Concurrent Acute Heart Failure and Renal Failure in Amyloid Light Chain Amyloidosis

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ABSTRACT

Introduction: Amyloid light chain (AL) amyloidosis is a multisystem disease with significant variability in patient presentation. This case describes the presentation and workup of a patient with unique multiorgan involvement on initial presentation.

Case Presentation: A 69-year-old African American male presented with weakness, leg swelling, and shortness of breath. Initial workup demonstrated acute heart failure and acute-on-chronic renal failure with nephrotic range proteinuria (5.78 protein to creatinine ratio). Further workup showed elevated serum protein electrophoresis, urine protein electrophoresis, and light chains. Subsequent renal biopsy showed lambda-restricted AL-type renal amyloidosis.

Discussion: A variety of systemic presentations have been described in the literature; however, concurrent heart and renal failure as primary presentation is uncommon.

Conclusions: This case emphasizes the importance of considering systemic inflammatory diseases, such as amyloidosis, in the differential diagnoses of patients with unexplained multiorgan disease. Early diagnosis and treatment initiation are essential for improving patient outcomes. Improved recognition of common clinical manifestations and laboratory abnormalities will likely improve outcomes through earlier diagnosis.

INTRODUCTION

Amyloid light chain (AL) amyloidosis is a plasma cell clonal proliferation that produces monoclonal light chains; and with a reported incidence of 9 to 14 per million people in the United States, it is the most common cause of systemic amyloidosis. Prevalence is greatest in African American males between 60 and 70 years old.[1] Amyloid fibrils form a beta-pleated sheet structure that stains with Congo red and demonstrates light green birefringence under polarized light. Multiorgan involvement is present in more than two-thirds of patients and can include cardiac, renal, liver, soft tissue, and neurovascular involvement.[1] Due to nonspecific multisystem involvement, diagnosis is often delayed. Our case demonstrates unique multisystem organ injury and includes key clinical and diagnostic findings that may be helpful when considering AL amyloidosis as a diagnosis.

CASE PRESENTATION

A 69-year-old African American male with a past medical history of hypertension, hyperlipidemia, peripheral artery disease status post right below-knee amputation, stroke, atrial septal defect, chronic kidney disease (CKD) stage 2, and asthma presented to the emergency department (ED) after he was unable to extract himself from a bathtub. His daily medications included amlodipine, aspirin, atorvastatin, furosemide, hydrochlorothiazide, and prazosin. Over the previous 2 months, he had had symptoms of progressive weakness with frequent falls. He also was noted to have increased left lower leg swelling, persistent shortness of breath, and poor appetite. Symptoms were severe enough that he had been unable to work due to mobility issues.

Vitals on presentation included heart rate 88 beats per minute, respiratory rate 19 breaths per minute, blood pressure 150/93, temperature 97.7 °Fahrenheit, and 99% oxygen saturation on room air. Labs in the ED were notable for sodium 137 mmol/L, potassium 6.9 mmol/L, creatinine 10.65 mg/dL, serum urea nitrogen 108 mg/dL, hemoglobin 8.0 g/dL, and hematocrit 27%. Cardiac workup included troponin 245 ng/L; electrocardiogram (ECG) showed normal sinus rhythm, nonspe-

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cific T wave changes, and prolonged QTc interval at 369 ms; and B-type natriuretic peptide was >70 000 pg/mL. Urinalysis was positive for proteinuria and was quantified with protein to creatinine ratio of 5.78 g/g. More than 3g/g or 300 mg/dl is the common definition of nephrotic range proteinuria and can indicate nephrotic syndrome.[2]

The patient was admitted to the medical intensive care unit (ICU) to address renal failure complicated by hyperkalemia, anuria, and azotemia with the initiation of hemodialysis by nephrology. A point-of-care ultrasound indicated heart failure with reduced ejection fraction. Cardiology was consulted with the working diagnosis of ischemic cardiomyopathy with acute decompensation given past history of pitting lower extremity edema while in clinic several years prior. Formal transthoracic echocardiogram (TTE) showed reduced ejection fraction of 33%, global hypokinesis, left atria/ventricle enlargement, left-sided systolic and diastolic dysfunction, elevated left atrial pressure >15 mmHg, normal right heart size and function, and mild aortic and mitral valve dysfunction. However, the TTE did not show any stippled or irregular edges that would indicate a focal mass or noninvasive diagnosis. His worsening cardiomegaly, progressive edema, and development of ascites not responsive to diuresis, in addition to persistent shortness of breath and weakness, supported the diagnosis of heart failure. Cardiology recommended guideline-directed medical therapy, including carvedilol 12.5 mg twice daily, aspirin 81 mg once daily, hydralazine 5 mg 3 times daily, and isosorbide dinitrate 10 mg 3 times daily. This was consistent with the American Heart Association 2022 Guidelines.[3] With initiation of dialysis and goal-directed medical therapy for heart failure, the patient had gradual symptomatic improvement, including increased strength and decreased subjective shortness of breath. His level of care was decreased, and he was transferred out of the ICU.

Given anuria, hyperkalemia, and proteinuria, nephrology further evaluated the renal failure. Results included a renal ultrasound that did not reveal hydronephrosis or nephrolithiasis and was suggestive of a chronic medical renal disease given small echogenic kidneys (9.6 cm on the right and 7.8 cm on the left). Simple cysts and large-volume ascites also were noted. Given significant and persistent nondiabetic proteinuria, further workup included urine microscopy that revealed dysmorphic red blood cells. Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) also were obtained. SPEP showed elevated lambda (1.04 IgG), UPEP showed elevated free kappa (84.6 mg/L), lambda(125.5 mg/L), and monoclonal IgG lambda. With no clear timeline of progression of his renal disease, and because his labs showed nephrotic range proteinuria (5.78 g/g), dysmorphic red blood cells on urine microscopy, and elevated IgG and lambda on UPEP, we were concerned for monoclonal gammopathy of renal significant or rapidly progressive glomerulonephritis. Therefore, a renal biopsy was obtained and showed lambda-restricted AL-type renal amyloidosis, focal global glomerular sclerosis (72%), and severe interstitial fibrosis and tubular atrophy (70%-80%). See Table 1 for a summary of lab results from his 12-day admission.

Table 1. Relevant Laboratory Values During 12-Day Admission

Labs		Reference Range
Troponin at admission	245 ng/L	0 – 16 ng/L
Troponin at discharge	268 ng/L	0 – 16 ng/L
B-type natriuretic peptide (BNP)	>70 000 pg/mL	0 – 125 ng/mL
Creatinine at admission[a]	10.65 mg/dL	0.7 – 1.3 mg/dL
Free kappa	84.6 mg/L	1.97 – 5.71 mg/L
Free lambda	125.5 mg/L	5.7 – 26.3 mg/L
Kappa/lambda ratio	0.67	0.26 – 1.65
IgG serum	1808 mg/dL	700 – 1600 mg/dL
IgA serum	151 mg/dL	70 – 400 mg/dL
IgM serum	10 mg/dL	40 – 230 mg/dL
IgG lambda monoclonal protein	1.24 g/dL	0.00 g/dL
Hemoglobin range	6.5 – 8.8 g/dL	13.7 – 17.5 g/dL
Calcium range	7.3 – 8.3 g/dL	8.6 – 10.2 mg/dL
Total protein range	6.4 – 6.6 g/dL	6.1 – 8.2 g/dL
Albumin	3.0 g/dL	3.8 – 5.0 g/dL

[a]Patient's baseline creatinine was 2.03 mg/dL prior to admission

Table 2. Relevant Laboratory Values at 10-Day Post-discharge Follow-up

Labs		Reference Range
Troponin	194 ng/L	0 – 16 ng/L
B-type natriuretic peptide (BNP)	>70 000 pg/mL	0 – 125 ng/mL
Creatinine[a]	4.26 mg/dL	0.7 – 1.3 mg/dL
Calcium	8.1 g/dL	8.6 – 10.2 mg/dL
Beta-2 microglobulin	20.9 mg/L	0 – 3.0 mg/L
Bone marrow biopsy	Lambda restricted plasma cell myeloma and negative Congo Red stain for amyloidosis	

[a]Patient's baseline creatinine was 2.03 mg/dL prior to admission

Hematology/oncology was consulted given monoclonal gammopathy of renal significance, and continued outpatient workup was decided given the patient's hemodynamic stability and improvement in subjective symptoms. He was discharged on vitamin D3 2000 units daily for CKD supplementation, epoetin 8000 units subcutaneously 3 times weekly at dialysis for anemia secondary to CKD, and carvedilol l2.5 mg twice daily and isosorbide dinitrate/hydralazine 20mg 3 times daily with meals for new-onset heart failure with reduced ejection fraction (HFrEF). See Table 2 for a summary of lab results at his 10-day post-discharge follow-up. He was referred to oncology for outpatient management and discharged on hemodialysis 3 times per week. A bone marrow biopsy obtained during his outpatient workup and treatment showed lambda restricted plasma cell myeloma <10%, not suggestive of multiple myeloma, which

was treated with cyclophosphamide, bortezomib, and dexamethasone (CyBordD). Over the next several months, the patient had repeated hospitalizations due to heart failure progression and further reduction in left ventricular ejection fraction (13%), which ultimately led to his death.

DISCUSSION

Amyloid deposition can occur in any organ, but organ toxicity is most often seen in cardiac, renal, and soft tissues. Cardiac amyloidosis is the most important determinant of survival, and early diagnosis is critical for successful treatment. Our patient presented with unexplained acute heart failure and acute-on-chronic renal failure, causing high concern for systemic inflammatory diseases, such as amyloidosis. Due to multisystem involvement and high clinical suspicion for a systemic disease, a definitive diagnosis was obtained prior to further outpatient cardiac workup. Other diagnoses considered included focal segmental glomerulosclerosis due to acute onset nephrotic syndrome, peripheral edema, hypoalbuminemia, and increased prevalence in African Americans, but this would not have explained the patient's new heart failure. Diabetes must also be considered in patients with significant proteinuria, but this would not have explained the heart involvement or profound and progressive fatigue in our patient. Lastly, labs also were concerning for multiple myeloma, but organ biopsy – a renal biopsy in this case – was critical in making the definitive diagnosis. Due to the invasive nature of organ biopsy, ruling out more common causes of renal or cardiac disease should be the first step in working up these patients. When other diagnoses are ruled out, clinicians should consider multiorgan systemic diseases in their differential diagnosis.

Symptoms of amyloidosis are always preceded by monoclonal gammopathy, but presymptomatic diagnosis is not always possible and high clinical suspicion must guide medical workup. Initial symptoms often are nonspecific, and routine laboratory tests often are not sensitive enough for diagnosis. A wide variety of clinical manifestations should warrant further investigation.

Cardiac involvement is present in 71% of patients, renal involvement in 58%, nerve involvement in 23%, and liver involvement in 16%.[4] Abdominal organ involvement can manifest in many ways, including gastric cystic masses, amyloid deposits in the gallbladder, and even soft tissue infiltration.[5] Nondiabetic nephrotic range proteinuria and even renal failure can be caused by renal amyloidosis. Cardiac amyloidosis is a restrictive cardiomyopathy that presents with classic left heart failure symptoms. The characteristic clinical features of cardiac involvement include diastolic heart failure with preserved apical systolic function, thickened ventricles, and low voltage ECG. Peripheral neuropathy can be confused with diabetic neuropathy but can be caused by amyloidosis. Periorbital purpura is specific for AL amyloidosis and is caused by vascular fragility. Several clotting alterations of systemic amyloidosis have been described, including defective fibrinogen conversion, reduced factor X levels, and other fibrinogen or antiplasmin abnormalities.[6] However, our patient had an INR of 1.0 and no concerns for bleeding thus did not receive further hematology workup. Macroglossia can be seen and is caused by soft tissue deposition of amyloid. Hepatomegaly and gastrointestinal symptoms also can be seen in some patients, as well as anemia due to iron deficiency from high cell turnover.[7]

For suspected amyloidosis, the initial workup should include serum free light chain assay, serum immunofixation electrophoresis, or urine immunofixation electrophoresis to assess for monoclonal protein. Baseline testing of serum creatinine, estimated glomerular filtration rate, 24-hour urine protein, clotting studies, liver function testing, troponin, N-terminal pro b-type natriuretic peptide, and ECG are also normally obtained at this time. If monoclonal protein is present, bone marrow biopsy or fat aspirate can provide a definitive diagnosis. The type of tissue biopsy is often the organ of known involvement, but bone marrow biopsy or fat aspiration often should be considered first. Fat aspiration in particular is often underutilized and can provide adequate diagnosis in a less invasive manner than bone marrow biopsy or solid organ biopsy.[8] In patients with a negative bone marrow biopsy but with a high clinical suspicion of amyloidosis, a biopsy of an affected organ may be necessary to provide definitive diagnosis. Definitive diagnosis, including the type of amyloidosis, must be made by tissue biopsy. At this point, patients often are referred to a hematologist for further management. Diagnosis of AL amyloidosis carries a 20% 6-month mortality rate, but early diagnosis and treatment can improve prognosis from a matter of months to years in some patients. Treatment can include medications – such as monoclonal antibodies, which are constantly being developed – in addition to stem cell transplantation.[9]

CONCLUSIONS

Our patient presented with acute onset heart failure, acute-on-chronic kidney failure with nephrotic syndrome, anemia, diarrhea, and fatigue. These symptoms all can be explained by AL amyloidosis. Amyloidosis is a challenging diagnosis given a nonspecific presentation and multiorgan involvement. Clinical suspicion should be raised for patients with unexplained multiorgan involvement and the clinical findings described above. Early diagnosis and treatment initiation could lead to better outcomes and longer lifespans for these patients.

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