CLINICAL VIGNETTE

Diagnosis of Cardiac Amyloidosis in the Geriatric Patient

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Case Report

An 86-year-old male with a history of mild left ventricular hypertrophy (LVH) and grade 1 diastolic dysfunction presented with new onset dyspnea on exertion and bilateral lower extremity edema of one week duration. He was seen in urgent care a few days prior and ultrasound of the lower extremities was negative for deep venous thrombosis. Previously he was walking 1-2 miles per day without symptoms. He denied orthopnea or chest pain. His past medical and surgical history also included hyperlipidemia, prediabetes, sleep apnea, chronic left ankle edema and bilateral carpal tunnel release surgeries. His relevant medications were aspirin, lisinopril and atorvastatin. Family history was negative for cardiac infiltrative disease. He was a never smoker and had rare alcohol use. On exam his vital signs were normal and heart was regular rate and rhythm without murmurs, rubs or gallops. Lungs were clear and JVP was estimated to be 10 cm H_20. He had 1-2+ left lower extremity edema, and 2-3+ right lower extremity edema with normal pedal pulses. Routine lab work was ordered in addition to echocardiogram and he was empirically initiated on furosemide 20mg daily for new onset heart failure. Routine laboratory data returned normal except for an elevated BNP 339pg/mL. Echocardiogram showed moderate concentric LVH, increased LV myocardial wall texture (for which an infiltrative disease cannot be excluded), left ventricular ejection fraction (LVEF) 55-60%, grade 3 diastolic dysfunction, dilated left and right atrial size, and mild pulmonary hypertension. The patient was diagnosed with heart failure with a preserved ejection fraction (HFpEF) and a cardiac MRI was recommended to evaluate LVH and rule out amyloidosis. Cardiac MRI showed biventricular hypertrophy, biatrial enlargement, normal chamber size, EF 56%, and delayed enhancement pattern of scar/fibrosis (most prominent in the free wall and basal segments), most consistent with an infiltrative cardiomyopathy. Normal ferritin level excluded the possibility of iron overload as an etiology for the patients' cardiomyopathy.

Discussion

Cardiac amyloidosis, also called "stiff heart syndrome," is the most common form of restrictive cardiomyopathy in adults older than age 65.[1] Due to its illusory presentation and complicated diagnostic criteria, patients may see multiple providers for months to years before getting an accurate diagnosis.[1]

Cardiac amyloidosis is usually due to one of two main proteins - *a*myloid *l*ight-chain (AL) and amyloid transthyretin (ATTR). AL amyloidosis, formerly called primary systemic amyloidosis, is a plasma cell disorder in which there is an overproduction of immunoglobulin light-chains by plasma cells in the bone marrow. AL amyloidosis is the most common type of amyloidosis involving the heart with about 3000 new cases each year in the United States.[1,2] Transthyretin amyloidosis (ATTR) is caused by transthyretin (TTR), a protein produced in the liver that transports thyroxine and retinol. TTR is further divided into two subtypes - mutant transthyretin or wild-type transthyretin. In mutant transthyretin amyloidosis (ATTRm), also called hereditary or familial amyloidosis, a mutation in the transthyretin gene results in the formation of amyloid fibrils. In the United States, the most common mutation (Val122Ile) is seen in 3-3.5% of African-Americans.[1,3] In other countries, demographics differ. ATTRm usually causes cardiomyopathy and polyneuropathy or both.[2] In wild-type transthyretin amyloidosis (ATTRwt), also called age-related or "senile" amyloidosis, there is no mutation but, for unclear reasons, the protein becomes misfolded and causes amyloid deposits in the heart. ATTRwt has been increasingly recognized as an important and often underdiagnosed cause of heart failure and arrhythmia in the elderly, particularly in men over age 60.[3-5] Recent data suggest that a significant proportion of HFpEF in the elderly may be due to ATTRwt - with 25 to 30% of patients with HFpEF older than 75 years having evidence of ATTRwt on autopsy.[6] ATTRwt is a diagnosis of exclusion after AL and ATTRm amyloidoses are ruled out.

In cardiac amyloidosis, the myocardium is more affected than other parts of the heart. The ventricles become stiffer and thicker, leading to restrictive ventricular filling, elevated filling pressures, biatrial dilatation, and eventually diastolic dysfunction and congestive heart failure (CHF).[1] Myocardial wall thickness is not due to an increase in number of cardiac cells but rather from extracellular amyloid deposits forming in between the heart cells. Other parts of the heart can be affected leading to pericardial effusion, valvular dysfunction, ischemia, and conduction system abnormalities such as arrhythmias and heart block.[4] High-grade infiltration (>50%) of myocardium is most common in the AL variety, and 90% of cases have vascular involvement.[1] Epicardial vessels are typically spared but microvascular involvement is common, resulting in tissue ischemia and infarction. Dilated atria, a feature of restrictive cardiomyopathy, and progressive atrial enlargement can result in atrial arrhythmias, secondary atrioventricular regurgitation

and poor atrial contractility with subsequent thromboembolic complications.[1]

The clinical manifestations of cardiac amyloidosis include shortness of breath, fatigue, edema, and decreased exercise tolerance. Overt heart failure findings are predominantly right sided. Other cardiac manifestations can include chest pain (infrequent), palpitations, atrial fibrillation, conduction disease, mitral and tricuspid regurgitation, syncope and stroke (from cardiac embolus). There is a higher prevalence of conduction disease in ATTR including atrial fibrillation and heart block.[1,7,8] Atrial fibrillation is the most common type of arrhythmia (10-20%) in cardiac amyloidosis[7] due to left atrial distention in the setting of high filling pressures.[6] Patients may also have extracardiac manifestations. Peripheral nerves can be affected and autonomic fiber involvement can result in dysautonomia.[6] Aside from CHF, the presence of neuropathy, proteinuria (in nephrotic range), hepatomegaly, periorbital bleeding and macroglossia are diagnostic clues for AL amyloidosis.[1,2,7] While carpal tunnel syndrome occurs in less than 10% in AL amyloidosis, it occurs in about 35% of patients with ATTR amyloid.[1] Carpal tunnel syndrome (almost always bilateral) and spinal stenosis are present in about 50% of patients diagnosed with ATTRwt.[2]

In AL amyloidosis, any organ can be involved but it is rare to have involvement of all the organs. Mostly the heart or kidneys or both (70%) are affected.[4,7] AL amyloidosis may develop in patients with multiple myeloma (10-15%) or in those with monoclonal gammopathy of undetermined significance (MGUS) (9%).[1] These direct toxic effects of circulating free light-chains may account for discrepant findings in patients with severe cardiac symptoms but minimal or mild myocardial thickening.[1] AL amyloidosis is rare in people younger than 40 years old and, in advanced cases, has a median survival of less than 1 year.[7] Macroglossia and periorbital purpura are rare (<10%) but are hallmarks of the disease.[1]

Workup of cardiac amyloidosis should include the following laboratory data: brain natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP), troponin, serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) with immunofixation (IFE), serum free light-chain (FLC) assay, creatinine, liver function tests, and urinalysis. If clinically indicated, genetic testing of transthyretin gene can be obtained. Due to ongoing gradual destruction of cardiomyocytes, troponin can be chronically positive at low levels (0.1-1ng/mL).[2,3] SPEP and UPEP are inadequate screening tests for light-chains due to their low sensitivities and therefore IFE and serum FLC should be obtained in addition.[1,2] Serum FLC is a quantitative test that can detect light-chains with higher sensitivity. Serum FLC will be elevated in 95-100% of patients with AL amyloidosis[1] and can be used to monitor disease response to chemotherapy.[3]

Additional workup of cardiac amyloidosis should include EKG, echocardiogram and cardiac MRI. On EKG, there is often an inappropriately low QRS voltage in the limb leads (<5mV). The degree of low voltage (QRS complexes) and hypertrophy can be variable depending on clinical presentation and absence of a low QRS voltage does not rule out cardiac amyloidosis.[1,2,7] Low voltage on EKG is more common in AL amyloidosis (seen in about 45% of AL amyloidosis) than in ATTR. This is thought to be due to circulating light-chains having direct myocardial toxic effects independent of the degree of amyloid infiltration.[7] A "pseudoinfarct" pattern is seen in about 45% of AL amyloidosis. This includes features of an infarct on EKG but absence of wall motion abnormalities on echocardiogram.[1] On echocardiogram, there will be diastolic dysfunction, increased wall thickness of the left and right ventricles, normal or slightly reduced LV cavity size and marked atrial enlargement.[1,7] Systolic function is typically normal until late stages of the disease.[1,2] Normal or grade I diastolic dysfunction is rare in AL amyloidosis;[7] diastolic dysfunction grades 2-4 is usually present.[7] Strain imaging on echocardiogram can be used to assess how cardiac muscles shorten and contract. In cardiac amyloidosis, a "bull's eye" pattern can be seen on strain echocardiography (due to a significant decrease in LV longitudinal strain in mid and basal wall regions with preserved strain in the apex). In addition, a “granular sparkling” appearance can be seen in the LV myocardium on echocardiogram.[7]

Cardiac MRI findings in amyloidosis include a delayed gadolinium enhancement diffusely in the subendocardium, indicating inflammation or fibrosis.[1] This global delayed gadolinium enhancement is characteristic of cardiac amyloidosis and is not seen in other causes of LVH or restrictive cardiomyopathy.[7] While cardiac MRI has a sensitivity of 88% and specificity of 95%,[7] it does not distinguish amyloid type and cannot be used in patients who have renal dysfunction or presence of a pacemaker or defibrillator.[7] T1 mapping, however, does not require contrast[2] and can be used to quantify myocardial fibrosis; T1 mapping may be more sensitive than gadolinium for detecting early amyloid deposits and can help in the diagnosis if imaging findings are equivocal.[1] Nuclear scintigraphy (Technetium pyrophosphate (PYP) scan) is another imaging option for evaluation of cardiac amyloidosis. In the absence of plasma cell dyscrasias, a strongly positive nuclear scan can establish a diagnosis of ATTR without tissue biopsy.[1,7] If a monoclonal protein is present, tissue confirmation of amyloid type is important because nuclear scintigraphy can be mildly positive in AL amyloidosis.[7]

Endomyocardial biopsy provides the definitive diagnosis for cardiac amyloidosis but is invasive.[4] The sensitivity for endomyocardial biopsy is 100%.[1] Abdominal fat pad biopsy can also be done but has lower sensitivity;[3,5] positive in about 75% of cardiac amyloidosis and is a relatively simple procedure with low morbidity.[4] However, even if an abdominal fat pad biopsy returns positive, the amyloid deposits are usually few and inadequate for subtyping.[3,4] A negative biopsy does not rule out amyloidosis,[2,4] since the distribution of amyloid deposition could be nodular and patchy instead of diffuse and pericellular.[4] Biopsies of affected organs, including bone marrow, kidneys, heart have higher sensitivity and allows for adequate tissue for subtyping.[3] In ATTR, protein typing is important for guiding clinical trial options and predicting sites of organ involvement.[3]

For amyloid protein typing, mass spectrometry is the gold standard and more reliable than immunohistochemistry.[1,2,7]

With regard to the patient, SPEP showed 0.2 g/dL monoclonal protein and serum IFE showed IgA kappa reactivity. UPEP and urine IFE were initially negative but returned positive five months later. Kappa FLC was 19, lambda FLC was 3.1, and K/L ratio was increased at 3.1. Subsequent bone marrow biopsy revealed 15% plasma cells and he completed two cycles of dexamethasone and bortezomib. After an abdominal fat pad biopsy returned negative for amyloid deposition (based on Congo red and sulfated alcian blue stains), he underwent endomyocardial biopsy which confirmed his final diagnosis of ATTRwt cardiac amyloidosis and therefore bortezomib and dexamethasone were discontinued. Recently, (about two years from his initial CHF presentation), he developed complete heart block and underwent dual chamber permanent pacemaker placement. Interestingly, his carpal tunnel release surgeries preceded his biopsy proven diagnosis of ATTRwt by nine years. In ATTRwt, carpal tunnel syndrome may precede the cardiac manifestations by 10-15 years.[4]

Conclusion

Cardiac amyloidosis should be in the differential diagnosis of HFpEF (diastolic dysfunction grades 2-4), especially in setting of unexplained heart failure with LVH, nondilated LV,[9] and inappropriately low EKG voltages.[3] Due to its elusive nature, cardiac amyloidosis is often diagnosed in advanced stages of the disease, or can be missed entirely. Earlier recognition of cardiac amyloidosis and treatment can minimize irreversible changes, decrease mortality, and improve overall survival.[5,7,8,10] While providers must have a high index of suspicion, a thorough initial evaluation will include non-invasive testing with lab work evaluation for excess light chains, EKG, and echocardiogram as well as consideration for cardiac MRI. Definitive diagnosis requires endomyocardial biopsy. The presence of serum light chains does not necessarily imply a diagnosis of AL amyloidosis since ATTR can occur concomitantly with MGUS or multiple myeloma,[1] as we have seen with this patient.

Table: Cardiac Amyloidosis

Type & Source	Demographics	Organ Involvement	LVH	Therapy
AL (formerly "primary") (bone marrow)	M>F Age 40-80	Any (heart, kidneys, GI, tongue, nerves, liver, soft tissue) * Mostly heart and kidneys are involved	+	Chemotherapy and/or Autologous Stem-cell transplant
Mutant ATTR (Hereditary / Familial) (liver)	M>> F Age 55-75	Heart & nerves (& carpal tunnel)	+++	Supportive & Clinical Trials Liver transplant in select cases
Wild-Type ATTR (age-related or senile) (liver)	M>>>F Age 65-95	Isolated Heart (& carpal tunnel)	+++	Supportive & Clinical Trials

Adapted from Witteles. American College of Cardiology, 2016; Grogan et al. Heart 2017; Pereira et al. JACC, 2018.

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