

Revisiting transthyretin related cardiac amyloidosis: Case report and review of literature

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Abstract

Amyloidosis is a complex group of disorders that can involve many organs and cause their dysfunction. Cardiac involvement indicates worse prognosis and influences treatment strategies. Cardiac amyloidosis is an under-diagnosed entity and high index of clinical suspicion and careful interpretation of basic diagnostic tools such as electrocardiogram and echocardiography is needed for early detection. Congestive heart failure due to restrictive pattern and/or conduction system abnormality, in absence of coronary artery disease should raise suspicion. We present a case of transthyretin related cardiac amyloidosis and discuss the key clinical and diagnostic findings along with review of existing literature regarding its management and outcomes.

Introduction

Amyloidosis is a unique group of disorders caused by accumulation of insoluble protein fibers, known as amyloid fibrils in the extracellular spaces of tissues and organs. Involvement of different organs and tissues in amyloidosis is often responsible for missed or delayed diagnosis, and amyloidosis remains a considerable clinical challenge as it is implicated in 1/1000 death in developed countries.¹ Cardiac involvement can be primary, a part of systemic amyloidosis, or a result of chronic systemic diseases.

Case Report

On 3/2017, a 72-year-old female with history of CHF with preserved ejection fraction (EF) of 50-55 %, hypertension and Rheumatoid Arthritis (RA) was admitted to

our hospital with worsening shortness of breath (SOB) of 1-week duration. Her SOB was worse even on walking less than 50 meters on a flat surface. Her primary cardiologist at a different health facility had diagnosed her with CHF a year prior to this presentation. She was compliant with her home dose of furosemide 40 mg daily. She was primarily treated with intravenous furosemide 40 mg daily and her home medications including atenolol 50 mg daily and lisinopril 5 mg daily were continued. Patient did not have history of myocardial infarction in the past and did not have prior exercise/nuclear stress test or cardiac catheterization. On examination, her blood pressure was 110/70 mm Hg, heart rate was 62 bpm and regular, respiratory rate was 12 per minute, temperature 98.6 F and SaO₂ of more than 92% at room air. Her neck was supple and cardiovascular examination revealed muffled heart sounds, normal S1S2 with no appreciable murmur.

Her ECG showed normal sinus rhythm, ventricular rate of 64 bpm, left axis deviation, low voltage QRS complexes with Q waves in inferior and antero-septal leads (Figure 1). Her echocardiogram was significant for moderate concentric left ventricular hypertrophy (LVH), mild global hypokinesis of left ventricle (LV), EF of 40-45%, grade III diastolic dysfunction, trace mitral regurgitation (MR) and severe tricuspid regurgitation (TR). Pulmonary arterial systolic pressure was 45-50 mm Hg and estimated right atrial (RA) pressure of 3 mmHg. Interventricular septum was thickened and showed *granular sparkling* appearance (Figure 2). In contrast, her echocardiogram done on 10/2016 had shown an EF of 50-55%, grade I diastolic dysfunction with evidence of trace TR. Her left heart catheterization revealed no significant coronary artery disease while right heart catheterization showed; RA pressure 12 mm hg, right ventricle pressure = 55/10 mmhg, PA pressure = 55/25 (mean of 30 mmhg), pulmonary capillary wedge pressure (PCWP) = 20 mmhg, Aortic pressure (Ao)=134/64 (mean=97) mm hg, left ventricular end diastolic pressure (LVEDP) = 15 mm hg, cardiac output = 4.83 L/min, cardiac index (CI) = 2.71 L/min/m². A cardiac magnetic resonance imaging (MRI) showed global hypokinesis of the LV with diffuse myocardial delayed enhancement and hypertrophy of interventricular septum without any evidence of perfusion defect. This constellation of symptoms was consistent with cardiac amyloidosis (Figure 3). Right ventricular endomyocardial biopsy obtained during right heart catheterization showed deposits of amorphous material consistent with amyloid. No stainable iron

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was detected with a special stain (Figure 4). Urine protein electrophoresis and serum protein electrophoresis results were not significant. Liquid chromatography tandem mass spectrometry detected a peptide profile consistent with ATTR (transthyretin/prealbumin)-type amyloid deposition.

Patient wished to follow up with her primary heart failure specialist. She was discharged on her previous home regimen and new diagnosis of ATTR-type cardiac amyloidosis was conveyed to the primary cardiologist.

Discussion

Majority of cardiac amyloidosis is caused by one of the two different types of protein; light chains or transthyretin. Light chain (AL) amyloidosis occurs due to clonal proliferation of plasma cells in bone marrow producing large amount of light chains, which are mis-folded into beta-pleated sheets and get deposited in various tissues. AL amyloidosis is the most common type of cardiac amyloidosis. About 2000 to 3000 new cases of AL amyloidosis occur each year in the United States, two thirds of these patients are male, and almost all of them are over the age of 50. Transthyretin-related (TTR) amyloidosis is derived from transthyretin, which is produced by the liver. There are 2 types of TTR-related amyloidosis: a genetic form known as hereditary transthyretin-related amyloidosis (ATTR) and a nonhereditary form known as wild-type ATTR amyloidosis. In ATTR,

genetic mutation is present from the birth but the abnormal deposition into tissues starts from age 30 to 60 years. It is a slowly progressive disease that usually affects the heart of men, almost always in the sixth or seventh decade of life.²

Cardiac amyloidosis most commonly manifests as heart failure. Dyspnea and signs of right heart failure including peripheral edema, hepatomegaly and ascites are common presentation. Pulmonary edema is rare, although the left sided heart pressures are elevated. Rarely, due to disproportionate amyloid deposition in the inter-ventricular septum, cardiac amyloidosis may be misdiagnosed as hypertrophic cardiomyopathy.³ Presence of purpura, leg or jaw claudication or angina suggests involvement of small vessel. Typically, small and intramyocardial vessel involvement gives rise to normal coronary angiography. Syncope or pre-syncope are common and are associated with a high mortality in the 3 months following the event.⁴ Ventricular arrhythmias have not been found to be frequently associated with syncopal episodes in cardiac amyloidosis. It is more likely multifactorial; postural or exertional hypotension due to excessive diuresis and autonomic neuropathy are the possible mechanisms. The conduction system is very frequently affected. High-grade atrioventricular block and symptomatic sinus node dysfunction are uncommon. Infra-His conduction times have been found to have prolonged. But, this prolongation may not be suspected clinically if the QRS is narrow on the ECG. Prolongation of His-ventricular interval has been found in few studies to be the sole independent predictor of subsequent sudden death. In spite of this, the routine screening for such conduction system abnormalities have not been recommended as the benefit of pacemaker or implantable cardioverter defibrillator (ICD) in prevention of sudden cardiac death has not been established in cases of cardiac amyloidosis.^{5,6} Patients are also at risk for cardiac thromboembolism, especially those with AL amyloidosis or atrial fibrillation.⁷ The etiology of pericardial effusion is more commonly CHF rather than direct amyloid deposition. There has to be high degree of suspicion of cardiac tamponade in a patient with moderate to large pericardial effusion because the classic echocardiographic signs of cardiac tamponade, such as right atrial and right ventricular compression may be absent. Endomyocardial biopsy has a nearly 100% sensitivity/specificity and allows for definitive subtyping.⁸ Immunofluorescence can be performed for subtyping but in case of any doubt about the diagnosis, mass spectrometry should be performed. In patients with cardiac ATTR amyloidosis,

bone scintigraphy can be used reliable diagnosis without the need for histology especially in patients without monoclonal gammopathy.⁹ Low voltage in the limb leads is one of the most common ECG manifestations, mainly in AL cardiac amyloidosis (50% cases) compared to lesser frequency in familial disease (25%) and senile cardiac amyloidosis (40%).¹⁰

Echocardiographic findings generally appear in the latter stages of the disease. Typically, *granular* appearance of the myocardium is seen in conventional 2-D echocardiography. This finding is nonspecific and is highly dependent on the machine settings.¹¹ A normally sized ventricle with increased wall thickness in both ventricles is generally seen. Bi-atrial dilation and inter-atrial septal thickening are typically seen in the advanced stages. Ventricular dilation is also a feature gener-

ally seen in the late stages. EF is preserved until end stage but strain is impaired very early. In the late stages of the disease, a systolic dysfunction of the left ventricle is seen. Impairment of left ventricle diastolic function is the first functional sign of cardiac involvement. At first, a reduced E wave with an increased deceleration time and a reduced early diastolic velocity of the left ventricular wall (E') are noted. In the advanced stage of the disease, an overt restrictive pattern can be found with increased E wave and decreased A wave, shortened mitral inflow deceleration time and severely reduced E' wave velocity.¹² With the advent of new echocardiographic techniques related to deformation imaging, promising results have been seen in diagnosing subclinical cases.¹³

Cardiovascular magnetic resonance (CMR) is more sensitive than echocardiog-

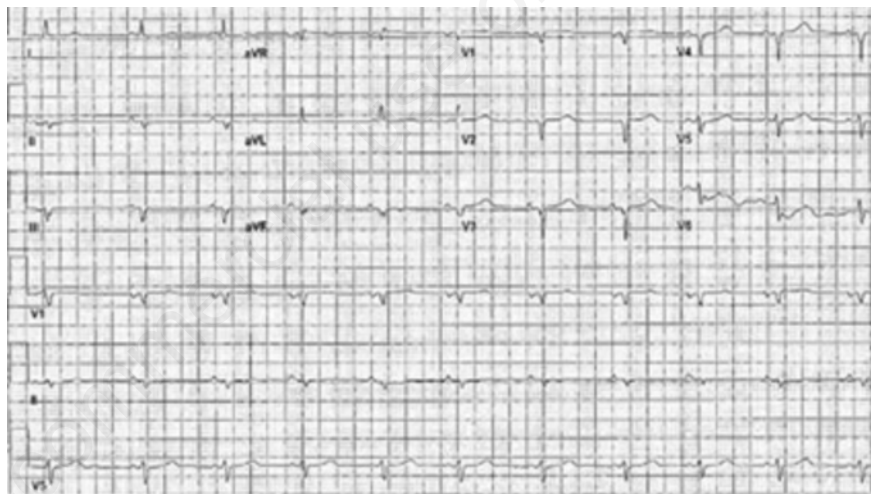


Figure 1. ECG revealing left axis deviation, low voltage QRS complexes with Q waves in inferior and anteroseptal leads (Pseudo-infarct pattern).



Figure 2. Granular sparkling pattern of thickened inter ventricular wall seen in echocardiogram.

raphy. A distinctive pattern of global left ventricular late gadolinium enhancement (LGE), which is rarely seen in other cardiomyopathies, provides strong clue to the diagnosis. Preliminary studies of the predicted value of LGE in patients with suspected cardiac amyloidosis have shown sensitivities of 86 and 88% and specificities of 86 and 90%. Supportive laboratory tests for AL amyloidosis like proteinuria, alkaline phosphatase and free light chain assays can be helpful in evaluating the likelihood of the disease prior to biopsy and monitoring diseases response to chemotherapy. Genetic testing for transthyretin gene in ATTR amyloidosis has relevance for family members and predicts sites of organ involvement as well as treatment options.

Prognosis depends mainly on the extent of cardiac involvement. It is generally better in ATTR amyloidosis compared to AL amyloidosis. A revised staging system for the disease published in 2012, includes circulating free light chain levels besides troponin (T or I) and N-terminal pro-B-type natriuretic peptide. It divides the disease into 4 stages with median survival of 94.1, 40.3, 14, and 5.8 months for Stages 1, 2, 3, and 4, respectively.¹⁴

The treatment of cardiac amyloidosis mainly encompasses therapy of heart failure and the treatment of the underlying disease. The treatment of heart failure differs from

standard recommendation in patients with diastolic or systolic heart failure. Salt and fluid restriction along with loop diuretics is the mainstay of treatment of cardiac amyloidosis. Due to autonomic dysfunction and inability to augment stroke volume in response to vasodilation in the presence of a small left ventricular cavity, angiotensin converting enzyme inhibitors and angiotensin receptor blockers are not suitable. Beta-blockers tend to exacerbate brady-arrhythmias while digoxin binds to amyloid fibrils and can lead to potential digoxin toxicity. Anticoagulation is recommended in patients with concomitant atrial fibrillation, systemic thromboembolism, and intra-cardiac thrombi or with atrial contractile dysfunction in presence of normal sinus rhythm.¹⁵ The role of ICD therapy in preventing sudden cardiac death (SCD) in cardiac amyloidosis is not clear. Since the electromechanical dissociation is the likely cause of SCD in these patients, efficacy of ICD therapy is doubted and safety has also not been well established.¹⁶

The main treatment option in patients with AL amyloidosis is chemotherapy. Administration of chemotherapy and/or autologous stem cell transplantation (ASCT) is done with an aim to eradicate the underlying plasma cell clone responsible for AL amyloid formation and to achieve a 90 percent or greater reduction in serum free light chain levels. The most common initial chemotherapy regimens used currently are bortezomib-based regimens such as

bortezomib, cyclophosphamide, and dexamethasone.

ATTR amyloidosis is not a malignant process and chemotherapy has no role. In ATTR amyloidosis, for specific mutations the source of the amyloidogenic protein is the liver and thus the evaluation for liver transplantation should be immediately initiated. Transplantation of the liver can be curative in selected patients with familial ATTR amyloidosis but not in wild-type ATTR. Unfortunately, there have been reports of cardiac disease progression even after liver transplantation in familial ATTR amyloidosis.¹⁷ If significant heart failure is concomitantly present, isolated liver transplantation is contraindicated and consideration should be given to a combined liver-heart transplant or just heart alone.

Conclusions

With the advent of newer diagnostic tools, more cases of cardiac amyloidosis have been diagnosed over the last decade. Early diagnosis and timely intervention after sub typing of amyloidosis is crucial in determining the outcome of the disease. Thus, high index of clinical suspicion for cardiac amyloidosis is required in patients presenting with established disease or with diagnostic clues such as unexplained ventricular hypertrophy with inappropriately low ECG voltages and unexplained heart

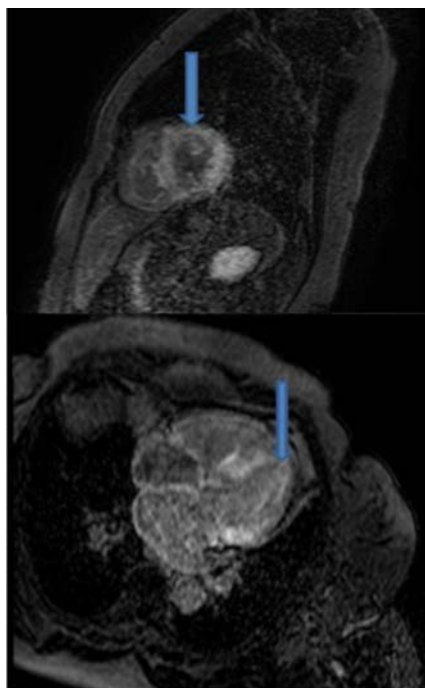


Figure 3. Diffuse delayed LV myocardial contrast enhancement seen in cardiac MRI (blue arrows) in two different views.

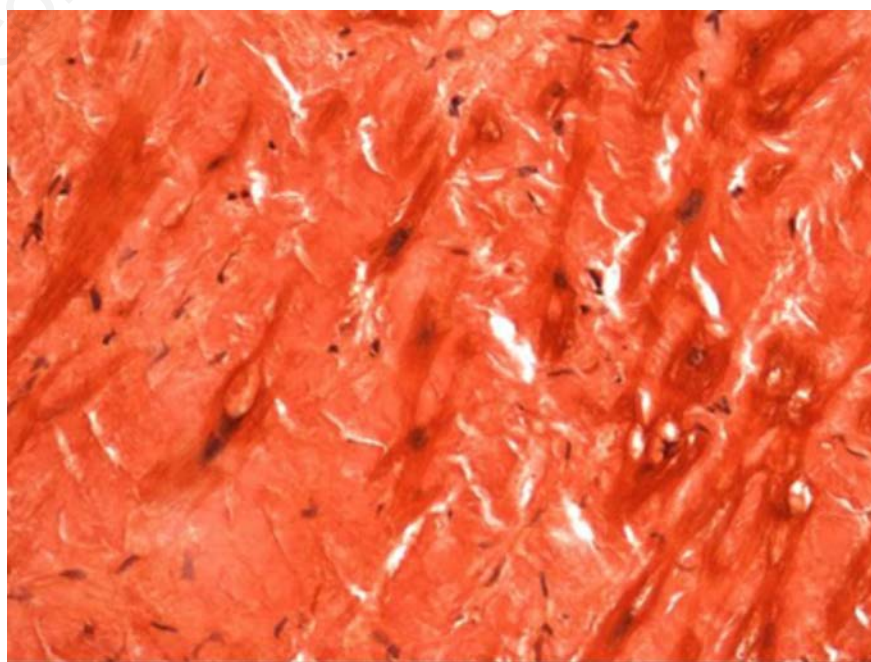


Figure 4. Congo red staining of myocardial tissue suggestive of cardiac amyloidosis.

failure occurring with characteristic dysfunction of other organs. Diuretic and rhythm management is the mainstay of medical management for cardiac involvement, along with anticoagulation when indicated. Chemotherapy and/or stem cell transplantation is reserved for AL amyloidosis. Liver and/or heart transplantation should be considered in familial ATTR amyloidosis. There are investigational drugs currently underway but not yet established for use.

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