





An Unusual Case of Acute Kidney Injury with AA Amyloidosis

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Abstract

Acute kidney injury (AKI) is an initial clinical diagnosis in patients with rapid renal function deterioration. Underlying etiologies of AKI include primary kidney diseases, such as acute glomerular and vasculitic diseases, tubulointerstitial nephritis (TIN); systemic insults, such as ischemia and toxins; and obstructive nephropathy. Acute TIN is a common cause of AKI and may be caused by systemic autoimmune conditions, such as immunoglobulin G4-related diseases (IgG4-RD). To date, only one case demonstrates the association of IgG4-RD and AA amyloidosis. Here we report an IgG4-related TIN (IgG4-TIN) and AA amyloidosis in a patient who presented with gross hematuria, proteinuria, and AKI. IgG4-TIN should be considered as a potential cause of AKI as well as chronic kidney disease regarding its long-term inflammatory effects on the kidney.

Keywords: Acute kidney injury, amyloidosis, immunoglobulin G4-related disease, tubulointerstitial nephritis

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INTRODUCTION

Primary kidney diseases, such as acute glomerular and vasculitic diseases; tubulointerstitial nephritis (TIN); systemic insults, such as ischemia and toxins; and obstructive nephropathy are the underlying causes of acute kidney injury (AKI) (1). Although acute TIN is commonly induced by a drug, it may also be caused by autoimmune disorders, infections, TIN, and uveitis syndrome (2). Recently, IgG4-related disease (IgG4-RD) of the kidney was recognized as an emerging clinicopathological entity that may cause acute or chronic renal dysfunction in addition to the systemic manifestations. TIN is the most dominant form of kidney involvement in IgG4-RD, which is diagnosed by renal biopsy findings in addition to elevated serum IgG4 levels (3-5).

We present the case of a 59-year-old woman with acute TIN and AA amyloidosis in addition to IgG4-positive plasma cells (PPC) in kidney biopsy with a mechanical heart valve who was successfully treated with corticosteroids.

CASE PRESENTATION

A 59-year-old woman with a history of mechanical mitral valve replacement was evaluated for polyuria, weight loss, and gross hematuria in another hospital. She was diagnosed with type 2 diabetes and primary hypertension on that admission. She was on warfarin, diclofenac, pantoprazole, premixed insulin, and amlodipine. Her known baseline serum creatinine level was 0.73 mg/dL, which was tested 6 months ago. On admission, it was found to be 1.5 mg/dL and increased to 3.75 mg/dL in 2 weeks at that hospital. Additionally, non-nephrotic range proteinuria (1.7 gr/d) was detected. She was referred to our center because of AKI with gross hematuria and proteinuria.

On admission to our hospital, her physical examination was unremarkable except for the sound of the mechanical heart valve. Laboratory findings were as follows: serum creatinine, 4.54 mg/dL; C-reactive protein, 18.8 mg/L; hemoglobin, 10.2 g/dL; international normalised ratio (INR), 2.33; 24-hour urine protein, 1,275



mg/dL; serum IgG, 16.8 g/L (7.51-15.6 g/L); serum IgG4, 2.13 g/L (0.039-0.864 g/L); serum IgA, 5.78 g/L (0.82-4.53 g/L); normal serum complement levels and kappa/lambda free light chain ratio; negative antinuclear antibodies, antineutrophil cytoplasmic antibodies, antidouble stranded DNA antibodies, antiglomerular basement membrane antibodies; and normal creatine kinase and angiotensin converting enzyme levels. Microscopic examination of the urine sediment showed erythrocytes with normal morphology without red blood cell casts. Urinary ultrasonography showed no abnormality. An ultrasound-guided kidney biopsy was performed after switching from warfarin to low molecular weight heparin and normalization of INR.

Light microscopy of the renal biopsy specimen showed three globally sclerotic glomeruli and one glomerulus with no abnormalities. Examination of the tubulointerstitial region demonstrated mononuclear inflammatory infiltrates mostly consisting of neutrophils and eosinophils. The wall of some arterioles showed acellular eosinophilic thickening, and these areas were positive for amyloid A and P components. There was prominent fibrointimal thickening in the arteries. Direct immunofluorescence microscopy showed no specific abnormalities on the specimen. There were three IgG4 PPC in two different focuses on the immunohistochemical examination (Figure 1). These findings were consistent with IgG4-TIN accompanied by secondary amyloidosis.

Based on the biopsy findings, she was started with methylprednisolone 125 mg/d for 3 days, continued orally as 48 mg/d, and tapered slowly over a duration of 4 months. Colchicine 0.5 mg was added to the therapy every other day.

There was no evidence suggesting familial Mediterranean fever (FMF) or other rheumatological diseases. Thoracic and abdominal computed tomography results were negative for any findings suggesting IgG4-RD. Gene mutation analysis was negative for FMF.

The patient's serum creatinine level decreased to 2.58 mg/dL on the third day of the glucocorticoid treatment. By the third month of the therapy, her creatinine level was 2.20 mg/dL, IgG4

level was normal (0.66 g/L), and proteinuria had decreased (urine protein/creatinine ratio 0.808 mg/mg). She is being followed-up with stable renal function with an estimated glomerular filtration ratio (eGFR) of 24 mL/dk/1.73 m² under conservative therapy.

DISCUSSION

IgG4-RD is a recently recognized systemic fibroinflammatory condition that may affect several organs including the kidneys (6). A connection of IgG4-RD and TIN was first reported in 2004 (7). Although AA amyloidosis is known to develop secondary to inflammatory conditions, to the best of our knowledge, its association with IgG4-RD has been reported in only one case (8). In that case report, the patient had nephrotic syndrome with normal kidney function, which was diagnosed as AA amyloidosis with a renal biopsy performed 16 years after he had been diagnosed with mesenteric IgG4 disease.

Our patient presented with AKI with hematuria and proteinuria, and she had a history of taking nonsteroidal anti-inflammatory drugs and warfarin. These findings led us firstly to the diagnosis of acute TIN and rapidly progressive glomerulonephritis. Anticoagulant-related nephropathy (ARN) was one of our differential diagnosis, which is diagnosed in patients who develop otherwise unexplained AKI in association with warfarin overdose and whose renal biopsy specimens reveal tubular injury and obstruction with red blood cells (9). Our patient's biopsy findings were not consistent with those of ARN or glomerulonephritis. In contrast, there were amyloid depositions on the biopsy, which were consistent with a more chronic process. There were no signs or symptoms associated with rheumatological disease, and the gene mutation analysis was negative for FMF; however, the history of rheumatic heart disease and IgG4-PPC on the biopsy suggested a systemic inflammatory activity. For pathological diagnosis of IgG4-TIN, the characteristic features are as follows: lymphoplasmacytic infiltrates dominantly with IgG4-PPC (>10 IgG4-PPC/high-power field), the ratio of IgG4-PPC over 40%, and obliterative phlebitis. However, renal involvement could be patchy in distribution; therefore, renal biopsy may not always be diagnostic. High serum IgG4 levels (>1.35 g/L) are observed in up to 93% of the patients with IgG4-TIN (5). In our patient, the level was 2.13 g/L (0.039-0.864 g/L) on diagnosis. For this patient, there was a prompt response to steroids, very high serum level of IgG4, concomitant existence of otherwise unexplained AA amyloidosis, and there was no evidence related to other rheumatological disease. Thus, the final diagnosis for her was IgG4-TIN without extrarenal manifestations. Glucocorticoids are the first-line treatment for TIN and IgG4-TIN. Prompt response in 2 to 3 weeks to the treatment is characteristic. Treatment should comprise of induction; tapering (with a duration of 4 to 6 months); and maintenance with low dose steroids, azathioprine, or other agents, such as mycophenolate mofetil, cyclophosphamide, and calcineurin inhibitors in

Main Points

- Tubulointerstitial nephritis is the most dominant form of kidney involvement in IgG4-related disease (IgG4-RD) which is diagnosed by renal biopsy findings in addition to elevated serum IgG4 levels.
- AA amyloidosis can develop secondary to inflammatory conditions, however its association with IgG4-RD is a new entity deserves to be noticed.
- In case of combination of acute kidney injury otherwise unexplained and proteinuria, performing a renal biopsy should be considered to guide proper treatment.

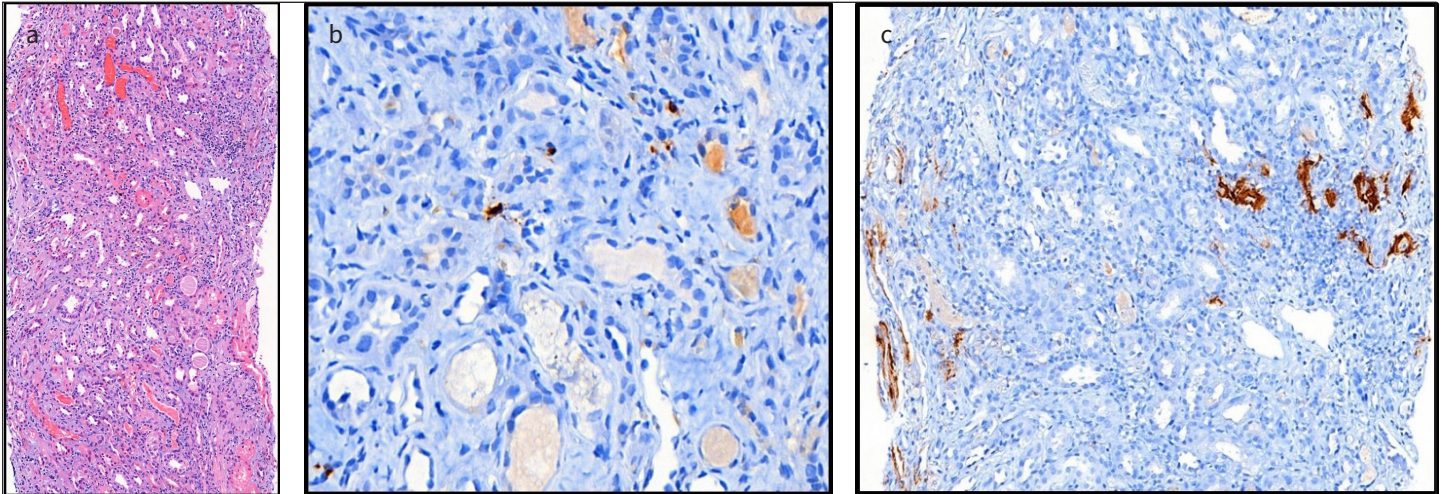


Figure 1. a-c. Histological examination of renal biopsy specimen. a) Light microscopy after staining with hematoxylin eosine (x10). b) Immunohistochemistry for IgG4 (x40). c) Immunohistochemistry for Amyloid A (x10).

multiorgan diseases. If the patient is intolerant or resistant to steroids, rituximab may be considered as an alternative for induction (6). Colchicine is an accepted therapy for AA amyloidosis (10). Our patient was treated with steroids and colchicine; however, she did not receive any maintenance therapy because there was no evidence of multiorgan disease.

CONCLUSION

In this case report, we observed that IgG4-TIN may manifest as an AKI without any systemic symptoms indicating other organ involvement, and long-term disease course may be associated with AA amyloidosis.

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