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A CASE OF CARDIAC AMYLOIDOSIS: DIAGNOSTIC VALUE OF RADIOLOGICAL FINDINGS AND HISTOLOGICAL FINDINGS

KEY WORDS: Cardiac amyloidosis; Restrictive cardiomyopathy; Transthyretin; Case report

Dr Chitneni Amanmahanya

Post Graduate, Department of General Medicine, Sri Ramachandra Institute of Higher Education and Research Porur, Chennai

ABSTRACT

Cardiac amyloidosis, a disease caused by the precipitation of amyloid proteins in the myocardial extracellular matrix has been historically difficult to diagnose due to lack of specific clinical manifestations and necessity of biopsy to demonstrate amyloid deposition. However, advances in cardiovascular imaging techniques have facilitated earlier recognition of this disease. In addition, while once thought of as incurable, treatment strategies are emerging for cardiac amyloidosis, making early diagnosis essential. We outline the case of a 69 years old Indian male who was admitted with exertional breathlessness. On further imaging with Echocardiogram and abdominal fat pad biopsy, Cardiac amyloidosis was diagnosed. Our objective is to highlight the diagnostic evaluation and clinical implications of cardiac amyloidosis.

INTRODUCTION

With an increasingly ageing population and advances in cardiovascular imaging techniques, conditions that previously went undiagnosed and thought to be uncommon are being increasingly identified. Cardiac amyloidosis is one of such conditions. In addition, with broad research ongoing on various modalities of treatment, early diagnosis may be crucial to limiting further amyloid deposition and thus, alter the disease course. In this case report, we discuss a 69 years old male admitted with exertional breathlessness with subsequent workup confirming a diagnosis of cardiac amyloidosis. A review of the condition focusing on the diagnosis and treatment is also included.

Case Presentation

A 69 years old Indian male presented to the OPD with exertional shortness of breath with no associated chest pain. He was admitted for further evaluation and management. His medical history was notable for congestive heart failure which includes paroxysmal nocturnal dyspnea, orthopnea and exertional shortness of breath with bilateral pitting pedal edema. He had a recent history of heart failure first diagnosed few months back with echocardiogram (ECHO) demonstrating restrictive pattern. His pre admission medications included Enalapril 5mg twice a day, furosemide 20 mg twice a day, metoprolol succinate 25 mg daily. On initial physical examination, He had macroglossia[Figure 3]. He had a blood pressure of 110/80 mmHg with pulse rate of 75 beats per minute (bpm). His jugular venous pressure was elevated. He had Bilateral basal crackles and normal heart sounds with no murmurs or gallops on auscultation. His lower extremities had mild pitting edema bilaterally. Laboratory testing was significant for N-terminal pro b-type natriuretic peptide (NT-ProBNP) elevation at 5000 pg/mL (Normal < 125 pg/mL). Complete blood count and comprehensive metabolic panel were within normal limits except for anaemia of chronic disease. Serum protein electrophoresis obtained to evaluate for an underlying gammopathy (seen in light chain amyloidosis) demonstrated moderate hypoproteinemia and hypoalbuminemia with no monoclonal spike (M spike). The serum free kappa to lambda light chain ratio was within normal limits. Electrocardiogram (ECG) showed 1st degree AV Block while the chest radiograph demonstrated bilateral patchy opacities consistent with pulmonary congestion. 24 hour Holter monitoring was done and showed 1st degree AV Block and polymorphic couplets(isolated and couplets)(Figure 1). Transthoracic ECHO revealed a dilated right and left atria, severe concentric LVH, Sparkling appearance noted in LV Septum, No obvious regional wall motion abnormality, EF 54% and Grade III Diastolic dysfunction. Due to the sparkling appearance of LV Septum, cardiac amyloidosis was considered as a possible etiology of the cardiomyopathy. Cardiovascular magnetic resonance imaging (MRI) showed Hypertrophic cardiomyopathy due to myocardial infiltration, Biventricular hypertrophy suggestive of Cardiac Amyloidosis(Figure 2). An abdominal fat pad biopsy was also done which showed adipocytes surrounded by pink acellular material morphologically resembling amyloid. Special stains for Congo red highlights amyloid with apple green birefringence on polarisation, confirming extracellular amyloid deposition(Figure 4). He was treated with Diuretics, ACE inhibitors and other symptomatic therapy.

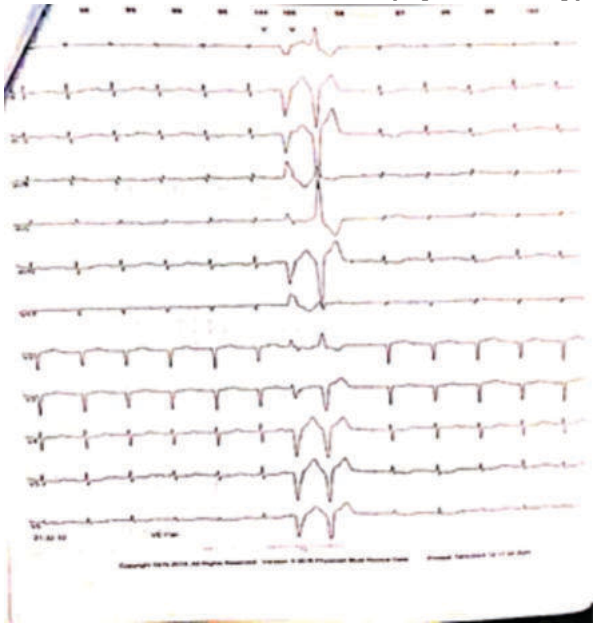

Figure 1: 24 Hour Holter Monitoring Report Showing Couplets.

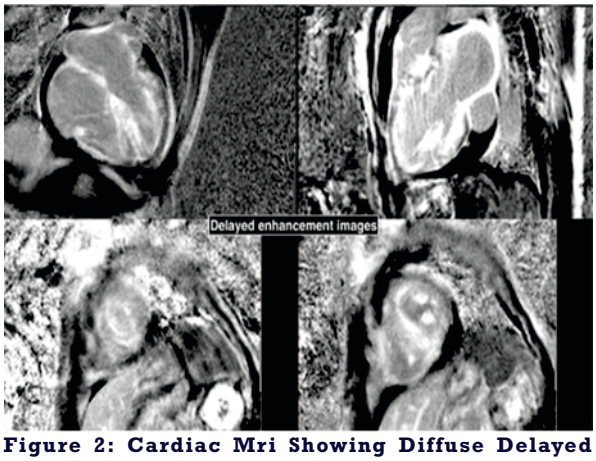

Figure 2: Cardiac Mri Showing Diffuse Delayed Enhancement, Thickened Myocardium Suggesting Cardiac Amyloidosis.

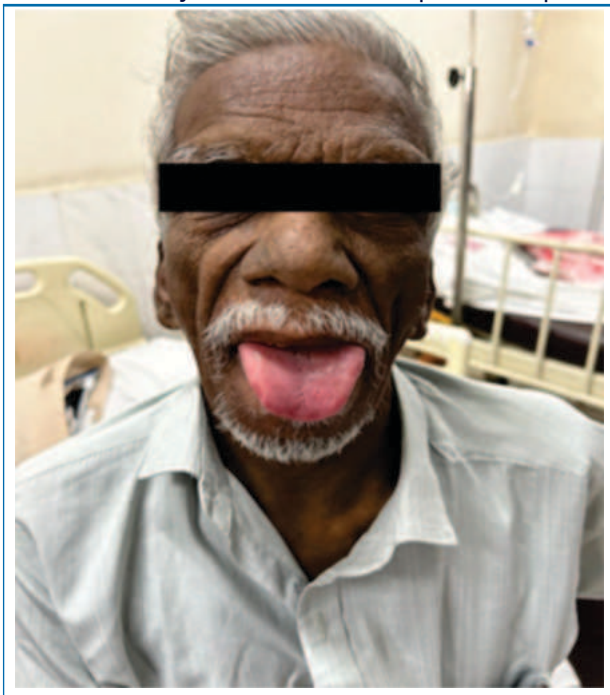

Figure 3: Patient Having Macroglossia.

Figure 4: HPE Of Abdominal Fat Pad Showing Apple Green Birefringence With Special Congo Red Staining.

Final Diagnosis
Cardiac Amyloidosis.

The main aim of treatment following diagnosis was optimizing his cardiac function and managing symptoms as there is no approved therapy for cardiac amyloidosis currently. Neurohormonal blocking agents were continued with titration of his diuretic depending on his volume status. In the future, he may be a good candidate for one of the amyloid specific therapies under investigation.

Outcome and Follow-up

He required regular clinic follow up since diagnosis. He has remained stable.

DISCUSSION

Amyloidosis is a systemic disorder characterized pathologically by the extracellular deposition of insoluble fibrils composed of misfolded proteins in various organs including the heart with resulting alteration in structure and function[1]. The amyloid fibrils are rigid, proteolytic resistant structures, typically less than 10 nanometers in diameter with a characteristic apple-green birefringence with Congo-red staining under polarized light microscopy[2].

Amyloidosis may be hereditary or acquired and the nature of the precursor protein of the fibrils forms the basis of classification[3]. More than 30 such precursor proteins have been identified and of these, 2 types are responsible for about 95% of cases of cardiac amyloidosis: Immunoglobulin light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR)[4].AL, although overall a rare condition, is the most frequently diagnosed form with about 0.3 cases per 100000 population in a large referral center[5]. AL occurs secondary to a plasma cell dyscrasia resulting in excessive production of immunoglobulin light chain units, with associated misfolding and deposition in extracellular tissue. In addition to cardiac manifestations, hepatic, renal and neurologic complications may be seen in AL. Early diagnosis and initiation of treatment in AL may alter disease outcome although mortality remains high[6].ATTR occurs due to the misfolding of the liver derived precursor protein transthyretin (TTR, previously called prealbumin). TTR has a tendency to dissociate into dimers and monomers and subsequently aggregate into insoluble fibrils[7,8]. Two variants of this form of amyloidosis have been described – the hereditary/mutant form caused by mutations in the TTR gene and the sporadic/wild type (systemic senile amyloidosis)[9]. Initial manifestations of wild type ATTR may include carpal tunnel syndrome (especially bilateral) and spinal stenosis and these may precede the cardiac complications by several years.The diffuse deposition of amyloid fibrils in the cardiac interstitial space produces significant thickening of both ventricles with associated stiffness which results in impaired diastolic relaxation and the characteristic restrictive physiology[2,9]. Fibril deposition within and/or around the smaller vessels of the heart with resulting narrowing may produce ischemia/infarction[10]. In addition, there is evidence pointing to the direct toxicity of the fibrils to the cardiac myocytes especially with AL[9,11]. The atria, valves and conduction system are also typically involved resulting in sequelae such as atrial fibrillation, valvular regurgitation and various degrees of heart block.The classic clinical presentation of cardiac amyloidosis is with symptoms of congestive heart failure including exertional dyspnea and orthopnea. Fatigue and weakness are also common, resulting from compromised CO. Symptoms of right ventricular failure including abdominal distension and lower extremity edema may be more prominent in certain patients[2,12].Coronary vessel involvement may manifest with angina while palpitations and syncope may be seen with the various conduction abnormalities associated with this condition, atrial fibrillation being the most commonly identified arrhythmia[[2,12]. A great variety of extra-cardiac symptoms/signs may be seen in amyloidosis including ecchymoses/petechiae, hepatomegaly, macroglossia, non-specific gastrointestinal symptoms such as diarrhea/weight loss and carpal tunnel syndrome (especially bilateral which is common in ATTR)[13,14].

Clinical Evaluation

Diagnosing cardiac amyloidosis requires a high index of suspicion due to its relatively low incidence. Typically, a combination of laboratory tests, ECG, cardiac imaging and histopathology is required.Plasma levels of the natriuretic peptides (BNP and NT-proBNP) tend to be high in cardiac amyloidosis irrespective of severity of heart failure. Work up for a monoclonal process to evaluate for AL is however always indicated when cardiac amyloidosis is suspected. The preferred test for this is the serum free light chain assay with immunofixation (as against the traditional serum and urine protein electrophoresis which are not sufficiently sensitive)[2]. An abnormal kappa to lambda ratio (< 0.26 or > 1.65) in combination with a M protein spike on immunofixation is highly suggestive of a monoclonal light chain process[2]. It is important to note that identifying an abnormal plasma cell clone alone is insufficient for diagnosis as a moderate increase in circulating light chains in not necessarily pathologic.The first clue which may prompt suspicion for cardiac amyloidosis is the ECG. The archetypal finding is low QRS voltages due to the electrically silent amyloid fibrils which are not detected by the ECG[2,12]. This is inconsistent with the degree of ventricular thickening seen on ECHO. ECG findings frequently encountered include atrial arrhythmias

such as atrial fibrillation, various degrees of atrioventricular block, interventricular conduction delays and bundle branch blocks.The ECHO findings in cardiac amyloidosis are nonspecific but highly suggestive in the right clinical context. The hallmark finding is symmetric biventricular wall thickening with a spectrum of diastolic abnormalities varying from abnormal relaxation to a restrictive filling pattern[2,9]. Cardiac MRI has taken on an increasingly important role in the screening and evaluation of cardiac amyloidosis. The typical finding is a transmural or subendocardial pattern of late gadolinium enhancement (LGE). Global involvement is more commonly encountered although a focal patchy pattern may be seen.

Nuclear scintigraphy with the use of bone seeking, phosphate-based radiotracers including ^{99m}Tc-PYP and ^{99m}Tc-DPD (technetium-3,3-diphosphono-1,2-pro- pano-dicarboxylic acid) has demonstrated excellent sensitivity and specificity in diagnosing cardiac amyloidosis and differentiating ATTR from AL.

There has been recent increased interest in the role of positron emission tomography/computerized tomography (PET/CT) in the imaging of cardiac amyloidosis. PET tracers, fluoride labelled radioisotopes including ^{18}F- florbetapir and ^{18}F-florbetapen, have been demonstrated to bind at sites of amyloid deposition irrespective of the nature of the precursor protein.

Despite these advances in cardiovascular imaging, histopathologic confirmation of amyloid deposits in tissue remains the gold standard. . Tissue may be obtained from extra-cardiac sites such as the abdominal fat pad and rectum by fine needle aspiration and apple green birefringence under polarized light microscopy after Congo-red staining is diagnostic.

Treatment

The treatment of cardiac amyloidosis is two pronged – treatment of symptoms arising from cardiac dysfunction and treatment of the underlying amyloidosis. The most commonly encountered manifestations of cardiac amyloidosis are congestive heart failure (CHF) and conduction system abnormalities. CHF in cardiac amyloidosis is most commonly diastolic in nature (heart failure with preserved ejection fraction) with systolic dysfunction occurring late in disease course. As a result, there is a distinct lack of therapies with demonstrated mortality benefit. The cornerstone of treatment remains restricting salt and fluids in addition to the judicious use of diuretics[2,12]. A combination of loop diuretics and aldosterone receptor antagonist appears to work best. Atrial fibrillation is the most common arrhythmia encountered[9] and usual rate controlling medications including beta blockers and calcium channel blockers are poorly tolerated due to their hypotensive side effects. There are 2 main approaches to treating the underlying amyloidosis – stopping further production of the precursor protein and reducing the burden of already deposited amyloid. In AL, therapy is directed towards the plasma cell clone with chemotherapy followed by autologous hematopoietic stem cell transplant (HSCT). The most commonly used chemotherapy regimen involves the use of bortezomib, dexamethasone and an alkylating agent – typically cyclophosphamide which has demonstrated benefit in lower risk patients[6]. A significant proportion of patients with AL have advanced cardiac disease at the time of diagnosis which limits their ability to receive high dose chemotherapy and HSCT.

With the liver being the primary site of TTR production, orthotropic liver transplantation (OLT) has been used as a curative strategy for the treatment of mutant ATTR. Although this brought about an improvement in neurologic symptoms, Dubrey et al noted a progression in ventricular thickening despite elimination of TTR production. This has been hypothesized to be due to the deposition of wild type TTR on the pre-existing focus of mutant $_{TTR}$.

In August 2018, the Food and Drug Administration (FDA) approved patisiran for the treatment of polyneuropathy associated with mutant ATTR after meeting the primary end point in the APOLLO clinical trial.

In a similar vein, the anti-sense oligonucleotide inotersen was approved by the FDA for the treatment of polyneuropathy associated with mutant ATTR in October 2018.

Diflunisal, a non-steroidal anti-inflammatory drug stabilizes the TTR molecule in a similar manner preventing amyloid fibrillogenesis.

The role of orthotropic heart transplantation (OHT) in the management of cardiac amyloidosis remains controversial due to concerns about recurrence of disease in transplanted hearts and long-term patient survival in an era with limited donors.

Prognosis

Despite advancements in the diagnosis and treatment of cardiac amyloidosis, the overall prognosis remains poor. In untreated patients, ATTR cardiac amyloidosis has a slowly progressive course and a better prognosis than AL cardiac amyloidosis. The Val122Ile mutation is associated with worse outcomes with a median survival from diagnosis of about 2 years In untreated AL cardiac amyloidosis, median survival is about 6 months from the onset of heart failure. In patients with early stage disease who undergo HSCT, reduced post-transplant mortality and improved survival has been demonstrated with 4 year overall survival of about 90%.

CONCLUSION

Cardiac amyloidosis remains a rare disease despite a recent uptick in diagnoses owing to increased physician suspicion and improved cardiovascular imaging techniques. With emerging therapies that have the potential to improve patient outcomes, early diagnosis has taken on an increasingly important role. This case report discusses the clinical evaluation of cardiac amyloidosis highlighting the utility of various laboratory tests and imaging modalities in arriving at a diagnosis.

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