

Review Article

IgG4-related renal disease: clinical and pathological characteristics

Naoto Kuroda¹, Tomoya Nao², Hideo Fukuhara², Takashi Karashima², Keiji Inoue², Yoshinori Taniguchi³, Mai Takeuchi⁴, Yoh Zen⁴, Yasuharu Sato^{5,6}, Kenji Notohara⁷, Tadashi Yoshino⁶

¹Department of Diagnostic Pathology, Kochi Red Cross Hospital, Kochi, Japan; Departments of ²Urology, ³Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University, Kochi, Japan; ⁴Department of Diagnostic Pathology, Kobe University Graduate School of Medicine, Kobe, Japan; ⁵Division of Pathophysiology, Okayama University Graduate School of Health Sciences, Okayama, Japan; ⁶Department of Pathology, Okayama Graduate School of Medicine, Dentistry, Pharmaceutical Sciences, Okayama, Japan; ⁷Department of Anatomic Pathology, Kurashiki Central Hospital, Kurashiki, Okayama, Japan

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Abstract: IgG4-related disease is a recently established systemic condition. Tubulointerstitial nephritis is the most common renal manifestation. Glomerular lesions, particularly membranous glomerulonephritis, can develop simultaneously. Some patients present with serological renal dysfunction associated with elevated IgG or IgE levels and hypocomplementemia, while others are incidentally found to have abnormalities in kidneys on imaging. A majority of patients with IgG4-related kidney disease have similar lesions at other anatomical sites, which help us to suspect this condition. Serum IgG4 elevation (>135 mg/dL) is the most, although not entirely, specific marker for the diagnosis. Imaging findings varies from small nodules to bilateral diffuse abnormalities. In addition to the renal parenchyma, the renal pelvis and perirenal adipose tissue can be affected. Histological features include dense lymphoplasmacytic infiltration, storiform or "bird's eye" fibrosis (highlighted by PAM stain), and IgG4-positive plasma cell infiltration (>10 cells/high-power field and IgG4/IgG-positive cell ratio >40%). Immune complex deposition is detectable in the tubular basement membrane by immunofluorescence and/or electron microscopy. Patients usually respond well to corticosteroids, but highly active diseases may require other immunosuppressive therapies. Further investigations will be required to fully understand pathophysiology underlying this emerging condition.

Keywords: IgG4-related disease, kidney, review

Introduction

IgG4-related disease is a recently discovered systemic condition. The possible involvement of IgG4 in sclerosing lesions was first suggested by Hamano et al. who described elevated serum IgG4 concentrations in patients with autoimmune pancreatitis (AIP) [1]. The unique sclerosing pancreatitis was originally described by Sarles in 1961, and was reported as an autoimmune condition by Yoshida et al. in 1995 [2, 3]. Kamisawa et al. discovered that abundant IgG4-positive plasma cells can be present in extrapancreatic lesions in patients with AIP, raising a possibility that IgG4-related pathology is not restricted to the pancreas [4]. Furthermore, Yamamoto et al. suggest the close link between Mikulicz's disease and

increased IgG4 level in 2004 [5]. Since then, IgG4-related sclerosing lesions have been identified at various anatomical sites [6-9], and IgG4-related disease has become a term of choice to describe the systemic condition [10, 11]. In this article, we review clinicopathological features of IgG4-related renal disease.

Patient characteristics

A precise incidence of IgG4-related disease remains uncertain. IgG4-related disease usually affects patients over 40 years of age. Most organ manifestations show significant male predominance (M/F=8/2), but an exception is head and neck lesions (sialadenitis and dacryoadenitis), for which the M/F ratio of patients is nearly 1/1 [8, 12-15].

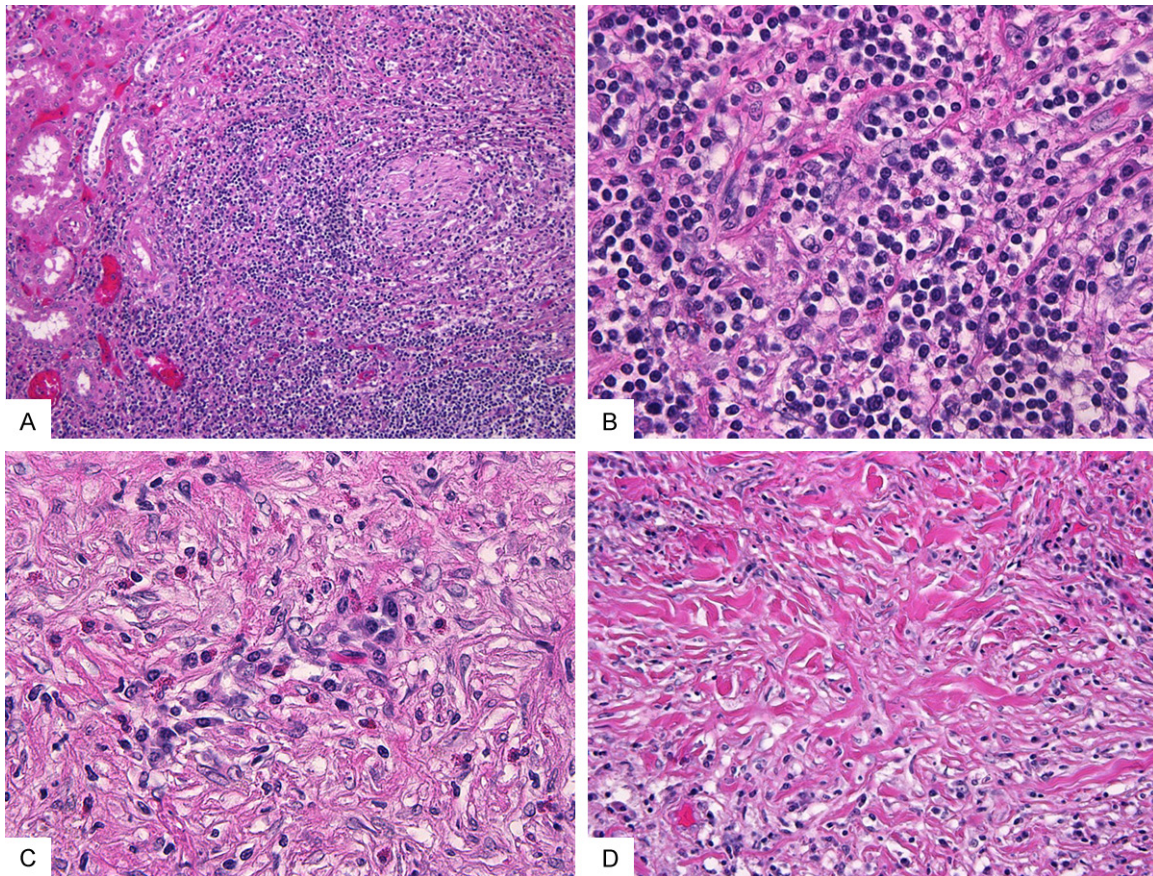


Figure 1. Histological findings of IgG4-related renal disease. A. The border between tubulointerstitial nephritis and non-lesional parenchyma is distinct. B. The inflammatory infiltrate consists predominantly of plasma cells and lymphocytes. C. Eosinophilic infiltration is observed. D. Fibrosis is arranged in a storiform pattern.

Clinical signs and symptoms

Some patients present with symptoms such as fever, fatigue, anorexia or abdominal pain, while others are incidentally found to have renal abnormalities by laboratory tests or imaging [16]. The presence of significant proteinuria and hematuria in the setting of IgG4-related tubulointerstitial nephritis (TIN) may suggest the association with glomerular disease [17, 18].

Laboratory findings

Patients with IgG4-related renal disease usually show hypergammaglobulinemia, elevated IgG concentrations, hypocomplementemia, or mild renal dysfunction [6, 13-15, 19-26]. Serum IgG4 concentrations exceed 135 mg/dl in about 80% of patients [8]. Serum IgE elevation is also seen in about 30% of patients [6, 15]. However, the elevation of IgA, IgM and CRP is

absent. Antinuclear antibodies and rheumatoid factor are sometimes detectable [13, 24]. In patients with TIN, elevation of urinary β 2-microglobulin can be seen [20, 27]. N-acetyl-beta-D-glucosaminase (NAG) and α 1-microglobulin can be also elevated [13]. As urinalysis usually shows only minor abnormalities [13], significant proteinuria and hematuria may suggest concomitant glomerulonephritis in addition to TIN [17, 18].

Imaging findings

Imaging plays an important role in the diagnosis, as IgG4-related renal disease almost always shows radiologically detectable abnormalities. The abdominal ultrasonography may show parenchymal swelling or low echoic lesions [21, 28]. The contrast-enhanced computed tomography (CT) may reveal isolated or multiple low-density lesions [22, 29]. Another possible abnormality is hydronephrosis caused

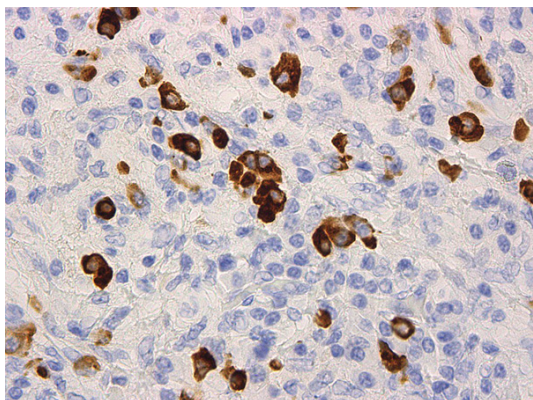


Figure 2. Immunohistochemical findings. IgG4-positive plasma cells per high-power field exceed 10 cells.

by a soft tissue mass affecting the renal pelvis or ureter [13, 16, 30]. The mucosal surface of the urinary tract is usually flat and smooth. Renal parenchymal lesions can be divided into small peripheral cortical nodules, round or wedge-shaped lesions, or diffuse involvement [24, 25, 30, 31]. On magnetic resonance imaging (MRI), renal lesions show iso- or hypointense on T1-weighted images and hypointense on T2-weighted images, and demonstrate mild contrast enhancement after contrast medium administration [28, 31, 32]. A rim sign detected by enhanced CT or MRI is a diagnostic clue for IgG4-related renal disease, the same as for AIP [33]. This finding likely represents an inflammatory process extending into the extrarenal adipose tissue. Diffusion-weight imaging on MRI was recently reported as a useful tool for diagnosing IgG4-related renal disease particularly in patients with significant renal dysfunction or failure [34, 35]. Gallium citrate scintigraphy and positron emission tomography help us to evaluate other organ involvement, but some manifestations may be falsely negative [20, 29, 36, 37].

Other organ manifestations

More than 90% of patients with IgG4-related renal disease have concomitant extrarenal lesions such as pancreatitis, sialadenitis, and retroperitoneal fibrosis, while isolated IgG4-related kidney disease is uncommon [38]. Multiorgan involvement in patients with IgG4-related renal disease (>90%) is significantly more common than in those with pancreatitis, sialadenitis, or dacryoadenitis (40 to 60%). AIP

is the most common extrarenal lesions, followed by sialadenitis and dacryoadenitis [13, 19, 23, 25, 29, 39-41]. Lymph node enlargement is also common, but histological examination is necessary to determine whether it is non-specific or IgG4-related lymphadenopathy [6, 42].

Pathological findings

Grossly, the renal parenchyma involved in this condition appears to be white, firm, and homogeneously solid [28]. Renal pelvic lesions are characterized by thickening of the renal pelvic wall [43].

IgG4-related TIN can be focal or diffuse, and sometimes creates tumor-like masses [12, 13, 29]. Both the renal cortex and medulla can be affected [14]. The lesions are usually well demarcated from the adjacent non-lesion parenchyma (**Figure 1A**). This is one reason that some needle biopsies are unexpectedly composed of the almost normal parenchyma. The inflammatory infiltrate consists of predominantly lymphocyte and plasma cells without cytologic atypia (**Figure 1B**) [6-8, 13-15]. Eosinophils are also frequently present, while neutrophils are exceptional (**Figure 1C**) [13, 14]. Cellular infiltration extending through the renal capsule occurs exclusively in IgG4-related lesion among various causes of TIN [44]. A characteristic pattern of fibrosis, designated as storiform (**Figure 1D**) or “bird’s eye” fibrosis, can be highlighted by periodic acid-methenamine silver stain (PAM) [6, 14, 25]. Obstruction or severe stenosis of collecting ducts due to the sclerosing process may cause cystic dilatation of ducts [45]. Although obliterative phlebitis is a characteristic finding in IgG4-related disease, it is uncommon in kidney specimens particularly needle biopsies. But, this may be simply because medium-sized veins are rarely sampled by needle biopsies [7]. Associated glomerular lesions include membranous glomerulonephritis, mesangial proliferative glomerulonephritis, IgA nephropathy, IgA vasculitis (Henoch-Shönlein purpura) nephritis, endocapillary proliferative glomerulonephritis and membranoproliferative glomerulonephritis [6, 13, 17, 18, 21, 24, 39, 46-54].

Immunostaining for IgG4 reveals abundant IgG4-positive plasma cells (>30 cells/high-power field for surgical specimens, >10 cells/high-

IgG4-related renal disease

power field for needle biopsies) (**Figure 2**) [8, 25]. The ratio of IgG4/IgG-positive plasma cells is usually over 40% [8, 25]. Only focal aggregation of IgG4-positive plasma cells is against the diagnosis of IgG4-related disease, even if it fulfills the number and ratio criteria. Membranous nephropathy in the setting of IgG4-related disease seems different from primary membranous nephropathy. In most cases with the former, immunofluorescent study demonstrates deposition of not only IgG4 but also other IgG subtypes and C3 [17, 49, 54]. Anti-phospholipase A2 receptor antibodies, which are demonstrated in the latter, are absent in the former [17, 49]. Therefore, although IgG4 deposition is predominant in primary membranous nephropathy, this finding itself does not necessarily support the diagnosis of IgG4-related disease. Electron-dense deposits can be observed in the tubular basement membrane [12, 20, 26, 39]. On immunofluorescence, immune complex deposits consist of predominantly IgG, C3, and kappa and lambda light chains [6, 12, 25, 26]. IgG4 is usually a predominant subclass involved in this process with minor constituents of IgG1 and IgG3 [6]. Ultrastructural and immunofluorescence findings in glomeruli depend on the presence or absence and types of associated glomerular diseases [39, 46, 53, 54].

Differential diagnosis

It is important to discriminate IgG4-related renal disease from other types of TIN. The presence of neutrophilic infiltration, severe tubulitis, severe peritubular capillaritis, granulomatous lesions, necrosis, or necrotizing angitis suggests other conditions [44]. Storiform fibrosis is deemed as a unique finding for IgG4-related lesions [44]. The presence of abundant IgG4-positive plasma cells triggers us to suspect IgG4-related disease, but a caveat is that IgG4-positive plasma cells can be present in other conditions such as granulomatosis with polyangiitis (Wegener's granulomatosis), diabetic nephropathy, idiopathic interstitial nephritis, membranous glomerulonephritis and lupus nephritis [19, 55-58]. The diagnosis of IgG4-related renal disease should be made based on not only histopathological features but also clinical and imaging features. Another differential diagnosis on imaging is malignant lymphoma, but this differential diagnosis is not difficult from the aspect of histopathology. The pres-

ence of cellular atypia, light-chain restriction, and lymphocyte-predominant infiltrate favors malignant lymphoma over IgG4-related disease. In the distinction from multicentric Castleman disease with lymphadenopathy, interleukin-6 and CRP level is important [59]. Regarding suspicious cases to IgG4-related disease, the diagnostic criteria or algorithm should be applied [8, 60].

Therapy and prognosis

IgG4-related TIN can not only progress rapidly but also pursue over a long period without significant urinary abnormalities [6, 20, 26]. Although spontaneous remission is known to occur in IgG4-related disease, most patients require immunosuppression to suppress renal inflammation [19]. Corticosteroids are effective for most cases [15, 16, 19, 20, 22, 25, 26, 30, 38, 40, 47, 48, 61, 62] IgG4-related renal disease shows better response to steroid therapy than IgG4-negative TIN [63]. However, relapses occur in approximately 20-30% of patients. Persistently elevated serum IgG4 concentrations or re-appearance of hypocomplementemia after steroid therapy may be an early indicator of relapse [6]. Steroid therapy may cause parenchymal atrophy, leading to persistent renal insufficiency [13, 61, 64]. The estimated glomerular filtration rate before steroid treatment may depend on the prognosis of patients [61]. If corticosteroids are not effective, the diagnosis of IgG4-related renal disease should be reviewed, before considering other immunosuppressive agents or rituximab [25, 46, 48, 65]. Surgical resection may not be avoidable for some patients with tumor-like lesions [28, 31]. Highly active diseases resistant to immunosuppression or leading to renal failure may require dialysis or renal transplantation [15, 49, 66].

Future perspectives

Since IgG4-related renal disease was discovered a decade ago, this condition has been widely recognized and accepted worldwide. The diagnostic process for this condition seems to be improved. Although some molecular studies have been carried out for IgG4-related disease, most of them examined pancreatitis and sialoadenitis. More studies are warranted to fully understand pathophysiology and long-term outcome of IgG4-related renal disease.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Naoto Kuroda, Department of Diagnostic Pathology, Kochi Red Cross Hospital, Shin-honmachi 2-13-51, Kochi City, Japan. Tel: +81-88-822-1201; Fax: +81-88-822-1056; E-mail: kurochankochi@yahoo.co.jp

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IgG4-related renal disease

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IgG4-related renal disease

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