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CLINICAL VIGNETTE

Cardiac Amyloidosis – A Race Against Time

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Case Presentation

A 71-year-old man with type 2 diabetes mellitus, prostate cancer treated with radiation therapy, essential hypertension, and hyperparathyroidism status post-parathyroidectomy developed dyspnea on exertion about seven months prior to being seen at UCLA. An echocardiogram at that time revealed normal left ventricular systolic function with a left ventricular ejection fraction of 60% with reversal of early (E) to late (A) ventricular filling velocities consistent with diastolic dysfunction. Initially, he was treated with furosemide with good response. However, over the next three months, he continued to have dyspnea on exertion with interval development of pleural effusions. Carvedilol, spironolactone, and atorvastatin were added to his regimen.

Three months prior, he presented to an outside hospital after a syncopal episode. He was initially bradycardic with episodes of tachycardia and bradycardia and a diagnosis of sick sinus syndrome was made leading to dual chamber pacemaker placement. His cardiac catheterization revealed non-obstructive coronary disease with an elevated left ventricular end-diastolic pressure of 28 mmHg. In addition, he had ultrasound guided thoracentesis with drainage of 1,500 milliliters of transudative fluid with negative cytology. His E/A wave velocity ratio was 2.75 on echocardiogram.

Two weeks later, he re-presented at the outside hospital with dyspnea at rest. It was worse when recumbent. Repeat thoracentesis removed 1,500 milliliters of transudative fluid. Cytology was again negative.

For the next two months, he continued to have dyspnea at rest with new symptoms of dizziness. His furosemide was adjusted and a magnetic resonance angiogram (MRA) was ordered but could not be completed due to his pacemaker. One month prior to UCLA evaluation, he had recurrent syncopal events and was taken to a different outside hospital where an electrophysiology study found inducible ventricular tachycardia. His pacemaker was upgraded to an automatic implantable cardioverter defibrillator (AICD), and he was transferred to our hospital for insurance reasons. At that time, he remained dyspneic at rest with recurrent pleural effusions. Cardiothoracic surgery was consulted with chest tube placement and talc pleurodesis. He initially did well with aggressive diuresis with intravenous furosemide achieving eleven liters negative fluid balance. He had averaged 1.5 liters daily negative fluid balance, but he became oliguric with an

acute elevation in his creatinine from 1.1 mg/dL to 1.9 mg/dL, serum calcium from 10.2 mg/dL to 12.4 mg/dL, and an elevated uric acid level of 11.4 mg/dL. Nephrology consult held his diuresis and initiated hypercalcemia workup. Urine protein electrophoresis was positive for a monoclonal spike and immunofixation revealed a monoclonal kappa light chain. Further testing included Kappa light chains 133 mg/dL, lambda light chains 51 mg/dL, kappa/lambda ratio of 2.61, and beta 2 microglobulin 4741.0 micrograms/L. He remained dyspneic at rest with a rising BNP and creatinine complicated by low blood pressure. Right heart catheterization revealed pulmonary capillary wedge pressure (PCWP) of 28 mmHg and a cardiac index of 1.49 L/min/m².

He was transferred to the intensive care unit (ICU) and started on dobutamine and furosemide infusions. This was complicated by sustained ventricular tachycardia and two episodes of his AICD firing. The dobutamine infusion was discontinued, and he was started on amiodarone. His pacemaker/AICD was reprogrammed for more anti-tachycardia pacing sequences. Despite his furosemide infusion, he was not diuresing; therefore, dopamine infusion was started but without effect. A repeat right heart catheterization again revealed a PCWP of 27 mmHg and a cardiac index of 1.32 L/min/m². Continuous renal replacement therapy was started. The following evening, he had a cardiac arrest with pulseless electrical activity (PEA). Return of spontaneous circulation (ROSC) was achieved and he was intubated and placed on mechanical ventilation. During his ICU stay, surgical consultation was requested for a fat pad biopsy; however, he was transferred prior to the procedure.

Patient was transferred to UCLA for further evaluation. His cardiac index was initially 0.8 L/min/m² and required vasopressor support with dopamine, phenylephrine, and milrinone. He had another cardiac arrest due to PEA arrest with ROSC after six minutes. He was started on norepinephrine for further hemodynamic support but again had a PEA arrest with ROSC achieved after nineteen minutes. A family meeting was held and he was changed to comfort care and succumbed to his illness. Autopsy determined cause of death to be cardiogenic shock from restrictive cardiomyopathy due to AL amyloidosis.

Discussion

Restrictive cardiomyopathy due to Amyloid light-chain (AL) amyloidosis can be easily missed in the evaluation of a new diagnosis of heart failure in a patient. Early recognition and initiation of treatments can possibly provide a survival advantage. AL amyloidosis, previously primary amyloidosis, remains a rare disease, approximately 6 to 10 cases per million person-years, caused by misfolded light chains that deposit into extracellular tissues as insoluble fibrils.¹ These proteins bind Congo red stain producing the characteristic apple green birefringence under polarized light microscopy. These light chains are produced by an underlying clonal plasma cell as a precursor protein and can be measured as free light chains in the plasma of patients. It is not clear what circumstances lead the precursor protein to misfold and deposit into various tissues. It is recognized that all forms of amyloidosis are co-deposited with other substances. AL amyloid fibrils bind and co-deposit with Serum amyloid P component (SAP), a protein member of a family that includes C-reactive protein. Studies have found that the ability to self-aggregate, underlying nucleotide sequence, and differences in light chain degradation and/or metabolism may all play a role in the development of tissue deposits.

The clinical manifestations of AL amyloidosis depend on the affected organs. Renal involvement is the most common, leads to nephrotic syndrome, and should be suspected in any non-diabetic with nephrotic range proteinuria. Restrictive cardiomyopathy, like in our case, is the result of the next most common organ involved. This can manifest as either systolic or diastolic dysfunction with subtle echocardiographic findings of a restrictive cardiomyopathy. Syncope and conduction system disease are less common but usually portend a more serious prognosis. Other organ involvement can lead to peripheral neuropathy, hepatomegaly, macroglossia, purpura, and bleeding diathesis. When suspected, initial testing should include serum and urine protein electrophoresis with immunofixation, serum free light chain analysis, and tissue diagnosis. Although direct organ tissue biopsy would provide the highest yield, fat pad aspirate and bone marrow biopsy combined are positive in over 90 percent of patients. Since AL amyloidosis co-deposits with SAP, SAP scintigraphy may reveal the extent of amyloid involvement in a target organ.²

The Mayo Clinic and the International Myeloma Working Group developed diagnostic criteria for AL amyloidosis. The diagnosis can be made if all four criteria are present: (a) Presence of an amyloid-related systemic syndrome, (b) positive amyloid staining by Congo red in any tissue, (c) evidence that amyloid is light-chain-related established by direct examination of the amyloid using mass spectrometry-based proteomic analysis or immunoelectronmicroscopy, and (d) evidence of a monoclonal plasma cell proliferative disorder.³

Treatment of heart failure due to AL amyloidosis differs from patients with systolic or diastolic heart failure. In AL amyloidosis, there are both compressed and disrupted myocardial cells due to amyloid deposits and decreased compliance. Loop diuretics such as furosemide are the

mainstay in the symptomatic management of heart failure in cardiac amyloidosis. Whereas beta-blockers and ACE inhibitors are commonly used for systolic heart failure, they may be ineffective and possibly even detrimental in AL amyloidosis due to dependence on heart rate and profound hypotension, respectively. Calcium channel blockers are contraindicated due their negative inotropic effect. Heart transplant is usually not an option due to non-cardiac organ involvement and availability of effective treatments using chemotherapy and autologous hematopoietic cell transplant.⁴

The Revised Mayo Stage I, II, III, or IV disease is scored zero, 1, 2, or 3 based on NT-proBNP $\geq$ 1800 ng/L, cardiac troponin T $\geq$ 0.025 mcg/L, and a difference between involved and uninvolved serum free light chains $\geq$ 18 mg/dL. These stages correspond to a median overall survival of 94, 40, 14, and 6 months and four-year survival for those receiving hematopoietic stem cell transplant as 87, 72, 56, and 46 percent, respectively.⁵

This case illustrates a rapidly progressive infiltrative restrictive cardiomyopathy presenting as dyspnea on exertion due to diastolic dysfunction, syncope, and conduction system disease manifesting as high degree AV block. Early establishment of the diagnosis may have improved medical management by avoiding beta-blockers and ACE inhibitors.

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