

# Recurrent syncope and cardiac arrest in a patient with systemic light chain amyloidosis treated with bortezomib

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## Abstract

About 10-15% of patients with multiple myeloma develop light chain (AL) amyloidosis. AL amyloidosis is a systemic disease that may involve multiple organs, often including the heart. It may present clinically with bradyarrhythmia and syncope. The proteasome inhibitor bortezomib has been used with clinical efficacy in treating patients with AL amyloidosis but also implicated as a possible cause of cardiomyocyte injury. We report a case of a 48-year-old man with AL amyloidosis and increased frequency of syncope and cardiac arrest after starting bortezomib. The biologic and clinical plausibility of a heightened risk for cardiac arrest in patients with cardiac AL amyloidosis and history of syncope being treated with bortezomib is a possibility that is not well documented in the medical literature and warrants further investigation.

## Introduction

We report a case of a 48-year-old man with multiple myeloma and light chain (AL) amyloidosis, who developed increased frequency of syncope and suffered cardiac arrest after starting treatment with the proteasome inhibitor bortezomib.

## Case Report

A 48-year-old Filipino man with a history of chronic Hepatitis B, chronic kidney disease (CKD), and syncopal episode of undetermined etiology 12 months prior, was admitted to the hospital for acute liver and kidney injury. He was jaundiced but otherwise asymptomatic. He was diagnosed with multiple myeloma and AL amyloidosis confirmed by the biopsy-proven presence of kappa-predominant light chain amyloid deposits with Congo red birefringence within the kidney, liver, and bone marrow. Cardiac involvement was also suspected based

on echocardiographic findings of diastolic dysfunction with sparkling left ventricular (LV) acoustic reflections and LV hypertrophy in the absence of hypertension. LV ejection fraction was normal with no valvular dysfunction. Electrocardiogram showed normal sinus rhythm with no conduction abnormalities. Brain natriuretic peptide (BNP) was markedly elevated at 1890 pg/mL; cardiac troponin-I was 0.43 ng/mL. He was initiated on treatment with bortezomib 0.7 mg/m<sup>2</sup> and received five concurrent treatments of plasmapheresis for high serum free kappa light chains (915 mg/dL). In response, he had notable improvement in liver and kidney function, but suffered a syncopal episode and was discharged from the hospital with an implanted loop recorder (ILR) recommended by cardiac electrophysiology consultant to guide further therapy. The patient did not undergo prophylactic insertion of an implantable pacemaker or cardioverter-defibrillator prior to his discharge from the hospital.

Six days later, he returned to the hospital for follow-up and suffered another witnessed syncopal episode followed by pulseless cardiac arrest with unsuccessful cardiopulmonary resuscitation (CPR) during which he was given epinephrine and vasopressin. The ILR demonstrated bradycardia as low as 34 beats per minute (bpm) preceding the cardiac arrest. During CPR, he had a heart rate ranging from 40-120 bpm, but no pulse, consistent with electromechanical dissociation. The ILR was otherwise unremarkable and did not show any events at home preceding his witnessed syncope and cardiac arrest. The patient did not undergo autopsy.

## Discussion and Conclusions

AL amyloidosis is a systemic disease that may occur in association with multiple myeloma and involve multiple organs, commonly including the heart. Cardiac amyloidosis is typically characterized by the extracellular deposition of 8-10 nm wide insoluble fibrils, predominantly in the myocardium, leading to thickening of the interventricular septum and ventricular wall. Restrictive cardiomyopathy may ensue with clinical manifestations of systolic or diastolic heart failure and cardiac conduction abnormalities. The treatment of AL amyloidosis is chemotherapy-based, and the proteasome inhibitor bortezomib has been used with clinical efficacy but also implicated as a possible cause of cardiomyocyte injury.<sup>1</sup> Hence, patients with cardiac amyloidosis may be at increased risk for syncope and sudden death due to a combination of these factors.

Our patient had biopsy-proven systemic AL amyloidosis with additional echocardiographic evidence of myocardial amyloid deposition and

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stage III cardiac involvement based on BNP and cardiac troponin levels.<sup>2</sup> Gadolinium-enhanced cardiac magnetic resonance imaging is more highly sensitive and specific for detecting myocardial amyloid,<sup>3</sup> but could not be done in this patient due to the presence of CKD and risk of gadolinium-induced nephrogenic systemic fibrosis.<sup>4</sup>

The patient's course was also notable for increased frequency of syncope after starting bortezomib. His first and only previous episode of syncope occurred 12 months before his formal diagnosis of AL amyloidosis and the patient self-reported having an unremarkable Holter and event monitor at the time. Because this event occurred before he began to receive care in our hospital system, we were unable to further determine whether additional workup was done or the etiology of his previous syncope. Nevertheless, the possibility of amyloidosis-induced cardiac conduction disturbance is certainly plausible considering that the median survival of a patient with untreated cardiac amyloidosis is only 6 months.<sup>5</sup> Bradyarrhythmias are the most common conduction disturbances reported in patients with AL amyloidosis and syncope, and they commonly precede terminal cardiac events.<sup>6</sup> In addition, bortezomib may induce cardiomyocyte injury through a mechanism related to the prevention of ubiquitin-proteasome mediated stabilization of atherosclerotic plaque with resultant vascular smooth muscle apoptosis and risk of cardiac arrhythmia, including ventricular fibrillation.<sup>1</sup> The timing between bortezomib administration and development of recurrent syncope in our patient after a long episode-free period raised concern that the proteasome

inhibitor may have played a role in increasing the frequency of his syncope. However, we cannot establish a causal relationship between bortezomib administration and the risk of cardiac conduction disturbance, syncope, or cardiac arrest in patients with cardiac AL amyloidosis based on this observation alone. Our experience nevertheless demonstrates the biologic and clinical plausibility of a heightened risk for cardiac arrest in patients with cardiac AL amyloidosis and history of syncope being treated with bortezomib, a possibility that is not well documented in the medical literature. This proposed hypothesis would need to be substantiated by more robust clinical studies. Whether these patients might benefit from prophylactic insertion of an implantable pace-

maker or cardioverter-defibrillator is also unknown and warrants further investigation.

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