Renal Lesions in IgG4-Related Systemic Disease

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Abstract

Objective  Recently, a new concept of IgG4-related systemic disease including autoimmune pancreatitis, characterized by a high serum IgG4 level and tissue infiltration by IgG4-positive plasma cells, has been proposed. Our aim was to investigate the renal involvement in this condition.

Patients and Methods  We investigated the results of laboratory and imaging studies of the kidneys in 7 patients with IgG4-related systemic disease, and examined the renal histology in four of them. All patients showed elevated serum IgG4 levels, and 4 had autoimmune pancreatitis. The other three patients showed involvement of various extrapancreatic organs (lymphadenopathy, sialadenitis or renal insufficiency), and abundant IgG4-positive plasma cell infiltration was confirmed in their affected tissues.

Results  Six of the 7 patients showed some renal abnormalities. In one patient, hydronephrosis was observed accompanied by retroperitoneal fibrosis. Another patient showed multiple low-density areas in both kidneys by computed tomography, and gallium citrate scintigraphy showed gallium-67 accumulation in both kidneys, although renal function was normal. Four patients had tubulointerstitial nephritis. In two of them, the tubulointerstitial nephritis was diffuse. In one patient, marked diffuse but patchily distributed lymphoplasmacytic infiltration of the renal interstitium was observed. In another patient, computed tomography showed a tumor-like low-density mass; open biopsy of the mass showed aggregates of lymphocytes and plasma cells in the renal interstitium.

Conclusion  Renal parenchymal lesions in IgG4-related systemic disease are due to dense lymphoplasmacytic infiltration of the renal interstitium, and the lesions vary from diffuse tubulointerstitial nephritis to tumor-like masses according to the distribution patterns of the infiltrating cells.

Key words: Autoimmune pancreatitis, tubulointerstitial nephritis, sclerosing sialadenitis, Mikulicz’s disease

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Introduction

Elevation of serum IgG4 concentration and abundant IgG4-positive plasma cell infiltration of the pancreas are well known characteristic findings in autoimmune pancreatitis (AIP) (1-3). AIP is also well known to be associated with various types of extrapancreatic organ involvement, and increased numbers of IgG4 positive plasma cells have been revealed not only within the pancreaticobiliary system but also in other organs (1, 2, 4). Therefore, a new concept of IgG4-related systemic disease has been proposed and AIP is suggested to be the pancreatic lesion in this condition (1, 4). On the other hand, Kitagawa et al reported the presence of abundant IgG4-positive plasma cell infiltration in chronic sclerosing sialadenitis, irrespective of the presence of AIP, and this infiltration was not observed in other forms of sialadenitis (5). Because the clinicopathological features of chronic sclerosing sialadenitis resemble those of AIP, they suggested that chronic sclerosing sialadenitis, like AIP, belongs to the IgG4-related disease spectrum. Similarly, serum IgG4 elevation and IgG4-positive plasma cell infiltration of the salivary glands have been documented in Mikulicz’s disease, but not in patients with ordinary Sjögren’s syndrome,
Table 1. Clinicopathological Findings of Seven Patients with IgG4-related Systemic Disease

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1) Laboratory Findings (Table 1)  
Mild proteinuria and/or hematuria were observed in three patients. No patient showed massive proteinuria. Increased serum creatinine levels were shown in five patients who had accompanying TIN or hydronephrosis. The levels of urinary β2-microglobulin (MG) and N-acetyl-β-D-glucosaminidase (NAG) elevated in 3 of 4 patients with TIN (patient 4, 6, and 7). Serum electrolytes were within the normal range in all patients, and renal tubular acidosis was shown in one patient with TIN (patient 7) (data not shown). Hypergammaglobulinemia, negativity for anti SS-A and anti SS-B antibodies, hypocomplementemia and eosinophilia were often observed, and Mikulicz’s disease has also been suggested to be one feature of IgG4-related systemic disease (6, 7). Recently, we reported some cases of tubulointerstitial nephritis (TIN) with high serum IgG4 (8, 9). None of the patients had notable pancreatic lesions when the TIN developed, but their clinicopathological findings were quite similar to those in AIP. We supported the concept of IgG4-related systemic disease and suggested that TIN is also one feature of this condition and can develop irrespective of the presence of AIP. In this way, the concept of IgG4-related systemic disease is becoming popular, although the nomenclature varies (“IgG4-related systemic disease” (6, 8-10), “IgG4-related disease” (5), “IgG4-related sclerosing disease” (1), “IgG4-related plasmocytic disease” (7), “autoimmune multi-organ lymphoproliferative syndrome” (11) or “IgG4 positive plasma cell disease” (12)). However, there have been only a few reports of extra-pancreatic lesions in this condition. Here, we investigated the renal lesions of patients with IgG4-related systemic disease.

Patients and Methods

From 1996 to 2006, we diagnosed seven patients as having IgG4-related systemic disease (Table 1). They were all middle-aged to elderly men and their serum IgG4 concentrations were elevated. Four patients (patients 1 to 4) were diagnosed as having AIP according to the criteria for AIP of the Japan Pancreas Society (13) or the criteria for AIP proposed by the Mayo Clinic (3). Patient 2 had retroperitoneal fibrosis with AIP. Patient 3 was diagnosed as having AIP and Mikulicz’s disease. The other three patients (patients 5, 6, and 7) had no notable pancreatic lesions. Patient 5 had a history of AIP, sialadenitis and idiopathic thrombotic purpura, and developed renal mass-like lesion and systemic lymphadenopathy after spontaneous remission of AIP. Because the patient had sicca complex, he was diagnosed as having primary Sjögren’s syndrome. Patient 6 showed renal insufficiency. Patient 7 showed systemic lymphadenopathy and renal dysfunction. In these three patients (patients 5-7), abundant IgG4-positive plasma cells infiltration to the affected organs (kidneys in all patients, lymph-nodes in patient 5 and 7, and salivary gland in patient 7) was histologically confirmed and steroid therapy was effective for the organ involvement.

We investigated the results of laboratory studies and imaging studies (computed tomography and gallium citrate scintigraphy) of the kidneys in all patients, and renal histology in four of the patients.

Results
as described previously in IgG4-related systemic disease (5-9).

2) Imaging studies (Table 1)

Six of 7 patients showed some abnormal renal findings in the imaging studies. In the patient with retroperitoneal fibrosis associated with AIP (patient 2), right hydronephrosis was observed; it was improved with steroid therapy. In the patient with AIP and Mikulicz’s disease (patient 3), multiple low-density areas in both kidneys were observed in the CT examination (Fig. 1A). Gallium citrate scintigraphy showed gallium-67 accumulation in both kidneys, the lacrimal glands, and pulmonary hila, in addition to the pancreas and both salivary glands (Fig. 1B), although the patient had normal urinalysis and normal renal function and had no swelling of lymph nodes or lacrimal glands on CT examination. Six months later, the swelling of the pancreas had diminished without therapy. The multiple low-density areas in both kidneys had also improved 9 months later, without therapy (Fig. 1C).

In all patients with TIN (patients 4 to 7), gallium citrate scintigraphy showed gallium-67 accumulation in both kidneys. Gallium-67 accumulation was also observed in the salivary glands in three patients although they had no salivary gland swelling. CT examination showed a tumor-like low-density mass in the left kidney of patient 5 (Fig. 2A), and diffuse kidney swelling in patient 7 (Fig. 2B). These findings were improved by steroid therapy (Fig. 2C and 2D).

3) Renal pathology

Percutaneous renal needle biopsies were conducted in three patients (patients 4, 6, and 7). In two patients (patients 4 and 7), light microscopic examination showed diffuse renal interstitial infiltration of lymphocytes and plasma cells, with fibrosis, tubular atrophy, and infiltration of a few eosinophils (Fig. 3A, B). In patient 6, three renal microscopic sections were obtained for light microscopic study. In all sections, the glomeruli showed only minor abnormalities. In two of the three sections, only a few cell infiltrations were observed in the renal interstitium, but marked cell infiltration composed of lymphocytes, plasma cells and a few eosinophils with fibrosis of the renal interstitium were observed in one section (Fig. 4A, B). In patient 5, open biopsy of the mass in the left kidney was performed. In the section, numerous lymphoplasmacytic infiltrations were observed. Although most glomeruli and tubules had vanished in the tissue of the mass, the remaining glomeruli had only minor abnormalities (Fig. 5). In all patients, immunohistochemistry revealed numerous IgG4-positive plasma cells that had infiltrated the renal interstitium (8, 9).
Figure 2. Renal CT findings in patient 5 (A, C) and 7 (B, D). A tumor-like low-density mass (arrow) was observed in the left kidney of patient 5 (A); it diminished with steroid therapy (C). Bilateral renal swelling was observed in patient 7 (B); it improved with steroid therapy (D).

Figure 3. Microscopic findings of renal biopsies in patient 4 (A) and patient 7 (B). Diffuse renal interstitial inflammation composed of lymphocytes and plasma cells, with fibrosis and tubular atrophy, was observed. (A: PAS (periodic acid-Schiff) stain ×40, B: PAM (periodic acid-methenamine-silver) - Masson (Masson trichrome) stain ×40).

Figure 4. Renal biopsy of patient 6. In two of three sections, only a few cell infiltrations are observed in the renal interstitium (A: PAM stain ×40). However, marked cell infiltration composed of lymphocytes and plasma cells, with fibrosis of renal interstitium, was observed in one section (B: PAM stain ×60).
Although the name and definition of the disease have not been established, the concept of IgG4-related systemic disease has been recognized recently (1, 2, 4-12). AIP is a representative condition of IgG4-related systemic disease, and Mikulicz’s disease, chronic sclerosing sialadenitis and TIN with serum IgG4 elevation are suggested to belong to the same disease spectrum. Although there are many common features in patients with IgG4-related systemic disease, predominant in middle-aged to elderly men, hypergammaglobulinemia, negativity for anti SS-A and anti SS-B antibodies, and sometimes hypocomplementemia and eosinophilia), the significant common features are as follows: 1) elevated serum IgG4 level; 2) abundant infiltration of affected organs by IgG4-positive plasma cells; and 3) marked improvement with corticosteroid therapy (1, 3, 5, 7-11, 14-16). Although some of the present 7 patients did not have AIP, their conditions fulfilled these criteria and were compatible with IgG4-related systemic disease (1, 8, 9). In the 7 patients with IgG4-related systemic disease, three patterns of renal involvement were observed: 1) extraparenchymal involvement such as hydronephrosis associated with retroperitoneal lesions; 2) diffuse tubulointerstitial nephritis; and 3) renal lesions composed of focal lymphoplasmacytict infiltration of the renal interstitium.

Hydronephrosis associated with retroperitoneal fibrosis in patients with AIP was first described in 2002 (17). In these patients, abundant IgG4-bearing plasma cells were observed in the retroperitoneal and pancreatic lesions and steroid therapy was effective for treatment of both types of lesions. These features were in accord with the concept of IgG4-related systemic disease; however, hydronephrosis was not the primary renal lesion, and had been caused by the retroperitoneal lesions.

In 2004, two separate case reports of TIN associated with AIP were published (18, 19). In both cases, renal biopsy revealed diffuse lymphoplasmacytic infiltrations of the renal interstitium. Since then, some cases of TIN associated with IgG4-related systemic disease, including AIP and Mikulicz’s disease, have been reported (8-10, 20, 21), and TIN has been recognized as a major renal lesion of IgG4-related systemic disease. We confirmed TIN by renal biopsy in 4 patients with IgG4-related systemic disease. In two patients (patients 4 and 7), renal biopsy showed diffuse TIN. In these patients, CT revealed normal or diffuse swelling of both kidneys and the levels of urinary β2-MG and NAG were markedly elevated. These findings are common in ordinary interstitial nephritis. However, in patient 6, the distribution of the lymphoplasmacytic infiltration was quite unique. Dense lymphoplasmacytic infiltration of the renal interstitium was observed not diffusely, but in focal areas. Although the renal CT findings were normal, gallium citrate scintigraphy showed gallium-67 accumulation in both kidneys, and deterioration of renal function with marked elevation of urinary β2-MG and NAG levels was observed. Therefore, we assumed that the renal interstitial lymphoplasmacytic infiltration extended to both kidneys widely but with a patchy distribution. Watson et al also noticed patchiness of the renal involvement in IgG4-related systemic disease, and they cautioned against sampling error in such circumstances (10).

Although the patchiness of renal involvement observed in patient 6 was at the microscopic level, macroscopic focality of the lymphoplasmacytic aggregation was also observed. In patient 5, a tumor-like mass composed of aggregations of numerous lymphocytes and plasma cells in the renal interstitium was observed. Although most of the glomeruli and tubules had vanished within the lesion, renal dysfunction was mild and urinary β2-MG and NAG levels were normal, suggesting that many intact glomeruli and tubules may well have remained in other areas. Recently, two cases of TIN presenting as multiple renal nodules mimicking tumors, and with AIP, were reported (22, 23). In these patients multiple low-density areas in both kidneys were observed on CT examination, and open renal biopsy of the renal masses revealed an inflammatory infiltrate composed of lymphocytes and plasma cells with fibrosis. There have been some reports of renal mass lesions associated with AIP, irrespective of the existence of renal dysfunction (24). Using CT and MR imaging, Takahashi et al demonstrated the frequent presence of renal peripheral cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement in patients with AIP, and also lymphoplasmacytic infiltration of the renal interstitium in one patient by renal biopsy (25). Our patient 3 also had multiple low-density areas in both kidneys on CT examination. Although this patient’s renal histology was not evaluated, the low-density lesions might have been composed of lymphoplasmacytic infiltration, because gallium citrate scintigraphy showed gallium-67 accumulation in both kidneys. Despite the presence of these abnormal findings on imaging studies, renal function was normal in this patient, suggesting that the lesion distribution.
was focal. Interestingly, the pancreatic swelling and low-density areas in both kidneys disappeared without therapy in this patient. Spontaneous remissions have been documented in some patients with AIP (14). It is also possible that the renal lesions could improve without therapy in some patients.

Thus, the renal lesions in IgG4-related systemic disease are characterized by dense lymphoplasmacytic infiltration of the renal interstitium in which the infiltrating plasma cells stain positively for IgG4 and have various distributions. According to the distribution patterns of the infiltrating cells, the lesions can be recognized as ranging from diffuse TIN to tumor-like masses. Such features are common in AIP and chronic sclerosing sialadenitis. In both diseases, tumor-like lesions composed of lymphoplasmacytic infiltrations are observed, in addition to diffuse enlargement of the pancreas and salivary glands (5, 26). Such focal lymphoplasmacytic aggregations are reminiscent of those seen in malignant lymphoma, but no patients had evidence of malignancy, even when tested by the DNA polymerase chain reaction method and immunohistochemistry (8, 9). Interestingly, gallium citrate scintigraphy often showed gallium-67 accumulation in the salivary glands or lacrimal glands of patients who had no enlargements of either organ. The findings suggest that IgG4-related systemic disease often affects the glandular tissues and that systemic surveys, including gallium citrate scintigraphy, are necessary to elicit the relationship between immune-complex and IgG4-related systemic disease. In addition, because dense lymphoplasmacytic infiltration with a patchy distribution is characteristic of IgG4-related systemic disease, we should also consider a mechanism of lymphoproliferative disorders. Further clinical, histological, immunological, and molecular examinations are necessary.

References