

Perspective

# Immunoglobulin G4-related kidney disease: Pathogenesis, diagnosis, and treatment

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## Abstract

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized clinical entity that often involves multiple organs; it is characterized by high levels of serum immunoglobulin G4 (IgG4), dense infiltration of IgG4+ cells, and storiform fibrosis. Cellular immunity, particularly T cell-mediated immunity, has been implicated in the pathogenesis of IgG4-RD. The most frequent renal manifestations of IgG4-RD are IgG4-related tubulointerstitial nephritis, membranous glomerulonephropathy (MGN), and obstructive nephropathy secondary to urinary tract obstruction due to IgG4-related retroperitoneal fibrosis, prostatitis, or ureter inflammation. Kidney function impairment can be acute or chronic. In IgG4-MGN, proteinuria can be in the nephrotic range. The diagnosis of IgG4-related kidney disease should not be based solely on serum IgG4 levels or the number of tissue-infiltrating IgG4+ plasma cells. Diagnosis should be based on specific histopathological findings, confirmed by tissue immunostaining and an appropriate clinical context. Steroid treatment is the first-line therapy. For relapsing or refractory cases, immunosuppressants could be combined with steroids. In hydronephrosis patients, appropriate immunosuppressive therapy could preclude the implantation of a double J ureteral catheter.

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**Keywords:** IgG4; Kidney; Pathogenesis; Diagnosis; Treatment

## Introduction

In 2001, serum immunoglobulin (Ig) G4 elevation was discovered in the context of autoimmune pancreatitis (AIP).<sup>1</sup> The term “IgG4-related systemic disease”

was first introduced in 2003.<sup>2</sup> Since then, a new clinicopathologic entity and systemic fibroinflammatory condition, IgG4-related disease (IgG4-RD), has gradually been recognized. It can involve nearly any organ system. The disease usually has multiple organ involvement, but it can also affect only a single organ, including the meninges, orbits, salivary and lacrimal glands, lymph nodes, thyroid, lungs, mediastinum, biliary tree, pancreas, aorta, kidney and urinary bladder, skin, or nerves.<sup>3</sup> The affected tissues have similar features, including lymphoplasmacytic infiltration of IgG4+ cells, storiform fibrosis, and

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obliterative phlebitis. Most cases also have elevated serum overall IgG and IgG4 levels.

The term IgG4-related kidney disease (IgG4-RKD) refers to any pattern of renal involvement in IgG4-RD.<sup>4</sup> The glomeruli, tubules, and interstitial vessels, as well as the renal pelvis, may all be affected. The most common IgG4-RKD is IgG4-related tubulointerstitial nephritis (IgG4-TIN). Approximately 15%–24.6% of IgG4-RD patients have IgG4-TIN.<sup>5,6</sup>

### What is IgG4?

IgG has 4 subclasses, from 1 to 4. In healthy individuals, IgG4 is the least abundant, accounting for less than 5% of total IgG.<sup>7</sup> IgG4 antibodies can be produced after prolonged antigen exposure. This process is believed to be controlled by T helper (Th) 2 cells.<sup>7,8</sup> Th2 cytokines like interleukin (IL)-4 enhance the production of IgE and IgG4, while the activation of regulatory T cells and the subsequent production of IL-10 shift the balance from IgE to IgG4.<sup>8</sup>

IgG4 antibodies are dynamic. They behave like monovalent antibodies. Their unique structure gives them distinct functions from the other IgG subclasses. The heavy chains of IgG4 molecules have inefficient disulphide bridges formed by non-covalent associations.

This phenomenon is induced by the proline-to-serine mutation in the hinge region.<sup>9</sup> Thus, “Fab arm exchange” occurs between IgG4 molecules. In Fab arm exchange, hemi-IgG4 molecules dissociate from each other and randomly recombine with distinct hemi-IgG4 molecules. The 2 recombined hemi-IgG4 molecules then have novel antigen-binding specificities (Fig. 1).<sup>7,10</sup> The newly formed IgG4 antibodies become “bi-specific” and asymmetric, and have the ability to bind 2 different antigens. The hetero-bivalent structure of IgG4 antibodies causes them to behave as monovalent antibodies that are unable to form large immune complexes. IgG4 antibodies have low affinity for both Fc $\gamma$  receptors and C1q, which limits their ability to activate classical complement pathway immune responses.<sup>11</sup> These distinct characteristics have led IgG4 to be considered a “non-inflammatory” antibody. In IgE-mediated allergy, IgG4 antibodies usually appear when symptoms are decreasing. The presence of IgG4 antibodies in the allergic context indicates that tolerance-inducing and anti-inflammatory mechanisms have been activated.<sup>7</sup>

### The role of IgG4 in IgG4-RD

IgG4-RD derives its name from the elevated serum IgG4 concentrations in patients and the characteristic pathologic finding of abundant IgG4+ lymphoplasm

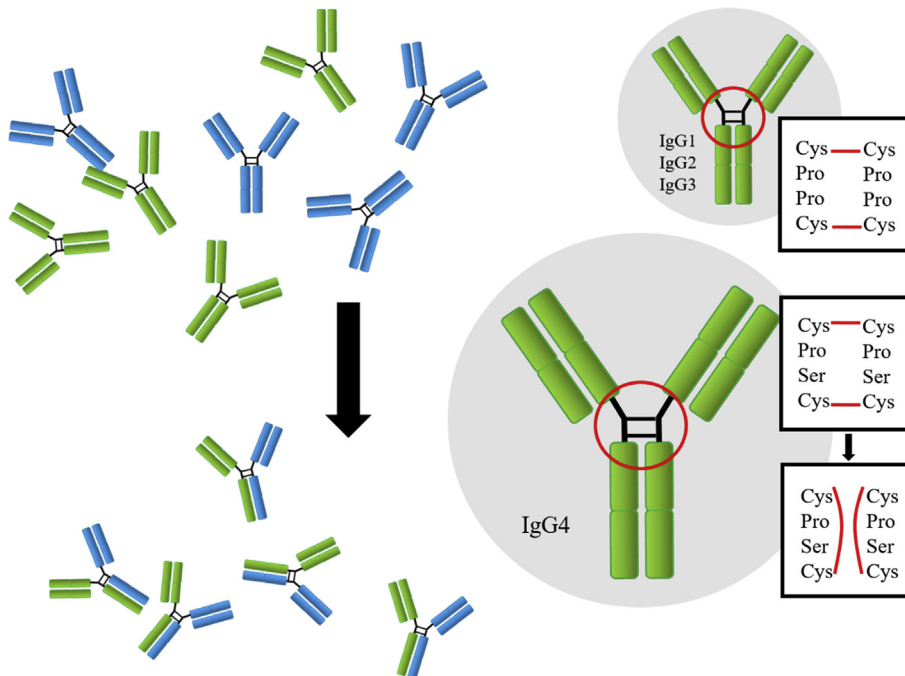


Fig. 1. The molecular basis of Fab arm exchange. IgG: immunoglobulin G; Cys: cysteine; Pro: proline; Ser: Serine.

cells in affected tissues. However, the role of IgG4 in the pathophysiology of IgG4-RD is still controversial.

Due to the non-inflammatory properties of IgG4 antibodies, the primary physiological function of IgG4 is to diminish, not incite or accelerate, chronic immune reactions. Thus, IgG4 may simply be overexpressed in response to an unknown initial inflammatory stimulus or an epiphenomenon, rather than as the disease driver. However, IgG4 can activate complement through other pathways, like the mannose-binding lectin pathway, or induce immune complex deposition in affected tissues.<sup>12</sup> Serum concentrations of IgG4 correlate with the number of organs involved.<sup>6</sup> In IgG4-TIN, IgG4 immune complexes and C3 were observed in the tubular basement membrane (TBM).<sup>5</sup> IgG4 may participate in the initiation of inflammation via these mechanisms.

### The possible pathogenesis of IgG4-RD and IgG4-RKD

IgG4-RD involves unrelated organs and systems. The affected tissues share similar histopathological

features. Based on these aspects, IgG4-RD should be considered a systemic disease.

Based on the infiltration of T cells, B cells, plasmablasts, and plasma cells into the affected organs, as well as the elevation of multiple inflammatory cytokines by oligoclonally expanded T and B cells, IgG4-RD could be characterized as an autoimmune disease. In the pathogenesis of IgG4-RD, the cellular immune system plays an important role. However, the triggers of IgG4-RD are unknown. Prolonged and chronic allergen exposure, infectious agents (such as *Helicobacter pylori*), and tissue damage induced by autoimmunity have all been considered as possible triggers. In the pathogenic model (Fig. 2), naïve/memory B cells and/or dendritic cells would present antigens from putative triggers to CD4+ T lymphocytes.<sup>10</sup> The signals from the B cells would polarize the T helper cells, which would differentiate into effector or memory T cells. The activated self-reactive T cells would facilitate germinal center formation and recruit naïve B cells into the germinal center, which would differentiate into plasmablasts or memory B cells.

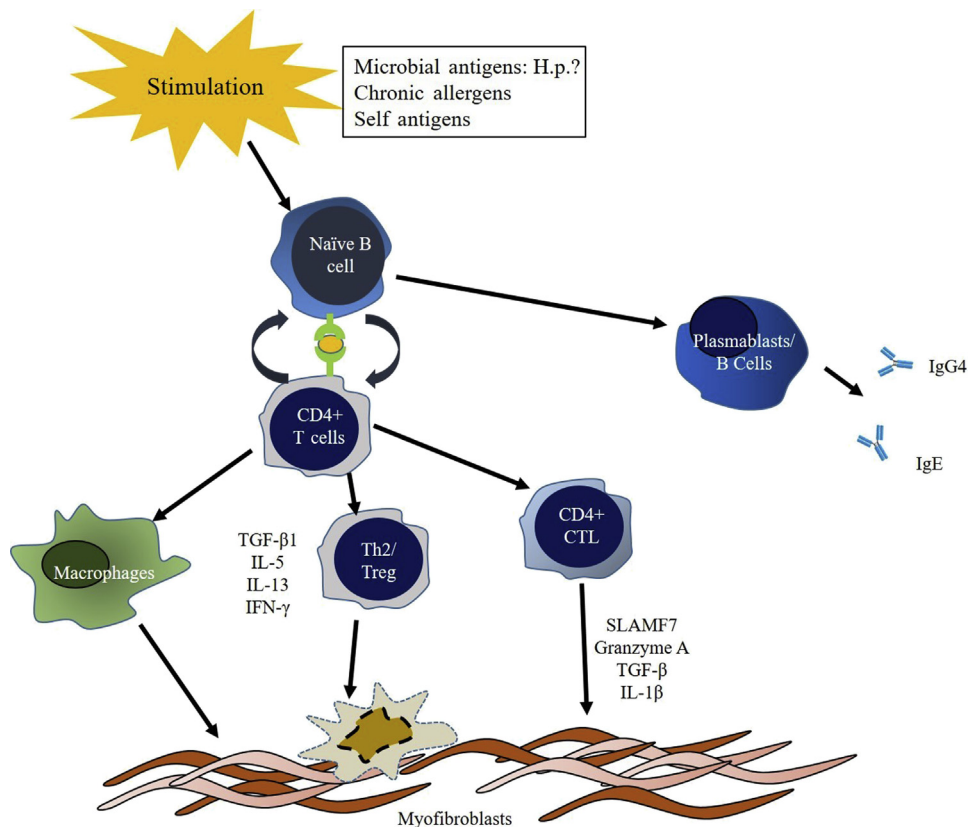


Fig. 2. The potential pathogenic model of IgG4-related disease. H.p: *Helicobacter pylori*; CD4: cluster of differentiation 4; TGF-β: transforming growth factor-β; IL: interleukin; IFN-γ: interferon-γ; Th2: T-helper 2; Treg: regulatory T cell; CD4+ CTL: CD4+ cytotoxic T lymphocyte; SLAMF7: signaling lymphocytic activation molecule F7; Ig: immunoglobulin.

Thus, a cycle of collaboration would be established between autoreactive T cells and B cells. The activated CD4+ Th2 and regulatory T cells would produce inflammatory cytokines, including IL-4, IL-5, IL-10, IL-13, interferon- $\gamma$  (IFN- $\gamma$ ), and transforming growth factor- $\beta$  (TGF- $\beta$ ). IL-4 and IL-10 would promote the differentiation of antigen-specific B cells into plasmablasts and plasma cells, and drive the switching of IgG antibodies to IgG4, in combination with the secretion of IgE. IL-5, IL-13, IFN- $\gamma$ , and TGF- $\beta$  would activate fibroblasts and inflammatory macrophages, which would mediate a dense storiform pattern of fibrosis.

B cells and T cells could engage in cross-talk, in which B cells would act as continuous antigen-presenting cells to Th2 cells, thereby maintaining CD4+ memory T cell activation and inducing prolonged proliferation of pathogenic T cells.

However, analysis of the polarization of circulating T cells in IgG4-RD patients has given conflicting results. Currently, more direct evidence for the role of Th1, Th2, and regulatory T cells in IgG4-RD pathogenesis is required.

Recently, Mattoo et al<sup>13</sup> identified clonally expanded CD4+ effector/memory T cells with a cytolytic phenotype (CD4+ cytotoxic T lymphocytes, CD4+ CTLs) in the peripheral blood and inflammatory tissue lesions of IgG4-RD patients. These CD4+ CTLs expressed signaling lymphocytic activation molecule F7 (SLAMF7), granzyme A, TGF- $\beta$ 1, and IL-1 $\beta$ . These findings support a role for cellular immunity in IgG4-RD.

Plasmablasts have also been found in the bloodstream of patients. These plasmablasts differentiated from CD20+ naïve B cells in germinal centers, and homed to the bone marrow where they differentiated into short-lived or long-lived plasma cells.<sup>14</sup> The expansion of plasmablasts was closely related to disease activity. In addition, several plasmablast-derived antibody clones from active IgG4-RD patients reacted with autoantigens in the cytosol of Hep2 cells.<sup>15</sup> These findings provided new evidence that IgG4-RD is an autoimmune disease.

Classically activated (M1) macrophages and alternatively activated (M2) macrophages have been identified in IgG4-RD patients; M1 macrophages are induced by Th1 responses, while M2 macrophages are induced by Th2-derived IL-4 and IL-13, and regulatory T cell-derived IL-10.<sup>16</sup> In patients with Mikulicz's disease, Furukawa et al<sup>17</sup> demonstrated that CD163+ M2 macrophage infiltration correlated with the degree of tissue fibrosis. In IgG4-related AIP,

activated macrophages secreted B cell-activating factor to induce B cell production of IgG4.<sup>18</sup>

The pathophysiology of IgG4-RKD is poorly understood compared to that of IgG4-RD. Most of the studies on the cytokines and lymphocytes involved in IgG4-RD have been in patients without kidney involvement.

In IgG4-RKD, no definite target antigens have been found. Most of the limited putative triggers for IgG4-RD were identified in AIP and sialadenitis, such as carbonic anhydrase II and IV in duct epithelia<sup>19</sup>; lactoferrin; amylase, alpha 2A; pancreatic trypsinogens and the pancreatic secretory trypsin inhibitor in acinar cells; and *Helicobacter pylori*.<sup>20–23</sup> It would be hard to explain renal involvement initiated by these stimuli.

In IgG4-TIN patients, IL-4, IL-10, and TGF- $\beta$  were expressed in kidney tissue.<sup>24</sup> This indicated that Th2 and regulatory T cells may play important roles in IgG4-TIN. Kawamura et al<sup>25</sup> showed that, in the kidney tissues of IgG4-RKD patients, TGF- $\beta$ 1+ cells and Foxp3+ cells colocalized in the interstitium. The ratios of interstitial TGF- $\beta$ 1+ to total infiltrating cells and Foxp3+ to CD3+ cells were higher than in Sjögren's syndrome and idiopathic TIN patients. There were correlations between the severity of fibrosis and the ratios of TGF- $\beta$ 1+ to total infiltrating cells, Foxp3+ to CD3+ cells, and ratio of IgG4+ to IgG+ plasma cells.

In IgG4-RKD, many questions remain to be answered. We need to know about the detailed cross-talk between different kinds of inflammatory cells in IgG4-RKD, the reasons that some patients have kidney-specific disease, and whether the IgG4 immune complexes in the TBM of IgG4-TIN patients and the glomerular basement membrane (GBM) in patients with membranous glomerulonephropathy (MGN) secondary to IgG4-RD indicate that humoral immunity is also involved in IgG4-RD pathogenesis.

## The clinical manifestations of IgG4-RKD

### Clinical features

IgG4-RKD predominantly affects middle-aged to elderly men.<sup>26,27</sup> Similar to IgG4-RD, it is a relapsing–remitting fibroinflammatory condition. Multiple organs or systems may be involved, as manifested in AIP, lymphadenopathy, retroperitoneal fibrosis, sclerosing cholangitis, dacryoadenitis, and sialadenitis. The other organs can be affected metachronously or simultaneously with the kidneys.

According to the definition of IgG4-RKD, any pattern of renal involvement in IgG4-RD qualifies as

IgG4-RKD.<sup>4</sup> Kidney impairment could be due to effects on the renal parenchyma and/or post-renal obstruction due to urinary tract, prostate, or posterior peritoneum (retroperitoneal fibrosis) involvement in IgG4-RD. IgG4-TIN is the most common kidney manifestation of IgG4-RD. Approximately 15%–24.6% of IgG4-RD patients have IgG4-TIN.<sup>5,6</sup> The second commonest kind of renal parenchyma involvement is MGN secondary to IgG4-RD. MGN is present in approximately 7% of kidney biopsy specimens from IgG4-RD patients.<sup>28</sup> Both MGN with and without IgG4-TIN have been reported.<sup>29–31</sup> As Alexander et al<sup>31</sup> reported in the largest series of IgG4-MGN cases, 55% of patients (5 of 9) had concurrent IgG4-related TIN.

Obstructive nephropathy is common in IgG4-RD. As indicated by the definition of IgG4-RKD,<sup>4</sup> this pattern of renal involvement should also be regarded as IgG4-RKD.

Most of the symptoms of IgG4-RKD are non-specific, including fatigue and lumbago. The major clinical features are progressive renal function decline and characteristic radiological changes, which account for nearly all of the patients who underwent renal biopsy.<sup>32</sup>

#### Laboratory features

Serum creatinine elevation, which is typically insidious, can be chronic or rapidly progressive.<sup>26,27</sup> In IgG4-RKD, proteinuria (typically tubular) was mild to moderate, and patients with MGN had nephrotic-range proteinuria.<sup>3,5,32</sup> Mild hematuria has been observed in a few cases.<sup>5</sup>

Elevated serum IgG and IgG4 (greater than 135 mg/dl) levels are common. Between 40% and 60% of IgG4-RD patients have hypocomplementemia, for complement C3 and C4.<sup>5,32</sup> Hypocomplementemia was more frequently found in IgG4-RKD patients than in IgG4-RD patients.<sup>32,33</sup> Thus, hypocomplementemia could be a hint for IgG4-TIN. Elevated serum IgE levels, peripheral eosinophilia, weak positivity for anti-nuclear antibodies (30%, but negative for specific antibodies associated with Sjögren's syndrome), and rheumatoid factor were also found in IgG4-RKD patients.

Serum C-reactive protein levels are usually normal in IgG4-RKD patients. This is a useful marker to distinguish IgG4-RD from Castleman disease or anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis.<sup>3</sup>

In patients with nephrotic-range proteinuria that indicated MGN secondary to IgG4-RD, serum anti-M-

type phospholipase A2 receptor (PLA2R) antibodies are usually negative.<sup>31,34,35</sup> The antibodies facilitate differentiation of these patients from those with primary MGN.

#### Imaging features

Contrast computed tomography (CT) is useful in diagnosis, as it delineates the characteristics and distribution of the renal lesions. Multiple round or wedge-shaped, low-density parenchymal lesions or diffuse, marked enlargement of the kidneys are common on contrast CT in IgG4-RD patients.<sup>32,36</sup> Mass or solitary lesions can also be observed; in such cases, malignant tumors should first be ruled out. Besides the renal parenchymal lesions, hydronephrosis can often accompany IgG4-RD with retroperitoneal fibrosis or urinary tract involvement.<sup>26,27</sup> The hydronephrosis could be bilateral or unilateral.

However, in patients with impaired kidney function, the use of contrast CT is limited. In this situation, conventional magnetic resonance imaging (MRI) with diffusion weighted imaging (DWI) is an alternative radiologic diagnosis method. In particular, DWI is a useful method for the detection of IgG4-RKD. The characteristic MRI findings of IgG4-RKD are multiple, bilateral, renal parenchymal nodules with T2 hypointensity (Fig. 3); diffusion restriction; and a progressive enhancement pattern.<sup>36,37</sup>



Fig. 3. MRI of an IgG4-RKD patient with bilateral renal parenchymal nodules with T2 hypointensity. MRI: magnetic resonance imaging; IgG4-RKD: IgG4-related kidney disease.



$^{18}\text{F}$ -fluorodeoxyglucose (FDG) positron emission tomography/CT (PET/CT) is useful in assessing organ involvement, guiding interventional treatment, and monitoring therapeutic responses. In PET/CT, IgG4-related lesions show high metabolic activity, with typical standardized uptake values ranging from 1 to 8.<sup>38,39</sup> This technique may also be helpful in diagnosing IgG4-RKD, especially in cases that must be distinguished from malignant diseases.

### Histopathological features

IgG4-TIN and MGN secondary to IgG4-RD are the 2 main types of histopathology described in the kidney. IgG4-RKD may cause cystic formations due to severe narrowing and obstruction of the collecting duct.<sup>40</sup>

IgG4-TIN has the classic pathological features of IgG4-RD, including lymphoplasmacytic infiltration of the renal interstitium and storiform fibrosis (Fig. 4). Obliterative phlebitis is observed less frequently in the kidney than in other organs.<sup>41</sup> The infiltration of mononuclear cells can be diffuse or multifocal. Eosinophil infiltration, tubulitis, and inflammatory cell

infiltration extending into the renal capsule may also be observed in IgG4-TIN; to the contrary, severe tubulitis, neutrophil infiltration, severe peritubular capillaritis, necrotizing angitis, and granulomatous lesions are rare in IgG4-TIN.<sup>32,42</sup>

Immunostaining for IgG4 shows infiltration of IgG4+ plasma cells into the interstitium, with more than 10 IgG4+ plasma cells per high-power field (HPF) (Fig. 5). At the same time, IgG4+ plasma cells should account for more than 40% of IgG+ plasma cells.

As assessed by an immunofluorescence assay, over 80% of IgG4-TIN patients had TBM immune complex deposits, and these TBM deposits were more likely to be present in patients with expansile fibrosis than in those with acute interstitial nephritis.<sup>32</sup>

In patients with MGN secondary to IgG4-RD, an immunofluorescence assay showed granular deposits of C3 and IgG, of which IgG4 was the dominant subclass, along the glomerular basement membrane (GBM). In these patients, renal tissue is typically negative for staining with anti-PLA2R antibodies, similar to the serum anti-PLA2R staining.<sup>31,35</sup>

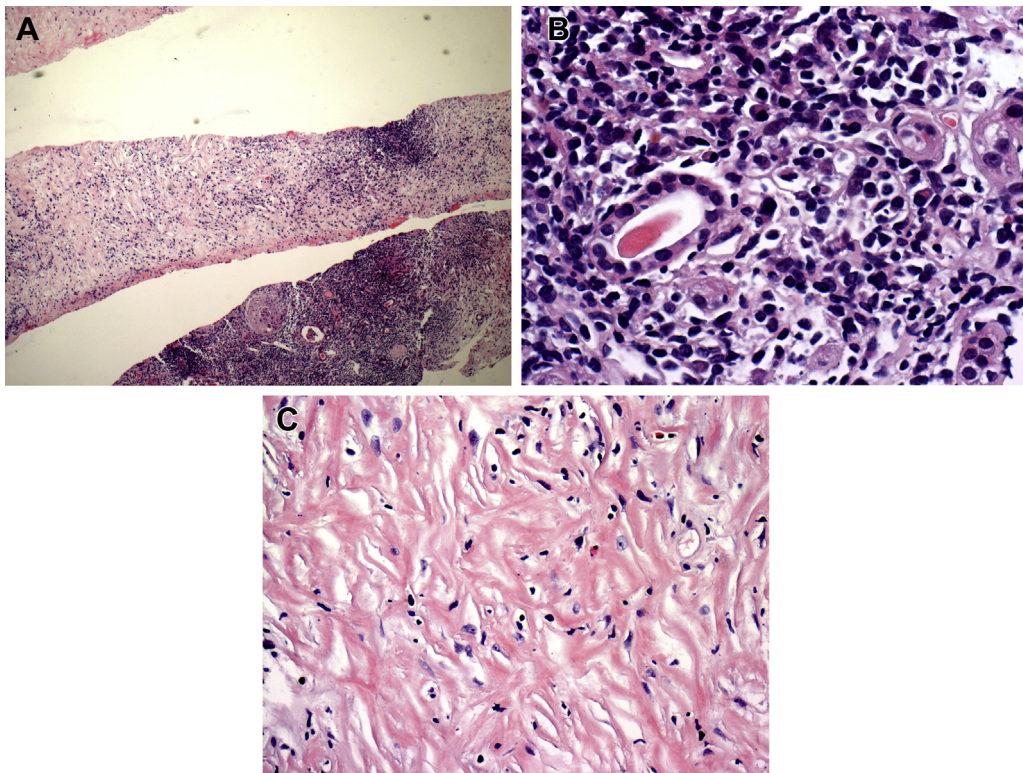


Fig. 4. Pathological features of IgG4-TIN. A: The infiltrates of inflammatory cells may be focal or diffuse (H&E stain, original magnification  $\times 40$ ). B: lymphoplasmacytic infiltration in renal interstitium (H&E stain, original magnification  $\times 400$ ). C: Storiform fibrosis in renal interstitium (H&E stain, original magnification  $\times 100$ ).

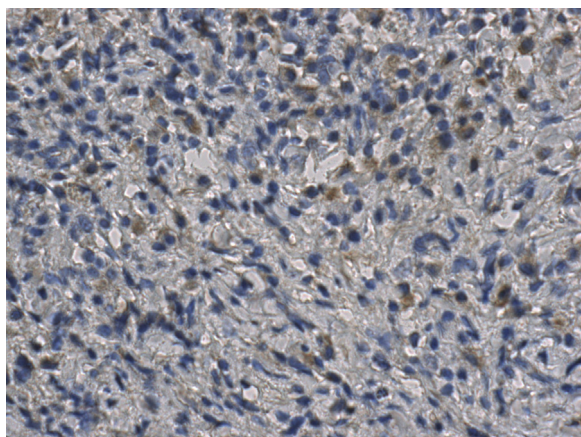


Fig. 5. IgG4+ plasma cell infiltration in the renal interstitium, >10 IgG4+ cells/high-power field. Immunohistochemical staining for IgG4, original magnification  $\times 400$ .

### The diagnosis of IgG4-RKD

Diagnosis of IgG4-RKD requires both histopathological confirmation and clinicopathological correlation.

Two sets of diagnostic criteria have been proposed for IgG4-TIN by Raissian et al.<sup>32</sup> and Kawano et al.<sup>33</sup> Raissian et al.<sup>32</sup> suggested that the histological feature of plasma cell-rich TIN with more than 10 IgG4+ plasma cells per HPF in the most concentrated field is required for the diagnosis of IgG4-TIN. In addition, patients should have at least 1 other feature: imaging (small peripheral low-attenuation cortical nodules, diffuse patchy involvement, or diffuse enlargement of kidneys), serology (elevated serum IgG4 or total IgG level), or other organ involvement. TBM immune complex deposits strengthen the diagnosis. In the criteria suggested by Kawano et al.,<sup>33</sup> clinical manifestations of kidney damage were also taken into consideration, and the diagnosis was defined as “definite”, “probable”, or “possible”, depending on the number of coincident criteria. These criteria are useful in the diagnosis of IgG4-TIN, but other kinds of kidney involvement in IgG4-RD should be considered when this algorithm is used in diagnosis.

In the majority of the literature, “MGN secondary to IgG4-RD” has been used to refer to the MGN associated with IgG4-RD. In 2012, IgG4-related MGN was proposed by Alexander et al.,<sup>31</sup> and this nomenclature fits the principles of the nomenclature for IgG4-RD. Unfortunately, IgG4-related MGN has not been well accepted. Currently, there is still no uniform diagnostic standard for MGN secondary to IgG4-RD. The

diagnosis of MGN secondary to IgG4-RD should be made in the context of IgG4-RD in other organs or IgG4-TIN. The rapid remission of proteinuria in response to steroids can be regarded as supporting evidence.

Similar to MGN secondary to IgG4-RD, there are no diagnostic criteria for IgG4-related obstructive nephropathy. Its diagnosis should be based on the diagnosis of IgG4-RD, usually in the context of IgG4-related retroperitoneal fibrosis, prostatitis, or urinary tract involvement. Other reasons for urinary tract obstruction, including cancer and urinary calculi, should be cautiously ruled out in these patients.

### Controversies in the diagnosis of IgG4-RD and IgG4-RKD

#### *The role of serum IgG4 in IgG4-RD*

In the clinic, serum IgG4 is a good indicator of IgG4-RD and relative to disease activity. However, a diagnosis should not be made solely on the basis of serum IgG4 levels, because there are both false positives and negatives in serum IgG4 testing. Elevated serum IgG4 does not equate to IgG4-RD. From 3% to 7% of the healthy population may have elevated serum IgG4 concentrations. Elevated serum IgG4 can be associated with multiple non-IgG4-RD conditions including connective tissue disorders such as Sjögren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis; systemic vasculitis, particularly granulomatosis with polyangiitis; infections such as chronic sinusitis, chronic sialadenitis, osteomyelitis, and invasive aspergillosis; malignancies such as acute lymphoblastic leukemia, chronic myelomonocytic leukemia, Castleman disease, and malignant lymphoma; pancreato-biliary diseases such as alcoholic pancreatitis and hepatitis; and immunodeficiency.<sup>43–45</sup>

On the other hand, normal serum IgG4 levels do not exclude IgG4-RD. Only 60%–80% of IgG4-RD patients have elevated serum IgG4 levels.<sup>45,46</sup> Between 30% and 50% of patients with biopsy-proven IgG4-RD had normal serum IgG4 concentrations when the disease was diagnosed, prior to therapy.<sup>47,48</sup> In IgG4-TIN, the ratio of elevated serum IgG4 will be higher than in IgG4-RD of other organs; 88% of IgG4-TIN patients had elevated serum IgG4, total IgG, or hypergammaglobulinemia.<sup>32</sup>

Serum IgG4 levels greater than 1350 mg/L had a sensitivity of 81%–97% and a specificity of 60%–85.5% in diagnosing IgG4-RD.<sup>43,45,49</sup> The negative predictive value of a serum IgG4 assay was 96%, but

the positive predictive value was only 34%.<sup>43</sup> A study from the Peking Union Medical College Hospital used a higher serum IgG4 level (1575 mg/L) as the cutoff value.<sup>45</sup> The sensitivity and specificity (78.9% and 80.0%, respectively) of the assay with this adjustment were similar to the 1350 mg/L cutoff values. Caruthers et al<sup>43</sup> suggested doubling the cutoff for IgG4 levels. Using this approach, the specificity of the assay would rise from 60% to 91%, but the sensitivity would drop to an unacceptably low 35%.

Therefore, a serum IgG4 level greater than 1350 mg/L is still suggested as the cutoff value for the diagnosis of IgG4-RD. However, the measurement of serum IgG4 should be used only as a useful screening tool for IgG4-RD. Serum IgG4 levels should not be regarded as a stand-alone diagnostic marker.

Recently, elevated circulating plasmablasts have been observed in IgG4-RD, even in patients with normal serum IgG4 concentrations. Circulating plasmablasts could be a potential biomarker for diagnosis, as a supplement to the assessment of serum IgG4 levels.<sup>48</sup>

#### *Differential diagnosis by renal biopsy*

As with serum IgG4 levels, the number of IgG4+ lymphoplasmacytic cells in the tissues may be misleading. The diagnosis of IgG4-RD and IgG4-RKD requires exclusion of all other diseases. The infiltration with IgG4+ cells can be observed in conditions other than IgG4-RD, such as ANCA-associated vasculitis, Rosai–Dorfman disease, Castleman disease, IgG4+ lymphoma, inflammatory myofibroblastic tumor, cutaneous plasmacytosis, and inflammatory bowel disease.<sup>50</sup> Approximately 32% of pauci-immune glomerulonephritis tissue specimens showed moderately or severely increased numbers of IgG4+ plasma cells by IgG4 staining.<sup>32</sup> However, in cases of granulomatosis with polyangiitis and eosinophilic GPA (EGPA), in addition to IgG4+ plasma cells, there should also be evidence of vasculitis or granulomas. In IgG4+ lymphoma, although increased IgG4+ plasma cells could be found, these plasma cells were not mature. These distinctions may be helpful for differential diagnosis.

To the contrary, in the progressive stage of IgG4-RD, fibrosis will become the dominant lesion. In such circumstances, lymphoplasmacytic cell numbers will be reduced. Thus, IgG4+ lymphoplasmacytic cell infiltration may not fulfill the diagnosis criteria. At this time, the ratio of IgG4+ to IgG+ cell should be considered a useful metric for diagnosis.

In conclusion, the diagnosis of IgG4-RD and -RKD should not be based solely on serum IgG4 levels or the number of tissue-infiltrating IgG4+ plasma cells. The diagnosis of IgG4-RD and -RKD should be based on specific histopathological findings, confirmed by tissue immunostaining, in an appropriate clinical context.

#### **How to treat IgG4-RKD**

The treatment concept for IgG4-RD comes from the treatment of type I AIP. The first-line therapy is steroids. The recommended initial dose to induce remission is 0.6 mg·kg<sup>-1</sup>·d<sup>-1</sup> or 30 or 40 mg/d of prednisolone.<sup>51</sup> The initial dose should be continued for 2–4 weeks, then tapered gradually (by 5 mg every 1–2 weeks), and the maintenance dose is usually 5–10 mg/d. The maintenance period is recommended to be 1–3 years.

In IgG4-RKD, the initial dose of prednisolone should be raised to 40–60 mg/d.<sup>12,51</sup> The reports of Saeki et al<sup>5</sup> and Raission et al,<sup>32</sup> as well as our own,<sup>26,27</sup> all showed a good, rapid response rate to prednisone in patients who had elevated serum creatinine (SCr). Even patients with markedly increased SCr and/or diffuse interstitial fibrosis on biopsy responded to this therapy. In refractory or frequently recurrent cases, immunosuppressants, including mycophenolate, cyclophosphamide, and azathioprine, could be combined with steroid therapy.<sup>26,27,31</sup> If the above treatment does not suffice, or patients have poor prognostic features including advanced renal insufficiency, B cell-depletion therapy with rituximab should be considered.<sup>12,52,53</sup>

In patients with MGN, especially with nephrotic syndrome, prolongation of the initial dose of prednisolone for 1–2 months is reasonable. A combination of immunosuppressants should also be administered in the initial period.

In patients with hydronephrosis, unlike hydro-nephrosis with alternative causes, placement of a double J ureteral catheter should be delayed. In our experience, if a patient has a relatively short disease duration, steroids should still be the first choice. For some patients, after administration of steroids, a double J stent can be avoided. Even if the patient already has a double J stent, it could be successfully removed after steroid administration.<sup>26,27</sup>

Although IgG4-RKD could be diagnosed as acute kidney injury or chronic kidney disease, with appropriate immune suppressive treatment, kidney function could be preserved in most patients.



## Conclusion

IgG4-RD is a clinical entity and is a systemic, autoimmune disease that can involve nearly all organs or systems. The diagnosis of IgG4-RKD should be based on hallmark histopathological features, serum IgG4 levels, and clinical context. The 3 main kinds of kidney involvement are TIN, MGN, and obstructive nephropathy. The hallmark histopathological features of IgG4-TIN are dense lymphoplasmacytic infiltrate and storiform fibrosis; obliterative phlebitis is not common in the kidney. Assessment of serum IgG4 levels and the number of IgG4+ plasma cells is essential for the diagnosis. Recently, assessment of plasmablasts in the bloodstream has been helpful in the diagnosis and monitoring of IgG4-RD. Glucocorticoids are the first-line treatment for most patients with acute disease. For refractory or frequently recurrent cases, immunosuppressants can also be considered. B cell-depletion with rituximab is also thought to be an effective and safe therapy.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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