IgG4-Related Tubulointerstitial Nephritis

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Immunoglobulin G4 (IgG4)–related disease (IgG4-RD) is a fibroinflammatory disorder that can involve nearly any organ. The disorder has increasingly become known as a distinct clinical entity during the last decade. IgG4-related tubulointerstitial nephritis (IgG4-TIN) is the most common manifestation of IgG4-RD in the kidney. Many patients with IgG4-TIN are diagnosed after IgG4-RD has been recognized in other organ systems, but the kidney may also be the first or only site involved. The presenting clinical features of IgG4-TIN are most commonly kidney insufficiency, kidney mass lesion(s), or both. On biopsy, IgG4-TIN shows a dense lymphoplasmacytic infiltrate, increased IgG4+ plasma cells, storiform fibrosis, and often tubular basement membrane immune complex deposits. Elevation of serum IgG4 often accompanies IgG4-RD; however, it is not specific in reaching the diagnosis. Like IgG4-RD in other organs, IgG4-TIN characteristically responds promptly to steroids, although there is a high relapse rate on discontinuation of immunosuppression. The pathogenesis of IgG4-RD is not understood.

Key Words: IgG4-related disease, Interstitial nephritis, Immune complex, Plasma cell

INTRODUCTION

Immunoglobulin G4 (IgG4)–related disease (IgG4-RD) is a fibroinflammatory disorder and has become increasingly known as a distinct clinical entity in the past decade.[1,2] IgG4-RD was first recognized in 1961 in the pancreas as sclerosing or autoimmune pancreatitis (AIP)[3,4]; many years later, investigators began to recognize extrapancreatic inflammatory lesions in patients with AIP.[5] This condition became known as a systemic immune-mediated disease that may not even have pancreatic involvement. Now, we recognize that IgG4-RD can affect nearly any tissue or organ system. Across different organ systems, the main histopathologic features remain similar, which are a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis.[6] Because of similar clinical and pathologic findings, many previously known disparate diseases, such as Mikulicz disease, Küttner tumor, and Riedel thyroiditis, have been unified under the diagnosis of IgG4-RD.[1]

As a systemic disease, IgG4-RD can affect a range of different organs, and patients often present with multiple organs involved, either synchronously or at different time points, potentially over years or decades.[2] Alternatively, patients may present with single organ involvement, including kidney-only involvement.[7,8] The fibroinflammatory manifestations of IgG4-RD in the kidney may take the form of tubulointerstitial nephritis (TIN)[7,9,10] or chronic sclerosing pyelitis.[11] Obstruction due to IgG4-related retroperitoneal fibrosis (RPF) may lead to kidney dysfunction. In addition, membranous glomerulonephritis (MGN) is now recognized as part of IgG4-RD, although this pattern represents a different histopathologic entity from the usual fibroinflammatory pattern seen in TIN and in other organs.[1,8,12] Other glomerular diseases have been associated with IgG4-RD, including IgA nephropathy, and mild mesangial immune complex glomerulonephritis not otherwise specified.[7,9] Finally, the arteries in the kidney can be affected by IgG4 plasma cell arteritis.[13] Of these disease patterns, IgG4-TIN is the most common form of IgG4-RD in the kidney and is the focus of this review.[14] Between 2004 and 2006, a few case reports of TIN in patients with AIP were published.[15-19] Following these case reports, 2 small series of IgG4-TIN cases were reported in 2007.[10,20] Later, 2 larger biopsy- or nephrectomy-based series from Japan and the United States (Mayo Clinic) were published, with 23 and 35 patients.[7,9] This review focuses on the clinical, radiographic, laboratory, and histopathologic features of IgG4-TIN. A brief discussion of IgG4-RD–associated membranous glomerulonephritis, RPF, and chronic sclerosing pyelitis is also included.

CLINICAL AND DEMOGRAPHIC FEATURES OF IgG4-TIN

Demographically, patients with IgG4-TIN are similar to those with IgG4-RD. IgG4-RD tends to affect middle-aged to elderly individuals with male preponderance.[7,9] At the time of writing, 2 main tissue-based studies of patients with IgG4-TIN have been published: one from a Japanese population and the other from a predominantly white population but also including African-American and American Indian patients.

In the Japanese study, 20 of 23 patients (87%) were men with an average age of 65.2 years, ranging from 40 to 83 years.[9] At the time of kidney diagnosis, nearly all patients (96%) had extra-kidney involvement, including sialadenitis (82.6%), lymphadenopathy (43.5%), dacryoadenitis (30.4%), and interstitial pneumonitis/nodular lesions (26.0%). Similarly, the series from Mayo Clinic included mostly men (86%) with an average age of 65 years, ranging from 20 to 81 years.[7] Twenty-nine of 35 patients (87%) had extrarenal involvement other than lymphadenopathy.

The 2 major clinical features of patients with IgG4-TIN are kidney insufficiency and kidney mass lesions. In an early series of 5 patients with IgG4-TIN, all patients had mass lesions in the kidney, although this series was biased

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toward mass lesions, as specimens originated from a large surgical pathology service.[10] At a large medical kidney pathology service, IgG4-TIN accounts for approximately 2% of cases of TIN (LD Cornell, unpublished data). The majority of IgG4-TIN patients present with kidney dysfunction, which may be acute or chronic, and whether there is a mass lesion(s).

In the Japanese series, 57% of the patients were investigated due to kidney insufficiency.[9] Two patients had membranous glomerulonephritis in addition to IgG4-TIN; these 2 patients also had proteinuria at >1.0 g/d. Similarly, about 80% of patients in the Mayo series had acute or progressive kidney insufficiency at the time of biopsy, with mean serum creatinine of 3.6 mg/dL.[7] The primary indications for biopsy (with some overlap) were as follows: (1) kidney insufficiency (77%); (2) kidney mass lesion(s) (26%); and (3) nephrotic-range proteinuria (6%). Patients who underwent biopsy for kidney insufficiency had a higher serum creatinine on average (4.2 mg/dL) than those who underwent biopsy or nephrectomy for a mass lesion (mean creatinine 1.4 mg/dL). The kidney insufficiency could be acute or chronic and progressive. Two patients had membranous glomerulonephritis in addition to IgG4-TIN, and both these patients underwent biopsy for nephrotic-range proteinuria.

CLINICAL SUMMARY

- Immunoglobulin G4 (IgG4)–related tubulointerstitial nephritis (IgG4-TIN) is a distinct type of autoimmune interstitial nephritis associated with a systemic disease.
- IgG4-TIN may present with acute or chronic kidney insufficiency, kidney mass lesions, or both.
- On biopsy, IgG4-TIN shows a plasma cell–rich tubulointerstitial nephritis with increased IgG4+ plasma cells, storiform fibrosis, and often tubular basement membrane immune complex deposits.
- IgG4-TIN, like other organ involvement by IgG4-related disease, shows a rapid response to steroids in most cases.

LABORATORY FEATURES OF IgG4-TIN

As opposed to other organ involvement by IgG4-RD, in IgG4-TIN, nephrologists and kidney pathologists have the advantage of access to a number of laboratory tests ordered as part of the nephrology evaluation in preparation for kidney biopsy. Among routine nephrology tests, the most helpful results in the diagnosis of IgG4-TIN are polyclonal hypergammaglobulinemia on serum protein electrophoresis, hypocomplementemia, and peripheral blood eosinophilia. Additional laboratory tests, in particular serum IgG4, may be helpful in evaluating and monitoring patients with IgG4-TIN.

In the study from Mayo Clinic, 88% of patients with IgG4-TIN had elevated total serum total IgG or IgG4 levels, and 56% had hypocomplementemia with decreased C3 (42%) and/or C4 (46%).[7] In the Japanese study, all patients had increased IgG and IgG4.[9] However, IgG4 is not specific for IgG4-RD,[14] although the higher the serum level of IgG4, the more specific that result is for the diagnosis of IgG4-RD. Mild elevation of IgG4 is seen in many conditions, such as bronchiectasis biliary diseases, and pancreatic malignancies; moreover, a normal serum IgG4 does not exclude a diagnosis of IgG4-RD. The clinician and pathologist must be aware of the serum IgG4 testing technique: the nephelometry method can give falsely low-serum IgG4 due to the prozone effect as the test was designed to test for IgG subclass deficiency, not excess as is seen in IgG4-RD. Falsely, low-serum IgG4 due to the prozone effect has been reported in 26% of IgG4-RD patients.[21] Accommodations to this laboratory anomaly include using a dilution step if using the nephelometry method or using a mass spectrometry method to quantitate serum IgG4.

Although IgG4-RD is a systemic inflammatory process, elevation of the systemic acute phase reactant C-reactive protein is observed in only 18% of patients.[22] Kawano and colleagues[23] reported that normal C-reactive protein can be used as a useful marker to differentiate IgG4-RD from antineutrophil cytoplasmic antibody–associated vasculitis or Castleman disease. Other laboratory results commonly seen in IgG4-RD with any organ involvement are eosinophilia in 34%, hypocomplementemia in 36%, elevated serum IgE in 58%, and positive ANA in 32%.[22]

RADIOGRAPHIC FEATURES

Contrast-enhanced computed tomography (CT) is the most useful tool to detect the structural abnormalities of IgG4-TIN. The kidney in IgG4-TIN may show multiple or bilateral small low-attenuation round or wedge-shaped lesions, diffuse heterogenous enhancement of the kidneys, diffuse soft tissue changes surrounding the kidneys, or well-defined low-attenuation exophytic mass(es).[24] On ultrasound, the kidneys may be markedly enlarged.[7] In the Japanese series,[9] 69.6% of patients (16 of 23) showed abnormal parenchymal lesions with diffuse swelling in 7 patients, patchy attenuated lesions in 10, kidney pelvic tumor in 2, and dilatation of the calices in 4. For the Mayo Clinic cohort,[7] 18 of 23 (78.3%) patients had radiographic abnormalities with bilateral and multiple small low-attenuation or mass-like lesions in 14 patients and bilateral markedly enlarged kidneys (>14.5 cm) on ultrasound in 4 patients.

Of note, these lesions may not be visible on non–contrast-enhanced CT or T1-weighted MRI.[24] In addition, when a solid mass lesion is encountered, the finding raises a suspicion of malignant neoplasm and may lead to unnecessary nephrectomy.[25] When the use of contrast is contraindicated, MRI is a promising alternative, especially in detecting IgG4-TIN in a very early stage. Hypointensity lesions are typical on T2-weighted images. Using diffusion-weighted MRI, a recent study revealed 100% sensitivity