



IgG4-related kidney disease

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IgG4-related kidney disease is a term that refers to any form of renal involvement by IgG4-related disease (IgG4-RD), a recently recognized systemic immune-mediated disease. The most common renal manifestation is IgG4-related tubulointerstitial nephritis (IgG4-TIN), which presents as acute or chronic renal insufficiency, renal mass lesions, or both. On biopsy, IgG4-TIN shows a plasma cell-rich interstitial inflammatory infiltrate with increased IgG4+ plasma cells, along with expansile interstitial fibrosis; tubular basement membrane immune complex deposits are common. IgG4-TIN usually shows a brisk response to immunosuppressive therapy. Glomeruli may be affected by IgG4-RD, usually in the form of membranous glomerulonephritis. Other patterns of glomerular disease include IgA nephropathy, membranoproliferative glomerulonephritis, and endocapillary or mesangioproliferative immune complex glomerulonephritis. IgG4-related plasma cell arteritis has also been observed in the kidney. This review describes the histopathologic and immunophenotypic patterns of renal involvement by IgG4-RD, with associated clinical, radiographic, and serologic features.

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IgG4-related kidney disease (IgG4-RKD) is the term used to refer to any pattern of renal involvement by IgG4-related disease (IgG4-RD).¹ As with other medical kidney diseases, IgG4-RKD can be described in terms of changes to the different “compartments” in the kidney: the tubules and interstitium, the glomeruli, and the vessels. In the kidney, IgG4-RD manifests most commonly as tubulointerstitial nephritis (TIN), which may be mass forming and detected on radiographic examination. Glomerular disease, in particular membranous glomerulonephritis (MGN), may also be seen in IgG4-RD, with or without concurrent IgG4-related TIN (IgG4-TIN). A lesion of the arteries, IgG4-related plasma cell arteritis, has also been observed.² The kidney may also be affected by extrarenal manifestations of IgG4-RD, including ureteral inflammatory pseudotumor or retroperitoneal fibrosis.³⁻⁵ This article will review the different

patterns of renal involvement by IgG4-RD, with associated clinical, radiographic, and serologic features.

Clinical presenting features of IgG4-RKD

IgG4-TIN in the kidney may present as masses evident on radiographic studies, as acute or progressive chronic renal failure, or both.⁶ Tissue samples of radiographic lesions reveal TIN.⁷ Patients with TIN may have mild proteinuria and microscopic hematuria on urinalysis, and those with MGN usually present with heavy proteinuria or nephrotic syndrome.⁸ IgG4-related retroperitoneal fibrosis or ureteral inflammatory pseudotumor may lead to renal failure due to obstruction.³⁻⁵

IgG4-related tubulointerstitial disease

IgG4-TIN, the most commonly recognized pattern of renal involvement by IgG4-RD, is a specific type of immune-mediated TIN that can be distinguished from other

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types of TIN by clinical, radiographic, laboratory, histologic, and immunophenotypic features.⁹ IgG4-TIN has been observed in IgG4-RD patients both with and without pancreatic involvement; in some patients the disease is confined to the kidney. A lesion similar to IgG4-TIN, chronic sclerosing pyelitis, an inflammatory mass that affects the renal pelvis, has also been described.¹⁰ Raissian et al and Saeki et al have collected data on the two largest biopsy series of IgG4-TIN at 35 and 23 cases, respectively.^{6,11} Both of these series showed many of the clinical and histologic features that have been encountered in other organs affected by IgG4-RD, namely, radiographic tumoral lesions, plasma cell-rich inflammatory infiltrates with increased IgG4+ plasma cells, elevated total IgG or IgG4 levels in the serum, presence of other organ involvement, and rapid response to steroid therapy in most patients. Features specific to the kidney are detailed below.

Clinical features of IgG4-TIN

The average age of patients with IgG4-TIN is 65 years; most (~80%) are male. The Saeki et al study from Japan included only Japanese patients; the Raissian series from North America included patients from other racial and ethnic groups, although the majority of cases were Caucasian.^{6,11} Most patients (57%-76%) had acute or progressive chronic renal failure. In the remaining patients, the primary indication for biopsy or nephrectomy was a renal mass lesion. Many patients had both renal failure and kidney mass lesions. Other organs were involved by IgG4-RD in >80% of patients in the Raissian et al biopsy series, either concurrently or before the recognition IgG4-TIN. The most common extrarenal sites involved were the pancreas, liver, and salivary or lacrimal glands.

Laboratory features of IgG4-TIN

Similar to autoimmune pancreatitis, almost 80% of IgG4-TIN patients had elevated serum total IgG or IgG4 levels.¹² Not all of these patients had serum IgG subclass levels measured; of the subset that did, 92% had an elevated serum IgG4.⁶ Elevated serum IgG4 alone is not specific for IgG4-RD, and the results of these serum studies should be interpreted with caution.¹³ Other common laboratory features are decreased serum C3 and/or C4 levels (56%-78% of IgG4-TIN patients), peripheral blood eosinophilia (33%-48%), and low-titer positive anti-nuclear antibody (~30%).^{6,11}

Radiographic features of IgG4-TIN

Radiographic lesions of IgG4-TIN are best visualized on contrast-enhanced computed tomography scan. The lesions are commonly bilateral and multiple and predominantly involve the renal cortex. Renal parenchymal lesions can be classified as small peripheral cortical nodules, round or wedge-shaped lesions, diffuse patchy involvement, or a large solitary mass.¹⁴ The radiographic differential diagnosis of renal parenchymal lesions includes lymphoma, vasculitis, pyelonephritis, and metastatic cancer.

Histologic, immunophenotypic, and ultrastructural features of IgG4-TIN

By light microscopy, IgG4-TIN shows a plasma cell-rich interstitial inflammatory cell infiltrate. There is a spectrum of histologic appearances, ranging from acute TIN with minimal fibrosis, to an intermediate pattern with some interstitial fibrosis but a marked inflammatory infiltrate, to a densely fibrotic paucicellular pattern with extensive tubular destruction and atrophy.⁶ The fibrosis is expansile, pushing apart the tubules, and often has a "storiform" pattern as seen in other organs involved by IgG4-RD.¹⁵ Along with plasma cells and mononuclear cells, some tissue specimens show numerous eosinophils and thus may be confused with allergic TIN due to a drug. Focal mild mononuclear cell tubulitis is seen in most cases, and eosinophilic or plasma cell tubulitis may also be seen. In some cases, tubules are destroyed and only fragments of tubular basement membranes (TBMs) can be appreciated on periodic acid-Schiff (PAS)- or silver-stained sections (Figure 1).

By immunofluorescence, >80% of cases show focal or diffuse TBM immune complex deposits, which stain for IgG and kappa and lambda light chains, usually for C3, albeit lesser intensity, and in approximately 10% of cases, for C1q in approximately 10% of cases.⁶ TBM deposits are found more frequently in specimens with interstitial fibrosis. Deposits are found only in areas of the fibroinflammatory process and not in adjacent unaffected areas.⁶

Specimens with deposits seen by immunofluorescence show corresponding amorphous TBM electron-dense deposits by electron microscopy.⁶ Glomeruli are negative by immunofluorescence and electron microscopy unless there is a concurrent immune complex glomerulonephritis.

Immunostaining for IgG4+ plasma cells is helpful in distinguishing IgG4-TIN from other types of plasma cell-rich tubulointerstitial inflammatory infiltrates that could mimic IgG4-TIN clinically and histologically.⁶ Using a cutoff of focal moderate (11-30 IgG4+ cells/40× field) to marked (>30 IgG4+ cells/40× field) increase in IgG4+ plasma cells, the authors of one study found a sensitivity of 100% (95% confidence interval: 0.9-1) and specificity of 92% (95% confidence interval: 0.86-0.95) for distinguishing IgG4-TIN from other forms of TIN, after excluding cases of inflammatory infiltrates in pauci-immune necrotizing and crescentic glomerulonephritis.⁶

In kidney biopsies with interstitial inflammation related to pauci-immune glomerulonephritis, approximately 30% of cases showed a focal moderate to marked increase in IgG4+ plasma cells⁶; others have made this observation in the kidney as well.¹⁶ Similar findings have been noted in granulomatosis with polyangiitis (Wegener's granulomatosis) affecting other organs.¹⁷ The absence of a serum anti-neutrophil cytoplasmic antibody (or anti-myeloperoxidase or -proteinase 3 antibodies) and necrotizing or crescentic glomerulonephritis on the tissue specimen helps to exclude pauci-immune glomerulonephritis as a cause of the interstitial inflammation. Focally increased IgG4+ plasma cells

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