Case in Point

A 37-Year-Old Man With Symptoms of Fatigue, Malaise, and Dizziness

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This case reviews the presentation, workup, management, and clinical course of a patient with renal amyloid associated amyloidosis resulting in nephrotic syndrome.

A common abnormal test result in adults in any primary care practice is proteinuria, whose cause can range from the benign to the more serious. Urinary protein excretion of more than 3 g per 24 hours is likely a result of a glomerular disease and defines the nephrotic syndrome when associated with hypoalbuminemia, edema, hyperlipidemia, and lipiduria. Glomerulonephropathy has a myriad of causes, among which amyloidosis is considered a secondary cause. We report a case of nephrotic syndrome caused by amyloid associated (AA) amyloidosis, which we suspected was due to chronic systemic inflammation from hidradenitis suppurativa.

CASE PRESENTATION

A 37-year-old man with a history of hidradenitis suppurativa was seen in the emergency room (ER) for symptoms of worsening fatigue, malaise, and dizziness that persisted for 1 week. The patient had been to the ER 1 week prior for fatigue secondary to anemia, which required transfusion. The patient refused admission but then returned with worsening symptoms. His chief concern was weakness and dizziness lasting 15 to 20 minutes, which was alleviated by rest. His dizzy spells were sporadic but more frequent on awakening. On review of his systems, the patient described an unintentional weight loss of about 5 to 6 pounds per week, with a 40-pound loss over the last 2 years, attributed to an ongoing loss of appetite.

The patient had no headaches, visual disturbances, tinnitus, fever, or sore throat. He had no shortness of breath, cough, sputum, and hemoptysis. He also had no chest pain, palpitations, and claudication, but he did notice swelling of his legs. He did not have abdominal pain, melenic stools, and hematemesis. He also did not have any lower urinary tract symptoms, but he did notice foamy urine. He did not have polydipsia, polyphagia, and heat or cold intolerance. He also noted generalized xerosis with small amounts of drainage from his right axilla, lower back, neck, and groin lesions.

The patient did not have any musculoskeletal concerns. In addition to hidradenitis suppurativa, his past medical history was significant for sickle cell trait (SCT) and beta thalassemia, hypertension, hyperlipidemia, and subclinical hypothyroidism (probably renal related due to the loss of the total binding globulin in his urine, as he became euthyroid later in the course of the disease).

He had allergies to gatifloxacin, infliximab (chosen based on case reports of anti-tumor necrosis factor (TNF) therapies being effective with hidradenitis suppurativa), and isotretinoin. His current medications included alendronate, calcium with vitamin D, simvastatin, prednisone, hydrochlorothiazide (HCT), gabapentin, morphine, and topical anesthetics. His past surgical history was notable for surgeries for multiple abscesses (right axilla, groin, scrotum, and posterior neck) and an aortic-valve replacement surgery following infectious endocarditis secondary to line sepsis—this admission was for a hidradenitis suppurativa flare and the peripherally inserted central catheter (PICC line) was for intravenous antibiotics. Unfortunately, records of this admission showed no echocardiogram report, although the physicians reported it was done.

The patient lived with his wife and sons and did not smoke or drink alcohol. He said he never used illicit substances. His family history was significant for a 30-year-old brother who died of renal-cell carcinoma.

INITIAL EXAM

The patient's temperature was 98.6°F,

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Table 1. Laboratory tests

Test name	Result	Reference range
Transferrin	140 mg/dL	180-329 mg/dL
TIBC[a] calculator[b]	188 mcg/dL	240-400 mcg/dL
Ferritin	121.5 ng/mL	22-322 ng/mL
Hb F	0.0%	0.0-2.0%
Hb S	31.4%	0.0-0.0%
Hb C	0.0%	0.0-0.0%
Hb A	64.6%	94-98%
Hb A2	4.0%	1.5-3.0%
Hb solution	Positive	Negative
QIG-IgA[c]	412 mg/dL	82-453 mg/dL
QIG-IgM	93.6 mg/dL	46-304 mg/dL
QIG-IgG	1,150 mg/dL	751-1,560 mg/dL
QIG-κ	924 mg/dL	629-1,350 mg/dL
QIG-λ	530 mg/dL	313-723 mg/dL

[a]TIBC: Total iron-binding capacity; [b]Evaluation: TIBC calculator = Transferrin x 1.34; [c]QIG: Quantitative immunoglobulin.

pulse 71 beats per minute, blood pressure 124/73 mm Hg, respirations 19 breaths per minute, and oxygen saturation 98% on room air. He was well-groomed, in no apparent distress, and well nourished. He was alert and fully oriented. His head was normocephalic, atraumatic, pupils equally round and reactive to light, extraocular muscles were intact, conjunctivae were pale, sclera anicteric, and the oropharynx was nonerythematous. His chest had a healed sternotomy scar.

The cardiovascular examination was unremarkable with a jugular venous pressure estimated to be 6 cm. The lungs were clear to auscultation bilaterally. The abdomen was rotund with striae, soft and nontender, without evidence of organomegaly. Bowel sounds were normal. He had bilateral lower extremity pitting edema without clubbing or cyanosis. Pulses were strong bilaterally. His skin had multiple areas of scarring and fibrosis of the posterior neck, bilateral axillae, perianal, perineal, and buttock regions.

Laboratory data revealed an increase in serum creatinine from baseline of 0.8 mg/dL to 1 mg/dL to 2.4 mg/dL and an increase in blood urea nitrogen from baseline of 6 mg/dL to 10 mg/dL to 44 mg/dL. The complete blood count was significant for hemoglobin (Hb) of 6.9 g/dL and hematocrit of 21.8%, with baseline indexes of 9 g/dL and 28%, respectively. The mean corpuscular volume was 60.6 fL and mean corpuscular Hb was 19.4 pg. His platelets were at 478,000. His white blood cell (WBC) count had been chronically elevated and on presentation was 21.7 K/uL, which was at his baseline value WBC. The differential diagnosis was significant for an increased absolute neutrophil count of 207,000 uL. His urinalysis revealed a proteinuria range of 300 to 600 mg/dL but bland sediment on microscopy without evidence of infection.

Plain radiograph of the chest was normal with no pulmonary infiltrates or effusions and post sternotomy changes with aortic valve replacement noted. The patient was admitted for treatment of acute renal failure and anemia.

DIAGNOSIS AND TREATMENT

Over the course of the patient's 3-day hospitalization, he received a transfusion of 2 units of packed red blood cells, which increased his Hb to 8.1 g/dL. The laboratory workup of his anemia revealed a mixed anemia consistent with chronic disease, iron deficiency, SCT, and beta thalassemia (Table 1). Previous outpatient workup for proteinuria revealed a 24-hour proteinuria of 5.9 g/day with hypoalbuminemia and an elevated low-density lipoprotein cholesterol. A 2.5 g increase of 24-hour urine protein was observed within a 2-week period. A partial immunologic workup was then conducted and completed at his admission. During his hospitalization, his serum creatinine increased from 2 mg/dL to 4 mg/dL, with continuing proteinuria, and the nephrology service was consulted.

A common approach to the differential diagnosis of nephrotic syndrome is to identify whether the nephrotic syndrome may be due to a primary or secondary cause (Table 2). In adults, systemic diseases such as diabetes, systemic lupus erythematosus, and amyloidosis can account for almost 30% of nephrotic syndrome cases. Primary renal disorders make up the remaining cases with minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy leading the group. Interestingly, published reports cite mem-

branous nephropathy, followed by minimal change disease, as the most common malignancy-associated glomerulonephropathy, occurring with many carcinomas and occasionally with leukemia and lymphoma.[1]

Pathological Diagnosis

A transjugular needle biopsy of the kidney was performed to determine the cause of the proteinuria. Unfortunately, there was not sufficient tissue to evaluate for glomerular disease. However, tissue from the cortico-medullary junction stained with Congo red was diagnostic of AA amyloidosis.

TREATMENT AND OUTCOME

This 37-year-old man had nephrotic syndrome due to secondary amyloidosis. Treatment of nephrotic syndrome can be divided into general and specific modalities.[2] General treatments aim to reduce proteinuria and lessen peripheral edema. It is generally necessary to administer angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers to control the proteinuria, and a loop diuretic is usually required to treat the peripheral edema. The associated hyperlipidemia typically resolves or reverses with resolution of the nephrotic syndrome. Initiation of anticoagulant treatment may be necessary as these patients have a higher incidence of thromboembolic events.

Specific control of the underlying inflammatory process, giving rise to the amyloid, ideally helps control the nephrotic syndrome. Renal amyloidosis, which is rapidly progressive and associated with a poor prognosis, has no standardized therapy. Prognostic factors in amyloidosis include the quantity of amyloid deposition in the kidney and the extent of glomerular, tubulointerstitial, and vascular damage.[3] Frequent measurements of the serum amyloid A (SAA) protein concentrations may guide empiric anti-inflammatory treatment in similar patients.[4]

Colchicine has become the accepted therapy for secondary amyloidosis, particularly in cases due to familial Mediterranean fever. Newer agents that specifically interfere with fibril formation are still under development.[5] Administration of immunosuppressive and cytostatic drugs can be initiated only after the evaluation of the renal histology and determination of overall risk status of the patient. Steroids, used as immunosuppressives, can be supplemented with other cytostatic treatments. New therapies, such as mycophenolate mofetil or rituximab, can be used in resistant cases.

Our patient was treated symptomatically with fluid restriction, irbesartan, a low-salt diet, and HCT. He also received a blood transfusion. However, he opted to leave the hospital in 3 days and follow up as an outpatient to specialty clinics.

DISCUSSION

Secondary AA amyloidosis is a systemic disorder caused by tissue deposition of fibrils composed of SAA protein fragments. The SAA protein is an acute phase reactant whose levels may be persistently elevated in rheumatic or chronic inflammatory conditions (eg, chronic infections). Unlike light chain amyloidosis (AL), AA amyloidosis has become a less prevalent

Table 2. Differential diagnosis of nephrotic syndrome

Primary

- Minimal change disease
- Focal segmental glomerulosclerosis
- Membranous nephropathy
- Membranoproliferative glomerulonephritis
- Rapidly progressive glomerulonephritis
- Congenital/genetic syndromes
  - -Denys-Drash syndrome, Frasier syndrome, familial focal segmental glomerulosclerosis, Galloway-Mowat syndrome, oculocerebrorenal syndrome

Secondary

- Infections
  - -Hepatitis B, hepatitis C
  - -HIV/AIDS
  - -Syphilis, malaria, CMV, rubella, toxoplasmosis
- Drugs
  - -Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - -Interferon
  - -Heroin
  - -Gold, mercury, lithium
  - -Penicillamine
  - -Pamidronate
- Systemic illnesses
  - -Diabetic nephropathy
  - -Vasculitides: Wegner's granulomatosis, Churg-Strauss syndrome, polyarteritis nodosa, Henoch-Schönlein purpura, systemic lupus erythematosus
  - -Malignancies: carcinoma, lymphoma, leukemia
  - -Immune complex deposition: IgA nephropathy, postinfectious glomerulonephritis (later stage), primary amyloidosis, secondary amyloidosis

Adapted from Seldin DC, Skinner M. Amyloidosis. In: Fauci AS, Braunwald E, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine.* 17th ed. New York, NY: McGraw-Hill Companies, Inc; 2008:chap 28.

disease entity due to the reduced incidence of diseases such as tuberculosis, osteomyelitis, or bronchiectasis in the Western Hemisphere.[6]

In one study, renal involvement represented by nephrotic syndrome and renal failure were observed in 59% and 54% of cases, respectively.[6] The presence of lambda light chains, either in serum or urine, is associated with higher levels of proteinuria and reduced renal function. The distribution pattern of glomerular amyloid deposits and the glomerular inflammatory reaction are independent factors influencing proteinuria level. Tubular atrophy and the abundance and distribution pattern of glomerular amyloid deposits at the time of biopsy are independent predictors of renal outcome.

Since patients with AA amyloidosis show decreased renal function at presentation relative to patients with AL amyloidosis, patients with chronic inflammatory disorders should be routinely evaluated for amyloidosis.[6] Despite the possible significant latency between the onset of inflammation and clinical presentation with AA amyloidosis, amyloid progression can be rapid, thus a timely diagnostic tissue biopsy should be pursued.

The factors associated with a poor prognosis include older age, a reduced serum albumin concentration, preexisting renal dysfunction at baseline, and the degree of SAA elevation during follow-up. Increased production of SAA was the most powerful risk factor for end-stage renal failure and death but was also one that could be ameliorated through anti-inflammatory treatment; in one study, stabilization or regression of amyloid deposits and prolonged survival were inversely related.[3,7] Glomerular involvement can thus be considered as the determining histological factor for predicting clinical manifestations and final outcome of renal AA amyloidosis.[8]

In our patient, despite the multitude of infections over time, including treatment-related adverse effects, the original reason for these infections were hidradenitis suppurativa flareups, and we dare to postulate that hidradenitis suppurativa caused the AA amyloidosis. Hidradenitis suppurativa is the only recurrent infection for all the years of patient care and hospitalizations. A similar case report by Titze et al recounted a male of the same age at presentation who had the same fistulization in both axillary, inguinal, and perineal area, cardiac involvement, and multiple surgeries.[9] He was treated for secondary infections with intravenous antibiotics. He also developed progressive kidney disease and nephrotic syndrome treated in the same manner as our case (ramipril, triamterene, and HCT). The major difference from our case is a strong family history of hidradenitis suppurativa, which, according to our patient, was not part of his family history. The other concomitant diagnosis in our patient of SCT was beta thalassemia, which has no documented relationship with nephrotic syndrome. A PubMed review did not reveal any correlation as of this writing. According to the case series report, the optimal method for diagnosis of AA amyloidosis remains controversial.[10]

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