CASE REPORT

IgG4-Related Infiltrative Kidney Disease without Extrarenal Organ Involvement: A Case Report

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Background: IgG4-related disease (RD) is a systemic condition that can affect nearly all organs. Renal involvement encompasses interstitial nephritis, membranous nephropathy, and renal infiltrative lesions. Symptomatic IgG4-related kidney disease (RKD) without extrarenal organ manifestations is an exceptionally rare occurrence.

Case Report: The authors present a case of 48-year-old male with isolated renal IgG4-RD presented with abdominal pain. Laboratory investigations revealed acute kidney injury, proteinuria, and hypoalbuminemia. Whole abdominal computed tomography (CT) scan disclosed infiltrative lesions in both kidneys and ureters, accompanied by hydronephrosis. Kidney biopsy demonstrated lymphocytic and plasma cell infiltration, with 82 plasma cells per high power field (HPF), storiform fibrosis, and the absence of obliterative phlebitis. After receiving corticosteroid treatment, the patient's renal function improved, and the infiltrative lesions went into remission.

Conclusion: Isolated renal IgG4-RD is a rare and challenging diagnosis. The disease can manifest as acute interstitial nephritis, glomerular disease, retroperitoneal fibrosis, or, rarely, as mass or infiltrative lesions. Corticosteroid therapy is likely to yield favorable responses, hence, prompt diagnosis is crucial. Delayed diagnosis may result in organ fibrosis and dysfunction.

Keywords: IgG4-related disease; IgG4-related kidney disease; Infiltrative renal disease

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A 48-year-old Thai male presented with right side abdominal pain for three months. His pain was dull aching in nature and radiated to the right groin. He reported experiencing nocturia twice per night and noted an increase in foamy urine. He also had weight loss of 13 kilograms, from 92 kg to 79 kg, within three months. One month prior to admission, his pain was worsening. He also noticed a bilateral pitting edema on both legs, so he decided to go to the hospital. He was previously healthy and had no underlying disease. At hospital, his vital signs were body temperature of 37°C, blood pressure of 126/82 mmHg, and heart rate of 80 bpm. The physical examination showed unremarkable except bilateral pitting edema 1+ both legs, and mild tenderness at right side of his abdomen with no guarding or rigidity. His laboratory investigations were hemoglobin 15.8 mg/dL, white blood cell (WBC) 7.9 $\times 10^3/\mu L$, with neutrophil 34%, lymphocyte 28%, monocyte 10%, and eosinophil 25%, absolute eosinophil count 1,975/µL, platelets 345 $\times 10^3/\mu L$, blood urea nitrogen (BUN) 20 mg/dL, serum creatinine 1.77 mg/dL, estimated glomerular filtration rate (eGFR) 46 mL/kg/1.73 m^2, sodium138 mEq/L, potassium 4.3 mEq/L, chloride 100 mEq/L, bicarbonate 26 mEq/L, total bilirubin 0.8 mg/dL, direct bilirubin 0.17 mg/dL, serum glutamic oxaloacetic transaminase (SGOT) 20 U/L, serum glutamic pyruvic transaminase (SGPT) 10 U/L, alkaline phosphatase (ALP) 72 IU/L, total protein 9.4 g/dL, albumin 3.2 g/dL, and globulin 6.2 g/dL. His urinary analysis showed specific gravity (spgr.) 1.021, protein 1+, blood negative, red blood cells (RBC) 2 to 3 per high power field (HPF), and WBC 0 to 1 per HPF. His urine protein per creatinine ratio (UPCR) was 1.0. Since he had right flank pain radiating to the groin, at that time, the differential diagnosis included 1) right ureteric calculi, 2) renal abscess,

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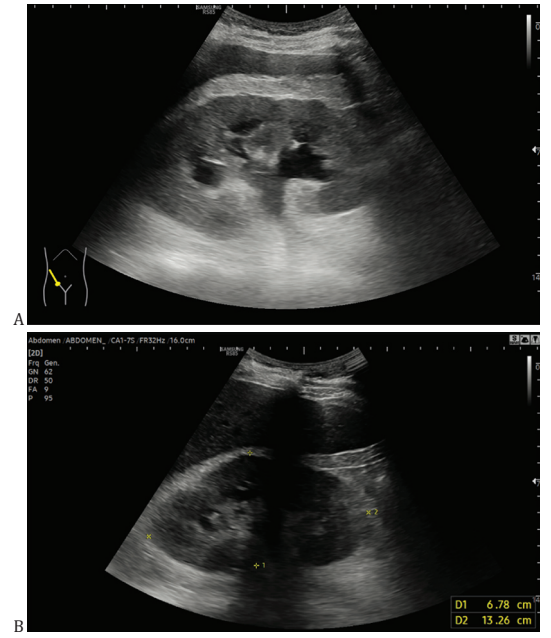

Figure 1. Ultrasound of right (A) and left (B) kidney showed bilateral kidneys enlargement and hydronephrosis. No cause of hydronephrosis was found.

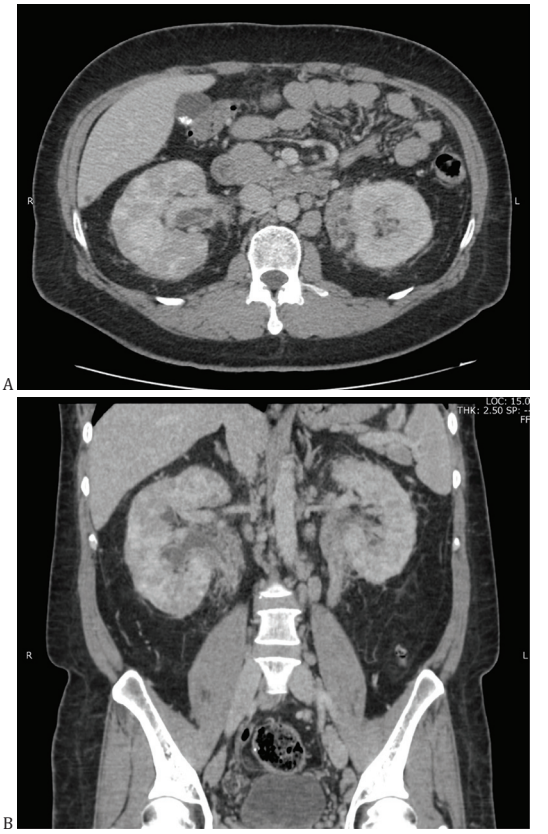

Figure 2. Post venous contrast CT whole abdomen in axial view (A) and coronal view (B) showed bilateral kidneys infiltrated with heterogenous infiltrative lesions. The lesions extended to bilateral proximal ureters resulting in obstructive nephropathy and hydronephrosis. After 6 months of treatment, post venous contrast CT whole abdomen in axial view (C) and coronal view (D) revealed complete remission of infiltrative lesions, complete remission of hydronephrosis, and subsided of enlarged intraabdominal lymph nodes.

and 3) acute appendicitis. So, the patient was sent for an ultrasound KUB.

His ultrasound KUB revealed bilateral kidney enlargement with right at 7.1×12.9 cm and left at 6.8×13.3 cm, with bilateral hydronephrosis. No ureteric stone or cause of obstruction was found (Figure 1). His CT whole abdomen demonstrated kidneys with bilateral heterogeneous infiltrative kidney lesions (Figure 2A, B). These lesions also involved proximal ureters resulting in bilateral hydronephrosis. He also had multiple lymph nodes enlargement along the para-aortic, aortocaval, retrocaval, bilateral common iliac, bilateral external iliac, and bilateral inguinal regions. The patient was suspected to have infiltrative kidney diseases, including malignancies such as lymphoma, urothelial carcinoma, and multiple myeloma.

His kidney biopsy was performed and revealed interstitial infiltration with lymphocytes, plasma cells, eosinophils, and some neutrophils (Figure 3A). Focus of storiform fibrosis is shown in Figure 3B. Immunohistochemical study for IgG and IgG4 demonstrated diffuse infiltration of 82 IgG4-positive plasma cells per HPF with IgG4-positive plasma cells/IgG-positive plasma cells ratio greater than 40% (Figure 3C, D). However, the PAS stain and immunofluorescence were not performed in the present case, potentially limiting the visualization of the glomerular basement membrane. His IgG4 level was 4,480 mg/dL when the normal range is 30 to 330 mg/dL. Workup for hematologic malignancy showed no monoclonal protein in serum electrophoresis, a normal bone marrow biopsy, and no kappa or lambda dominance of serum free light chain.

The present patient had met the definite diagnosis for IgG4-related disease (RD) by the 2020 revised comprehensive diagnostic (RCD) criteria and consensus statement on the pathology of IgG4-RD for the following reasons[1,2]. Firstly, our patient exhibited renal infiltration, clearly visible on the computed tomography (CT) scan. Secondly, he had serum IgG4 levels exceeding 135 mg/dL. Lastly, he demonstrated dense plasma cell infiltration, with more than 10 cells per HPF and a ratio of IgG4-positive plasma cells to IgG-positive cells exceeding 40%, accompanied by

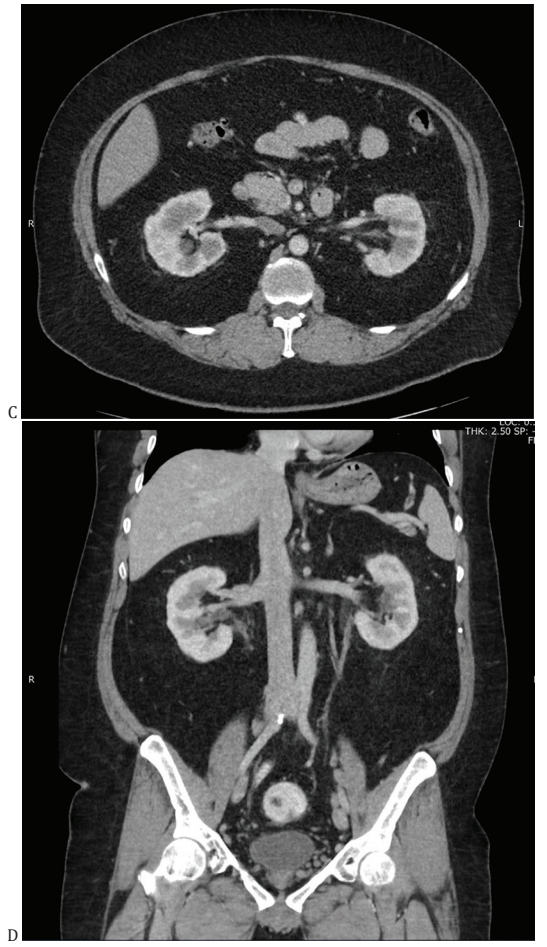

Figure 2. (continued).

typical storiform fibrosis.

He was treated with oral prednisolone 40 mg/day for three months. The prednisolone was gradually tapered, and azathioprine 50 mg/day was introduced to address steroid-related side effects. His symptoms showed improvement throughout the treatment course. Within one month after initiation of treatment, his serum creatinine decreased from 1.76 to 1.22 mg/dL, further reducing to 1.0 mg/dL within four months. Concurrently, his serum albumin increased from 3.2 to 4.0 mg/dL three months after treatment. The serum IgG4 levels decreased from 4,480 to 493 mg/dL within six months, eventually normalized at one year. A repeat CT scan of the entire abdomen at six months post-treatment revealed complete remission of kidney and ureter infiltration, as well as bilateral hydronephrosis (Figure 2C, D). Multiple intra-abdominal lymphadenopathies had also disappeared. Medications were gradually tapered and completely discontinued after two years of treatment.

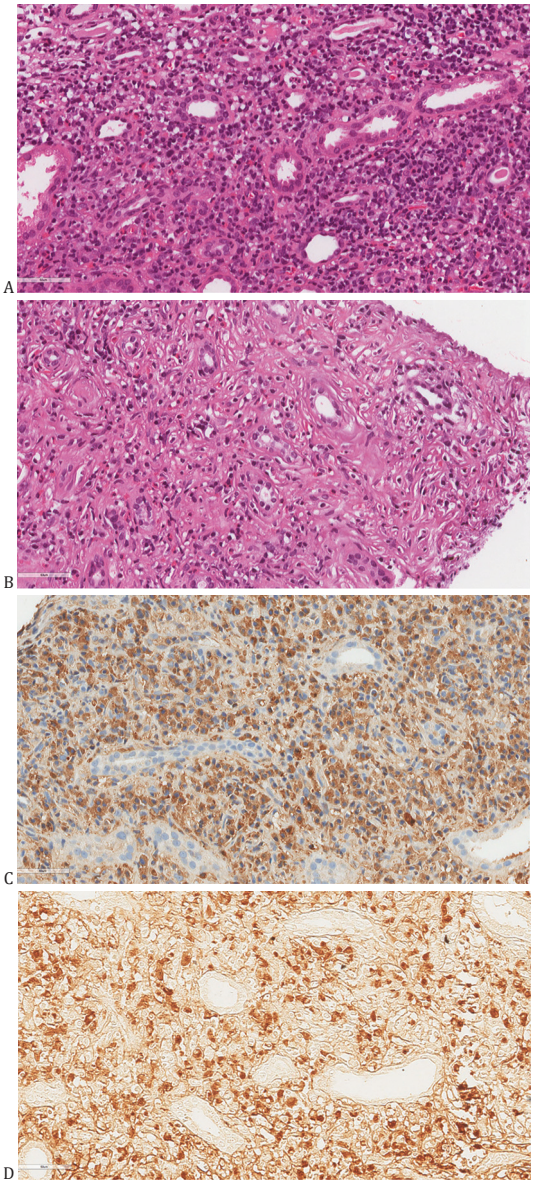

Figure 3. The kidney biopsy demonstrates interstitial infiltration with lymphocytes, plasma cells, eosinophils, and some neutrophils (A, H&E 400x). Focus of storiform fibrosis is shown (B, H&E 400x). Immunoperoxidase staining of renal interstitial shows IgG staining plasma cells (C, 400x), and IgG4 staining plasma cells (D, 400x).

He currently attends regular nephrology clinic visits every four months for disease monitoring.

Discussion

IgG4-RD is an uncommon inflammatory disease that causes fibrosis in nearly every organ. The estimated annual incidence rate is about 1 per 100,000 persons in Asian population. The disease

was first discovered in early 2001 in patients with sclerosing pancreatitis[3]. The pathophysiology involves the infiltration of corresponding organs by IgG4-producing plasma cells and lymphocytes[4]. This disease is systemic and typically affects multiple organs simultaneously; therefore, isolated renal disease is exceptionally rare[5,6].

Renal involvements include tubulointerstitial nephritis (TIN), glomerular disease, and obstructive nephropathy from retroperitoneal fibrosis[7-9]. Interestingly, the disease can also manifest as a renal mass that mimic kidney tumor or malignancy[10]. Only a few cases of isolated renal mass or infiltrative lesion involvement of IgG4 have been reported[11,12]. These patients also experienced acute kidney injury (AKI) and albuminuria. However, when compared to their cases, the present case presented with abdominal pain rather than abnormal serum creatinine, contributing to a different differential diagnosis, choice of imaging study, and clinical judgment. This different clinical presentation is useful as a reminder for clinicians to consider IgG4-RD as a differential diagnosis when treating patients with abdominal pain.

Radiologically, IgG4-related kidney disease can involve kidney parenchyma in three forms including 1) multiple nodular lesions, 2) patchy infiltrative lesions, and 3) single nodular lesion (rare). These lesions usually appear to be hypoattenuation on CT scan, representing fibro-inflammatory nature of the disease[13,14]. The most common site of the infiltrative lesion is renal cortex, but renal medulla, perinephric space, and renal pelvis can also be involved. Urogenital organ, such as prostate and bladder can also be involved[14]. The involvement of ureter is even more rare and usually cause hydronephrosis, similar to the present patient[15-17]. The authors summarized renal involvement in IgG4-RKD in Figure 4. To the authors' knowledge, the present case is the first case of isolated bilateral kidneys and ureters IgG4-RD.

Fortunately, there are clinical clues to aid in the diagnosis of IgG4-RD. Demographically, this disease shows male predominance, with a male to female prevalence ratio of 4:1, and the most prevalent age group is from middle age to the elderly. The authors' patient had an increased absolute eosinophils count of 1,975/μL consistent with eosinophilia. Eosinophilia is defined as an absolute eosinophils count greater than 500/μL which is also found in various conditions such as autoimmune disease, parasitic disease, and allergies[18-20]. There are hypotheses that eosinophils have a strong association with IgG4-RD and play a key role in the pathogenesis of IgG4-RD. A significant

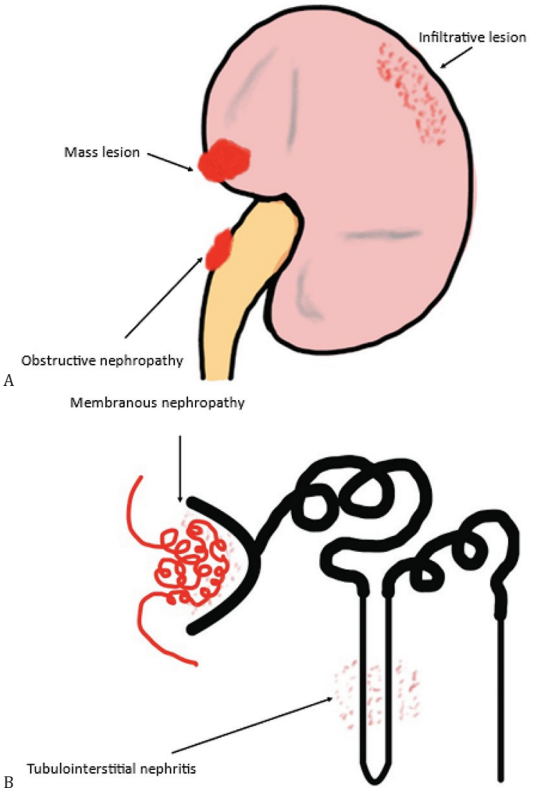

Figure 4. Diagram of kidney (A) and nephron (B) involved by IgG4-related kidney disease. IgG4-related kidney disease can be presented as mass lesion or infiltrative lesion. Direct ureter compression from IgG4-related mass can cause obstructive nephropathy and hydronephrosis. Retroperitoneal fibrosis can also be the cause of obstructive nephropathy in advance disease. IgG4-RD can cause nephrotic syndrome from membranous nephropathy. Tubulointerstitial involvement of the disease can cause acute kidney injury and sub nephrotic range proteinuria.

* This figure was drawn by the author.

number, from 20% to 40%, of IgG4-RD patients present with eosinophilia[21,22]. Moreover, eosinophils can also be found in 51% to 86% in pathological tissues in IgG4-RD patients[21]. The functions of eosinophils in the pathogenesis of IgG4-RD are still uncertain but there are hypotheses that eosinophils help to maintain plasma cell survival and function, T lymphocyte activation, antigen presentation, and tissue fibrosis formation[20,23,24]. Therefore, if the eosinophilia was found without a justifiable cause in a clinical suspected patient, clinicians should consider the increased possibility of IgG4-RD. About 30% of IgG4-RD patients had a low complement level, and this increased to about 50% in patient with renal involvement[25].

Currently, glucocorticoids are the first line treatment for IgG4-RD that generates a rapid response

in over 80% to 90% of patients[9,26,27]. The current guideline recommends an oral prednisolone at 0.6 mg/kg/day for three months to induce remission and subsequently taper to a maintenance dose of 2.5 to 5 mg/day for 6 to 36 months[28,29]. Patients who do not respond to steroids should undergo a workup for other causes such as concurrent malignancy and infection. Other immunosuppressants, such as azathioprine, mycophenolate mofetil (MMF), or anti-CD20 antibody, can be used as a second line drug when corticosteroids are not effective or cannot be used[30,31]. The author's patient received prednisolone at 40 mg/day (0.6 mg/kg/day) for three months and was tapered off to avoid long term side effects. Azathioprine was used in the present patient as a maintenance therapy for two years. From previous study, there was about an 80% therapeutic response rate with this approach[32]. Up until now, the patient continues to follow up regularly at nephrology clinic Somdech Phra Pinklao Hospital and has had no recurrence of the disease.

Conclusion

IgG4-RD is a systemic immune-mediated disorder. Isolated renal involvement is infrequent and may manifest as masses or infiltrative lesions, posing challenges in differentiation from other diseases. The condition exhibits a favorable response to corticosteroid therapy. Delayed diagnosis or uncontrolled disease may lead to organ fibrosis, contributing to morbidity, and mortality[29].

What is already known on this topic?

IgG4-RD is an immune mediated disease that can involve nearly all organs. Renal isolated IgG4-RD is rare and can be presented as a mass or infiltrative lesion. Tissue biopsy is required to make a diagnosis. Delay in diagnosis could lead to unfavorable outcome.

What does this study add?

Even though this is a single case report without a control group for comparison, the authors have presented a distinctive case involving isolated IgG4-RD characterized by the presentation of abdominal pain and AKI. This serves as a notable reminder for clinicians to consider IgG4-RD as a potential differential diagnosis for abdominal pain, even in the absence of other manifestations associated with IgG4-RD. Elevated serum IgG4 levels and the presence of infiltrative lesions serve as pertinent clinical indicators for this disease. Nevertheless, a definitive diagnosis necessitates a tissue biopsy.

Ethical approval

The case presentation was approved by the Research Ethics Committee Naval Medical Department (No. RP0027/66). The consent form was waived due to the retrospective nature of the presentation, using only de-identified data.

Conflicts of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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