CLINICAL VIGNETTE

An Atypical Presentation of Cardiac Amyloidosis

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A 55-year-old male with past medical history of diabetes type II, Gout, hypertension, and obstructive sleep apnea on CPAP, presents with sudden onset chest pain. He describes it as chest tightness that radiates to his jaw, and rated at 8/10. Symptoms last about 30 seconds. Pain is aggravated by exertion and improved with rest. He also notes shortness of breath associated with chest pain. He can walk about 50 feet before getting out of breath. He also has bilateral leg swelling for the past few weeks and has been wearing compression hose without improvement. He denies palpitations, orthopnea, presyncope or syncope.

Current medications include allopurinol 300 mg daily and metformin 500 mg twice daily. He is a truck driver with a sedentary lifestyle and smokes cigars a few times a week for 15 years.

On exam his vital signs were unremarkable. He was obese with no elevated JVD or carotid bruits, heart rate was regular, with normal S1S2 and no murmurs, rubs or gallops. Respiratory exam was clear to auscultation, without crackles or wheezes. He had trace bilateral non pitting edema to his shin.

After further evaluation in the emergency department (ED) he was diagnosed with non-ST elevation myocardial infarction (NSTEMI) based on troponin elevation as well as acute on chronic heart failure with preserved ejection fraction. Troponin initially measured 0.05 ng/mL (N=0 – 0.4 ng/mL) and increased to 0.1 ng/ml. B-type natriuretic peptide (BNP) 581 pg/mL (N= <100 pg/mL) and ProBNP was 2,346 pg/mL electrocardiogram (EKG) was notable for old inferior Q waves. The rest of the labs including complete blood count, comprehensive metabolic panel, thyroid function test, and TSH were normal. HgA1c was 6.1%. Our patient underwent a left heart cath which was significant for non-obstructive coronaries and evidence of pulmonary hypertension. Transthoracic echo showed moderate to severe left ventricular hypertrophy and grade 3 diastolic dysfunction. Computed tomography (CT) pulmonary angiogram was negative for pulmonary emboli. Cardiac magnetic resonance imaging (MRI) was consistent with amyloidosis.

Nuclear CARD Myocardial PYP 9 Pyrophosphate Amyloid scan was equivocal for TTR- transthyretin amyloidosis. The quantitative portion was negative for TTR, however quality analysis was suspicious/suggestive of TTR amyloidosis. Due to this discrepancy endomyocardial biopsy was performed and was consistent with AL amyloidosis. UPEP/serum protein electrophoresis (SPEP)/immunofixation was suspicious for a bone marrow disorder /AL amyloidosis. Lambda LC - 1212 with kappa - 6 (L/K ratio >100). S-M spike - 1.41g/dL (IgAL) Beta-2-microglobulin (B2M)=4.57 mg/L, Lactate Dehydrogenase (LDH)=429 U/L.

He was diagnosed with AL amyloidosis and also met new SLIM criteria (sixty percent or more plasma cells in bone marrow, serum-free light chain ratio >100 and more than one focal bone lesion on MRI) for multiple myeloma with L/K ratio being >100. Immunochemistry stain was positive for lambda light chain. He also had mild renal involvement with proteinuria. Bone survey did not show any destructive/erosive lesions. Bone marrow biopsy findings were consistent with amyloid with 80% plasma cells. R-ISS=stage 2 MM, ISS Stage 2. Urgent treatment was started to prevent further cardiac deposition. He started DaraVCD (daratumumab, velcade, cyclophosphamide and dexamethasone) and responded well. After one month, lambda decreased to <200 and to < 26 after two-month treatment.

Discussion

Amyloidosis is the pathologic condition resulting from tissue accumulation of insoluble aggregates of misfolded protein. This is known as cardiac amyloidosis when it involves the myocardium. Although not a common cause of heart failure, cardiac amyloidosis is often overlooked in the differential diagnosis of diastolic heart failure. Our patient was initially felt to have NSTEMI and after further evaluation was diagnosed with cardiac amyloidosis.

There are 2 main types of amyloidosis: AL amyloidosis (light chain) and ATTR (transthyretin) amyloidosis. AL type has nonspecific symptoms including poor appetite, early safety, weight loss, and fatigue. It is often associated with kidney disease, peripheral neuropathy, carpal tunnel syndrome, gastrointestinal involvement, macroglossia and bleeding diathesis. ATTR amyloidosis can develop autonomic or peripheral nerve disease. Spinal stenosis and biceps tendon rupture are common in patients with ATTR amyloidosis.

Initial identification of cardiac amyloidosis is based on history, labs, and EKG. Lab abnormalities include: proteinuria with or without BUN (blood urea nitrogen) and creatinine elevation, elevated bilirubin and/or elevated LFTs (liver function tests) may be present with liver involvement. Elevated troponin and natriuretic peptides are seen in patients with cardiac amyloidosis as in this case.

For suspected cardiac amyloidosis, echocardiograms are the initial cardiac imaging. Echocardiograms are generally non-specific, but may include findings that are pathognomonic for cardiac amyloidosis. Relative apical sparing of longitudinal strain is highly suggestive, with appropriate clinical presentation.[1] Echo may note ventricular wall infiltration with hypertrophy frequently biventricular with no dilation. Common findings include thickening of the valves and the interatrial septum along with atrial dilation. There are echocardiogram differences for AL and ATTR type of amyloidosis. ATTR amyloidosis has an increase in left ventricular (LV) and right ventricular (RV) mass and more systolic dysfunction. Left ventricular hypertrophy (LVH) is symmetric in AL and asymmetric with septal hypertrophy in ATTR type.[2] Despite some differences on echo there is notable similarity and echo is not routinely used to differentiate the two types.[3]

Other imaging modalities including cardiovascular magnetic resonance (CMR) with contrast. CMR is able to detect early cardiac amyloidosis before the development of LVH. It is unable to distinguish between cardiac AL vs ATTR amyloidosis. CMR with late gadolinium enhancement (LGE) has distinctive findings, initially with diffuse subendocardial LGE. As the disease progresses there may be transmural myocardial LGE pattern.[4]

Other tests used are bone tracer cardiac scintigraphy and monoclonal protein. Presence of monoclonal protein with echo combined with CMR findings of cardiac amyloidosis is highly suggestive of amyloidosis. Tissue biopsy is done in certain clinical scenarios but not always required, however, can differentiate the type of amyloidosis. In this patient the diagnosis was questionable. Generally, if AL amyloidosis is suspected, bone marrow biopsy and endomyocardial biopsy are done. On microscopic exam, tissue with amyloid infiltration shows amorphous hyaline deposits in extracellular space. Apple-green birefringence with Congo red under polarized light microscopy is pathognomonic.

Differential diagnoses to consider in the setting of LVH include hypertrophic cardiomyopathy, hypertension associated LVH, heart failure with preserved ejection fraction and Anderson Fabry disease. Cardiac amyloidosis is generally associated with heart failure with preserved ejection fraction (HFpEF) and systolic dysfunction generally occurs in the later stages of the disease process.

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