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Case Report

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Delayed Diagnosis of Cardiac Amyloidosis Secondary to Multiple Myeloma

Ahmad Qatanani[a, e], Shereen Dahab[a], Steven Douedi[a], Yumna Hamid[a], Sameh Girgis[a], Steven Daniels[b], Gurpreet Lamba[c], Mohammad Zafar[d]

Abstract

Cardiac amyloidosis is a rare condition with only 2,500 new cases reported yearly in the United States of America (USA). The prognosis of cardiac amyloidosis is particularly grim. The median survival is 6 months from onset of congestive heart failure (CHF) symptoms. CHF is a common presentation as the second leading cause of hospitalization in the senile population in the USA. We report a case of an 83-year-old man who presented with the classic symptoms of CHF including bilateral lower extremity edema, shortness of breath, and weight gain. Upon further workup, an echocardiogram revealed strain patterns suggestive of cardiac amyloidosis and bone marrow biopsy confirmed the diagnosis of multiple myeloma. Unfortunately, despite starting treatment with steroids and chemotherapy, the patient succumbed to his condition in a matter of weeks. We report this case to highlight that cardiac amyloidosis secondary to multiple myeloma can present in the form of new onset, quickly deteriorating CHF long before any classic multiple myeloma symptoms manifest.

Keywords: Cardiac amyloidosis; Congestive heart failure; Multiple myeloma

Introduction

Multiple myeloma is a neoplastic proliferation of monoclonal plasma cells. Plasma cells are mature B-cell lymphocytes that manufacture and secrete immunoglobulins. Malignant plasma cells produce excess quantities of immunoglobulin light chains and hinder the body's ability to fight infections. Multiple myeloma typically presents in the form of four symptomatic conditions included in the mnemonic "CRAB": hypercalcemia ("stones, bones, moans and psychiatric overtones"), renal failure, anemia (fatigue) and bone lesions (pain or factures). Furthermore, the neoplastic production of immunoglobulin chains increases the amount of misfolded proteins. The excess misfolded proteins, termed "paraproteins" due to their lack of functionality, aggregate to create beta-pleated sheets of protein fibrils called amyloid. Amyloid then deposits into tissues throughout the body disrupting their function and causing end organ damage. Examples of pathologic amyloid deposition include nephrotic syndrome leading to renal failure and restrictive cardiomyopathy leading to diastolic heart failure. It is possible, though less common, for patients to present with end organ damage secondary to amyloidosis prior to the manifestations of the typical multiple myeloma symptoms [1, 2].

Case Report

Investigations

An 83-year-old man with a past medical history significant for coronary artery disease, hyperlipidemia, hypertension, and chronic kidney disease presented to the emergency department with a 6-week history of worsening bilateral lower extremity swelling and 1 week of increased shortness of breath. He also endorsed dyspnea on exertion and a weight gain of 8 pounds in the past 2 weeks. Of note the patient did not have a prior history of congestive heart failure (CHF) and previous echocardiograms revealed normal heart function.

Approximately 3 weeks prior to presentation, the patient underwent preoperative testing at a different facility in preparation for primary hip arthroplasty. Nuclear stress test at the time showed multivessel coronary artery disease, left ventricular ejection fraction of 40% and abnormal myocardial perfusion. Echocardiogram revealed the presence of severe left ventricular hypertrophy with an abnormal strain pattern and an inferobasilar aneurysm. The patient was then scheduled at that facility for a coronary angiogram but was deferred due to elevated creatinine. His anti-hypertensives losartan and chlorthalidone were discontinued at discharge due to the elevated creatinine. The patient was directed to follow up with his

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[a]Department of Medicine, Jersey Shore University Medical Center, Neptune, NJ 07753, USA
[b]Department of Cardiology, Jersey Shore University Medical Center, Neptune, NJ 07753, USA
[c]Department of Hematology & Oncology, Jersey Shore University Medical Center, Neptune, NJ 07753, USA
[d]Department of Nephrology, Jersey Shore University Medical Center, Neptune, NJ 07753, USA
[e]Corresponding Author: Ahmad Qatanani, Department of Medicine, Jersey Shore University Medical Center, Neptune, NJ 07753, USA.
Email: ahmad.qatanani@gmail.com

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Table 1. Vitals on Presentation

Measurement	Value
Blood pressure	127/77 mm Hg
Heart rate	84 beats/min
Respiratory rate	14 breaths/min
Pulse oximetry	98%

cardiologist whom he scheduled an appointment in 4 weeks' time.

In the time between the preoperative testing and presentation to our hospital, the patient reported initially feeling well. He endorsed a healthy lifestyle with the ability to exercise and walk miles without any difficulty. He was employed as a physical education teacher. As the lower extremity swelling worsened, he started to develop shortness of breath limiting his activity level which prompted his visit to the emergency room.

On arrival to our hospital, the patient's vital signs were all within normal limits and his blood pressure was well controlled despite the recent discontinuation of some of his antihypertensives (Table 1). Physical examination exhibited leg edema, crackles on auscultation and flat neck veins. Laboratory results showed an elevated brain-type natriuretic peptide (BNP) (1,761 ng/L), troponin (0.31 ng/mL), blood urea nitrogen (BUN) (55 mg/dL) and creatinine (3.46 mg/dL) (Table 2). According to medical records, his baseline creatinine ranged 1.4 - 1.8 mg/dL. Urine analysis revealed hematuria and proteinuria suggesting nephrotic syndrome (Table 3). Electrocardiogram (EKG) displayed low-voltage normal sinus rhythm. Repeat echocardiogram at our hospital confirmed the severe left ventricular hypertrophy with reduced ejection fraction of 46-50% but also revealed a strain pattern suggestive of cardiac amyloidosis.

Table 2. Laboratory Results

Measurement	Value
Sodium	142 mmol/L
Potassium	5.0 mmol/L
Chloride	110 mmol/L
Glucose	116 mg/dL
Calcium	9.1 mg/dL
Blood urea nitrogen	55 mg/dL
Creatinine	3.46 mg/dL
Total protein	4.0 g/dL
Anion gap	10
White blood cells	7,200/µL
Hemoglobin	14.4 g/dL
Mean corpuscular volume	93.8 fL
Platelet count	360,000/µL
Brain-type natriuretic peptide	1,761 pg/mL
Initial troponin	0.28 ng/mL
Second troponin (4 h later)	0.31 ng/mL

Table 3. Urine Analysis

Measurement	Value
Appearance	Hazy
Urine protein	> 500 mg/dL
Glucose	Negative
Bilirubin	Negative
Ketones	Negative
Blood	Moderate
Nitrites	Negative
Leukocytes	Negative
Urobilinogen	< 2.0 mg/dL

Diagnosis

The patient underwent laboratory investigation for amyloidosis due to the echocardiogram findings. Total urine protein was elevated (1.19 g/L) and positive for monoclonal free lambda light chains (Bence-Jones protein). Serum protein electrophoresis (SPEP) showed markedly decreased total protein, hypoalbuminemia, hypogammaglobulinemia and increased alpha-2-globulin. It also revealed a monoclonal protein peak migrating in the beta-globulin region making up 0.21 g/dL of the total 0.67 g/dL, a second monoclonal protein peak migrating in the gamma globulin region making up 0.10 g/dL of the total 0.22 g/dL with markedly increased free lambda light chains and markedly decreased kappa/lambda ratio.

Diagnostic testing for amyloidosis was initiated with a fat pad biopsy that upon Congo red staining was indeterminate for amyloid deposition. Bone marrow biopsy of the left iliac crest showed extensive interstitial infiltrate of atypical plasma cells (80-90%) in the form of diffuse sheets that is consistent with multiple myeloma. An X-ray skeletal survey was negative for any osteolytic lesions. The patient was scheduled for positron emission tomography (PET) on a later date at an outpatient center.

Treatment

The patient was initially started on a daily dose of 40 mg intravenous dexamethasone. Once the multiple myeloma diagnosis was confirmed with bone marrow biopsy, the patient received two rounds of "CyBorD" chemotherapy treatment: cyclophosphamide, bortezomib and dexamethasone. CHF medications and diuretics were administered to manage volume overload secondary to cardiac amyloidosis. As treatment progressed, serial labs indicated increased uric acid production (12.3 mg/dL) that was treated with one-time rasburicase and managed thereafter with allopurinol. He also received "Granix" (tbofilgrastim) to reduce the duration of severe neutropenia while

undergoing chemotherapy. After 9 days of initial hospitalization, the patient was scheduled for a third chemotherapy session and discharged to home.

Follow-up and outcomes

Seven days later, the patient presented again to our facility with continued symptoms of worsening dyspnea and generalized edema. Additionally, he tested positive for a urinary tract infection and was started on antibiotics. Blood work revealed acute on chronic kidney disease with significantly worse creatinine of 5.40 mg/dL compared to previous admission. He was promptly started on hemodialysis. Next morning, the patient became hypoxic and hypotensive requiring transfer to the intensive care unit where vasopressors, inotropes and bilevel positive airway pressure (BiPAP) were initiated. Shortly thereafter, the patient went into cardiac arrest and resuscitation efforts were unsuccessful.

Discussion

Multiple myeloma is the third most common hematologic malignancy after diffuse B-cell lymphoma and chronic lymphocytic leukemia [3]. Over the past 30 years, the global incidence rate of multiple myeloma has increased 126% to a rate of 2.1 per 100,000 persons [4]. Continually, the mortality of rate increased 94% to 1.5 deaths per 100,000 persons in that time frame. Much of this surge in numbers can be attributed to the growth of an aging global population. Nonetheless, a rise in age-specific incidence rate still contributed a 32.6% increase. In the United States of America, the incidence rate is expected to be 5.9 per 100,000 translating to 32,000 new cases expected in 2020.

AL amyloidosis, previously called primary systemic amyloidosis, is the most common type of systemic amyloidosis. There are studies indicating this disorder is underdiagnosed because primary care doctors may not recognize when and how to test for AL amyloidosis. Worse yet it is often misdiagnosed because of the wide range of clinical manifestations [5, 6]. Amyloidosis is diagnosed through biopsies usually obtained from the abdominal fat pad or rectum. However, due to the asymmetric nature of amyloid deposition, it is sometimes necessary to conduct more invasive biopsy of end organs such as the heart or bone marrow. This is performed when there is evidence or strong suspicion of underlying malignancy such as multiple myeloma.

Approximately 20% of multiple myeloma patients will develop AL amyloidosis simply due to the pathological nature of the disease [7]. Conversely, only 10% of patients with AL amyloidosis meet the diagnostic criteria for multiple myeloma. It is unclear of the chronologic order of disease in our patient, but the confirmed diagnosis of both diseases is highly suggestive that the multiple myeloma caused the cardiac amyloidosis. Furthermore, we purport that the speed of onset of CHF symptoms and rapid deterioration of our patient indicate they were more likely due in large part to the cardiac amyloidosis. His medical records including prior echocardiograms suggest his presentation was less likely due to a combination of his underlying coronary artery disease and hypertension. Further evidence to this effect is the patient's high activity level only weeks or months prior to presentation. As such, it is our goal to highlight the prospect of atypical presentation of multiple myeloma in the form of end organ damage secondary to AL amyloidosis.

Over the past 20 years, advances in treatment have led to an increase in relative survival rates from multiple myeloma [8]. Treatment modalities now include stem-cell transplantation and new chemotherapy agents. From 1990 to 2016, the 5- and 10-year survival rates of multiple myeloma patients have nearly doubled [9].

Despite the challenges in managing cardiac amyloidosis, understanding the outcomes is a vital aspect of management and patient education. Lee et al suggested the most important indicators of prognosis are old age, elevation of cardiac troponin as well as left ventricular dysfunction [10]. Milani et al reported in a landmark study of 754 patients from Mayo Clinic that stroke volume index (SVI) could serve as the preferred echocardiographic measure to predict outcomes in AL amyloidosis patients [8]. Furthermore, they developed the "Mayo staging system" as a prognostic predictor based on three measurements: N-terminal pro-brain natriuretic peptide (NT-proBNP), troponins TnT/TnI and the difference between involved and uninvolved free light chains (dFLC). Our patient met the criteria for stage IIIb which carried a median survival rate of less than 1 year.

Learning points

We thought it was prudent to report this case primarily due to the numerous manifestations of multiple myeloma and the ubiquity of CHF presentation. Our patient developed lower extremity swelling only 6 weeks prior to presentation or 3 weeks prior to his preoperative testing at the previous facility. It is critical for clinicians to recognize the more subtle presentations of multiple myeloma and cardiac amyloidosis in the form of CHF. It would have been more ideal if our patient underwent prompt workup and conceivably received earlier treatment for his multiple myeloma. It is obvious that any delay in initiating treatment increases the mortality rate [11-13]. The 5-year mortality rate is currently 53% and only 5% of the patients with primary amyloidosis survive beyond 10 years [14, 15]. Prompt diagnosis and effective treatment of multiple myeloma and cardiac amyloidosis is essential in decreasing patient mortality.

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Conflict of Interest

The authors declare no conflict of interest for this publication.

Informed Consent

The patient described in the case report had given informed consent for the case report to be published.

Author Contributions

Ahmad Qatanani: case selection, discussion and drafting manuscript; Shereen Dahab: drafting manuscript and revision; Steven Douedi: drafting manuscript and revision; Yumna Hamid: drafting manuscript and revision; Steven Daniels: manuscript revision and final approval; Gurpreet Lamba: manuscript revision and final approval; Mohammad Zafar: case selection, planning, manuscript revision and final approval.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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