CASE REPORT

Transthyretin Amyloid Cardiomyopathy – Setting the Diagnosis Step by Step

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Abstract

Introduction: Transthyretin amyloid cardiomyopathy (ATTR-CM) can be diagnosed in the absence of histology with typical echocardiographic findings and skeletal scintigraphy showing grade 2 or 3 myocardial tracer uptake, when clonal plasma cell dyscrasia is excluded. Aim: To present a patient diagnosed with ATTR-CM, who was hospitalized with clinical signs of congestive heart failure. Case Report: An 84-year-old man was hospitalized with clinical signs of heart failure. Echocardiography showed concentric left ventricular hypertrophy (LVH) with reduced systolic function, along with impaired LV global longitudinal strain (GLS) with apical sparing (-9.9%). Serum and urine protein electrophoresis with immunofixation were obtained and were negative for plasma cell dyscrasia. Bone scintigraphy showed similar radiotracer uptake in the myocardium and ribs (Perugini grade 2). The diagnosis of ATTR-CM was confirmed. Conclusion: ATTR-CM is an underdiagnosed condition and should be suspected in patients with heart failure and unexplained LVH.

Keywords: amyloidosis, cardiomyopathies, diagnosis, rare diseases.

Learning Objectives

- To consider infiltrative cardiomyopathy in patients with "red flag" signs related to transthyretin amyloid cardiomyopathy (ATTR-CM), including LV hypertrophy.
- To understand the ATTR-CM diagnostic approach.
- To understand that ATTR-CM can be diagnosed in daily clinical practice via non-invasive means.
- Early diagnosis of ATTR-CM is a key to improving patient outcomes.

INTRODUCTION

Transthyretin amyloid cardiomyopathy (ATTR-CM) can be diagnosed in the absence of histology with typical echocardiographic findings (or cardiac magnetic resonance findings) when skeletal scintigraphy with 99mTc-pyrophosphate (PYP), 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), or 99mTc-(hydroxy) methylene diphosphonate ((H)MDP) shows grade 2 or 3 myocardial tracer uptake, and clonal plasma cell dyscrasia is excluded (1-3). ATTR-CM is often an unrecognized pathology, and it has been found in 25% of people aged over 85 years in autopsy studies (1-3). It was reported in up to 16% of patients with aortic stenosis who underwent transcatheter aortic valve implantation, and 13% of patients with heart failure with preserved ejection fraction (HFpEF) (4). Echocardiography is the primary diagnostic test for cardiac amyloidosis, revealing infiltration of the ventricular walls characterized by a speckled appearance of the myocardium (5). The hallmark echocardiographic feature of cardiac amyloidosis is the relative apical sparing of longitudinal strain (5-7). There is a discrepancy between LV (left ventricular) wall thickness and electrocardiogram (ECG) voltage (4). The aim of the case report was to present a patient diagnosed with ATTR-CM, who was admitted initially due to clinical manifestations of heart failure and exhibited pleural effusions, ascites, and free fluid in the pelvic cavity.

CASE PRESENTATION

An 84-year-old man was admitted to the hospital presenting clinical symptoms of congestive heart failure, including dyspnea and peripheral edema. His past medical history included permanent atrial fibrillation (AF), hypertension, chronic kidney disease (CKD) grade IV, megaloblastic anemia and periurethral adenoma. The initial chest X-ray upon admission revealed bilateral pleural effusions. A pulmonologist was consulted, and a thoracocentesis was performed for diagnostic and therapeutic purposes. The analysis of the pleural fluid indicated it was a transudate. Abdominal ultrasound confirmed congestive hepatopathy with ascites. The ECG revealed atrial fibrillation alongside the left bundle branch block and low voltage. Transthoracic echocardiography revealed concentric left ventricular hypertrophy (LVH) with global hypokinesia and reduced systolic function (left ventricular ejection fraction (LVEF) of 36%, assessed using the Simpson biplane method). Cardiac chamber sizes were normal, with right ventricular free wall hypertrophy (13mm). Mild mitral regurgitation and moderate tricuspid regurgitation were detected, along with moderate pulmonary hypertension. The inferior vena cava (IVC) diameter was 2.5cm with inspiratory collapse of less than 50%. Subsequent analysis of global longitudinal strain (GLS) showed GLS reduction (-9.9%) with an apical sparing pattern ('cherry on top'). We suspected infiltrative cardiomyopathy and obtained serum and urine protein electrophoresis with immunofixation and the kappa/lambda ratio, which were negative for clonal plasma cell dyscrasia. The next diagnostic modality was bone scintigraphy with 99Tc MDP, which showed similar radiotracer uptake in the myocardium and ribs (Perugini grade 2) with a region of interest (ROI) ratio of 1.54. Additionally, a rest myocardial perfusion scan with 99m-technetium methoxy isobutyl isonitrile (99mTc MIBI) was performed, and an irreversible perfusion defect of the inferolateral wall was detected.

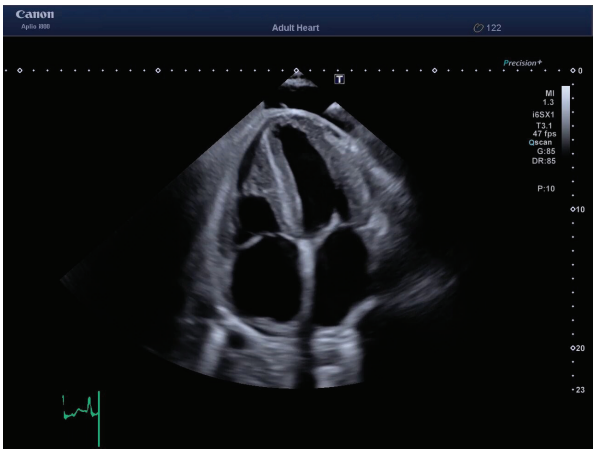

Figure 1. Assessment of cardiac muscle by transthoracic echocardiography

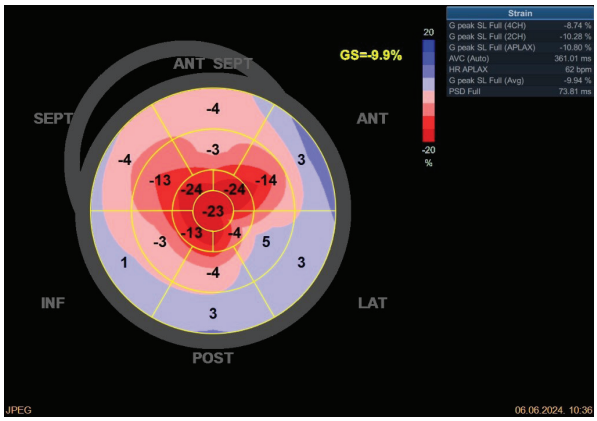

Figure 2. Apical sparing pattern (global longitudinal strain of left ventricle)

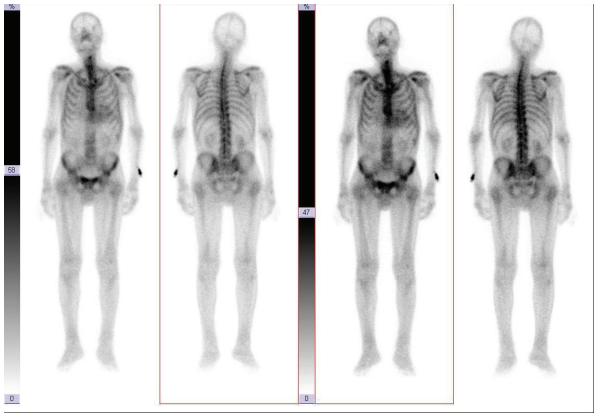

Figure 3. Perugini grade 2 on skeletal scintigraphy

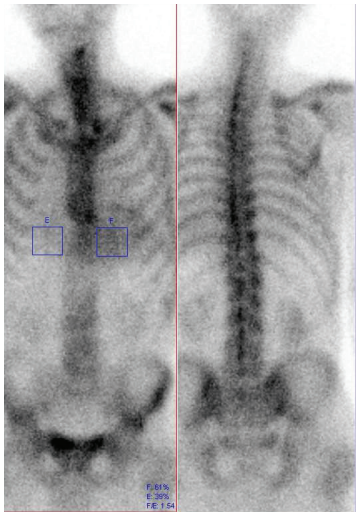

Figure 4. ROI ratio 1.54

DISCUSSION

Unexplained LVH, especially in patients with HFpEF, should raise suspicion for cardiac amyloidosis (3, 5). It is important to differentiate amyloid light chain (AL) amyloidosis which causes the deposition of misfolded immunoglobulin light chains, produced by a plasma cell clone, and ATTR amyloidosis which causes deposition of the transthyretin (TTR), a protein produced by the liver (3). ATTR amyloidosis can be hereditary (variant type, ATTRv) or acquired (senile or wild-type, ATTRwt) (3). Systolic function can be impaired in earlier stages of amyloidosis, reduced end-diastolic volume decreases the stroke volume (6). LVEF is preserved until the end-stage disease, but we commonly diagnose patients when LVEF is already mildly reduced (3, 6). Extracardiac signs and symptoms can be helpful in earlier detection of the disease, they vary among the types of amyloidosis. ATTR amyloidosis primarily involves the heart and peripheral nervous system (3). ATTRwt is associated with bilateral carpal tunnel syndrome (often precedes cardiac manifestations by 10 years), biceps tendon rupture and spinal canal stenosis. ATTRv is associated with peripheral sensorimotor neuropathy and autonomic dysfunction including gastrointestinal dysautonomia and orthostatic hypotension (3). Our patient did not present with classic extracardiac manifestations. He was previously diagnosed with CKD, which was described by a nephrologist as cardio-renal syndrome type 2. Our diagnosis was suspected based on echocardiography. Echocardiographic findings in ATTR amyloidosis are non-specific and include infiltration of the ventricular walls, which produces the appearance of pseudohypertrophy (wall thickness ≥12mm; relative wall thickness (RWT)≥ 0,42) with increased LV mass (5). Pericardial effusion, enlarged atria, thickening of the atrioventricular valves and interatrial septum are common (5, 6). Amyloid deposition can cause 'granular speckling' of the myocardium, however, it is a non-specific finding commonly seen in other infiltrative cardiomyopathies and end-stage renal disease (3, 6). Reduction in GLS with relative apical sparing has high sensitivity (93%) and specificity (82%) for cardiac amyloidosis (1). Apical sparing in the bulls-eye plot with an apex:base ratio of > 2.1 helps distinguish cardiac amyloidosis from other causes of LV hypertrophy (such as hypertensi-

on, Fabry disease and Friedreich's ataxia) (5). In suspected cases, serum and urine protein electrophoresis with immunofixation should be performed first to exclude AL (3). If a monoclonal protein was identified by these tests, the patient would need a referral to a hematologist, bone marrow biopsy or other tissue biopsies may be required (1). If monoclonal protein is not identified, as in our case, we proceed to bone scintigraphy. Bone scintigraphy showing myocardial uptake equal to or greater than in ribs (Perugini score 2 or 3), coupled with a lack of evidence of plasma cell dyscrasia, is sufficient to diagnose cardiac ATTR amyloidosis and tissue biopsy is not required (9). The role of cardiac magnetic resonance (CMR) depends largely on local accessibility, it is indicated if echocardiographic findings are inconclusive and if there is a broader differential diagnosis (4, 10). ATTR amyloidosis typically demonstrates transmural late gadolinium enhancement (LGE), whereas AL amyloidosis shows subendocardial LGE (4). T1 mapping detects the combined signal of myocytes and extracellular matrix. Native T1 signals are increased in regions with amyloid deposits or diffuse fibrosis. T2 signals are increased in AL compared to ATTR and the general population (10). Genetic testing is recommended to distinguish ATTRv from ATTRwt (3).

CONCLUSION

Cardiac amyloidosis is an underdiagnosed disease and should be included in differential diagnosis for patients presenting with heart failure and increased LV wall thickness on echocardiography. In suspected cases, negative serum and urine protein electrophoresis, with bone scintigraphy showing a Perugini score of 2 or 3, are sufficient to diagnose ATTR amyloidosis.

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