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The Hidden Cardiac Amyloidosis and Red Flags: Case Report

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Abstract It is imperative that internists and hospitalists who are the frontier of care seen by the patient are aware of the red flags associated with cardiac amyloidosis. This case report discusses the clinical evaluation of cardiac amyloidosis highlighting the utility of various laboratory tests and imaging modalities utilized to facilitate reaching a diagnosis. Herein, we discuss the clinical evaluation of a 69-year-old male with suspected cardiac amyloidosis highlighting the utility of various laboratory tests and imaging modalities to reach a diagnosis. Additionally, we discuss the pitfalls of delayed diagnosis.

Keywords: *amyloidosis, echocardiography, red flags*

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1. Introduction

Cardiac involvement in amyloidosis is significantly underdiagnosed and is increasingly recognized as a cause of heart failure with preserved ejection fraction (HFpEF), in its early stages [1]. Internists and clinicians should be familiar with the disease and have early suspicions to initiate early diagnostic workup. The disease overlaps with hypertensive heart disease or hypertrophic cardiomyopathy, all resulting in thickening of the myocardium. However, initiating the workup for cardiac amyloidosis can be considered when left ventricle wall thickness on echocardiography is ≥12 mm with the following but not limited to family history of amyloidosis, cardiac conduction involvements, elevated biomarkers, and non-cardiac involvement including peripheral neuropathy, autonomic dysfunction, proteinuria, macroglossia, skin bruising, or bilateral carpal tunnel syndrome. Despite the wide range of non-invasive imaging modalities for detecting cardiac amyloidosis, limitation still exists by the decreased availability and cost of such modalities [2].

Our case highlights the importance of raising awareness for early diagnosis of cardiac amyloidosis among internists and hospitalists who are the frontier and first care providers seen by the patient. The patient was informed that data concerning the case would be submitted for publication, and he provided an informed consent.

2. Case Description

A 69-years-old Latin American male with a past medical history of hypertension, type 2 diabetes mellitus, cerebrovascular accident, former smoking, and Parkinson's disease presented to our hospital with shortness of breath and bilateral leg swelling for several days. The patient denied chest pain, palpitations, fever, night sweats, orthopnea, or paroxysmal nocturnal dyspnea. His family history was unremarkable. On a physical exam, the patient is alert and oriented x2 (oriented to self and date), vital signs were as follows: blood pressure 169/74mmHg, heart rate 52 beats per minute, 98.0 F temperature, respiratory rate 22 /min and the patient was saturating at 99% on room air. The patient had distant heart sounds but regular S1 and S2, right sided S3, no murmurs, rubs, or gallops. The patient had an equal breathing sound bilateral, without any wheezes or rhonchi. Abdominal examination was unremarkable with no evidence of hepatomegaly. Lower Extremities revealed bilateral 2+ pitting edema up to the knee. His preadmission medications included atorvastatin 40 mg daily, losartan potassium 100 mg daily, 2.5 mg twice daily, apixaban 2.5 mg twice daily, carbidopa-levodopa 10-100 mg twice daily, regular insulin and aspirin 81 mg daily. Chest Xray showed enlarged cardiac silhouette with no focal pulmonary consolidation or pleural effusion (Figure 1). Electrocardiogram (EKG) demonstrated atrial fibrillation with controlled ventricular rate and exhibited

low voltage criteria. (Figure 2). An echocardiogram revealed a left ventricular (LV) ejection fraction of 50%, concentric left ventricular (LV) hypertrophy, severely increased left atrial volume measuring 83.7 ml/m^2, thickening of the right ventricular free wall, moderate pulmonary hypertension with right ventricular systolic pressure of 52.9 mmHg, thickened interatrial septum, diastolic dysfunction with restrictive mitral in-flow filling pattern on Doppler evaluation, and mild pericardial effusion behind LV (Figure 3). Given the discordance between the degree of LV thickness on echocardiography and QRS voltage on ECG, cardiac amyloidosis was considered as a possible etiology of heart failure with preserved ejection fraction (LVpEF). Computerized tomography (CT) of the chest revealed mild cardiomegaly, and mild pericardial effusion. Selected laboratory workup over hospital admission is summarized in Table 1. There was no liver involvement (i.e., liver function tests were normal) with no isolated alkaline phosphatase elevation. There were high levels of brain natriuretic peptide (BNP). Renal involvement was demonstrated with borderline increased creatinine levels and marked total 24 hours protein levels. Serum protein electrophoresis was further obtained to evaluate for an underlying gammopathy (which is commonly found in light chain amyloidosis). There was a high pathological serum level of kappa chains (66.4 mg/L) with a pathological kappa/lambda ratio. Serum and urine immunofixation showed a free lambda light chain. The patient was offered a fat pad biopsy and cardiac MRI for further confirmation of the diagnosis of Amyloidosis. The main aim of treatment following diagnosis was direct at optimizing cardiac function and managing symptoms with titration of her diuretic and heart failure medications depending on the volume status, close monitoring of intake/output and body weight. Rate control of the atrial fibrillation was enhanced, and oral anticoagulation therapy was continued. The lower extremities edema subsided on the 3rd hospital day with no relapse. Patient cardiac medications were adjusted to include Losartan 100 mg, furosemide 40 mg twice daily, Atorvastatin 40 mg, apixaban 2.5 mg twice daily, and aspirin 81 mg daily. Patient was also instructed that in the future, a hematology oncology consult might be warranted.

Table 1. Select laboratory workup during hospital admission

Lab	Value	References
WBC Count	6.0	4.50-11.00 x 10*3/uL
Hemoglobin	11.9 L	12.0-15.7 g/dL
Hematocrit	33.2	38-50%
Platelet Count	229	140-440 x 10*3/ uL
BUN	34 H	7-22 mg/dL
Creatinine	1.77 H	0.50-1.50 mg/dL
BUN/Creatinine	19 H	10-14 mg/dL
BNP	293 H	0-125ug/mL
MALB	14.1	0-30mg/dL
MICRO/CR	73	0-30 mg/g
UPROT	30	0-12 mg/dL
USOD	88	30-90 mmol/L
IGG	871	603-1613 mg/dL
IGA	300	61-437 mg/dL
CYSTC	1.70	0.62-1.16 mg/L
IGM	72	20-172 mg/dL
TP24C	216 H	30-150 mg/24 hours
MSPIKE %	Not observed	
A1 GLOB	0.2	0.0-0.4 g/dL
A2 GLOB	0.9	0.4-1.0 g/dL
BETA GLOB	1.3	0.7-1.3 g/dL
GLOTOT	3.4	2.2-3.9 g/dL
FRKAPLC	66.4 H	3.3-19.4 mg/L
FRLAMLC	22.4	5.7-26.3 mg/L
KAP/LAM	2.96 H	0.26-1.65
IGE	7	6-495 IU/mL
AMYBETAP	42	20-80 pg/mL

Table Abbreviations: BUN, Blood Urea Nitrogen**, BNP,** Brain Natriuretic peptides**; MALB,** microalbumin in urine; **MICRO/CR,** microalbumin in urine /creatinine ratio**; UPTOT,** Urinary Proteins**; USOD, Urinary sodium; IGG,** Immunoglobulin G**; IGA,** Immune globulin A**; IGM,** Immune globulin M; IGE, Immune globulin E; **TP24C**, Total Protein collection in 24 hours; **CYSTC,** cytochrome c **; MSPIKE %,** M spike protein ; **AMYBETAP,** Amyloid Beta protein**; A1 GLOB**; alpha 1 globulin; **A2 GLOB,** alpha 2 globulin**; BETA GLOB,** Beta A globulin **; GLOTOT,** Total globulins**; FRKAPLC,** serum free kappa light chain **; FRLAMLC,** serum free lambda light chain; **KAP/LAM,** Kappa/lambda light chain ratio.

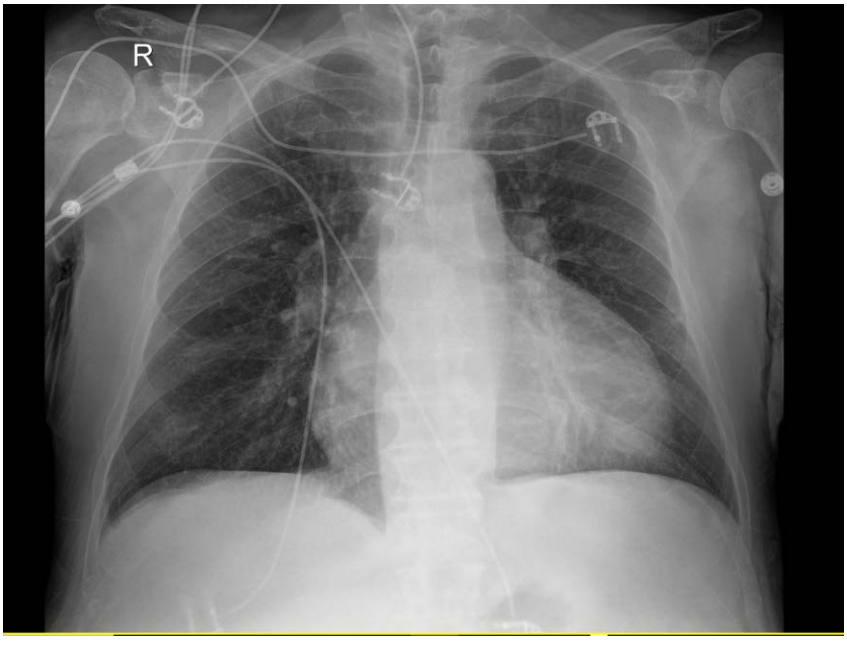

Figure 1. Chest X Ray showed enlarged cardiac silhouette with no focal pulmonary consolidation or pleural effusion

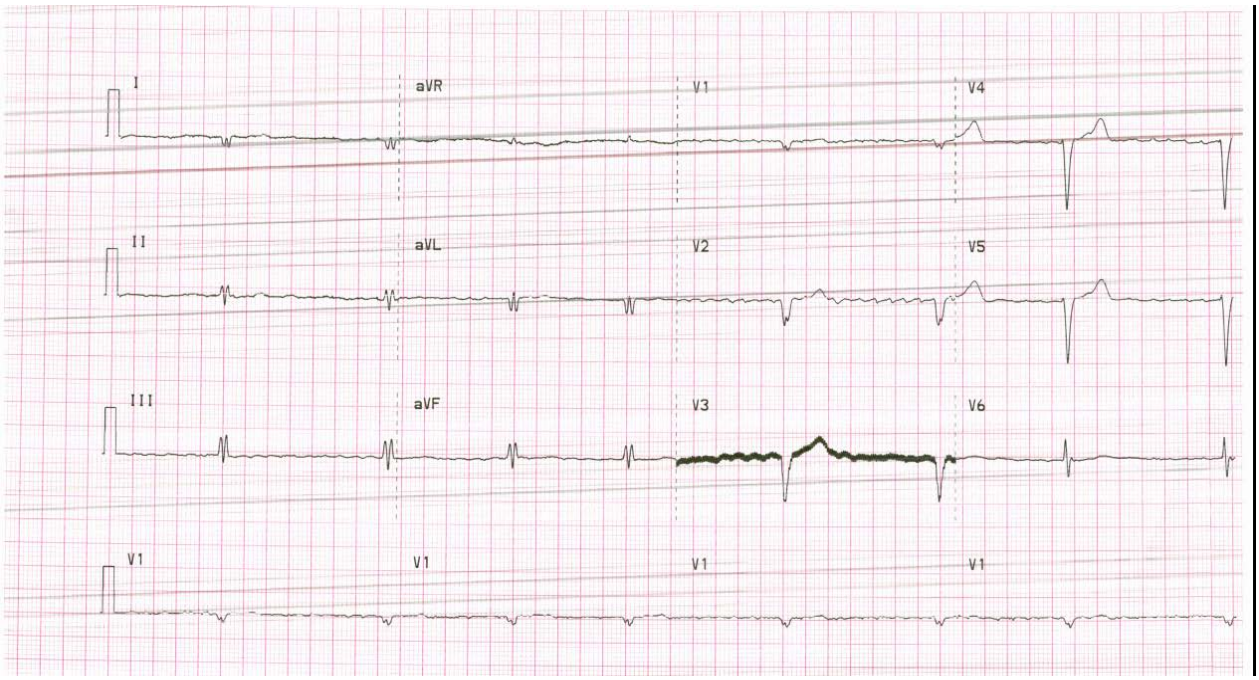

Figure 2. Electrocardiography in a patient with cardiac amyloidosis. Rhythm is atrial fibrillation. Note the low voltage QRS in criteria (QRS complexes in the limb leads are < 5 mm; or the amplitudes of all the QRS complexes in the precordial leads are < 10 mm)

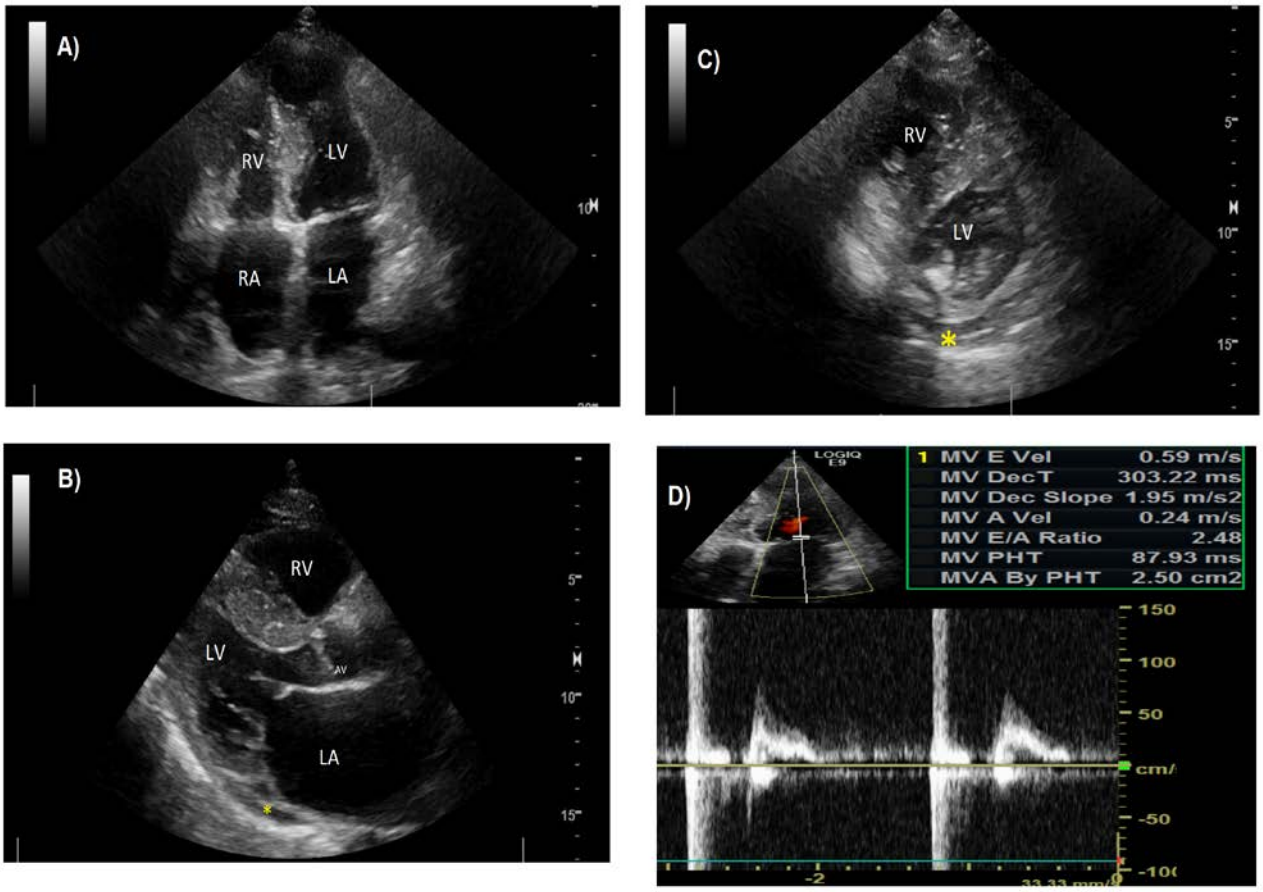

Figure 3. Transthoracic echocardiography showing **A)** Four chamber echocardiographic view demonstrating bi atrial enlargement, left ventricular hypertrophy, small pericardial effusion, **B)** Short axis echocardiographic view demonstrating severe concentric left ventricular hypertrophy with small pericardial effusion (*)**, C)** Parasternal long axis echocardiographic view demonstrating severe concentric left ventricular hypertrophy with small pericardial effusion (*), **D)** Doppler demonstrating restrictive physiology with an E velocity of 0.59 cm/s and E/A 2. 48, and her E' velocity of 2.78 cm/s and E/Med E' 18.75

MOVIE FILES

Movie File: Movie file 1 and Movie File 2 Transthoracic echocardiogram showing 4 chamber and parasternal long axis view illustrating Bi-atrial dilatation, valve thickening, Thick ventricular walls, and interatrial septum thickening, with speckled appearance suggestive of amyloid infiltration.

3. Discussion

Amyloidosis is a progressive disease in which misfolded insoluble amyloid protein deposits in one or more organs, including cardiac tissues. Five of more than 30 amyloid protein deposits causes cardiac amyloidosis includ87iing immunoglobulin light chain (AL or primary amyloidosis), immunoglobulin heavy chain, amyloid transthyretin (ATTR), and serum amyloid A [1]. Recent advances in diagnostic imaging and treatments can delay or prevent the accumulation of amyloid proteins. However, misdiagnosis or delayed diagnosis is still very common. One of the major challenges in cardiac amyloidosis diagnosis is the awareness among internists and hospitalists who are the frontier and first care providers seen by the patient. In addition, many hospitalists lack familiarity with the latest non-invasive diagnostic imaging tests in cardiac amyloidosis [3].

In this case report, we tried to generate a differential diagnosis for our patient that presented signs and symptoms consistent with cardiac amyloidosis. Indeed, such variability in initial presentations coupled with red flags from lab workup and discrepancy between ECG and echocardiography raised our suspicion of diagnosis by searching for clues for amyloidosis. A distinctive sign of cardiac amyloidosis is the abnormal ratio between LV thickness and the low voltage of QRS on ECG. However, it must be noted that absence of low QRS voltage alone does not rule out cardiac amyloidosis. The importance of interpretation of cardiac imaging alongside clinical findings is crucial and different non-invasive imaging techniques are complementary. On echocardiography, we have shown the characteristic features of amyloid heart include ventricular thickening with myocardial “speckled” appearance, decreased left ventricular volume, enlarged atria, and restrictive diastolic physiology, which could be found in all types of cardiac amyloidosis [4]. However, our case was limited by the lack of availability of myocardial deformation imaging (longitudinal systolic function in all myocardial segments, GLS), which typically shows the “apical sparing” phenomena in amyloidosis that reflects 82% specificity and 93% sensitivity. However, the presence of a monoclonal protein in the serum or urine and the abnormal serum kappa/lambda free light chain ratio, raises the sensitivity (>99%) for the detection of AL amyloidosis [2]. This lab test is unique for identifying the underlying substrate of AL cardiac amyloidosis which is the consequence of plasma cell dyscrasia leading to the production of amyloidogenic monoclonal immunoglobulin light chain, in contrast no blood test can identify TTR oligomers to diagnose ATTR cardiac amyloidosis. While mild elevations in serum kappa/lambda free light chain ratio are common in patients with kidney disease with normal serum and urine immunofixation electrophoresis which was not the case in our patient but again the kappa/lambda ratio was elevated [5]. Fat pad and endomyocardial biopsy with Congo red staining, immune-electron microscopy or mass-spectrometry are the gold standard for definitive diagnosis, however adding to the challenges of confirming diagnosis, not all patients will consent for such procedure which was the case in our patient refused to proceed with the biopsy. Notably, failure to consider cardiac amyloidosis or often misdiagnosing it for non-amyloid heart failure preserved ejection fraction (HFpEF), hypertensive heart failure, or hypertrophic cardiomyopathy is an important reason for delaying treatment [6]. Delayed diagnosis of cardiac amyloidosis has been reported in a survey of > 500 patients with AL amyloidosis (37% of whom with cardiac involvements) with average time from initial symptoms to diagnosis of 2 years [3].

Once diagnosis of AL amyloidosis is confirmed, therapy is usually directed towards the plasma cell clone with chemotherapy (bortezomib, dexamethasone and an alkylating agent – typically cyclophosphamide) followed by autologous hematopoietic stem cell transplant. However, delay in diagnosis comes at a price which is advancing cardiac involvement and in ability to receive the appropriate dosage of chemotherapy or being a candidate for hematopoietic stem cell transplant [2].

In conclusion, we have demonstrated in this case that several factors may hinder the correct and timely diagnosis of cardiac amyloidosis including heterogeneity of symptoms, the need for tissue biopsy which requires expert centers, and the expensive diagnostic imaging modalities which may not be accessible to the population of certain demographics which was in our case.

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