**Proposal for diagnostic criteria for IgG4-related kidney disease**

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**Abstract**

Background

Recently, IgG4-related disease is attracting wide attention. 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 (JSN) has established a working group to prepare diagnostic criteria of 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 IgG4RKD: clinical features including extra-renal organ involvement, urinalysis and serological features including serum IgG4 levels, imaging findings demonstrated by computed tomography, 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 show abnormal renal imaging findings: multiple low density lesions on enhanced computed tomography, 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 exceeds 135mg/dl. 4. Renal histology shows two abnormal findings: a) Dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells >10/HPF and/or ratio of IgG4 positive plasma cells/IgG positive plasma cells >40%. b) Characteristic ‘striform’ fibrosis surrounding nests of lymphocytes and/or plasma cells. 5. Extra-renal histology shows 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 conditions as above.

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.

## Introduction

After the recognition of autoimmune pancreatitis (AIP) as an IgG4-related disease [1], similar lesions in other organs have attracted wide paid attention. IgG4-related kidney disease (IgG4-RKD) was first reported as a complication or an extrapancreatic manifestation of autoimmune pancreatitis (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 sialoadenitis and dacryoadenitis [8] using enhanced computed tomography (CT) have been additionally accumulated. And lately, IgG4-RKD without AIP or chronic sclerosing sialoadenitis 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 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-RD without TIN with decreased renal function; 1 Sjogren's syndrome with TIN; 1 minimal change nephritic disease; 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 Japanese Society of Nephrology. 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 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 β2 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 Laboratory, 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-related kidney disease, 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**

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 creatinine (Cr) level was 1.7 mg/dl, and 24 patients had elevated serum creatinine 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. When decreased renal function existed and administration of contrast medium was deemed inadvisable, diffuse bilateral renal swelling was another feature (n = 2). The third characteristic radiologic finding of IgG4-related kidney disease was diffuse thickening of the renal pelvis wall with smooth intra-luminal surface, and this finding was sometimes detected in patients with IgG4-related disease without obvious clinical symptoms. 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 very rarely pointed out to be an IgG4-related kidney lesion, with only one such case detected in this study. 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, and without fibrosis in one. Interstitial fibrosis surrounding nests of lymphocytes was characteristic and resembled the “striform’ shape in AIP [14, 15]. Of these, marked IgG4-positive plasma cell infiltration was confirmed immunohistochemically in all patients. On the other hand, glomerular

lesions were not specific, although those were found in 11 patients. 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 Figure 1. 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 autoimmune pancreatitis, 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 sialoadenitis 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 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 (Figure 2, 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 (SLE), 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 [16, 17], sarcoidosis [18] 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 more than 10 infiltrating IgG4-positive plasma cells /HPF and/or a ratio of IgG4/IgG positive plasma cells exceeding 40%, b. characteristic fibrosis surrounding several infiltrating cells, c. other useful findings for the differential diagnosis [positive findings : lesions beyond renal capsule, eosinophil infiltration, clear border between affected and unaffected areas, marked fibrosis, negative findings : (necrotizing) angiitis, 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 (Figure 3). 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 its being an extrapancreatic manifestation of AIP [2-11, 19-24]. This disease has many features helping to distinguish it from other types of tubulointerstitial nephritis radiographically [25-29] and pathologically [11, 20. 22], 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 [30]. This prompted us to prepare by consensus a set of diagnostic criteria for IgG4-RKD.

To prepare diagnostic criteria, characteristic radiological 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 [25-29]. Of these, the most common radiological finding was multiple low-density lesions on enhanced CT [25-29], with 46.3% showing this type of abnormality in our study. Takahashi et al [25] 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 [29, 31]. In 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 [25, 27-29].

Hypergammaglobulinemia or elevated serum IgG levels, hypocomplementemia, and elevated serum IgE levels are all frequently observed serological features of IgG4-RKD [2-11]. In our series as well we confirmed that 90.2% had 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 [32-34]. In contrast, our criteria do not consider the presence of IgG4-RKD with 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 normal serum IgG4 patients might lead to misdiagnosis. However, a case report with IgG4-related inflammatory pseudotumor of the kidney with normal serum IgG4 level is available [31], and this represents one of the limitations of our criteria.

Chari et al considered histologic criteria to be the gold standard for the diagnosis of AIP [13]. In addition to the immunohistochemical findings obtained by IgG4 staining, distinguishing fibrosis called “striform fibrosis” and obliterative phlebitis are very important for the diagnosis of type 1 AIP as well [14, 15]. Interestingly, it was identified that the same kind of fibrosis was detected in the involved kidney and in a previous study found that this characteristic fibrosis was very useful in distinguishing IgG4-RKD from other tubulointerstitial nephritides [35]. In contrast, obliterative phlebitis was not detected in any renal biopsy specimens in this study (data not shown). Glomerular lesions also seem non-specific so far, although some cases associated with glomerulopathy have been reported [22,23],

Considering the above-mentioned features of IgG4-RKD and referring to several sets of previously established diagnostic criteria for AIP [12,13,36,37], 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 added other organ involvement and response to steroid therapy as useful findings in making the diagnosis of AIP [13]. 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 (more than 10/hpf and/or IgG4/IgG more than 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 tubulointerstitial nephritis is in general responsive to it.

On the basis of this analysis of 41 patients with IgG4-RKD, we proposed a diagnostic algorithm (Figure 2) 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 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 et al showed that all the kidney lesions that they experienced were associated with extrarenal IgG4-related disease [38]. 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 creatinine levels, the renal histology of which turned out to be nephrosclerosis and diabetic nephropathy in one each (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 tubulointerstitial nephritis.

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**Figure legend**

Figure 1. Frequency distribution of the number of affected organs. The mean number of affected organs was 3.4.

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

Figure 3. 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.

Table 1　Clinical and pathological characteristics of 41 patients

| Characteristic | The number of cases* (percentage) |
|---|---|
| Age-----yr | 63.7±12.3 |
| Male sex-----no. (%) | 30 (73.2) |
| Patients with preceding IgG4-related disease-----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. (%) | 18/36 (50.0) |
| Hematuria-----no./total no. (%) | 12/36 (33.3) |
| Elevated serum creatinine-----no./total no. (%) | 24/41 (58.5) |
| Serum creatinine level | 1.7±1.5 |
| Elevated serum IgG-----no./total no. (%) | 37/41 (90.2) |
| Serum IgG level | 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 | 754.3±876.8 |
| Elevated serum IgG4-----no./total no. (%) | 41/41 (100.0) |
| Serum IgG4 level | 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) |
| Periaorta | 2 (4.9) |
| Breast, liver, nerve, thyroid gland, peritoneum, bile duct, or joint # | 1 (2.4) |

*Plus-minus values are mean ± SD.

#The number of each organ involvement is the same.

Table 2 Diagnostic algorithm for IgG4-related kidney disease (IgG4-RKD)

Supplement

Boxed numbers correspond to Figure 2.

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, β2 microglobulin and/or α1 microglobulin excretions in urinalysis.
3. ② At least one of 3 abnormalities (elevated serum IgG, hypocomplementemia and elvated serum IgE) is necessary.
4. ③The 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. ④Autoimmune 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 sialoadenitis)

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 more than 10 infiltrating IgG4-positive plasma cells / high power field and/or a ratio of IgG4/IgG positive plasma cells exceeding 40%

b. characteristic 'striform' fibrosis surrounding infiltrating cells

c. other useful findings for differential diagnosis

1. positive findings : lesions extending into the renal capsule, eosinophil infiltration, well-defined reginal lesion distribution, marked 'striform' fibrosis

2. negative findings : (necrotizing) angiitis, granulomatous lesion, neutrophil infiltration,

advanced tubulitis

Table 3 Diagnostic criteria for IgG4-related kidney disease

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 ≧ 135 mg/dl)
4. Histological 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 (sclero-)fibrosis surrounding nests of lymphocytes and/or plasma cells
5. Histological 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)

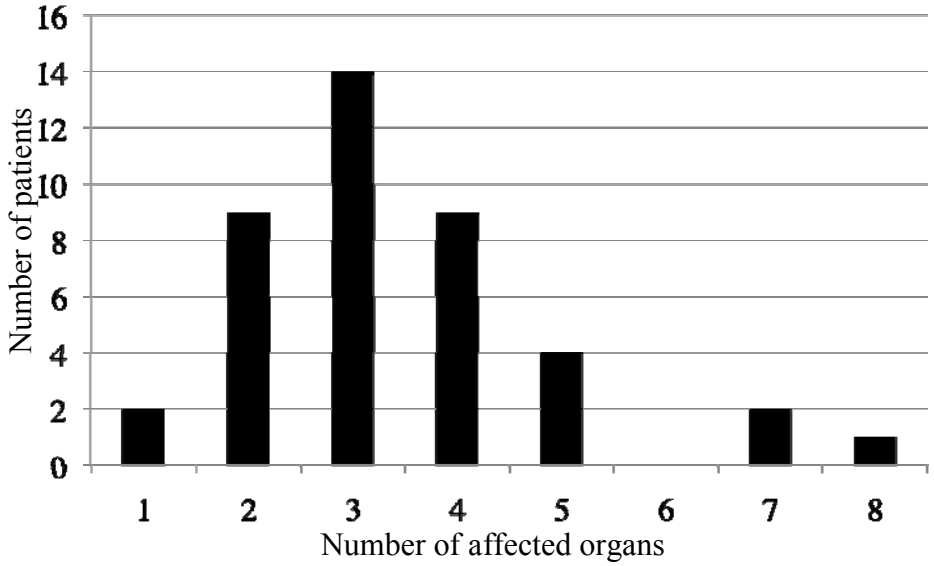
Probable : 1) + 4) a, b
2) + 4) a, b
2) + 5)
3) + 4) a, (b)

Possible : 1) + 3)
2) + 3)
1) + 4) a
2) + 4) a

Appendix:

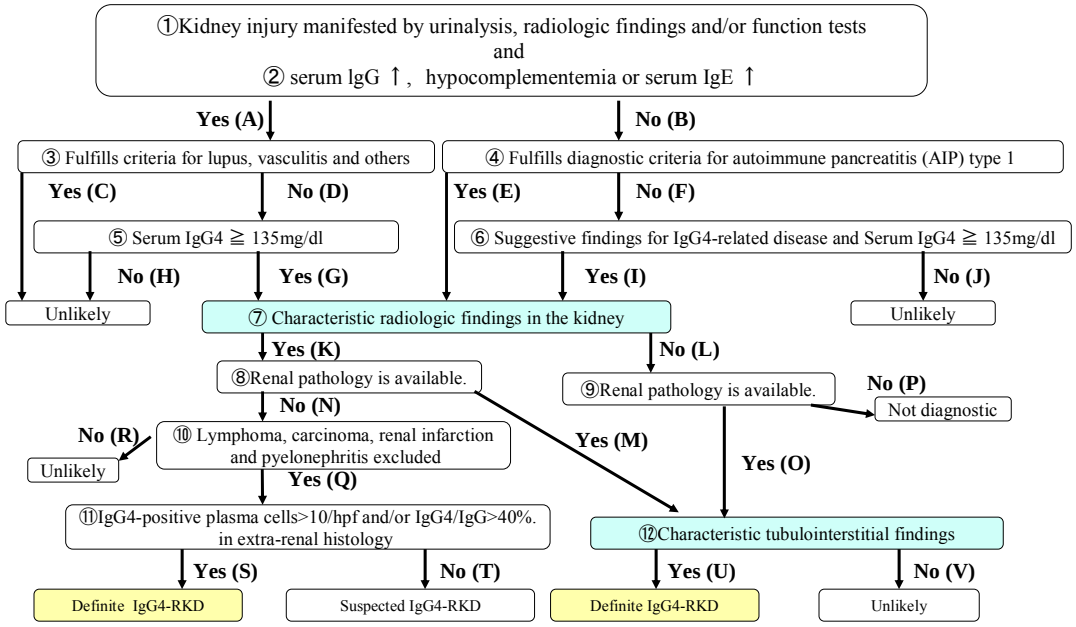
1. Clinically and histologically, the following diseases should be excluded:
   Wegener's granulomatosis, Churg-Strauss syndrome, extramedullary plasmacytoma
2. Radiologically, the following diseases should be excluded:
   Malignant lymphoma, urinary tract carcinomas, renal infarction and pyelonephritis
   (Rarely, Wegener's granulomatosis, sarcoidosis and metastatic carcinoma)

Figure 1. Frequency distribution of the number of affected organs




The mean number of affected organs was 3.4

Figure 2. Diagnostic algorithm for IgG4-related kidney disease (IgG4-RKD)



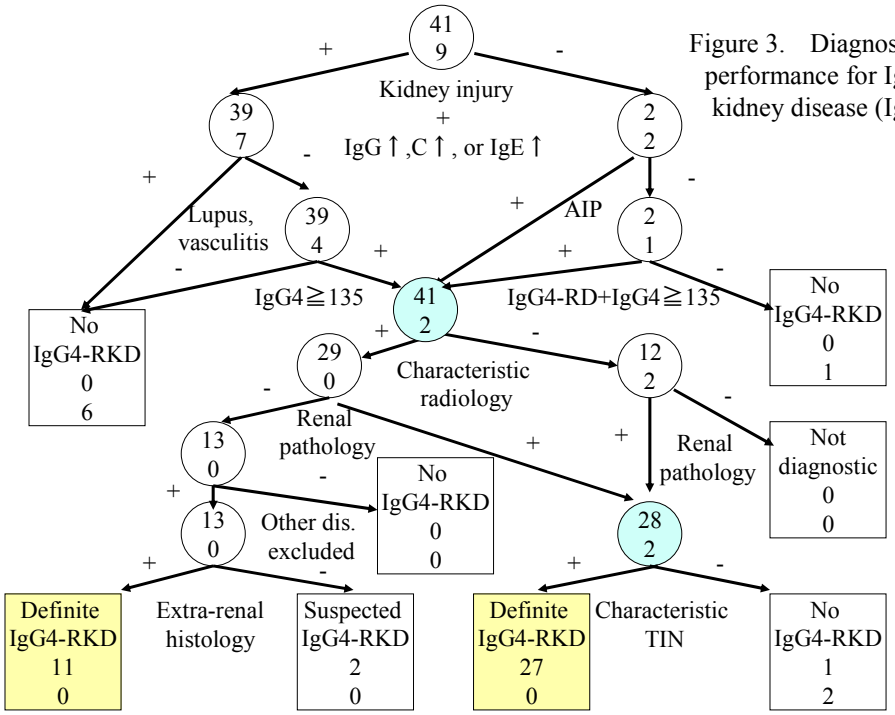



Figure 3. Diagnostic algorithm performance for IgG4-related kidney disease (IgG4-RKD)