CLINICAL VIGNETTE

A Case of Amyloid Cardiomyopathy

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A 65-year-old male presented with episodes of chest pain and shortness of breath. He had a long history of medical non-compliance with smoking, obesity and hypertension. Myocardial perfusion test showed nonspecific apical changes more apparent at rest, suggestive of prior injury versus artifact. His left ventricular chamber size appeared enlarged with hypertrophied muscle mass. Initial prior echocardiogram showed left atrial enlargement with moderately increased ventricular wall thickness. This progressed to severely increased left ventricular wall thickness and severe bi-atrial enlargement on repeat echocardiogram a few years later. He still had preserved ejection fraction of 65 to 70%, with no evidence of pulmonary hypertension.

As his shortness of breath worsened, chest CT scan demonstrated persistent enlargement of the main pulmonary artery with pleural effusion. Abdominal ultrasound showed hepatosplenomegaly.

With suspicion of infiltrative heart disease, cardiology ordered studies for restrictive cardiomyopathy. Kappa/Lambda ratio was abnormal, and Hematology recommended obtaining tissue for possible amyloid infiltration. Abdominal fat pad biopsy showed only benign fibrofatty tissue. Endomyocardial biopsy and cardiac catheterization confirmed left ventricular hypertrophy, normal right heart and pulmonary capillary wedge pressures. Biopsies of septal wall supported the diagnosis of amyloidosis and indicated AL (lambda)-type amyloid deposition. Bone marrow biopsy was compatible with plasma cell myeloma. Flow cytometry demonstrated monotypic lambda restricted plasma cells, in addition to evidence of amyloid deposit by Congo red stain. He was started on chemotherapy with CyBorD Regimen. Disease progression coupled with medication non-compliance and delayed treatments led to worsened cardiomyopathy, heart failure and atrial flutter with left atrial thrombus and he was started on anticoagulation. Renal involvement progressed to end stage renal disease dependent on dialysis.

He developed hepatomegaly with elevated liver enzymes, which worsened to acute liver failure likely due to ischemic hepatic insult with occasional low blood pressures.

With further deterioration treatment was directed at comfort and he died less than two years after his diagnosis of AL cardiac Amyloidosis.

Introduction

Amyloidosis is caused by the deposition of one of over 30 different precursor proteins which fold abnormally into a beta pleated sheet configuration. The unstable tertiary structure of these proteins cause them to aggregate and deposit as insoluble amyloid fibrils in the extracellular space of different organs including the heart.[1]

Amyloidosis is classified based on the precursor protein type. Amyloid deposits stained with Congo red dye show an apple-green birefringence, while they display a cross-beta-pleated sheet configuration under electron microscopy.

More than 95% of all clinical cardiac amyloidosis cases are attributed to transthyretin amyloidosis (ATTR) or light chain amyloidosis (AL).[2-4] ATTR is caused by deposition of dissociated monomers and oligomers of TTR as amyloid fibrils. Transthyretin (TTR), previously known as prealbumin is synthesized in the liver, circulates as a stable tetramer which transports thyroid hormone and vitamin A. “Wild type ATTR” is an under-diagnosed cause of heart failure, found in about 13% of the patients who present with heart failure with preserved ejection fraction.[5]

Primary systemic amyloidosis (AL) is due to immunoglobulin light chain deposits related to a plasma cell dyscrasia. This type of amyloidosis is rare, with incidence of about 1 per 100,000 representing about 2500-5000 new cases per year in the United States.[6]

Other rare causes of amyloid cardiomyopathy are serum amyloid A amyloidosis (AA) and apolipoprotein A-1 (ApoA-1) amyloidosis which are not discussed.

Clinical Manifestation

Age of onset of amyloidosis symptoms varies based on the type of amyloid deposit.[6] AL (light chain) cardiac amyloidosis usually has an age of onset of above 40, compared to ATTR cardiac amyloidosis which usually presents at above 60-year-old patients. Systemic AL amyloidosis can involve the liver, kidneys, spleen, autonomic and peripheral nervous system, lungs and heart. Fatigue, carpal tunnel syndrome, GI bleed, macroglossia, periorbital purpura and bleeding diathesis are some manifestations.

Majority of AL amyloidosis patients (50-70%) have cardiac infiltration which determines their prognosis.[7,8] Cardiac

amyloidosis usually presents with restrictive cardiomyopathy with right ventricular failure symptoms, including lower extremity edema, elevated JVP, hepatic congestion, ascites and dyspnea. As the disease progresses, low cardiac output symptoms develop.

The worse outcome of amyloidosis caused by AL (light chains) compared to ATTR patients may be attributed to the toxicity of light chains to the myocardial cells.[9,10] Bradyarrhythmia and advanced atrioventricular block are most common causes of syncope in amyloidosis patients. Progressive conduction system disease needing pacemaker implantation is more common in ATTR cases. High degree atrioventricular block or symptomatic sinus node dysfunction is not as prevalent in AL amyloidosis.[11]

The risk of cardiac thromboembolism is increased in AL amyloidosis with atrial fibrillation. amyloid deposition in atrial and ventricular walls contributes to electromechanical dissociation during sinus rhythm which increases the risk of atrial thrombus formation.[12,13]

Restrictive cardiomyopathy associated with ATTR can lead to low gradient, low flow aortic stenosis.[14] Some non-cardiac manifestations of wild type ATTR are spinal stenosis, biceps tendon rupture, and bilateral carpal tunnel syndrome with amyloid deposits found with decompression procedures.[15]

Diagnosis

Initial tests can reveal proteinuria and renal failure, elevated liver enzymes with congestive hepatopathy, elevated natriuretic peptide and troponin levels. Cardiac enzymes are usually mildly elevated in ATTR compared to higher levels in AL amyloidosis which is likely secondary to light chains cardiotoxicity. Common EKG findings are increased left ventricular wall thickness and reduced QRS voltage, the latter seen most in AL amyloidosis compared to ATTR cases.[16,17]

About 30 percent of patients with wild type ATTR, have left ventricular hypertrophy or left bundle branch block with pseudo-infarction patterns seen in 70 percent of the cases in addition to conduction abnormalities. About 15 percent of patients also have atrial fibrillation. Cardiac amyloidosis should be suspected when unexplained LVH is noted on echocardiogram, low gradient/low flow aortic stenosis and heart failure.[14,18]

Early impaired ventricular relaxation leads to diastolic dysfunction with progression to restrictive physiology.[19] Marked elevation in LV diastolic pressure can cause pulmonary hypertension. In AL amyloidosis, small pericardial and pleural effusions may also be present.

After physical exam, echocardiograms are initially ordered in suspected cases with reduced global longitudinal strain as an early marker with high sensitivity and specificity.[20] Left ventricular hypertrophy is usually non-dilated with small ventricles. Thickening of the valves and interatrial septum, speckled myocardium and bi-atrial dilatation are common. Symmetric LVH is seen more in AL amyloidosis versus asymmetry with predominant septal hypertrophy being more common in ATTR. Cardiovascular magnetic resonance imaging (CMR) can detect cardiac abnormalities prior to LVH development. It can assess cardiac structure, function and tissue characteristics, but cannot distinguish cardiac AL from ATTR.[21,22]

Inconsistent results usually make diagnosis of cardiac amyloidosis unlikely, other cause of LVH including hypertrophic cardiomyopathy, hypertension or other etiologies should be considered if the above tests are not conclusive.[23]

If the CMR results are consistent with possible diagnosis, serum kappa/lambda free light chain ratio analysis, serum protein immunofixation and urine protein immunofixation should be obtained to identify monoclonal proteins and bone marrow biopsy and evaluation for treatment options. Tissue biopsy from fat pad or other organs may be indicated for both diagnostic and typing purposes. In majority of the case, noncardiac tissue biopsy in addition to CMR findings is sufficient.[24] Typical apple-green birefringence with Congo red dye under polarized light microscopy and cross-beta-pleated sheets under electron microscopy are the diagnostic characteristics of extracellular amyloid deposits. Although immunohistochemistry, immunofluorescence and immunoelectron microscopy are used to determine the type of amyloid fibril, laser microdissection with mass spectrometry is considered the gold standard.[25]

If monoclonal proteins are not detected in above tests, a bone tracer cardiac scintigraphy scan can be performed for cardiac uptake evaluation and grading. Grade zero suggests that cardiac amyloidosis is unlikely and other causes of LVH should be considered. Grade 1 suggests additional tests including endomyocardial biopsy for confirmation. Grade 2 or 3, in addition to lack of evidence of plasma cell dyscrasia, is highly specific for ATTR cardiac disease and in these cases tissue biopsy is not needed.[26]

Treatment

The two approaches in treating patients with amyloidosis are management of heart failure and treatment of the underlying disease. Heart failure treatment is more responsive in wild type ATTR compared to AL amyloidosis in which control of the plasma cell dyscrasia leads to rapid decrease in serum biomarkers of heart failure.[27]

In amyloidosis heart failure, treatment with loop diuretics is commonly used in addition to aldosterone therapy. The treatment options in these patients differs from other types of heart failure due to potential hypotension side effects of beta blockers, ACE inhibitors and calcium channel blockers. Amyloid fibrils can also bind to digoxin which can increase its toxicity. However, if atrial fibrillation is present, low dose beta

blockade and digoxin can be used cautiously to assist with rate control and symptom management. Amiodarone seems to be well tolerated in these patients as well.[28] Anticoagulation is used to decrease the increased risk of intraatrial thrombus, regardless of their CHADS2 or CHADS2VA2SC score. It is even suggested in patients with normal sinus rhythm due to associated atrial thrombus in AL type group.[29,30]

Since sudden cardiac death is common in cardiac AL amyloidosis patients and prophylactic implantable cardioverter-defibrillators (ICDs) have been suggested despite its unclear role in electromechanical dissociation.[31]

Heart transplant is not usually recommended for these patients as most of them have significant extracardiac amyloid associated disease. Heart transplant would not treat the underlying plasma cell dyscrasia which leads to its progression and involvement the transplanted heart.[32-34]

Prognosis of AL amyloidosis patients depends on the degree of their multiple organ involvement. Routine therapy for underlying plasma cell clones include chemotherapy and/or autologous stem cell transplant, with the goal of 90 percent reduction in serum free light chains. NYHA functional class III or IV Heart failure is considered a contraindication for autologous stem cell transplant.[35]

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