the ventricular septum (15 mm), and late gadolinium enhancement was observed in the left ventricular, endocardium, and artium.

If there are above mentioned clues, further tests are needed to exclude ATTR-CM. According to the scientific statement from the American Heart Association,[11] measurement of serum immunofixation electrophoresis (IFE), urine IFE, and serum free light chain should be conducted to exclude light-chain CM. If the light-chain CM is excluded, 99mTc-PYP should be administered, and if there is grade 2–3 cardiac uptake or a heart/contralateral chest ratio >1.5, ATTR-CM can be diagnosed; if not, endomyocardial biopsy should be conducted in a highly suspected case. For definitive ATTR-CM, genetic testing is used to distinct hATTR-CM and wild-type transthyretin amyloidosis.

In our case, the main presentation was exertional angina, which was atypical in patients with ATTR-CM. Previously, there were also some cases reported with atypical chest pain in patients with CM,[12–16] and recently, a relatively bigger sample size with 174 CM patients revealed that 66 (38%) presented with chest pain,[17] indicating that chest pain is actually a relatively common symptom in patients with CM; moreover, in this study, those who presented with chest pain were more likely to have a history of coronary artery disease, heart failure symptoms, and higher troponin I level. However, in our present case and some other reported cases,[12–16] patients had no symptoms of heart failure or coronary artery disease, suggesting the symptoms of CM are substantially heterogeneous.

The mechanisms of chest pain in patients with CM are multifactorial,[13] including accumulation of amyloid within the walls of the small coronary arteries, perivascular and interstitial amyloid deposits leading to extramural compression and reduced diastolic perfusion time, obstruction of small coronary arteries by amyloid infiltration, and coronary microvascular dysfunction such as significantly lower myocardial blood flow, lower coronary flow reserve, and higher minimal coronary vascular resistance, which cause an imbalance between the myocardial oxygen supply and the myocardial oxygen demand, especially in the setting of increased cardiac load.

Although the presentation in our case is not rare, it is indeed atypical. When encountering patients complaining of exertional chest pain without angiographically apparent lesions, clinicians should consider amyloidosis as a differential diagnosis. Besides, the prognostic impact of chest pain in patients with CM should be addressed because previous studies have shown angina symptoms may precede the onset of heart failure in some patients with CM[6] and chest pain was a reflection of a more advanced cardiac impairment and predicted future heart failure hospitalization.[17] Early and timely diagnosis, along with appropriate treatment, is conducive to improving the prognosis of patients with CM.

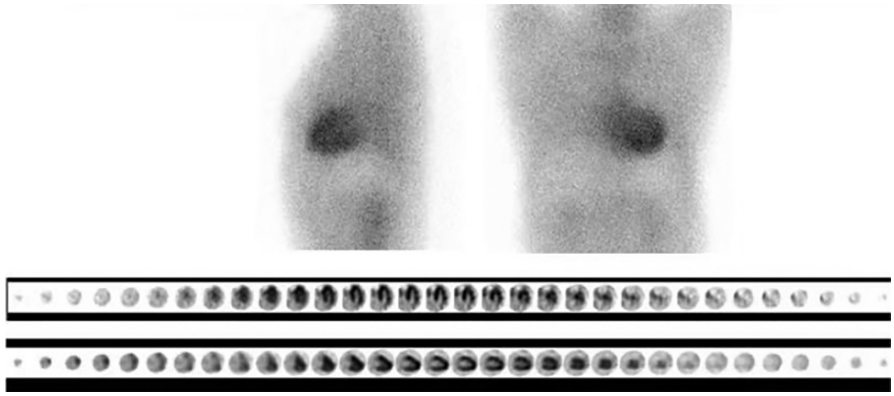

FIGURE 5 The technetium-99m pyrophosphate (99mTc-PYP) imaging showed a cardiac scintigraphy with a visual score of 3.

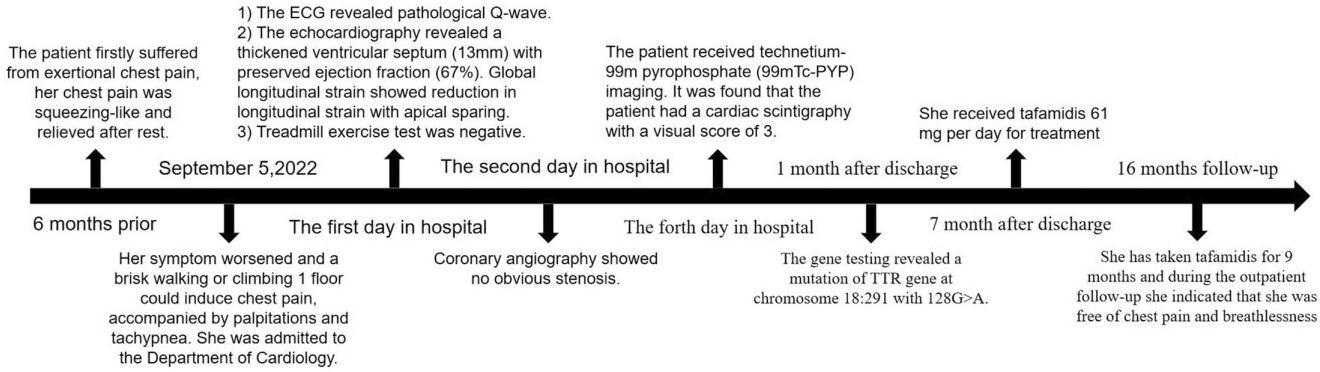

FIGURE 6 The process from the symptom onset to treatment with tafamidis and the conditions during follow-up period.

In conclusion, our case showed that a patient presented with exertional angina and was finally diagnosed with hATTR-CM. Although patients with ATTR-CM commonly present with dyspnea, fatigue, and edema, some atypical symptoms such as exertional chest pain, should be recognized. As long as there are clinical clues for ATTR-CM, further examinations should be arranged no matter, how atypical the symptom is.

AUTHOR CONTRIBUTIONS

Linfeng Xie: Conceptualization; data curation; formal analysis; writing – original draft. **Suxin Luo:** Supervision. **Bi Huang:** Supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this case report are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study complied with the Declaration of Helsinki and was approved by the Human Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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