CASE REPORT

IgG4-related Kidney Disease in Which the Urinalysis, Kidney Function and Imaging Findings Were Normal

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Abstract

IgG4-related kidney disease (IgG4RKD) is recognized as a fibroinflammatory disease characterized by storiform fibrosis, lymphoplasmacytic infiltration and a high serum IgG4 level. A renal biopsy is necessary to diagnose IgG4RKD in patients without any lesions in other organs. Nephrologists typically perform renal biopsies in patients with abnormal urinalysis, such as proteinuria or hematuria, or renal failure. However, we experienced a patient with IgG4RKD without abnormalities in the urinalysis, renal function or imaging, who had severe interstitial lesions. We therefore propose that renal biopsies should be considered if patients do not show abnormal urinalysis findings and are suspected to have IgG4RKD.

Key words: IgG4-related kidney disease, storiform fibrosis, interstitial nephritis

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Introduction

IgG4-related disease is a rare autoimmune disorder associated with elevated serum IgG4 concentrations, a lymphoplasmacytic infiltrate of IgG4-positive plasma cells, and storiform fibrosis in the kidneys. We herein present a case of IgG4-related kidney disease in which both the urinalysis findings and kidney function were normal.

Case Report

A 58-year-old man, who had undergone treatment for sinusitis and allergic rhinitis, visited a hospital because of occult blood in his stool. Colon fibroscopy indicated rectal cancer. His computed tomography findings showed lymphadenopathy of the bilateral hilar region of the lung, the mediastinum, the neck, and the subclavian region. He was diagnosed with rectal cancer and laparoscopy-assisted colectomy was performed in June, 2011. After that, the patient had swelling of his bilateral upper eye lids and enlargement of the bilateral submandibular glands. He was referred to the department of respiratory medicine for evaluation of multiple lymphadenopathies in July. With a high level of IgG4, the patient was suspected to have an IgG4-related disease. A submandibular lymph node biopsy was performed in August, and it showed follicular hyperplasia and an IgG4/IgG positive plasma cell ratio <40% via immunostaining. A lip biopsy was performed in June, 2012 which showed an infiltration of lymphocytes and plasma cells [more than 10/HPF in the interstitium] and an IgG4/IgG positive plasma cell ratio of approximately 40% via immunostaining. However, previous reports have shown that the infiltration of IgG4-positive cells also may be seen in patients with rheumatoid arthritis or in oral inflammatory diseases. We considered that the infiltration of the cells was not specific for IgG4-related kidney disease (IgG4RKD) and decided to perform a renal biopsy to make a definitive diagnosis.

On the physical examination, the patient had swollen bilateral upper eyelids and an enlargement of the bilateral submandibular glands without tenderness or redness. His chest

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and abdomen were intact. Edema was not seen in his extremities and swelling of the lymph nodes was not palpable in the axillae or the inguinal region. His urinalysis was completely normal: negative for proteinuria, negative for hematuria, RBC <1/HPF, WBC 1-4/HPF. The N-acetyl-beta-D-glucosaminidase (NAG) and beta 2-microglobulin levels in his urine were 2.5 U/L and 102 μg/L, respectively. His serum creatinine level was 0.78 mg/dL and the estimated glomerular filtration rate (eGFR) was 80.2 mL/min/1.73 m². The total leucocyte count was 5,830/μL and hypereosinophilia was seen (31%). The patient’s C-reactive protein concentration was 0.2 mg/dL. Immunological tests showed the patient was negative for antinuclear antibody and anti-SS-A/SS-B antibodies. His serum angiotensin-converting enzyme (ACE) was 12.6 U/mL and IL-2R was 1,112 U/mL. The serum levels of IgG, IgG4 and IgE were elevated (4,721 mg/dL, 2,990 mg/dL, and 1,571 IU/mL, respectively). However, his serum levels of IgA and IgM were decreased, 84 mg/dL and 23 mg/dL, respectively. He showed hypocomplementemia (C3 26 mg/dL, C4 2 mg/dL, CH50<15 U/mL).

A chest X-ray showed lymphadenopathy of the bilateral hilar region of the lung. Positron emission tomography (PET)-CT scan showed lesions of the bilateral submandibular glands, the bilateral hilar region of the lung, the mediastinum, the subclavian region, the para-aorta, and the prostate. The kidneys were not enlarged and multiple patchily distributed hypoattenuated lesions, renal pelvic tumor, or thickening of the renal pelvic wall were not seen in the enhanced abdominal CT. Ga scintigraphy was not available in our hospital. We performed a renal needle biopsy in late August 2012 because we strongly suspected IgG4RKD in this patient due to his hypocomplementemia, lymphadenopathies and enlargement of the lacrimal glands. We punctured the patient’s left kidney with a biopsy gun (16G, 16 cm) and took two samples of the renal cortex (Fig. 1). For immunostaining, we used mouse monoclonal antibodies to human IgG4 and IgG (ZYMED Laboratories, South San Francisco, USA) and stained samples by VENTANA BENCHMARK-XT (Roche, Tucson, USA). Interestingly, one of them appeared to be almost normal. Infiltration of the inflammatory cells was seen in about 40% of the interstitium. The infiltrate was predominantly composed of lymphocytes and plasma cells (Fig. 2A). Collagen fibers encircled the inflammatory cells, which were organized in a storiform pattern (Fig. 2B). Eosinophils were not seen in the interstitium. The IgG4/IgG positive plasma cell ratio reached as high as 40% (Fig. 2C, D). Approximately 4% global sclerosis was detected but other glomerular changes were not detected. Furthermore, significant IgG or complement deposition was not observed via immunofluorescence. Based on the results of a renal biopsy, the patient satisfied the criteria for IgG4RKD proposed by the Japanese society (1); therefore, he was diagnosed with IgG4RKD. At the time of the diagnosis, the patient was fine. Moreover, the swelling of his lacrimal and submandibular glands was slightly decreased. However, we elected to begin treatment to protect the patient’s renal function because his renal biopsy showed severe infiltration of lymphocytes and plasma cells with fibrosis. We started to administer oral prednisolone 20 mg/day (0.4 mg/kg/day) in October. Swelling of the patient’s lacrimal and submandibular glands completely disappeared two months after receiving treatment. Similarly, swelling of the lymph nodes of the bilateral lung hilar, the mediastinum, the subclavian and the thickening of the wall of abdominal aorta were improved in the CT images (Fig. 3). The concentrations of IgG and IgG4 decreased to 1,800 mg/dL and 470 mg/dL, respectively.

**Discussion**

IgG4RKD is now broadly recognized as a fibroinflammatory disease characterized by storiform fibrosis, lymphoplasmacytic infiltration and a high level of serum IgG4. IgG4RKD was first described as an organ complication associated with auto-immune pancreatitis (AIP) by in 2004 (2, 3). Thereafter, many cases were reported in Japan and Kawano et al. proposed a diagnostic guideline for IgG4-related kidney disease in 2011 (4). They proposed five conditions: 1) the presence of kidney damage, as manifested by abnormal urinalysis or urine marker(s) and/or decreased kid-
Figure 2. Renal biopsy. (A) The infiltrate was predominantly composed of lymphocytes and plasma cells (Hematoxylin and Eosin staining, ×400 magnification). (B) Collagen fibers encircled the inflammatory cells which were organized in a storiform pattern (periodic acid silver methenamine, ×400 magnification). (C, D) The IgG4/IgG positive plasma cell ratio was as high as 40% (immunostaining, ×400 magnification). IgG is depicted in blue; IgG4 in brown.

Figure 3. Enhanced CT: The lymph nodes of the bilateral lung hilar and the mediastinum were swollen on admission (A), and the wall of abdominal aorta was thickened (B). These improved after the patient received treatment for 2 months (C, D).
ney function with either elevated serum IgG levels, hypocomplementemia, or elevated serum IgE levels; 2) abnormal renal imaging findings comprising multiple low density lesions on enhanced computed tomography, diffuse kidney enlargement, hypovascular solitary masses in the kidney, or hypertrophic lesions of the renal pelvic wall without irregularity of the renal pelvic surface; 3) serum IgG4 levels exceeding 135 mg/dL; 4) renal histology showing either dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells (>10/HPF) and/or an IgG4/IgG positive plasma cell ratio >40% or characteristic storiform fibrosis surrounding nests of lymphocytes and/or plasma cells; and 5) extra-renal histology showing dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells >10/HPF and/or an IgG4/IgG positive plasma cell ratio <40%. The diagnosis is classified into three stages as “definite,” “probable” or “possible” according to the combinations of conditions described above. In this case, the patient’s serum IgG4 level was as high as 2,990 mg/dL and his lip biopsy showed the infiltration of inflammatory cells and an IgG4/IgG positive plasma cell ratio <40%. In conclusion, we experienced a case of IgG4RKD in which the urinalysis findings and kidney function were both normal, but nevertheless showed a severe infiltration of inflammatory cells in the renal interstitium. A renal biopsy should thus be considered to make a definitive diagnosis of IgG4RKD and to also protect the renal function even when the urinalysis findings and kidney function are normal in such patients.

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

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