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Review

IgG4-related kidney disease – A review

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ABSTRACT

IgG4-related disease (IgG4-RD) is a recently recognized systemic autoimmune disorder characterized by high levels of serum IgG4 and dense infiltration of IgG4-positive plasma cells in multiple organs. The condition was first described as a disease of the pancreas, and has since been recognized in various organ systems including the kidneys. IgG4 related kidney disease (IgG4-RKD) signifies any form of renal involvement by IgG4-RD. The most common renal involvement by IgG4-RD is tubulointerstitial nephritis. Glomerular disease, in particular membranous glomerulonephritis, may also be seen. Other co-existent glomerular diseases such as IgA nephropathy, membranoproliferative glomerulonephritis, and mesangioproliferative immune complex glomerulonephritis may be identified. IgG4-related plasma cell arteritis has also been noted in the kidney. As with IgG4-RD in general, IgG4 related kidney disease (IgG4-RKD) usually occurs in middle-aged to elderly men. Common findings in IgG4-RKD are plasma cell-rich interstitial inflammatory infiltrate either in a focal or diffuse pattern with increased IgG4+ plasma cells, expansile swirling interstitial fibrosis, high levels of serum IgG and IgG4, hypocomplementemia, high serum IgE levels and/or peripheral blood eosinophilia. By immunofluorescence, most of the cases show IgG4 dominant tubular basement membrane immune complex deposits. Similar to IgG4-RD, IgG4-RKD often shows a rapid response to steroid therapy. In this review, we discuss the current knowledge on IgG4-RKD and its clinical relevance.

Contents

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Introduction

IgG4-related disease (IgG4-RD) is a recently recognized systemic autoimmune disorder characterized by high levels of serum IgG4 and dense infiltration of IgG4-positive cells in multiple organs [1,2]. The diagnosis of IgG4-related disease depends on the characteristic morphologic appearance, which includes a dense lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, and increased numbers of IgG4+ plasma cells. Deshpande et al. [3] nevertheless stresses careful clinicopathologic correlation, which cannot be superseded by the morphologic criteria alone.

This systemic disease was first recognized as a disease of the pancreas [sclerosing lymphoplasmacytic pancreatitis also referred as autoimmune pancreatitis (AIP)] by Sarles et al. in 1961 [4]. IgG4-RD disease has now been described in nearly every organ system, including the kidney, liver (sclerosing cholangitis, pseudotumor), gallbladder (IgG4-related cholecystitis), salivary and lacrimal glands (chronic sclerosing sialadenitis/Kuttner's tumor; dacryoadenitis; Mikulicz disease), lung and pleura (interstitial pneumonitis, inflammatory pseudotumor, fibrinous pleuritis), orbit (pseudotumor), breast (sclerosing mastitis, inflammatory pseudotumor), retroperitoneum (retroperitoneal fibrosis), cardiovascular system (periaortitis; inflammatory aortic aneurysm; pericarditis), lymph nodes (lymphadenopathy with various histologic patterns), skin (cutaneous pseudolymphoma), pituitary gland (infundibulohypophysitis), thyroid (Riedel thyroiditis; Hashimoto thyroiditis), and prostate (prostatitis) [5–16]. The fibroinflammatory lesions show remarkable histologic similarity in these different organs [3,17].

Renal involvement in IgG4-RD in any form is collectively referred to as IgG4-related kidney disease (IgG4-RKD) [18–20]. The most common renal involvement by IgG4-RD is in the form of plasma cell rich tubulointerstitial nephritis (IgG4-TIN). Other renal manifestations and associations of IgG4-RD include membranous glomerulonephritis (MGN) with or without IgG4-TIN, IgA nephropathy, membranoproliferative glomerulonephritis, mesangioproliferative immune complex glomerulonephritis, sclerosing pyelitis, IgG4-related plasma cell arteritis and hydronephrosis associated with IgG4 related retroperitoneal fibrosis or ureteral inflammatory pseudotumor [1,18–21]. To date, sporadic case reports and occasional series of IgG4-RD have been described in the literature. In this review, we discuss the recent literature related to IgG4-RD as it affects the kidney.

Clinical and radiologic features

IgG4-RKD like other IgG4-RD is found mostly in older men. It presents commonly as acute or progressive chronic renal failure, radiographic mass lesion, or both [22]. The mean serum creatinine in the Raissian et al. [22] biopsy series, was lower in patients with renal tissue specimens obtained primarily for mass lesions compared to those biopsied for renal failure (1.4 mg/dl versus 4.2 mg/dl, respectively). Patients with IgG4-TIN alone may have mild proteinuria and microscopic hematuria; those with concurrent membranous glomerulonephritis present with heavy proteinuria or nephrotic syndrome. Other patients may present with obstruction related to retroperitoneal fibrosis or ureteral inflammatory pseudotumor [18,20]. Over 80% of patients in the Raissian et al. [22] biopsy series had other organ involvement, either concurrently or prior to the recognized renal involvement. The most common extrarenal sites affected were the pancreas, liver and salivary or lacrimal glands [22]. IgG4-TIN is commonly bilateral and multiple. These lesions predominantly involve the renal cortex. Diffuse swelling of bilateral kidneys or patchily distributed hypoattenuated mass lesions may be evident on imaging [1]. Renal parenchymal lesions as best seen on contrast enhanced computed tomography (CT) scan can be classified as a large solitary mass, small multiple peripheral cortical nodules, wedge shaped or round lesions, or diffuse patchy involvement [23]. The mass lesion appears hypoattenuated on contrast-enhanced CT and is not visible on non-contrast-enhanced CT. Lymphoma, pyelonephritis, metastases, or vasculitis may simulate this condition radiologically and so renal biopsy becomes important [23].

Laboratory features

Almost 80% of patients with IgG4-RKD, have hypergammaglobulinemia or elevated serum total IgG and/or IgG4 levels [1,24]. The finding of an elevated serum IgG4 alone is not specific for IgG4-RD, as 5% of the normal population and 10% of pancreatic cancer patients have an elevated serum IgG4 level [25]. Other common laboratory features are hypocomplementemia (decreased serum C3 and/or C4 levels), a high serum IgE level, and peripheral blood eosinophilia (33–48%) [1,22]. Some patients have a positive antinuclear antibody (ANA, in about 30%), mostly with low titer levels [1,22].

Pathologic features

Macroscopic features

IgG4-RKD is mostly diagnosed on renal biopsies and so gross findings have not been studied extensively.

Microscopic features

IgG4-RKD can be described histologically as changes to the different compartments in the kidney, including the tubules and interstitium, the glomeruli, and the vessels.

IgG4-TIN

IgG4-RKD displays a diffuse or multifocal TIN with increased plasma cells, as well as a mononuclear cell-rich interstitial inflammatory infiltrate (Figs. 1 and 2) [20]. There is a spectrum of microscopic appearances, which include acute TIN with minimal fibrosis, an intermediate pattern with some interstitial fibrosis and a marked inflammatory infiltrate, and a densely fibrotic, paucicellular pattern with extensive tubular destruction and atrophy [22].

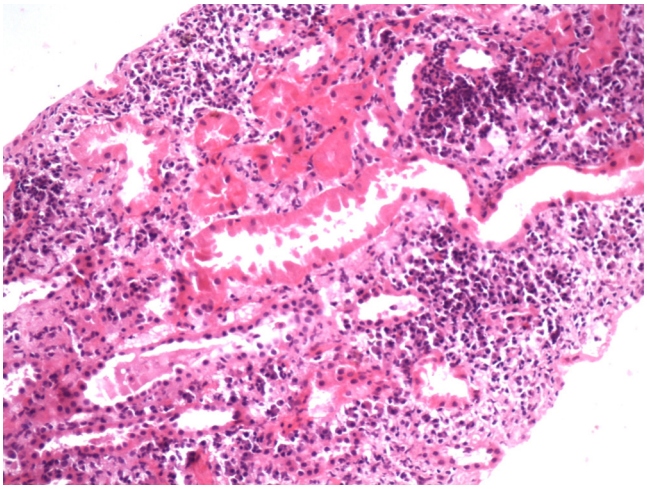

Fig. 1. Microscopic picture of IgG4-related kidney disease (IgG4-RKD): renal parenchyma showing interstitial plasma cell rich chronic inflammatory infiltrate; the tubules are histologically unremarkable (hematoxylin–eosin, original magnification 200×).