IgG4-related kidney disease

Lynn D Cornell

Abstract

IgG4-related disease (IgG4-RD) is a recently recognized systemic immune-mediated disease that can affect nearly any organ or tissue. The most common manifestation in the kidney is IgG4-related tubulointerstitial nephritis (IgG4-TIN), which can present as renal insufficiency, renal mass lesions, or both. Histologically, IgG4-TIN is a plasma cell-rich interstitial inflammatory infiltrate with mononuclear cells, eosinophils, and increased IgG4+ plasma cells, along with expansile interstitial fibrosis that often has a "storiform" appearance. Tubular basement membrane immune complex deposits, best visualized on immunofluorescence staining, are present in most cases. IgG4-TIN usually shows a rapid response to steroid therapy. Glomeruli may be affected by IgG4-RD, usually in the form of membranous glomerulonephritis; other glomerular lesions have also been described. This review describes the different histopathologic patterns of renal involvement by IgG4-RD, with associated clinical, radiographic, and serologic features.

Keywords autoimmune pancreatitis; IgG4-related sclerosing disease; immune complex; interstitial nephritis; membranous glomerulonephritis; membranous nephropathy

Introduction

IgG4-related disease (IgG4-RD) is a recently recognized systemic immune-mediated disease. IgG4-RD was first recognized in the pancreas as a disease now termed autoimmune pancreatitis type I (AIP). Other organs were noted to be involved with histopathologic and clinical manifestations similar to AIP. AIP, or sclerosing pancreatitis, was first described by Sarles et al. in 1961.[1] These authors surmised that sclerosing pancreatitis was an autoimmune condition due to the presence of hypergammaglobulinemia in some affected patients and the lack of evidence for an infection.

In 2001, Hamano et al. elucidated the link between IgG4 and AIP: the hypergammaglobulinemia in AIP patients was largely due to increased serum IgG4.[2] Hamano and colleagues later demonstrated tissue infiltration by IgG4+ plasma cells in the pancreas in AIP.[3] Thereafter, Kamisawa et al. expanded the spectrum of AIP to a systemic disease by showing increased IgG4+ plasma cells in AIP patients compared to controls in organs and tissues other than the pancreas.[4] These findings, supplemented by IgG4 immunostaining of tissue, helped to identify other organs involved by IgG4-RD.

Histologically, the fibroinflammatory lesions in different organs often show striking histologic similarity.[5] Some diseases, including Mikulicz's disease, Riedel's thyroiditis, and some cases of idiopathic hypocomplementemic tubulointerstitial nephritis,[6–10] were previously thought to represent diseases of a single organ system and now have become recognized as part of IgG4-RD. The International Symposium on IgG4-related disease, held in Boston, Massachusetts in October 2011, produced consensus statements on the nomenclature and pathology of IgG4-RD with its different organ manifestations.[11,12]

IgG4-related kidney disease (IgG4-RKD) is the term used to refer to any or all patterns of renal involvement by IgG4-related disease (IgG4-RD).[12] 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. The most common pattern of kidney involvement by IgG4-RD is IgG4-related tubulointerstitial nephritis (IgG4-TIN). IgG4-TIN may be mass-forming and detected on radiographic examination, or may be present clinically as acute or progressive chronic renal insufficiency. Glomerular disease, in particular membranous glomerulonephritis (MGN), may also be seen in IgG4-RD, with or without concurrent IgG4-TIN.[13] A lesion of the arteries, IgG4-related plasma cell arteritis, has also been observed.[14] The kidney may also be affected by ureteral inflammatory pseudotumor or retroperitoneal fibrosis.[3,15,16] This article will review the different patterns of renal involvement by IgG4-RD, with associated clinical, radiographic, and serologic features.

IgG4-related tubulointerstitial nephritis

IgG4-TIN is a specific type of immune-mediated TIN that can be distinguished from other types of TIN by clinical, radiographic, laboratory, histopathologic, and immunophenotypic features.[17] IgG4-TIN may present as masses evident on radiographic studies, as acute or progressive chronic renal failure, or both.[18] Tissue samples of mass lesions reveal TIN.[19] IgG4-TIN patients may have mild proteinuria and microscopic hematuria on urinalysis. IgG4-TIN has been observed in IgG4-RD patients both with and without pancreatic involvement, and some patients appear to have renal involvement only. Saeki et al. and Raissian et al. have collected data on the two largest biopsy series of IgG4-TIN, at 23 and 35 cases respectively.[18,20] These series showed clinical and histologic features that have been encountered in other organs affected by IgG4-RD: radiographic abnormalities, plasma cell-rich inflammatory infiltrates with increased IgG4+ plasma cells, elevated serum total IgG or IgG4, presence of other organ involvement (either at the same time as renal involvement or at another time), and rapid response to steroid therapy in most patients.

Clinical features of IgG4-TIN

The average age of patients with IgG4-TIN is approximately 65 years, and most patients (~73–80%) are male.[18,20,21] Patients in IgG4-TIN studies represent a variety of racial and ethnic groups. Most patients (57–76%) have acute or progressive chronic renal failure. In the remaining patients, the primary indication for biopsy or nephrectomy is a renal mass lesion. Many patients have both kidney mass lesions and some degree of renal insufficiency. There was other organ involvement by IgG4-RD in >80% of patients in the Raissian et al. biopsy series, either concurrent with or prior to the recognized IgG4-TIN. The most common

Lynn D Cornell *MD Assistant Professor of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN, USA.*
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extra-renal sites involved were the pancreas, liver, and salivary or lacrimal glands.

Laboratory features of IgG4-TIN

Elevated serum total IgG and IgG4 has been observed in ~70–80% of patients with AIP[22] and can be an indicator of IgG4-RD in the appropriate clinical setting. Similarly, in IgG4-TIN, almost 80% of patients with measurements available in a series of IgG4-TIN had elevated serum total IgG or IgG4 levels. Of the subset that had IgG4 subclass levels measured, 92% had elevated serum IgG4.[18] Elevated serum IgG4 alone is not specific for IgG4-RD, however, and so results of these serum studies should be interpreted with caution.[23] Other common laboratory features are hypocomplementemia (56–78% of IgG4-TIN patients), peripheral blood eosinophilia (33–48%), and positive ANA (~30%), which is usually low-titer.[18,20]

Radiographic features of IgG4-TIN

Renal radiographic involvement has been observed in 35% of patients with AIP[24]; biopsy of such lesions reveals IgG4-TIN.[19] Radiographic lesions of IgG4-TIN are best visualized on contrast-enhanced CT scan. The lesions are commonly bilateral and multiple and predominantly involve the renal cortex. Renal parenchymal lesions can be variable, and can appear as small peripheral cortical nodules, round or wedge-shaped lesions, diffuse patchy involvement, or a large solitary mass.[24] The radiographic differential diagnosis of renal parenchymal lesions includes lymphoma, vasculitis, pyelonephritis, and metastatic cancer. Renal ultrasound may show markedly enlarged kidneys.[18]

Biopsy features of IgG4-TIN

By definition, IgG4-TIN shows a plasma cell-rich interstitial inflammatory cell infiltrate on light microscopic examination. There is a spectrum of histologic appearances, ranging from acute tubulointerstitial nephritis with minimal fibrosis, to an intermediate pattern with some interstitial fibrosis but still a marked inflammatory infiltrate, to a densely fibrotic, paucicellular pattern with extensive tubular destruction and atrophy.[18] (See Figure 1) The different degrees of fibrosis may represent different stages of disease: on nephrectomy samples, the innermost part of a mass lesion is more fibrotic, surrounded by a more inflammatory lesion; and patients who have been treated for a long history of other organ involvement show more fibrotic and less inflammatory lesions. The fibrosis is expansile and pushes the tubules apart. The fibrosis often has a "storiform" pattern as seen in other organs involved by IgG4-RD.[25] (Figure 2) The interstitial infiltrate is composed of plasma cells, mononuclear cells, and sometimes numerous eosinophils. The presence of many eosinophils may cause confusion with allergic TIN due to a drug. Mild mononuclear cell tubulitis is seen, sometimes also with occasional eosinophilic or plasma cell tubulitis. Granulomatous inflammation, neutrophils, and necrosis are absent. In some cases, particularly those with extensive fibrosis, tubules are destroyed and only fragments of tubular basement membranes (TBMs) can be appreciated on PAS − or silver-stained sections. (Figures 3 and 4) A lesion similar to IgG4-TIN, chronic sclerosing pyelitis, an inflammatory mass that affects the renal pelvis, has also been described.[26]

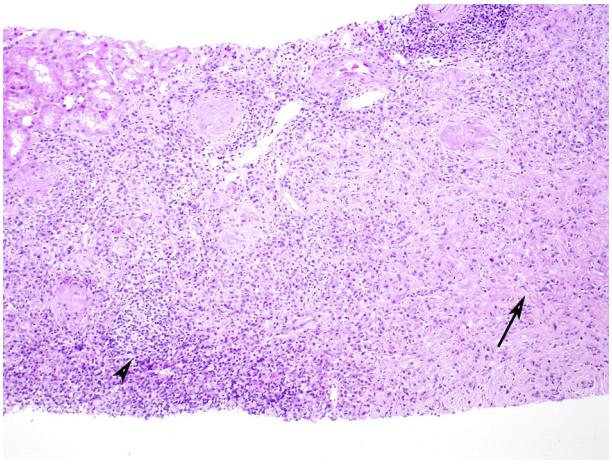

Figure 1 IgG4-related tubulointerstitial nephritis (IgG4-TIN). This biopsy is from a 67-year-old woman with proteinuria (4 g/day), hematuria, and a serum creatinine of 1.2 mg/dl. The biopsy shows a multifocal TIN with highly cellular areas with little fibrosis (arrowhead) and other areas with increased fibrosis with a storiform pattern (arrow). In addition to IgG4-TIN, the biopsy showed IgG4-related membranous glomerulonephritis, which explains the heavy proteinuria. (Hematoxylin and eosin).

More than 80% of IgG4-TIN cases show focal or diffuse TBM immune complex deposits, usually in the absence of glomerular deposits. By immunofluorescence (IF), there is bright granular TBM staining for IgG and kappa and lambda light chains, usually for C3 with lesser intensity, and for C1q in ~10% of cases.[18] (Figure 5). Rarely, dim TBM granular IgA staining may also be present. TBM deposits are found more frequently in specimens with interstitial fibrosis, and the deposits are found only in areas of the fibroinflammatory process and not in adjacent unaffected areas.[18] By electron microscopy, corresponding amorphous TBM electron dense deposits are seen in cases with deposits seen by IF.[18] (Figure 6) Of interest, similar immune complex deposits are seen in basement membranes in the pancreas affected by AIP,[27] which also supports a common immune-mediated mechanism in different organs in IgG4-RD. Glomeruli are negative by IF and electron microscopy unless there is a concurrent immune

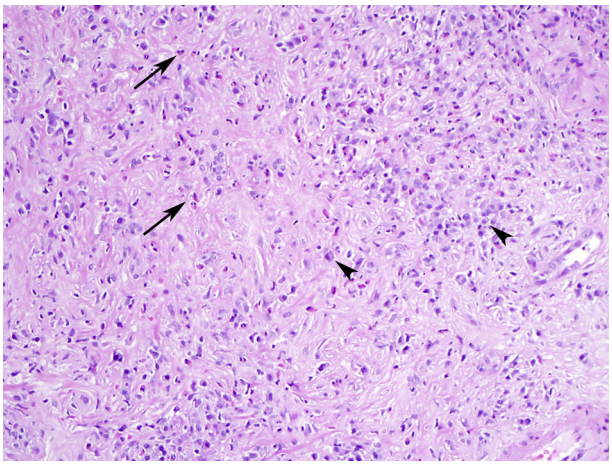

Figure 2 Higher magnification of the biopsy in Figure 1 reveals a pattern of storiform fibrosis. Numerous eosinophils are present in the infiltrate (arrows), along with plasma cells (arrowheads). (Hematoxylin and eosin).