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Multiple myeloma and amyloidosis as an often-missed cause of heart failure: A case report

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Abstract

Amyloidosis is a clinical disorder in which a protein-based infiltrate deposits in tissues (eg, heart, liver, kidney, skin, eyes, lungs, nervous system) as beta-pleated sheets. Cardiac amyloidosis (CA) thought to be a rare disease, now is increasingly recognized due to enhanced clinical awareness and advanced diagnostic imaging. In amyloidosis Cardiac involvement is a progressive disorder resulting in early death due to congestive heart failure (CHF) and arrhythmias. The subtype of the disease is determined by which protein is depositing; although dozens of subtypes have been described.

Immunoglobulin light-chain amyloidosis (AL) associated with Multiple Myeloma (MM) is the most common type of amyloidosis. AL amyloidosis associated with MM is characterized by the deposition of immunoglobulin light chain fragments within the heart. It is thus very important to be able to understand, diagnose, and treat this often overlooked and misunderstood cause of heart failure for timely treatment.

Keywords

multiple myeloma; amyloidosis; heart failure

Introduction

Amyloidosis is a rare disease that occurs when proteinaceous deposits called amyloid build up in tissues and organs either locally or systemically. Amyloid is formed from insoluble fibrils or misfolded protein subunits. These fibrils deposit between cells, causing physiologic dysfunction. There are several types of amyloidosis including Primary (systemic AL type) amyloidosis, Secondary (systemic AA type) amyloidosis, Senile systemic amyloidosis (SSA), Hereditary Amyloidosis (ATTR) or abnormal transthyretin protein, dialysis-related amyloidosis and organ-specific amyloidosis [1]. AL amyloidosis is the most common type of amyloidosis in the U.S. which tends to have a higher incidence in males with an average age of diagnosis

at 63 years old [2]. MM is a commonly known etiology of AL amyloidosis and is 2 x more common in African Americans with an associated younger age of onset compared to European Americans [3]. AL amyloidosis associated with multiple myeloma and can present with a variety of signs and symptoms [4]. The heart, however, is the most common organ affected followed by the kidney, soft tissue, liver, and peripheral/autonomic nervous system [5]. In cardiac amyloidosis, amyloid fibrils deposit between the cardiac myocytes and reduce cardiac compliance, ultimately leading to congestive heart failure, ventricular arrhythmias, and sudden cardiac death [1]. Diagnosis of this uncommon etiology historically relies on obtaining blood work, an EKG, ECHO, and endomyocardial biopsy. Therapy involves treating the different aspects of the disease including eliminating the amyloid precursor, removing the fibrils, and effectively managing heart failure. We report a case of amyloidosis that presents with congestive heart failure as the initial sign of amyloidosis disease relating to multiple myeloma.

Case Report

A 65-year-old African American male with a past medical history of systolic heart failure (ejection fraction of 45-50%), coronary artery disease status post-stenting of the left anterior descending artery, hypertension, hyperlipidemia, and diabetes mellitus presented to the ED complaining of chest pain and shortness of breath for a one-month duration. The patient was compliant with all of his existing medications. Vital signs revealed BP of 78/50mmHg with HR of 78bpm. The patient was hypoxic on room air. Physical exam findings showed jugular venous distention, muffled S1-S2 heart sounds, crackles at lung bases, and 2+ pitting edema of the lower extremities. Significant labs revealed a troponin level of .09 ng/mL and a BNP of 665 pg/mL. His EKG was significant for low voltage QRS and T-wave inversion in lateral leads (Figure 1). The patient was diagnosed with a congestive heart failure exacerbation. A 2D echo performed revealed normal LV size, concentric LVH, mild diffuse LV hypo kinesis with EF of 40-45%. The limited 2D echo showed all LV segments to have reduced strain, with sparing of the apex (Figure 2). A left heart catheterization did not find any concerning lesions. Heart pressures were elevated in all four chambers with a low cardiac output and cardiac index. An endo-myocardial biopsy revealed positive Congo red staining, indicating cardiac amyloidosis (Figure 3). A bone marrow biopsy was then performed which showed plasma cells and lambda cell light chains, pointing towards AL amyloidosis with an underlying diagnosis of Multiple Myeloma (Figure 4). The patient was then started on Cyclophosphamide, Bortezomib, and Dexamethasone.

Discussion

In cardiac amyloidosis, amyloid fibrils deposit within the myocardial vessels between the cardiac myocytes leading to a reduction in cardiac compliance, ischemia, arrhythmias and ultimately congestive heart failure. Due to the involvement of small coronary vessels, patients may present with chest discomfort and cardiac ischemic signs, such as elevated troponin and dyspnea [1]. Patients may often present with weight loss, anorexia, and malaise. Some patients may also display purpurain the periorbital region as a sign of small vessel disease. Often times, patients can also present with hepatomegaly, nephrotic syndrome, and macroglossia, which was not noted in our patient [6]. Unfortunately, a delayed diagnosis occurs in approximately 40% of patients with AL amyloidosis as well as 25% of patients presents with advanced car-

diac disease [5], as in our case.

As far as EKG readings are concerned, low QRS voltages (all limb leads <5 mm in height) with poor R-wave progression in the chest leads (pseudo infarction pattern) occurs in upto 50% of patients with cardiac AL amyloidosis [4]. In our case, the patient's EKG was significant for low voltage QRS and T-wave inversion in the lateral leads. Furthermore, the combination of low ECG voltage with concentrically increased wall thickness is highly suspicious for cardiac amyloidosis, but voltage criteria for LV hypertrophy can nevertheless sometimes occur. Other findings indicative of AL amyloidosis, but not noted in our patient include first-degree atrioventricular blocks in 21% of patients, nonspecific intraventricular conduction delays in 16% patients, second- or third-degree atrioventricular blocks in 3% of patients, atrial fibrillation/flutter in 20% of patients, and ventricular tachycardia in 5% of pateints [7].

Measurements of BNP in its more stable form, N-terminal fragment (NT-proBNP), and cardiac troponins are extremely informative in AL amyloidosis [8]. In fact, NT-proBNP has been shown to improve risk stratification and accuracy in regard to an accurate diagnosis. Recently, sensitive mass spectrometry technologies are being used for monoclonal FLC quantification as well as detection [5].

Diastolic dysfunction is the earliest echocardiographic abnormality and may occur before cardiac symptoms develop [9,10]. While echocardiography has been the historic diagnostic modality to detect cardiac amyloid, recent advances in cardiac magnetic resonance imaging taking advantage of T1 mapping has been used to help diagnose cardiac amyloid [5].

Despite all possible diagnostic techniques, a biopsy is mandatory to definitively diagnose amyloidosis. Endomyocardial biopsy is the gold standard for diagnosing cardiac amyloidosis with Congo red staining to confirm the specific type of amyloidosis present. If staining with Congored does not provide a clear answer, electron microscopy can be used to confirm or reject the diagnosis [8]. This immunofluorescence technique uses fluorescein isothiocyanate (FITC) labeled antibodies that are used for typing [5].

Treatment of AL cardiac amyloidosis is based on treating the underlying pathologies with rapid elimination of the amyloid precursor, removing the fibrils, and effectively managing the heart failure. In this case, the patient had a co-existent diagnosis of Multiple Myeloma and was treated with a protease inhibitor, an alkylating agent, and a glucocorticoid. Bortezomib, Dexamethasone, and Cyclophosphamide was the combination of drugs chosen and is commonly referred to as CyBorD, CVD, VCD, or CBD. In a study evaluating the effectiveness of this frontline regimen, 94% of patients received a positive hematologicalresponse, with 71% of patients achieving a completehematological response [11].

Other proteasome inhibitors that can be used in treating this etiology include Ixazomib and Carfilzomib. Regarding are cent study done on refractory patients with AL amyloidosis, Ixazomib was able to produce a positive hematologic response in 52% of patients. A study done on Carfilzomib, this drug showed a 63% response rate in refractory AL amyloidosis. However, this drug also showed signs of cardiopulmonary toxicity in 36% of patients. For these reasons, Bortezomib is still the first choice proteasome inhibitor used in cardiac amyloidosis due to its good safety profile and rare cardiotoxicity effects [12].

Other forms of treatment for patients with AL amyloidosis is high dose Melphalan (HDM) with autologous stem cell transplantation (ASCT) as well as oral Melphalan with Dexamethasone (MDex). HDM with ASCT is the most cytotoxic therapy used against plasma cells and in a study done achieved a positive hematological response in >70% of patients and a complete hematologic response in 30-40% of patients. However, this treatment plan was most probably not chosen for our patient because this drug is not used for patients with severe cardiac involvement as it is associated with fluid retention and hypotension. MDex is a regimen for patients not eligible for ASCT and has proven to be effective and well-tolerated. In a recent study, this regimen showed a positive hematologic response rate in 76% of patients and a complete hematologic response in 31% of patients. Furthermore, 37% of patients had a positive cardiac response and this regime showed an overall median survival of 7.4 years. This treatment option was probably an option in treating our patient, however, our initial treatment plan has better positive outcomes [12].

Newer approaches to treating AL amyloidosis include the use of immunomodulatory drugs including Thalidomide, Lenalidomide, and Pomalidomide. While these drugs are usually reserved for refractory amyloidosis, they can also be implemented as part of initial therapy. These options are used with caution as their mechanisms of action are not fully understood and can lead to adverse events like neurotoxicity associated with Thalidomide and worsening cardiac function associated with Lenalidomide. However, Pomalidomide has proven to have positive effects in a phase 2 trial and has a better safety profile when compared to similar immunomodulatory agents [12]. Another novel approach to treating AL amyloidosis as an etiology of heart failure includes the use of a human monoclonal antibody, Daratumumab. This drug targets the CD38 surface antigen on plasma cells and is well tolerated among patients with severe cardiac involvement. A recent study found that daratumumab was able to rapidly lower circulating light chains, without significant adverse effects [12,13].

Another option in the treatment of cardiac amyloidosis is fibril directed therapy such as the use of Doxycycline has been shown to interfere with fibril formation. This takes advantage of the bacteriostatic abilities of doxycycline to bind to specific ribosomal subunits to inhibit protein synthesis [12].

In managing the heart failure directly, the traditional heart failure treatment plan of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, B-blockers, and mineralocorticoid receptor antagonists are often poorly tolerated in patients with severe cardiac amyloidosis. Thus, treatment of the congestion most often requires loop diuretics like Torsemide and Bumetanide [12].

The past few years have seen massive improvements in treating AL amyloidosis as this once fatal disease has become treatable [12]. Despite treatment advances, cardiac amyloidosis continues to have apoor prognosis [11]. While cardiac amyloidosis is a rare disease, it is crucial to always consider this etiology associated with Multiple Myeloma for patients presenting with heart failure.

Figures

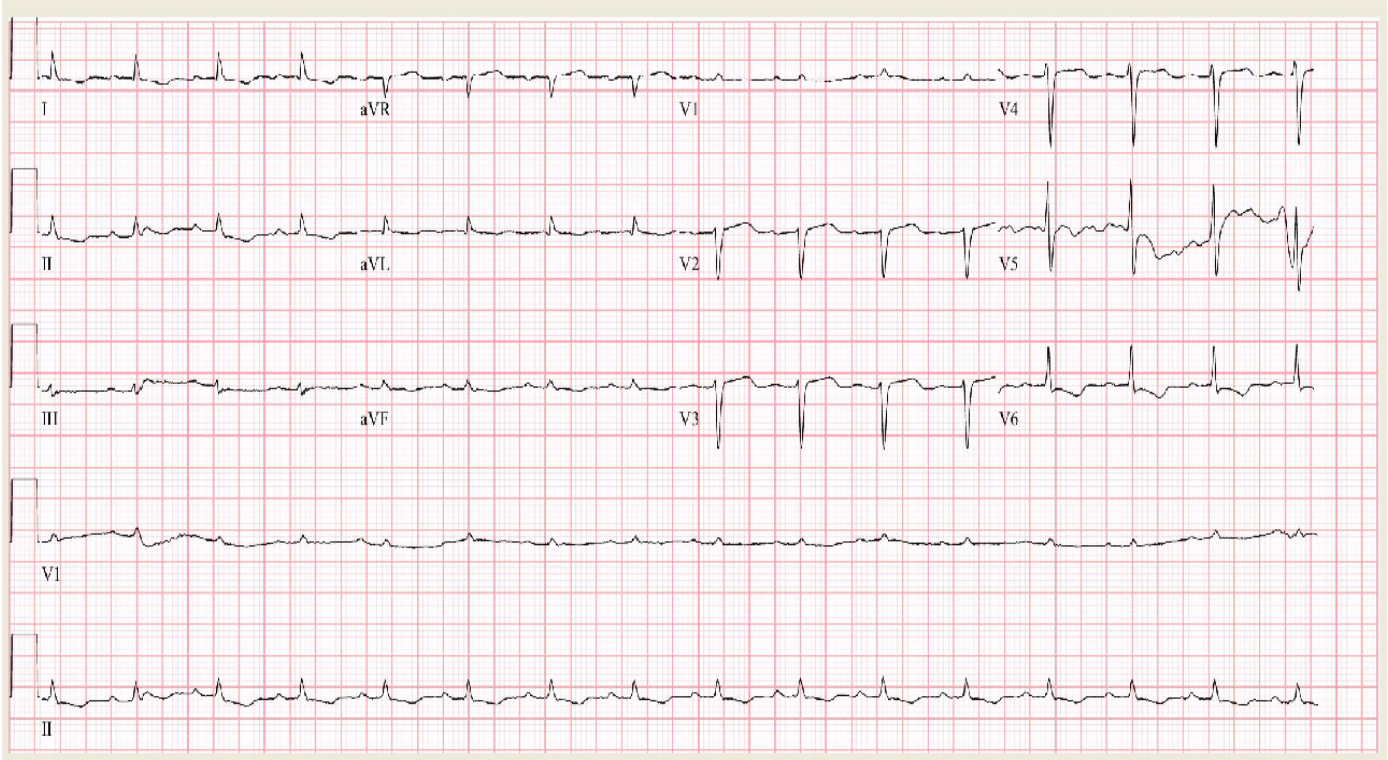

Figure 1: Low voltage EKG.

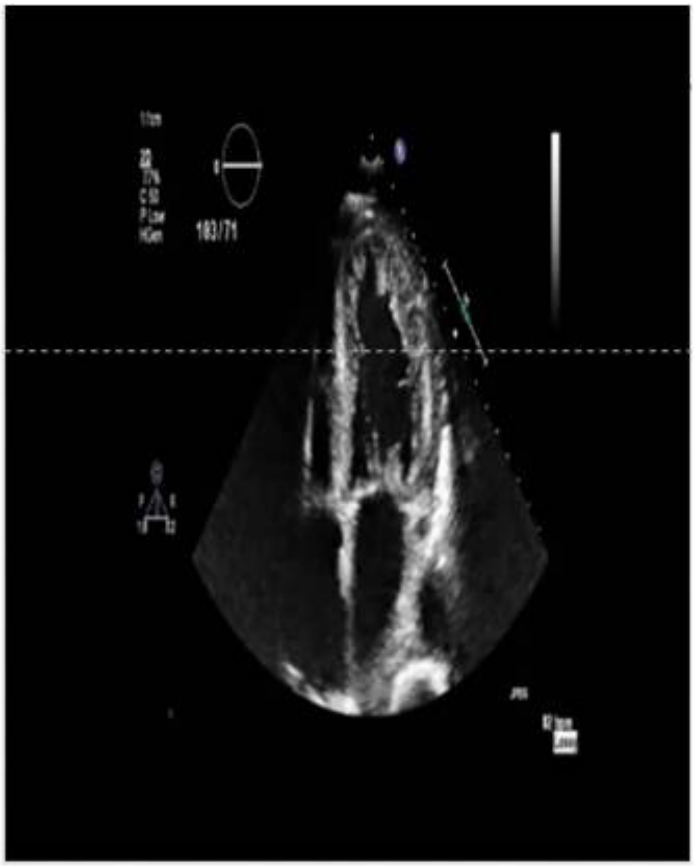

Figure 2: Echocardiography - All segments have reduced strain with some sparing of the apex.

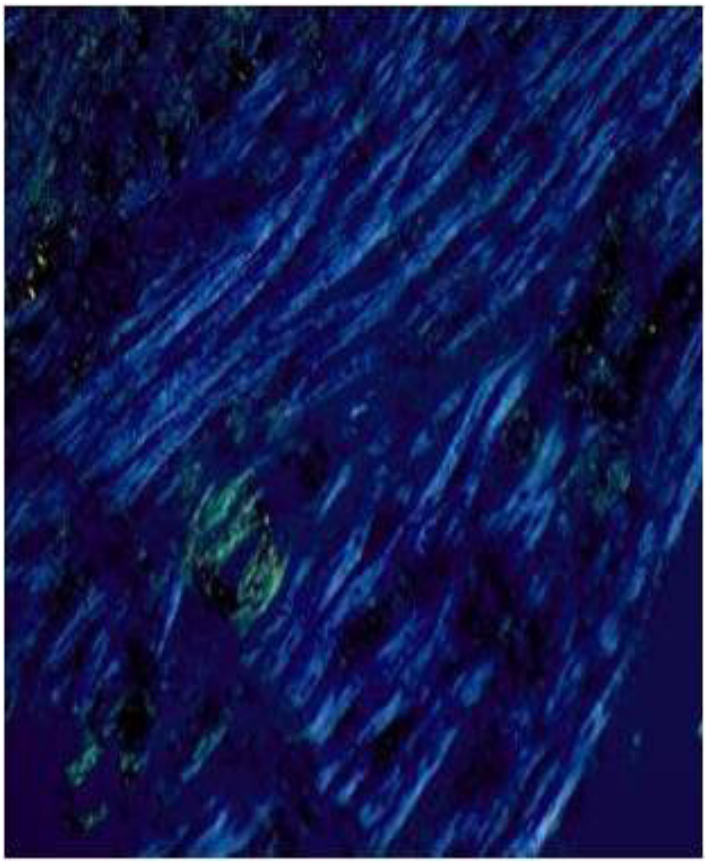

Figure 3: Apple green birefringence on Congo Red stain of endo-myocardial biopsy.

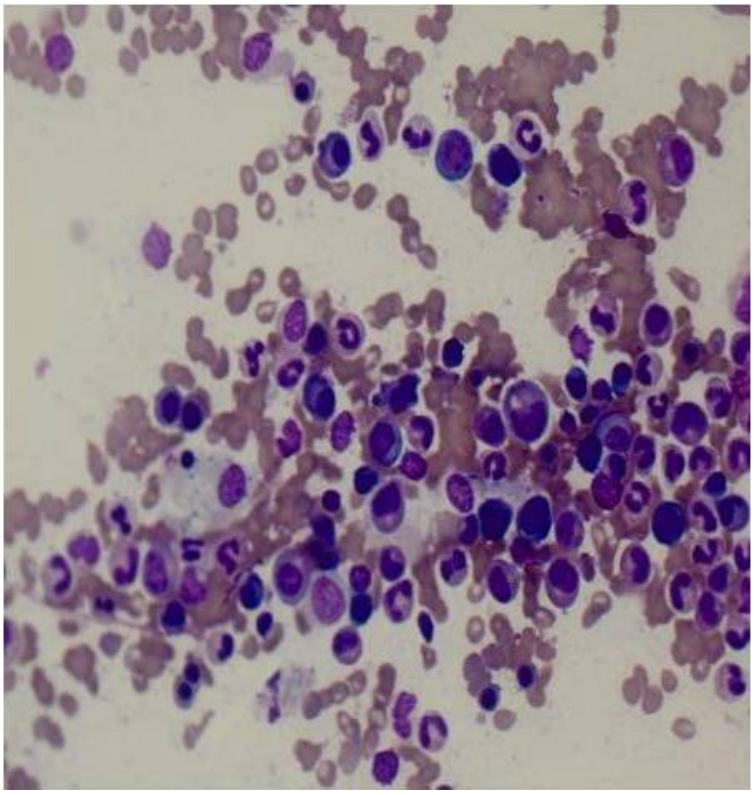

Figure 4: Hyper-cellular marrow with increased plasma cells

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