Functional Role of Amyloidosis in the Pathophysiology of Heart Failure with Preserved Ejection Fraction and Cardiorenal Syndrome

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Abstract
We present our experience of an elderly male patient with unexplained rapidly progressive left ventricular hypertrophy that resulted in clinically significant heart failure with preserved ejection fraction (HFpEF). During repeated hospitalizations, his condition progressed to a state of refractory low output cardiac failure and diuretic resistant end-stage cardiorenal syndrome that eventually lead to his demise. Cardiac amyloidosis, a diagnosis frequently overlooked, is an important cause of severe HFpEF in the elderly population. The disease often presents with subtle clinical findings that mimic hypertensive heart disease and can present with acute cardiorenal syndrome, as was the case in our patient. This report reviews the functional role of cardiac amyloidosis in the pathophysiology of rapidly progressive HFpEF and cardiorenal syndrome. In addition, we also illustrate the diagnostic approach one should consider in dealing with patients with severe unexplained HFpEF to assess for alternative etiologies in the presence of subtle diagnostic findings, such that timely and potentially life-saving therapies can be instituted.

Keywords — cardiac amyloidosis, cardiorenal syndrome, heart failure with preserved ejection fraction

INTRODUCTION
The incidence of heart failure with preserved ejection fraction (HFpEF) continues to rise with advancing age. Renal dysfunction in patients with HFpEF is commonly encountered. Although most patients with HFpEF tend to have relatively slow disease progression, some decline much rapidly towards end-stage heart failure and associated cardiorenal syndrome. Identifying this high-risk subgroup of patients by recognizing the underlying disease process early on in the clinical course remains crucial for providing appropriate and timely therapies aimed at improving survival and quality of life.

Systemic hypertension, especially in the elderly, frequently leads to left ventricular hypertrophy (LVH) and resultant HFpEF. However, the presence of other underlying systemic disorders that can lead to rapid disease progression, pose a unique diagnostic challenge. Given the rarity of diagnosis of other non-hypertension related entities leading to severe HFpEF, a strong index of suspicion for alternative diagnoses is often the cornerstone of appropriate clinical management in these patients. We present one such case of an elderly male patient who presented with rapidly progressive LVH that eventually progressed to treatment refractory low-output cardiac failure and end-stage cardiorenal syndrome.

Figure 1. Initial 12-lead ECG showed a normal sinus rhythm with first-degree atrio-ventricular block, right axis deviation, normal voltage in the limb leads and a non-specific inter-ventricular conduction delay.
OUR EXPERIENCE

An 84-year-old male was admitted from the nephrology clinic with worsening renal dysfunction and progressive dyspnea. He had been recently started on diuretics for volume overload with a presumptive diagnosis of HFpEF noted by a prior 2D echocardiogram.

The patient had a remote history of coronary artery bypass graft surgery but denied recurrent chest pains. Physical examination was significant for an elderly male in no distress, with an initial BP of 100/60 mmHg, HR of 80 beats/min and signs of bi-ventricular failure as evidenced by an elevated jugular venous pressure of ~18 cm, bibasilar lung crackles, and bilateral lower extremity edema.

A 12-lead ECG (Figure 1) demonstrated sinus rhythm with first-degree AV block, right axis deviation, normal QRS voltage in the limb leads, and a non-specific pattern of inter-ventricular conduction delay. Significant labs included an elevated blood urea nitrogen and serum creatinine of 81 mg/dl and 2.6 mg/dl respectively, which had increased from 34 mg/dl and 1.6 mg/dl since starting diuretics. An N-terminal pro brain natriuretic peptide (NT-proBNP) was markedly elevated at 52,000 pg/ml (normal <100 pg/ml). His hospital course was complicated by hypotension during an initial attempt to advance low dose parenteral diuretic therapy.

An echocardiogram was performed shortly thereafter that demonstrated marked LVH, preserved LV systolic function and a markedly dilated inferior vena cava. Doppler parameters were suggestive of elevated LV filling pressures, as noted by an E/A ratio >2.5 and an E/e’ >25 in both the medial and lateral mitral annuli. Of interest, despite the absence of a history of hypertension, was the severe circumferential thickening of the myocardial walls (Figure 2). These findings were prominent, with an interval progression noted when compared to a prior echocardiogram three-months earlier.

Concerns were expressed about an infiltrative myocardial process in the setting of severe concentric LVH in the absence of systemic hypertension. Serum protein electrophoresis and immunofixation were requested and revealed a monoclonal kappa-chain immunoglobulin spike. With the provisional diagnosis of cardiac amyloidosis, an abdominal fat pad biopsy was obtained for tissue confirmation that demonstrated strongly positive Congo red staining and apple-green birefringence upon polarization, consistent with a clinical diagnosis of systemic amyloidosis (Figure 3). Final confirmatory results revealed AL-type amyloid with kappa light chains. Attempts to manage the patient conservatively failed because of hypotension and progressive renal dysfunction. Following a lengthy discussion with the patient’s primary care providers and family, the patient elected hospice care and subsequently passed away few weeks later.

DISCUSSION

Our patient’s clinical course and work up suggested a presentation consistent with acute type 1 cardiorenal syndrome in the setting of severe underlying HFpEF.1 Given the presence of significant LVH in the absence of long-standing systemic hypertension, consideration of an infiltrative myocardial process was reasonable. Although a cardiac MRI may have yielded diagnostic results, it was deferred at patient’s request. An endomyocardial biopsy was considered high-risk and as our case demonstrates, it was reasonable to consider alternative sites to access tissue. In our patient an abdominal fat-pad biopsy was deemed the best alternative and yielded a confirmatory diagnosis of AL-amyloidosis. Given the clinical context, LVH and HFpEF were considered to be secondary to cardiac involvement in systemic amyloidosis.
Figure 3. Biopsy tissue was obtained from the abdominal fat pad and histological preparation shown with (A) Congo red staining at 100X magnification and (B) polarized Congo red staining at 50X magnification, showing typical apple-green birefringence of the amyloid protein. (Images courtesy of Dr. Gloria Niehans, Minneapolis VA Medical Center Department of Pathology)

Cardiac amyloidosis has been well described as an infiltrative disease of the myocardium induced by either transthyretin-related (TTR) amyloid proteins or AL-type amyloid. TTR amyloidosis can be hereditary due to familial genetic mutations or present as non-hereditary disease (also referred to as senile systemic amyloidosis) that is commonly seen in patients >70 years of age. This disease type is usually associated with milder symptoms and a slower clinical progression. AL-amyloid, on the other hand, is a plasma cell dyscrasia that often leads to multi-system involvement, is associated with a more malignant course that causes rapid decline in cardiovascular function as seen in our patient, and carries poorer prognosis.2

Amyloid protein deposition in the heart often leads to restrictive disease that presents as HFpEF with secondary pulmonary venous hypertension and/or right ventricular dysfunction. Physical examination is usually consistent with signs of HFpEF with marked peripheral edema, congestive hepatomegaly, and prominent X and Y descents on neck vein exam in the absence of Kussmaul’s sign. While heart failure is the commonest presenting symptom, atrial fibrillation, intra-cardiac thrombus formation, brady-arrhythmias, syncope, and/or sudden cardiac death may be presenting manifestations.3 Systolic left ventricular dysfunction is usually a late manifestation and is associated with grave prognosis,3 with prior studies reporting a median survival of ~6 months in patients with overt heart failure.2,4

Cardiac imaging plays an important role in early diagnosis. Echocardiographic parameters for cardiac amyloidosis have been extensively studied but are largely non-specific; with LVH, right ventricular free wall thickening, and dilated atria with diastolic dysfunction being the commonest findings.5 Granular or “sparkling” appearance of the myocardium is usually a late sign with high specificity (71-81%) but very low sensitivity (26-36%).6,8 Cardiac MRI has been gaining popularity for disease detection when echo diagnosis is uncertain. Delayed gadolinium enhancement, in addition to global myocardial and sub-endocardial longitudinal relaxation times, can help in differentiating cardiac amyloidosis from hypertensive LVH.9,10 Definitive diagnosis, however, is usually based on histopathology. To that regard, abdominal fat pad, salivary gland, and endomyocardial biopsies can be utilized for obtaining tissue, all with relatively high diagnostic specificity.11,12

Our report has recognized limitations. First, cardiac tissue confirmation for amyloidosis was not performed in our patient. Secondly, it remained unclear if renal dysfunction was solely from HFpEF related low-output state and passive renal congestion, or intrinsic renal involvement with amyloid proteins. Despite these limitations, several clinical features pertinent to the current case are interesting and merit discussion. First, the presence of severe concentric LVH on echo, in the absence of ECG voltage criteria and a history of hypertension, was notable. This combination of increased myocardial mass with a low-normal QRS voltage on ECG is a strong predictor for cardiac amyloidosis.7 Secondly, the traditional teaching of bright echogenic granular speckling on 2D echocardiogram was not visualized in this case, and further confirms the lack of sensitivity of this finding.7 On the other hand, the presence of rapidly increasing myocardial thickness and worsening filling patterns on serial echo studies was highly suggestive of an infiltrative cardiac process.5 Third, the disproportionate elevation in NT-pro BNP levels (52,000 pg/ml) was interesting. In addition to being a marker of increased volume overload, elevation of NT-pro BNP levels to this degree have been observed in cases of amyloidosis, presumably as a result of direct myocyte damage and inflammation by extracellular deposits of amyloid.13 Finally, although our clinical suspicion was high for senile systemic amyloidosis (TTR amyloid) in this elderly patient, tissue biopsy revealed AL-type disease. As expected with this disease form, our patient had a malignant clinical course with rapid progression to end-stage HFpEF and diuretic resistant renal dysfunction.

CLINICAL PERSPECTIVE

This experience demonstrates that systemic amyloidosis with cardiac involvement ought to be considered as a possible, albeit unusual, cause of severe LVH with rapidly progressing refractory HFpEF. Importantly, in the presence of systemic
hypertension, the presence of low-normal QRS voltage on ECG in the setting of imaging evidence of LVH should prompt a search for myocardial infiltration. Given that it is nearly impossible to screen every patient with LVH for amyloidosis or other infiltrative diseases, an understanding of these subtle differentiating features can aid clinical decision-making and thereby improve patient outcomes.

REFERENCES