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Kidney Biopsy Teaching Case

Recurrent AA Amyloidosis in a Kidney Transplant

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Recurrent AA amyloidosis in a kidney transplant is rare, especially when the underlying inflammatory condition is controlled. We present a 59-year-old man who underwent a living donor kidney transplant 17 years ago for kidney failure due to AA amyloid nephropathy in the setting of long-standing Crohn disease. His Crohn disease was quiescent before and after the kidney transplant. Transplant function had been stable until a month before presentation, when he developed worsening proteinuria and decreased kidney function. A transplant biopsy showed recurrent AA amyloidosis despite excellent clinical and histologic control of Crohn disease.

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INDEX WORDS: AA amyloidosis; kidney transplant; Crohn disease; proteinuria; recurrence; decreased kidney function.

INTRODUCTION

Kidney transplant is an accepted treatment for patients with end-stage kidney failure due to AA amyloidosis. Recurrent AA amyloidosis in the kidney transplant is rare, especially when the underlying inflammatory condition is controlled. We present a case of AA amyloidosis associated with long-standing Crohn disease that recurred in the kidney transplant 17 years after transplant despite excellent control of Crohn disease.

CASE REPORT

Clinical History and Initial Laboratory Data

A 59-year-old man presented in September 2010 with progressive weakness, fatigue, and hypotension. Crohn disease was diagnosed when he was 20 years old, and he underwent multiple small-bowel resections in 1982-1989, resulting in ~120 cm of small bowel remaining. After the bowel resections, Crohn disease was well controlled and he was taken off medications for Crohn disease in 1990. He had symptoms of short gut syndrome, which he controlled through dietary modification; he ate small meals 8 times a day and on average had 2-3 soft to firm stools daily. In 1992, he developed heavy proteinuria and decreased kidney function, and AA amyloid nephropathy was diagnosed by means of kidney biopsy. In 1993, shortly after he developed kidney failure, he underwent a living donor kidney transplant at the age of 42; the kidney was donated by his brother. Apart from an episode of acute cellular rejection that resolved with steroid treatment, during the next 17 years, transplant function was stable with serum creatinine concentrations of 1.4-1.7 mg/dL (123.7-150.3 μmol/L) and estimated glomerular filtration rate (eGFR) of 45-60 mL/min/1.73 m^2 (0.75-1 mL/s/1.73 m^2; calculated using the 4-variable MDRD [Modification of Diet in Renal Disease] Study equation[1]). He was maintained on a stable regimen of azathioprine and low-dose prednisone. A kidney transplant biopsy was performed in April 2009 for evaluation of proteinuria with protein excretion of 283 mg/24 h (predicted from a spot urine protein to osmolality ratio). Serum creatinine concentration was stable at 1.5 mg/dL (132.6 μmol/L), and eGFR was 51 mL/min/1.73 m^2 (0.85 mL/s/1.73 m^2) at that time. The biopsy specimen showed that 4 of 10 glomeruli were globally sclerotic. Glomeruli showed no mesangial matrix expansion or hypercellularity, no segmental scar, and no glomerular basement membrane thickening. Approximately 5%-10% focal interstitial fibrosis and tubular atrophy were present. One artery was present and had minimum fibrotic intimal thickening and no evidence of endothelialitis. No amyloid fibrils were detected on electron microscopy.

In July 2010, the patient developed bacterial bronchitis requiring intravenous antimicrobials administered through an upper-arm peripherally inserted central catheter. In the course of the treatment, he developed deep vein thrombosis in the arm and anticoagulation therapy was started. In August, he noted lower-extremity fluid retention, and evaluation showed proteinuria with a urine protein to osmolality ratio of 2.9, sharply increased from baseline. Proteinuria was confirmed using a 24-hour urine collection that showed 2.13 g of protein excretion. Serum creatinine level subsequently increased to 2.6 mg/dL (229.8 μmol/L; eGFR, 27 mL/min/1.73 m^2 [0.45 mL/s/1.73 m^2]) from 1.5 mg/dL (132.6 μmol/L; eGFR, 51 mL/min/1.73 m^2 [0.85 mL/s/1.73 m^2]) 2 months prior, and serum albumin level decreased to 2.4 g/dL (24 g/L) from 3.7 g/dL (37 g/L) 3 months prior. The following month, serum creatinine level increased further to 3.2 mg/dL (282.8 μmol/L; eGFR, 21 mL/min/1.73 m^2 [0.35 mL/s/1.73 m^2]), urine protein excretion increased to 4.3 g/24 h, and serum albumin level decreased to 1.8 g/dL (18 g/L; Fig 1). In light of these changes, anticoagulation therapy was withheld temporarily and a transplant kidney biopsy was performed.

Kidney Biopsy

The sample submitted for light microscopy contained 20 glomeruli, of which 3 were globally sclerosed. Glomeruli showed mild mesangial expansion with periodic acid–Schiff–negative acellular material. Proliferative features were not present. Glomerular base-

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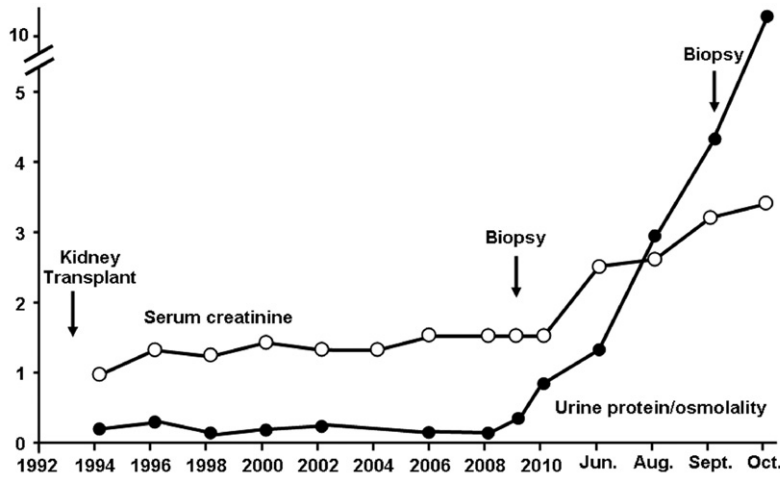

Figure 1. Time course of the patient's urine protein to osmolality ratio, serum creatinine (mg/dL), estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2), and serum albumin (S. Alb; g/dL) values after kidney transplant is shown. Arrows indicate the time of transplant biopsies. Conversion factor for units: serum creatinine concentration in mg/dL to μmol/L, $\times$88.4; eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, $\times$0.01667; serum albumin in g/dL to g/L, $\times$10.

ment membranes were slightly thickened with acellular material along the capillary walls; basement membrane spikes or pinholes were not present along the capillary walls. Significant interstitial inflammation was not present, and there was mild tubular atrophy and interstitial fibrosis. Arteries and arterioles showed moderate thickening of vessel walls with periodic acid–Schiff–negative acellular material. Congo Red stain was positive, showing reddish-brown material in glomeruli, interstitium, and vessels. The material showed apple-green birefringence under polarized light. Immunoperoxidase staining for serum amyloid A was strongly positive, and serum amyloid A was present predominantly in the vessels and focally in the interstitium and glomeruli. Immunofluorescence microscopy was negative for all immunoglobulins, including κ and λ light chains. Electron microscopy showed small collections of amyloid fibrils in the mesangium and along the basement membranes; vascular amyloid fibrils also were noted. Mean fibril thickness was 9.3 nm (Fig 2).

Diagnosis

AA amyloidosis in the kidney transplant involving vessels, interstitium, and glomeruli.

Clinical Follow-up

The patient was evaluated by pulmonology and gastroenterology. Bronchoscopy was positive for *Pneumocystis jirovecii*. Esophageal gastroscopy and colonoscopy showed no evidence of active Crohn disease. He was treated with concomitant prednisone and trimethoprim-sulfamethoxazole for *P jirovecii* infection and responded well. However, he subsequently developed pneumonia caused by *Pseudomonas aeruginosa*, and ertapenem therapy was started. At the 2-month follow-up, the bronchitis had resolved, but serum creatinine level remained at 3.6-3.8 mg/dL (318.2-335.9 μmol/L; eGFR, 16-18 mL/min/1.73 m^2 [0.26-0.3 mL/s/1.73 m^2]) off renal replacement therapy.

DISCUSSION

Recurrent AA amyloidosis in a kidney transplant typically presents as proteinuria and decreased transplant function, which clinically may resemble allograft nephropathy. However, transplant loss related to this entity is uncommon. We describe a patient with recurrent AA amyloidosis in the kidney transplant related to Crohn disease presenting as worsening proteinuria and decreased transplant function 17 years after the kidney transplant.

AA amyloidosis is caused by extracellular deposition of amyloid A protein formed from the precursor serum amyloid A, an acute-phase protein produced and secreted by hepatocytes in response to inflammation. AA amyloidosis occurs in up to 6% of patients with any condition associated with a sustained acute-phase response or chronic inflammatory disorders, including familial Mediterranean fever, rheumatoid arthritis, ankylosing spondylitis, chronic infection (eg, tuberculosis, osteomyelitis, and bronchiectasis), and inflammatory bowel disease. The incidence of AA amyloidosis due to long-standing Crohn disease varies widely depending on geographic areas. In the United States, ~0.5%-0.9% of patients with Crohn disease develop AA amyloidosis.[2,3]

The kidney is the major organ affected by AA amyloidosis: >80% of patients with AA amyloid show kidney involvement. The clinical features of AA amyloid nephropathy are proteinuria and kidney failure. End-stage renal failure is the cause of death in 40%-60% of cases.[4]

Kidney transplant has been accepted as a treatment for patients with kidney failure due to AA amyloidosis.[5] These patients show a lower rate of transplant rejection compared with patients without amyloido-