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Case Reports

Myocardial Scintigraphy in Diagnosing Cardiac Transthyretin Amyloidosis

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Myocardial scintigraphy with technetium-99m pyrophosphate is a minimally invasive technique that can distinguish between transthyretin amyloidosis (ATTR) and light-chain amyloidosis. We present a case in which it helped determine the amyloidosis type in a 74-year-old man with cardiac amyloidosis and multiple previous admissions for acute decompensated heart failure.

The patient presented with increasing abdominal girth and bilateral lower extremity edema. His medical history also included atrial fibrillation, liver cirrhosis, hypertension, stage 3 chronic kidney disease, and peripheral vascular disease. We prescribed guideline-directed medical therapy for his acute decompensated heart failure with cardiorenal syndrome and his decompensated cirrhosis.

Two years previously, a presumptive diagnosis of ATTR cardiomyopathy had been made on the basis of the patient's age, predominantly cardiac involvement, an unremarkable serum protein electrophoresis result, and an abnormal free κ/λ light-chain ratio of 2.24. Over the next year, the patient's clinical condition had worsened with the development of liver cirrhosis and peripheral neuropathy, and his free κ/λ light-chain ratio had become even more abnormal. At the current presentation, a technetium-99m pyrophosphate nuclear scintigram revealed a free κ/λ light-chain ratio of 1.52. This, combined with the patient's age and slow progression of primarily cardiac disease, supported the diagnosis of ATTR, and we prescribed tafamidis.

This case suggests that technetium-99m pyrophosphate scintigraphy is valuable in definitively diagnosing ATTR cardiomyopathy and selecting patients who may benefit from disease-modifying therapy. ***(Tex Heart Inst J 2022;49(4):e207379)***

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Transthyretin amyloidosis (ATTR) is a systemic disease in which fibrils of misfolded transthyretin proteins are deposited in different organs. Transthyretin amyloidosis may be hereditary or acquired through the accumulation of wild-type transthyretin.[1] A frequent but often unrecognized manifestation is ATTR cardiomyopathy (ATTR-CM), which is associated with poor prognosis. Amyloid light-chain (AL) amyloidosis can also result in cardiomyopathy. This creates a diagnostic challenge that may delay initiation of disease-modifying therapy. We present a case in which myocardial scintigraphy with technetium-99m pyrophosphate (^{99m}Tc-PYP) helped distinguish between cardiomyopathy associated with ATTR versus that associated with AL amyloidosis.

Case Report

A 74-year-old man with cardiac amyloidosis and a history of multiple admissions for acute decompensated heart failure (ADHF) presented at our institution with increasing abdominal girth and worsening bilateral lower extremity edema. His medical history also included atrial fibrillation, liver cirrhosis, hypertension, stage 3 chronic kidney disease, and peripheral vascular disease. Physical examination revealed jugular

vein distention, irregular heart rhythm, ascites, and 3+ bilateral pitting edema of the lower extremities. The patient was prescribed guideline-directed medical therapy for ADHF as well as for possible cardiorenal syndrome and decompensated cirrhosis, and he showed subsequent clinical improvement.

Cardiac amyloidosis had first been suspected 2 years previously, when an electrocardiogram (ECG) revealed low QRS voltage with poor R-wave progression in the precordial leads (Fig. 1), and a transthoracic echocardiogram (TTE) revealed biventricular failure (left ventricular ejection fraction [LVEF], 35%) with prominent ventricular wall thickening (Fig. 2). The TTE also showed granular sparkling on the myocardial wall, a small LV cavity, biatrial enlargement, atrial septal thickening, and a restrictive transmitral Doppler filling pattern. We did not perform strain imaging at the time because the ECG and TTE findings already suggested cardiac amyloidosis. Strain imaging can reveal signs of cardiac amyloidosis such as an apical sparing pattern, apical-to-basal strain ratio >2.1, and LVEF-to-strain ratio >4. Amyloidosis was confirmed by the positive results of a fat biopsy with Congo red staining. Our presumptive diagnosis was ATTR-CM, given the patient's age, predominantly cardiac involvement, unremarkable serum protein electrophoresis result, and free κ/λ light-chain ratio of 2.24 (κ, 77.8 mg/L; λ, 34.7 mg/L). An implantable cardiac defibrillator (ICD) was subsequently placed for the primary prevention of sudden cardiac death. Given the patient's multiple admissions for ADHF, we considered prescribing tafamidis, which had recently been approved by the United States Food and Drug Administration (FDA) to increase functional capacity and quality of life and decrease hospitalizations in patients with heart failure.[2]

In the 2 years after our initial presumptive diagnosis of amyloidosis, the patient developed liver cirrhosis and peripheral neuropathy. His κ/λ light-chain ratio also became even more abnormal (κ, 146.0 mg/L; λ, 52.8 mg/L; ratio, 2.8). These findings suggested AL amyloidosis. Because tafamidis treatment is expensive and does not clinically improve AL-CM, we decided to obtain a ^{99m}Tc-PYP scan to differentiate between the 2 amyloidal types. We did not perform magnetic resonance imaging either initially (because the previous TTE and ECG findings had already suggested cardiac amyloidosis) or later (because of his ICD). The ^{99m}Tc-PYP scintigram revealed substantial radiotracer uptake in the heart, resulting in a heart-to-contralateral lung ratio of 1.52 at 1 hour (Fig. 3). This finding was strongly consistent with ATTR-CM, and it confirmed the initial diagnostic impression suggested by the patient's age and clinical course. We also considered performing a bone marrow biopsy to rule out AL amyloidosis. However, an oncology consultant concluded that the patient's abnormal κ/λ ratio was likely secondary to his advanced age and chronic kidney disease, because the ^{99m}Tc-PYP scintigram was consistent with ATTR and because the initial serum protein electrophoresis result was normal. We also attributed the patient's cirrhosis to right ven-

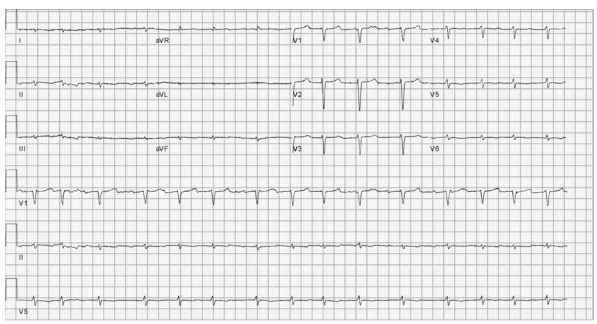
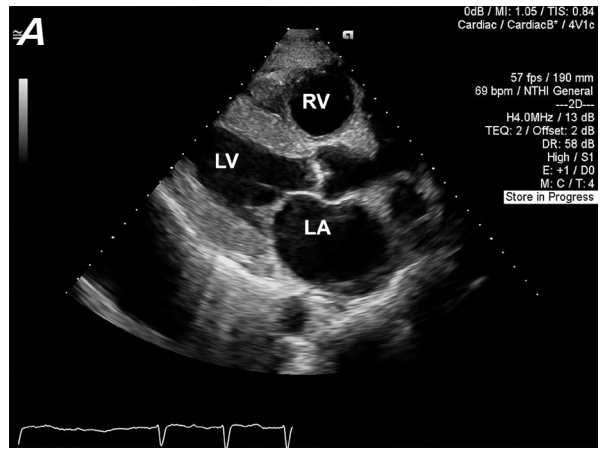


Fig. 1 *Electrocardiogram reveals a QRS amplitude <5 mV in all frontal leads and <10 mV in most precordial leads, consistent with low voltage.*



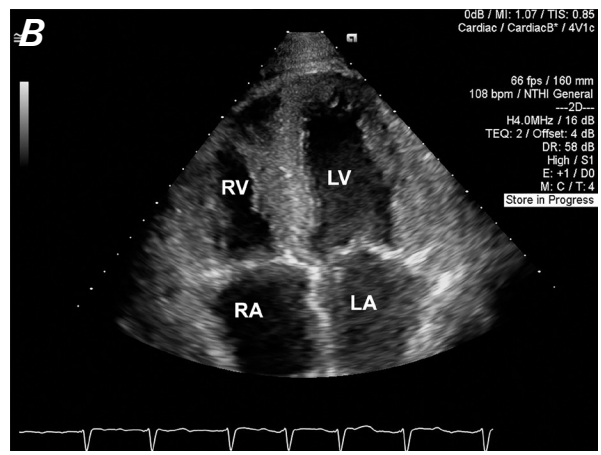


Fig. 2 *Two-dimensional transthoracic echocardiograms in **A**) parasternal long-axis and **B**) apical 4-chamber views show substantial thickening of the left ventricular (LV) and right ventricular (RV) walls, granular sparkling on the myocardial wall, a small LV cavity, biatrial enlargement, and atrial septal thickening, findings consistent with cardiac amyloidosis.*

LA = left atrium; RA = right atrium

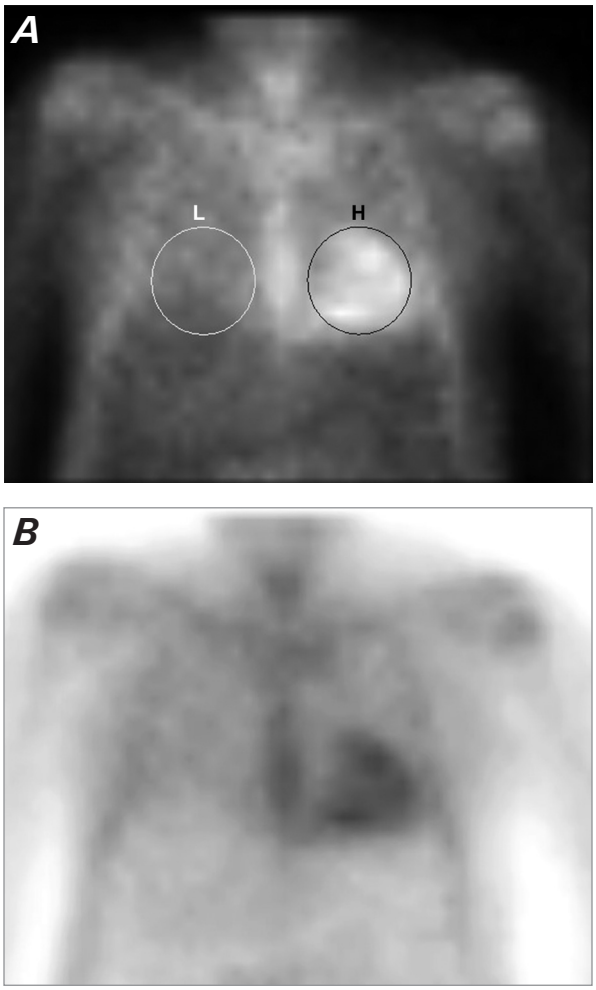


Fig. 3 *Myocardial scintigrams in **A**) inverted and **B**) standard views show substantial cardiac uptake in the heart (H) versus the contralateral lung (L) 1 hour after radiotracer administration, resulting in an H-to-L ratio of 1.52 consistent with transthyretin amyloidosis cardiomyopathy.*

tricular failure, not hepatic amyloidosis. The patient was prescribed tafamidis (20 mg/d) and was discharged from the hospital. Nevertheless, he died one month later of an unspecified cause, precluding the ATTR genotyping that we had planned to perform during the follow-up period.

Discussion

Transthyretin amyloidosis is often unrecognized or is diagnosed late in its course because of its plethora of symptoms, ranging from autonomic dysfunction to heart failure.[1] A diagnosis of cardiac amyloidosis requires a high level of suspicion, and it should be considered in patients with heart failure whose hemodynamic status renders them intolerant of renin-angiotensin system inhibitors and β-blockers, and whose ECGs and echocardiograms are consistent with amyloidosis.[1,3]

Transthyretin amyloidosis is more likely when symptoms progress slowly and when associated cardiac disease appears late in life. However, distinguishing ATTR from AL can be challenging and can lead to potential harm if not done. Although the signs and symptoms of different types of amyloidosis overlap with each other and with those of other causes of HF, some more strongly suggest ATTR. On echocardiograms, the LV is often thicker in patients with ATTR-CM than in patients with AL amyloidosis. Patients with ATTR-CM often exhibit both low QRS voltage on ECGs and LV septal thickness >12 mm on echocardiograms.[1,4] Magnetic resonance imaging scans in patients with cardiac amyloidosis typically show diffuse subendocardial or transmural late gadolinium enhancement (LGE), myocardial nulling of the blood pool, and elevated native T1 relaxation time and extracellular volume.[1] Left ventricular LGE is seen in all patients with cardiac amyloidosis; in comparison, right ventricular LGE is seen in all patients with ATTR and in 72% of patients with AL.[4] The criterion standard for definitive diagnosis is endomyocardial biopsy together with either immunohistochemistry or mass spectroscopy.[3,4]

Myocardial scintigraphy with the bone-imaging agent ^{99m}Tc-PYP is a simple, cost-effective diagnostic method with high sensitivity (97%) and specificity (100%) for ATTR-CM that can preclude more invasive procedures and expedite diagnosis.[1,3,4] It is particularly helpful when magnetic resonance imaging is neither logistically nor clinically feasible or when, in the early stages of cardiac disease, echocardiographic findings may not indicate amyloidosis.[1,3,4] Myocardial ^{99m}Tc-PYP uptake is quantified by calculating the ratio between mean pixel counts in the heart and the contralateral right lung. This ratio accounts for background noise and rib uptake. A ratio of at least 1.5 at 1 hour after radiotracer administration strongly suggests ATTR.[3,4]

Current therapies for ATTR amyloidosis include transthyretin stabilizers, silencers, and disruptors.[2] In May 2019, the FDA approved tafamadis, a transthyretin tetramer stabilizer that can slow disease progression, reduce cardiovascular mortality, and decrease the number of hospitalizations in patients with ATTR-CM while increasing their functional capacity and quality of life.[2] However, the effectiveness of tafamidis depends on timely diagnosis and early administration.[2]

Conclusion

Our case suggests that ^{99m}Tc-PYP myocardial scintigraphy is a valuable, cost-effective, and minimally invasive tool for definitively diagnosing ATTR-CM and for promptly selecting patients who may benefit from disease-modifying therapy.

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