Recent advances in IgG4-related kidney disease

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Abstract

Recent advances in the management and understanding of IgG4-related kidney disease (RKD) have emphasized the importance of urgent treatment in IgG4-related tubulointerstitial nephritis. On the other hand, to avoid long term glucocorticoid toxicity, strategies for early withdrawal of steroid or combination of immunosuppressants, such as rituximab, and the minimum dose of steroid have been pursued. However, disease recurrence after reducing or stopping steroid therapy hampers early withdrawal of glucocorticoid maintenance therapy. In addition, knowledge has accumulated in diagnostic approaches including differential diagnosis of anti-neutrophil...
cytoplasmic antibodies (ANCA)-associated vasculitis, idiopathic multicentric Castleman’s disease, and Rosai-Dorfman disease with kidney lesion, which leads to earlier and precise diagnosis of IgG4-RKD. This review summarizes recent progress in the differential diagnosis of IgG4-RKD and related treatment strategies, and recent topics of hypocomplementemia, membranous glomerulonephritis, and IgG4-related pyelitis and perirenal lesion.

1. Introduction

The renal parenchyma is one of the major targets of IgG4-related disease (IgG4-RD), with plasma cell-rich tubulointerstitial nephritis (TIN) being a frequent renal manifestation of IgG4-RD, which is called IgG4-TIN [1-3]. In addition to the kidneys, IgG4-RD affects various other organs throughout the body, including the lacrimal glands, salivary glands, pancreas, and periaorta/retroperitoneum, with about 7.0% to 24.6% of patients with IgG4-RD having kidney lesions [4-14]. The renal pelvis is also a major target of IgG4-RD, but most renal pelvic lesions result in little damage to patients clinically [1,2]. Although glomerular lesions are relatively rare, membranous glomerulonephritis (MGN) is the most common, with the response of these patients to glucocorticoid therapy being very different from that of patients with IgG4-TIN [15]. IgG4-related kidney disease (IgG4-RKD) is the comprehensive term for kidney lesions, which includes specific disease types such as TIN (IgG4-TIN), a variety of glomerular lesions including membranous glomerulonephritis, and renal pelvic lesions. This review describes important clinical updates on IgG4-related kidney disease (IgG4-RKD), in particular methods of diagnosis, differential diagnosis from other diseases, and treatment.

2. Diagnosis

IgG4-positive (IgG4+) plasma cell-rich TIN is a frequently encountered kidney lesion in patients with IgG4-RD. Because IgG4-RD also affects the kidney pelvis in a number of patients, IgG4-RKD has been defined as IgG4-RD involving the renal parenchyma and pelvis [1-3,16,17]. Although two sets of organ specific criteria for IgG4-RKD and IgG4-TIN had been developed [2,18], their usefulness had not been confirmed in a validation study. The diagnostic criteria for IgG4-TIN requires histopathological confirmation of IgG4+ plasma cell-rich TIN, while that for IgG4-RKD is either biopptic proof or characteristic imaging findings with or without biopptic proof. In 2020, the 2011 Japanese diagnostic criteria for IgG4-RKD were evaluated in a study involving 55 patients with IgG4-RKD and 50 patients with conditions mimicking IgG4-RKD [19]. That study found that the
Japanese criteria had sufficient specificity (90.0%), but relatively low sensitivity (72.7%) in diagnosis of IgG4-RKD. Fifteen patients with actual IgG4-RKD did not fulfill the diagnostic criteria due to the absence of storiform fibrosis and/or the inability to histopathologically confirm IgG4+ plasma cell infiltration into extrarenal organ(s). Although removal of the criterion “storiform fibrosis” from the diagnostic criteria increased the sensitivity of diagnosis from 72.7% to 94.5%, it reduced the specificity of diagnosis from 90.0% to 76.0%. In contrast, most true negative patients had lesions in other representative organs, including the pancreas, lacrimal glands, salivary glands, and/or periaorta/retroperitoneum, although these lesions were not histopathologically confirmed. The inclusion of clinical and/or imaging findings of these other organ lesions improved the sensitivity of IgG4-RKD diagnosis from 72.7% to 90.1% without affecting specificity. These results led to the formulation of new 2020 diagnostic criteria for IgG4-RKD (Table 1).

In 2019, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed alternative classification criteria for IgG4-RD [16,17]. These criteria were validated in 55 patients with IgG4-RKD and in 50 patients with conditions mimicking IgG4-RKD. The ACR/EULAR criteria had a sensitivity of 90.9% and a specificity of 98.0% [20], perhaps because these criteria excluded patients with IgG4+ plasma cell-rich TIN associated with conditions mimicking IgG4-RD, most patients with IgG4-RKD (92.7%) underwent renal biopsy, and 74.5% of patients with IgG4-RKD had typical extrarenal lesions that were clinically or radiologically confirmed. These findings indicated that the ACR/EULAR criteria for IgG4-RD could diagnose most patients with IgG4-RKD as having IgG4-RD.

3. Differential diagnosis
   a. ANCA-associated vasculitis

   Some patients with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) have plasma cell-rich TIN with many IgG4+ plasma cells in kidney lesions [21-23]. Thus, patients with AAV and increased numbers of IgG4+ plasma cells in the kidneys can be misdiagnosed as having IgG4-RD. Similarly, because serum IgG4 levels are elevated in a subgroup of AAV patients, particularly in those with eosinophilic granulomatosis with polyangiitis (EGPA) [22] or granulomatosis with polyangiitis (GPA) [23], AAV patients with elevated serum IgG4 levels can be misdiagnosed as having an overlap of AAV and IgG4-RD. Therefore, the 2019 ACR/EULAR classification criteria for IgG4-RD define positivity for anti-proteinase (PR) 3 or anti-myeloperoxidase (MPO) ANCA by ELISA as excluding a diagnosis of IgG4-RD [16,17]. The key points to differentiate between IgG4-RKD and AAV are summarized in Table 2.
ANCA positivity in patients with high serum IgG4 concentrations does not always indicate a diagnosis of AAV rather than of IgG4-RD [24,25]. An analysis of 162 patients with IgG4-RD showed that, although four of these patients had elevated serum ANCA levels by ELISA, none had true AAV; rather, all four were serologically positive for ANCA with true IgG4-RD [24]. This finding suggests that ANCA-positivity alone, without clinical or histopathological features of AAV such as necrotizing vasculitis or primary granulomatous formation, was insufficient to rule out IgG4-RD. Similarly, an analysis of 29 patients with IgG4-RD found that although three (10.3%) of these patients had low ANCA titers, none overlapped with AAV, with all three being diagnosed with IgG4-RD, not AAV [26]. An analysis of ANCA in 31 patients with IgG4-RD by indirect immunofluorescence microscopy (IIF) or ELISA [25] found that 14 patients were ANCA positive by IIF and five by ELISA (PR3- or MPO-ANCA), only one patient was diagnosed with an overlap of AAV and IgG4-RD, whereas the others were diagnosed with IgG4-RD. Furthermore, an analysis of 18 patients who fulfilled both the ACR and Chapel Hill criteria for AAV and the Comprehensive Diagnostic Criteria for IgG4-RD found that two of these patients had features typical of IgG4-TIN with neutrophilic infiltrates, a pathological feature characteristic of AAV, supporting the overlap of these two diseases [27].

These findings suggest the need for careful differential diagnoses of patients with the clinical and histopathological features of IgG4-RD and ANCA-positivity. Moreover, because the overlap of AAV and IgG4-RD is extremely rare, such a diagnosis should be made only in patients with histopathologically confirmed features of both IgG4-RD and AAV, as most patients suspected of having an overlap IgG4-RD and AAV actually had only one of these conditions.

b. Multicentric Castleman’s disease

Idiopathic multicentric Castleman’s disease (iMCD) usually affects the lymph nodes, although extra-nodal lesions have been reported [28-32]. These extra-nodal lesions are usually present in the lungs and/or skin, iMCD can also affect the kidneys and retroperitoneum [33]. We recently described two patients with serologic, histopathological and radiologic features similar to those of IgG4-RD [34]. Histopathological findings included plasma cell-rich tubulointerstitial nephritis with copious IgG4-positive plasma cells, findings similar in patients with IgG4-RD and iMCD. A recent review article showed that about 73.3% of patients with iMCD have elevated serum IgG4 levels [35], but their response to glucocorticoids, serum CRP levels and extra-nodal involvement differed markedly from those of patients with IgG4-RD. Moreover, although IgG4-RD frequently involves the
lacrimal glands, salivary glands and pancreas, these organs are rarely involved in patients with iMCD. In addition, although patients with IgG4-RD respond well to glucocorticoids, the response of patients with iMCD to steroids is sometimes partial, with these patients frequently needing additional treatment, with, for example, immunosuppressants and/or anti-IL-6 therapy [34,35]. Finally, although serum CRP levels are usually elevated in patients with iMCD, reflecting hyper IL-6 disease, serum CRP concentrations are usually normal or slightly elevated in patients with IgG4-RD [34,35]. Whereas serum IgA levels are often elevated in patients with iMCD, those are usually within normal range in patients with IgG4-RD [35]. Although it has been shown that anti-IgA immunostaining of affected lymph node may be useful to differentiate these two diseases [36], no data regarding IgA immunostaining of kidney lesions associated with iMCD or IgG4-RD is currently available. The key points to differentiate between IgG4-RD and iMCD are summarized in Table 3 [37,38].

c. Rosai-Dorfman disease

The 2019 ACR/EULAR classification criteria for IgG4-RD exclude patients with Rosai-Dorfman disease (RDD), a condition mimicking IgG4-RD. RDD has features of a macrophage/histiocytic disorder, with S100-positive macrophages demonstrating emperipolesis [16,17]. Histopathologically, histiocyte infiltration into affected organs is frequent, with many lymphoplasmacytic infiltrates in the affected organs of some patients, including a subset of RDD patients characterized by copious IgG4-positive plasma cell infiltrates [39,40]. Although RDD mainly affects the lymph nodes (nodal RDD), about 92% of patients were found to have extranodal RDD, with about 9% having kidney lesions [41]. A recent case report described infiltration by many IgG4-positive plasma cells into a kidney lesion in a patient with RDD [42], suggesting that histopathological features of IgG4-RKD could be present in some patients with RDD in kidney lesions. Importantly, the presence of S100-positive macrophages in the kidney lesion was a characteristic feature that differentiated RDD from IgG4-TIN in this patient.

4. Membranous glomerulonephritis

Membranous glomerulonephritis (MGN) is a representative glomerular disease of IgG4-RD, with about 7% of patients with IgG4-RKD reported to have MGN [15]. Although a variety of glomerular lesions associated with IgG4-RD have been reported, the presence of a nephrotic level of proteinuria in patients with IgG4-RD suggests that MGN may be the most likely overlapping glomerular lesion. Interestingly, the first patient reported to have IgG4-TIN also had MGN, with subepithelial electron dense deposits in the glomerular basement membrane.
(GBM) and focal effacement of podocyte foot processes on electron microscopy [43]. Since then, more than 30 patients have been reported to have MGN associated with IgG4-RD [15, 43-66]. A review of these patients (Table 4) showed that 62% of patients had concomitant tubulointerstitial nephritis, whereas 38% had only MGN without IgG4-TIN in the kidneys [15, 43-66]. IgG4-RD associated lesions in other organs, such as autoimmune pancreatitis or IgG4-related dacryoadenitis and sialadenitis, and MGN occur simultaneously in 44% of patients, whereas IgG4-RD occurs one to six years before the onset of MGN in most remaining patients. Although very rare, IgG4-RD developing during the clinical course of idiopathic MGN was observed in three patients. Most patients with IgG4-RD and MGN were treated with glucocorticoid (steroid) alone or in combination with immunosuppressants, although eight (26%) of the 31 patients experienced recurrence(s). Interestingly, the responses to steroids differed in patients with IgG4-TIN and IgG4-MGN. Glucocorticoid monotherapy may be only partially effective in treating IgG4-MGN, with some of these patients requiring additional immunosuppressants to reduce proteinuria.

Although almost all patients with IgG4-MGN were negative for anti-M-type phospholipase A2 receptor (PLA2R) antibody, suggesting that IgG4-MGN was secondary, two patients with IgG4-TIN and MGN were found to be positive on immunostaining with anti-PLA2R antibody [62,65] and one patient was positive for serum anti-PLA2R antibody [57]. The mechanism underlying the development of MGN in IgG4-RD includes C1q deposition in the glomerular basement membrane (GBM), as observed in ten (42%) of 24 patients [15, 43-66]. Of the three complement activation pathways, i.e., the classical, alternative, and lectin pathways, only the classical pathway included C1q activation. C1q immunostaining is usually negative in patients with primary MGN, but positive in patients with secondary MGN, such as lupus nephritis. In addition, some patients with IgG4-MGN are positive for anti-PLA2R antibodies, suggesting the involvement of the lectin pathway in some but not all patients with IgG4-MGN [45]. Evaluation of IgG subclasses deposited in the GBM showed that IgG4 is predominant in most patients, although IgG1 [57,60], IgG2 [15,47], and IgG3 [48] dominance has also been reported.

Questions remain regarding the relationship between IgG4-TIN and IgG4-MGN. For example, it has not yet been determined whether IgG4-MGN has a specific relationship with IgG4-producing plasma cells or whether IgG4-positive plasma cells that produce IgG4 molecules in TIN lesions target unknown antigens in the deposits on the GBM. Additional studies are needed to resolve the pathophysiological significance of MGN in IgG4-RD.

5. Hypocomplementemia
Hypocomplementemia is a major laboratory feature of IgG4-RD [1-3,16,17]. Lupus nephritis (LN) is a representative disease, in which activation of the complement system plays a key role in inducing renal tissue damage through immune complex formation. Severe hypocomplementemia compatible with LN has been encountered in more than 50% of untreated patients with IgG4-TIN [1-3], but its significance in the pathogenesis of IgG4-RD or as a mere biomarker of this disease has not been determined. We show the comparison of clinical and serological features between IgG4-related kidney disease with and without hypocomplementemia [68] (Supplemental table 1). The possibility of the frequent recurrence of IgG4-RD indicates a need for maintenance glucocorticoid therapy or alternative agents such as rituximab [69]. Because IgG4-RD is usually asymptomatic or only slightly symptomatic, an ideal biomarker is necessary to monitor any relapses [69]. Although circulating plasmablasts may be a promising candidate biomarker [70], their evaluation in daily clinical practice is unrealistic at present. Monitoring of complement titer may be useful for the early detection of metachronous or recurrent lesions in patients with IgG4-RD, particularly those with IgG4-TIN [68,71]. More experience with monitoring serum complement levels in patients with IgG4-RD is needed to determine whether serum complement titer can serve as a biomarker of IgG4-RD.

a. A representative case summary

Because granular deposits of IgG4 and/or C3 have been detected only in the tubular basement membrane (TBM) of affected areas but are rarely detected in the TBM of normal tubules (unaffected area) [18, 21, 72], IgG4 and/or C3 deposits have been regarded as the result, not the cause, of IgG4-TIN. We describe here the clinical findings in a patient with IgG4-RD who experienced hypocomplementemia prior to the development of TIN. Findings in this patient suggest a possible direct causative relationship between hypocomplementemia and the development of IgG4-TIN.

Patient

A 72-year-old Japanese man visited our hospital because of a 2-month history of bilateral submandibular masses without tenderness. His serum IgG4 level was 364 mg/dL (normal; <135 mg/dL), and IgG4-RD was suspected. Contrast-enhanced computed tomography (CT) showed swelling of the bilateral submandibular glands, left supraclavicular lymph node and mediastinal lymph nodes without abdominal abnormalities. Imaging analysis and physical examination did not detect enlargement of the lacrimal and parotid glands. A submandibular gland biopsy showed a diffuse lymphoplasmacytic infiltrate with lymphoid follicles and atrophic
acini. The absence of immunoglobulin light chain restriction supported suspected non-neoplastic inflammation. Although he was negative for typical storiform fibrosis, the presence of obstructive phlebitis and many IgG4 positive plasma cell (IgG4+PC) infiltrates resulted in a diagnosis of IgG4-RD. Because his IgG4-RD did not involve any critical organs, the patient elected to undergo observational follow-up without glucocorticoid administration. At that time, his CH50, C3, and C4 concentrations were 19 U/mL (normal range; 32-47 U/mL), 75 mg/dL (normal range; 65-135 mg/dL), and 7 mg/dL (normal range; 13-35 mg/dL), respectively. His serum IgG was slightly increased (2,000 mg/dL), with mild eosinophilia. Renal function, liver function, and electrolytes were normal.

Although he had no new symptoms, his complement concentrations gradually decreased, with CH50, C3, and C4 concentrations 9 months later declining to 0 U/mL, 32 mg/dL and 3 mg/dL, respectively, accompanied by increases in his serum IgG (3,426 mg/dL) and IgG4 (1,230 mg/dL) concentrations (Figure 1). Contrast-enhanced CT showed newly developed pancreatic tail swelling and thickening of the walls of the abdominal aorta and common iliac arteries, in addition to new multiple small peripheral cortical nodules with rim-like lesions in both kidneys (Figure 2). Because the pancreatic lesion was restricted to the tail of the pancreas, he had no subjective symptoms such as abdominal or back pain or signs such as jaundice. Thus, despite imaging analysis showing multiple new lesions, the patient remained completely asymptomatic.

Urinalysis showed no evidence of proteinuria or leukocyturia, and his renal function was normal. A renal biopsy showed a small lesion with lymphoplasmacytic infiltration by IgG4+PC, but without obvious fibrosis. The patient was successfully treated with glucocorticoid, with almost all imaging abnormalities having disappeared and serum complement concentrations becoming normalized 1 year after starting glucocorticoid therapy. Thirty-six months after starting glucocorticoid therapy, the patient was continued on maintenance treatment with 5 mg/day prednisolone (PSL). Almost all lesions had improved substantially, with only a very mild scar in the pancreas, and his serum concentrations of CH50 (65 U/mL), C3 119 (mg/dL) and C4 (24 mg/dL) were normal. These findings suggested that hypocomplementemia may be a direct cause of IgG4-TIN.

6. IgG4-related pyelitis and periureteral lesion

The renal pelvis and ureter can be affected in IgG4-RD [73,74]. Because renal pelvis wall thickening with a smooth intraluminal surface is frequently observed on imaging of patients with IgG4-RD (Figure 3A, B) [2], the 2019 ACR/EULAR classification criteria for IgG4-RD regard this lesion as a kidney manifestation of IgG4-RD [16,17]. In the absence of involvement of other representative organs in IgG4-RD, renal pelvic and periureteral
lesions may be mistakenly diagnosed as ureteral malignancies, leading to nephrectomy [75,76]. Although deterioration of renal function is rarely observed in patients with renal pelvic lesions, ureteral lesions can lead to hydronephrosis, reducing renal function. Histopathologically, renal pelvic and ureteral lesions are very similar to lacrimal gland and salivary gland lesions, which resemble lymph nodes with many lymphoid follicles (Figure 3C, D) [73]. In contrast, lymphoid follicles are very rare in renal parenchymal lesions.

7. Treatment

Subclinical disease in a subgroup of patients with IgG4-RD can lead to severe, irreversible damage to affected organs [77]. Urgent treatment is recommended for patients with IgG4-TIN to avoid irreversible kidney damage [77]. Because almost all patients with IgG4-RD respond well to glucocorticoid therapy, glucocorticoid is a first-line drug for inducing remission. A meta-analysis of five observational studies that included 140 patients showed that the mean starting dose of PSL in patients with kidney lesions was 42.7 mg/day [78], a dose higher than that in patients with salivary gland (27.6 mg/day), pancreas/biliary tract (34.7 mg/day), ocular (39.0 mg/day), and lymph node/skin lesions (20.0 mg/day). However, high dose induction therapy may not be needed to stop the progression of organ damage or frequent relapse in patients with IgG4-RKD [79]. That study found that induction treatment with 0.5 mg/kg/day PSL was sufficient in patients with IgG4-TIN and renal dysfunction. Following the recovery of renal function, these patients could be maintained for more than 36 months on low-dose glucocorticoid maintenance therapy (≤5 mg/day PSL). Similarly, relapse rates were found to differ significantly in patients with type 1 autoimmune pancreatitis who were treated with maintenance PSL doses of <5 mg/day and ≥5 mg/day, indicating that a maintenance dose of 5 mg/day PSL could reduce the relapse rate [80].

A recent long-term retrospective study showed that most patients responded well to glucocorticoid therapy, with rapid improvement of renal function, with the recovery of renal function maintained for about 5 years, even in patients with low eGFR (stage 4 or 5) [81].

That study also found that patients with histological stage B (active cellular infiltration with mild but distinct fibrosis) had significantly lower eGFR than those with histological stage A (active cellular infiltration with little fibrosis) throughout the entire period, suggesting that already advanced histological fibrosis may be irreversible, despite glucocorticoid or immunosuppressant therapy. Several patients with IgG4-TIN receiving maintenance glucocorticoid therapy have been followed-up for ≥10 years. Although only anecdotal evidence is currently available, with no studies following up patients for more than 10 years, the long-term preservation of renal
function is not as bad as we had previously feared (Figure 4A,4B). Actually, even in some patients who experienced several recurrences and re-escalation of the dose of PSL (Figure 4A,4B), maintenance glucocorticoid therapy prevented end stage renal failure. However, the effects of glucocorticoid toxicity on long-term prognosis may have been underestimated. Efforts are underway to reduce maintenance glucocorticoid doses as much as possible, thereby minimizing the possibility of glucocorticoid toxicity.

In contrast to results showing long-term preservation of renal function in patients with IgG4-TIN, partial renal damage may be unavoidable in some patients [82]. Imaging analysis showed partial atrophy of the kidneys in 11 (47.8%) of 23 patients after successful glucocorticoid therapy even if renal function had been preserved. The average eGFR in the patients who developed partial atrophy of the kidneys was 85.5 ml/min/1.73m² at the last review. Because pre-treatment eGFR was a risk factor for the development of renal atrophy, it was recommended that glucocorticoid therapy for IgG4-TIN be started as early as possible.

The adverse effects of glucocorticoid may be avoided by the addition of an immunosuppressant such as azathioprine. Rituximab is an alternative possibility with promising results [83,84]. However, since a retrospective study found that 37% of patients treated with rituximab experienced relapses [85], maintenance therapy remains important even in patients receiving rituximab-based treatment for IgG4-RD.

8. Conclusion

The high frequency of relapse is an important feature of IgG4-RD. Reductions in serum complement levels may be an important biomarker of relapse in patients with IgG4-TIN. Future analyses of pathogenesis may contribute to the development of treatment strategies.

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Conflict of interest

None.

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Figure legends

**Figure 1**
Clinical course of IgG4-RD in this patient. CT, computed tomography

![Figure 1. Clinical course](image)

**Figure 2**
Contrast-enhanced computed tomography findings before (A–D) and after (E–H) the development of metachronous new lesions in the patient with IgG4-related disease. E, newly developed swelling of the
pancreatic tail; F: newly developed thickening of the walls of the common iliac arteries; G,H: newly developed small peripheral cortical nodules with rim-like lesions in the both kidneys.

Figure. 3

Contrast-enhanced computed tomography findings in patients with IgG4-related pyelitis. Bilateral (A) or unilateral (B) renal pelvis wall thickening with a smooth intraluminal surface is seen. Light microscopy findings in the periureteral lesion of a patient, showing that (C) the ureteral lesions resemble lymph nodes with many lymphoid follicles (hematoxylin and eosin staining x10) and (D) the presence of many IgG4-positive plasma cell infiltrates (IgG4 immunostaining x100).
A patient (case 1) with IgG4-related kidney disease followed-up for more than 10 years while receiving successful glucocorticoid therapy: Although the patient experienced kidney recurrences twice, maintenance steroid therapy prevented end stage renal failure. Serum creatinine concentrations at the initial and latest visits were 7.26 mg/dL and 1.58 mg/dL, respectively.

*PSL, prednisolone*

A patient (case 2) with IgG4-related kidney disease followed-up for more than 10 years. Although this patient experienced kidney recurrences twice and received methylprednisolone pulse therapy, his serum creatinine level showed almost no change throughout the clinical course of disease. Diagnostic imaging, however, showed the development of partial renal atrophy, suggesting permanent renal damage.

*AZA, azathioprine; mPSL, methyl prednisolone; PSL, prednisolone*

**Figure 4A. Ten-year clinical course in case 1**

![Graph showing clinical course](image-url)
Supplemental figure 1

Immunofluorescence findings in a representative patient with IgG4-related tubulointerstitial nephritis. Granular deposits of IgG subclasses in the tubular basement membrane are seen. Not only IgG4 but also other subclasses of IgG are deposited in the tubular basement membrane.
Table 1 Diagnostic criteria for IgG4-related kidney disease (IgG4-RKD) 2020

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 > 135mg/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. Extra-renal organ(s):
   a. Dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells > 10/HPF and IgG4/IgG-positive plasma cells > 40% in extra-renal organ(s).
   b. Imaging or clinical findings in extra-renal organ(s): existence of one of the following items:
      1) Bilateral lacrimal gland swelling
      2) Bilateral submandibular or parotid gland swelling
      3) Imaging findings compatible with type 1 autoimmune pancreatitis
      4) Imaging features of retroperitoneal fibrosis
Appendix
1. Clinically and histologically, exclusion of the following diseases should be considered: ANCA-associated vasculitis, multicentric Castleman’s disease, malignant lymphoma, and extramedullary plasmacytoma.
2. Radiologically, exclusion of the following diseases should be considered: malignant lymphoma, urinary tract carcinoma, renal infarction and pyelonephritis (rarely, granulomatosis with polyangiitis, sarcoidosis and metastatic carcinoma).

Table 2. Differential diagnosis between IgG4-related kidney disease and ANCA-associated vasculitis

|                          | IgG4-related kidney disease | ANCA-associated vasculitis |
|--------------------------|----------------------------|---------------------------|
| Serum IgG level          | Elevated (rarely normal)   | Elevated or normal        |
| MPO or PR3-ANCA          | Usually - (rarely low titer positive) | +                          |
| Serum CRP level          | Normal                     | Elevated                  |
| Response to glucocorticoid| Good                      | Partially effective       |
| Salivary gland lesion    | Often                      | Quite rare                |
| Lacrimal gland lesion    | Often                      | Quite rare                |
| Pancreas lesion          | Often                      | Quite rare                |
| Histopathological findings|                           |                           |
| Necrotizing vasculitis   | -                         | +                         |
| Primary granulomatous formation| -                        | + (GPA or EGPA)          |
| Prominent neutrophil infiltrate| -                        | +                         |

ANCA, anti-neutrophil cytoplasmic antibodies; CRP, C-reactive protein; EGPA, eosinophilic granulomatous polyangiitis; GPA, granulomatosis with polyangiitis.
granulomatosis with polyangiitis; GPA, ranulomatosis with polyangiitis; MPO, myeloperoxidase; PR, proteinase

Table 3. Differential diagnosis between IgG4-related disease and idiopathic multicentric Castleman's disease

|                           | IgG4-related disease | Idiopathic multicentric Castleman's disease |
|---------------------------|----------------------|---------------------------------------------|
| Serum IgG level           | ↑                    | ↑                                          |
| Serum IgA level           | Normal               |                                             |
| Serum IgG4/IgG ratio      | ↑                    | Normal or slightly elevated                |
| Serum CRP level           | Normal               | ↑                                          |
| Thrombocytosis            | No                   | Yes                                        |
| Anemia                    | No                   | Yes                                        |
| Hypoalbuminemia           | No                   | Yes                                        |
| Hypcholesterolemia        | No                   | Yes                                        |
| Response to glucocorticoid| Good                 | Partially effective                        |
| Histopathological finding| + or -               |                                             |
| Storiform fibrosis        | + or -               | -                                          |

CRP, C-reactive protein

Table 4. Summary of previously reported cases with IgG4-related membranous glomerulonephritis

| Case | Age (years) | Gender | TIN | PLAR2 R | Cr at diagnosis (mg/dL) | u-protein at diagnosis (g/day) | Relapses | Treatment | Most dominant IgG subclass(s) in GBM | C1q in GBM | The timing of occurrence of MGN | Refs |
|------|-------------|--------|-----|---------|-------------------------|-------------------------------|----------|-----------|-----------------------------------|-----------|----------------------------------|------|
| 1    | 64          | M      | +   | -       | 4.5                     | 1.5                           | 0        | mPSL      | ND                                | ND        | G4 = MGN                         | [43] |
| 2    | 67          | M      | +   | ND      | 3.4                     | 2.4                           | 0        | PSL       | ND                                | ND        | G4 → MGN                        | [44] |
| 3    | 83          | M      | +   | ND      | 1.48                    | 2.3                           | 0        | PSL       | G1=G4                             | -         | G4 = MGN                        | [45] |
|   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|
|   |   |   |   |   |   |   |   |
| 4 | 68 | M | - | ND | 1.2 | 1.5 | 0 | PSL | G4 | ND | G4 → MGN | [46] |
| 5 | 67 | F | + | - | 1.2 | 4 | 0 | PSL | G2 | - | G4 = MGN | [47] |
| 6 | 54 | M | - | - | 1.15 | 3.9 | 1 | RTX | G3 | + | G4 → MGN | [48] |
| 7 | 72 | M | + | ND | Normal | 15.6 | NA | PSL+RTX | ND | + | G4 = MGN | [49] |
| 8 | 59 | M | - | - | 0.7 | 4.3 | 1 | PSL | G1=G4 | - | MGN → G4 | [50] |
| 9 | 67 | F | + | - | 1.2 | 4 | 0 | PSL | G2 | - | G4 → MGN? | [15] |
|10 | 75 | M | + | - | 6.6 | 16 | 0 | PSL | G4 | - | G4 = MGN? | [15] |
|11 | 53 | M | - | - | 0.8 | 16 | 1 | PSL+MMF | G4 | - | G4 → MGN? | [15] |
|12 | 50 | M | - | - | 1.3 | 3.5 | 0 | RTX+MMF | ND | - | G4 → MGN? | [15] |
|13 | 46 | F | + | - | ND | >3.5 | 0 | Transplant | ND | - | G4 → MGN? | [15] |
|14 | 67 | M | + | - | 1.8 | 4.5 | 0 | PSL+IVCY | G4 | - | G4 → MGN? | [15] |
|15 | 65 | F | - | ND | 0.7 | 8.5 | 0 | PSL+MMF | ND | + | G4 → MGN? | [15] |
|16 | 64 | M | + | - | 3.4 | 1.7 | NA | unknown | ND | - | G4 = MGN | [15] |
|17 | 34 | M | - | - | 1.6 | 12.4 | NA | unknown | G4 | + | G4 → MGN? | [15] |
|18 | 50 | M | - | ND | 0.87 | 9.4 | 2 | mPSL+PSL+CY | G1=G4 | unknown | G4 → MGN | [51] |
|19 | 55 | M | + | ND | 0.8 | 5.5 | 0 | mPSL | G4 | unknown | G4 → MGN | [52] |
|20 | 58 | M | - | ND | 0.7 | 15.7 | 1 | PSL+CsA+CY | G4 | - | G4 = MGN | [53] |
|21 | 69 | M | + | ND | 1 | 1.4 | 0 | PSL+MZM | G4 | + | G4 = MGN | [54] |
|22 | 80 | M | + | ND | 0.9 | 2.73 | 2 | PSL | G4 | + | G4 = MGN | [54] |
|23 | 54 | M | + | - | 7.4 | 8.3 | 0 | PSL | ND | unknown | G4 = MGN | [55] |
|24 | 63 | M | + | ND | 2.8 | 1.8 | 0 | mPSL | ND | - | G4 = MGN | [56] |
|25 | 64 | M | - | Ab+ | 2.58 | 12 | 0 | PSL+CY | G1 | unknown | G4 → MGN | [57] |
|26 | 40 | M | + | ND | 3.51 | >3.5 | 2 | GC | ND | unknown | G4 = MGN | [58] |
|27 | 62 | M | + | - | 2.5 | 2.22 | 0 | PSL | ND | - | G4 = MGN | [59] |
|28 | 58 | M | + | - | 0.8 | 12.2 | 0 | PSL+MZM+IVCY+CsA | G1 | + | G4 → MGN | [60] |
|   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|
| 25 | 81 | M  | + | ND | 2.09 | 2.78 | 0 | PSL | G4 | + | G4 = MGN | [61] |
| 30 | 45 | M  | - | IF + | 0.9 | 7 | 0 | PSL+RTX+CY | G4 | unknown | G4 → MGN | [62] |
| 31 | 70 | M  | - | - | 0 | PSL | G4 | unknown | MGN → G4 | [63] |
| 32 | 46 | M  | - | - | 1.09 | 5.23 | 1 | unknown | ND | - | MGN → G4 | [64] |
| 33 | 69 | M  | + | IF + | 1.24 | 12.8 | 0 | mPSL+PSL+LDL-A | G1=G4 | + | G4 = MGN | [65] |
| 34 | 62 | F  | + | - | 1.1 | 7 | 0 | mPSL, PSL | G4 | - | G4 → MGN | [66] |

TIN, tubulointerstitial nephritis; PLAR2R, anti-M-type phospholipase A2 receptor; Cr, creatinine; GBM, glomerular basement membrane; MGN, membranous glomerulonephritis; Refs, references; ND, not determined; Ab, antibodies; IF, immunofluorescent; NA, not available; mPSL, methylprednisolone; PSL, prednisolone; RTX, rituximab; MMF, mycophenolate mofetil; IVCY, intravenous cyclophosphamide; CsA, cyclosporin A; MZR, mizoribine; LDL-A, low-density lipoprotein apheresis.