Recurrent AA Amyloidosis Combined With Chronic Active Antibody-mediated Rejection After Kidney Transplantation

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Kidney transplantation for amyloidosis remains a contentious issue. Recurrence of amyloidosis is one of the risks of transplantation. Chronic active antibody-mediated rejection is an important cause of chronic allograft dysfunction. A 47-year-old woman underwent kidney transplantation due to renal AA amyloidosis with unknown etiology. Six years posttransplantation, a kidney biopsy showed AA amyloidosis with chronic active antibody-mediated rejection. Donor-specific antibody class II was positive. The patient underwent intravenous plasmapheresis and treatment with rituximab and colchicine. The relationship between recurrence of amyloidosis and rejection was not obvious. Clinical characteristics of kidney transplantation for AA amyloidosis were subjected to literature review and 315 cases were identified. The incidence of amyloidosis recurrence and acute and chronic rejection rates were 15%, 15%, and 8%, respectively. Five-year patient and graft survival rates were 77% and 82%, respectively. Clinical courses of kidney transplantation in AA amyloidosis were, thus, identified.

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Case Report

INTRODUCTION

Kidney transplantation is a contentious issue in patients with amyloidosis. Recurrence of amyloidosis can be a risk to the implanted kidney and to extrarenal organs. Chronic active antibody mediated rejection is known as a main cause of late kidney allograft dysfunction.[1] Because of the rarity of transplantation for amyloid A (AA) amyloidosis, the rate of recurrence and incidence of rejection are not well documented. Herein, a case of AA amyloidosis recurrence combined with chronic active antibody mediated rejection in a transplanted kidney is presented.

CASE REPORT

A 31-year-old woman was admitted to Chungnam National University Hospital during a routine health checkup in 1999. During the workup, azotemia (serum creatinine, 3.8 mg/dL) was identified with subsequent kidney biopsy leading to a diagnosis of renal amyloidosis. Serum and urine electrophoresis showed no evidence of monoclonal gammopathy. There were no other findings of extrarenal or bone marrow involvement and underlying inflammatory disease. Colchicine and regular hemodialysis were started in 2002 and kidney transplantation was performed in 2008 from a deceased donor. Kidney function initially maintained within the normal range, followed by slow deterioration beginning in May 2013. In December 2015, laboratory analysis revealed a serum creatinine level of 2.5 mg/dL; serum total protein of 6.8 g/dL; serum albumin of 3.5 g/dL; blood urea nitrogen of 44 mg/dL; glomerular filtration rate of 24.1 mL/min/1.73 m^2; serum tacrolimus level of 5.6 ng/mL; urine dipstick protein of trace positive; urine spot protein-creatinine ratio of 0.444 g/g; negative donor specific antibody class I; and positive donor

specific antibody class II to DR15.

A posttransplant kidney biopsy showed significant arterial, arteriolar, and glomerular basement thickening with accumulation of acellular eosinophilic materials (Figure 1A). Congo red staining was positive (Figure 1B) with apple-green birefringence under a polarizing microscopy (Figure 1C). Immunohistochemical staining for serum AA was positive (Figure 1D). Mild tubular atrophy with interstitial scarring was associated with sparse lymphocytic infiltration (Figure 2A). Peritubular capillaries were dilated and infiltrated by mononuclear cells (Figure 2B). Double-contoured glomerular basement membranes were identified (Figure 2C). C4d immunohistochemical staining was diffusely positive along peritubular capillaries and glomerular basement membranes (Figure 2D). Electron microscopy showed collections of amyloid fibrils with average thickness of 8 nm to 10 nm. The glomerulus showed a subendothelial electron-lucent area with glomerular basement membrane duplication. Patient diagnosis was recurrent AA amyloidosis with chronic active antibody mediated rejection, which was treated with intravenous plasmapheresis with rituximab for removal of antibody and a restart of colchicine. She kept being treated with mycophenolate mofetil, prednisolone, and tacrolimus. During the follow-up, kidney function was maintained for 4 months, but slowly deteriorated with no recurrence of amyloidosis.

DISCUSSION

Current understanding of clinical characteristics after kidney transplantation with AA amyloidosis is limited. A literature review for AA amyloidosis with kidney transplantation using the PubMed

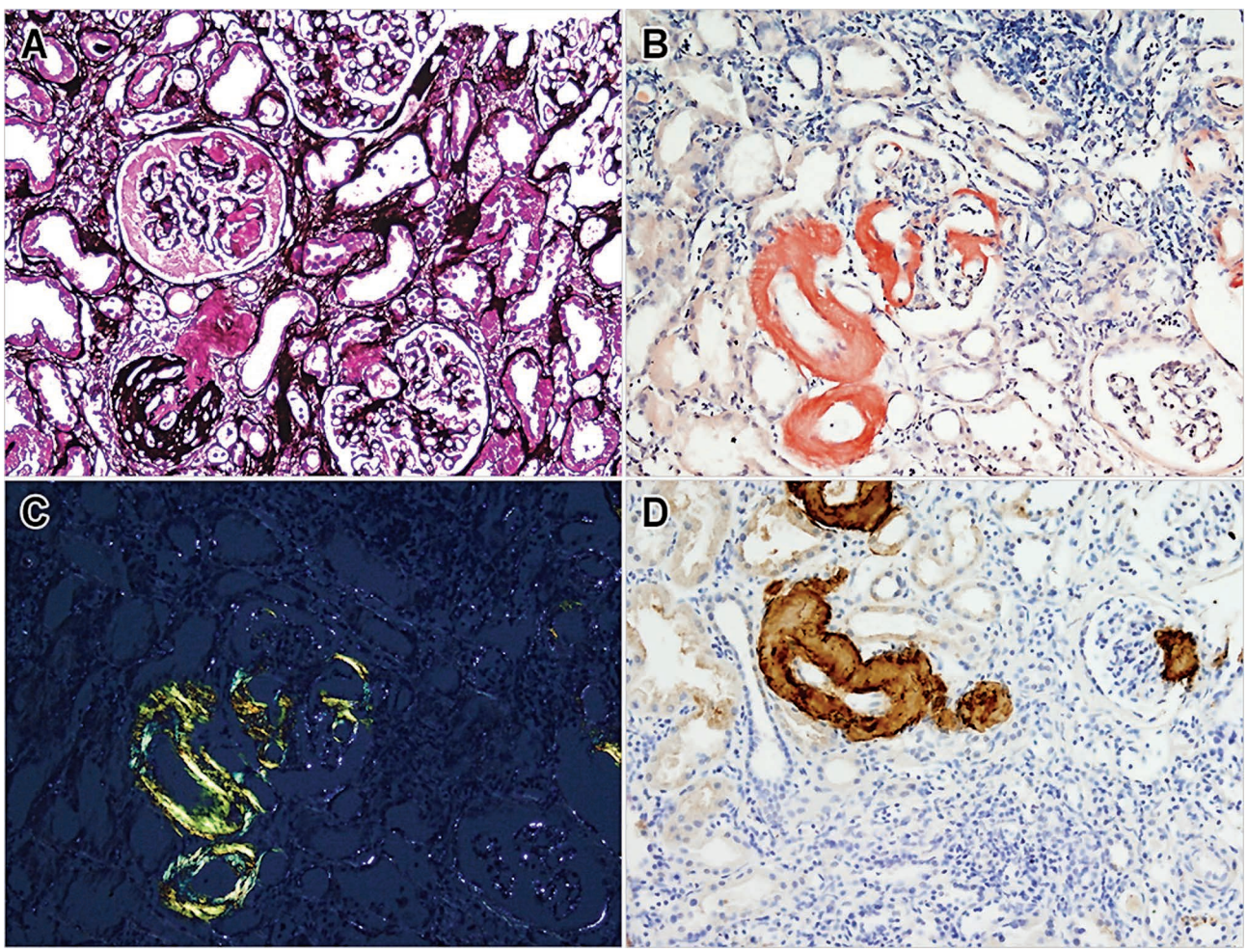

Figure 1. A, Light microscopy showing nodular mesangial expansion and arteriolar thickening with silver-negative materials. **B,** Congo-red stain showing pink-reddish mesangial and vascular staining. **C,** A section showing typical apple-green birefringence under polarized light microscopy. **D,** Immunohistochemical staining for serum amyloid A is positive.

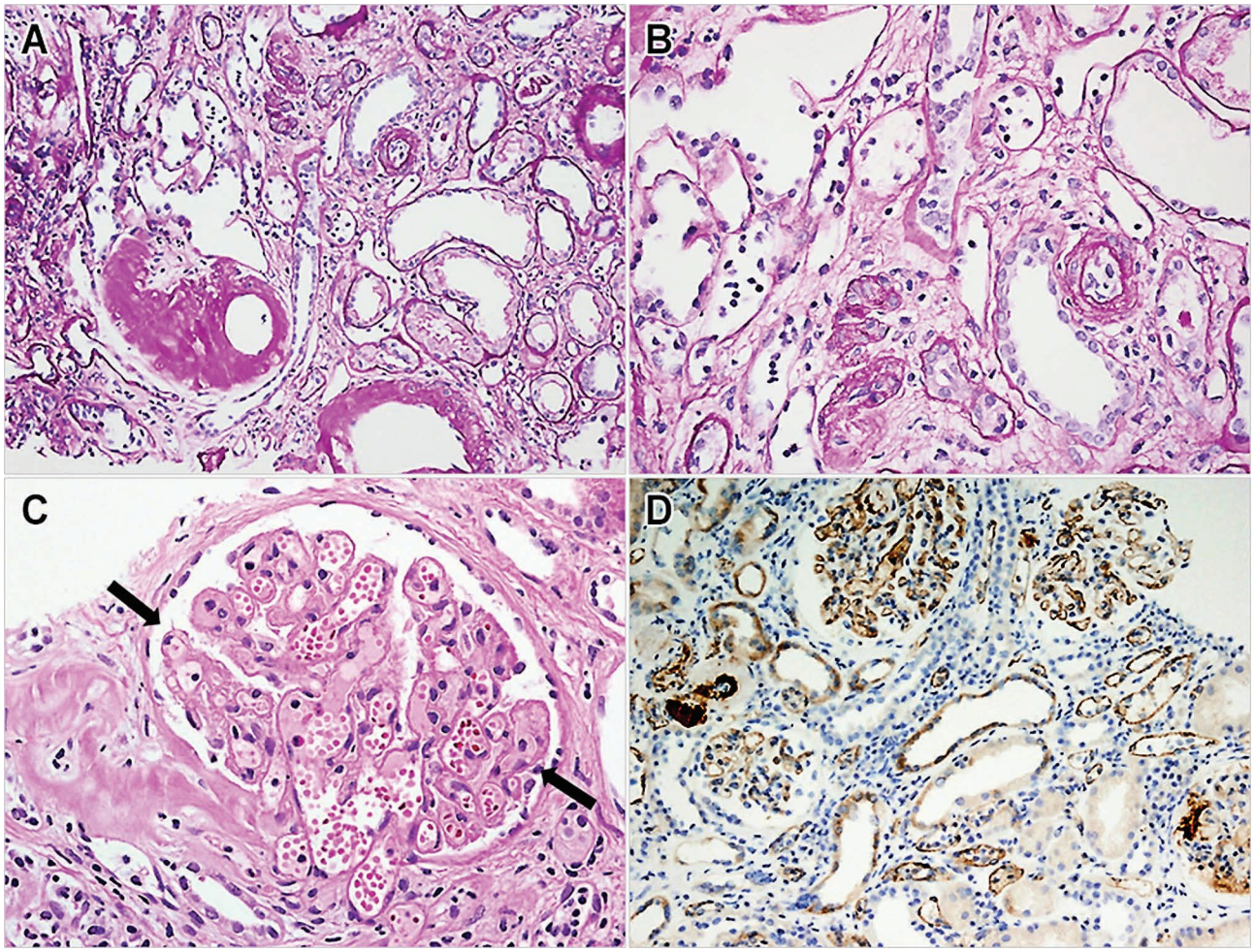

Figure 2. A, Mild tubular atrophy with interstitial scarring is associated with sparse lymphocytic infiltration. **B,** Peritubular capillaries are dilated and contain infiltration of mononuclear cells. **C,** Double contoured (arrow) glomerular basement membranes are identified. **D,** Immunohistochemical staining for C4d is diffusely positive along peritubular capillaries and glomerular basement membranes.

(www.ncbi.nlm.nih.gov/pubmed) was performed resulting in identification of a total of 315 cases from 10 articles between 1990 and 2016 (excepting case reports) (Table and Supplementary Table).[2-11] The average age and sex of transplantation was 37.7 years with a male-female ratio of 1.6:1. Most cases report were from Turkey (n = 5) with others from Iran (n = 1), Egypt (n = 1), Norway (n = 1), France (n = 1), and the United Kingdom (n = 1). The most common underlying disease was periodic fever syndrome (52%) and the next most common was chronic inflammatory arthritis (28%).

Transplantation was considered an acceptable treatment for patients with renal amyloidosis caused by familial Mediterranean fever, which represented the most frequent underlying cause of chronic kidney failure.[12] The rate of amyloid recurrence was 15%, which occurred approximately after 5.2 years posttransplantation. Acute and chronic rejection rates were 15% and 8%, respectively. The acute rejection rate of transplanted patients for AA amyloidosis between control groups generally showed no difference, except for the report of Sherif and coworkers,[11] in which low incidence of acute rejection in amyloidosis cases.[3,5,9-10] Infection was found in 33% of cases and was the most common cause of death (48%). The mean 5-year patient and graft survival rates were 77% and 82%, respectively. The 5-year patient survival rate of transplanted patients for AA amyloidosis was significantly lower than for control groups, whereas 5-year graft survival not significantly different from control groups.[6,10,11] Frequent infection and cardiovascular and cerebrovascular events of transplanted patients for AA amyloidosis suggested a reason for decreased patient survival.[6] With a review of 315 cases and

Clinical Characteristics of 315 Kidney Transplant Patients With AA Amyloidosis Reported in the Literature

Characteristic	Value (%)
Male-female ratio	186:120
Mean age, y	37.7 (13 to 69)
Living-deceased donor ratio	157:135
Underlying disease of AA amyloidosis	
Periodic fever syndrome	165 (52)
Chronic inflammatory arthritis	88 (28)
Chronic infection	17 (6)
Inflammatory bowel syndrome	16 (5)
Castleman disease	2 (1)
Unknown	27 (9)
Amyloid recurrence	48 of 315 (15)
Acute rejection	38 of 247 (15)
Chronic rejection	8 of 95 (8)
Infection	77 of 230 (33)
Death	88 of 297 (30)
Cause of death	
Infection	42 (48)
Cardio-/cerebrovascular disease	18 (20)
Amyloid deposits	5 (6)
Gastrointestinal disease	4 (5)
Malignancy	2 (2)
Renal infarction	1 (1)
Guillan-Barre syndrome	1 (1)
Unknown	13 (15)
Prognosis	
5-year patient survival, %	77
5-year graft survival, %	82

the present case report, the understanding of clinical courses of kidney transplantation in AA amyloidosis is improved.

CONFLICT OF INTEREST

None declared.

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