HEART FAILURE

FELLOWS CASE OF THE MONTH

Cardiac Effects of Bortezomib Therapy in a Case of AL Amyloidosis Presenting with Bradycardia and Heart Failure

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ABSTRACT. We report a case of a 68-year-old woman who presented with conduction system disease in the setting of light chain amyloidosis, which subsequently improved with bortezomib chemotherapy. This case demonstrates the potential reversibility of atrioventricular conduction delay in cardiac amyloidosis with timely therapy, highlighting the importance of early diagnosis of cardiac amyloidosis.

KEYWORDS. atrioventricular nodal dysfunction, bortezomib, cardiac amyloidosis.

Introduction

Amyloidosis is a protein misfolding disease in which different soluble proteins aggregate as insoluble fibrils that precipitate in the extracellular space, causing organ dysfunction and death.1 Patients with clinically significant cardiac involvement have historically been considered to have an extremely poor prognosis.2 Herein, we present the case of a 68-year-old female patient who presented with atrioventricular (AV) nodal dysfunction and heart failure secondary to cardiac light chain amyloidosis, with subsequent improvement after chemotherapy based on bortezomib.

Case report

A 68-year-old female with a history of heart failure with preserved ejection fraction presented to the emergency department at our institution (Loyola Medical Center) for worsening dyspnea on exertion and a pre-syncopal episode of 1-day duration. Her past medical history was notable for right carotid artery occlusion, transient ischemic attack, and hypothyroidism. Medications included aspirin, clopidogrel, carvedilol, lisinopril, atorvastatin, furosemide, metolazone, and levothyroxine. There was no family history of cardiac disease. On presentation she had a blood pressure of 92/59 mmHg and pulse of 51 bpm. Pertinent findings on examination include markedly elevated jugular venous pulsation (12 cmH2O), decreased breath sounds over the right lung field, regularly irregular heart rate, hepatomegaly, and bilateral pitting edema up to the level of the thighs. Laboratory tests at initial evaluation were notable for elevated blood urea nitrogen (72.0 mg/dl), serum creatinine (2.4 mg/dl), beta natriuretic peptide (BNP) (898 pg/dl), and troponin I (0.34 ng/dl). Electrocardiogram (ECG) on admission revealed profound sinus bradycardia with junctional escape rhythm and prolonged PR interval >500 ms (Figure 1). Transthoracic echocardiogram revealed moderate concentric left ventricular thickening (1.5 cm) (Figure 2) with restrictive filling pattern (E/e' ratio = 30) (Figures 3 and 4) and an ejection fraction of 65%. It is worthwhile mentioning that she had a similar presentation at an outside facility 2 weeks prior to presentation at our institution. Pertinent work-up at that time included ECG that showed normal sinus rhythm with first degree AV block and cardiac catheterization that did not demonstrate any evidence of coronary artery disease (Figures 5 and 6). In light of her symptoms and findings...
Figure 1: On admission, atrial fibrillation with slow atrioventricular conduction and junctional escape rhythm. The precordial lead meets low voltage criteria (<10 mV).

Figure 2: Parasternal long axis view of the transthoracic echocardiogram at presentation revealed left ventricle hypertrophy, left atrial enlargement, and possible thickening of the mitral valve.
Figure 3: Mitral valve inflow pulse Doppler waveform.

Figure 4: Tissue Doppler image with significantly decreased septal e'.
on ECG during this current admission, she underwent permanent pacemaker placement for symptomatic bradycardia. Active fixation lead placement was attempted initially, but mapping of the right atrial appendage and other right atrial lesions yielded very poor sensing with no capture. Although passive fixation lead placement also yielded poor results, this was eventually used despite sensing at 0.7 mV, extreme latency from pacing to capture, and delayed AV conduction.

The constellation of findings, low-voltage ECG, restrictive filling pattern, and poor sensing of the pacemaker lead suggested infiltrative cardiomyopathy as the etiology of heart failure. The patient underwent abdominal fat pad biopsy, which revealed amyloid deposition (Figure 7). Serum immunofixation showed a monoclonal immunoglobulin A (IgA) lambda spike (0.9 g/dl). Serum free light chain measurement revealed an excess of lambda light chains (263 mg/l), with a mildly increased kappa light chain level at 32.7 mg/l and abnormal kappa/lambda ratio at 0.12 mg/l. Bone marrow biopsy revealed a slightly hypercellular bone marrow (40–50%) and increased percentage of plasma cells (13%). Eventually, immunoperoxidase staining revealed expression of cytoplasmic immunoglobulin lambda light chains leading to a diagnosis of AL amyloidosis. Cardiac magnetic resonance imaging (MRI) was not performed.

Figure 5: Right anterior oblique caudal view with no obstruction in left anterior descending (LAD) and left circumflex artery (LCx).
as we already had a conclusive diagnosis, and performing an additional test would not have altered management. Following medical optimization, the patient was subsequently discharged home with outpatient hematology follow-up.

Two weeks after discharge, the patient was started on weekly CyBorD therapy (subcutaneous bortezomib 1.5 mg/m², oral cyclophosphamide 300 mg/m², and oral dexamethasone 40 mg weekly). She tolerated chemotherapy well except for severe paresthesia, which required dose reduction of bortezomib. Levels of free light chain normalized after one cycle of chemotherapy (Figure 8). At 3 months, she was found to be in atrial fibrillation and anticoagulation with warfarin was started (Figure 9). At 9 months’ follow-up, her PR interval improved to 300 ms, and at 10 months’ follow-up, the PR interval improved to 260 ms (Figure 10). Despite two admissions for heart failure exacerbation during chemotherapy, she had interval improvement in BNP (Figure 8). Currently, she is clinically doing well 2 years later and has had no more recurrences of her heart failure exacerbations.

Discussion

AL amyloidosis is a plasma-cell dyscrasia with monoclonal immunoglobulin light chains forming amyloid fibril precursors. Clinical cardiac involvement occurs in up to 50% of cases and is a poor prognostic sign with a life expectancy of less than 6 months if left untreated. The condition was once viewed as a death sentence, but treatment for AL amyloidosis has improved progressively over the past 25 years since the introduction of melphalan therapy in the 1990s. Currently, high-dose melphalan therapy with autologous stem cell transplantation is considered the standard of care. However,
patients with cardiac involvement similar to ours, or patients with involvement of two or more organs, are at higher risk of early death from stem cell transplantation and are usually not eligible. Other novel therapies such as therapy based on bortezomib or lenalidomide have been introduced recently; they show promising results, even in patients who are ineligible for high-dose melphalan therapy with autologous stem cell transplant. In one study, a hematologic response was seen in 94% of patients who were ineligible for stem cell transplant. Although this is based on case series, prospective validation studies are currently underway. Conduction disturbances are commonly seen in patients with AL amyloidosis and have a negative prognostic impact. Our case is unique in that AV conduction delay (thought to be from amyloid deposition) showed improvement after complete hematologic response with bortezomib therapy. Although there have been prior reports in the literature describing regression of ventricular wall thickness and a decrease in BNP level with bortezomib therapy in patients with cardiac amyloidosis, we did not find any reports describing improvement of AV conduction delay with bortezomib chemotherapy in patients with cardiac amyloidosis.

Our case suggests that with appropriate treatment, AV conduction delay could be improved in cardiac amyloidosis. This highlights the importance of early diagnosis leading to timely therapy. Therefore, amyloidosis should be suspected when patients present with left ventricular hypertrophy (LVH), low-voltage ECG with no evidence of hypertension, and difficulty pacing with high threshold, as was the case in our patient. Cardiac MRI is recommended in such situations as it is a useful modality with high accuracy for detection of cardiac amyloidosis. In our patient, cardiac MRI was not performed since the definitive diagnosis was reached by fat pad biopsy, and MRI would not have changed our treatment plan.

Our case report has multiple limitations. First, we did not perform intracardiac recording. It would have been interesting if AH (supra-his) and HV (his-ventricle) intervals had been assessed. A second limitation to consider is that we cannot exclude the confounding effect of steroids, given as part of the CyBorD therapy, on AV nodal conduction.

In conclusion, therapy based on bortezomib may have a potential role in improving cardiac manifestations of AL amyloidosis.

Figure 7: Congo red stain of the fat pad under polarized light revealed the typical apple-green birefringence appearance.
Figure 8: Free lambda light chain improved dramatically after the first cycle of CyBorD therapy and remained in the normal range throughout the chemotherapy.

Figure 9: At 3 months’ follow-up, electrocardiogram showed atrial fibrillation with ventricular conduction.
References


