A Right-atrial Variant of Wild-type Transthyretin Cardiac Amyloidosis

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Abstract

Amyloidosis is caused by extracellular deposition of amyloid protein in various organs and tissues. Light-chain amyloidosis is the most common systemic amyloidosis, whereas transthyretin amyloid cardiomyopathy is emerging as the underdiagnosed variant, especially in the elderly. Cardiac MRI and technetium-99m-pyrophosphate scintigraphy are specific non-invasive modalities that have simplified the diagnostic accuracy of cardiac amyloidosis. Identifying the type of amyloidosis is of paramount importance, given the differences in management protocols. Increased left-ventricular wall thickness and diastolic dysfunction are the most easily detectable manifestations of cardiac amyloidosis. Atrial involvement is early in both light-chain and transthyretin amyloidosis and is associated with high risk of arrhythmias and thromboembolic events. We report a case of wild-type transthyretin amyloid cardiomyopathy with predominant involvement of the right atrium and patchy involvement of the right and left ventricles.

Keywords

Wild-type transthyretin amyloid cardiomyopathy, cardiac MRI, case report, hereditary transthyretin amyloid cardiomyopathy, technetium-99m-pyrophosphate scintigraphy

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Amyloidosis is a group of diseases characterized by the extracellular deposition of misfolded proteins with a highly ordered abnormal cross β-sheet conformation in various organs.[1] Among various amyloidogenic proteins, cardiac amyloidosis typically arises from misfolded transthyretin (TTR) proteins (TTR amyloidosis; ATTR) or immunoglobulin light-chain aggregation (light-chain amyloidosis; AL).[2] ATTR amyloidosis is classified by the sequence of the *TTR* gene: either wild-type ATTR (wtATTR) cardiomyopathy (wtATTR-CM) in which no mutation is present, or hereditary ATTR cardiomyopathy (hATTR-CM) in which a mutation is present.[3] The prevalence of wtATTR in older adults with heart failure is being recognized more frequently.[3] In wtATTR there is predominant involvement of the left ventricle in the form of increased left ventricular thickness and mass.[4] Amyloid deposits in the atria may be focal or diffuse and impair both the atrial reservoir and contractile function.[5] This electromechanical dissociation in the atria can lead to supraventricular arrhythmias such as AF and increase the risk for thromboembolic events.[6] We hereby report a case of wtATTR with predominant pyrophosphate (PYP) uptake in the right atrium. Right- and left-ventricle uptake was present, but was lower and patchy.

Case Report

A 66-year-old woman with a history of type 2 diabetes and hypertension was diagnosed with hypertrophic cardiomyopathy (HCM) 5 years prior to presentation. At that time, coronary angiography was negative for significant epicardial coronary disease. She was diagnosed with AF after presenting with a stroke 3 years prior to presentation. She was referred to our center for routine cardiac evaluation.

The patient had New York Heart Association class II dyspnea. Examination revealed an irregularly irregular pulse. There was no macroglossia or periorbital bruising. There were no features of carpal tunnel syndrome. Peripheral pulses were brisk. Cardiovascular examination was normal.

Investigations

Serum and urine immune-electrophoresis were negative and the kappa/lambda ratio was normal (1.55). High-sensitivity troponin I was elevated (63.5 pg/ml). The ECG showed AF with a controlled rate and left-ventricular hypertrophy (LVH) by voltage criteria (*Figure 1*). The echocardiogram showed LVH with thickened inter-ventricular septum (21 mm) and asymmetrical septal hypertrophy with a left-ventricular outflow tract gradient of 35 mmHg (*Figure 2*). Global longitudinal strain (GLS) of the left ventricle was reduced (−10.5%); there was no apical sparing pattern. The ratio of ejection fraction (EF) and GLS was elevated at 5.71 (normal <4.1). Right ventricle free wall thickness was increased (7 mm) and right ventricle GLS was also reduced (−14.5%).

Cardiac MRI showed diffuse sub-endocardial late gadolinium enhancement (LGE) of the left and right ventricles (*Figure 3*). The technetium-99m-PYP (Tc-99m-PYP) scintigraphy for ATTR cardiac

Figure 1: ECG Showing AF with Controlled Rate and Left-ventricular Hypertrophy by Voltage Criteria

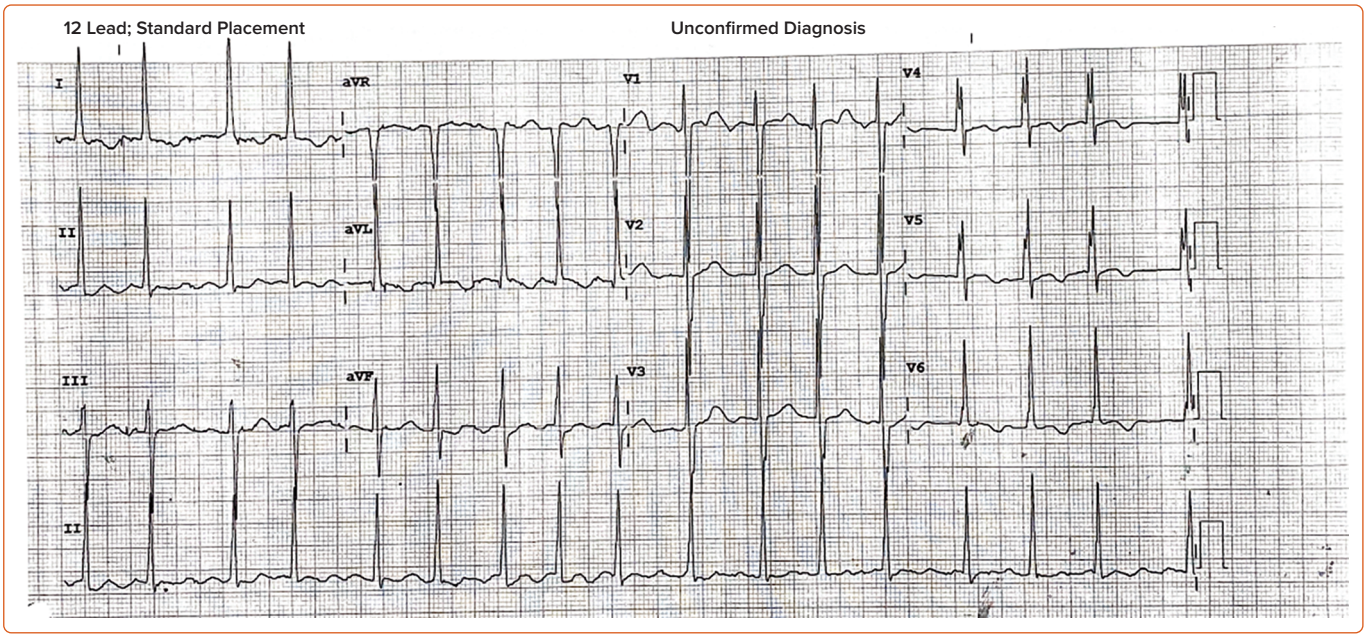
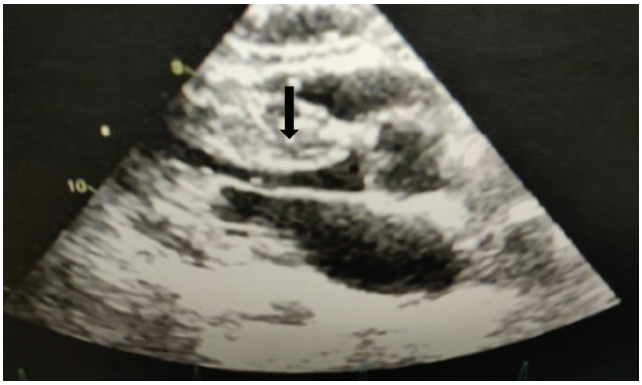


Figure 2: Echocardiogram



The echocardiogram shows left-ventricular hypertrophy with a thickened inter-ventricular septum and asymmetrical septal hypertrophy with thickened right atrium and ventricle and valves. The arrow indicates thickened inter-ventricular septum with myocardial speckling.

amyloidosis showed semiquantitative tracer uptake in the right atrium in comparison with rib uptake suggestive of Grade 3 (more than rib) and mild uptake in the right and left ventricles at 3 hours (*Figure 4*).

ATTR genotyping of 8,332 clinical exome assay genes showed no evidence of a mutant protein, thus ruling out hATTR-CM. This confirmed the diagnosis of wtATTR-CM. Our patient was started on 61 mg tafamidis once a day. The patient is symptomatically better and has been receiving regular follow up since then.

Discussion

Cardiac amyloidosis often escapes recognition, being correctly diagnosed in approximately only one-third of the patients during their lifetime.[7] Clinical red flags include being elderly, having heart failure, peripheral neuropathy, bilateral carpal tunnel syndrome, rupture of the biceps tendon, lumbar spinal stenosis, and low voltage complexes on the ECG in the context of LVH on echocardiography.[8]

In the context of a thickened left ventricle, the following features on the echocardiography should be considered red flags for cardiac amyloidosis:[8] pericardial and/or pleural effusions, thickened right ventricle, thickened heart valves, thickened inter-atrial septum, small left ventricle cavity size with low stroke volume, and paradoxical low flow, low-gradient aortic stenosis. Amyloid infiltration impairs GLS with characteristic left ventricle apical sparing (a 'cherry on top' appearance). The red flags in our case were an inter-ventricular septum thickness of 21 mm, EF/GLS ratio of 5.71, right ventricle thickening of 7 mm, and elevated high-sensitivity troponin I levels.

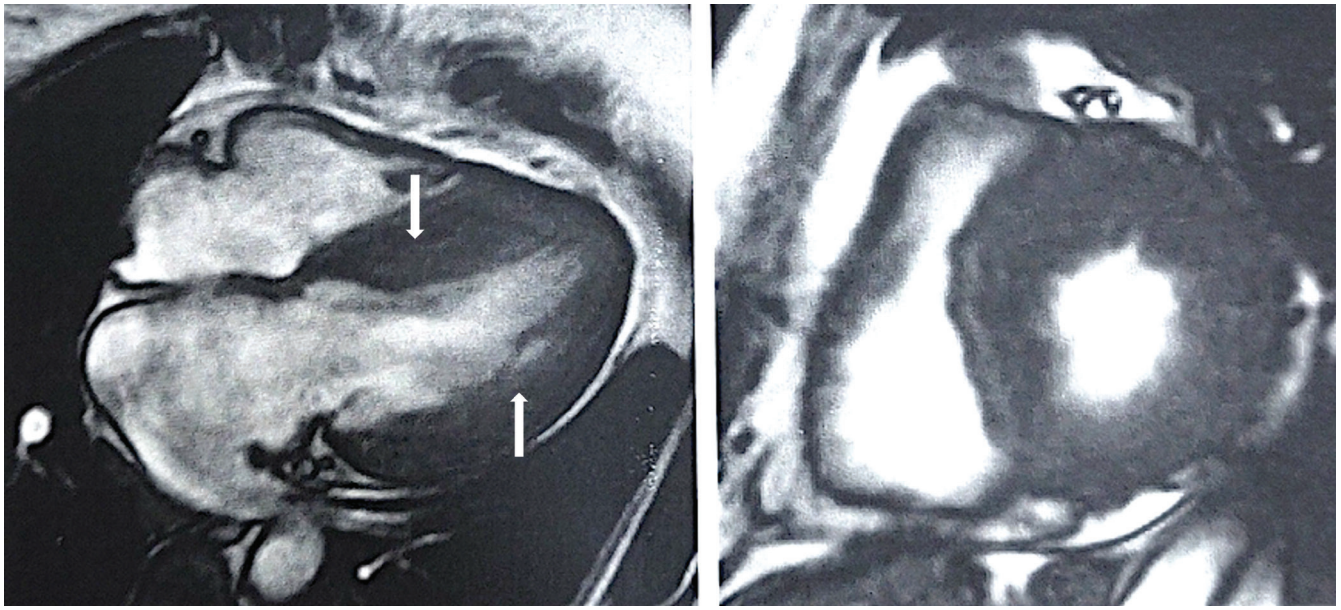
Cardiac MRI features of amyloidosis include LGE, an inability to suppress or 'null' the myocardial signal, or the presence of diffuse sub-endocardial or transmural enhancement patterns with a sensitivity and specificity that approach 85–90%.[9] Cardiac MRI may not be necessary for the diagnosis of cardiac amyloidosis if clinical, electrocardiographic, and echocardiographic features are all consistent.

The accurate diagnosis of ATTR-CM without the need for invasive cardiac biopsy can be made with nuclear scintigraphy using bone-avid radiotracers. Nuclear imaging with bone-avid tracers has been reported to confer a 100% specificity for ATTR-CM when there is Grade 2 or 3 tracer uptake in a patient with clinical suspicion for cardiac amyloidosis in whom serum and urine testing are negative for a gammopathy, ruling out light-chain systemic amyloidosis.[10]

Atrial involvement in amyloidosis could be secondary to systemic amyloidosis or as an isolated atrial amyloidosis. Amyloid deposits in the atria may be found as focal, multifocal, or diffuse nodules disrupting the normal tissue architecture. They are associated with extensive atrial remodeling and lead to atrial electromechanical dissociation causing arrhythmias such as AF. Blood stasis in the atria may occur even in patients in sinus rhythm due to ineffective atrial contractions and lead to thrombosis and thromboembolism.[6]

Isolated atrial amyloidosis is limited to the atria and is the result of the overproduction of atrial natriuretic peptide, a peptide synthesized by atrial cardiomyocytes.[11] The deposits are more common in women and in

Figure 3: Cardiac MRI



The left panel shows a cardiac MRI demonstrating diffuse sub-endocardial late gadolinium enhancement of the left and right ventricle with diffuse left-ventricular wall and inter-ventricular septal thickening (arrows). The right panel shows the late gadolinium enhancement of the left and right ventricles in short axis.

patients undergoing mitral valve replacement with pronounced left-atrial deposits.[12]

Tc-99m-PYP scintigraphy has been shown to have atrial uptake in 78% and right ventricle uptake in 93% of cases.[13] However, our patient had predominant right-atrial uptake compared with mild uptake in the right and left ventricles, in contrast with previous reported cases, suggesting a predominantly right-atrium variant.[13]

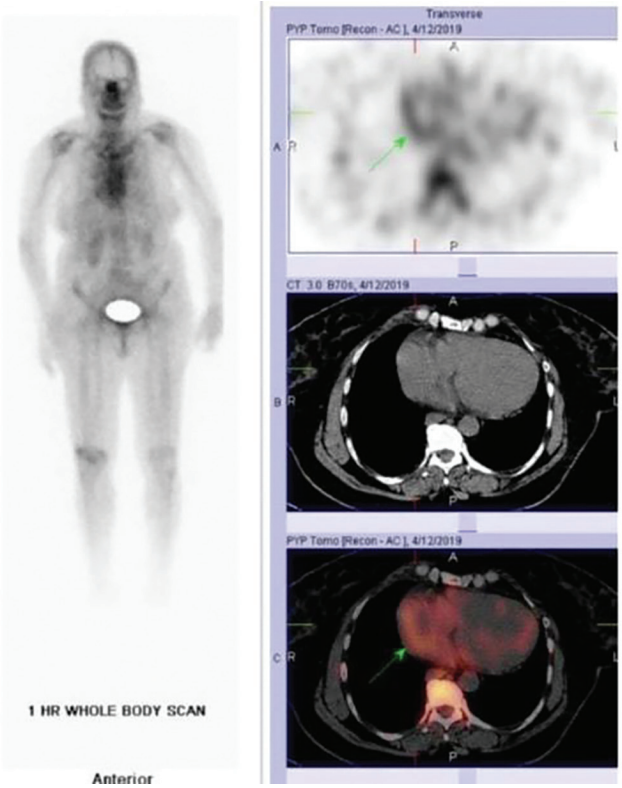
There have been reports of AL-type amyloidosis from India. However, the first proven case of familial amyloid polyneuropathy was reported in 2018 resulting from a heterozygous missense mutation of Val30Ala.[14] Another case of mutant-type ATTR with ulcerative colitis was reported from India in 2019, which showed a pathogenic disease-causing mutation in exon 3 with a resultant amino acid change at position 55 from leucine to proline.[15]

Our patient was initially misdiagnosed as having HCM. After reviewing the patient's symptoms and noticing red flag signs on her echocardiography, non-invasive imaging (cardiac MRI and nuclear imaging) along with genetic testing helped us reach the diagnosis of wtATTR-CM. A high index of suspicion is needed to diagnose ATTR-CM, which is a mimic of HCM and can cause asymmetric septal hypertrophy. A literature search revealed no other published report of a genetically proven right atrium variant of wtATTR-CM in India.

Conclusion

Amyloidosis is no longer considered an orphan disease. The clinician should be aware of the red flags for early detection and treatment. Atrial involvement can influence clinical outcomes by hastening the occurrence of AF and thromboembolism. Advanced imaging modalities, in particular cardiac MRI and Tc-99m-PYP scintigraphy, simplify the diagnosis of ATTR-CM. To the best of our knowledge this is the first wtATTR confirmed by genetic studies from India. Preferential involvement of the right atrium as evidenced by increased uptake of pyrophosphate by Tc-99m-PYP scintigraphy in comparison with the left ventricle indicates a right atrium variant of ATTR. ❑

Figure 4: Technetium-99m-pyrophosphate Scintigraphy



Technetium-99m-pyrophosphate scintigraphy shows cardiac uptake of tracer with maximum uptake in the right atrium compared with the right and left ventricles. A: The green arrow indicates maximum tracer uptake in right atrium. B: Baseline cardiac scintigraphy before tracer uptake. C: Cardiac uptake of tracer predominantly in the right atrium as denoted by green arrow. The left and right ventricles show mild uptake. HR = hour.

Clinical Perspective

- Amyloidosis is characterized by the extracellular deposition of misfolded protein in various organs.
- The diagnosis of wild-type transthyretin amyloidosis is simplified with nuclear scintigraphy using bone-avid radiotracers.
- Atrial amyloidosis develops in the early stages of light-chain and transthyretin amyloidosis and is associated with an increased risk of supraventricular arrhythmias and thromboembolic events.
- Atrial amyloidosis can be found even in the absence of systemic disease and left-ventricular involvement.

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