

A misdiagnosed transthyretin in an elderly with myocardial hypertrophy and atrioventricular block: a case report

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Cardiac amyloidosis (CA) is an infiltrative and restrictive cardiomyopathy that leads to heart failure (HF), decreased quality of life, and death.^[1–3] There are two main subtypes of the disease, transthyretin cardiac amyloidosis (ATTR-CA) and immunoglobulin light chain CA. The former was further subdivided into wild-type (ATTRwt-CA) and or variant (ATTRv-CA) according to the presence or absence of a mutations in the transthyretin (TTR) gene.^[4,5] The majority of patients with ATTRwt-CA are over 75 years of age and 80%–90% are male.^[2,3]

The patients suffering from ATTRwt-CA display symptoms of HF with atrioventricular block (AVB) as the first symptom in more than 73.5% of patients.^[4] The median survival following diagnosis ranges from 43 months to 57 months with poor life quality and low survival rates.^[4] An autopsy study of people over 85 years showed that 25% of them had TTR deposits in their hearts.^[6] ATTR-CA is a systemic disease that necessitates multidisciplinary approaches for diagnosis and treatment.^[5] However, with insufficient clinical knowledge, ATTR-CA showed a high rate of misdiagnosis and missed diagnosis.

A 91-year-old man presented to Beijing Friendship Hospital, Capital Medical University, Beijing, China with complains of shortness of breath after exercise and lower limb edema for three weeks. Seven years ago, he was diagnosed with hypertrophic cardiomyopathy with interventricular septum of 16–18 mm, third-degree AVB and had a dual chamber implantable cardioverter defibrillator implantation two years ago. His medical history was hypertension, coronary atherosclerotic heart disease, and cardiac dysfunction (NYHA class III). He denied on family history of related diseases, his both brothers have high life expectancy and

the two daughters have normal electrocardiogram (ECG) and echocardiogram.

His physical examination showed a heart rate of 82 beats/min, blood pressure of 119/67 mmHg, no significant cardiovascular signs such as pulmonary rales, cardiac murmurs, or lower extremity edema were observed. Laboratory test showed: troponin T of 0.063 ng/mL (0.01–0.017 ng/mL), N-terminal pro-B-type natriuretic peptide of 7100 ng/L (< 1800 ng/L). Serum and urine protein electrophoresis were negative. An initial ECG from 2009 (Figure 1A) to 2020 showed a progressive prolongation of the PR interval (221–315 ms) until third-degree AVB (Figure 1B), and junctional fugitive rhythm. The ECG in Beijing Friendship Hospital, Capital Medical University, Beijing, China showed pacing rhythm, low voltage in limb conduction, and poor R-wave progression in chest conduction, no ST-T segments change (Figure 1C). Echocardiography showed widening of the ascending aorta (3.8 cm), enlargement of the left atrium (3.9 cm), thickening of the left ventricular wall (1.5–2.2 cm), stenosis of the left ventricular outflow tract (1.9 cm), left ventricular ejection fraction of 66.5%, valvular degeneration in old age, and reduced left ventricular diastolic function (E/E': 28.2) (Figure 2). Cardiac function assessment: 6-min walk test distance of 270 m.

The patient had a longevity family history and no malignant ventricular arrhythmias, and ATTR-CA was suspected despite the diagnosis of hypertrophic cardiomyopathy for many years. However, the patient could not tolerate magnetic resonance imaging due to the pacemaker. Therefore, after completing serum and urine protein electrophoresis to exclude amyloid light chain, cardiac scintigraphy with technetium Tc 99m pyrophosphate (^{99m}Tc-PYP) was performed.

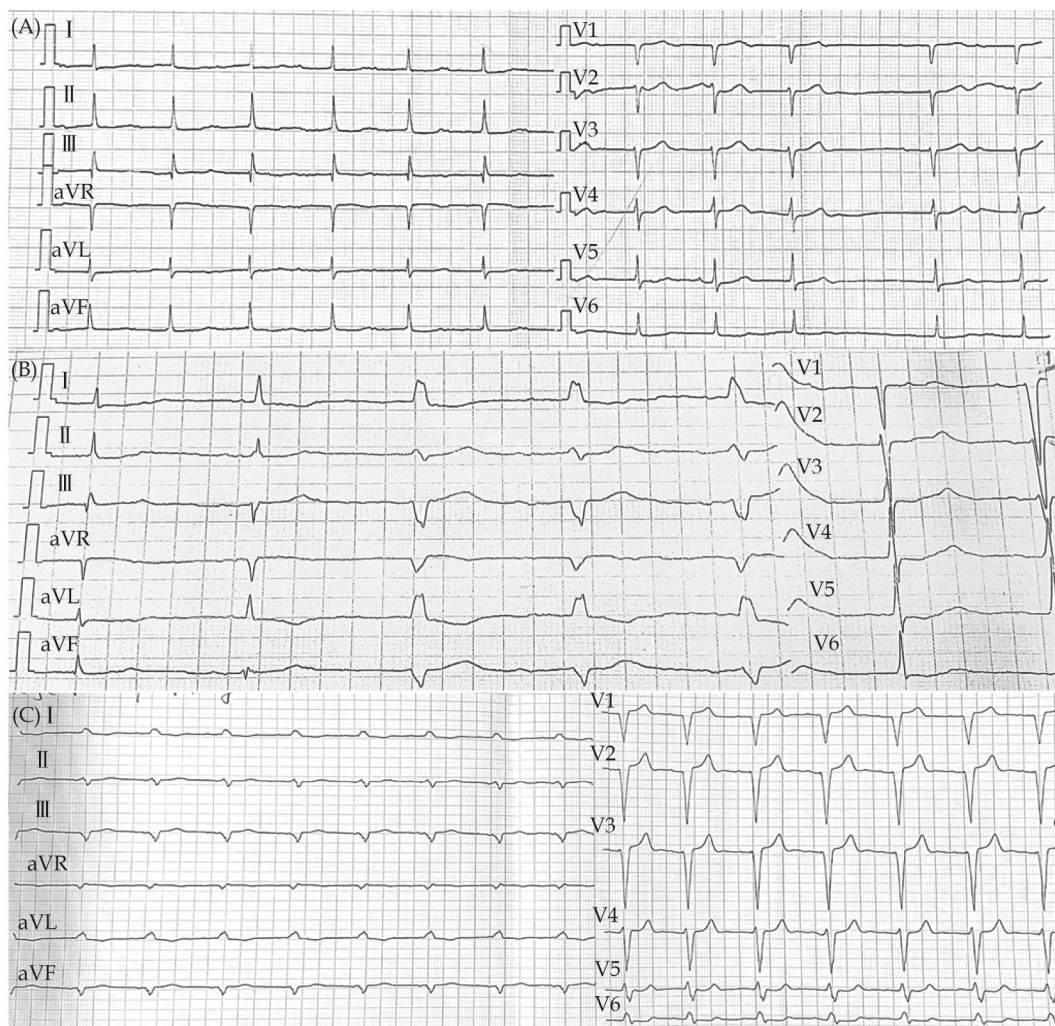


Figure 1 Recordings of electrocardiogram. (A): Heart rate of 86 beats/min, PR interval of 221 ms in 2009; (B): heart rate of 55 beats/min, PR interval of 253 ms, borderline escape rhythm ventricular autonomic rhythm in 2020; and (C): heart rate of 66 beats/min, pacing rhythm, limb lead low voltage, chest lead R-wave increasing poorly, no ST-T segments change in 2022.

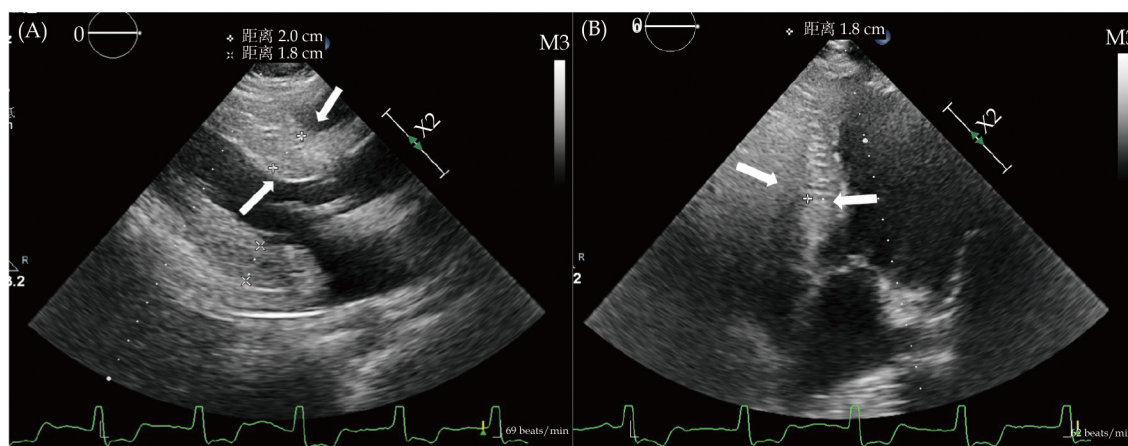


Figure 2 Echocardiogram recorded on admission. The interventricular septum thickness (arrows) of long axis section (A) and four chamber section (B).

The results of cardiac scintigraphy imaging with ^{99m}Tc -PYP showed the increased thorax at 1-hour radiotracer uptake at the region of the heart with heart-to-contralateral (H/CL) ratio of 1.9 (Figure 3A & 3B). Anterior and posterior views of the whole body bone scintigraphy scan in 3 h demonstrated increased tracer uptake at the region of the heart with associated apparent attenuation of the skeletal bone uptake, which was consistent with Perugini score 3 (Figure 3C). The diagnosis of ATTR-CA was clear. Followed by the TTR gene testing, no mutations was found, ATTRwt-CA was confirmed eventually.

The patient was treated with loop diuretics, potassium-sparing diuretics, and beta-blockers diuretics. Tafamidis, the only marketed the United States Food and Drug Administration drug for ATTR-CA (61 mg/d), was also applied. In addition, patients received appropriate cardiac rehabilitation training instruction and exercise prescriptions. The patient did not complain of shortness of breath after walking 2000 meters. Reexamination of echocardiography showed that left ventricular ejection fraction was 61.3%, left atrium of 3.9 cm and left ventricular wall (1.5–2.2 cm) had no significant change six months later.

ATTR-CA is an infiltrative cardiomyopathy and is the most common form of CA other than immunoglobulin light chain CA. ATTR-CA, manifested as progressive HF clinically, resulting from erroneously dissociation of TTR to form monomers and misfolding into amyloid, which is deposited in the myocardial interstitium.^[1] Although ATTR-CA is considered a rare disease, there is increasing evidence that the disease (AT-

TRwt in particular) may be more common than previously recognized.^[5,7] It was found that 13.3% of patients with HF with preserved ejection fraction and left ventricular hypertrophy were finally diagnosed as ATTRwt-CA by ^{99m}Tc -PYP scintigraphy.^[8] ATTRwt-CA mainly affects the heart, resulting in ventricular wall thickening, progressive HF, and arrhythmias.^[3] ATTR-CA has been shown to be frequently misdiagnosed, or delayed due to low awareness/misunderstanding of the disease.^[3,9]

The most frequent age of ATTRwt-CA is between 47 years and 94 years but past 90 years are rare phenotypes.^[1] Among 360 cases of ATTRwt-CA diagnosed from 1965 to 2013 reported by Mayo Clinic in 2016, only 3 cases (0.83%) were older than 90 years.^[1] Since then, few cases of ATTR-CA over 90 years have been reported. We hope that our case will have a certain impact on the ATTRwt-CA diagnosis and management in elderly people.

With the development of noninvasive diagnostic techniques and the availability of effective drugs, more ATTR-CA patients are being treated and favorably influence clinical outcomes. Guidelines have been updated to help cardiologists and physicians in recognizing, diagnosing and treating patients with CA. The 2021 European Society of Cardiology guidelines published some clinical “red flags” for ATTR disease, including proteinuria, polyneuropathy, bilateral carpal tunnel syndrome and so on.^[10] The heart warning signs included: (1) disproportionally elevated N-terminal pro-B-type natriuretic peptide to degree of HF; (2) out of proportion to the “objective” findings of echocardiography;

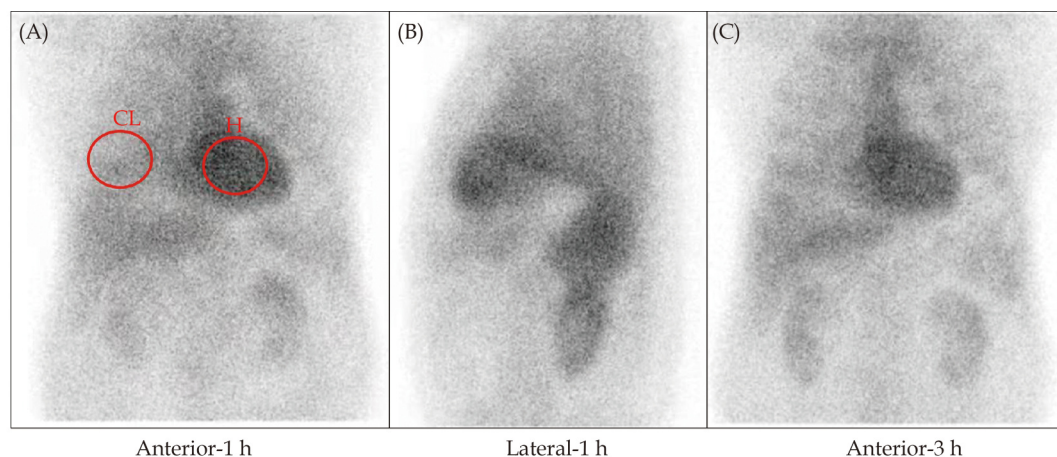


Figure 3 Cardiac scintigraphy with ^{99m}Tc -PYP. (A & B): Cardiac scintigraphy with ^{99m}Tc -PYP showed the increased thorax at 1-hour radiotracer uptake at the region of the heart with H/CL ratio of 1.9; and (C): ^{99m}Tc -PYP in 3-hour demonstrated myocardial uptake (Perugini score 3). H/CL: heart-to-contralateral.

(3) increased right ventricular wall/valve thickness; (4) persisting elevated troponin level; and (5) ECG: pseudoinfarct pattern, low/decreased QRS voltage to degree of left ventricular thickness AV conduction disease.^[10] These are the signs that clinicians need to look for as causes of CA. For patients with “warning signs”, they may consider for ATTR-CA diagnosis process. In our case, AVB in ECG was the initial presentation, and the PR interval was gradually prolonged (221–315 ms) from 2009, ventricular septal thickening on echocardiography, and clinical manifestations of HF, there are four “red flags” heart signs of ATTR-CA.

Endocardial biopsy for amyloid fibrils has long been the gold standard of diagnosis for CA, but it is often seriously delayed because it is invasive and requires expertise and knowledge to interpret the results. Guidelines are now confirmed ATTR-CA is the only subtype of CA that can be diagnosed by noninvasive testing after excluding light chain CA.^[3] ^{99m}Tc-PYP, ^{99m}Tc-D and ^{99m}Tc-HMDP scintigraphy emerged as a noninvasive diagnostic test that sensitivity is 92% and specificity of 95%.^[11,12] Patients with clinical “red flags” and negative immunoglobulin light chain had 100% specificity and positive predictive value for the diagnosis of ATTR-CA, when the cardiac scintigraphy with ^{99m}Tc-PYP scintigraphy in 1-hour planar scan having H/CL ratio of > 1.5 (qualitative assessment) and Perugini score 2 or 3 cardiac uptake (semi-quantitative assessment) in 3 h.^[10,13,14] Genetic testing is recommended for all patients diagnosed with ATTR, which is necessary for prognosis, family screening and genetic counseling.^[10] The guidelines also suggest that simultaneous initiation of immunoglobulin light chain exclusion and PYP test can improve the diagnostic rate and efficiency of ATTR-CA, which is an important means to early intervention.^[13]

Clinical trials confirmed that Tafamidis stabilized TTR tetramer within six weeks of taking Tafamidis.^[15] In this phase 3 trial of 441 patients with ATTR-CA, Tafamidis showed a reduction in cardiovascular hospitalization rate (relative risk ratio of 0.68) and a reduction in all-cause mortality after approximately 18 months of treatment.^[16]

In conclusion, we reported the misdiagnosed TTR in a 91-year-old man with ATTRwt-CA. To date, ATTRwt-CA cases past 90 years over the world have rarely been reported. In our case, some etiologies of myocardial hy-

pertrophy, like hypertension, ischemia, and hypertrophic cardiomyopathy were excluded. Immunoglobulin light chain CA was not considered as the negative results of serum and urine protein electrophoresis. ^{99m}Tc-PYP scintigraphy confirmed the diagnosis of ATTR-CA (myocardial uptake grade 3, H/CL ratio of 1.9). There was no myocardial disease family history and this case was identified by genetic test as ATTRwt-CA. Until now, no extracardiac manifestations such as peripheral sensory and motor neuropathy, carpal tunnel syndrome was found in this patient, which was more prevalence in ATTRwt-CA.^[17] As the research results and drug instructions, there is a turning point in the survival curve at approximately 18 months after administration of Tafamidis, and we will continue to follow up and provide regular rehabilitation instructions to the patient.

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