Renal manifestations of IgG4-related systemic disease

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While autoimmune pancreatitis (AIP) has been recognized since the first description by Sarles et al in 1961, its involvement of other organs has been recognized more recently. Now, some form of IgG4-related systemic disease (IgG4-RSD) has been described in nearly every organ system, including the liver, gallbladder, other gastrointestinal sites, kidney, salivary and lacrimal glands, orbit, breast, lung, retroperitoneum, aorta, lymph nodes, skin, pituitary gland, and prostate. Involvement usually consists of inflammatory masses but may also manifest as a skin rash or as inflammatory bowel disease.

In the kidney, IgG4-RSD can also present as an inflammatory mass or masses. Biopsy of these masses reveals a histologic pattern of tubulointerstitial nephritis (TIN); glomerular disease has been reported in a subset of cases. Besides radiographic findings of a mass or masses, renal involvement by IgG4-RSD may also present clinically as acute or chronic renal failure, proteinuria with associated glomerular disease, or obstruction related to retroperitoneal fibrosis.

**Tubulointerstitial nephritis**

In the kidney, we attempt to classify TIN according to its cause. In general, TIN/nephropathy can be divided into broad categories of drug-related, autoimmune, hereditary/toxic/metabolic, infectious (direct infection or reactive to a distant infection), and idiopathic/other. Some overlap exists between the different categories.

The cause of TIN in a particular case can be determined by biopsy features by light microscopy, immunofluorescence (IF), and electron microscopy (EM) in conjunction with clinical history and clinical laboratory results, and correlation with radiographic studies in some entities. By light microscopy, the renal pathologist recognizes the pattern of inflammation and types of cells in infiltrate; by IF, the presence or absence of immune deposits and anatomic and immunophenotypic pattern of deposition; and by EM, the absence or presence of immune deposits, pattern of deposition, and presence of any substructure to the deposits.

Autoimmune TIN may be may be associated with systemic autoimmune disease. Examples of systemic autoimmune disease with associated TIN are interstitial inflammation as part of systemic lupus erythematosus (usually accompanied by glomerular disease), sarcoidosis, and Sjögren syndrome. Although not always present, some types of autoimmune TIN show tubular basement membrane (TBM) immune complex deposits, which can suggest an autoimmune etiology.

**IgG4-related tubulointerstitial nephritis**

TIN as part of IgG4-RSD is an autoimmune TIN, which we term IgG4-related TIN. TIN is the most common renal manifestation of IgG4-RSD. Indeed, 30% of patients with AIP
show evidence of renal parenchymal involvement by TIN based on the distinctive radiographic appearance. A history suggestive of IgG4-RSD is helpful in making the diagnosis, but this history is not always present in patients at the time of renal biopsy, or particular aspects of the history are not recognized by the clinician as relevant. Certain laboratory results, along with radiographic findings, can also help make the diagnosis of IgG4-related TIN.

Common clinical, radiographic, and clinical laboratory features in IgG4-related TIN include radiographic abnormalities (present in 85% of cases), elevated serum IgG4 or total IgG levels or hypergammaglobulinemia on serum protein electrophoresis (present in 81%), eosinophilia (present in 28%), and a history of other organ involvement by associated inflammatory conditions including inflammatory masses (present in 84%). Patients may show some but not all of these clinical, radiographic, and laboratory features together. Seventy-five percent of patients with renal specimens had renal failure, either acute or chronic and progressive, as the main indication for renal biopsy, while ~25% of patients with renal specimens had a renal mass or masses as the indication for biopsy or nephrectomy.

Pathologic features of IgG4-related TIN

By light microscopy, the biopsy may show diffuse, multifocal, or focal involvement of the renal cortex by TIN. The infiltrate is composed of mononuclear cells, many plasma cells, and sometimes numerous eosinophils. Often, cases show a distinctive expansion of the interstitium by a fibroinflammatory process with prominent myofibroblasts, resulting in the residual tubules being pushed apart. Tubules are atrophic, sometimes with thickened basement membranes containing immune deposits. Residual fragments of basement membranes of destroyed tubules may be seen focally. Mononuclear cell (sometimes plasma cell) tubulitis and tubular injury are present. Individual cases show a range of appearances, ranging from a very cellular, less fibrotic lesion to a very sclerotic lesion with fewer inflammatory cells. The inflammatory involvement of the kidney resembles that of other organs involved by IgG4-RSD.

Approximately 84% of cases show TBM immune complex deposits. By immunofluorescence, there is granular TBM staining for IgG, C3, and kappa and lambda light chains, sometimes with accompanying interstitial granular staining. Some cases show lesser TBM staining for IgM or C1q. Corresponding amorphous electron dense deposits can be seen by electron microscopy. Immune deposits may be focal, and are present in areas of interstitial inflammation. In some cases, TBM deposits may be seen on an immunohistochemical stain for IgG4.

Value of IgG4 immunohistochemical staining

The pancreatic literature categorizes IgG4+ infiltrates according to the number of IgG4+ plasma cells per 40x field (hpf) in the most concentrated area(s): 0-5 IgG4+ cells, no increase; 5-10, mild increase; 11-30, moderate increase; and >30, marked increase. In the pancreas, increased IgG4+ plasma cells distinguish inflammatory infiltrates of AIP from those associated with other conditions. In a study by Zhang et al (Mod Pathol 2007), 72% of AIP cases showed moderate to marked increase in IgG4+ plasma cells, compared to 11 and 12% of cases of chronic alcoholic pancreatitis and pancreatic adenocarcinoma.
A series of 32 IgG4-related TIN cases from Mayo Clinic, Nephropath, and Massachusetts General Hospital (Raisian USCAP 2011 abstract and Cornell 2007) used as one criterion for IgG4-related TIN diagnosis the presence of increased IgG4+ plasma cells; consequently, 100% of these cases showed moderate to marked increased IgG4+ plasma cells. In comparison, only 10 of 114 (9%) renal biopsies with plasma cell-rich interstitial inflammation due to other causes showed at least moderate increase in IgG4+ plasma cells (excluding cases of pauci-immune necrotizing and crescentic glomerulonephritis; see below). These results provide a sensitivity of 100%, a specificity of 91%, and a positive predictive value of 76% for IgG4-related TIN with at least moderately increased IgG4+ plasma cells.

### Differential diagnosis and pitfalls of IgG4 staining

Some other causes of interstitial inflammation with increased plasma cells show increased IgG4+ plasma cells, usually with a moderate increase (11-30/hpf focally). Most notably, 25% of cases of pauci-immune necrotizing and crescentic glomerulonephritis show at least moderate increase in IgG4+ plasma cells, in both the kidney and in extra-renal ANCA-associated disease. This disease can be mass-forming and may resemble IgG4-RSD. Rare cases of TIN in other categories may also show increased IgG4+ plasma cells, including chronic pyelonephritis, Sjögren syndrome (<10% of cases), and drug reactions. These entities should not show the other clinical or radiographic features of IgG4-RSD, however.

One entity similar to IgG4-related TIN is “idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits” (Kambham, *Am J Kid Dis* 2001), some cases of which may represent IgG4-RSD.

### Proposed diagnostic criteria for IgG4-related TIN

| **Histology** | Plasma cell-rich tubulointerstitial nephritis with >10 IgG4+ plasma cells/hpf field in the most concentrated field*  
|              | Tubular basement membrane immune complex deposits by immunofluorescence and/or electron microscopy** |
| **Imaging**  | Small peripheral cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement  
|              | Diffuse enlargement of kidneys |
| **Laboratory results** | Elevated serum IgG4 or IgG level  
|                  | Hypergammaglobulinemia  
|                  | Eosinophilia |
| **Other organ involvement** | Includes autoimmune pancreatitis, sclerosing cholangitis, inflammatory masses in any organ, salivary/lacrimal gland involvement, inflammatory aortic aneurysm, lung involvement, retroperitoneal fibrosis |

* Mandatory criterion  
** Present in ~84% of cases
To make the diagnosis of IgG4-related TIN, a typical histologic appearance with >10 IgG4+ plasma cells/hpf in the most concentrated area must be present, along with at least one other feature in the categories of Imaging, Laboratory, or Other organ involvement. Other organ involvement need not be concurrent with renal manifestations. Supporting features are the presence of TBM immune complex deposits, as well as marked improvement with steroid therapy, particularly with respect to masses or other radiographic abnormalities.

**Treatment of IgG4-related TIN**

The standard therapy for AIP with pancreatic involvement is steroid therapy. Patients typically show a marked response to steroids, but there is a high relapse rate. A small subset of patients does not respond to steroids; in these patients, rituximab has been used, with a good response. Some AIP patients have been reported to respond to azathioprine, mycophenolate mofetil, or cyclophosphamide, sometimes in combination with steroids.

Less is known about the response to treatment in IgG4-related TIN. In a Mayo Clinic IgG4-related TIN biopsy series (Raissian USCAP 2011 abstract), 11 of 12 patients with elevated serum creatinine showed a response to prednisone therapy (one responder also received mycophenolate mofetil), while 2 untreated patients showed continued elevated creatinine. One patient with a mass lesion was treated with prednisone and mycophenolate mofetil. Similarly in the Saeki series, 10 of 11 patients with elevated creatinine at diagnosis showed decreased creatinine 1 month after prednisolone therapy, while another patient presented with a high creatinine and remained on hemodialysis even after treatment.

**Other renal involvement**

*Glomerular disease*

Glomerular diseases have also been seen in patients with IgG4-RSD. Membranous glomerulonephritis (MGN) is most commonly observed, present in 9% of IgG4-RSD patients in the largest published series of renal parenchymal involvement (Saeki, *Kidney Int* Nov 2010). MGN has also been noted in association with AIP in various case reports. MGN in patients with IgG4-RSD may or may not have concurrent interstitial nephritis. Of interest, MGN is also an IgG4-dominant disease.

In the series of Saeki et al of 23 patients with IgG4-related TIN, 6 (26%) patients had concurrent glomerular disease: 2 with membranous glomerulonephritis, one with IgA nephropathy, and 3 with mesangial immune deposits with mesangial or endocapillary proliferative GN without a more definitive glomerular diagnosis.

A few individual cases have been reported of membranoproliferative glomerulonephritis, IgA nephropathy, and an endocapillary proliferative GN.

*Obstruction related to retroperitoneal fibrosis or ureteral mass(es)*

Extra-renal manifestations may give rise to hydronephrosis, with or without accompanying renal parenchymal involvement.
Pathogenesis of IgG4-RSD

IgG4 is an unusual molecule, with some unusual physical characteristics. Compared to IgG1, IgG4 has weaker inter-chain bonds, resulting in a high rate of dissociation of immunoglobulin half-molecules. In this way, the IgG4 molecule cannot fix complement and cannot form large immune complexes. IgG4 may block antigen from the more pathogenic IgG1 or IgE.

Despite being thought of as an “anti-inflammatory” immunoglobulin, IgG4 nevertheless is found in high levels in IgG4-related autoimmune disease. IgG4 class switching depends on IL-4 and/or IL-13 mainly secreted by T-helper 2 cells. IL-10 has an effect on IgG4 versus IgE class switching and may be required for IgG4 class-switched B cells to differentiate into IgG4-secreting plasma cells. One may speculate that, in IgG4-related systemic disease, an initial insult and process involving production of anti-inflammatory cytokines, including IL-10 and tumor necrosis factor-alpha, along with fibrogenic IL-13, drives increased fibrosis, induction of IgG4 class-switched B cells, and production and massive expansion of IgG4-secreting plasma cells.

Selected references