

■ CASE STUDY

An Unusual Presentation and Etiology of Hypotension Seen in Nephrotic Syndrome

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Objective and Clinical Importance

An unusual clinical case of hypotension and acute kidney injury seen in a patient with underlying nephrotic syndrome is presented with an emphasis on understanding the differential diagnosis as well as the pathophysiology of the underlying disease.

Case History

A woman, age 58 years, reported having experienced presyncopal dizziness for two weeks. During her physical examination, her systolic blood pressure was found to be approximately 70 mm Hg. She reported that for two weeks, she had taken 20 mg of furosemide daily for lower-extremity edema. She said that she had not had any chest pain, palpitations, shortness of breath, fever, or hypothermia and did not have any history of bleeding, diarrhea, polydipsia, dysuria, seizures, or abdominal pain. She did exhibit gastrointestinal symptoms of nausea and early satiety as well as urinary symptoms of polyuria and nocturia. Her medical history included hyperlipidemia and rheumatoid arthritis. She had no history of diabetes, liver disease, or cardiac disease. She had at one time undergone a hysterectomy and an appendectomy. She reported that she did not use

tobacco, alcohol, or street drugs. Her prescribed daily dosages of oral medications included 20 mg of furosemide; 20 mg of simvastatin; 20 mg of omeprazole; 40 mg of benazepril; 200 mg of Oysco 500; and hydrocodone-acetaminophen, which she had been taking for several months. She was not taking any disease-modifying agents for her rheumatoid arthritis. Her vital signs were as follows: blood pressure, 70/30 mmHg; temperature, 98.6°F (37°C); pulse rate, 96 beats per minute; respiration rate, 18 breaths per minute; oxygen saturation, 99%; weight, 75 kg. The physical examination demonstrated bilateral 2+ pedal edema, several bruises on her back and legs, and right-eye subconjunctival hemorrhage. Jugular venous pressure was not elevated, and there were no rales. The patient did not have any joint deformities. The patient had negative results on guaiac testing.

Case Workup

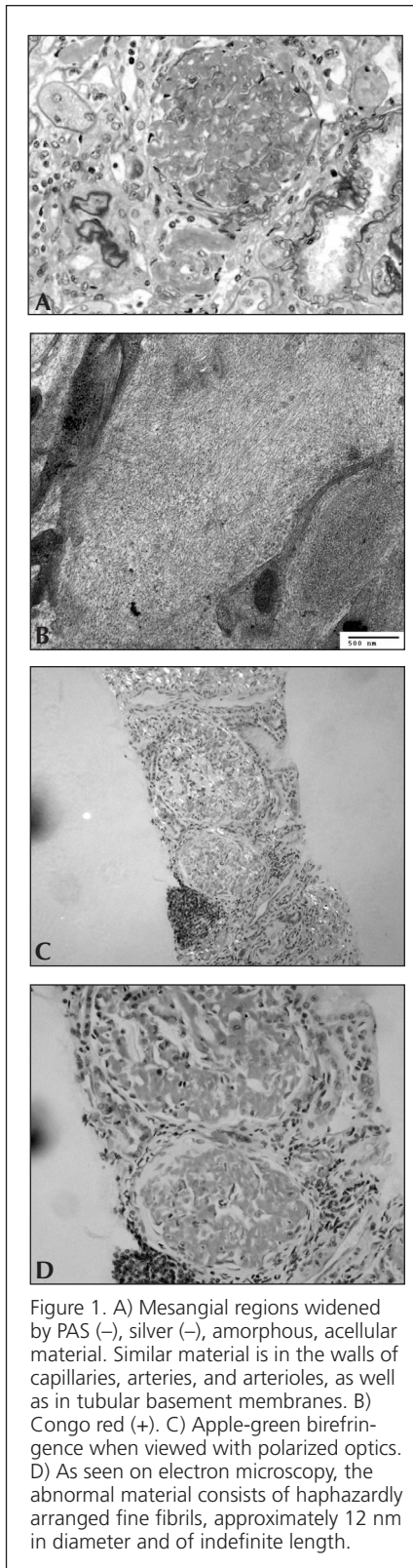
Initial investigative workup produced normal echocardiography findings, negative findings on tests for cardiac enzymes, negative findings on blood cultures, a finding of a low level of thyroid-stimulating hormone, and a finding of a normal level of free T₄, the latter three of which ruled out cardiac dysfunc-

tion, septicemia, and hypothyroidism, respectively. Her laboratory testing also revealed acute kidney injury, with a creatine level of 7.3 mg/dL (compared with a baseline of 1.1 mg/dL). Dipstick urinalysis revealed 2+ protein, no blood, and 1+ glucose, although her serum glucose was 100 mg/dL with no history of diabetes mellitus. A 24-hour urine quantitation revealed 19 g of protein and a urine albumin level of 10 g in a collection of 2.4 L. Her proteinuria, together with her clinical presentation of peripheral edema and later laboratory findings of hypoalbuminemia and hyperlipidemia, indicated that she had nephrotic syndrome. The differential diagnosis included primary glomerular diseases, such as minimal-change disease, focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis, as well as secondary causes such as systemic diseases, including diabetes, human immunodeficiency virus, hepatitis B or C, myeloma, and amyloidosis.

The discrepancy between the total urine albumin and total urine protein quantitation suggested a paraproteinemic process. The chemistry panel also revealed a nonanion-gap metabolic acidosis with a serum bicarbonate of 14 mEq/L.

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The urinalysis also demonstrated glucosuria despite a normal serum glucose level, further suggesting renal tubular dysfunction. A renal infiltrative process was suspected. The decrease in blood pressure after the patient began taking a low dose of furosemide also suggested possible vascular rigidity and involvement. Renal ultrasonography demonstrated normal kidney size and echogenicity bilaterally. Urine and serum protein electrophoresis produced negative findings for any light chains (LCs) or monoclonal spikes by immunofixation, respectively.

Diagnosis

A renal biopsy was performed and revealed both renal and vascular amorphous material deposition in the mesangium, capillary walls, interstitium, arteries, and arterioles (Figure 1). Congo red staining produced positive results, and apple-green birefringence was present on polar spectroscopy. Immunofluorescence demonstrated immunoglobulin A (IgA) (4+), IgM (1–2+), and λ LCs (3+) in the capillary walls and mesangial regions of all the glomeruli in a diffuse pattern, in the interstitium, and in tubular casts. Electron microscopy revealed fibrillary deposition in the mesangial regions of the glomeruli, interstitium, and walls of the arteries and arterioles. The abnormal material consisted of haphazardly arranged fine fibrils, approximately 12 nm in diameter and of indefinite length. The definitive diagnosis was primary systemic (AL) amyloidosis.

Discussion

Amyloidosis, a multisystem disease, can manifest in different ways with varying severity. Its major classifications are AL amyloidosis, composed of Ig LCs and arising from a clonal B-cell disorder; familial (AF)

amyloidosis, most commonly due to transthyretin; and secondary (AA) amyloidosis, which is composed of the acute-phase reactant serum amyloid A protein that occurs in the setting of chronic inflammatory or infectious diseases. Clinically relevant renal involvement mainly occurs in AL or AA amyloidosis.¹

AL amyloidosis is the most common type of systemic amyloidosis in North America. It is estimated to affect 5 to 12 people per million each year, although autopsy studies suggest that the incidence might be higher.² More than 90% of patients have a serum or urine monoclonal Ig protein that can be detected by immunofixation electrophoresis or free-LC assay.³ The standard serum protein electrophoresis and urine protein electrophoresis are not useful screening tests because the clonal Ig in AL amyloidosis, unlike in multiple myeloma, is often not present in sufficient quantity in the serum to produce a monoclonal “M spike” on these tests.⁴ This phenomenon was illustrated in the patient discussed here whose urine and serum protein electrophoresis produced negative findings for any LCs or monoclonal spikes by immunofixation, respectively. The clonal Ig was detected in the patient, however, by immunofluorescence on the renal biopsy, revealing IgA (4+), IgM (1–2+), and λ LCs (3+) in the capillary walls and mesangial regions of all the glomeruli in a diffuse pattern, in the interstitium, and in tubular casts.

AL amyloidosis is usually a rapidly progressive disease that presents with characteristic clinical syndromes, recognition of which is key to making the diagnosis. The kidneys are the most frequently affected organs in approximately 80% of patients with the disease.⁵ The paraproteinemia, proteinuria,

hypoalbuminemia, and edema seen in the patient discussed here were the result of amyloidosis having caused nephrotic syndrome with tubular dysfunction and glomerular injury. Cardiac dysfunction, which the patient did not exhibit, is the second most common presentation. Involvement of the nervous system can include peripheral sensory neuropathy, carpal tunnel syndrome, and autonomic dysfunction with gastrointestinal motility disturbances (early satiety, diarrhea, constipation) and orthostatic hypotension. Our patient did exhibit certain clinical features suggesting the presence of autonomic dysfunction, such as dizziness, nausea, early satiety, and polyuria; however, her hypotension and dizziness quickly resolved after minimal fluid resuscitation.

Occasional patients have a different renal presentation because the amyloid deposits are primarily limited to the vessels, leading to narrowing of the vascular lumens. These patients usually present with slowly progressive chronic kidney disease with little or no proteinuria. Along with both glomerular and tubular involvement, the patient discussed here had vascular involvement, illustrated by deteriorated renal function, with low-dose diuresis causing further worsening of renal function, which was aggravated by the presence of angiotensin-converting inhibitor in the setting of

low blood pressure. As mentioned earlier, the patient also had several areas of ecchymosis on her back and legs as well as subconjunctival hemorrhage, further suggesting the presence of peripheral capillary vascular compromise due to amyloid infiltration. Vasculature with amyloid infiltration cannot respond normally with appropriate vasoconstriction when presented with slight hypovolemia due to mild diuresis.⁶ As expected, the patient's hypotension quickly resolved after minimal fluid resuscitation, given the increased vascular rigidity caused by the amyloid infiltration. This allowed for adequate perfusion to the kidneys, resulting in the rapid correction of the patient's acute kidney injury.

Conclusion

Amyloidosis is a multisystem disease that can manifest in different ways with varying severity. The case discussed here illustrates an unusual presentation of hypotension due to amyloid infiltration of the vasculature, leaving the patient susceptible to acute kidney injury even from what is generally considered mild diuresis. Paraproteinemia and proteinuria were due to the amyloidosis having caused nephrotic syndrome with tubular dysfunction and glomerular injury. The patient's hypotension and acute kidney injury, which likely occurred because of the in-

creased vascular rigidity caused by amyloid infiltration, did eventually resolve with volume resuscitation. It was planned for the patient to be evaluated by a hematologist for a more specific workup and therapy, but she left and did not return. ♦

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Urine

All we know for certain about the kidney is that it makes urine.

— Homer William Smith, ScD, 1895 – 1962, *American physiologist and advocate for science*