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CASE REPORT

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A rare case: IgG4-related chronic inflammatory disease with kidney involvement

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Abstract

IgG4-related disease is an inflammatory, multisystemic disease that affects the immune system. The disease progresses to fibrosis due to inflammation. Retroperitoneal fibrosis is a serious complication. Pancreas, biliary tract, glands, thyroid, lymph nodes, etc. may be involved. Prognosis is usually subacute, and seen in middle age and advanced men. It is characterized histopathologically by IgG4 positive plasma cells, lymphoplasmocytic cell infiltration, and storiform fibrosis. In our case, we evaluated a patient who referred to our clinic from an external center with the complaints of generalized pain, itching, tearing and redness in eyes, involvement of bilateral large joints, and impaired renal function. Diagnosis, treatment and management of the disease are important. Response to glucocorticoid therapy is good.

KEYWORDS

acute kidney injury, IgG4 related disease, tubulointerstitial nephritis

1 | INTRODUCTION

IgG4-related disease (IgG4-RD) is an immune-mediated chronic inflammatory disease that progresses to fibrosis. It is a multisystemic disease with involvement of secretory glands, kidney, etc. It usually has a subacute course and is frequently observed in middle-aged and older male population. The pathogenesis of IgG4-RD is still unclear, but elevated IgG4 levels and the good response of IgG4-RD patients to treatment with rituximab (B-cell depletion treatment) suggest a role of the humoral immune system in the pathogenesis of IgG4-RD. Glucocorticoids and rituximab are used in the treatment of the disease. Early diagnosis, treatment, and follow-up are important for prognosis and recurrence of the disease[1–4] (Table 1).

In our case, we evaluated a patient who had arthritis, pain, itching, tearing, and redness and referred to our clinic with impairment in renal function tests from an external center.

2 | CASE PRESENTATION

A 52-year-old male patient had arthritis, pain, itching, and redness of the eyes and referred to our clinic with a history of allergic rhinitis and not using any medication before evaluated. Serum urea 102.1 mg/dL (12.84–42.8 mg/dL), creatinine 4.66 mg/dL (0.70–1.20 mg/dL), eGFR 13 mL/min/1.73 m^2 (60–120 mL/min/1.73 m^2), serum albumin 30.4 gr/L (35–52 gr/L), blood eosinophil

TABLE 1 The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-RD.[4]

Step	Categorical assessment or numeric weight
Step 1: Entry criteria	**Yes**[b] or No
Characteristic[a] clinical or radiologic involvement of a typical organ (e.g., pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges, or thyroid gland [Riedel's thyroiditis]) OR pathologic evidence of an inflammatory process accompanied by a lymphoplasmacytic infiltrate of uncertain etiology in one of these same organs	
Step 2: Exclusion criteria: domains and items[c]	Yes or **No**[d]
Clinical	
Fever	
No objective response to glucocorticoids	
Serologic	
Leukopenia and thrombocytopenia with no explanation	
Peripheral eosinophilia	
Positive antineutrophil cytoplasmic antibody (specifically against proteinase 3 or myeloperoxidase)	
Positive SSA/Ro or SSB/La antibody	
Positive double-stranded DNA, RNP, or Sm antibody	
Other disease-specific autoantibody	
Cryoglobulinemia	
Radiologic	
Known radiologic findings suspicious for malignancy or infection that have not been sufficiently investigated	
Rapid radiologic progression	
Long bone abnormalities consistent with Erdheim–Chester disease	
Pathologic	
Cellular infiltrates suggesting malignancy that have not been sufficiently evaluated	
Markers consistent with inflammatory myofibroblastic tumor	
Prominent neutrophilic inflammation	
Necrotizing vasculitis	
Prominent necrosis	
Primarily granulomatous inflammation	
Pathologic features of macrophage/histiocytic disorder	
Known diagnosis of the following:	
Multicentric Castleman's disease	
Crohn's disease or ulcerative colitis (if only pancreatobiliary disease is present)	
Hashimoto thyroiditis (if only the thyroid is affected)	
If case meets entry criteria and does not meet any exclusion criteria, proceed to step 3	
Step 3: Inclusion criteria: domains and items[e]	
Histopathology	
Uninformative biopsy	0
Dense lymphocytic infiltrate	+4
Dense lymphocytic infiltrate and obliterative phlebitis	+6
Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis	+13

TABLE 1 (Continued)

Step	Categorical assessment or numeric weight
Immunostaining[f]	0–16, as follows:
	Assigned weight is 0 if the IgG4+:IgG+ ratio is 0–40% or indeterminate and the number of IgG4+ cells/hpf is 0–9[g] Assigned weight is 7 if 1) the IgG4+:IgG+ ratio is ≥41% and the number of IgG4+ cells/hpf is 0–9 or indeterminate; or 2) the IgG4+: IgG+ ratio is 0–40% or indeterminate and the number of IgG4+ cells/hpf is ≥10 or indeterminate
	Assigned weight is 14 if 1) the IgG4+:IgG+ ratio is 41%–70% and the number of IgG4+ cells/hpf is ≥10; or 2) the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is 10–50
	Assigned weight is 16 if the IgG4+ :IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is ≥51
Serum IgG4 concentration	
Normal or not checked	0
>Normal but <2× upper limit of normal	+4
2–5× upper limit of normal	+6
>5× upper limit of normal	+11
Bilateral lacrimal, parotid, sublingual, and submandibular glands	
No set of glands involved	0
One set of glands involved	+6
Two or more sets of glands involved	+14
Chest	
Not checked or neither of the items listed is present	0
Peribronchovascular and septal thickening	+4
Paravertebral band-like soft tissue in the thorax	+10
Pancreas and biliary tree	
Not checked or none of the items listed is present	0
Diffuse pancreas enlargement (loss of lobulations)	+8
Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+11
Pancreas (either of above) and biliary tree involvement	+19
Kidney	
Not checked or none of the items listed is present	0
Hypocomplementemia	+6
Renal pelvis thickening/soft tissue	+8
Bilateral renal cortex low-density areas	+10
Retroperitoneum	
Not checked or neither of the items listed is present	0
Diffuse thickening of the abdominal aortic wall	+4
Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	+8
Step 4: Total inclusion points	
A case meets the classification criteria for IgG4-RD if the entry criteria are met, no exclusion criteria are present, and the total points is ≥20	

[a]Refers to enlargement or tumor-like mass in an affected organ except in 1) the bile ducts, where narrowing tends to occur, 2) the aorta, where wall thickening or aneurysmal dilatation is typical, and 3) the lungs, where thickening of the bronchovascular bundles is common.

[b]If entry criteria are not fulfilled, the patient cannot be further considered for classification as having IgG4-related disease (IgG4-RD).

(Continues)

TABLE 1 (Continued)

[c]Assessment for the presence of exclusion criteria should be individualized depending on a patient's clinical scenario.

[d]If exclusion criteria are met, the patient cannot be further considered for classification as having IgG4-RD.

[e]Only the highest-weighted item in each domain is scored.

[f]Biopsies from lymph nodes, mucosal surfaces of the gastrointestinal tract, and skin are not acceptable for use in weighting the immunostaining domain.

[g]"Indeterminate" refers to a situation in which the pathologist is unable to clearly quantify the number of positively staining cells within an infiltrate yet can still ascertain that the number of cells is at least 10/high-power field (hpf). For a number of reasons, most often pertaining to the quality of the immunostain, pathologists are sometimes unable to count the number of IgG4+ plasma cells with precision yet even so, can be confident in grouping cases into the appropriate immunostaining result category.

1.23 10^3/μL (0.03–0.59 10^3/μL), C-reactive protein 69.8 mg/L (0–5 mg/L), and 1 + proteinuria in complete urine analysis. Hematuria and leukocyturia were absent in urine analysis, urine microscopy was normal, and 1527.5 mg/day proteinuria was detected in 24-h urine. C3c 0.38 g/L (0.9–1.8 g/L), C4 < 0.02 (0.1–0.4 g/L), serum amyloid A 50.70 mg/dL (5.7–8.2 mg/dL), IgG 37.83 g/L (7–16 g/L), α1 globulin 6% (2.9–4.9), β1 globulin 3.2% (4.7–7.2), β2 globulin% in protein electrophoresis 7.8 (3.2–6.5), and γ globulin 39.4% (11.1–18.8) were found in laboratuary assessment. The patient's liver and thyroid function tests and pancreatic enzymes were normal. There was no growth in the blood and urine cultures. Rheumatoid factor and autoantibody tests were negative in his examinations in our clinic. Contrast-enhanced abdominal computed tomography of the patient revealed an inflamed appearance in the adipose tissue in the left pararectal region, loss of corticomedullary separation, and hypodense patchy areas in both kidneys detected (Figures 1 and 2). Contrast nephropathy, tubulointerstitial nephritis (TIN), or vasculitis considered in the differential diagnosis.

The patient's respiratory system examination was normal, she had no rashes suggestive of vasculitis, her antibodies were negative (ANA, pANCA, cANCA, antiGBM, etc.), and there was no clinical picture of rapidly progressive glomerulonephritis.

In the needle biopsy, samples taken from the left pararectal region of the patient, mononuclear inflammatory cells infiltration rich with eosinophil leukocytes and plasma cells observed in fibrolipomatous tissues showing fibrosis. More than 10 IgG4-expressing plasma cells counted in one high magnification field in plasma cells that showed CD68 negative and CD138 positive staining. These histopathological findings were found to be significant in terms of IgG4-RD (Figure 3).

The patient had normal kidney size and proteinuria over 1.5 g/day. Kidney was biopsy performed. No endocapillary or extracapillary proliferative or necrotizing lesions were observed in the biopsy. Intense fibrocollagenous connective tissue increase in the interstitium, and tubular atrophy, coarsening, and wrinkling of the tubular basement membranes are noted. Mononuclear cell infiltration rich

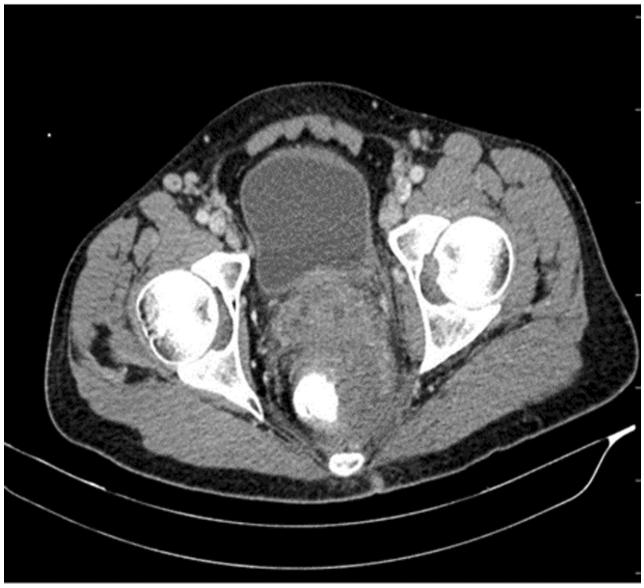

FIGURE 1 Contrast-enhanced abdominal computed tomography. Inflammation in pararectal adipose tissue.

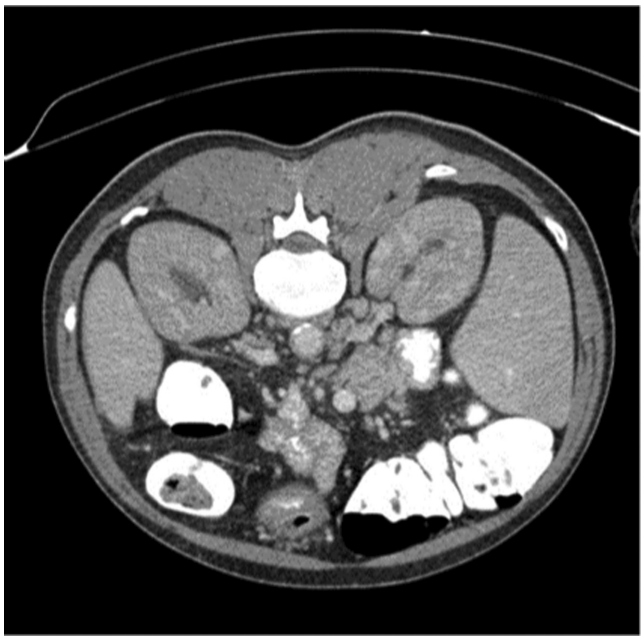

FIGURE 2 Contrast-enhanced abdominal computed tomography. Loss of corticomedullary separation and hypodense patchy areas in both kidneys.

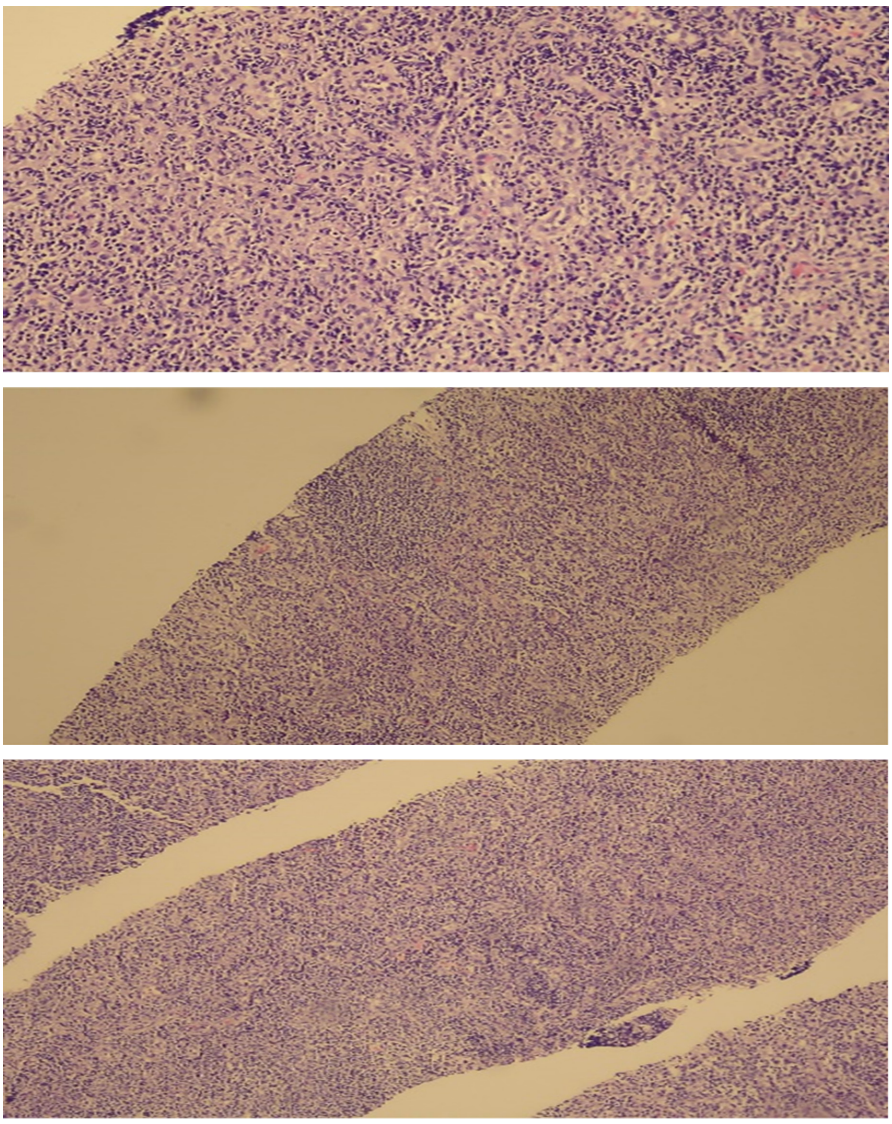

FIGURE 3 Examples of pararectal lymphatic tissue biopsy. Lymphoid tissue samples with increased plasma cells in hematoxylin–eosin staining.

with plasma cells was observed. In the IgG4 staining, it was seen that the plasma cells stained positively in 16–20/one large magnification. These findings supported tubulointerstitial nephritis (Figure 4). No significant vasculopathy, arteriolar concentric sclerosis, or hyalinosis detected in the arteries.

Considering IgG4-related tubulointerstitial nephritis, 250 mg/day intravenous prednisolone was started for 3 days, followed by maintenance of 0.5 mg/kg/day oral prednisolone. Angiotensin-converting enzyme, proton pump inhibitor, calcium + vitamin D were given. At the first follow-up after 15 days, the patient stated that his current complaints had regressed dramatically. Laboratuary values were found as serum urea 95.7 mg/dL (12.84–42.8 mg/dL), creatinine 1.96 mg/dL (0.70–1.20 mg/dL), and 24-h urine protein 238.5 mg/day (0–140 mg/dL). The patient's follow-up and treatment continue in our unit.

3 | DISCUSSİON

IgG4-RD is a fibroinflammatory disease involving almost all organs. Patients may be asymptomatic or have severe symptoms. Clinical diagnosis of the disease may be difficult, or the findings may be confused with other diseases. The American College of Rheumatology/European League Against Rheumatism IgG4-RD determined classification criteria.[4] The disease progresses with tissue and organ involvement; IgG4 level is usually high, and it can also be found normal. IgG4-RD can lead to fibrosis and can cause to organ failure. Tissue biopsy is important to support the diagnosis.[1,5] While the disease is first described as associated with autoimmune pancreatitis, it can affect organs such as the thyroid, salivary gland, biliary tract, kidney etc.[6,7]

The kidney is involved in approximately 20% of patients with IgG4-RD. The most common kidney disease

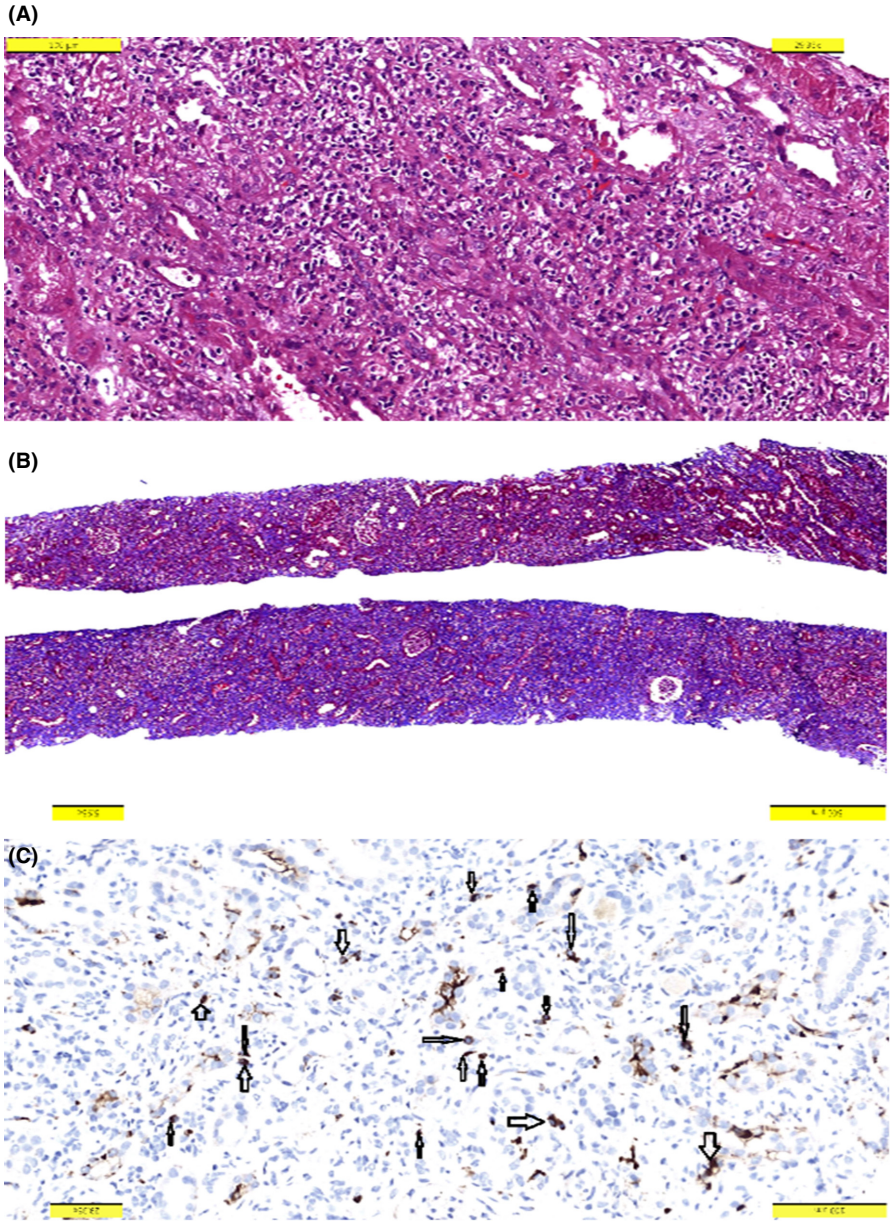

FIGURE 4 Kidney biopsy samples. IgG4-secreting plasma cells with (A) hematoxylin–eosin staining, (B) Masson trichrome staining, (C) IgG4 immunohistochemical staining.

is TIN. Retroperitoneal fibrosis can cause to obstructive acute renal injury (ARI). Rarely, IgG4-RKD can represent as a glomerular disease, especially as membranous nephropathy (MN).[8]

IgG4-related TIN has been identified as a part of systemic IgG4-RD. On biopsy, TIN shows an IgG4+ plasma cell-rich infiltrate and may show tubulointerstitial immune complex deposits. Saeki et al evaluated 23 patients with renal parenchymal injury, and more than 60% of them had TIN. Light microscopy demonstrated dense cell infiltration with fibrosis and tubular atrophy. The infiltrate was predominantly composed of plasma cells and lymphocytes, and also eosinophils in some patients.[8–10] IgG4-RD with TIN cases presented with hypertension, elevated serum creatinine and IgG4, proteinuria, and eosinophilia have been reported.[11,12]

CT is the primary imaging modality used to examine patients with suspected IgG4-RD. Multiple low-density lesions on enhanced CT are the most common radiologic finding in IgG4-related TIN, but diffuse bilateral renal swelling may be observed when severe renal failure is a contraindication for the administration of contrast medium. Kidney abnormalities on CT imaging have been observed in nearly 70% of patients with IgG4-RD.[13–16]

In a study, nine patients described with IgG4-RD MN. All patients showed MGN on biopsy, presented with proteinuria (mean 8.3 g/day), and most had elevated serum creatinine (mean 2.2 mg/dL). All biopsies showed a pattern of MGN with subepithelial deposits in a membranous pattern seen by immunofluorescence (IF), electron microscopy, or light microscopy, including immunoperoxidase staining for IgG4. In another study about IgG4-RD

MN, interstitial IgG4+ plasma cell infiltration (>10/hpf) and IgG4-positive plasma cells account for more than 40% of IgG+ plasma cells detected in immunohistochemistry staining.[14,15,17]

The efficacy of glucocorticoids and rituximab (RTX) in the treatment of IgG4-RD has been demonstrated. IgG4-related disease usually responds to high-dose glucocorticoids, with an average dose of 40 mg/day, which is subsequently tapered. In a study, partial and complete responses were observed in all patients after glucocorticoid and RTX treatment. International consensus recommends a much more gradual tapering of the dose, over a period of 3–6 months. With this dosing scheme, the rate of relapses was 23%.[2,18,19] In a French study, patients who received rituximab treatment at 375 mg/m^2 once a week (4 doses) and 1000 mg on the 1st and 15th days were evaluated, and the response to the treatment was 93.5%. The relapse rate was 41.9% (after mean 19.0 ± 11.5 months), and relapse after retreatment was 27.2%.[20]

In our study, we evaluated a 52-year-old patient who presented with proteinuria and acute kidney injury. The diagnosis of IgG4-RD was made according to American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease in our case[4] [hypocomplementemia (6 points), IgG4 levels (4 points), IgG4 staining level in biopsy (14 points), and radiological kidney involvement (10 points), total 34 points] (Table 1). The patient's clinical course was stable, and proteinuria regressed after steroid treatment. The complete urinalysis, protein, erythrocyte, and leukocyte were negative. In his control, after 60 days, serum urea decreased to 53.1 mg/dL and creatinine to 1.71 mg/dL. Glucocorticoid dose reduced to 15 mg/day.

In conclusion, renal involvement in IgG4-related disease is rare. Early diagnosis and treatment and management of the disease are important for survival and progression of the disease.

AUTHOR CONTRIBUTIONS

Fatos Mete: Data curation; resources. **Tuba Mengeneci:** Conceptualization; data curation. **Emre Albayrak:** Conceptualization; visualization. **Yavuz Ayar:** Conceptualization; data curation; formal analysis; investigation. **Melike Nalbant:** Data curation; methodology. **Ilknur Ozudeniz Mutlucan:** Data curation; formal analysis; investigation. **Zeliha Fusun Baba:** Investigation; resources; software.

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Contribution to Data: writing YA, TM, FM, EA; analyzing YA, MN, IOM, ZFB; review YA, IOM, ZFB.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest between authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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