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Cases report

TRANSTHYRETIN CARDIAC AMYLOIDOSIS REVEALED BY MULTIMODALITY IMAGING IN AN ELDERLY PATIENT WITH HFpEF

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ABSTRACT: Amyloid cardiomyopathy is an infiltrative disease caused by extracellular deposition of amyloid fibrils within the myocardium, most commonly from immunoglobulin light-chain (AL) or transthyretin (ATTR) sources, leading to progressive heart failure, arrhythmias, and conduction disturbances. We present the case of an 80-year-old man with heart failure with preserved ejection fraction (HFpEF) and comorbidities who was admitted for acute onset dyspnea accompanied by profound hypotension at home. Together with a non-clonal free light-chain profile, these findings supported a diagnosis of transthyretin (ATTR) cardiac amyloidosis. This case highlights the value of integrating electrocardiogram, echocardiography, cardiac magnetic resonance, and bone-avid tracer scintigraphy to establish the diagnosis of ATTR cardiomyopathy and guide management in settings where disease-modifying therapy remains limited.Keywords: supraclavicular brachial plexus nerve block, adductor canal block, popliteal sciatic block, heart failure, limb amputation.

Key words: Amyloid cardiomyopathy, transthyretin, scintigraphy.

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1. OVERVIEW

Cardiac amyloidosis is an infiltrative cardiomyopathy resulting from extracellular deposition of misfolded amyloid fibrils within the myocardium, leading to progressive diastolic dysfunction, arrhythmias, and heart failure [1]. Immunoglobulin light-chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis account for the majority of contemporary cases. ATTR amyloidosis occurs either as a hereditary form (ATTRv), caused by pathogenic mutations in the transthyretin gene, or as wild-type ATTR (ATTRwt), which is increasingly recognized as an underdiagnosed cause of HFpEF and unexplained left ventricular hypertrophy in elderly patients.

We describe a case of ATTR cardiac amyloidosis in an elderly man presenting with acute dyspnea and hypotension, in whom characteristic electrocardiographic abnormalities and multimodality imaging including CMR and technetium-99m pyrophosphate (99mTc-PYP) scintigraphy supported the diagnosis. This report highlights the importance of maintaining a high index of suspicion for ATTR-CM in older patients with HFpEF and extracardiac manifestations and demonstrates the value of a systematic, guideline-based, noninvasive diagnostic approach.

2. CASES PRESENTATION

An 80-year-old male presented to the emergency department with acute-onset dyspnea of approximately three hours' duration, accompanied by severe hypotension at home (blood pressure 70/50 mmHg). His medical history was significant for HFpEF, chronic coronary artery disease with prior percutaneous coronary interventions in 2017 and 2020, paroxysmal atrial fibrillation, sustained ventricular tachycardia requiring implantable cardioverter defibrillator implantation in 2018, hypertension, and dyslipidemia. His surgical history included carpal tunnel release surgery in 2016.

On arrival, the patient was tachypneic; however, his blood pressure had stabilized at 110/70 mmHg, and oxygen saturation was within normal limits.

Electrocardiography demonstrated atrial fibrillation with a slow ventricular response (heart rate approximately 55 beats/min), an intermediate QRS axis, low QRS voltage, and nonspecific ST-segment and T-wave abnormalities in the limb leads [Figure 1]. High-sensitivity cardiac troponin T was elevated at 70.9 pg/mL, and NT-proBNP was markedly increased at 3,081 pg/mL.

Transthoracic echocardiography revealed concentric left ventricular hypertrophy, biatrial enlargement, and thickening of the interatrial septum (10–15 mm). Left ventricular systolic function was preserved (LVEF 65%), biatrial enlargement and coexistence of right ventricular diastolic dysfunction (TAPSE 14mm). Speckle-tracking echocardiography demonstrated markedly impaired global longitudinal strain with a characteristic relative apical sparing pattern, producing the typical bull's-eye appearance associated with cardiac amyloidosis. Longitudinal strain reduction predominantly involved basal and mid-ventricular segments, while apical segments exhibited relatively preserved deformation [Figure 2].

Cardiac magnetic resonance imaging demonstrated subendocardial perfusion defects involving the basal inferior wall and mid-interventricular septum on resting perfusion imaging. Late gadolinium enhancement revealed diffuse, circumferential subendocardial enhancement extending to the papillary muscles, with focal transmural enhancement predominantly in the basal-to-mid interventricular septum and inferior wall. Parametric mapping showed mildly elevated native myocardial T1 (1054 ms) and markedly increased extracellular volume fraction (64%), while native T2 values were within normal limits [Figure 3].

Serum free light-chain analysis revealed mildly elevated kappa (26.9 mg/L) and lambda (33.7 mg/L) concentrations with a normal kappa-to-lambda ratio (0.798), reducing the likelihood of AL amyloidosis. Technetium-99m PYP scintigraphy demonstrated significant myocardial tracer uptake with a heart-to-contralateral lung ratio of 1.88, consistent with ATTR cardiac amyloidosis [Figure 4]. Abdominal fat pad biopsy was negative for amyloid deposition on Congo red staining, with no light-chain restriction on immunofluorescence [Figure 5].

Following diagnosis of transthyretin cardiac amyloidosis (ATTR-CM),

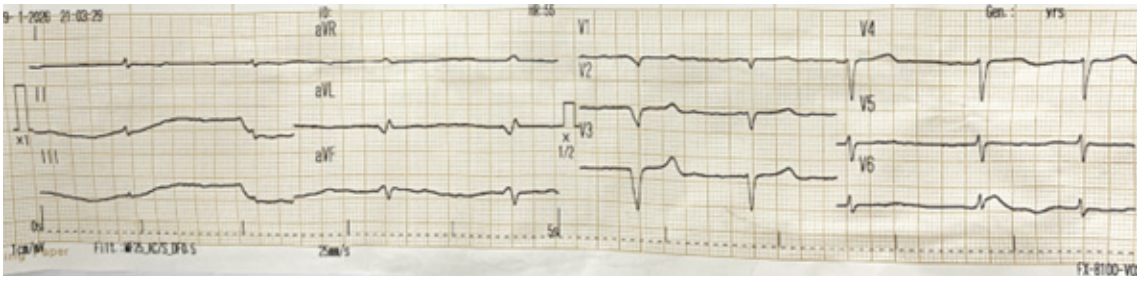

Figure 1. Standard 12-lead ECG showing atrial fibrillation with slow-ventricular response with heart rates 55 beat per; an intermediate QRS axis; low QRS voltages in and non-specific ST segment/T wave changes in limb leads

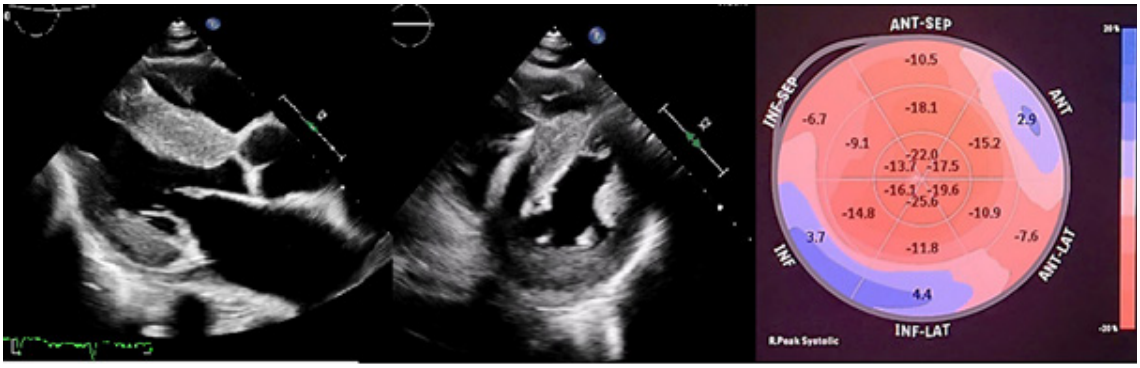

Figure 2. Transthoracic echocardiography (TTE) showing concentric left ventricular hypertrophy, diffuse granular sparkling appearance and markedly impaired global longitudinal strain with a characteristic relative apical sparing pattern

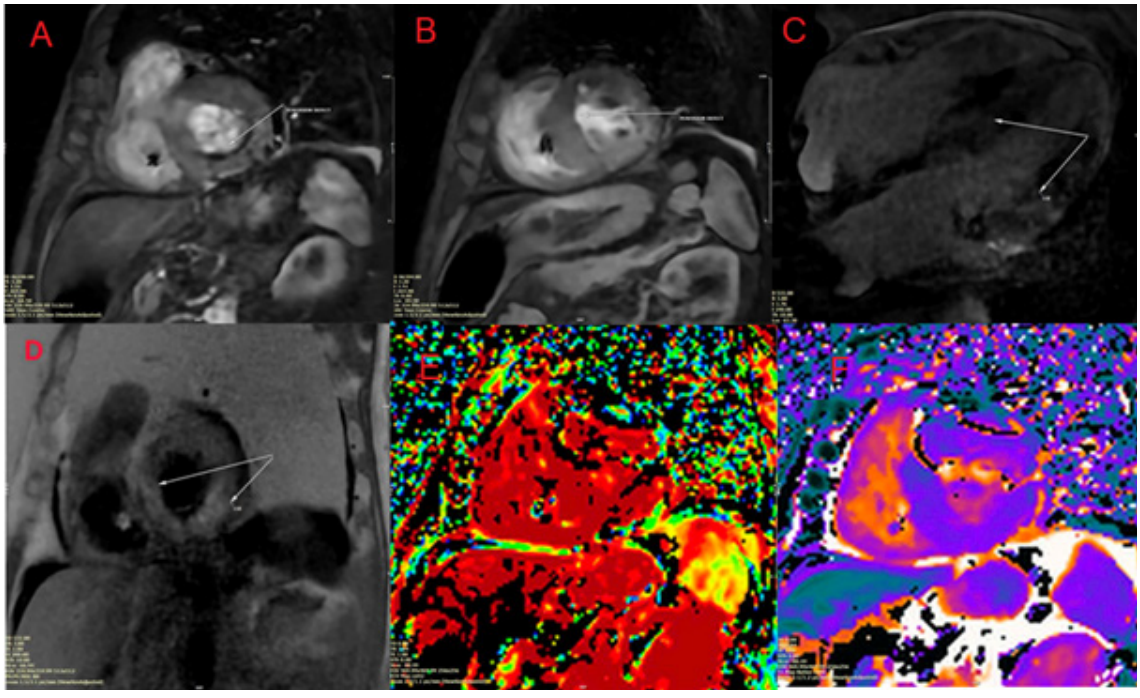

Figure 3. Cardiac magnetic resonance (CMR) demonstrated subendocardial perfusion defect involving the basal inferior wall and the mid interventricular septum of the left ventricle (A and B); late gadolinium enhancement (LGE) showed heterogeneous, circumferential, diffuse subendocardial enhancement (C, D); global ECV > 0.40 with mildly increased native myocardial T1 (native T1=1054ms) and markedly elevated extracellular volume fraction (ECV=64%) (E and F)

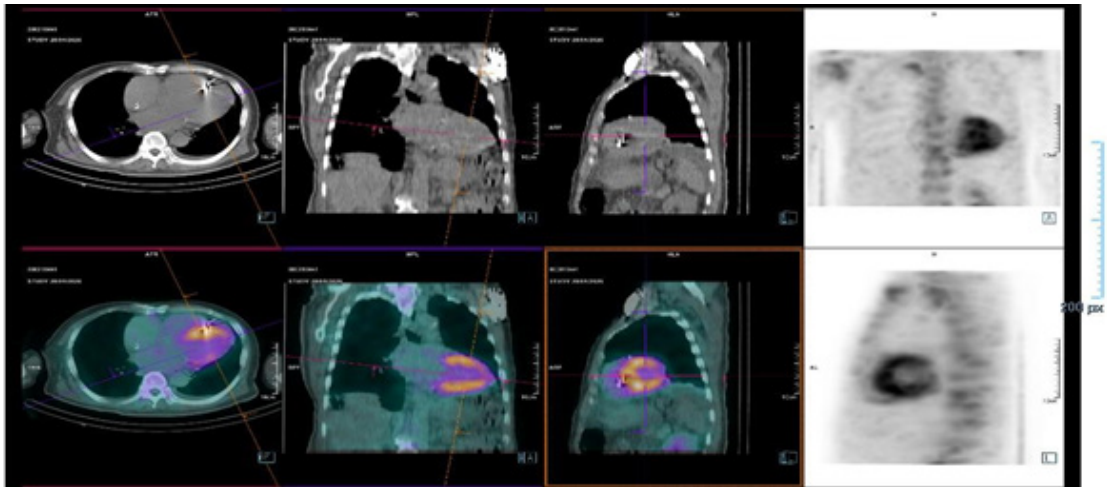

Figure 4. Myocardial Scan PYP-99mTc-PYP showing that 99mTc-PYP grade ≥ 2 myocardial uptake of radiotracer and absence of a clonal plasma cell process and using Heart to Contralateral Lung (H/CL) ratio = 1.88

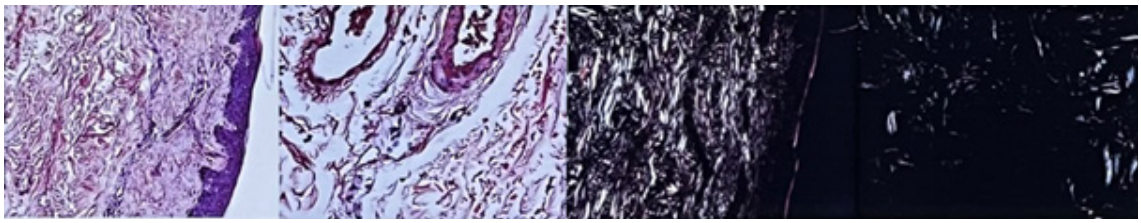

Figure 5. Abdominal fat pad biopsy demonstrating adipose and fibrous connective tissue without amyloid deposition. Congo red staining was negative for apple-green birefringence under polarized light. Immunofluorescence showed no specific deposition and no significant difference between kappa and lambda light chains.

treatment focused on stabilization of heart failure symptoms and prevention of thromboembolic complications, as disease-modifying therapies such as tafamidis are not yet widely available locally. Congestion was managed with oral furosemide 20 mg once daily, carefully titrated given the preload dependence and risk of hypotension typical of amyloid cardiomyopathy. Because cardiac amyloidosis carries a high thromboembolic risk in atrial fibrillation, rivaroxaban 20 mg once daily was initiated for stroke prevention. Secondary prevention therapy with atorvastatin 20 mg daily was continued for established coronary artery disease. Management emphasized individualized therapy, as conventional heart failure medications are often poorly tolerated in amyloid cardiomyopathy.

3. DISCUSSION

Transthyretin is a hepatically synthesized transport protein responsible for thyroxine and retinol delivery [2]. ATTR amyloidosis is a protein misfolding disorder characterized by destabilization of the transthyretin tetramer, leading to amyloid fibril deposition in extracellular tissues and progressive organ dysfunction [3]. Prior to the advent of disease-modifying therapy, ATTR-CM was associated with poor prognosis, with historical median survival ranging from 2 to 6 years following diagnosis [4]

Carpal tunnel syndrome is a frequently overlooked extracardiac manifestation of ATTR amyloidosis and may precede the diagnosis of cardiac involvement by several years. Amyloid deposition within the tenosynovium and transverse carpal ligament results in median nerve compression and is particularly common in ATTRwt . Screening studies have demonstrated a substantial prevalence of ATTRwt among older patients undergoing carpal tunnel release, reinforcing its role as an early clinical "red flag" [5].

In a screening study of individuals aged ≥60 years with a history of carpal tunnel release, Ladefoged et al. reported a notable prevalence of wild-type transthyretin

amyloidosis (ATTRwt) (≈8.3%) [6], further supporting carpal tunnel syndrome (CTS) as a potential "window" manifestation for early recognition of ATTR cardiac amyloidosis (ATTR-CM). CTS is most frequently observed in ATTRwt, but it may also occur in hereditary/variant ATTR, depending on the specific mutation and the predominant clinical phenotype [6].

According to the 2023 guidelines of the European Society of Cardiology (ESC), the diagnostic process begins with the recognition of clinical "red flags," including heart failure with preserved ejection fraction, unexplained left ventricular wall thickening, conduction system abnormalities, low QRS voltage on electrocardiography, and extracardiac manifestations such as bilateral carpal tunnel syndrome, macroglossia, or proteinuria of unclear etiology. Transthoracic echocardiography (TTE) represents a key initial screening modality, enabling the detection of increased ventricular wall thickness, diastolic dysfunction, and characteristic features such as a granular or "sparkling" myocardial appearance. Cardiac magnetic resonance imaging (CMR) provides high diagnostic value by allowing myocardial tissue characterization, particularly through diffuse late gadolinium enhancement and abnormal T1 mapping [1].

In our patient, both serum free light chains (kappa and lambda) were mildly elevated, while the kappa/lambda ratio remained normal, which reduced the likelihood of a monoclonal light-chain (AL) process in the appropriate clinical context. Our patient also exhibited multiple features suggestive of amyloid cardiomyopathy: the ECG and transthoracic echocardiography. Notably, in older adults, cardiac amyloidosis commonly presents with heart failure particularly heart failure with preserved ejection fraction (HFpEF). When left ventricular systolic function becomes impaired, prognosis is typically worse [7].

Nguyen Van Te (2021) reported a cohort of 10 patients with suspected amyloid restrictive cardiomyopathy who underwent 99mTc-MDP cardiac scintigraphy with SPECT/CT; scans were defined as positive when diffuse myocardial uptake was present with a Perugini score of 2–3 and an H/CL ratio >1.5. The study found that 20% of patients had positive scintigraphy without evidence of monoclonal protein disease, supporting this method as a safe, non-invasive, and highly accurate method for diagnosing ATTR cardiomyopathy, potentially eliminating the need for endomyocardial biopsy when monoclonal proteins are excluded [8].

The management of heart failure secondary to cardiac amyloidosis is challenging, as patients with amyloid cardiomyopathy have been largely excluded from major clinical trials of heart failure therapies. Heart failure management in cardiac amyloidosis remains challenging. Conventional heart failure therapies including ACE inhibitors, ARBs, ARNIs, and beta-blockers have not demonstrated clear prognostic benefit and are often poorly tolerated due to hypotension and autonomic dysfunction. Careful individualized therapy is therefore essential. Tafamidis, a selective transthyretin stabilizer, is the first disease-modifying therapy shown to improve outcomes in transthyretin cardiac amyloidosis. In the ATTR-ACT trial, tafamidis significantly reduced all-cause mortality and cardiovascular hospitalizations compared with placebo in patients with ATTR-CM, and attenuated decline in measures of cardiac function over 30 months [9]. However, despite its proven efficacy, access to tafamidis remains limited in Viet nam due to high cost and restricted availability.

4. CONCLUSION

This case illustrates a representative presentation of transthyretin amyloid cardiomyopathy in an elderly Vietnamese patient with HFpEF and prior carpal tunnel syndrome. It emphasizes the importance of early clinical suspicion, recognition of extracardiac manifestations, and application of multimodality imaging to establish a non-biopsy diagnosis. Increased awareness of ATTR-CM is essential to improve recognition and management of this underdiagnosed condition, particularly in resource-limited settings.

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