

[CASE REPORT]

Rapidly Progressive Kidney Failure Associated with Perirenal Capsular Lesion Due to IgG4-Related Disease

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Abstract:

A 71-year-old Japanese man with progressive kidney failure was referred to our hospital. Laboratory tests showed elevated IgG4 levels. Contrast-enhanced computed tomography (CT) revealed soft tissue surrounding the left kidney and right atrophic kidney. A histopathological examination revealed inflammation and fibrosis with rich IgG4-positive cells in the thickened kidney capsule, but not in the kidney parenchyma. Poor enhancement in the left kidney on contrast-enhanced CT and wrinkling of glomerular capillaries in pathological tissues were also observed. These findings indicated IgG4-related perirenal lesions leading to low renal perfusion and kidney failure. The perirenal lesions and kidney failure were improved by corticosteroid therapy.

Key words: IgG4-related disease, perirenal capsule, rapidly progressive kidney failure, retroperitoneal fibrosis

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Introduction

Kidney involvement in IgG4-related disease (IgG4-RD) can manifest as tubulointerstitial nephritis (TIN), glomerular lesions represented by membranous nephropathy, mass lesions, and retroperitoneal fibrosis (1). Several characteristic imaging abnormalities have been reported (2). Multiple low-density areas on contrast-enhanced computed tomography (CT) are often observed. Mass lesions are relatively rare and should be distinguished from malignant tumours. Hydronephrosis associated with retroperitoneal fibrosis is another common abnormality. Perirenal lesions are a rare presentation of IgG4-RD and few studies have reported on their clinical significance in detail (3, 4).

We report a case of rapidly progressive kidney failure with unique imaging abnormalities, including soft tissue around the kidney and retroperitoneal fibrosis.

Case Report

A 71-year-old Japanese man with dyspnea and pleural effusion was referred to our hospital. Initially, he was diagnosed with heart failure due to severe mitral regurgitation.

Although his symptoms improved with diuretics, he developed progressive kidney failure and was referred to our nephrology department.

At presentation, a physical examination revealed the following: blood pressure, 150/61 mmHg; heart rate, 85 beats/min; body temperature, 37-38°C. He had no rash, lymphadenopathy or edema of the limbs.

On day 23 of hospitalization, the patient's laboratory test results revealed an impaired renal function with a serum creatinine (Cr) level of 5.27 mg/dL, which was 1.34 mg/dL on admission. His white blood cell count was 7,300/mm³ and his hemoglobin level was 10.0 g/dL. His C-reactive protein (CRP) level was mildly increased (3.44 mg/dL). Urine tests showed no proteinuria or microscopic hematuria. Immunological tests revealed serum IgG4 elevation, without IgG elevation (263 mg/dL and 1,339 mg/dL, respectively). His serum complement levels (C3, C4, and CH50) were within normal range. Tests for autoantibodies, including antinuclear, anti-neutrophil cytoplasmic, anti-SS-A, and anti-SS-B antibodies, were negative. His soluble interleukin-2 receptor (sIL-2R) level was elevated (5,316 U/mL). The patient's laboratory results are summarized in Table.

Contrast-enhanced CT showed diffuse soft tissue infiltration in the left perirenal space, as well as mild infiltration in

Table. Laboratory Data at the Time of Referral.

CRP	3.44 mg/dL	IgG	1,339 mg/dL	WBC	7,300 / μ L
TP	5.8 g/dL	IgA	264 mg/dL	Eos	3.4 %
Alb	2.7 g/dL	IgM	49 mg/dL	Neu	72.8 %
AST	7 U/L	IgE	1,926 IU/mL	Lymph	13.7 %
ALT	4 U/L	IgG4	263 mg/dL	Mono	10 %
LDH	107 U/L	C3	107 mg/dL	RBC	329 \times 10 ⁴ / μ L
ALP	149 U/L	C4	31 mg/dL	Hb	10.0 g/dL
Na	132 mmol/L	ANA	1:40	MCV	91.7 fL
K	5.4 mmol/L	Anti-SSA Ab	<1.0 U/mL	Platelet	12.8 \times 10 ⁴ / μ L
Cl	103 mmol/L	Anti-SSB Ab	<1.0 U/mL	Urinalysis	
Ca	7.7 mg/dL	sIL-2R	5,316 U/mL	Protein	0.1 g/gCr
P	2.8 mg/dL			RBC	<1 /HPF
BUN	61 mg/dL			WBC	<1 /HPF
Cre	5.27 mg/dL			NAG	5.9 U/L
HbA1c	5.4 %			β 2-MG	3,300 μ g/L

CRP: C-reactive protein, TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, BUN: blood urea nitrogen, Cre: creatinine, HbA1c: hemoglobin A1c, ANA: antinuclear antibody, sIL-2R: soluble interleukin-2 receptor, Hb: hemoglobin, Ht: hematocrit, MCV: mean corpuscular volume, HPF: high power field, NAG: N-acetyl- β -D-glucosaminidase, β 2-MG: β 2-microglobulin

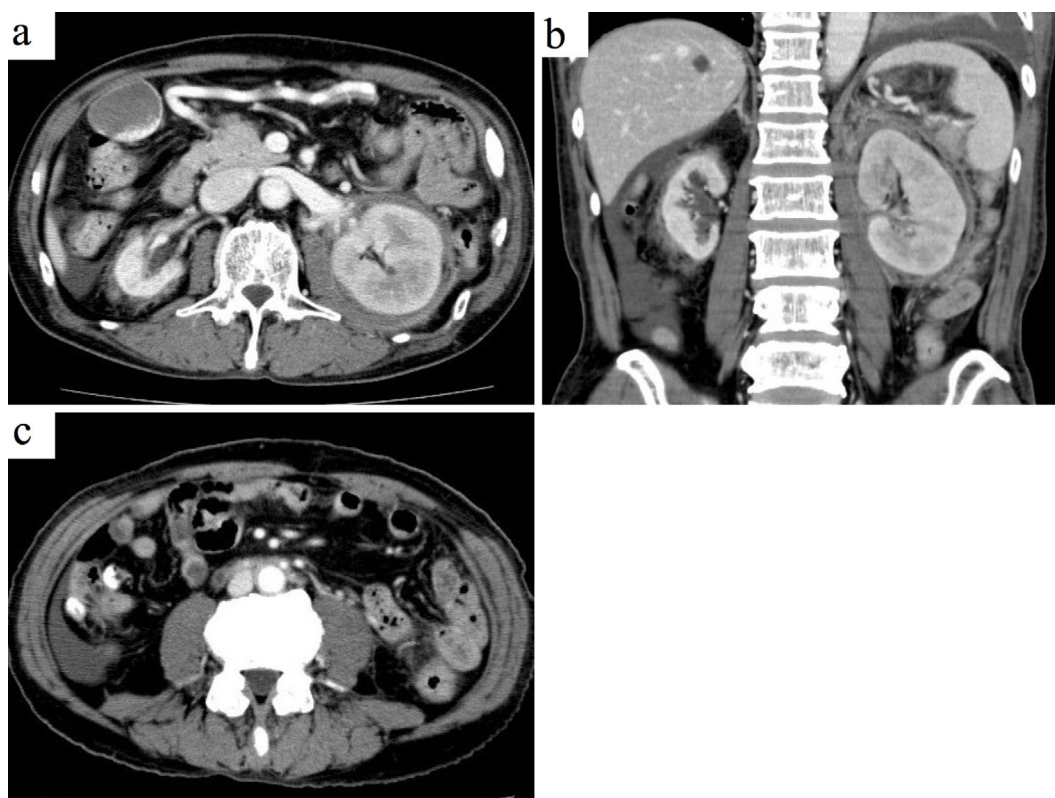


Figure 1. The contrast-enhanced CT findings before corticosteroid therapy. (a, b) A soft tissue lesion surrounded the left kidney, including the renal hilum. The left kidney enhancement was weaker than that of the ischemic right kidney. (c) A periaortic soft tissue lesion and right hydronephrosis were also observed.

the right perirenal space and right-sided hydronephrosis due to periaortic fibrosis (Fig. 1). Although the right kidney was atrophic and showed hydronephrosis, the left kidney was less enhanced than the right. Chest CT revealed slight ground glass opacities in the bilateral lungs. There was no

significant enlargement of the lymph nodes. In addition, no obvious renal abnormalities were observed on a contrast-enhanced CT scan performed 8 years before his hospitalization.

On day 26 of admission, his kidney failure worsened with

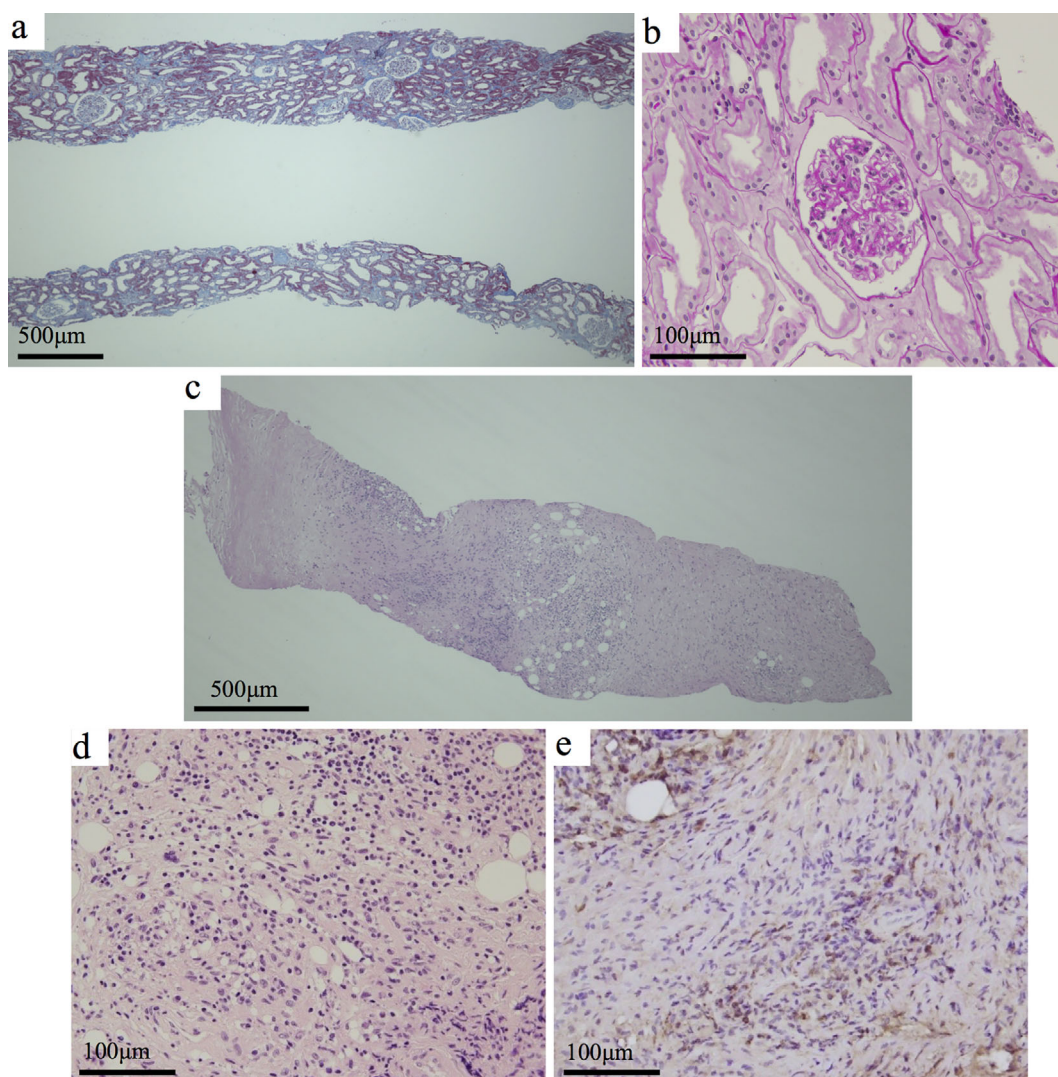


Figure 2. Histopathologic findings of the kidney biopsy specimen. (a, b) Light microscopy revealed the absence of tubulointerstitial nephritis, but diffuse mild wrinkling of the glomerular capillary was present (Masson trichrome staining $\times 40$, periodic acid-Schiff staining $\times 400$). (c, d) The kidney capsule was thickened due to inflammatory infiltration of lymphocytes and plasma cells with fibrosis (Hematoxylin and Eosin staining $\times 40$, $\times 400$). (e) Immunostaining with an anti-IgG4 antibody revealed the presence of IgG4-positive cells ($\times 400$).

elevated levels of Cr and CRP (Cr 8.59 mg/dL, CRP 8.94 mg/dL) and symptoms of uremia, such as nausea and fatigue. Hemodialysis was initiated with vascular access catheters.

Based on these findings, we considered that his progressive kidney failure was induced by IgG4-RD. However, the exact etiology was unknown. We therefore performed a laparoscopic biopsy of the left kidney and retroperitoneum.

The kidney biopsy showed no tubulointerstitial nephritis but diffuse mild wrinkling of the basement membranes of the glomerular capillaries (Fig. 2a, b). No other glomerular lesions, such as membranous nephropathy or glomerulonephritis, were observed. Immunofluorescence microscopy showed no significant deposition of IgG, IgA, IgM, C3, C4 or C1q. Electron microscopy demonstrated no significant abnormalities. The kidney capsule tissues were thickened with inflammatory infiltration of lymphocytes and plasma cells,

in addition to fibrosis (Fig. 2c, d). Immunohistochemical staining indicated an average IgG4-positive plasma cell count of approximately 20/high power field, and an IgG4/IgG-positive cell ratio of 70% in the kidney capsules (Fig. 2e). Retroperitoneal biopsy revealed dense connective tissues infiltrated with lymphocytes, macrophages, and plasma cells, which was consistent with peritoneal fibrosis. There were no signs of malignancy. Collectively, the kidney capsular lesions associated with IgG4-RD were considered to be the main cause of kidney failure.

Prednisolone (30 mg; 0.5 mg/kg) was administered on hospital day 32, followed by tapering at 2- to 3-week intervals. Signs of systematic inflammation, such as fever and his CRP level rapidly improved. His kidney function gradually improved, and hemodialysis was terminated on hospital day 45. His kidney function was well maintained after 6 months (Cr 1.5-2.0 mg/dL). Follow-up CT showed improve-



Figure 3. The plain CT findings at 6 months after treatment. The soft tissue surrounding the left kidney showed remarkable improvement.

ment in the perirenal capsular lesions and retroperitoneal fibrosis (Fig. 3).

Discussion

IgG4-RD is a fibroinflammatory disease that affects various organs, resulting in organ dysfunction (5). The most dominant kidney disease caused by IgG4-RD is tubulointerstitial nephritis, which leads to kidney failure without apparent proteinuria or hematuria (1). Glomerular lesions, such as membranous nephropathy with proteinuria have also been reported. Renal pelvic and periureteral lesions or retroperitoneal fibrosis often result in postrenal renal failure. Some patients with IgG4-RD have very mild or no symptoms, as their lesions progress slowly.

The comprehensive diagnostic criteria for IgG4-RD are: (i) serum IgG4 > 135 mg/dL; (ii) > 40% of IgG-positive plasma cells being IgG4 positive and > 10 cells/HPF on biopsy (6). However, the sensitivity and specificity of the serum IgG4 level are inadequate. The histopathological findings should be interpreted in the context of the clinical and radiological findings, because IgG4-positive cells are also seen in many other conditions, including malignancies, Castleman disease, granulomatosis with polyangiitis, and Sjogren's syndrome (7). Recently, the American College of Rheumatology/European League Against Rheumatism classification criteria including characteristic clinical, serologic, radiologic and pathologic features were reported to have excellent reliability (8). This present case met these criteria adequately.

Progressive kidney disease during the first month after hospitalization in this case was atypical of IgG4-RD. Before the kidney biopsy, we suspected that the main cause of kidney failure was interstitial nephritis because with the exception of the detection of urinary β_2 -microglobulin, the results of a urinalysis were almost normal. However, the pathological significance of the perirenal capsular lesion was unclear. The histopathological examination showed no signs of interstitial nephritis or glomerular lesions, with the exception of

diffuse mild wrinkling of the basement membranes of the glomerular capillaries, suggesting renal ischemia, although IgG4-related lesions might have been missed during biopsy. The kidney capsule was involved in inflammation and fibrosis with rich IgG4-positive cells, which was consistent with IgG4-RD.

On contrast-enhanced CT, the contrast effect of the left kidney was weaker than that of the right kidney, despite atrophy of the right kidney. This finding was also suggestive of decreased perfusion of the left kidney. The soft tissue of kidney capsules surrounded the left kidney entirely, including the renal hilum.

Based on these findings, we considered that the inflammatory lesion around the left kidney reduced the perfusion of the kidney leading to renal failure. Page kidney is a pathological condition in which external compression of the kidney due to hematoma or mass lesions causes renal ischemia, leading to hypertension and kidney failure (9). Considering that retroperitoneal fibrosis causes compression of the ureter and impairs the ureteral passage, it was reasonable to consider that perirenal inflammation and fibrosis due to IgG4-related disease induced low renal perfusion and kidney failure by the same mechanism as in Page kidney. Perirenal soft tissue infiltration associated with IgG4-RD is rare (2). Cho et al. and Chen et al. reported perirenal capsule infiltration due to IgG4-RD (3, 4). Kidney failure was mild and not rapidly progressive in these cases, and the detailed mechanism underlying the development of kidney failure was not explained. No cases of rapidly progressive kidney failure requiring temporary dialysis, as occurred in the present case, have been reported. Usually, in patients with IgG4-RD, the CRP levels are low and symptoms progress slowly. It has been reported that CRP elevation is associated with periaortitis or periarteritis in patients with IgG4-RD, and the present patient also had periaortic lesions (10). The elevated CRP or low-grade fever in the present case might reflect relatively active vascular inflammation. Although most cases of Page kidney show hypertension or mild renal damage, a few cases of severe kidney failure have been reported in patients with solitary kidney, such as patients who have undergone kidney transplantation (11). In this case, the right kidney was impaired by atrophy and hydronephrosis. However, due to a lack of information on the patient's state before his current presentation, it remains unclear whether or not this atrophy of the right kidney had been caused by conditions other than hydronephrosis. Based on these findings, in addition to right kidney impairment, continued compression of the left kidney by perirenal lesions was considered to have induced low renal perfusion and progressive kidney failure. To the best of our knowledge, this is the first report to describe rapidly progressive kidney failure caused by perirenal lesions associated with IgG4-RD in detail.

IgG4-RD can affect various multiple organs and can cause inflammation and fibrosis, resulting in various clinical symptoms. Malignant lymphoma can be considered as a differential diagnosis in patients presenting with perirenal or

retroperitoneal soft tissue masses. In this case, we performed renal biopsy to exclude malignant lymphoma, considering the high serum IL-2R levels. However, renal biopsy is an invasive procedure and is often impossible if the patient's general condition is poor. Atypical imaging findings and clinical symptoms can lead to a better understanding of IgG4-RD, allowing for a more efficient approach to its diagnosis and treatment. This atypical case highlights the clinical diversity of IgG4-RD.

The authors state that they have no Conflict of Interest (COI).

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