

Noninvasive diagnosis of hereditary transthyretin-related cardiac amyloidosis

A case report

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Abstract

Rationale: Cardiac transthyretin amyloidosis is a progressive and fatal cardiomyopathy for which several promising therapies are in development. The diagnosis is frequently delayed or missed because of the limited specificity of clinical manifestations, routine electrocardiogram, echocardiography and the traditional requirement for endomyocardial biopsy confirmation.

Patient concerns: A 68-year-old female had suffered from lumbago for 5 years with progressive weakness, numbness in both lower limb.

Diagnosis: The patient's clinical signs were not specific, but cardiac amyloidosis was suspected based on relative left ventricular apical sparing of longitudinal strain on echocardiography and continuous elevated serum levels of cardiac biomarkers (ultrasensitive cardiac troponin I and NT-proBNP). She was finally diagnosed hereditary transthyretin-related cardiac amyloidosis by specific findings of cardiovascular magnetic resonance imaging (CMR), ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) scintigraphy and genetic testing.

Interventions: The patient received medications including diuretics, beta-blockers and angiotensin-converting enzyme inhibitors at the time of hospitalization. Ultimately, however, she refused further treatments and requested discharge from our hospital.

Outcomes: A series of noninvasive technique enables the diagnosis of hereditary transthyretin-related cardiac amyloidosis.

Lessons: While endomyocardial biopsy is not able to performed, this case demonstrates that a combination of noninvasive techniques, especially CMR, nuclear imaging, and genetic testing, may help us to make a correct diagnosis of hereditary transthyretin-related cardiac amyloidosis.

Abbreviations: AL = light-chain immunoglobulin, ATTR = transthyretin-related amyloidosis, ATTR-CA = transthyretin-related cardiac amyloidosis, ATTRm = mutated ATTR, CMR = cardiovascular magnetic resonance imaging, ECG = electrocardiogram, ECV = extracellular volume, FAP = familial amyloid polyneuropathy, H/CL = heart-to-contralateral lung ratio, LGE = late gadolinium enhancement, LS = longitudinal strain, LV = left ventricle, TTE = transthoracic echocardiography, TTR = transthyretin.

Keywords: ^{99m}Tc-PYP scintigraphy, cardiovascular magnetic resonance imaging, genetic testing, hereditary transthyretin-related cardiac amyloidosis

1. Introduction

Amyloidosis is a relatively rare multisystem disease characterized by deposition of fibrils in extracellular tissue that involves the

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kidney, liver, heart, autonomic nervous system, and several other organs.^[1] Cardiac involvement indicates an unfavorable prognosis and influences treatment strategies.^[2] Although early diagnosis is a critical step in treating cardiac amyloidosis, diagnosis is usually delayed because amyloid deposition can involve multiple systems with a wide variety of clinical appearances. Therefore, increasingly studies are focused on novel diagnostic and surveillance approaches, particularly combined application of noninvasive methods. We present a case of hereditary transthyretin-related cardiac amyloidosis and discuss the key clinical and diagnostic findings along with the existing literature regarding its treatment and outcomes.

1.1. Consent statement

The ethical approval was obtained from the Ethics Committees of Tongji Hospital. Written informed consent was obtained from the patient for the publication of this case report.

2. Case report

In June 2018, a 68-year-old female was admitted to the orthopedic ward of our hospital with lumbago for 5 years and

Table 1
Admission laboratory data.

Test	Value	Normal values
Hemoglobin	107.0 g/L	115.0-150.0 g/L
Blood urea nitrogen	4.81 mmol/L	3.1-8.8 mmol/L
Creatinine	85 umol/L	45-84 umol/L
eGFR (mL/min)	60.8 ml/min/1.73m ²	>90 ml/min/1.73m ²
Alkaline phosphatase	57 U/L	35-105 U/L
Aspartate aminotransferase	26 U/L	≤32 U/L
Glucose	4.64 mmol/L	4.11-6.05 mmol/L
Coagulation studies	Normal	normal
Creatine kinase	71 U/L	≤190 U/L
Creatine kinase MB isoenzyme	1.6 ng/mL	≤3.4 ng/mL
High-sensitivity troponin I	313.3 pg/mL	<15.6 pg/mL
NT-proBNP	3822 pg/mL	<285 pg/mL
Urine protein	Negative	negative

progressive weakness, numbness in both lower limb. On examination, her blood pressure was 120/70 mmHg, heart rate was 70 bpm and regular, respiratory rate was 18 per minute, temperature 36.5°C and SaO₂ of more than 97% at room air. Her neck was supple and cardiovascular examination revealed muffled heart sounds, normal S₁S₂ with no appreciable murmur. The remainder of the examination was almost normal. Admission laboratory data are presented in Table 1. We noted ultrasensitive cardiac troponin I (cTnI) was elevated to 313.3 pg/mL (normal <15.6 pg/mL), and NT-proBNP assay was 3822 pg/mL (normal <285 pg/mL). Her electrocardiogram (ECG) showed normal sinus rhythm with a ventricular rate of 84 beats/min and poor R wave progression in precordial leads with ST-segment changes in antero-lateral leads (Fig. 1). A 24-hour Holter monitoring manifested dynamic changes of ST segments. Diagnostic coronary computed tomographic angiography

(CTA) revealed the absence of significant luminal narrowing on epicardial arteries. Due to the continuous elevated troponin I levels and deteriorating cardiac function, she was transferred to the cardiovascular medicine department.

Her transthoracic echocardiogram was significant for moderate concentric left ventricular hypertrophy, hypokinesis of diastolic function with a ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e', E/e' ratio) of 22, and preserved left ventricle ejection fraction (EF, 53%). Pulmonary arterial systolic pressure was 30mm Hg and right atria (RA) was dilated. No significant valvular heart disease was found. Relative apical sparing was seen in the 2D strain analysis which led to the suspicion of cardiac amyloidosis (Fig. 2). And then, the patient underwent cardiac magnetic resonance imaging (CMR), which showed global hypokinesis of the left ventricle (LV) (an absolute cardiac output 2.6L/min) with diffuse myocardial late gadolinium enhancement (LGE) and hypertrophy of interventricular septum without any evidence of perfusion defect. The native T1 values and extracellular volume (ECV) values were significantly high (Fig. 3). This constellation of symptoms was consistent with cardiac amyloidosis.

A complete work-up was then performed to distinguish different types of amyloidosis. Immunoelectrophoresis of the proteins and research for light chains were negative in blood and urine. Bone marrow examinations including bone marrow smear and biopsy plus flow cytometry were not found abnormal plasma cells. Further investigated with ^{99m}-technetium pyrophosphate (^{99m}Tc-PYP) scintigraphy, cardiac retention of radiotracer was assessed quantitatively by drawing a region of interest over the heart followed by the contralateral right lung and calculating a heart-to-contralateral lung ratio (H/CL). The patient was injected with 20.0 mCi of ^{99m}Tc-PYP and planar images were acquired 1 hour later, which showed significantly increased radiotracer activity in the heart with a calculated H/CL of 1.90 (normal <1.5) (Fig. 4A), consistent with a cardiac transthyretin amyloidosis.

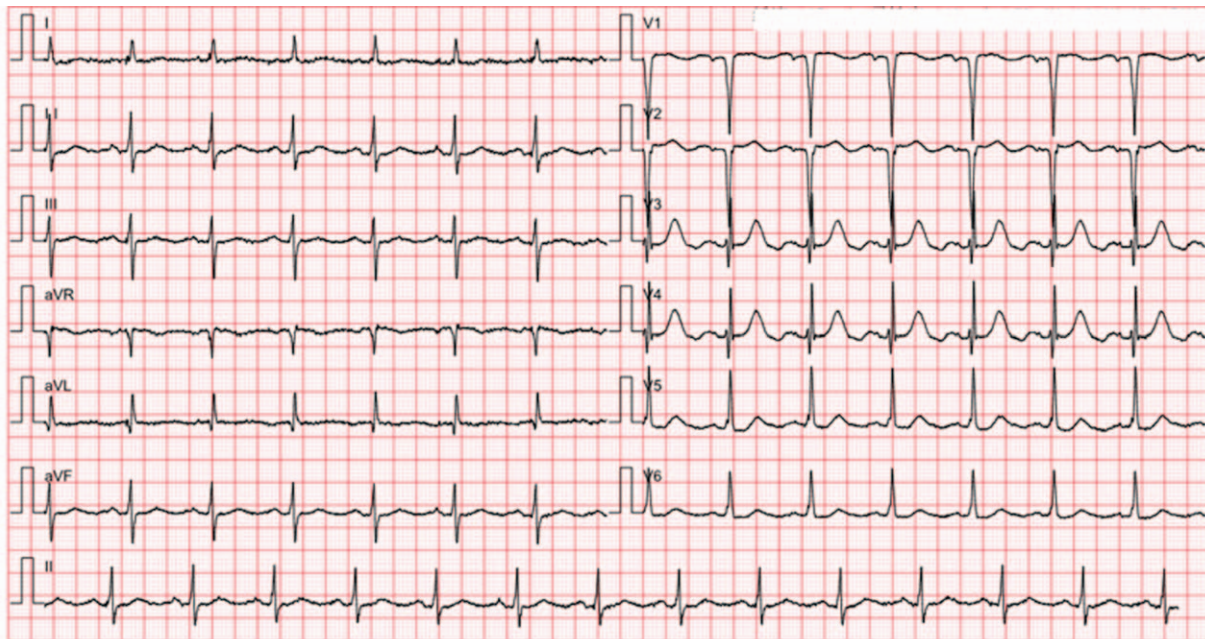


Figure 1. 12-lead electrocardiogram demonstrating poor R wave progression in precordial leads with ST segment changes in V5-V6.

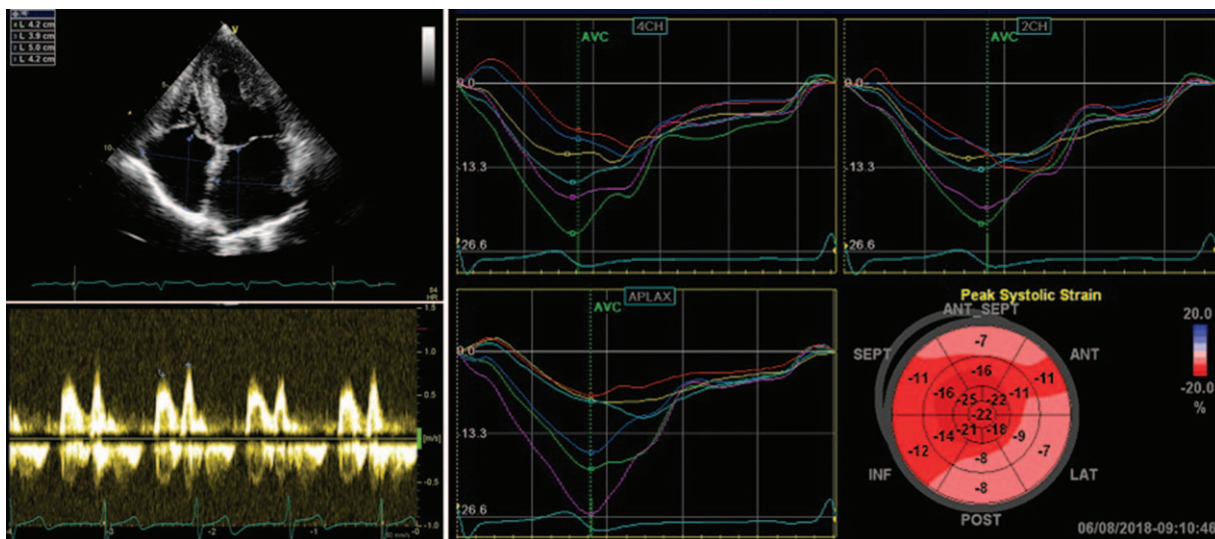


Figure 2. (A) Cardiac image section 4 cavities of an echocardiography: thickening of the interventricular septum measured at 16 mm; (B) TDI: E/e' measured 22 as an indication for a diastolic dysfunction; (C) 2D strain analysis with “apical sparing” as a typical sign for amyloidosis. TDI=Tissue Doppler.

After obtaining informed consent, DNA sequencing of the transthyretin (TTR) gene and amino acid sequence analysis of serum TTR was performed and identified a c. 349G >T transversion (p. Ala117Ser) in TTR gene exon 4 (Fig. 4B). No other mutations were present in TTR. The patient had no family history of cardiomyopathy, and a diagnosis of sporadic hereditary transthyretin-related amyloidosis (ATTR) was finally made.

The patient received medications including diuretics, beta-blockers and angiotensin-converting enzyme inhibitors at the time of hospitalization. Ultimately, however, she refused further treatments and requested discharge from our hospital.

3. Discussion

Cardiac amyloidosis is increasingly recognized as an important cause of heart failure with preserved ejection fraction, which marked by endogenous proteins mis-folded into beta-pleated sheets and get deposited in myocardium.^[2,3] Cardiac involvement may occur in the 3 main types of amyloidosis (acquired monoclonal light-chain, hereditary transthyretin, and senile amyloidosis) and has a major impact on prognosis. Cardiac amyloidosis due to the deposition of light-chain immunoglobulin

(AL) is present in about 50% of cases, and almost all of them are over the age of 50. Transthyretin (TTR)-related amyloidosis is derived from transthyretin, which is produced by the liver. There are 2 types of TTR-related amyloidosis: a genetic form known as hereditary transthyretin-related amyloidosis (mutant ATTR or ATTR_m), which associated with an autosomal dominant genetic mutation, and a senile TTR amyloidosis form known as wild-type ATTR amyloidosis (wild-type ATTR [ATTR_w]).^[4] It is important to distinguish these various types of cardiac amyloidosis because disease progression and prognosis of each type are different; however, in any forms, myocardial involvement is the critical effect factor of prognosis.

Cardiac involvement in ATTR_m amyloidosis (ATTR_m-CA) develops in about half of the patients with ATTR_m amyloidosis. ATTR_m-CA most frequently manifests clinically as heart failure with normal systolic function, conduction blocks, atrial and/or ventricular arrhythmias, or sometimes sudden cardiac death (SCD).^[4] Timely identification of ATTR_m-CA facilitates selection of appropriate managements and provides valuable prognostic insight, including genetic counseling of family members.

As we know, the gold standard for diagnosing cardiac amyloidosis is endomyocardial biopsy. But myocardial biopsies

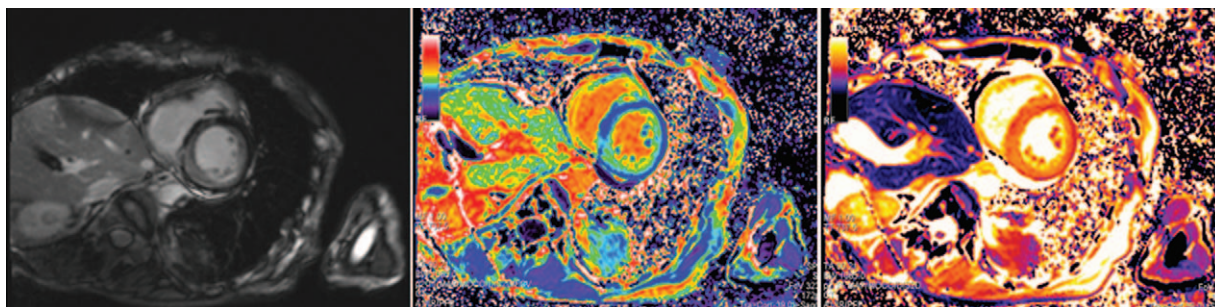


Figure 3. Images from a cardiac MRI. (A) Diffuse subendocardial LGE of the left ventricle demonstrates high signal intensity patterns, typical for a clinical picture of cardiac amyloidosis; (B) ECV values indicating heavy cardiac amyloid burden; (C) Contrast-free T1-mapping reveals elevated values for T1-times indicating increased amount of diffuse myocardial fibrosis. ECV= elevated extracellular volume.

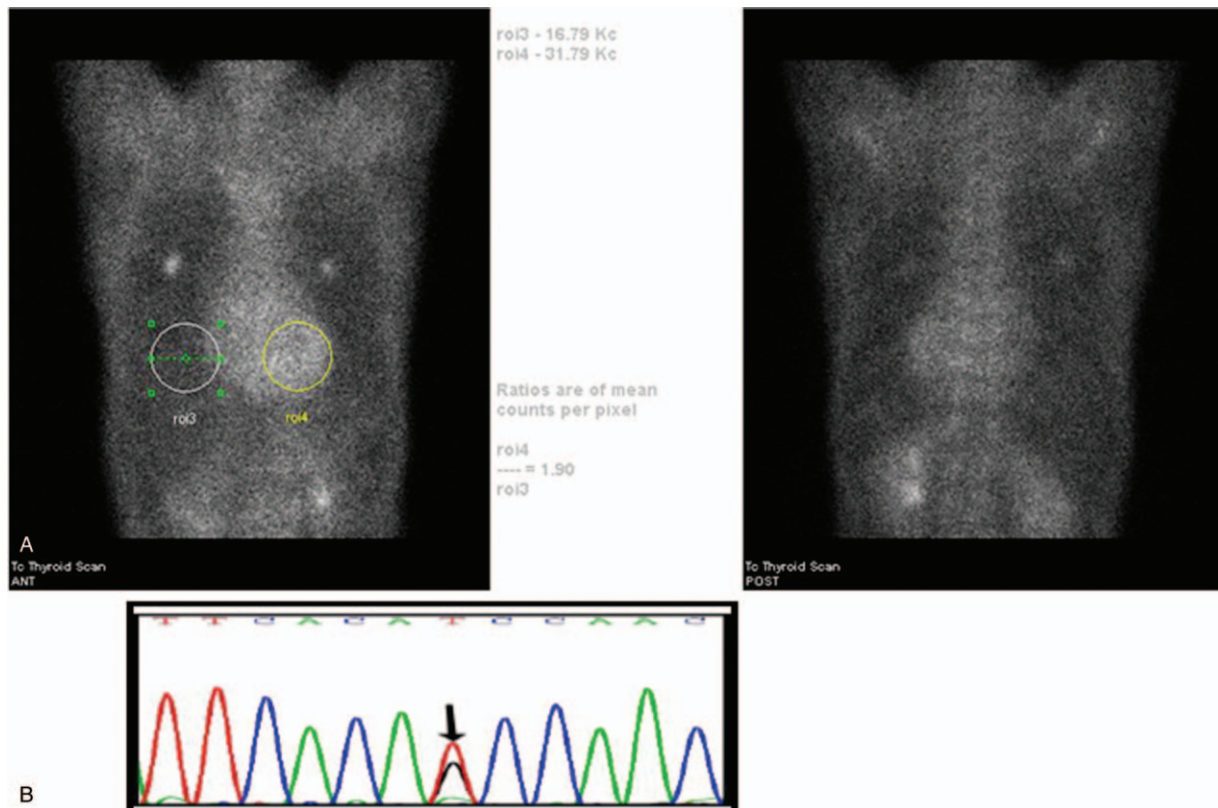


Figure 4. (A) ^{99m}Tc -PYP scintigraphy showed increased isotope uptake in the heart; (B) DNA sequencing of the TTR gene showed a c. 349G>T transversion (p. Ala117Ser) in TTR gene exon 4.

are rarely carried out routinely in clinical practice because of a non-negligible risk of complications, particularly in old patients. Therefore, noninvasive imaging methods are being increasingly used to allow safer and earlier detection. Here, the patient finally confirmed the presence of the hereditary transthyretin-related cardiac amyloidosis via combining application of noninvasive methods.

Previous studies had revealed that ECGs were abnormal in 90% of cases with cardiac amyloidosis. Murtagh et al reported that the 2 most common abnormalities were low voltage QRS complex (defined as all limb leads <5 mm in height) and a pseudo-infarct pattern on the precordial leads, which were seen in about 50% of the patients included.^[5] Other changes such as atrial fibrillation could occur in roughly 15% of patients.^[6] Right and left bundle branch block were uncommon. Another study mentioned that a fragmented QRS (notches and R_sR' pattern in the absence of QRS prolongation) was significantly more frequent in patients with cardiac amyloidosis (28.5% vs 11.7%; $P = .0008$).^[7] However, these ECG findings are not specific to cardiac amyloidosis.^[8] Another common method using to identify cardiac amyloidosis is transthoracic echocardiography (TTE). The typical features include:

- (1) increased LV wall thickness ≥ 12 mm with a “brilliant” speckled or granular appearance of the myocardium,
- (2) preserved LV ejection fraction (LVEF) >50% (at least in the early stage of the disease),
- (3) poor longitudinal function and altered LV relaxation,
- (4) mild or moderate LV diastolic dysfunction,
- (5) normal or small LV cavity,

- (6) left atrial enlargement (diameter >23 mm/m², area >20 cm² or maximal volume >28 mL/m²).^[9]

Advanced echocardiographic techniques are beginning to reveal more about the underlying pathology and functional abnormalities in TTR type cardiac amyloidosis (ATTR-CA). A recent study published by Phelan et al showed that the amyloid heart was characterized by reduced basal strain and regional variations in longitudinal strain (LS) from base to apex. And that a relative “apical sparing” pattern in LS is considered to be an easily recognizable, accurate and reproducible means of differentiating cardiac amyloidosis from other causes of LV hypertrophy.^[10] In our case, the clinical signs that revealed the condition were not specific. But characteristic changes showed in her TTE and continuous elevated of cTnI and NT-proBNP sparked our thinking.

Next, CMR provides strong clue to the diagnosis of cardiac amyloidosis. The extent or severity of cardiac involvement in amyloidosis can be described by ventricular wall thickness, left ventricular mass, the degree of LGE, T1 mapping and ECV at CMR. Tissue characterization specifically with LGE imaging, including transmural LGE, large diffuse annular LGE, global heterogeneous LGE of “patch” LGE, has been reported to be 1 of the most accurate predictors of endomyocardial biopsy-positive amyloidosis.^[11] In normal myocardium, gadolinium is not retained after administration, a phenomenon known as “nulling of myocardium.” In amyloid heart, the distribution kinetics of gadolinium are altered due to extracellular deposition of amyloid, leading to retained contrast that produces the characteristic LGE. Preliminary studies of the predicted value

of LGE in patients with suspected cardiac amyloidosis have shown sensitivities of 86 and 88% and specificities of 86 and 90%.^[12] And myocardial enhancement on LGE sequence is reported to be more intense in ATTR than in AL amyloidosis, with predominant transmural enhancement and frequent right ventricular (RV) involvement.^[13] More recently, Fontana et al. reported that ATTR amyloid deposits were larger than AL amyloid deposits and were associated with a ~20% increase in cell volume by using parametric imaging.^[14] Martinez et al. have further found that quantification of ECV measures cardiac amyloid deposition in both types of amyloidosis and shows that amyloid deposition is more extensive in patients with ATTR than in those with AL.^[15] Conversely, the myocardial native T2 relaxation time is significantly increased in AL compared to ATTR patients.^[16] Therefore, CMR has been a promising tool to detect cardiac amyloidosis and also provide useful additive insights to distinguish cardiac amyloid subtypes in a sense.

Positive CMR results of our patient contributed to establish the diagnosis of cardiac amyloidosis, and also prompted further investigation with ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) scintigraphy. The phosphate derivative single-photon emission computed tomography tracers, labeled with ^{99m}Tc, have been used to detect cardiac involvement of amyloidosis. Most commonly, ^{99m}Tc-DPD (technetium-3,3-diphosphono-1,2-propionic acid) and ^{99m}Tc-PYP are used, despite displaying different properties with respect to bone and soft tissue uptake. ^{99m}Tc-DPD is not approved by the Federal Drug Administration in the United States but has been mainly used in Europe. The exact mechanism by which these radiotracers accumulate in myocardium is not clear, although various hypotheses have been proposed. Of these, 1 suggests that phosphate in the radiotracers binds to high calcium level in the amyloidosis. Another hypothesis is based on duration of amyloid deposition that occurs in less time frame in patients with AL relative to more indolent course of patients with ATTR. As ^{99m}Tc-PYP preferentially binds to ATTR relative to AL fibrils, this technique also uses to distinguish the aforementioned amyloidosis subtypes.^[17] Bokhari et al. have described the diagnostic accuracy of ^{99m}Tc-PYP scintigraphy in identifying patients with ATTR and distinguishing ATTR from AL. In this study, patients with AL were also found to have radiotracer uptake, but H/CL can differentiate ATTR from AL.^[18] Now, using the quantitative measure H/CL with a cutoff value > 1.5, ATTR subtype amyloidosis can be detected with a 97% sensitivity and 100% specificity.^[19] The calculated H/CL of our patient was 1.90. At this point, our patient was diagnosed with ATTR-CA. Concerning about the risk of radiation exposure associated with nuclear imaging, Einstein et al. also performed an analysis to estimate cancer-risk associated with ^{99m}Tc-PYP scintigraphy for cardiac amyloidosis work-up. Findings demonstrated that the highest excess ^{99m}Tc-PYP-related risk of cancer was that of urinary bladder cancer. And the conclusion of the study suggested that there were very low cancer risks associated with ^{99m}Tc-PYP scintigraphy.^[20] Therefore, ^{99m}Tc-PYP scintigraphy has high diagnostic accuracy for detection of ATTR-CA and has the potential to evolve into a screening tool in the at-risk population.

Considering that the additional genetic test on the TTR gene revealed there was a mutation c. 349G>T in exon 4 of the TTR gene, resulting in replacement of alanine with serine at position 117 of the mature protein (Ala117Ser), a definitive diagnosis of hereditary ATTR-CA was established. The mutation c. 349G>T

in TTR gene is relatively common in Chinese population. Yuan et al. have reported a familial amyloid polyneuropathy (FAP) case with chronic paroxysmal dry cough, which with a proven heterozygous missense mutation c. 349G>T by whole-exome sequencing.^[21] Chen et al. studied the genetic features of Han Chinese family with FAP. And a c. 349G>T transversion in TTR gene exon 4 was identified in the proband with typical autonomic neuropathy and peripheral motor neuropathy.^[22] Our patient was hospitalized because of lumbago, but there were no overt signs of peripheral neuropathy except for numbness in both lower limb and the result of electromyography was normal. Some specific TTR mutations are more frequent in patients with a specific ethnic background and show many distinguishing characteristics in the genotype-phenotype correlation in different nationalities. For example, the V30M mutation, which is the most prevalent mutation associated with ATTR amyloidosis, is mainly found in endemic areas of Portugal, Japan, and northern Sweden and has a prevalence of 1:1000 in these areas. The characteristic phenotype of this mutation comprises sensori-motor polyneuropathy of the legs, carpal tunnel syndrome, autonomic dysfunction, constipation, and impotence.^[23] While the V122I TTR mutation is notable for its high prevalence in patients of African origin. Roughly 3% to 4% of African Americans are heterozygous for this mutation. The phenotype associated with the V122I mutation is mainly a late-onset amyloid cardiomyopathy without or with less evident polyneuropathy.^[24] Liu et al. proposed a possible hot-spot mutation of the TTR gene, Ala97Ser, in the Chinese-Taiwanese population, which presented with a constellation of late-onset sensorimotor polyneuropathy, and relentless progression to a great disability.^[25] According to incomplete statistics, there were over 70 single point mutations in TTR amyloidosis.^[26] Obviously, genetic testing can be useful to make the exactly diagnosis and distinguish amyloidosis from phenocopies, and large-scale study is still needed to establish the full picture of these mutations.

The treatment of cardiac amyloidosis mainly encompasses therapy of heart failure and the treatment of the underlying disease. The mainstays of therapy are loop diuretics, potentially in combination with thiazide diuretics and aldosterone antagonist. While other medications recommended in patients with diastolic or systolic heart failure, such as digitalis, calcium channel blockers, beta-blockers, or angiotensin-converting enzyme inhibitors can have significant adverse effects on amyloid-associated cardiomyopathy. Recent development of targeted therapies involved TTR stabilization, TTR suppression, and TTR disruption. Rosenblum et al. have demonstrated that the combined primary outcome of mortality and heart transplantation could be decreased in the patients treated with TTR stabilizers diflunisal (nonsteroidal anti-inflammatory drug) and tafamidis. So far, these treatments are limited to patients with mild or moderate neuropathy and the cardiac effects of these drugs are going to be assessed shortly.^[27] Furthermore, orthotopic liver transplantation (OLT) with or without a heart transplant is also theoretically the choice of treatment.^[28] New gene therapies (with antisense oligonucleotides to suppress hepatic TTR synthesis) are also going to be tested in ATTR. Now small-molecule inhibitors are investigated which complicate the tyrosine-binding site at the dimer-dimer interface, which results in inhibiting TTR monomer release and suppressing TTR amyloid fibril formation.^[29] Besides these, an observational study in Germany reported reductions in amyloid burden and left ventricular mass on 1-year follow-up in patients using green tea

extract.^[30] These emerging newer therapeutic agents may be able to revolutionize the treatment of ATTR in future.

4. Conclusion

Hereditary transthyretin amyloidosis is a rare, progressive, and fatal disease that presents with a wide spectrum of clinical manifestations, making natural history difficult to accurately describe. Diagnosis can be easily overlooked as patients often present with common and non-specific symptoms, and there is limited data on the natural history of ATTRm amyloidosis. Diagnosing cardiac ATTR amyloidosis is challenging. This report presents a case of hereditary transthyretin-related cardiac amyloidosis through combining application of noninvasive methods, especially CMR, ^{99m}Tc-PYP scintigraphy and genetic test.

Author contributions

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Writing – original draft: Jin Qin.

Writing – review & editing: Jin Qin, Jiangtao Yan.

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