



Case report: IgG4-related renal disease co-existing with retroperitoneal fibrosis

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Abstract: A 51-year-old woman visited our clinic for orthopnea, chest discomfort, and facial and leg edema. Acute kidney injury and pleural effusion were diagnosed and she received hemodialysis. This is a rare case of IgG4-related disease diagnosed by renal biopsy in the patient with retroperitoneal fibrosis and severe acute kidney injury, which progressed rapidly and required hemodialysis without markedly elevated serum IgG4 level and urinary tract obstruction. Immunostaining of a kidney biopsy revealed IgG4-related renal disease and magnetic resonance imaging showed retroperitoneal fibrosis in the paraspinal and presacral areas. After 3 days of glucocorticoid treatment, renal function and bilateral pleural effusion were restored. Another 2 months of glucocorticoid treatment decreased the extent of retroperitoneal fibrosis on follow-up abdominal computed tomography. IgG4-related disease is a recently recognized fibro-inflammatory condition with a dense lymphoplasmacytic infiltration of IgG4-positive plasma cells. The kidney and retroperitoneum are the frequently associated organs in IgG4-related disease. This case shows that IgG4-related disease can involve the kidney and/or other organs and be diagnosed by kidney biopsy.

Keywords: IgG4-related renal disease; retroperitoneal fibrosis; case report; acute kidney injury; kidney biopsy

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Introduction

IgG4-related disease is a recently recognized fibro-inflammatory condition with a dense lymphoplasmacytic infiltration of IgG4-positive plasma cells. IgG4-related disease can involve various organs of humans (1). Retroperitoneal fibrosis was first described by Dr. John Ormond in 1948. It is a rare disease with fibro-inflammatory changes in the soft tissues in the retroperitoneal space (2). The kidney and retroperitoneum are frequently associated organs in IgG4-related disease (3). Although elevated serum IgG4 levels are not always specific for IgG4-related disease, the elevation of IgG4 level often correlates with the activity of the disease and the number of organs involved (4-6). This is a rare case of IgG4-related disease diagnosed by renal biopsy without markedly elevated serum IgG4 level. Sometimes the clinical manifestations

accompanying retroperitoneal fibrosis give an idea of the underlying condition of this disease. We herein report a case of IgG4-related disease which involves the kidney and retroperitoneum.

Case presentation

A 51-year-old woman visited our hospital for chest discomfort, orthopnea, and edema in the face and both legs. She had a medical history of hypertension, diabetes mellitus, and uterine myoma. No abnormal physical finding was presented except pitting edema on both lower extremities. Her baseline creatinine was 0.50 mg/dL (normal range, 0.5–1.3 mg/dL) a month ago. On admission day, her serum creatinine was elevated at 1.44 mg/dL (*Table 1*). Her urinalysis exam showed hematuria without proteinuria. Chest X-ray revealed bilateral pleural effusion (panel A

Table 1 Laboratory findings on admission

Laboratory parameters (Units)	Results [Normal ranges]
Complete blood cell count	
White blood cells ($\times 10^3/\mu\text{L}$)	6,900 [4,800–10,800]
Hemoglobin (g/dL)	9.4 [12–18]
Platelet count ($\times 10^3/\mu\text{L}$)	282 [130–450]
Blood chemistry	
BUN (mg/dL)	16.5 [8–23]
Creatinine (mg/dL)	1.44 [0.5–1.3]
Sodium (mEq/L)	140 [135–145]
Potassium (mEq/L)	3.5 [3.5–5.1]
Chloride (mEq/L)	110 [98–110]
Total protein (g/dL)	7.4 [6–8.3]
Albumin (g/dL)	3.4 [3.5–5.2]
CRP (mg/dL)	2.37 [0–0.3]
Troponin I (ng/mL)	0.007 [0–0.05]
ProBNP (pg/mL)	851.2 [0–270]
LDH (U/L)	600 [218–472]
Urinalysis	
Specific gravity	<1.005 [1.005–1.03]
pH	5.5 [5–8]
Protein	Negative
Glucose	Negative
Ketone body	Negative
Red blood cell	30–49/HPF
Casts	Negative
Immunoglobulins	
ANA	Nucleolar: 80[1+]
ANCA	Negative
IgG (mg/dL)	1,731.5 [700–1,600]
IgA (mg/dL)	498.4 [70–400]
IgM (mg/dL)	109.0 [40–230]
IgE (IU/mL)	11.7 [1.5–158]
IgG4 subclass (mg/dL)	93.07 [3.90–86.40]

BUN, blood urea nitrogen; CRP, C-reactive protein; proBNP, pro-brain natriuretic peptide; LDH, lactate dehydrogenase; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic autoantibody; Ig, immunoglobulin.

of *Figure 1*). Kidney ultrasonography showed increased cortical echogenicity with mild hydronephrosis (grade 1) (*Figure 2*) (7). Enhanced pelvic magnetic resonance imaging (MRI) showed an ill-defined soft tissue lesion with low signal intensity on T1 weighted image and relatively homogeneous enhancement on contrast-enhanced image, in the paraspinal and presacral area. These imaging studies did not suggest an obstructive lesion in both urinary tracts prominently, and her urine volume was maintained over 1.5 L/day. Thoracentesis was performed twice and the aspirated pleural fluid was a transudate (*Table 2*). The non-enhanced CT scan of the chest did not show a significant lesion, except pleural effusion. Despite of management for acute kidney injury, serum creatinine was increased at 9.22 mg/dL 10 days after admission and urine output was decreased. We inserted a permanent jugular catheter and performed hemodialysis.

A kidney biopsy was performed, which showed inflammatory cell infiltration consisting of lymphocytes and mast cells. Hematoxylin & eosin stain, Periodic acid-Schiff stain and Masson trichrome stain of kidney specimen was obtained and they showed dense lymphoplasmacytic infiltration (*Figure 3A,B,C*). More than 10 IgG4-positive plasma cells were observed per high power field in the immunostaining of kidney biopsy specimens with monoclonal antibodies for IgG4 (*Figure 3D*). Regrettably, the serum IgG level was not increased significantly (1,731.5 mg/dL, reference range 700–1,600 mg/dL), as well as serum IgG4 subclass level (93.07 mg/dL, reference range 3.90–86.40 mg/dL). We performed positron emission tomography-computed tomography (PET-CT) with ^{18}F fluorodeoxyglucose to rule out malignancy, it revealed a diffuse hypermetabolic soft tissue lesion along the retroperitoneal space without lymph node, lung or pleural involvement (*Figure 4*). The pathologic diagnosis for this kidney biopsy was compatible with IgG4-related kidney disease and radiologic diagnosis indicated retroperitoneal fibrosis.

We started 60 mg of prednisolone (1 mg/kg/day) for 3 days and her renal function improved rapidly from 9.22 to 1.22 mg/dL. After the administration of 30 mg/day of prednisolone for 12 days, serum creatinine was decreased to 0.6 mg/dL, and pleural effusion disappeared (*Figure 1B* and *Figure 5*). Two months after discharge, she underwent abdominal CT, which showed a decreased extent of the ill-defined soft tissue lesion involving both the paraspinal area

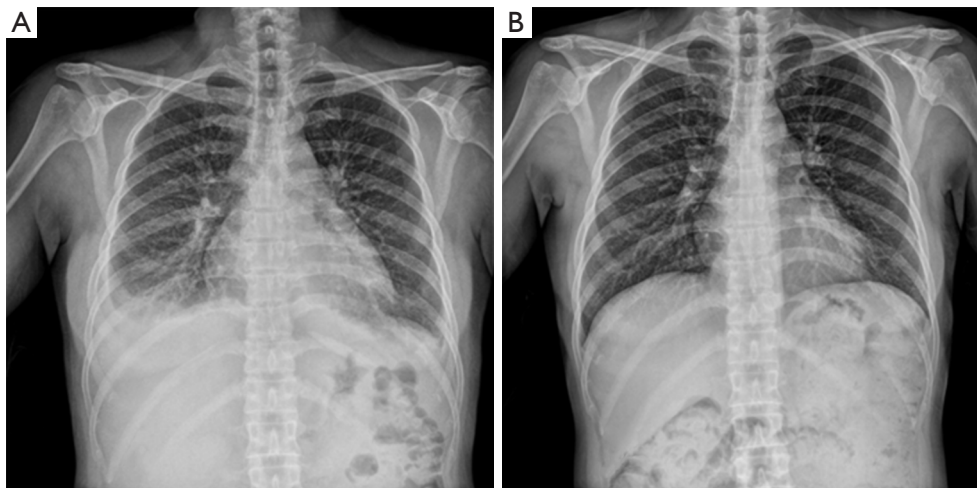


Figure 1 Chest X-rays before and after treatment. (A) Bilateral pleural effusion and pulmonary edema on chest simple X-ray. (B) Pleural effusion and pulmonary edema was disappeared after treatment.

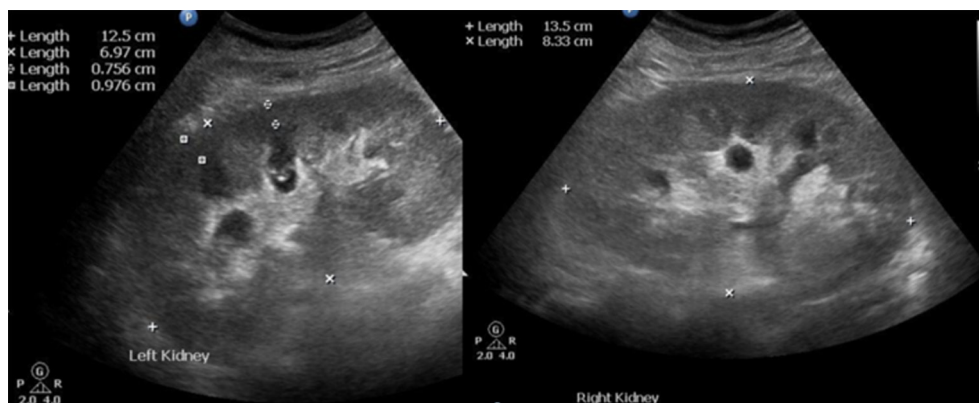


Figure 2 Kidney ultrasonography. Kidney ultrasonography showing increased cortical echogenicity with mild bilateral hydronephrosis (grade 1).

Table 2 Pleural fluid analysis

Laboratory parameters (Units)	Results
Total nucleated cells (mm^{-3})	503
Red blood cells (mm^{-3})	600
White blood cells (mm^{-3})	314
Polymorphonuclear leukocytes	2.2%
Mononuclear cells	97.8%
Specific gravity	1.015
pH	7.471
Glucose (mg/dL)	214
Lactate dehydrogenase (U/L)	232
Protein (g/dL)	3.0

of L5 and the presacral space (*Figure 6*). We maintained 10 mg of prednisolone during another 4 months for preventing relapse. She was followed up every month and showed good adherence and tolerance for treatment. Steroid-induced diabetes occurred, but it was well-controlled by the administration of oral hypoglycemic agents. She expressed satisfaction with the treatment and the response.

Discussion

We reported a case of IgG4-related disease with renal and retroperitoneal complications. IgG4-related disease was identified as a systemic condition in patients with autoimmune pancreatitis and extra-pancreatic manifestations in 2003 for the first time (1,6). The

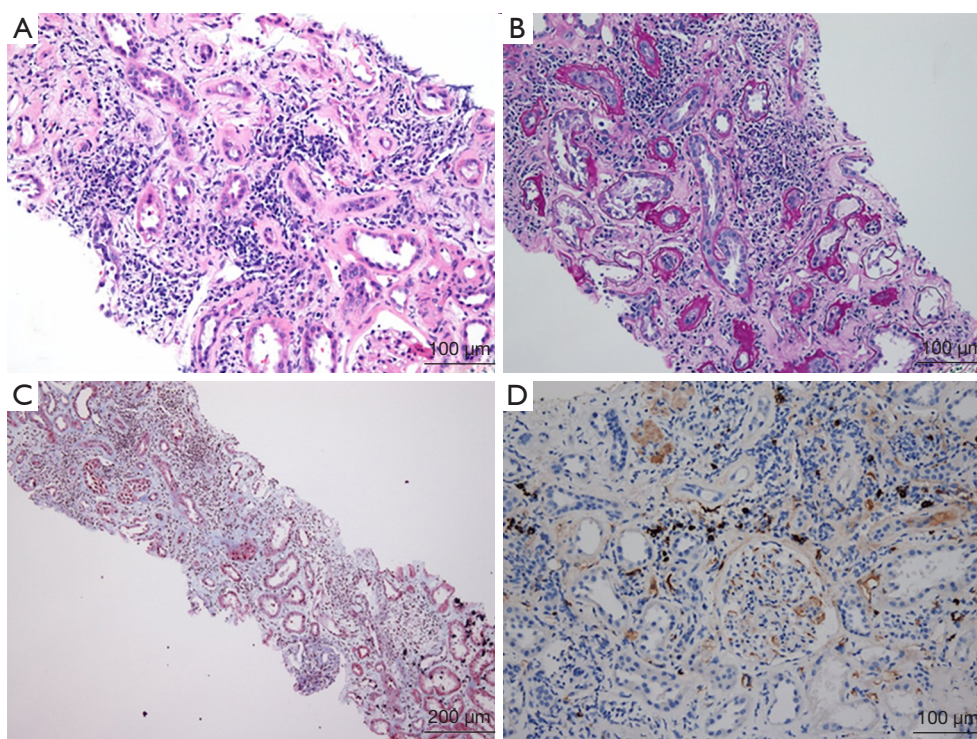


Figure 3 Kidney biopsy. A tissue specimen from kidney biopsy showed a dense lymphoplasmacytic infiltration (A, hematoxylin and eosin stain, $\times 200$; B, Periodic acid-Schiff stain, $\times 200$; C, Masson trichrome stain, $\times 100$). Immunohistochemical staining for IgG4 monoclonal antibody showed more than 10 IgG4-positive plasma cells per high-power field in the peritubular interstitial area (D, $\times 200$).



Figure 4 Positron emission tomography-computed tomography (PET-CT). PET-CT with 18 fluorodeoxyglucose revealed a diffuse hypermetabolic soft tissue lesion along the retroperitoneal space (arrow). There was no significant hypermetabolism in the lung and pleura.

frequency of renal involvement is 7.0% to 24.6% and that of retroperitoneal involvement is 9.6% to 27.0% in patients with IgG4-related disease (8-10). Two small studies in America and Japan represented that 57–59% of idiopathic retroperitoneal fibrosis were IgG4-related (11). And in a small retrospective study in South Korea, 59.3% of patients diagnosed idiopathic retroperitoneal fibrosis were found as IgG4-related (12). IgG4-related diseases are not always associated with an elevation of serum IgG4 concentration. Even if the serum IgG4 level was not significantly elevated in this case, an infiltration of IgG4-positive plasma cells in biopsy tissue could indicate a diagnosis of IgG4-related renal disease (1). IgG4-related renal disease is one of the most frequent forms of organ involvements in IgG4-related disease, and the most common type of IgG4-related renal disease is tubulointerstitial nephritis. Glomerular disease such as membranous glomerulonephritis, and renal pelvic lesion like IgG4-related pyelitis can be presented as other types of IgG4-related renal disease. Without glomerular lesions, IgG4-related renal disease leads to very mild or no symptoms in most patients. It usually

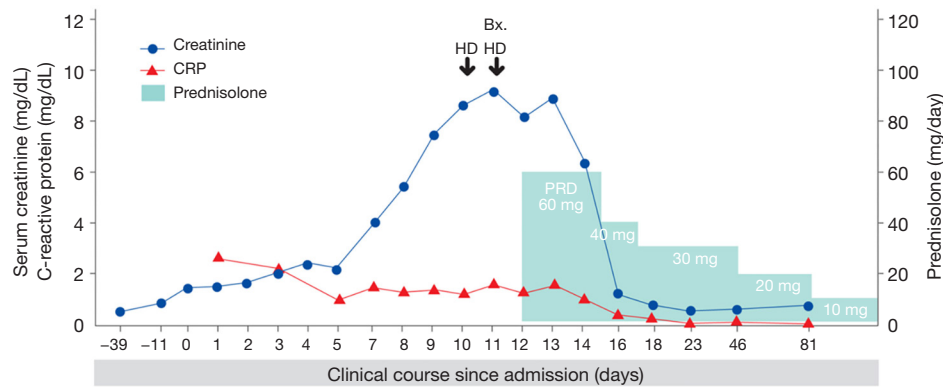


Figure 5 Clinical course of IgG4 related renal disease. HD, hemodialysis; Bx., Kidney biopsy; PRD, prednisolone; CRP, C-reactive peptide.

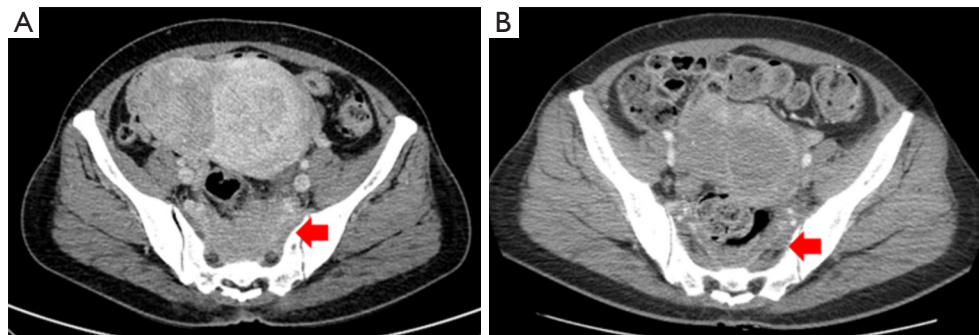


Figure 6 Enhanced CT scans of the abdomen, before and after treatment. Enhanced CT scan of the abdomen revealed diffuse prevertebral soft tissue thickening and enhancement at lower lumbar spine and sacrum (A, arrow). The CT scan after treatment showed a decreased extent of the ill-defined soft tissue lesion involving both the paraspinous area of L5 and the presacral space (B, arrow).

presents mild proteinuria less than 500 mg/gCr with or without hematuria. Retroperitoneal fibrosis associated with IgG4-related disease shows bilateral hydronephrosis in 25% of reported cases, and unilateral hydronephrosis in 75% of cases (8). In this patient, a post-renal obstructive lesion was not significant in various radiologic and ultrasound findings. And only 2 sessions of hemodialysis and 3 days of administration of glucocorticoids were needed for fast recovery from acute kidney injury, without any intervention such as percutaneous nephrostomy or ureteric stent insertion. The treatment of choice is glucocorticoids, 0.6 mg/kg/day of prednisolone, for 2 to 4 weeks. Then prednisolone can be tapered to 2.5–5 mg/day for 3 to 6 months (1,13–15). Glucocorticoids show a good response in the majority of patients, but flare-up of the disease often occurs (1,8,10–12). Several drugs like Rituximab, azathioprine, mycophenolate mofetil, and methotrexate can be used for refractory disease or for

preventing relapse (1,15–18). We successfully diagnosed IgG4-related renal disease and retroperitoneal fibrosis by kidney biopsy without findings suggesting IgG4-related disease such as the elevation of serum IgG4 level or abnormal imaging findings, and controlled them without significant adverse effects by administering glucocorticoid. Nevertheless, this case has some limitations. We did not perform surgical tissue biopsy of retroperitoneal fibrosis, itself. In addition, pleural effusion cytology and pleural biopsy were not conducted, so we could not check the possibility of accompanied IgG4-related pulmonary disease.

In conclusion, we successfully diagnosed and managed this case of IgG4-related renal disease with retroperitoneal fibrosis by glucocorticoid treatment. Retroperitoneal fibrosis can be a clue for hidden IgG4-related disease when manifestations in other organs are present, like acute kidney injury and pleural effusion.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tau.2020.02.06>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this Case report and any accompanying images.

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