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Letter to Editor

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Cardiac Amyloidosis

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Abstract
Cardiac amyloidosis is a rare and often underdiagnosed infiltrative cardiomyopathy characterized by the deposition of misfolded proteins, known as amyloids, within the heart tissue. Symptoms of cardiac amyloidosis often mimic other forms of heart failure and include restrictive cardiomyopathy, arrhythmias, and diastolic dysfunction. Diagnosis relies on a combination of echocardiography, cardiac MRI, nuclear imaging, and tissue biopsy, with the latter being the gold standard. Treatment strategies vary depending on the type of amyloidosis, ranging from chemotherapy and stem cell transplantation in AL amyloidosis to liver transplantation and novel pharmacologic agents in ATTR amyloidosis. Despite advancements in treatment, the prognosis remains variable, and early diagnosis is critical for improving outcomes. Further research into targeted therapies and early detection methods holds promise for better managing this complex disease. The condition is diagnosed with the use of an echocardiogram, a cardiac MRI, a nuclear imaging and a tissue biopsy. Chemotherapy, relapsed often chemotherapy and stem cell transplantation in systemic AL amyloidosis patients are quite common. In general, however, this aspect of the affairs here has not quite gained a normative public attention. Let's first conduct the most appropriate types of intervention as early as soon and treat these open-ended issues later.

Keywords: cardiac amyloidosis; nuclear imaging; cardiac MRI

Dear Editor

Cardiac amyloidosis constitutes a disease caused by the build-up of amyloid or abnormal protein deposits in the heart tissues [1]. Cardiac amyloidosis is among the cardiac infiltrative diseases with a bad outcome and is such that it necessitates exclusion of heart failure, with patients presenting with clinical symptoms. Such clinical outcomes depend on the degree of tissue injury and the nature of the amyloid protein. There are many types of amyloidosis: Primary or AL amyloidosis, Secondary or AA amyloidosis, Hereditary or ATTR amyloidosis, Dialysis ache amyloidosis, Senile systemic amyloidosis (SSA) [2]. Among these, the types most commonly causing cardiac involvement are AL, ATTR, and SSA while AA is infrequent in causing such over-involvement. Primary amyloidosis AL consists of monoclonal light chain amyloid proteins, which are usually associated with plasma cell disorder (exmultiple myeloma). Cardiac involvement is high and still it has the poorest prognosis from the type. Familial or genetic amyloidosis: The gene for transthyretin (TTR) is situated in the long arm of the chromosome 18. In the literature it has been described more than 120 morphs of TTR gene that all belong to the amyloidogenic subgroup. Usually as this disease has a late onset it usually manifests after the age of 30-40. Extracardiac manifestations of this type poly neuropathy, hepatomegaly, splenomegaly, carpal tunnel syndrome, epidural stenosis biceps tendon rupture, ocular infiltration. Senile systemic amyloidosis (SSA) which also is known as the wild type TTR is also a transport protein but it is produced in liver. This disease usually occurs in males above the age of seventy. Other lower extremity regions affected by the disease include the pancreas parenchyma the brain bilateral carpal tunnel syndrome and lumbar spinal stenosis the kidneys and lungs. Its progression is slower than that of AL. The disease is diagnosed through an endomyocardial biopsy noticing that the patient does not fall under AL nor ATTR. Often, there will be no symptoms related to the disease and the disorder will go unrecognized until late stages [3]. The degree of symptomatology is related to the organs involved. Relating to Cardiac amyloidosis, more symptoms are seen in right ventricular failure. A variety of tachycardia witnessed, syncope with all forms of exertion especially those of ischemia, myocardial infarction and postural htn. Apoptosis and fibrosis following the cytotoxic action of amyloid fibrils are part of the systolic dysfunction causing symptomatic heart failure with dyspnea and orthopnea on the patients. On examination, there

may be signs of raised jugular venous pressure, a right-sided S3 gallop, features suggestive of autonomic neuropathy, and in some cases of right heart failure, hepatomegaly and ascites. Bulging of the pupil or areas of the forehack or periorbital area with blood vessels are Extracardiac. If bilateral, activity in the carpal tunnel is more assignable to something like the SSA. Patients with Nephrotic syndrome or Hypoalbuminemia have this epic proportioned swelling of the legs that tends to get worse [4]. In laboratory evaluation, the free serum light chain assay measures the ratio of kappa to lambda light chains. The normal range for this ratio is 0.26 to 1.65 [5]. A kappa/lambda ratio greater than 1.65 indicates an excess of kappa light chains, which may suggest a monoclonal gammopathy, commonly associated with conditions like primary amyloidosis (AL). Conversely, a ratio below 0.26 may indicate an excess of lambda light chains. Elevated levels of BNP (B-type natriuretic peptide), proBNP (N-terminal proBNP), and troponin serve as predictors of significant cardiac injury before the onset of heart failure. In AL amyloidosis, a BNP level greater than 152 pg/mL is an indicator of an aggressive prognosis. These biomarkers are crucial in assessing the extent of cardiac damage and guiding treatment strategies. In electrocardiography, findings in cardiac amyloidosis may include:

- Low Voltage: Small voltage amplitudes (<5 mm) in the limb leads.
- Reduced Progression of the R Wave: A decrease in the progression of the R wave across the precordial leads, sometimes referred to as a pseudo infarct pattern.
- AV Block: Atrioventricular block, which can be partial or complete.
- Various Arrhythmias: Including atrial fibrillation and other arrhythmias.

These electrocardiographic abnormalities are indicative of the structural and functional changes in the heart due to amyloid deposits. In echocardiography, findings in cardiac amyloidosis include:

- Biatrial Dilatation: Enlargement of both the left and right atria.
- Increased Left Ventricular Wall and Valve Thickness and Echogenicity: Thickening and increased brightness of the left ventricular walls and valves.
- Increased Right Ventricular Wall Thickness: Thickening of the right ventricular walls.
- Speckled Myocardial Appearance: A granular or "speckled" appearance of the myocardium.
- Pleural and Pericardial Effusion: Fluid accumulation in the pleural and pericardial spaces.
- Restrictive Diastolic Pattern: Restricted filling of the heart during diastole.

A low ejection fraction associated with restrictive dysfunction is a negative prognostic indicator. In amyloidosis, left ventricular systolic function is typically preserved, but in advanced stages, right ventricular dysfunction may lead to right ventricular dilatation. Strain echocardiography often reveals impaired basal strain and preserved apical strain, with characteristic patterns such as "cherry" or "bull's-eye" patterns. Atypical symptoms of amyloidosis: In amyloidosis, ejection fraction is usually normal but sometimes a reduced ejection fraction may be seen [6]. In this group, despite normal epicardial coronary vessels, patients can present with angina due to systolic dysfunction, chronic myocardial ischemia, and small vessel damage. It would be indistinguishable clinically from hypertrophic cardiomyopathy, with features of septal hypertrophy and left ventricular outflow tract obstruction in a subset of patients, which might require myocardial biopsy for further differentiation. These conditions are quite difficult to distinguish from one another based solely on echocardiography; so, differentiation usually requires cardiac MRI with gadolinium contrast. Other examinations: CMR - Gadolinium accumulation occurs in amyloid tissue. Cardiac scintigraphy - although all ATTR is positive, it is not specific, it is also positive in some ALs. In nuclear imaging, specific radiotracers investigate amyloid deposits. Among these, PET is the most advanced technique compared with other forms of nuclear medicine imaging. It is possible that PET imaging could depict amyloid deposition in many tissues, including the heart, quite nicely, and conditions like cardiac amyloidosis could be effectively diagnosed. EMB with histopathology is the gold standard of diagnosis. Sensitivity of EMB to diagnose amyloidosis is 100%. The biopsy specimen obtained in EMB is usually from myocardial tissue; however, biopsy can also be obtained from other tissues such as abdominal fat, renal, rectal, and other affected organs. Amyloid fibrils show a characteristic apple-green birefringence when stained with Congo red dye under polarized light microscopy. Amyloidal arrhythmias in amyloidosis occur due to amyloid involvement of the

conduction system. These include bradyarrhythmia's, atrial arrhythmias (most commonly pacing arrhythmias), ventricular arrhythmias, AV block, syncope, and sudden cardiac death. Excitable arrhythmias occur in 10-20% of patients and increase the risk of thromboembolism [7]. There is a limitation in rhythm and pulse control in inducible arrhythmias due to the toxic effect of some drugs like B blockers, calcium channel blockers, digoxin. Amiodarone can be given but in judicious amounts only. Treatment of amyloidosis I Treatment of heart failure:

1. Loop diuretics, fluid and salt restriction [8].
2. ACE inhibitors, ARBs and Beta blockers are contraindicated, they worsen renal function and can cause postural hypotension.
3. Calcium channel blockers are not helpful and worsen left ventricular function.
4. Digoxin is not recommended due to high toxicity.
5. Oral anticoagulants should be used regardless of CHA2DS2-VASc-Score if there is concomitant arrhythmia.
6. Orthostatic Midodrine and compression stockings can be used in hypotension.

II Pacemaker and ICD Pacemakers are used in cases of symptomatic AV block to help regulate heart rhythm and improve cardiac function. In symptomatic cases, biventricular pacing may be utilized to address issues with both ventricles and improve overall cardiac output. The use of implantable cardioverter-defibrillators (ICDs) for prophylactic purposes in amyloidosis remains a subject of debate, as it does not always provide additional benefit in preventing sudden cardiac death compared to its risks and costs. The decision to implant an ICD is typically based on individual patient risk factors and the presence of specific indications, rather than as a routine preventative measure. III Heart Transplantation in AL amyloidosis, OHT is still controversial in view of the seeding of the transplanted heart and the progressive nature of the disease. However, age below 60 years without other plasma cell disorders and without significant damage to other major organs are considered as ideal indications for heart transplantation. Since they are less likely to suffer from complications related to amyloid deposition in the transplanted heart and their overall prognosis is better. AL specific treatment Chemotherapy and autologous stem cell transplantation form the cornerstone of treatment for AL amyloidosis, with the goal of reducing the production of light chains.

- Bortezomib: This protease inhibitor enhances early hematologic response when used alone or in combination with dexamethasone.
- Thalidomide: Although it improves response to treatment, it is associated with high toxicity.

Elevated levels of NT-proBNP (>8500 ng/mL) and low blood pressure (systolic <100 mmHg) are indicators of poor response to chemotherapy and high mortality risk. These markers help assess the severity of cardiac involvement and guide treatment decisions. ATTR specific treatment Since the 1990s, liver transplantation has been performed as a treatment for ATTR amyloidosis due to the synthesis of transthyretin (TTR) proteins in the liver. Combined liver and heart transplantation has shown favorable outcomes in selected patients. Additionally, pharmacological agents such as TAFAMIDIS are used in the treatment of ATTR amyloidosis. Tafamidis stabilizes the transthyretin protein, preventing it from misfolding and forming amyloid deposits, thereby helping to manage the disease and improve patient outcomes. SSA treatment Symptomatic treatment of heart failure in ATTR amyloidosis is ongoing. Future use of pharmacological agents like tafamidis and diflunisal is being explored, as they are in the research and development stage. Tafamidis, already in use, stabilizes the transthyretin protein to prevent amyloid formation, while diflunisal, a nonsteroidal anti-inflammatory drug, is being investigated for its potential to stabilize TTR and improve patient outcomes.

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