Proposal for diagnostic criteria for IgG4-related kidney disease

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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

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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 ≥ 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 $\times 40$, **b** PAM-Masson's trichrome stain $\times 100$, **c** CD138 immunostain $\times 400$, **d** IgG4 immunostain $\times 400$)

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 ($> 10/\text{HPF}$ and/or $\text{IgG4/IgG} > 40\%$) 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 assess 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.

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