Clin Exp Nephrol
DOI 10.1007/s10157-011-0521-2

SPEICIAL ARTICLE

Proposal for diagnostic criteria for IgG4-related kidney disease

Mitsuhiro Kawano · Takako Saeki · Hitoshi Nakashima · Shinichi Nishi · Yutaka Yamaguchi · Satoshi Hisano · Nobuaki Yamanaka · Dai Inoue · Motohisa Yamamoto · Hiroki Takahashi · Hideki Nomura · Takashi Taguchi · Hisanori Umehara · Hirofumi Makino · Takao Saito

Received: 29 July 2011

Abstract
Background IgG4-related disease has attracted wide attention recently. It is characterized by a high level of serum IgG4 and dense infiltration of IgG4-positive plasma cells into multiple organs, with the kidney being one representative target. Although several sets of diagnostic criteria for autoimmune pancreatitis (AIP) are available and renal lesion is recognized as an extra-pancreatic manifestation of AIP, it is difficult to differentiate IgG4-related tubulointerstitial nephritis (TIN) without AIP from other types of TIN. To clarify the entity of IgG4-related kidney disease (IgG4-RKD) and support in-depth studies, the Japanese Society of Nephrology has established a working group to prepare diagnostic criteria for IgG4-RKD.
Method The working group analyzed 41 patients with IgG4-RKD, and collected the following data to devise a diagnostic algorithm and diagnostic criteria for IgG4-RKD: clinical features including extra-renal organ involvement, urinalysis and serological features including serum IgG4

M. Kawano and T. Saeki equally contributed to this work.

M. Kawano
Division of Rheumatology, Department of Internal Medicine, Kanazawa University Hospital, Kanazawa, Japan

T. Saeki
Department of Internal Medicine, Nagaoka Red Cross Hospital, Nagaoka, Japan

H. Nakashima · T. Saito (✉)
Division of Nephrology and Rheumatology, Department of Internal Medicine, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan
e-mail: tsaito@fukuoka-u.ac.jp

S. Nishi
Division of Nephrology and Kidney Center, Kobe University Graduate School of Medicine, Kobe, Japan

Y. Yamaguchi
Yamaguchi's Pathology Laboratory, Chiba, Japan

S. Hisano
Department of Pathology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

N. Yamanaka
Tokyo Kidney Research Institute, Tokyo, Japan

D. Inoue
Department of Radiology, Toyama Prefectural Central Hospital, Toyama, Japan

M. Yamamoto · H. Takahashi
First Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

H. Nomura
Department of General Medicine, Kanazawa University Hospital, Kanazawa, Japan

T. Taguchi
Department of Pathology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

H. Umehara
Department of Hematology and Immunology, Kanazawa Medical University, Ishikawa, Japan

H. Makino
Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Okayama, Japan

Published online: 07 September 2011

levels, imaging findings demonstrated by computed tomography (CT), renal histology with IgG4 immunostaining, and response to steroid therapy.

Results The conditions for criteria are as follows. (1) Presence of some kidney damage, as manifested by abnormal urinalysis or urine marker(s) and/or decreased kidney function with either elevated serum IgG level, hypocomplementemia, or elevated serum IgE level. (2) Kidney imaging studies showing abnormal renal imaging findings, i.e., multiple low density lesions on enhanced CT, diffuse kidney enlargement, hypovascular solitary mass in the kidney, and hypertrophic lesion of the renal pelvic wall without irregularity of the renal pelvic surface. (3) Serum IgG4 level exceeding 135 mg/dl. (4) Renal histology showing two abnormal findings: (a) dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells >10/high power field (HPF) and/or ratio of IgG4-positive plasma cells/IgG positive plasma cells >40%. (b) Characteristic 'storiform' fibrosis surrounding nests of lymphocytes and/or plasma cells. (5) Extra-renal histology showing dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells >10/HPF and/or ratio of IgG4-positive plasma cells/IgG-positive plasma cells >40%. The diagnosis is classified into 3 stages of definite, probable and possible according to the combinations of the above conditions. Thirty-nine cases (95.1%) were diagnosed with IgG4-RKD according to the criteria.

Conclusion The provisional criteria and algorithm appear to be useful for clarifying the entity of IgG4-RKD and seeking underlying IgG4-RKD cases; however, further experience is needed to confirm the validity of these criteria.

Keywords IgG4-related kidney disease · Diagnostic criteria · IgG4 · Tubulointerstitial nephritis

Introduction

After the recognition of autoimmune pancreatitis (AIP) as an IgG4-related disease [1], similar lesions in other organs have attracted much attention. IgG4-related kidney disease (IgG4-RKD) was first reported as a complication or an extrapancreatic manifestation of AIP in 2004 [2, 3]. In the early reported cases, the development of renal dysfunction and/or proteinuria during the clinical course of AIP was the clue to the presence of renal involvement, and renal biopsy revealed tubulointerstitial nephritis (TIN) and fibrosis with dense infiltration of IgG4-positive plasma cells [2–4]. Thereafter, incidentally-detected IgG4-RKD cases in the course of close examination of AIP [5–7] or chronic sclerosing sialadenitis and dacryoadenitis [8] using enhanced computed tomography (CT) have been additionally accumulated. Recently, IgG4-RKD without AIP or chronic sclerosing sialadenitis and dacryoadenitis has also been reported [9–11].

Against this background of detection of IgG4-RKD with the kidney being the first recognized organ of IgG4-related disease [9–11], demand for practical diagnostic criteria for IgG4-RKD has been growing. To meet this demand and spread recognition of IgG4-RKD among nephrologists and other clinical practitioners, we organized a working group in the Japanese Society of Nephrology (JSN) consisting of specialists in clinical nephrology, renal pathology, clinical immunology and rheumatology. This report describes our proposal for a diagnostic algorithm and the diagnostic criteria for IgG4-RKD prepared by this working group.

Methods

Patients

Between 2004 and 2011, we identified 41 patients with IgG4-RKD in Kanazawa University Hospital, Nagaoka Red Cross Hospital, Niigata University Hospital, Sapporo Medical University Hospital, and Fukuoka University Hospital. Nine patients [3 Churg–Strauss syndrome; 2 IgG4-RKD without TIN with decreased renal function; 1 Sjögren's syndrome (SS) with TIN; 1 minimal change nephrotic syndrome; 1 allergic disease with hypocomplementemia; 1 relapsing polychondritis] were selected as a negative control. Written informed consent for all data and samples was obtained from each patient. The diagnosis of IgG4-RKD was made principally based on the histologic and immunohistochemical findings of the kidney or other organs with the support of a comprehensive analysis of the clinical picture including elevated serum IgG4 levels, and final clinical judgment was left to the observers at each hospital who had sufficient experience in IgG4-related disease and clinical nephrology. This study was approved by each institutional ethics board and ethics board of the JSN. The research was conducted in compliance with the Declaration of Helsinki.

Clinical features

The clinical picture including symptoms resulting from other organ involvement such as the pancreas, lacrimal and salivary glands, or lungs was noted. Diagnostic clues to IgG4-RKD were carefully evaluated, and important items were extracted. Serum IgG, IgG4, IgE, and complement levels were collected from the clinical data file. Serum creatinine (Cr) levels and any abnormalities of urinalysis including proteinuria and hematuria before corticosteroid therapy were noted in all cases. Urine *N*-acetyl-β-D-glucosaminidase and urine β_2-microglobulin levels were also noted if available.

Imaging

CT was the most recommended radiographic imaging method for IgG4-RKD. In general, contrast-enhanced CT was needed to make the correct diagnosis; however, the use of contrast medium required careful judgment in patients with impaired renal function. Without enhancement, diffuse enlargement of the kidney inconsistent with the degree of renal function was noted. Other modalities including gallium scintigraphy, magnetic resonance imaging, and fluorodeoxyglucose positron emission tomography were additionally used to identify renal lesions.

Histology and immunostaining

Renal histology was available in 28 patients. Bouin's fluid-fixed or formalin-fixed and paraffin-embedded renal specimens of patients with IgG4-RKD were analyzed, and the degree of lymphoplasmacytic infiltration in the interstitium, degree of fibrosis, eosinophilic infiltration, and glomerular lesions were recorded. In immunostaining, immunofluorescence was performed against IgG, IgA, IgM, C3, C1q, and fibrinogen. Immunostaining was performed using mouse monoclonal antibody against human IgG4 (Zymed Laboratories, San Francisco, CA, USA, or The Binding Site, Birmingham, UK), anti-human IgG (Dako, Glostrup, Denmark), and/or anti-human CD138 (AbD Serotec, Oxford, UK).

Diagnostic algorithm and criteria

We first analyzed 41 cases of IgG4-RKD, the preliminary diagnosis of which was made based on the clinical decision of observers who had sufficient experience with IgG4-related disease including AIP. To select the most sensitive and specific test for the diagnosis of IgG4-RKD, we referred to the revised clinical diagnostic criteria for AIP proposed by Okazaki et al. [12] and Mayo Clinic criteria for AIP proposed by Chari et al. [13]. On the basis of these analyses, a diagnostic algorithm and criteria were prepared.

Results

Clinical features

Table 1 summarizes clinical and histological characteristics of the 41 patients. The mean age of the 41 patients was 63.7 years (range 27–83). The ratio of male to female patients was 30:11. Eight patients without preceding IgG4-related disease were suspected to have renal disease because of decreased kidney function ($n = 4$), radiographic abnormalities ($n = 2$) and/or urinary abnormalities ($n = 1$). The remaining one patient was detected after close examination of highly suspected elderly-onset lupus with elevated serum IgG, hypocomplementemia, and polyarthritis without urinary abnormalities. In contrast, 33 patients were diagnosed as having IgG4-RKD during the clinical course of IgG4-related disease. Of these, 20 patients were incidentally detected when systemic examination for IgG4-related disease was performed through radiographic examination. Thirteen patients were suspected of having renal disease because of newly noted renal dysfunction.

Serological features

The mean serum IgG level was 3467 mg/dl (range 1480–9470 mg/dl), and 37 patients (90.2%) had elevated serum IgG level. In 21 patients (51.2%), serum IgG levels exceeded 3000 mg/dl. The mean serum IgG4 level was 991.2 mg/dl (range 152–2940 mg/dl), and all patients had elevated serum IgG4 levels. Hypocomplementemia was detected in 22 patients (53.7%), 16 of whom had low C3, C4, and CH50 levels. Two patients had both low C3 and CH50 levels, one had both low C3 and C4 levels, one had low C3 levels only, and two had low C4 levels only. Serum IgE level was evaluated in 33 patients. Mean serum IgE level was 754.3 U/ml (range 3–3960 U/ml), and 26 patients (78.8%) had elevated serum IgE levels. Mean serum Cr level was 1.7 mg/dl, and 24 patients had elevated serum Cr levels (serum Cr $\geq$ 1.0 mg/dl).

Imaging

Contrast-enhanced CT was performed in 29 patients. Twelve of 41 patients had no remarkable CT findings. In 10 of these, use of contrast enhancement was withheld because of decreased renal function. The remaining two patients had no remarkable CT findings despite the use of contrast enhancement. Multiple low-density lesions on enhanced CT were the most common radiologic finding in IgG4-RKD, and 19 patients (46.3%) showed this feature (Fig. 1a). When decreased renal function existed and administration of contrast medium was deemed inadvisable, diffuse bilateral renal swelling was another feature ($n = 2$) (Fig. 1b). The third characteristic radiologic finding of IgG4-RKD was diffuse thickening of the renal pelvis wall with smooth intraluminal surface, and this finding was sometimes detected in patients with IgG4-related disease without obvious clinical symptoms (Fig. 1d). This radiologic finding was usually pointed out incidentally during the close systemic evaluation of IgG4-related disease patients, and 6 patients had this type of pelvic lesion. A hypovascular solitary nodule of the renal parenchyma was

Table 1 Clinical and pathological characteristics of 41 patients

Characteristics	The number of cases[a] (%)
Age (years)	63.7 ± 12.3
Male sex [no. (%)]	30 (73.2)
Patients with preceding IgG4-RD [no. (%)]	33 (80.5)
Clue to detect IgG4-RKD with preceding IgG4-RD [no./total no. (%)]	
Incidentally detected during systemic examination for IgG4-RD	20/33 (60.6)
Newly noted renal dysfunction	13/33 (39.4)
Clue to detect IgG4-RKD without preceding IgG4-RD [no./total no. (%)]	
Decreased kidney function	4/8 (50.0)
Radiographic abnormalities	2/8 (25.0)
Urinary abnormalities	1/8 (12.5)
Urinalysis and serological features	
Proteinuria [no./total no. (%)]	
3+	1/36 (2.8)
2+	6/36 (16.7)
1+	11/36 (30.6)
±	3/36 (8.3)
Hematuria [no./total no. (%)]	
3+	1/36 (2.8)
2+	2/36 (5.6)
1+	9/36 (25.0)
±	3/36 (8.3)
Elevated serum creatinine [no./total no. (%)]	24/41 (58.5)
Serum creatinine level (mg/dl)	1.7 ± 1.5
Elevated serum IgG [no./total no. (%)]	37/41 (90.2)
Serum IgG level (mg/dl)	3467.4 ± 1658.2
Serum IgG levels exceeding 3000 mg/dl [no./total no. (%)]	21/41 (51.2)
Hypocomplementemia [no./total no. (%)]	22/41 (53.7)
Elevated serum IgE [no./total no. (%)]	26/33 (78.8)
Serum IgE level (U/ml)	754.3 ± 876.8
Elevated serum IgG4 [no./total no. (%)]	41/41 (100.0)
Serum IgG4 level (mg/dl)	991.2 ± 604.9
Imaging (CT)	
Contrast medium used [no./total no. (%)]	29/41 (70.7)
Multiple low-density lesions on enhanced CT [no./total no. (%)]	19/29 (65.5)
Diffuse bilateral renal swelling on enhanced CT [no./total no. (%)]	1/29 (3.4)
Diffuse bilateral renal swelling without enhanced CT [no./total no. (%)]	2/12 (16.7)
Diffuse thickening of the renal pelvis wall [no./total no. (%)]	6/41 (14.6)
Hypovascular solitary nodule [no./total no. (%)]	1/29 (3.4)
Histology	
Patients with tubulointerstitial lesions [no./total biopsied no. (%)]	28/28 (100.0)
Patients with glomerular lesions [no./total biopsied no. (%)]	11/28 (39.3)
Other organ involvement [no. (%)]	
Pancreas	13 (31.7)
Salivary gland	29 (70.7)
Lacrimal gland	12 (29.3)
Lung	12 (29.3)
Lymph node	17 (42.5)
Retroperitoneum	4 (9.8)
Prostate	3 (7.3)
Periaortic area	2 (4.9)
Breast, liver, nerve, thyroid gland, peritoneum, bile duct, or joint[b]	1 (2.4)

IgG4-RD IgG4-related disease; *IgG4-RKD* IgG4-related kidney disease; *no.* numbers

[a] Plus-minus values are mean ± SD

[b] The number of each organ involvement is the same

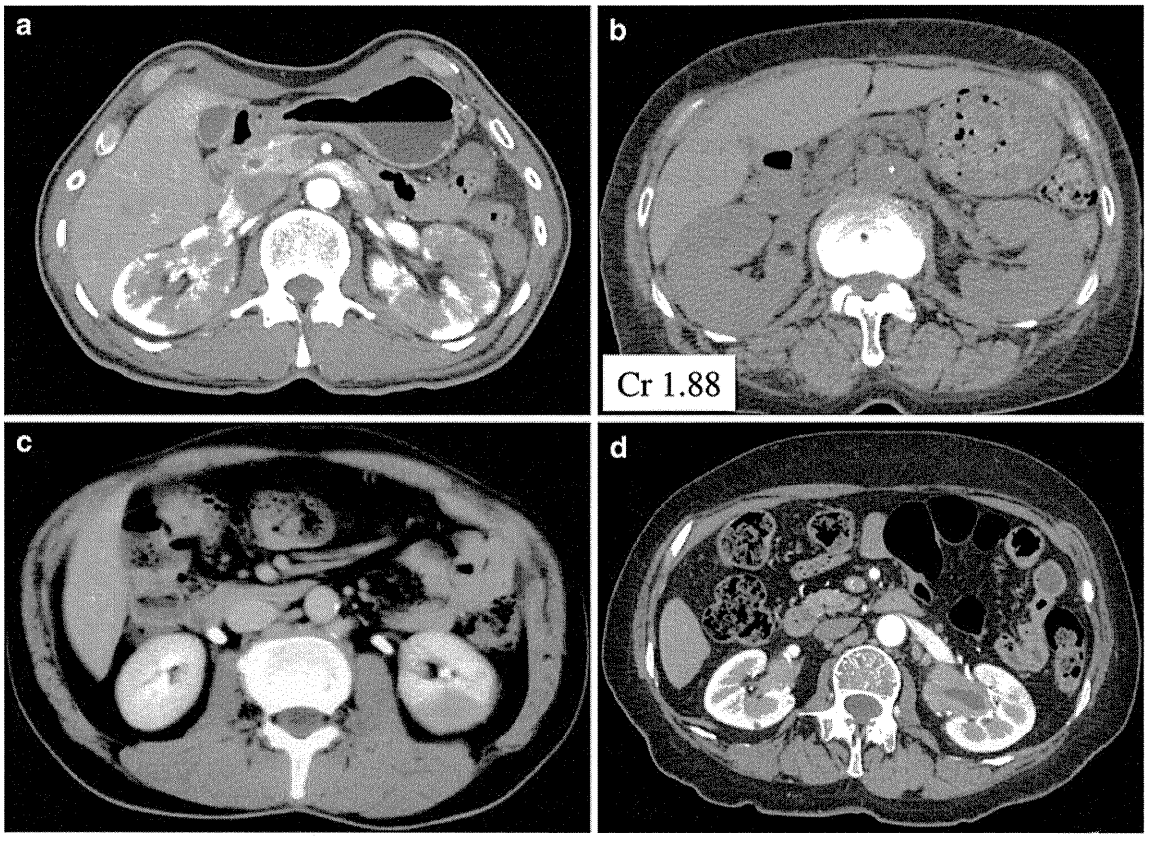

Fig. 1 Characteristic renal computed tomography (CT) imaging. **a** Multiple low-density lesions on enhanced CT. **b** Diffuse bilateral renal swelling. **c** A hypovascular solitary nodule. **d** Diffuse thickening of the renal pelvis wall with smooth intra-luminal surface

very rarely diagnosed as an IgG4-related kidney lesion, with only one such case detected in this study (Fig. 1c). Another patient had unilateral renal swelling probably because of a unilateral renal mass, but decreased renal function prevented more detailed analysis using contrast-enhanced CT.

Histology and immunostaining

A renal biopsy was performed in 28 of 37 patients (75.7%) with renal parenchymal lesions. Dense lymphoplasmacytic infiltration with fibrosis in the interstitium was found in 27 patients (Fig. 2a), and without fibrosis in one patient. Interstitial fibrosis surrounding nests of lymphocytes was characteristic and resembled the 'storiform' shape in AIP [14, 15], and also termed 'bird's eye' pattern [16] (Fig. 2b). Of these, marked IgG4-positive plasma cell infiltration was confirmed immunohistochemically in all patients (Fig. 2c, d). On the other hand, glomerular lesions were not specific, although they were found in 11 patients [3 membranous nephropathy (MN), 2 Henoch-Schönlein purpura nephritis, 2 IgA nephropathy, 2 focal and segmental endocapillary proliferative glomerulonephritis, 1 membranoproliferative glomerulonephritis, 1 mesangial proliferative glomerulonephritis]. Five patients who showed only diffuse pelvic wall thickening radiologically were excluded from the renal histological examination.

Other organ involvement

Other organ involvement was detected in 39 of 41 patients (95.1%). The average number of affected organs was 3.4 (range 1–8), and the distribution was shown in Fig. 3. The most frequently involved organ was the salivary gland, with 29 of 41 patients (70.7%) affected. Lymph node swelling was also frequently noted (17 of 41 patients; 42.5%). Thirteen patients (31.7%) had AIP, 12 (29.3%) had dacryoadenitis, 12 (29.3%) had lung lesion, 4 (9.8%) had retroperitoneal fibrosis, 3 (7.3%) had prostate lesion, and 2 (4.9%) had periaortic lesion. Breast, liver, nerve, thyroid gland, peritoneum, bile duct, or joint lesion was detected in one patient each. Eleven patients had both chronic sclerosing sialadenitis and dacryoadenitis.

Response to steroid therapy

Thirty-eight patients were treated with corticosteroid, 35 of whom had a favorable response to steroid therapy. One patient eventually required maintenance hemodialysis in spite of corticosteroid therapy. In the remaining two

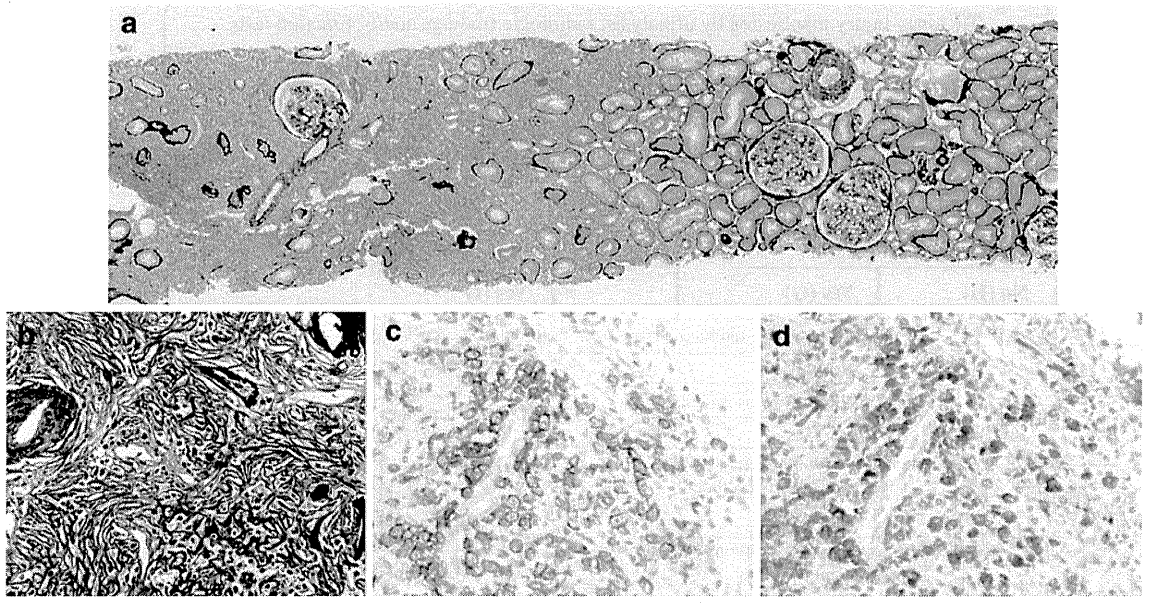

Fig. 2 Representative light microscopic histology. **a** Dense lymphoplasmacytic infiltration with fibrosis in the interstitium with clear border between affected and unaffected areas. **b** Typical fibrosis. **c**, **d** CD138 and IgG4 stain shows that >40% of plasma cells are IgG4-positive (**a** Periodic acid-Schiff stain ×40, **b** PAM-Masson's trichrome stain ×100, **c** CD138 immunostain ×400, **d** IgG4 immunostain ×400)

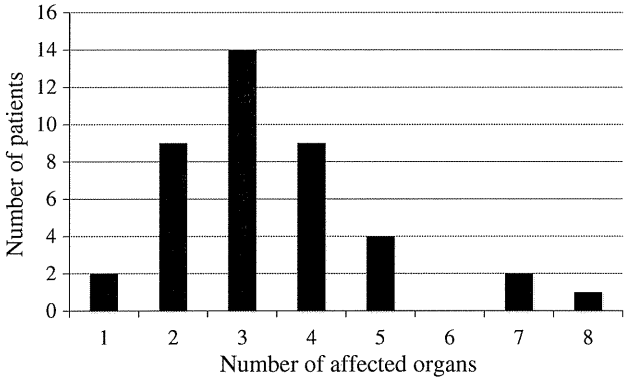

Fig. 3 Frequency distribution of the number of affected organs. The mean number of affected organs was 3.4

patients, reduction of serum Cr was not achieved probably because of a delay in the initiation of steroid treatment.

Diagnostic algorithm

Based on the analysis results of the diagnostic processes of these 41 cases and previously reported cases, our working group prepared a diagnostic algorithm of IgG4-RKD (Fig. 4; Table 2). Forty of 41 patients (97.6%) had either abnormal urinalysis or urine marker(s), abnormal radiologic findings, or decreased kidney function. Either elevated serum IgG level, hypocomplementemia, or elevated serum IgE level was detected in 40 of 41 patients (97.6%). In four patients with normal serum IgG level, three had increased serum IgE levels without hypocomplementemia. Therefore, the presence of some kidney damage, as manifested by abnormal urinalysis or urine marker(s), abnormal radiologic findings, or decreased kidney function, with either elevated serum IgG level, hypocomplementemia, or elevated serum IgE level was selected to be the first step to suspect the diagnosis of IgG4-RKD. However, as these features are shared with systemic lupus erythematosus, cryoglobulinemia, or vasculitis including Wegener's granulomatosis and Churg–Strauss syndrome, exclusion criteria were inserted in the next step. The third step was chosen to confirm an elevated serum IgG4 level, and the following step consisted of two complementary components: radiologic and histopathologic examinations. If renal pathology was not available, a careful differential diagnosis to rule out malignant lymphoma, urinary tract carcinomas, renal infarction, pyelonephritis, Wegener's granulomatosis [17, 18], sarcoidosis [19] and metastatic carcinoma was necessary, and non-renal histological finding with infiltrating IgG4-positive plasma cells >10/high power field (HPF) or IgG4/IgG >40% was necessary to support the radiologic findings. As the pathologic examination part, the following characteristic renal pathological findings of IgG4-RKD were listed: (a) marked lymphoplasmacytic infiltration, accompanied by >10 infiltrating IgG4-positive plasma cells/HPF and/or a ratio of IgG4/IgG-positive plasma cells >40%, (b) characteristic fibrosis surrounding several infiltrating cells, (c) other useful findings for the differential diagnosis [positive findings: lesions extending into the renal capsule, eosinophil infiltration, well-defined regional lesion distribution, marked fibrosis, negative findings: (necrotizing) angiitis,

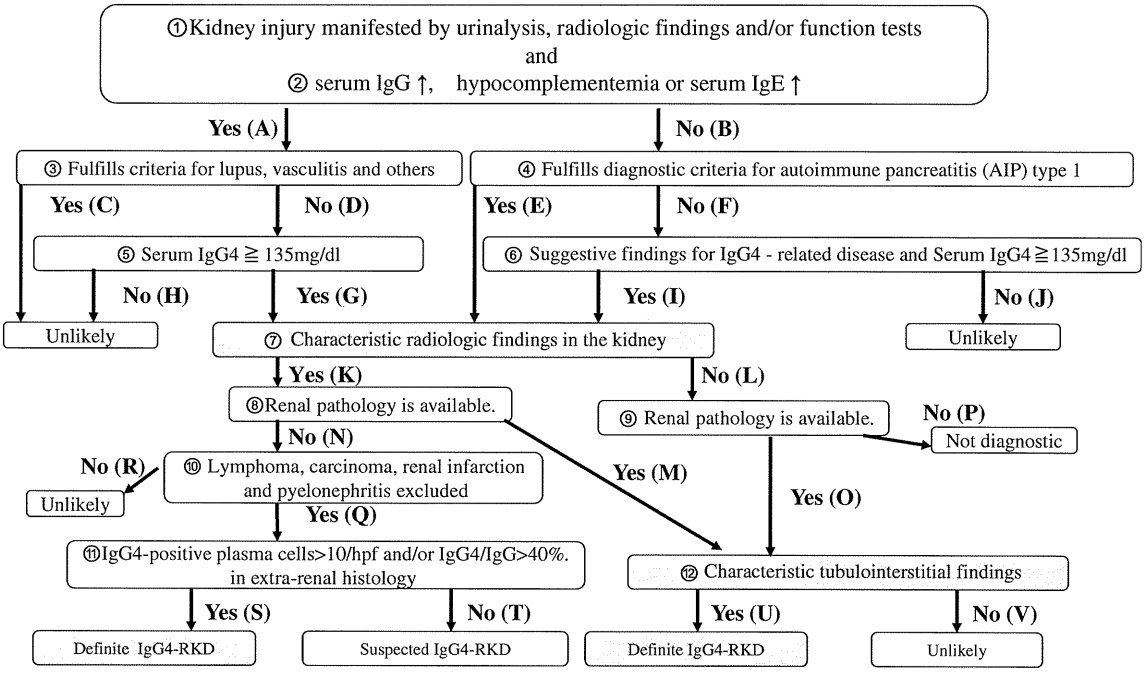

Fig. 4 Diagnostic algorithm for IgG4-related kidney disease (IgG4-RKD). Table 2 is a supplement of Fig. 4

granulomatous lesion, neutrophil infiltration, advanced tubulitis]. Since about 80% of patients were diagnosed as having IgG4-RKD during the close examination of IgG4-related disease other than IgG4-RKD, an alternative pathway was inserted in the algorithm. Then, the performance of the diagnostic algorithm procedure was tested on these 41 patients with IgG4-RKD (Fig. 5). In this way, 38 of 41 patients (92.7%) were diagnosed with definite IgG4-RKD, two with suspected IgG4-RKD. In contrast, none of the negative control patients were diagnosed with IgG4-RKD.

Diagnostic criteria

On the basis of the result of diagnostic algorithm procedure and referring to several diagnostic criteria for AIP, we propose criteria for diagnosis of IgG4-RKD (Table 3). Using the proposed criteria, 39 of 41 patients (95.1%) were diagnosed with definite, one with probable, and one with possible IgG4-RKD.

Discussion

IgG4-RKD is a new clinical entity in the field of nephrology, unrecognized before 2004, when the notion gradually emerged of it being an extrapancreatic manifestation of AIP [2–11, 20–25]. This disease has many features helping to distinguish it from other types of TIN radiographically [26–30] and pathologically [11, 21], and early detection provides the best chance for preservation of renal function because of its good responsiveness to corticosteroid therapy [2–11]. However, any delay in treatment increases the risk of kidney failure [31]. This prompted us to prepare by consensus a set of diagnostic criteria for IgG4-RKD.

To prepare diagnostic criteria, characteristic radiologic findings are a very important component because these are usually the first recognized distinctive features of this disease, while rarely being seen in other tubulointerstitial nephritides [26–30]. Of these, the most common radiologic finding was multiple low-density lesions on enhanced CT [26–30], with 46.3% showing this type of abnormality in our study. Takahashi et al. [26] found 9 patients with bilateral multiple renal lesions, which could be included in the same category as our multiple low-density lesions, in 14 renal involvement cases. If the presence of decreased renal function precludes use of contrast-enhanced CT, bilateral diffuse kidney enlargement in plain CT is another feature. In addition, very rarely, a hypovascular solitary mass in the kidney was also detected [30, 32]; with this type of CT finding, malignancy must be ruled out. The fourth radiologic finding was hypertrophic lesion of the renal pelvic wall without irregularity of the renal pelvic surface, with urinary tract carcinoma being the most important condition to consider in the differential diagnosis [26, 28–30].

Hypergammaglobulinemia or elevated serum IgG levels, hypocomplementemia, and elevated serum IgE levels are all frequently observed serologic features of IgG4-RKD [2–11]. In our series as well we confirmed that 90.2% had

Table 2 Diagnostic algorithm for IgG4-related kidney disease (IgG4-RKD)—Supplement to Figure 4

1. This diagnostic algorithm for IgG4-RKD covers renal parenchymal lesions and renal pelvic lesions
2. ① Kidney injury is recognized by proteinuria, hematuria, and elevated *N*-acetyl-β-D-glucosaminidase, β_2-microglobulin and/or α_1-microglobulin excretions in urinalysis
3. ② At least one of 3 abnormalities (elevated serum IgG, hypocomplementemia and elevated serum IgE) is necessary
4. ③ The following diseases: systemic lupus erythematosus, systemic vasculitis (Churg–Strauss syndrome and Wegener's granulomatosis), and cryoglobulinemia should be excluded. However, even if the patient fulfills the classification criteria of lupus or vasculitis, this may not be sufficient to completely rule out IgG4-related disease, and measurement of serum IgG4 level is recommended in atypical cases
5. ④ Autoimmune pancreatitis is diagnosed according to the previously proposed diagnostic criteria
6. ⑥ Systemic lesion(s) other than AIP suggesting IgG4-related disease are listed as follows:

   Biliary lesion (sclerosing cholangitis)

   Pulmonary lesion (interstitial pneumonia, pseudotumor)

   Retroperitoneal lesion (retroperitoneal fibrosis)

   (peri-)Arterial lesion (inflammatory aortic aneurysm)

   Lymph node lesion (hilar lymph node swelling, mediastinal lymph node swelling)

   Lacrimal and salivary gland lesion (Mikulicz's disease, chronic sclerosing dacryoadenitis and sialadenitis)

   Hepatic lesion (pseudotumor of the liver)
7. ⑦ Characteristic renal radiologic findings of IgG4-related kidney disease are listed as follows: (in general, contrast-enhanced CT is needed to make the correct diagnosis. However, the use of contrast medium requires careful judgment in patients with impaired renal function)
   a. Multiple low-density lesions on enhanced CT
   b. Diffuse kidney enlargement
   c. Hypovascular solitary mass in the kidney
   d. Hypertrophic lesion of renal pelvic wall without irregularity of the renal pelvic surface
8. ⑩ Malignant lymphoma, urinary tract carcinomas, renal infarction and pyelonephritis sometime have similar and confusing radiologic findings, and their exclusion is necessary. In particular, misdiagnosis of malignancy as IgG4-related disease must be avoided

   (rarely, Wegener's granulomatosis, sarcoidosis and metastatic carcinoma have similar radiologic findings)
9. ⑫ Characteristic tubulointerstitial findings of IgG4-related kidney disease are listed as follows:
   a. Marked lymphoplasmacytic infiltration, which must be accompanied by >10 infiltrating IgG4-positive plasma cells/high power field and/or a ratio of IgG4/IgG-positive plasma cells $>40\%$
   b. Characteristic 'storiform' fibrosis surrounding infiltrating cells
   c. Other useful findings for differential diagnosis:
      1. Positive findings: lesions extending into the renal capsule, eosinophil infiltration, well-defined regional lesion distribution, marked fibrosis
      2. Negative findings: (necrotizing) angiitis, granulomatous lesion, neutrophil infiltration, advanced tubulitis

Circled numbers correspond to those in Fig. 4

increased serum IgG levels, 53.7% hypocomplementemia, and 78.8% increased serum IgE levels. In addition, decreased renal function was detected 58.5%. Therefore, we considered that the presence of kidney damage, as manifested by abnormal urinalysis or urine marker(s) or decreased function, in combination with either elevated serum IgG level, hypocomplementemia, or elevated serum IgE level could obviate the need for characteristic radiographic renal findings.

Although elevated serum IgG4 level is a useful marker of IgG4-related disease including AIP, not all patients with AIP manifest it. In fact, 8–23% of AIP patients are thought to have normal serum IgG4 levels in Japanese patients [33–35]. In contrast, our criteria do not consider the presence of IgG4-RKD with a normal serum IgG4 level because we found that all our patients with IgG4-RKD had elevated serum IgG4 levels, and considered that the presence of a normal serum IgG4 patient might lead to misdiagnosis. In fact, recent studies [36–38] have shown that only the characteristic histologic finding of marked IgG4-positive plasma cell infiltration is not specific for IgG4-related disease but is also seen in other diseases such as vasculitis and Castleman's disease. However, a case report with IgG4-related inflammatory pseudotumor of the kidney with normal serum IgG4 level is available [32], and this represents one of the limitations of our criteria.

Chari et al. [13] considered histologic criteria to be the gold standard for the diagnosis of AIP. In addition to the immunohistochemical findings obtained by IgG4 staining, distinguishing fibrosis called 'storiform fibrosis' and obliterative phlebitis are also very important for the diagnosis of type 1 AIP [14, 15]. Interestingly, we identified that the same kind of fibrosis was detected in the involved

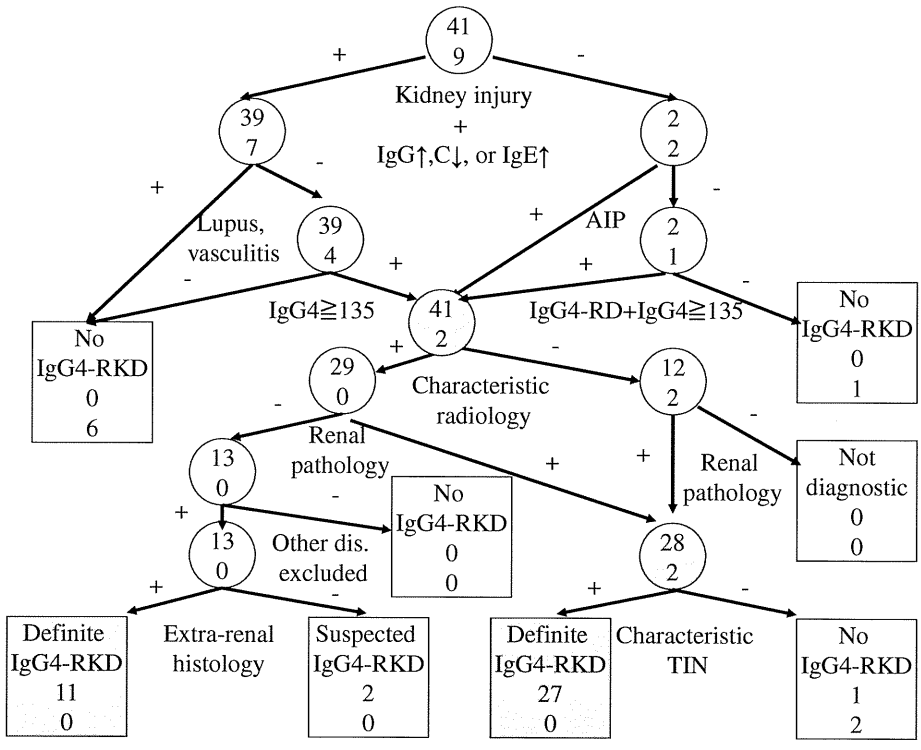

Fig. 5 Diagnostic algorithm performance for IgG4-related kidney disease (IgG4-RKD). This figure shows the results of performance of diagnostic algorithm for IgG4-RKD using 41 patients with IgG4-RKD and 9 patients as a negative control. *Upper number* in each *circle* or *box* shows the number of IgG4-RKD, and *lower number* shows that of the negative control. *Each box* shows the number of final diagnosis with IgG4-RKD or non-IgG4-RKD. Using this algorithm, 38 of 41 patients (92.7%) were diagnosed with definite IgG4-RKD, while none of the negative control patients were diagnosed with IgG4-RKD

kidney and in a previous study found that this characteristic fibrosis was very useful in distinguishing IgG4-RKD from other tubulointerstitial nephritides [16]. In contrast, obliterative phlebitis was not detected in any renal biopsy specimens in this study (data not shown). Therefore, lymphoplasmacytic TIN with fibrosis and prominent IgG4-positive plasma cells seems to be a representative histopathologic feature of IgG4-RKD.

Several kinds of glomerular lesions have been reported that overlap with those of typical lymphoplasmacytic TIN [11, 23, 24]. The most frequently reported lesion is membranous nephropathy (MN), and three patients had this type of glomerulopathy in this study. In addition, 8 other patients had various glomerular lesions other than MN. Although the significance of glomerular lesions in IgG4-RKD is unclear now, careful attention should be paid to glomerular lesions in cases of IgG4-RKD.

One of the important differential diagnoses in daily clinical practice is SS with TIN. Some investigators still consider that Mikulicz's disease and SS are the same disease because they have common clinical features such as hypergammaglobulinemia, salivary gland enlargement or dry symptoms. However, Mikulicz's disease rarely has positive serum anti-SSA/Ro or SSB/La antibodies as seen in SS [39, 40], and has gradually been accepted as a representative IgG4-related disease. On the other hand, patients with SS seldom have elevated serum IgG4 levels. Moreover, although both diseases have similar TIN in renal histology, IgG4 immunostaining is very useful to differentiate between them [39, 40]. Hence, IgG4-RKD is unlikely to be confused with SS.

Considering the above-mentioned features of IgG4-RKD and referring to several sets of previously established diagnostic criteria for AIP [12, 13, 41, 42], we prepared diagnostic criteria for IgG4-RKD. In the diagnostic procedure of AIP, pancreatic imaging, serology, and histology have been regarded as important factors by Japanese researchers [12]. In addition, Chari et al. [13] added other organ involvement and response to steroid therapy as useful findings in making the diagnosis of AIP. Application of the approach of AIP to IgG4-RKD based on renal imaging, serology, and histology appears reasonable and are similarly useful. In addition, if renal pathology is not available, histological findings of an extra-renal sample with abundant infiltrating IgG4-positive plasma cells ($>$ 10/HPF and/or IgG4/IgG $>$ 40%) with characteristic radiographic findings of kidneys seem to be sufficient to make a definite diagnosis. Responsiveness to corticosteroid therapy was not very useful in the diagnosis of IgG4-RKD because idiopathic TIN is in general responsive to it.

On the basis of this analysis of 41 patients with IgG4-RKD, we proposed a diagnostic algorithm (Fig. 4) and a set of diagnostic criteria (Table 3). Using this algorithm, 92.7% of patients were diagnosed with definite IgG4-RKD, and using these diagnostic criteria, 95.1% of them were diagnosed with definite IgG4-RKD.

A merit of our diagnostic algorithm and our set of diagnostic criteria in daily clinical practice is that it

Table 3 Diagnostic criteria for IgG4-related kidney disease (IgG4-RKD)

1. Presence of some kidney damage, as manifested by abnormal urinalysis or urine marker(s) or decreased kidney function with either elevated serum IgG level, hypocomplementemia, or elevated serum IgE level
2. Abnormal renal radiologic findings:
   a. Multiple low-density lesions on enhanced computed tomography
   b. Diffuse kidney enlargement
   c. Hypovascular solitary mass in the kidney
   d. Hypertrophic lesion of renal pelvic wall without irregularity of the renal pelvic surface
3. Elevated serum IgG4 level (IgG4 $\geq$ 135 mg/dl)
4. Histologic findings in the kidney
   a. Dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells $>$10/high power field (HPF) and/or IgG4/IgG-positive plasma cells $>$40%
   b. Characteristic fibrosis surrounding nests of lymphocytes and/or plasma cells
5. Histologic findings in extra-renal organ(s):
   Dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells $>$10/HPF and/or IgG4/IgG-positive plasma cells $>$40% in extra-renal organ(s)

Definite:	1) + 3) + 4) a, b
	2) + 3) + 4) a, b
	2) + 3) + 5)
	1) + 3) + 4) a + 5)
Probable:	1) + 4) a, b
	2) + 4) a, b
	2) + 5)
	3) + 4) a, b
Possible:	1) + 3)
	2) + 3)
	1) + 4) a
	2) + 4) a

Appendix:

1. Clinically and histologically, the following diseases should be excluded: Wegener's granulomatosis, Churg–Strauss syndrome, extramedullary plasmacytoma
2. Radiologically, the following diseases should be excluded: malignant lymphoma, urinary tract carcinomas, renal infarction and pyelonephritis (rarely, Wegener's granulomatosis, sarcoidosis and metastatic carcinoma)
3. Cases with suspected disease according to the diagnostic algorithm (Fig. 4) are classified into probable or possible IgG4-RKD according to these criteria

provides nephrologists and other clinical practitioners with the opportunity to identify patients with kidney-restricted IgG4-related disease among those with miscellaneous tubulointerstitial nephritides. In this study, only two patients (4.9%) had no extra-renal manifestations of IgG-related disease. Similarly, Zen and Nakanuma [43] showed that all the kidney lesions that they experienced were associated with extrarenal IgG4-related disease. These results can be interpreted in two ways; either kidney-restricted IgG4-related disease is very rare or it is often overlooked because of poor recognition. Our diagnostic algorithm and set of diagnostic criteria for IgG4-RKD may also provide a promising approach to elucidate this issue.

In contrast, decreased renal function associated with IgG4-related disease does not necessarily mean renal involvement by IgG4-related disease. We experienced two cases of IgG4-related disease with elevated serum Cr levels, the renal histology of which turned out to be nephrosclerosis in one case and diabetic nephropathy in the other case (data not shown). Other such diagnostic pitfalls will surely be recognized with the accumulation of greater numbers of cases in various populations. Because of the existence of such cases the diagnosis of IgG4-RKD must rely on characteristic radiographic findings or histopathologic findings.

In summary, we proposed the first diagnostic algorithm and a set of diagnostic criteria for IgG4-RKD. Prospective studies are required to access the sensitivity and specificity of these methods and to identify patients undiagnosed with IgG4-RKD among the patients with idiopathic TIN and other renal diseases.

Acknowledgments This proposal was prepared by the 'IgG4-related Kidney Disease' working group belonging to the Committee for Standardized Pathological Diagnosis of Kidney (Chair: Takashi Taguchi) of the Japanese Society of Nephrology (President: Hirofumi Makino). The members of the working group are Takao Saito (Chair), Mitsuhiro Kawano, Takako Saeki, Hitoshi Nakashima, Shinichi Nishi, Yutaka Yamaguchi, Satoshi Hisano and Nobuaki Yamanaka (Adviser). Dai Inoue, Motohisa Yamamoto, Hiroki Takahashi and Hideki Nomura collaborated in the study from the viewpoint of their respective specialties. This study was supported in part by Health and Labour Sciences Research Grants for the Study of Intractable Diseases (Establishment of a clinical new entity, IgG4-related multi-organ lymphoproliferative syndrome. Chief: Hisanori Umehara) from the Ministry of Health, Labour and Welfare, Japan. The working group also thanks Drs. Hideaki Hamano, Wako Yumura and Tohru Miyagi for their valuable advice and John Gelblum for his critical reading of the manuscript.

Conflict of interest The authors have declared that no conflict of interest exists.

References

1. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 2001;344:732–8.
2. Uchiyama-Tanaka Y, Mori Y, Kimura T, Sonomura K, Umemura S, Kishimoto N, et al. Acute tubulointerstitial nephritis associated with autoimmune-related pancreatitis. Am J Kidney Dis. 2004;43:e18–25.
3. Takeda S, Haratake J, Kasai T, Takaeda C, Takazakura E, et al. IgG4-associated idiopathic tubulointerstitial nephritis complicating autoimmune pancreatitis. Nephrol Dial Transplant. 2004;19:474–6.
4. Watson SJ, Jenkins DA, Bellamy CO. Nephropathy in IgG4-related systemic disease. Am J Surg Pathol. 2006;30:1472–7.
5. Rudmik L, Trpkov K, Nash C, Kinnear S, Falck V, Dushinski J, et al. Autoimmune pancreatitis associated with renal lesions mimicking metastatic tumours. CMAJ. 2006;175:367–9.
6. Nakamura H, Wada H, Origuchi T, Kawakami A, Taura N, Aramaki T, et al. A case of IgG4-related autoimmune disease with multiple organ involvement. Scand J Rheumatol. 2006;35:69–71.
7. Deshpande V, Chicano S, Finkelberg D, Selig MK, Mino-Kenudson M, Brugge WR, et al. Autoimmune pancreatitis: a systemic immune complex mediated disease. Am J Surg Pathol. 2006;30:1537–45.
8. Shimoyama K, Ogawa N, Sawaki T, Karasawa H, Masaki Y, Kawabata H, et al. A case of Mikulicz's disease complicated with interstitial nephritis successfully treated by high-dose corticosteroid. Mod Rheumatol. 2006;16:176–82.
9. Tsubata Y, Akiyama F, Oya T, Ajiro J, Saeki T, Nishi S, et al. IgG4-related chronic tubulointerstitial nephritis without autoimmune pancreatitis and the time course of renal function. Intern Med. 2010;49:1593–8.
10. Kim F, Yamada K, Inoue D, Nakajima K, Mizushima I, Kakuchi Y, et al. IgG4-related tubulointerstitial nephritis and hepatic inflammatory pseudotumor without hypocomplementemia. Intern Med. 2011;50:1239–44.
11. Saeki T, Nishi S, Imai N, Ito T, Yamazaki M, Kawano M, et al. Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. Kidney Int. 2010;78:1016–23.
12. Okazaki K, Kawa S, Kamisawa T, Naruse S, Tanaka S, Nishimori I, et al. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. J Gastroenterol. 2006;41:626–31.
13. Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol. 2006;4:1010–6.
14. Chari ST, Kloeppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T. Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu consensus document. Pancreatology. 2010;10:664–72.
15. Deshpande V, Gupta R, Sainani N, Sahani DV, Virk R, Ferrone C, et al. Subclassification of autoimmune pancreatitis: a histologic classification with clinical significance. Am J Surg Pathol. 2011;35:26–35.
16. Yamaguchi Y, Kanetsuna Y, Honda K, Yamanaka N, Kawano M, Nagata M. Characteristic tubulointerstitial nephritis in IgG4-related disease. Hum Pathol. 2011 [Epub ahead of print].
17. Krambeck AE, Miller DV, Blute ML. Wegener's granulomatosis presenting as renal mass: a case for nephron-sparing surgery. Urology. 2005;65:798.
18. Roussou M, Dimopoulos SK, Dimopoulos MA, Anastasiou-Nana MI. Wegener's granulomatosis presenting as a renal mass. Urology. 2008;71:547.e1–2.
19. Mizunoe S, Yamasaki T, Tokimatsu I, Kushima H, Matsunaga N, Hashinaga K, et al. Sarcoidosis associated with renal masses on computed tomography. Intern Med. 2006;45:279–82.
20. Murashima M, Tomaszewski J, Glickman JD. Chronic tubulointerstitial nephritis presenting as multiple renal nodules and pancreatic insufficiency. Am J Kidney Dis. 2007;49:e7–10.
21. Cornell LD, Chicano SL, Deshpande V, Collins AB, Selig MK, Lauwers GY, et al. Pseudotumors due to IgG4 immune-complex tubulointerstitial nephritis associated with autoimmune pancreatocentric disease. Am J Surg Pathol. 2007;31:1586–97.
22. Yoneda K, Murata K, Katayama K, Ishikawa E, Fuke H, Yamamoto N, et al. Tubulointerstitial nephritis associated with IgG4-related autoimmune disease. Am J Kidney Dis. 2007;50:455–62.
23. Morimoto J, Hasegawa Y, Fukushima H, Uesugi N, Hisano S, Saito T, et al. Membranoproliferative glomerulonephritis-like glomerular disease and concurrent tubulointerstitial nephritis complicating IgG4-related autoimmune pancreatitis. Intern Med. 2009;48:157–62.
24. Saeki T, Imai N, Ito T, Yamazaki H, Nishi S. Membranous nephropathy associated with IgG4-related systemic disease and without autoimmune pancreatitis. Clin Nephrol. 2009;71:173–8.
25. Naitoh I, Nakazawa T, Ohara H, Sano H, Ando T, Hayashi K, et al. Autoimmune pancreatitis associated with various extrapancreatic lesions during a long-term clinical course successfully treated with azathioprine and corticosteroid maintenance therapy. Intern Med. 2009;48:2003–7.
26. Takahashi N, Kawashima A, Fletcher JG, Chari ST. Renal involvement in patients with autoimmune pancreatitis: CT and MR imaging findings. Radiology. 2007;242:791–801.
27. Khalili K, Doyle DJ, Chawla TP, Hanbidge E. Renal cortical lesions in patients with autoimmune pancreatitis: a clue to differentiation from pancreatic malignancy. Eur J Radiol. 2008;67:329–35.
28. Sohn JH, Byun JH, Yoon SE, Choi EK, Park SH, Kim MH, et al. Abdominal extrapancreatic lesions associated with autoimmune pancreatitis: radiological findings and changes after therapy. Eur J Radiol. 2008;67:497–507.
29. Fujinaga Y, Kadoya M, Kawa S, Hamano H, Ueda K, Momose M, et al. Characteristic findings in images of extra-pancreatic lesions associated with autoimmune pancreatitis. Eur J Radiol. 2009;76:228–38.
30. Triantopoulou C, Malachias G, Maniatis P, Anastopoulos J, Siafas I, Papailiou J. Renal lesions associated with autoimmune pancreatitis: CT findings. Acta Radiol. 2010;51:702–7.
31. Saida Y, Homma N, Hama H, Ueno M, Imai N, Nishi S, et al. A case of IgG4-related tubulointerstitial nephritis showing the

progression of renal dysfunction after a cure for autoimmune pancreatitis. Jpn J Nephrol. 2010;52:73–9.
32. Shoji S, Nakano M, Usui Y. IgG4-related inflammatory pseudotumor of the kidney. Int J Urol. 2010;17:389–90.
33. Kawa S, Hamano H. Serological markers for the diagnosis of autoimmune pancreatitis. Suizo. 2007;22:641–5 (in Japanese with English abstract).
34. Kamisawa T, Takuma K, Egawa N, Tsuruta K, Sasaki T. Autoimmune pancreatitis and IgG4-related sclerosing disease. Nat Rev Gastroenterol Hepatol. 2010;7:401–9.
35. Kamisawa T, Kim MH, Liao WC, Liu Q, Balakrishnan V, Okazaki K, et al. Clinical characteristics of 327 Asian patients with autoimmune pancreatitis based on Asian diagnostic criteria. Pancreas. 2011;40:200–5.
36. Yamamoto M, Takahashi H, Suzuki C, Tabeya T, Ohara M, Naishiro Y, et al. Analysis of serum IgG subclasses in Churg-Strauss syndrome—the meaning of elevated serum levels of IgG4. Intern Med. 2010;49:1365–70.
37. Strehl JD, Hartmann A, Agaimy A. Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. J Clin Pathol. 2011;64:237–43.
38. Houghton DC, Troxell ML. An abundance of IgG4+ plasma cells is not specific for IgG4-related tubulointerstitial nephritis. Mod Pathol. 2011 [Epub ahead of print].
39. Yamamoto M, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, Takahashi H, et al. Elevated IgG4 concentrations in serum of patients with Mikulicz's disease. Scand J Rheumatol. 2004;33:432–3.
40. Masaki Y, Dong L, Kurose N, Kitagawa K, Morikawa Y, Yamamoto M, et al. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. Ann Rheum Dis. 2009;68:1310–5.
41. Otsuki M, Chung JB, Okazaki K, Kim MH, Kamisawa T, Kawa S, et al. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. J Gastroenterol. 2008;43:403–8.
42. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 2011;40:352–8.
43. Zen Y, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. Am J Surg Pathol. 2010;34:1812–9.

NDT Advance Access published January 6, 2012

Nephrol Dial Transplant (2012) 0: 1–7
doi: 10.1093/ndt/gfr761

Original Article

NDT
Nephrology Dialysis Transplantation

Light-microscopic characteristics of IgG4-related tubulointerstitial nephritis: distinction from non-IgG4-related tubulointerstitial nephritis

Kazuhiro Yoshita[1,*], Mitsuhiro Kawano[2,*], Ichiro Mizushima[2], Satoshi Hara[2], Yumi Ito[1], Naofumi Imai[1], Mitsuhiro Ueno[3], Shinichi Nishi[4], Hideki Nomura[5], Ichiei Narita[1] and Takako Saeki[6]

[1]Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [2]Division of Rheumatology, Department of Internal Medicine, Kanazawa University Hospital, Kanazawa, Japan, [3]University Health Center, Joetsu University of Education, Joetsu, Japan, [4]Division of Nephrology and Kidney Center, Kobe University Graduate School of Medicine, Kobe, Japan, [5]Department of General Medicine, Kanazawa University Hospital, Kanazawa, Japan and [6]Department of Internal Medicine, Nagaoka Red Cross Hospital, Nagaoka, Japan

Correspondence and offprint requests to: Takako Saeki; E-mail: saekit@nagaoka.jrc.or.jp
*Both authors contributed equally to this work.

Abstract

Background. IgG4-related disease is a multi-organ disorder characterized by a high level of serum IgG4 and dense infiltration of IgG4-positive cells into affected organs. In routine studies, however, IgG subclasses are not estimated. In the present study, we attempted to clarify the light-microscopic characteristics of IgG4-related tubulointerstitial nephritis (TIN) to facilitate distinction from non-IgG4-related TIN in specimens obtained by renal biopsy using routine staining.

Methods. In specimens from 34 cases of TIN (13 IgG4-related and 21 non-IgG4-related), 9 nephrologists independently reviewed the following histological features of interstitial lesions: (i) cell infiltration extending into the renal capsule, (ii) cell infiltration into the renal medulla, (iii) regional lesion distribution, (iv) lymphoid follicles, (v) granulomatous lesions, (vi) necrotizing angiitis, (vii) eosinophil infiltration, (viii) neutrophil infiltration, (ix) tubulitis, (x) peritubular capillaritis, (xi) storiform fibrosis and (xii) the stage of interstitial fibrosis. The modified nominal group technique was applied to obtain a consensus in the pathological interpretation.

Results. Consensus was successfully attained among the diagnosticians for all but one pathological feature (regional lesion distribution). Storiform fibrosis was demonstrated in 12 of 13 (92.3%) cases of IgG4-related TIN but in none of the cases of other types of TIN. Cell infiltration extending into the renal capsule was also observed only in IgG4-related TIN. Conversely, neutrophil infiltration, severe tubulitis, severe peritubular capillaritis, granulomatous lesions and necrotizing angiitis were evident only in non-IgG4-related TIN.

Conclusion. This study revealed some useful and characteristic features for distinguishing IgG4-related from non-IgG4-related TIN on the basis of light-microscopic observation.

Keywords: IgG4; light microscopy; storiform fibrosis; tubulointerstitial nephritis

Introduction

IgG4-related disease (IgG4-RD) is a new clinical entity that has been attracting worldwide attention, being characterized by a high level of serum IgG4 and dense infiltration of IgG4-positive cells into affected organs [1–3]. The prototype of this condition was sclerosing pancreatitis [4] (also known as Type 1 autoimmune pancreatitis [5]), but it is known to affect various organs including the salivary glands, hepatobiliary tract, lymph nodes, lungs, retroperitoneum and kidneys [1, 2, 6, 7]. Recently, we reported that the major renal parenchymal lesion associated with IgG4-RD is tubulointerstitial nephritis (TIN) [8]. Because steroid therapy is usually quite effective, diagnosis of IgG4-related TIN is important. However, IgG4-related TIN is difficult to recognize in the absence of autoimmune pancreatitis or Mikulicz's disease, which are representative conditions of the disease [1–3] because serum IgG subclasses are not examined routinely and immunostaining for IgG subclasses is not a routine part of renal pathologic studies. Furthermore, recent studies have revealed that high serum IgG4 levels and/or IgG4-positive plasma cells can also be present in some inflammatory conditions that are not associated with IgG4-RD, including anti-neutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitis [9–11]. On the other hand, several studies have revealed that certain common pathological features of IgG4-RD are evaluable in routine examinations, such as storiform fibrosis, eosinophilic infiltration, lymphoid follicles and obliterative phlebitis, and that these are also useful for diagnosis [5–8, 12–16]. In fact, we have observed that some pathological features including storiform fibrosis in IgG4-related TIN were

similar to those observed in Type 1 autoimmune pancreatitis [8]. However, it is still unclear whether the pathological features of IgG4-related TIN are actually characteristic in comparison with those of non-IgG4-related TIN and whether a consensus can be obtained among diagnosticians in the interpretation of pathological features such as storiform fibrosis, because tubulointerstitial lesions have not been fully examined from this perspective in ordinary TIN. These background factors prompted us to examine the light-microscopic characteristics of IgG4-related TIN, in which pathological consensus is attainable among diagnosticians, to allow its distinction from non-IgG4-related TIN using routine staining.

Materials and methods

Patients

This study included 13 patients with IgG4-related TIN (IgG4 group) and 21 patients with the other types of TIN (non-IgG4 group). The cases in both groups were selected from the renal biopsy pathology files at the Division of Clinical Nephrology, Niigata University (including cases seen at Nagaoka Red Cross Hospital) and the Division of Rheumatology, Kanazawa University Hospital, between 1998 and 2010 (IgG4 group) and between 2004 and 2010 (non-IgG4 group), respectively. Cases in which the specimens included over 100 glomeruli (obtained by surgery, open biopsy or autopsy) were excluded. The diagnosis of IgG4-related TIN was based on both (i) a high serum IgG4 level (>135 mg/dL) [17] and (ii) infiltration of numerous IgG4-positive plasma cells into the renal interstitium (IgG4-positive plasma cells/IgG-positive plasma cells >40% and/or IgG4-positive plasma cells >10/high power field), along with clinical features [18, 19]. The patients in the IgG4 group were all Japanese (11 males and 2 females) with an average age of 69.2 years (range 55–83 years). Twelve of the 13 patients had some IgG4-related extra-renal lesions (autoimmune pancreatitis, sialadenitis, dacryoadenitis, lymph node swelling, lung lesion, prostatitis or pseudo-tumor of the liver). The serum creatinine levels were within the range 0.9–6.17 mg/dL (average 2.55 ± 1.89). The levels of serum IgG4 before steroid therapy were 486–1860 (mean 1091, normal range <105). Hypocomplementemia was evident in 61.5% of the patients. None of them met the criteria for systemic lupus erythematosus, ANCA-associated vasculitis or sarcoidosis. Nine of the 13 patients had been included in our earlier study [8] and four were newly enrolled and had not been previously described.

The patients in the non-IgG4 group had a main renal pathological diagnosis of TIN, excluding IgG4-related TIN, renal allograft rejection and TIN associated with progressive chronic primary glomerular disease. The etiology of TIN included drug use ($n = 6$), vesicoureteral reflux ($n = 1$), malignant hypertension ($n = 1$), sarcoidosis ($n = 2$), Sjögren's syndrome ($n = 3$), ANCA-related vasculitis ($n = 3$) and idiopathic ($n = 5$). They were all Japanese (11 males and 10 females) with an average age of 55.7 years (range 11–80 years). Sialadenitis was present in three patients with Sjögren's syndrome and a patient with sarcoidosis showed lung lesions. The other 17 patients had no extra-renal lesions. Serum creatinine levels were 0.96–14.4 mg/dL (average 3.52 ± 3.07). Serum IgG4 levels were examined in three patients (two idiopathic and one Sjögren's syndrome) and were within the normal range in all of them. No patient showed hypocomplementemia. In all cases of idiopathic TIN, immunostaining for IgG4 revealed no or only few IgG4-positive plasma cells in the renal interstitium (data not shown).

Histological evaluation

Renal tissues were obtained by needle biopsy from all patients, except one patient with vesicoureteral reflux. For routine light-microscopic studies, renal biopsy specimens were fixed in formalin or alcohol-Bouin, embedded in paraffin and stained with hematoxylin and eosin, periodic acid-Schiff, periodic acid-methenamine silver (PAM) and Masson's trichrome or Azan. All tissue slides were anonymized and reviewed independently by nine nephrologists (all experts in renal pathology and routinely involved in the diagnosis of renal biopsy samples), who were blinded to the clinical and serological data and the IgG4/non-IgG4 status of the patients.

The estimated items pertaining to histological features were decided on the basis of previous pathological studies of IgG4-RD [5–8, 12–16]: (i) cell (inflammatory cell) infiltration extending into the renal capsule (absent, present or not evaluable due to lack of a renal capsule in the specimens), (ii) cell (inflammatory cell) infiltration into the renal medulla (absent, present or not evaluable due to lack of a renal medulla in the specimens), (iii) regional lesion distribution, well defined and excluding small patchy lesions (absent or present), (iv) lymphoid follicles with germinal centers (absent or present), (v) granulomatous lesions (absent or present), (vi) necrotizing angiitis (absent or present), (vii) eosinophil infiltration (0, no; 1+, occasional and 2+, numerous), (viii) neutrophil infiltration (0, no; 1+, occasional and 2+, numerous), (ix) tubulitis (0, no inflammatory cells in tubules; 1, mild; 1–4 cells per tubule cross section; 2, moderate; 5–10 cells per tubule cross section; 3, severe; >10 cells per tubule cross section, judged from the highest number of all types of cells infiltrating each tubule in the whole specimen), (x) peritubular capillaritis (0, no; 1, mild; 2, moderate; 3, severe; assigned a 'ptc' score of 0–3 in the Banff 07 classification [20]), (xi) storiform fibrosis (absent or present), (xii) stage of interstitial fibrosis (0, no fibrosis; 1, mild; scattered fibrosis; 2, moderate; degree of fibrosis less predominant than that of cell infiltration; 3, severe; degree of fibrosis more predominant than that of cell infiltration; 4; only fibrosis). In each specimen, all stages and the main stage were described respectively.

'Storiform fibrosis' is a characteristic swirling pattern of fibrosclerosing inflammation consisting of inflammatory cells and irregular fibrosis evident in Type 1 autoimmune pancreatitis [12]. In our earlier study, we demonstrated a similar pattern of fibrosis in IgG4-related TIN and showed that the irregular fibrosis surrounded nests of inflammatory cells in PAM-stained preparations [8]. In the present study, we defined 'storiform fibrosis in IgG4-related TIN' as a pattern of fibrosclerosing inflammation consisting of both (i) dense collagen fibers, into which inflammatory cells had infiltrated, exhibiting a swirling or arabesque pattern in the renal interstitium and (ii) irregular fibers surrounding nests of inflammatory cells in PAM-stained preparations. Representative photographs of storiform fibrosis in IgG4-related TIN are shown in Figure 1. Reference photographs of the stages of interstitial fibrosis (Stage 4 was not evident in any of the cases examined) are shown in Figure 2. Storiform fibrosis was evaluable in Stages 2 and 3. In our earlier study of IgG4-related TIN [8], obliterative phlebitis was not evident although phlebitis was shown in some patients (data not shown). Therefore, obliterative phlebitis was not investigated in this study.

The modified nominal group technique developed by the RAND Corporation [21] was applied to obtain consensus in the histopathological interpretation of renal biopsy specimens among the nine nephrologists. Briefly, each nephrologist recorded his/her assessments according to the rating system for TIN described later. These ratings were collected centrally, and the most frequent ratings were chosen as tentative interpretations. Then, the nephrologists anonymously rated the tentative interpretations on a 9-point scale, in which 1 = extremely inappropriate, 5 = uncertain and 9 = extremely appropriate. After anonymous feedback of the distribution of the ratings made by their colleagues and anonymous discussion via electronic mail, a second round of ratings was undertaken confidentially for all specimens regardless of the initial degree of agreement. To determine the final degree of agreement and disagreement, a statistical definition using a binomial distribution was applied. Consensus was considered to exist when no more than two individuals rated a particular indication outside a 3-point range (i.e. 1–3, 4–6 and 7–9). Items for which the nine nephrologists were unable to reach an agreement were discussed further in a group meeting. Attempts were made to modify the wordings of the rating system, and subsequently the third anonymous rating round was undertaken for these particular items. If a consensus was still not attainable after the third round of ratings, the item was described as 'consensus failure'.

Statistical analysis

Statistical analyses were done using the Fisher's exact probability test or the Mann–Whitney's *U*-test. A probability of $P < 0.05$ was considered to indicate statistical significance.

Results

Renal pathology

The histological features of the IgG4 and non-IgG4 groups are summarized in Table 1. Consensus was successfully attained among the nine nephrologists for all but one

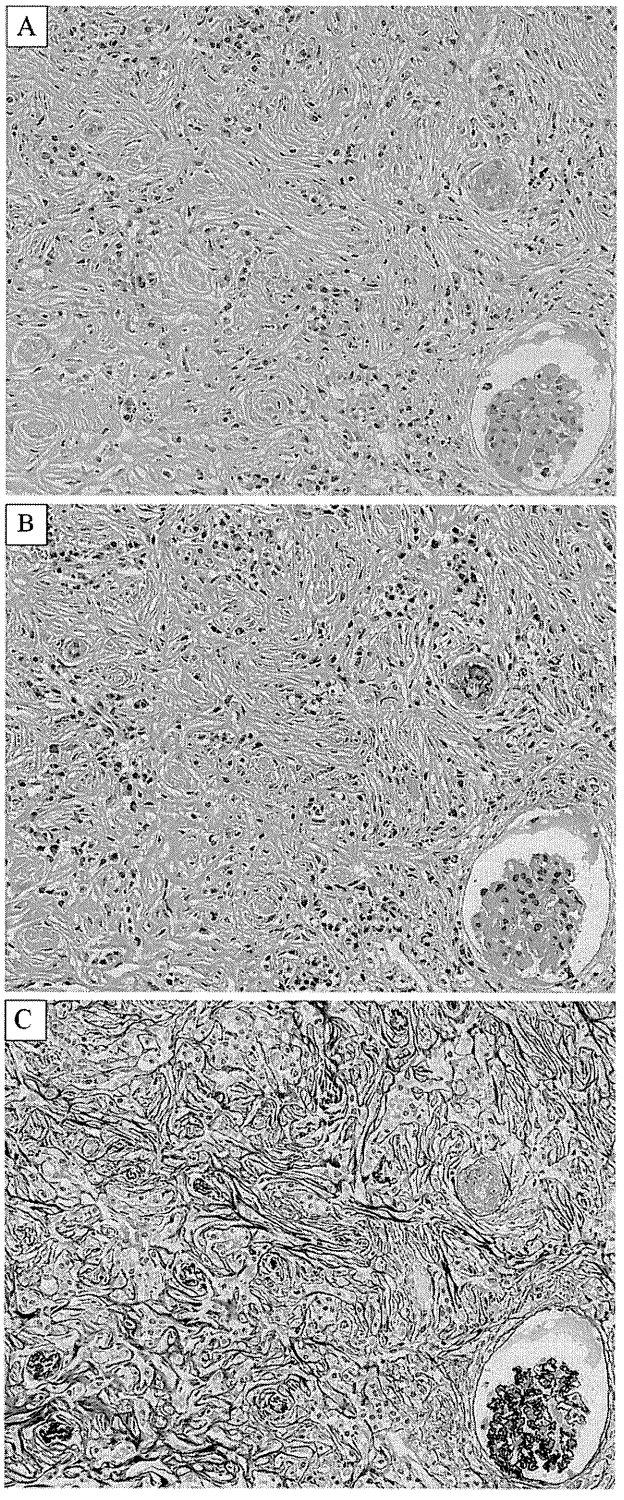

Fig. 1. Storiform fibrosis in IgG4-related TIN. A swirling or arabesque pattern consisting inflammatory cells and collagen fibers, corresponding to storiform fibrosis in Type 1 autoimmune pancreatitis, is evident (**A** and **B**). In PAM stain, irregular fibers surround nests of inflammatory cells (**C**). (**A**) Hematoxylin and eosin, (**B**) Elastica–Masson trichrome, (**C**) PAM. All images ×200 in almost the same field .

pathological feature (a regional lesion distribution) in two cases. The features that were evident only in the IgG4 group were storiform fibrosis and 'cell infiltration extending into the renal capsule'. Storiform fibrosis was evident in 12/13 patients (92.3%) in the IgG4 group but in none of the non-IgG4 group ($P < 0.0001$) (Figure 3). Cell infiltration extending into the renal capsule, although this feature was not evaluable in many patients in the both groups, was evident in two patients in the IgG4 group (Figure 4). Conversely, neutrophil infiltration, granulomatous lesions and necrotizing angiitis were evident only in the non-IgG4 group [neutrophil infiltration = 12/21 ($P = 0.0010$), granulomatous lesions = 5/21 ($P = 0.1317$) and necrotizing angiitis = 5/21 patients ($P = 0.1317$)]. The grades of tubulitis were significantly lower in the IgG4 group (in the IgG4 group, stage of tubulitis was 0 in 7.7%, 1 in 76.9%, 2 in 15.4% and 3 in 0%, whereas in the non-IgG4 group, it was 0 in 0%, 1 in 33.3%, 2 in 47.6% and 3 in 19.0%, $P = 0.0026$). Severe tubulitis was evident only in the non-IgG4 group. Although the grades of peritubular capillaritis were not significantly different between the two groups, severe peritubular capillaritis was also evident only in the non-IgG4 group. A regional lesion distribution was observed more frequently in the IgG4 group (5/12 in the IgG4 and 1/20 in the non-IgG4, $P = 0.0185$); however, consensus in the pathological interpretation was not attainable in two patients. Cell infiltration into the renal medulla was observed in both groups (5/6 in the IgG4 and 12/15 in the non-IgG4, P = not significant). Eosinophil infiltration was evident in 30.8% of the patients in the IgG4 group and 9.5% in the non-IgG4 group, but the difference was not significant. Lymphoid follicles were evident in only one patient in the non-IgG4 group.

The results of interstitial fibrosis staging are summarized in Table 2. The stages of fibrosis were mixed in most cases in both groups. The IgG4 group had significantly higher stages of fibrosis than the non-IgG4 group (in the IgG4 group, main stage of fibrosis was mild in 15.4%, moderate in 61.5% and severe in 23.1%, whereas in the non-IgG4 group, it was mild in 57.1%, moderate in 42.9% and severe in 0%, $P = 0.0054$).

Discussion

Although the etiology of IgG4-RD has not been elucidated, some common pathological characteristics of this disease have been demonstrated. Dense lymphoplasmacytic infiltration with fibrosis and infiltration of numerous IgG4-positive plasma cells are the most characteristic features [1–8, 12–16, 18, 19] and storiform fibrosis, eosinophil infiltration, lymphoid follicles, inflammation around the margins of affected tissues, a regional lesion distribution and obliterative phlebitis have also been considered to be common features [5–8, 12–16, 22]. On the other hand, neutrophil infiltration and inflammation of the duct epithelium in affected organs are rare [7, 12, 13, 16]. In IgG4-related TIN, lymphoplasmacytic infiltration with numerous IgG4-positive plasma cells and fibrosis are also very important features [8]. Recently, Raissian *et al.* [18] revealed that the presence of plasma cell-rich TIN with numerous IgG4-positive plasma cells has diagnostic utility, with a sensitivity of 100% and specificity of 92%, for IgG4-related TIN, excluding pauci-immune necrotizing and crescentic glomerulonephritis. However,

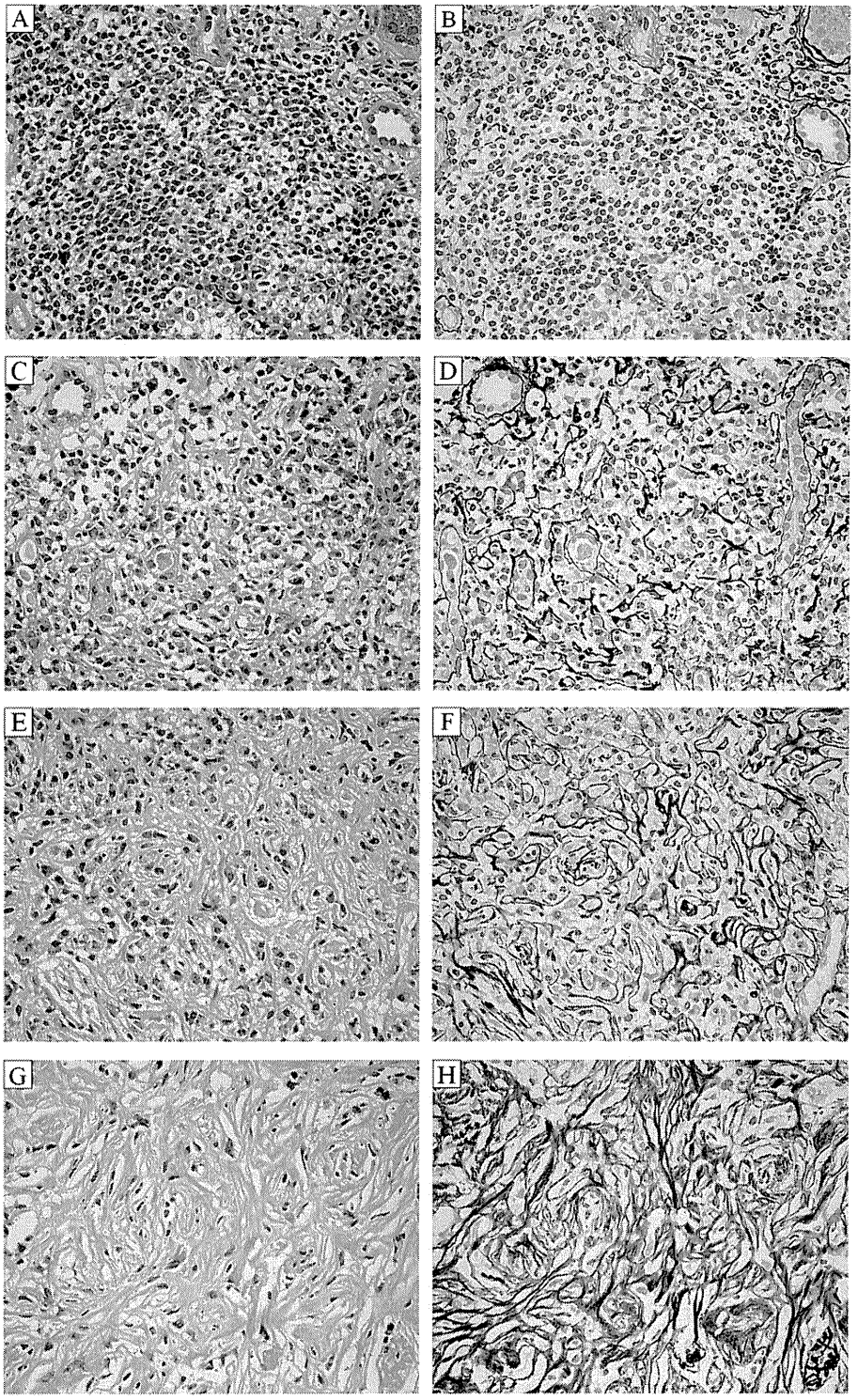

Fig. 2. The stages of interstitial fibrosis. Stage 0, no fibrosis (**A** and **B**); 1, mild; scattered fibrosis (**C** and **D**); 2, moderate; degree of fibrosis less predominant than that of cell infiltration (**E** and **F**); 3, severe; degree of fibrosis more predominant than that of cell infiltration (**G** and **H**). (**A**, **C**, **E** and **G**): Elastica–Masson trichrome, (**B**, **D**, **F** and **H**) PAM (×400). Each stage is from almost the same field in IgG4-related TIN.

lymphoplasmacytic infiltration is a non-specific finding in TIN, and immunostaining is not performed routinely. Furthermore, recent studies have revealed that numerous IgG4-positive plasma cells can also be present in conditions not associated with IgG4-RD [9–11]. Houghton *et al.* [9] described that the presence of numerous IgG4-positive plasma cells is essential to, but not sufficient for, the diagnosis of IgG4-related TIN. In addition, there is organ specificity in the pathological features of IgG4-RD [7]. For example, storiform fibrosis is not evident in the lymph nodes, minor salivary glands [7] or lung lesions [23]. It is important to examine the pathological findings closely in

Table 1. Histological features of IgG4-related and non-IgG4-related TIN[a]

	IgG4 (n = 13)	Non-IgG4 (n = 21)	P
Cell infiltration extending into the renal capsule	2/7 (NE 6)	0/7 (NE 14)	0.4615
Cell infiltrations into the renal medulla	5/6 (NE 7)	12/15 (NE 6)	>0.9999
Regional lesion distribution	5/12 (CF 1)	1/20 (CF 1)	0.0185
Lymphoid follicles	0/13 (0%)	1/21 (4.8%)	>0.9999
Granulomatous lesions	0/13 (0%)	5/21 (23.8%)	0.1317
Necrotizing angiitis	0/13 (0%)	5/21 (23.8%)	0.1317
Storiform fibrosis	12/13 (92.3%)	0/21 (0%)	<0.0001
Eosinophil infiltration			
Grade 0	9/13 (69.2%)	19/21 (90.5%)	0.1084
Grade 1	3/13 (23.1%)	2/21 (9.5%)	
Grade 2	1/13 (7.7%)	0/21 (0%)	
Neutrophil infiltration			
Grade 0	13/13 (100%)	9/21 (42.9%)	0.0010
Grade 1	0/13 (0%)	9/21 (42.9%)	
Grade 2	0/13 (0%)	3/21 (14.3%)	
Tubulitis			
Grade 0	1/13 (7.7%)	0/21 (0%)	0.0026
Grade 1	10/13 (76.9%)	7/21 (33.3%)	
Grade 2	2/13 (15.4%)	10/21 (47.6%)	
Grade 3	0/13 (0%)	4/21 (19.0%)	
Peritubular capillaritis			
Grade 0	5/13 (38.5%)	5/21 (23.8%)	0.0649
Grade 1	5/13 (38.5%)	4/21 (19.0%)	
Grade 2	3/13 (23.1%)	8/21 (38.1%)	
Grade 3	0/13 (0%)	4/21 (19.0%)	

[a]NE, not evaluable; CF, consensus failure; grade of eosinophil and neutrophil infiltration: Grade 0, no; 1+, occasional and 2+, numerous; grade of tubulitis and peritubular capillaritis: Grade 0, no; 1, mild; 2, moderate and 3, severe.

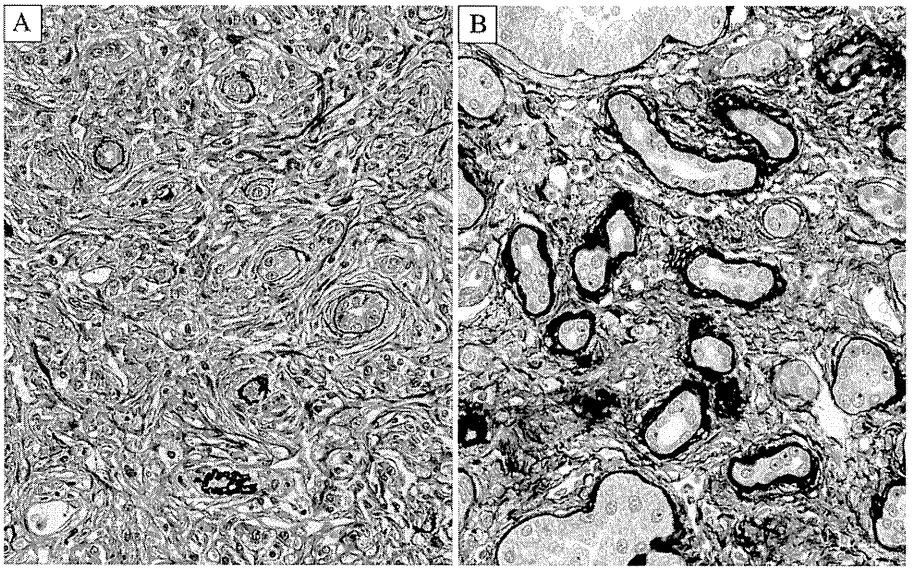

Fig. 3. Interstitial fibrosis of IgG4-related TIN and non-IgG4-related TIN. Characteristic storiform fibrosis is evident in IgG4-related TIN (**A**) but not in non-IgG4-related TIN (**B**) (PAM–Masson trichrome, ×400).

each organ and elucidate points of similarities and differences. In this study, we have revealed some useful and characteristic features for distinguishing IgG4-related from non-IgG4-related TIN on the basis of light-microscopic observation using routine staining, with consensus among diagnosticians. In particular, storiform fibrosis was revealed to be quite characteristic and useful for diagnosis of IgG4-related TIN. Because renal biopsy is usually applied to non-atrophic kidneys, dense interstitial fibrosis is noted relatively rarely in specimens obtained by biopsy. Interestingly, however, most of the patients with IgG4-related TIN showed high grades of fibrosis, even those with mild renal dysfunction, and the characteristic pattern was easy to recognize.

Cell infiltration extending into the renal capsule was evident in two patients in the IgG4 group. Because this feature is ordinarily not evident in other types of TIN, it might also be diagnostic of IgG4-related TIN. However, this feature was not evaluable in many of the patients in

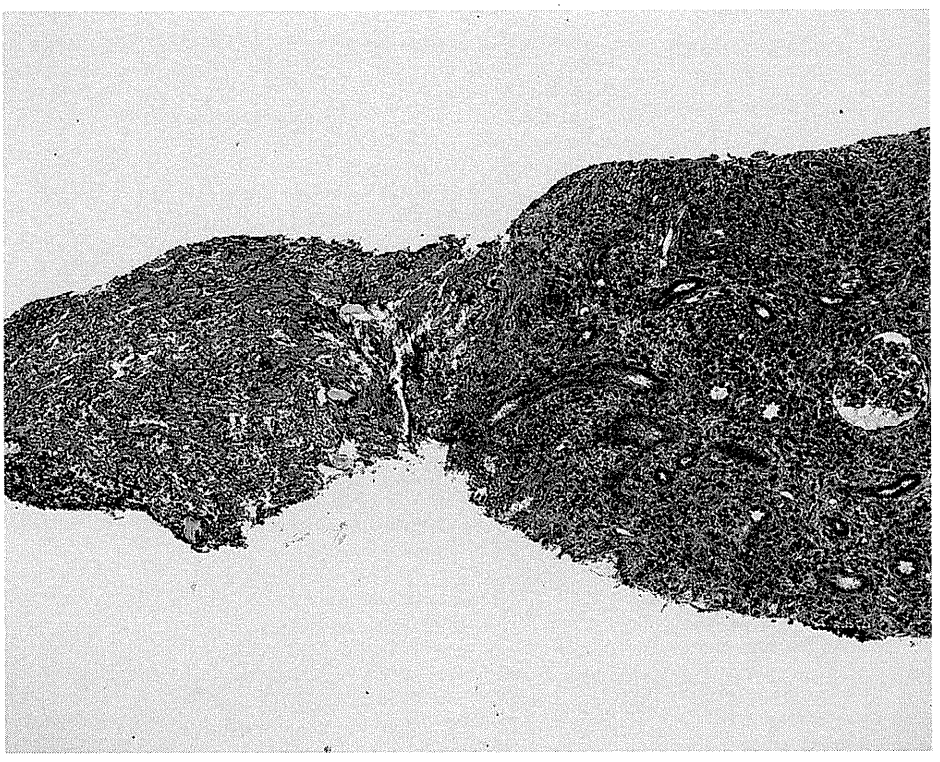

Fig. 4. Cell infiltration extending into the renal capsule. Inflammatory cells are evident within the renal capsule (Masson's trichrome, ×100).

Table 2. Stages of interstitial fibrosis of IgG4 and non-IgG4-related TIN[a]

	IgG4 (n = 13)	Non-IgG4 (n = 21)	P
Mean s-Cr (mg/dL) (range)	2.55 (0.9–6.17)	3.52 (0.96–14.4)	0.2719
Main stage			
1	2/13 (15.4%)	12/21 (57.1%)	0.0054
2	8/13 (61.5%)	9/21 (42.9%)	
3	3/13 (23.1%)	0/21 (0%)	
All stages			
0 + 1	1/13	1/21	
1	0/13	2/21	
0 + 1 + 2	0/13	4/21	
1 + 2	2/13[b]	5/21	
0 + 1 + 2 + 3	2/13[b]	3/21	
1 + 2 + 3	8/13[b]	6/21	

[a]s-Cr, serum creatinine; Stage 0, no fibrosis; 1, mild fibrosis; 2, moderate fibrosis and 3, severe fibrosis.
[b]Storiform fibrosis was evident.

both groups, because specimens obtained by renal biopsy and subjected to light microscopy often lack the renal capsule. Therefore, further study to confirm this will be necessary. Neutrophil infiltration and severe tubulitis were not evident in IgG4-related TIN. Neutrophil infiltration has been described as rare in head and neck, hepatic and pancreatobiliary and retroperitoneal lesions in IgG4-RD [7]. Also, rarity of inflammation of the duct epithelium has been demonstrated in Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis [6, 12], suggesting these features are common in IgG4-RD. A regional lesion distribution was evident more frequently in the IgG4 group, suggesting that this may also be useful for the diagnosis of IgG4-related TIN. However, pathological interpretation of this feature was difficult in some patients, and a consensus could not be reached in two patients. Lymphoid follicles were evident in only one of all patients. Because specimens obtained by needle renal biopsy are quite small, lymphoid follicles with germinal centers might be difficult to discern. Eosinophil infiltration was often evident in IgG4-related TIN and so, IgG4-related TIN should be considered in the differential diagnosis of TIN with eosinophils. But there was no significant inter-group difference in this respect. Because eosinophil infiltration has also been reported as a common feature of non-IgG4-related TIN [24], it should be considered as not being diagnostic but rather a supportive feature of IgG4-related TIN. Granulomatous lesions and necrotizing angiitis, which are sometimes observed in sarcoidosis or ANCA-related vasculitis, were not evident in IgG4-related TIN, suggesting that they are useful features for distinguishing between these diseases, although granulomas have rarely been observed in extra-renal organs associated with IgG4-RD [7].

Except for the items examined in this light-microscopic study using routine staining, immune complex deposits in the renal tubule basement membranes by immunofluorescence, immunohistochemistry and/or electron microscopy have been shown to be a characteristic feature of IgG4-related TIN [18, 25]. On the basis of these pathological features, nephrologists might be able to recognize IgG4-related TIN in specimens obtained by renal biopsy using routine methods, even when no data for IgG subclass are available.

In this study, each item was examined closely by nine diagnosticians in a blinded manner, and a modified nominal

group technique was used to elucidate whether consensus can be obtained among diagnosticians in the interpretation of pathological features. For this purpose, the study employed a relatively small cohort size, and addition of TIN cases proven to have non-IgG4 status as controls was unfortunately impossible. However, including more non-related TIN cases would make the P-values more significant for certain features (granulomatous lesion or necrotizing angiitis). Further studies employing a larger cohort size and including all types of TIN as a control will be necessary to clarify the positive and negative predictive values of each item for diagnosis of IgG4 TIN.

In conclusion, the present study identifies some useful and characteristic features for distinguishing IgG4-related TIN from non-IgG4-related TIN in specimens examined by light microscopy. However, the significance of these pathological findings and the etiology of IgG4-RD remain poorly understood. Further studies will be necessary to elucidate the underlying mechanisms.

Acknowledgements. This work was supported by Health and Labour Sciences Research Grants for the Study of Intractable Diseases from the Ministry of Health, Labor and Welfare, Japan.

Conflict of interest statement. None declared.

References

1. Kamisawa T, Okamoto A. IgG4-related sclerosing disease. *World J Gastroenterol* 2008; 14: 3948–3955
2. Masaki Y, Dong L, Kurose N *et al.* Proposal for a new clinical entity, IgG4-positive multi-organ lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis* 2009; 68: 1310–1315
3. Yamamoto M, Takahashi H, Ohara M *et al.* A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. *Mod Rheumatol* 2006; 16: 335–340
4. Hamano H, Kawa S, Horiuchi A *et al.* High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; 344: 732–738
5. Chari ST, Kloeppel G, Zhang L *et al.* Histopathologic and clinical subtypes of autoimmune pancreatitis. The Honolulu consensus document. *Pancreas* 2010; 39: 549–554
6. Cheuk W, Chan JK. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. *Adv Anat Pathol* 2010; 17: 303–332
7. Zen Y, Nakanuma Y. IgG4-related disease. A cross-sectional study of 114 cases. *Am J Surg Pathol* 2010; 34: 1812–1819
8. Saeki T, Nishi S, Imai N *et al.* Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. *Kidney Int* 2010; 78: 1016–1023
9. Houghton DC, Troxell ML. An abundance of IgG4+ plasma cells is not specific for IgG4-related tubulointerstitial nephritis. *Mod Pathol* 2011; 24: 1480–1487
10. Yamamoto M, Takahashi H, Suzuki C *et al.* Analysis of serum IgG subclasses in Churg-Strauss syndrome—the meaning of elevated serum levels of IgG4. *Intern Med* 2010; 49: 1365–1370
11. Strehl JD, Hartmann A, Agaimy A. Numerous IgG4-positive plasma cells are ubiquitous in diverse localized non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. *J Clin Pathol* 2011; 64: 237–243
12. Notohara K, Wani Y, Fujisawa M. Pathologic findings of autoimmune pancreatitis and IgG4-related disease. *Curr Immunol Rev* 2011; 7: 212–220
13. Zen Y, Inoue D, Kitao A *et al.* IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. *Am J Surg Pathol* 2009; 33: 1886–1893
14. Zen Y, Onodera M, Inoue D *et al.* Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. *Am J Surg Pathol* 2009; 33: 1833–1839
15. Nakanuma Y, Zen Y. Pathology and immunopathology of immunoglobulin G4-related sclerosing cholangitis: the latest addition to the sclerosing cholangitis family. *Hepatol Res* 2007; 37: S478–S486
16. Deshpande V, Gupta R, Sainani N *et al.* Subclassification of autoimmune pancreatitis: a histologic classification with clinical significance. *Am J Surg Pathol* 2011; 35: 26–35
17. Okazaki K, Kawa S, Kamisawa T *et al.* Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. *J Gastroenterol* 2006; 41: 626–631
18. Raissian Y, Nasr SH, Larsen CP *et al.* Diagnosis of IgG4-related tubulointerstitial nephritis. *J Am Soc Nephrol* 2011; 22: 1343–1352
19. Kawano M, Saeki T, Nakashima H *et al.* Proposal for diagnostic criteria for IgG4-related kidney disease. *Clin Exp Nephrol* 2011; 15: 615–626
20. Solez K, Colvin RB, Racusen LC *et al.* Banff 07 classification of renal allograft pathology: updates and future directions. *Am J Transplant* 2008; 8: 753–760
21. Murphy MK, Black NA, Lamping DL *et al.* Consensus development methods, and their use in clinical guideline development. *Health Technol Asess* 1998; 2: i–iv, 1–88
22. Saeki T, Nishi S, Ito T *et al.* Renal lesions in IgG4-related systemic disease. *Intern Med* 2007; 46: 1365–1372
23. Shrestha B, Sekiguchi H, Colby TV *et al.* Distinctive pulmonary histopathology with increased IgG4-positive plasma cells in patients with autoimmune pancreatitis. *Am J Surg Pathol* 2009; 33: 1450–1462
24. Nadasdy T, Sedmak D. Acute and chronic tubulointerstitial nephritis. In: Jennette JC (eds). Heptinstall's Pathology of the Kidney. 6th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2007, pp. 1083–1137
25. Cornell LD, Chicano SL, Deshpande V *et al.* Pseudotumors due to IgG4 immune-complex tubulointerstitial nephritis associated with autoimmune pancreatocentric disease. *Am J Surg Pathol* 2007; 31: 1586–1597

Received for publication: 7.9.11; Accepted in revised form: 2.12.11

Mod Rheumatol
DOI 10.1007/s10165-011-0589-2

ORIGINAL ARTICLE

Clinical and histological changes associated with corticosteroid therapy in IgG4-related tubulointerstitial nephritis

Ichiro Mizushima · Kazunori Yamada · Hiroshi Fujii · Dai Inoue · Hisanori Umehara · Masakazu Yamagishi · Yutaka Yamaguchi · Michio Nagata · Masami Matsumura · Mitsuhiro Kawano

Received: 11 November 2011 / Accepted: 26 December 2011

Abstract
Objectives This study aimed to investigate the clinicopathological changes induced by corticosteroid therapy in immunoglobulin (Ig)G4-related tubulointerstitial nephritis (TIN).
Methods We studied six IgG4-related TIN patients receiving renal biopsies before and after corticosteroid therapy. Their clinical data and histological findings were evaluated before and after therapy.
Results Elevated serum creatinine levels rapidly improved after corticosteroid therapy except for two patients, in whom it persisted. Abnormal radiological findings improved in all patients, although focal cortical atrophy persisted in three. Histologically, TIN-like dense lymphoplasmacytic infiltration, interstitial fibrosis, IgG4-positive plasma cell, CD4+CD25+ T cell, and Foxp3+ cell infiltration were characteristic before therapy. After therapy, the area with cell infiltration decreased and regional fibrosis became evident in the renal interstitium. The number of IgG4-positive plasma cells and Foxp3+ cells significantly diminished even in the early stage of therapy, whereas low to moderate numbers of CD4+ and CD8+ T cells still infiltrated where inflammation persisted in the later stage.
Conclusions Our study shows that persistent renal insufficiency associated with macroscopic atrophy and microscopic fibrosis is not so rare in IgG4-related TIN. Pathologically, the behavior of regulatory T cells during the clinical course is quite similar to that of IgG4-positive plasma cells, and the behavior pattern of those cells is distinctive.

Keywords IgG4-related disease · Tubulointerstitial nephritis · IgG4-positive plasma cell · Regulatory T cell · Corticosteroid therapy

I. Mizushima · K. Yamada · H. Fujii · M. Kawano (✉)
Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8640, Japan
e-mail: mk0920@mac.com

D. Inoue
Department of Radiology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

H. Umehara
Department of Hematology and Immunology, Kanazawa Medical University, Kanazawa, Ishikawa, Japan

M. Yamagishi
Division of Cardiology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

Y. Yamaguchi
Yamaguchi Pathology Laboratory, Matsudo, Chiba, Japan

M. Nagata
Department of Kidney and Vascular Pathology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

M. Matsumura
Research Center for Medical Education, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

Introduction

Immunoglobulin (Ig)G4-related disease (IgG4-RD) is a recently recognized systemic inflammatory disease with multiorgan involvement [1–5], including the kidney. Since 2004, accumulated case reports and case series have defined the radiographic and histopathological characteristic findings of IgG4-related kidney disease [6–20]. Two large

Published online: 20 January 2012