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Review Article

IgG4-related Disease of the Genitourinary Tract

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Abstract

IgG4-related disease (IgG4-RD) is a recently established albeit well recognized fibro-inflammatory condition with distinctive features including a characteristic histopathological appearance; a propensity to develop tumefactive lesions in multiple body sites; and oft elevated serum IgG4 levels. The consensus statement on IgG-4 RD equips practicing pathologists with a set of working guidelines for the diagnosis of pathologic lesions identified in a host of different organ system affected with this disease. The diagnosis of IgG4-RD requires the combined presence of the characteristic histopathological appearance and increased numbers of IgG4-positive plasma cells. The essential histopathological features include a dense lymphoplasmacytic infiltrate, a storiform pattern of fibrosis, and obliterative phlebitis. Tissue IgG4-positive plasma cell counts and IgG4: IgG ratios are significant ancillary aids in establishing the diagnosis. The spectrum of IgG4-RD continues to expand and involve multiple body sites. The genitourinary system comprising of the kidneys, ureters, urinary bladder, urethra, prostate gland, testes and penis is one of the multiple organ systems to be affected by IgG4-RD. This review describes the clinical and histopathologic patterns of involvement of the genitourinary system by IgG4-RD, in association with serologic and radiological features.

INTRODUCTION

IgG4-related disease (IgG4-RD) is a well reported albeit recently established fibroinflammatory disease condition which is best characterized by a dense lymphoplasmacytic infiltrate rich in IgG4+ plasma cells; prominent fibrosis that is at least focally storiform; mass forming lesions at multiple body sites and elevated serum IgG4 concentrations [1-3].

Although this disease phenomenon was initially reported as occurring in the pancreas (type 1 autoimmune pancreatitis), it is now well known that there are several other body sites that manifest variable signs and symptoms of this multi-system disease [3]. IgG4-RD has been reported to involve several organ systems including salivary glands, periorbital tissues, biliary system, lymph nodes, kidneys, aorta, mesenteric soft tissue, thyroid gland, lungs, meninges, breast, prostate, and skin [4]. Of note, the morphological features of disease involvement in all these organs show significant overlap along with elevated serum IgG4 levels and these varying lesions usually respond to immunosuppressive treatment.

Guidelines for the diagnosis of IgG4-RD have been published following an international symposium on IgG4-RD held in Boston, Massachusetts in October 2011. The organizing committee comprised of 35 IgG4- related disease experts from across the world representing all pertinent subspecialties. The main aim of the consensus statement is to provide clinicians with a working panel of guidelines for the diagnosis of IgG4-RD to be employed in practice [1].

It is imperative to state that the guidelines proffered in the consensus statement do not supersede the organ-specific diagnostic criteria in IgG4-RD [5, 6]. Many lesions reported as IgG4-RD fulfill the mandated organ-specific criteria, including histologic requirements as elucidated in the consensus statement guidelines. However, inclusion of cases which do not meet all the diagnostic criteria must be performed on a case by case basis with interdisciplinary correlation. A definitive diagnosis of IgG4-RD does not rest solely upon the recognition of histopathologic features with increased IgG4+ plasma cells on immunohistochemical staining but also includes correlation with the clinical presentation and radiologic findings [1, 6].

The three major histopathological criteria associated with a diagnosis of IgG4-RD are (1) dense lymphoplasmacytic infiltrate, (2) fibrosis, which demonstrates a storiform pattern at least focally and (3) obliterative phlebitis [1, 7, and 8]. Two other histopathological features associated with IgG4-RD are (1) phlebitis without luminal obliteration and (2) increased numbers of eosinophils [1]. On a morphologic basis, a diagnosis of IgG4-RD usually mandates the presence of two of the three major histological features listed above. The most frequently encountered histopathologic features include a dense lymphoplasmacytic infiltrate and storiform-type fibrosis. The solitary presence of phlebitis without luminal obliteration or increased eosinophils is neither sensitive nor specific for diagnosing IgG4-RD [1]. Indeed, there are exceptions in organs including lung, lymph nodes, minor salivary glands, and lacrimal glands where one or more of the aforementioned features viz. storiform-type fibrosis or obliterative phlebitis may be present only focally or entirely absent altogether [9-11].

In regard to serological correlation, the serum IgG4 concentration may either be elevated as is often the case or may even be normal as reported in up to 40% of patients with IgG4-RD diagnosed on biopsy [12]. In any situation, an isolated increase in serum IgG4 or the lone finding of increased numbers of IgG4+ plasma cells in tissue material does not permit the case to be reported as IgG4-RD. In addition to characteristic morphologic findings, the diagnosis of IgG4-RD also requires an increased number of IgG4+ plasma cells (or an elevated IgG4/IgG ratio) in tissue as demonstrated by immunohistochemical staining [1, 6].

If epithelioid cell granulomas or a prominent neutrophilic infiltrate are identified on microscopic examination, then the reporting pathologist must be extremely cautious of rendering a diagnosis of IgG4-RD as the presence of either of these two features is not compatible with the diagnosis [7]. It is prudent to accept the presence of granulomas in IgG4-RD only when they are indicative of another concomitant lesion that might occur in a background of IgG4-RD [4, 7, 8]. A prominent neutrophilic infiltrate with possible abscess formation may be seen in cases of IgG4-RD with associated erosion and ulceration. This finding is more often encountered in cases from the upper respiratory and digestive tract [1].

As per the consensus statement, organ specific cutoffs have been suggested for the diagnosis of IgG4-RD in different body sites. Prominent and diffuse infiltrates of > 50 IgG4+ plasma cells /hpf are reported to be highly specific. A much lower cutoff of > 10 IgG4+ plasma cells/hpf is recommended for biopsy specimens evaluating histologic features in cases being worked up for IgG4-RD [7,13-15]. The presence of varying amounts of fibrosis coupled with sampling issues may lead to differing yields of IgG4+ plasma cells. Determination of the IgG4+/IgG+ plasma cell ratio is of greater significance than relying purely on obtaining IgG4+ plasma cell counts in establishing the diagnosis of IgG4-RD. IgG4+ plasma cell estimation alone may not help to distinguish between IgG4-RD and other inflammatory disorders as both situations can exhibit increased positivity for IgG4 plasma cells on immunohistochemical staining [7, 16-19]. With reference to determining IgG4 and/or /IgG counts, it is recommended to count three high power (x 40) fields with the greatest number of IgG4+ plasma cells (hot spots) and determining the average number of IgG4+ or IgG+ plasma cells in these fields [1, 16].

It has been proposed by several researchers that an IgG4+/IgG+ plasma cell ratio of > 44% be employed as a comprehensive cutoff value in any organ [10, 16, 19]. While this may be applicable in many cases, it is even more essential to correlate this ratio with the histopathologic findings and overall clinical picture [7, 10, 16-19]. A host of other conditions, including inflammatory bowel diseases, oral inflammatory diseases, immunological diseases such as rheumatoid arthritis, vasculitis, as well as lymphoproliferative disorders like Castleman's disease may be associated with elevated serum IgG4 levels and increased IgG4+/IgG+ ratios. Low grade B-cell lymphomas and malignancies with peritumoral or intratumoral increased IgG4+ plasma cells and a florid lymphoplasmacytic infiltrate are also excluded from the consideration of IgG4-RD [1].

Over the last decade, several new developments have been reported in the incidence and diagnostic parameters of IgG4-RD in different organ systems. In this review, we aim to provide a targeted summary of the recent developments in IgG4-RD involving the genitourinary system (Refer to Table 1).

Table 1: Genitourinary system involvement by IgG4-RD.

Body Site	Clinicopathologic presentation
Kidney	Tubulointerstitial nephritis, membranous glomerulonephritis
Ureter	Inflammatory pseudotumor, secondary involvement by IgG4- associated retroperitoneal fibrosis
Urinary Bladder	Inflammatory pseudotumor, proposed role in subset of interstitial cystitis
Urethra	Inflammatory pseudotumor, proposed role in subset of urethral caruncle
Prostate gland	Prostatitis
Testis	Paratesticular fibrous pseudotumor

KIDNEY

Several IgG4-RD lesions within the kidney involving the renal parenchyma and collecting system have been characterized by radiologic studies and pathologic examination. Therefore, the term "IgG4-related kidney disease (IgG4-RKD)" has been coined as a comprehensive descriptor for this group of renal lesions [20-21]. The most commonly encountered manifestation of IgG4-RKD is plasma cell-rich tubulointerstitial nephritis (TIN) with increased IgG4+ plasma cells and may be associated with mass formation detected on radiologic examination [22-23]. However, the spectrum of IgG4-RKD lesions also includes various glomerular lesions, including membranous glomerulonephritis (MGN), which have been reported [21-28].

Clinical features of IgG4-RKD

IgG4-TIN involving the kidneys may present as either acute or chronic renal failure or as a mass forming lesion identified on imaging studies or a combination of both processes [22,27]. Clinical work-up, including urinalysis of patients highlights cases of TIN with mild proteinuria and MGN with heavy proteinuria or nephrotic syndrome [22-28].

IgG4-RKD occurs far more commonly in males with an average patient age of 65 years [22-26]. IgG4-RKD may be seen either with or without associated IgG4-RD extrarenal lesions involving the pancreas, salivary glands, lacrimal glands, lymph nodes and liver. Other organs were involved by IgG4-RD in > 80% of patients in the Raissian et al biopsy series, either concurrently or before the recognition IgG4-TIN [22-28]. Protein loss may result in development of edema, especially in cases with glomerular lesions. Systemic manifestations may be variable but are commonly mild, and associated with renal dysfunction and radiographic mass lesions which are often detected during work up of systemic involvement by IgG4-RD [21-23].

Laboratory Findings in IgG4-RKD

The vast majority of patients (80%) with IgG4-RKD have elevated serum total IgG or IgG4 levels [21, 23]. In the study by Kawano et al. [21], the serum total IgG level was greater than 3000 mg/dl in half of the cases whereas the mean serum IgG4 level was 990 mg/dl (normal < 105 mg/dl). The effect of IgG4-RKD on kidney function varies significantly and clinical presentations range from acute renal failure to chronic progressive disease. Up to 50% of patients with IgG4-RKD demonstrate the presence of proteinuria; it is mild in the majority of cases and may also be accompanied by hematuria in some instances. Cases of IgG4-RKD with glomerular lesions and membranous nephropathy are associated with relatively increased proteinuria which is rarely in the nephrotic syndrome range. One of the typical findings noted is polyclonal hypergammaglobulinemia. Other characteristic features including decreased complement levels and an elevated serum IgE level which have been reported in up to 78% of IgG4-RKD cases [21-26]. Peripheral blood eosinophilia (33-48%) is frequently detected but total white cell and platelet counts are not increased. Rheumatoid factor (RF) and antinuclear (ANA) antibodies are often positive (in up to one third of cases) but other antibodies including anti-DNA and anti-RNP antibodies are usually negative. C-reactive protein levels are not increased and paraproteinemia, cryoglobulinemia, and antineutrophil cytoplasmic antibodies (ANCA) are not observed [21-26].

Imaging Features of IgG4-RKD

TIN that develops as a consequence of IgG4-RKD leads to the development of renal abnormalities which are identified on imaging modalities [21-26]. Contrast-enhanced computed tomography (CT) is the modality of choice for the radiologic diagnosis of IgG4-RKD lesions, but the risk versus benefit ratio must be considered while using contrast in patients with abnormal renal function. The most frequently documented finding of contrast CT is multiple low-density round or wedge shaped small peripheral cortical lesions, and was recorded in 65% of IgG4-RKD cases worked up with the aid of this modality in a prior study [21]. Diffuse kidney enlargement has been identified in 20–30% of patients with IgG4-TIN on both contrast and plain CT studies. Renal mass lesions are relatively rarer and the differential diagnosis involves distinction from a primary renal neoplasm, metastatic lesions, lymphoproliferative disorders and vasculitis. Imaging findings are confirmed on open biopsy or radiologically guided biopsies depending upon the setting and magnitude of the lesions. IgG4-RKD can also involve the pelvicalyceal system as diffuse thickening of the pelvic wall albeit with a smooth intraluminal surface. Other modalities that may be employed for detection of renal or extrarenal IgG4-RKD include gallium scintigraphy and fluorodeoxyglucose positron emission tomography (FDG-PET) [21-26].

Pathological Features of IgG4-RKD

Tubulointerstitial Lesions

The most common finding in TIN lesions associated with IgG4-RKD is plasma cell-rich TIN with an increased number of IgG4-positive plasma cells with accompanying fibrosis [21-30]. In keeping with the diagnostic criteria for IgG4-RD, storiform fibrosis is also a component of the fibroinflammatory lesions in IgG4-TIN. The amount of fibrosis identified in biopsies however, may be variable and is dependent on

sampling issues. The histologic appearance in these cases extends across a broad spectrum which includes acute TIN with minimal fibrosis at one end, an intermediate pattern with a prominent inflammatory infiltrate and focal interstitial fibrosis, in addition to a densely fibrotic pattern with extensive tubular damage and atrophy in the more severely affected patients [22, 29, 30]. Yamaguchi et al. [30] have reported a morphologic pattern referred to as "bird's-eye fibrosis" which describes nests of inflammatory cells surrounded by irregular fibers and highlighted by periodic acid-methenamine silver staining. This pattern is named as such owing to its resemblance to the "bird's eye" grain pattern of maple wood. Obliterative phlebitis is rarely seen in IgG4-TIN, but this might be accounted for by the fact that renal needle biopsies sample a relatively limited volume of lesional tissue [29-30]. A mild degree of mononuclear cell tubulitis is ubiquitously present in most instances, but eosinophilic or plasma cell tubulitis are documented in some cases. Tubular destruction results in fragments of tubular basement membranes (TBMs) that are identified with the help of periodic acid-Schiff (PAS) or silver-based stains. The presence of eosinophils amidst the lymphoplasmacytic inflammatory infiltrate might raise the possibility of drug related TIN in some cases [24]. An example of IgG4-related TIN from our institution is highlighted in the images in Figure 1.

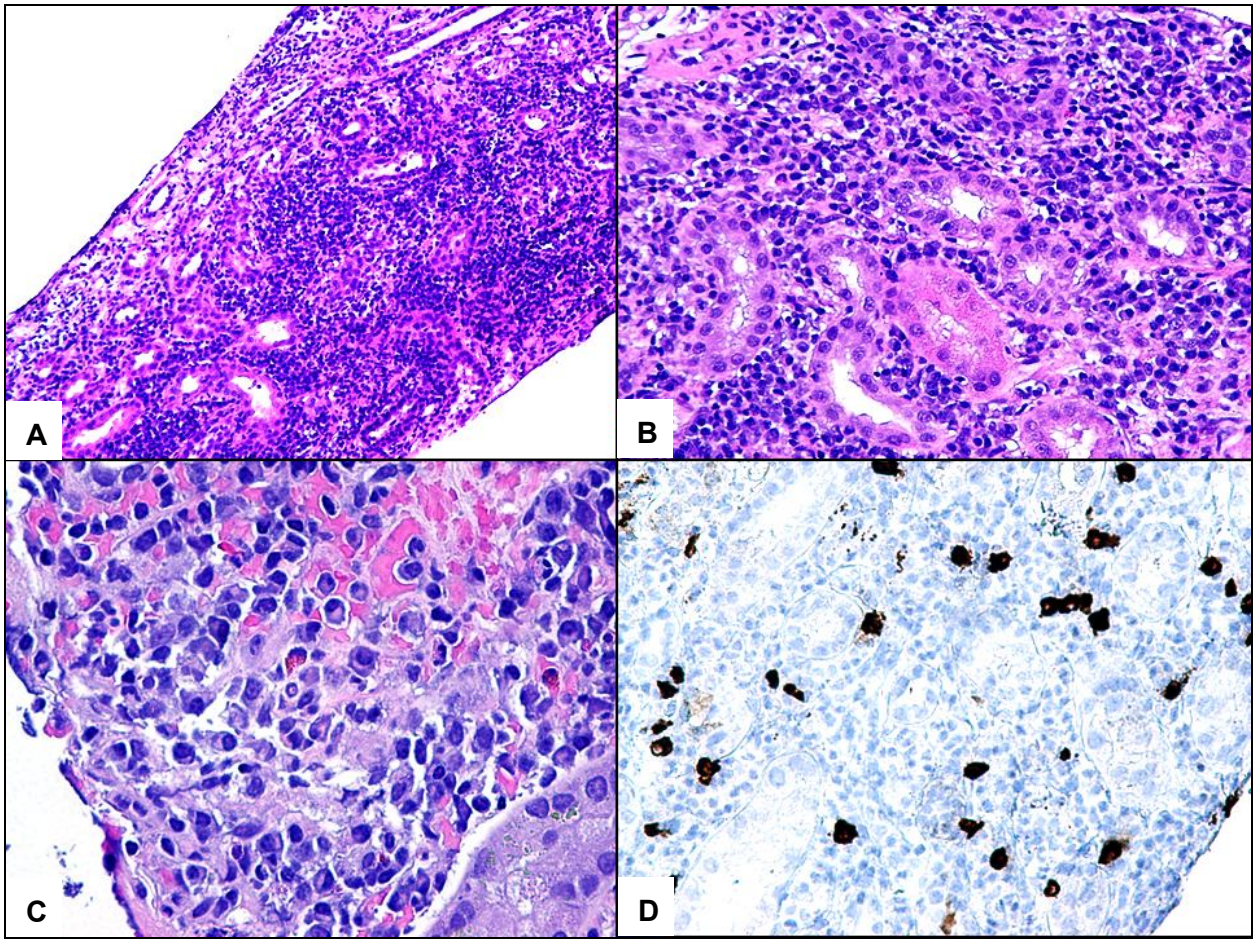

Figure 1: Microscopic features of IgG4-related tubulointerstitial nephritis (TIN) in a renal biopsy from a 66 year old male with bilateral enlarged kidneys and fluctuating serum creatinine levels. (A) Dense expansile interstitial lymphoplasmacytic inflammatory infiltrate masking foci of interstitial fibrosis (H&E stain, original magnification x 100). (B) Severe tubulitis with a plasma cell rich cell interstitial inflammatory infiltrate and intracytoplasmic accumulation of eosinophilic droplets (H&E stain, original magnification x 200).(C) Scattered eosinophils seen amidst the predominant plasma cell inflammatory infiltrate (H&E stain, original magnification x 400). (D) An IgG4 immunoperoxidase stain shows a marked increase in IgG4 plasma cells (H&E stain, original magnification x 200).

On immunofluorescence studies performed in cases with IgG4-TIN, immune complex deposition in the tubular basement membrane (TBM) has been identified in the vast majority of cases [22, 24, 30, 31]. Focal or diffuse immune complex deposition in the TBM in >80% of patients with IgG4-TIN in the study by Raissian et al. [22], granular deposits of IgG with kappa and lambda light chains and/or C3 (and C1q in a minority of cases) on the TBM have been documented in 50–80% of patients with IgG4-TIN [22, 30, 31]. In addition, electron-dense deposits have also been demonstrated in the TBM in > 80% of IgG4-TIN patients on electron microscopic examination [22]. TBM deposits are more commonly reported in specimens with interstitial fibrosis and are present only in fibroinflammatory foci but not in uninvolved renal parenchyma [22, 30]. Several types of IgG might be included in the TBM immune complexes seen in IgG4-TIN apart from the IgG4 subclass. Immunostaining for IgG4+ plasma cells is certainly of benefit in distinguishing IgG4-TIN from other types of plasma cell–rich tubulointerstitial inflammatory infiltrates that mimic IgG4-TIN on a clinical and morphologic basis [22, 30, 31]. Granulomatous inflammation, neutrophilic infiltration, necrotizing angiitis and advanced tubulitis are exceedingly rare in IgG4-TIN, and when present would rule out the diagnosis of IgG4-TIN. Elevated numbers of IgG4+ plasma cells may also be identified in a significant proportion of renal biopsies from patients with interstitial inflammation related to pauci-immune glomerulonephritis and granulomatosis with polyangiitis (Wegener's granulomatosis) [22, 32, 33]. Correlation with serum antineutrophil cytoplasmic antibody (or anti-myeloperoxidase or -proteinase 3 antibodies) and biopsy findings of necrotizing or crescentic glomerulonephritis is mandated to establish a definitive diagnosis in such cases.

Glomerular Lesions

IgG4-related membranous nephropathy (MN) has also been reported either in conjunction with IgG4-TIN or as part of IgG4RD also affecting other organs. Many of the patients have heavy proteinuria or nephrotic syndrome [22-33]. Membranous nephropathy is the most frequently reported glomerular lesion in IgG4-RKD, with an incidence of 7–10% in cases with IgG4-TIN [24, 25]. In the series reported by Kawano et al. [21], 39% (11/28) patients showed the presence of glomerular involvement. In recent studies, patients with membranous nephropathy developing in a background of IgG4-RD but without co-existing TIN have been reported [28, 34].

The glomeruli are morphologically unremarkable or exhibit thickened glomerular capillary loops on H&E-stained sections in IgG4-MN. Subepithelial immune complex deposits may be identified on a trichrome stain and PAS-silver stains may show scattered GBM "spikes". Segmental or global granular GBM bright staining for IgG, C3, and both kappa and lambda light chains is seen on immunofluorescence studies [24]. IgG4 deposition is notably present over the glomerular basement membrane in most, if not all cases, and usually concurrent with other types of IgG subclasses [26, 28, 34].

As documented by Alexander et al. [28], membranous nephropathy may be seen in cases of IgG4-RKD, regardless of the presence or absence of TIN. According to this study, membranous nephropathy represents another spoke in the wheel of IgG4-RKD, although the pathogenesis is different than that seen in conjunction with other fibro-inflammatory lesions in IgG4-RKD. Immunohistochemical stains for the phospholipase A2 receptor, which is usually present in primary MN, was negative in all 8 biopsies stained, thus favoring IgG4-MN arising as a secondary MN [28]. In this series, 5 of 9 patients (56%) showed concurrent IgG4-TIN on biopsy. TBM deposits were less common in IgG4-MN, and seen in 33% of cases as compared to IgG4-TIN [28].

Other glomerular diseases reported in association with IgG4-RKD, include IgA nephropathy, Henoch-Schönlein purpura, and membranoproliferative glomerulonephritis [21, 23, 35, 36]. A few cases of endocapillary proliferative glomerulonephritis, including cases with crescents, have been described [21, 23, 36, 37]. A rare pattern of non-specific mesangial proliferative glomerulonephritis with IgG-containing mesangial immune complex deposits has also been reported [23, 27]. Plasma cell–rich renal arteritis involving small and medium-sized arteries has also been recently reported in a patient with a renal biopsy for IgG4-TIN [38]. A severe transmural inflammatory infiltrate composed of plasma cells and lymphocytes, including many IgG4+ plasma cells, was noted in the arterial wall. Fibrinoid necrosis and neutrophilic infiltrate were absent. Venulitis, akin to that seen in extra-renal IgG4- RD, can also be identified in IgG4-TIN on nephrectomy specimens, but is not mandatory for diagnosis [27].

Proposed Criteria for Diagnosis of IgG4-TIN

Sets of diagnostic criteria for IgG4-TIN have been proposed by a North American group and the Japanese Society of Nephrology and are as listed in Tables 2 and 3 respectively [21, 22]. Both sets of recommendations encompass pertinent features including serology, histopathology, renal imaging, and involvement of other organs as important diagnostic criteria, and emphasize exclusion of other diseases prior to implementation.

Table 2: Proposed diagnostic criteria for IgG4-TIN (Raissian et al [22]).

Histology	Plasma cell–rich TIN with > 10 IgG4+ plasma cells/hpf in the most concentrated field TBM immune complex deposits by immunofluorescence, immunohistochemistry, and/or electron microscopy
Imaging	Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement
Serology	Elevated serum IgG4 or total IgG level
Other organ involvement	Characteristic findings of IgG4-RD in other organs

Table 3: Japanese Society of Nephrology criteria for IgG4-RKD [21].

Clinical features	Clinical or laboratory evidence of kidney damage, including abnormal renal function or abnormal urinalysis with elevated serum IgG or IgE level or hypocomplementemia
Imaging	Abnormal radiographic findings: Multiple low-density lesions on contrast-enhanced computed tomography scan, diffuse kidney enlargement, hypovascular solitary kidney mass, hypertrophic lesion of the renal pelvic wall
Serology	Elevated serum IgG4 or total IgG level
Histology	a. Dense lymphoplasmacytic infiltrate with >10 IgG4+ plasma cells/hpf and/ or IgG4 + plasma cells /IgG + plasma cells ratio of > 40% b. Characteristic storiform fibrosis
Other organ involvement	Characteristic findings of IgG4-RD in other organs

As per the criteria proposed by Raissian et al. [22] the presence of plasma cell-rich TIN with an increased number of IgG4-positive plasma cells is required along with at least one other feature based on imaging, serology (an elevated serum IgG4 or total IgG level), or IgG4-related involvement of another organ. This group excluded cases of pauci-immune necrotizing and crescentic glomerulonephritis and obtained a sensitivity of 100% and a specificity of 92% for IgG4 immunohistochemical staining in their cohort of cases.

According to the Japanese criteria put forth by Kawano et al. [21], "Definite" IgG4-RKD can be diagnosed with three of the following: 1) clinical features, serology, and histologic features (a and b); 2) imaging, serology, and histologic features (a and b); 3) imaging, serology, or other organ involvement; or 4) clinical features, serology, histologic features (a only), and other organ involvement. "Probable" and "possible" disease can be reported if fewer criteria are fulfilled.

Treatment and Clinical Course of IgG4-RKD

IgG4-RD lesions usually respond to corticosteroid therapy as a first line measure. The vast majority (90%) of patients with raised serum creatinine on initial presentation who were treated with steroids showed declining creatinine levels at follow-up. IgG4-TIN tends to show a response even in cases where baseline biopsies show severe interstitial fibrosis. One of the caveats is that IgG4-TIN may relapse after treatment, but this phenomenon is not restricted to IgG4-RKD alone and is seen in other organs also [25, 39]. Corticosteroid therapy also elicits a rapid response in most cases of IgG4-TIN although no controlled clinical trial has been undertaken and the protocol used for corticosteroid therapy is different between countries and even within institutions in the same country [22, 23]. There is limited data available regarding the efficacy of other treatments for IgG4-TIN. Six IgG4-MN patients in a small series were treated with various immunosuppressive drugs. All six patients showed decreased proteinuria and the majority showed a drop in elevated serum creatinine levels at an average of 39-month follow- up (range: 4-184 months) [24]. Immunosuppressant therapy or B-cell depletion with rituximab therapy are reported to be beneficial in some cases with recurrent or refractory IgG4-RD [40].

Corticosteroid treatment in a cohort of 19 Japanese patients with IgG4-TIN resulted in an improvement of renal function, increase in complement levels and improved renal radiologic findings at 1 month after the start of therapy in 18 patients (94.7%) [23]. Another recent study reported the renal function recovered for a relatively longer period (median follow-up, 34 months) under the low-dose maintenance steroid therapy [41]. However, renal function did not recover completely, and irreversible renal failure necessitating hemodialysis could not be prevented in treated patients with advanced renal damage due to IgG4-TIN [23, 41]. A sizable proportion of patients developed renal atrophy, including cases wherein advanced renal injury was established prior to initiating therapy. Relapse of IgG4-RD, including kidney lesions, occurred in 20% of treated patients with IgG4-RKD during maintenance therapy [41]. These findings undermine the crucial

need for early diagnosis and treatment for IgG4-TIN as well as the development of additional treatment strategies.

URETER

The spectrum of IgG4-RD lesions has also been expanded to include ureteral involvement with mass forming "pseudotumoral" lesions. Inflammatory pseudotumor (IPT) lesions are characterized by proliferation of fibroblasts or myofibroblasts with a variable chronic lymphoplasmacytic inflammatory infiltrate amidst myxoid or collagenized stroma [42, 43]. Many authors have proposed that IPTs with increased IgG4+ plasma cells are distinct entities in the IPT category, and are better characterized as belonging to the spectrum of IgG4-RD lesions [43-47]. Recent case reports have suggested that lesions of the ureters otherwise resembling an IPT with increased IgG4+ plasma cells may be associated with systemic IgG4-RD and should be distinguished from other similar lesions viz. inflammatory myofibroblastic tumor and fibrohistiocytic-type inflammatory pseudotumor [48-51].

Kim et al. [48] described 3 cases of ureteral IPT of IgG4-associated lymphoplasmacytic type, with abundant IgG4+ plasma cells accompanied by infiltration with increased eosinophils and histiocytes and presence of obliterative phlebitis. This case series included two males aged 45 and 47 years respectively and an 84-year-old female, who all presented with flank pain of varying duration and ureteral narrowing with accompanying mass effect. Detection of a mass in each case on radiologic examination resulted in either an ureterectomy in one case or nephrouretectomy in the remaining two cases for a presumptive diagnosis of malignancy. The mass forming lesions ranged from 1.5 cm to 3 cm in largest dimension. Microscopic examination of the resected ureters showed suburothelial mass lesions with proliferation of fibroblasts/myofibroblasts without atypia, abundant plasma cells, and scattered eosinophils and histiocytes. The lesion was confined to subepithelial connective tissue in one case, involved the muscularis propria in the second case and extended into periureteric adipose tissue in the third case. The lesion in the 47-year-old male also demonstrated obliterative phlebitis. The lesion in the 84-year-old female demonstrated concomitant urothelial carcinoma in situ in the overlying urothelium. The spindle cells in all 3 cases were diffusely or focally positive for smooth muscle actin whereas they were negative for anaplastic lymphoma kinase (ALK) in all 3 cases, thus providing further basis for categorizing these lesions as being different from inflammatory myofibroblastic tumors. The number of IgG4+ plasma cells was markedly elevated in each case with an average of 154, 112, and 50 plasma cells per high-power field and this aided significantly in establishing a diagnosis feature of IgG4-RD inflammatory pseudotumor. The IgG4+/IgG+ plasma cells ratio was not studied in this case series. Serum IgG4 level was determined in only one of the 3 cases and was recorded within normal range. There were no other significant laboratory test findings in all 3 cases. The postoperative course was unremarkable and no disease recurrence was noted in 9 and 8 months for patients in two of the cases. The third patient was disease free until 36 months after surgery at the age of 87 years, but was subsequently lost to follow-up.

IPTs with IgG4-positive plasma cells in several organs such as liver, breast, and lung have been described [43-47]. All IgG4-RD associated IPTs show histopathologic features similar to sclerosing pancreatitis, including prominent lymphoplasmacytic infiltrates, fibrosis with a storiform pattern, obliterative phlebitis, and elevated counts of IgG4+ plasma cells [43-48]. These case series and reports highlight the need for IgG4 immunostaining in any IPTs with an increased plasma cell inflammatory infiltrate. Correlation with serum IgG4 levels, clinical presentation and imaging studies for detection of involvement of other organ systems by IgG4-RD is also recommended.

Abe et al. [50] reported a case of IgG4- related periureteral fibrosis presenting as a stenotic ureteral mass in a 39 year old male. The presenting symptom was abdominal pain and CT-imaging showed a 3x1.1 cm mass in the lower left ureter with stenosis present on ureteroscopy. A segmental ureterectomy showed an ill-defined, circumferential firm white lesion encasing the ureter. Microscopic examination demonstrated the presence of striking fibrosis and obliterative phlebitis with a dense lymphoplasmacytic inflammatory infiltrate and increased IgG4+ plasma cells on immunostaining (85 IgG4+ plasma cells/hpf, equivalent to 86% of IgG+ plasma cells). Scattered eosinophils and histiocytes were also noted. An ALK immunostain was performed since the differential diagnosis included inflammatory myofibroblastic tumor and was reported as negative. This rare case represents another unique presentation since fibrosis and IgG4+ plasma cell infiltration were localized in the periureteral area. The post-operative serum IgG4 level was slightly elevated above the reference value. More recently, Marando et al. [49] described the clinicopathological features of two cases of ureteral IgG4-RD. An 82-year-old female and a 77-year-old male were treated with ureteral resection owing to findings of severe ureteral wall thickness and lumen stenosis suggestive of urothelial carcinoma. Morphological findings showed transmural fibro-inflammatory lesions, with abundant IgG4+

plasma cells and mixed inflammation with histiocytes, lymphocytes, fibroblasts, and scattered eosinophils. Kim et al. [51] reported a case of a 70 year old male with a left pelvicalyceal soft tissue mass obstructing outflow and extending to the left mid-ureter with resultant hydronephrosis. A laproscopic biopsy showed extensive inflammation and fibrosis with greater than 50 IgG+ plasma cells/ hpf and a simultaneous measurement of serum IgG4 also demonstrated an elevated level of 0.420 g/L (normal range, 0.061 to 0.214 g/L). The serum IgG level was also elevated to 1,839 mg/dL (reference range, 870 to 1,700 mg/dL). The patient was treated with corticosteroid therapy for 3 months and follow-up imaging showed minimal hydronephrosis. Characteristic findings in IgG4-related inflammatory pseudotumor of the ureter are depicted in Figure 2.

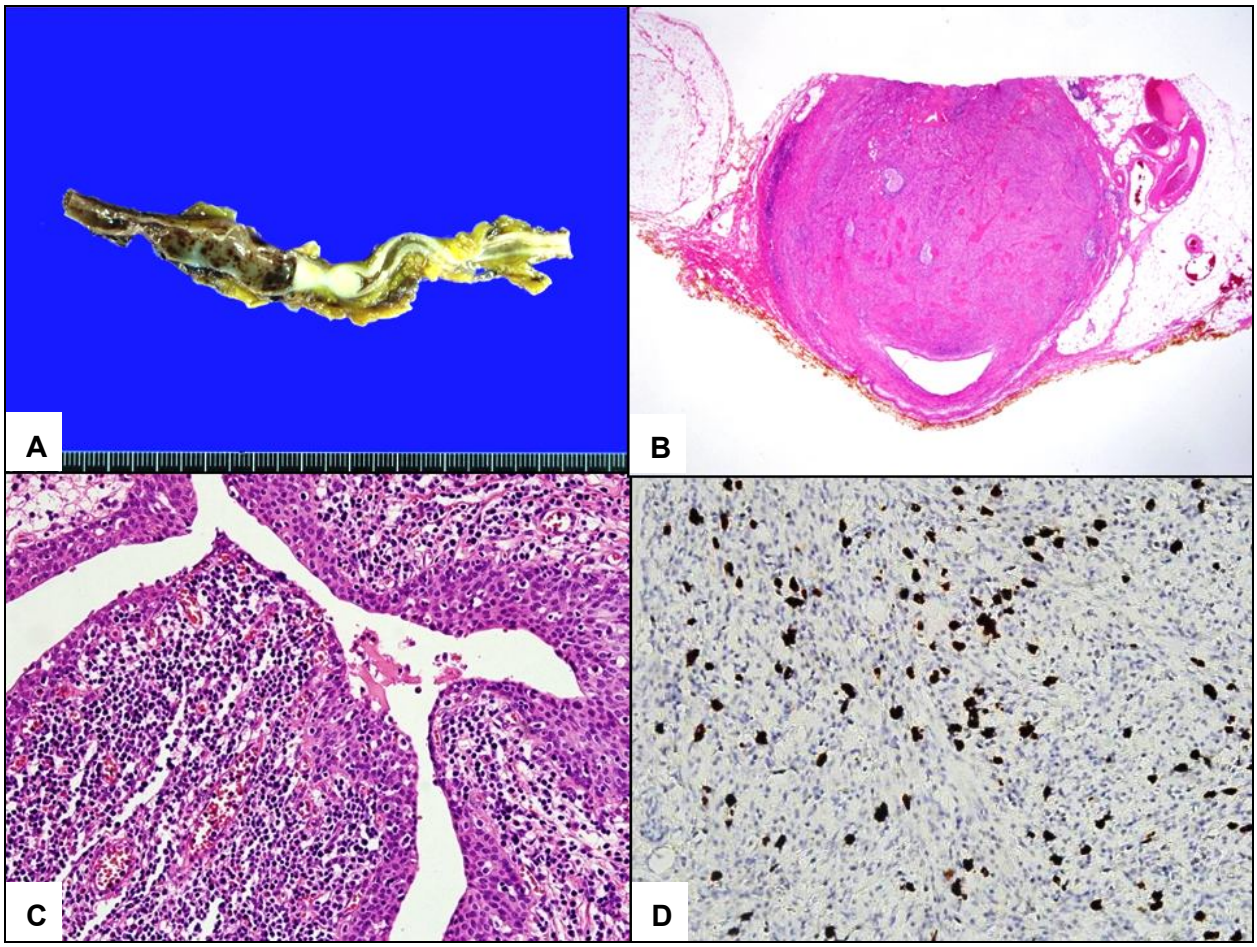

Figure 2: (A) Gross image of IgG4-related inflammatory pseudotumor of ureter with a firm stenotic mass lesion in the lumen demonstrating a yellow-tan and fibrotic cut surface. (B-D) Microscopic features of IgG4-associated inflammatory pseudotumor of ureter: (B) Fibroinflammatory lesion with transmural involvement of ureter wall and focal extension into periureteral adipose tissue (H&E stain, original magnification x12.5). (C) Abundant subepithelial lymphoplasmacytic inflammatory infiltrate with overlying benign urothelium (H&E stain, original magnification x100). (D) A significant subset of plasma cells is positive for IgG4 (immunoperoxidase stain, original magnification x200).

There may be synchronous or metachronous involvement of more than one organ system in cases of IgG4-RD. In cases with confined periureteral fibrosis, development of metachronous IgG4-related autoimmune pancreatitis has been reported in three patients within 1 year after the diagnosis of ureteral IgG4-RD [52, 53]. Ureteric involvement may also be seen in cases of retroperitoneal fibrosis (RPF) which comprise a subset of IgG4-RD [54]. According to Zen et al. [55] immunostaining showed significantly elevated numbers of IgG4+ plasma cells in 10 out of 17 cases (59%) of RPF. In these cases, there were 24–144 IgG4+ plasma cells/hpf, corresponding to 35–76% of the IgG+ plasma cells in IgG4-RD associated cases of

RPF. The IgG4/IgG ratio ranged from 9.6–60.8% in this cohort. Corradi et al. [54] found that a high percentage (92.5 ± 4.5%) of CD138-positive plasma cells were also IgG4-positive, thus providing firm evidence in favor of IgG4-RD occurring in the retroperitoneum. As many of these mass forming ureteral lesions cannot be distinguished for a malignant process, surgery is often undertaken to establish a definitive diagnosis [48-51]. However, suspicion or confirmation of IgG4-RD on ureteroscopic or CT-guided biopsies from these cases would enable treatment with corticosteroids and might even preclude extensive surgical intervention in some cases.

URINARY BLADDER

Involvement of the urinary bladder by IgG4-RD as an isolated occurrence is rare and a few cases have been recently reported [56]. Park et al. [56] reported the first case of IgG4-related inflammatory pseudotumor of the urinary bladder. A 72-year old female with no other comorbidities presented with a 4 month history of gross hematuria and fecaluria. CT scan demonstrated a lobulated intravesical exophytic mass adherent to the sigmoid colon and the differential diagnosis included bladder carcinoma invading the sigmoid colon with fistulization or vice-versa. Frozen section evaluation of the bladder mass revealed an inflammatory lesion resulting in a partial cystectomy with segmental resection of the adherent sigmoid colon. Microscopic examination showed a suburothelial fibro-inflammatory lesion, with transmural inflammation extending into the adjacent sigmoid colon. Dense bands of fibrosis composed of spindle cells without significant atypia and sclerotic areas admixed with abundant lymphocytes, plasma cells, and some scattered eosinophils were noted. Chronic inflammation surrounding nerve bundles, with prominent lymphoid follicle formation was seen amidst the fibrotic areas and increased IgG4+ plasma cells were identified on immunostaining. No urothelial and colonic dysplasia or malignancy was identified. Immunostaining showed an average of 57 IgG4+ plasma cells/hpf with an IgG4/IgG ratio > 40%, enabling a diagnosis of IgG4-associated inflammatory pseudotumor (IPT), arising in the bladder with the secondary involvement of the sigmoid colon.

On a related note, interstitial cystitis (IC) is an interesting disease wherein the exact mechanism of etiopathogenesis has not been fully elucidated yet. The presence of inflammation plays an important role in these cases and is usually accompanied by an increase in mast cells within the detrusor muscle of the urinary bladder. In the recently published study by Crumley et al. [57], a unique concept is proposed in which the authors state that a subset of patients with IC may represent manifestations of bladder involvement by IgG4-RD. The authors identified a set of patients with IC and increased plasma cells as a component of the inflammatory infiltrate in surgical pathology specimens from the urinary bladder. The study comprised of a series of 44 cases accrued from 2006-11 including 42 bladder biopsies and 2 cystectomy specimens. The patients ranged in age from 18 to 92 years (average age of 49.5 years) and this study included 7 male and 37 female patients. Immunostains for IgG, IgG4 and tryptase were carried out, and the results were correlated with both clinical and cystoscopic findings. Four cases showed a significant increase in IgG4-positive plasma cells, with greater than 30 IgG4+ plasma cells/hpf and an IgG4+/IgG+ plasma cells ratio > 50%. Microscopic examination of the surgical specimens also exhibited the presence of dense storiform fibrosis in addition to the inflammatory foci. Statistically significant differences were found between IC with IgG4+ plasma cells versus IgG4-negative cases. The IgG4+ IC patients were older in age and had increased severity of disease as well as decreased bladder capacity when compared with the IgG4-negative group. Figure 3 highlights characteristic findings in IgG4-related interstitial cystitis identified in a cystectomy specimen from our institution. Per the authors, the limitations of this study included the fact that it was only a small subset of IC cases with features of IgG4-RD and a control group was not included owing to the inherent difficulties in obtaining nonneoplastic bladder biopsies. Also, most of the cases were biopsies, which may not be entirely representative of the disease process. The authors recommend examining larger prospective cohorts in conjunction with serum IgG4 levels, clinical symptoms, disease progression and response to corticosteroid treatment in order to achieve a better understanding of this disease process.

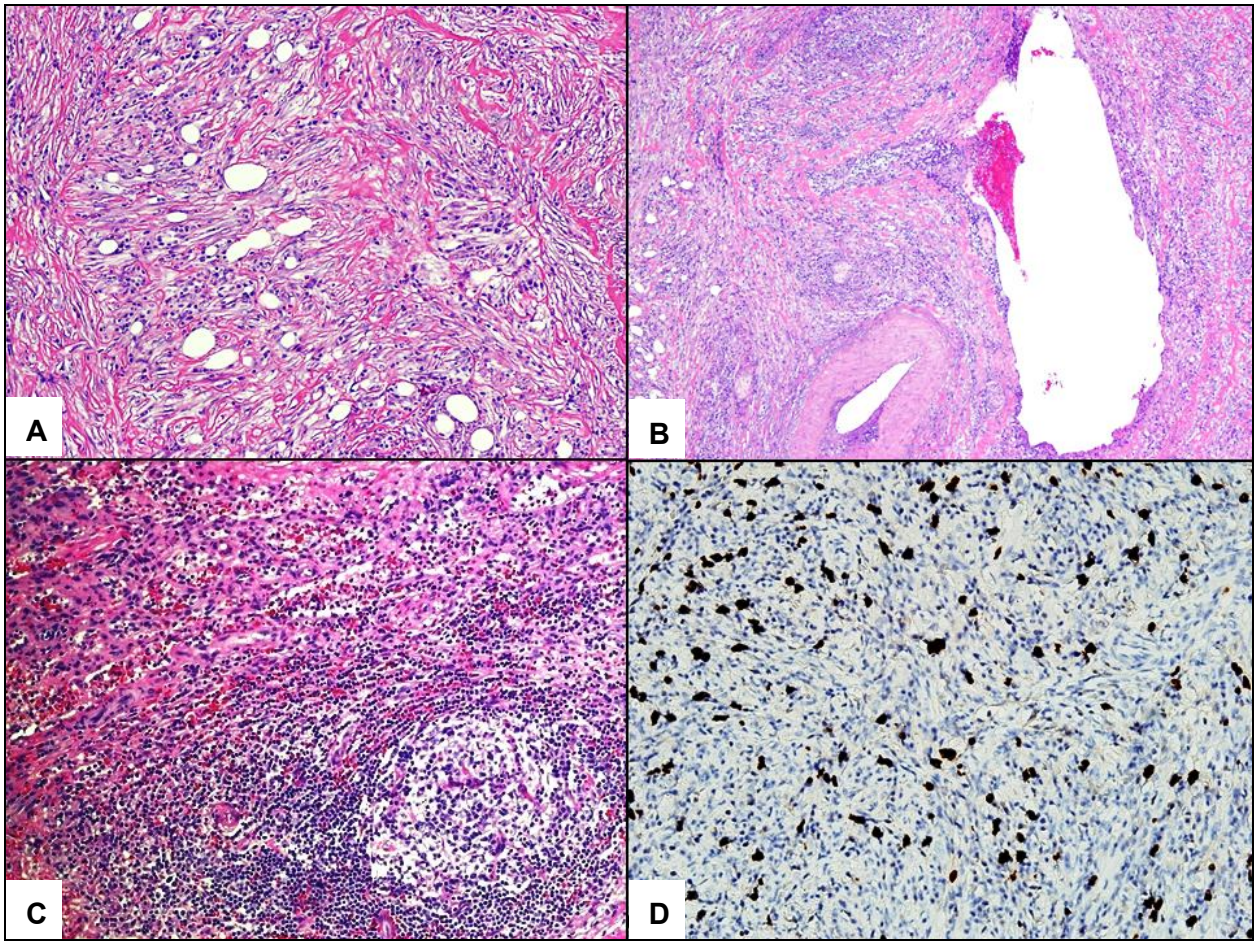

Figure 3: Microscopic features of IgG4-related interstitial cystitis: (A) Dense fibrosis in a storiform pattern with an accompanying inflammatory infiltrate in a cystectomy specimen (H&E stain, original magnification x 100). (B) Obliterative phlebitis involving a large vein with a circumferential inflammatory infiltrate extending along the branch pint of the vessel. Note the uninvolved arterial blood vessel adjacent to the vein. (H&E stain, original magnification x 100). (C) Severe inflammation with formation of lymphoid follicles within the muscularis propria of urinary bladder wall (H&E stain, original magnification x 100). (D) A prominent population of IgG4+ plasma cells (Immunoperoxidase stain, original magnification x100).

URETHRA

Urethral involvement by IgG4-RD with mass formation is limited to case reports in the existing literature. A case report of an IgG4-related IPT in the urethra by Choi et al. [58] describes a mass arising in the posterior urethral wall in a 72 year old female with slight hyperintensity and rim enhancement on magnetic resonance imaging (MRI). Interestingly enough, the patient had a history of IgG4-related autoimmune pancreatitis and an IgG4-related orbital IPT several years prior to the urethral lesion. Biopsy findings demonstrated an IPT with proliferation of smooth muscle actin positive spindle cells and an increased IgG4+ plasma cell infiltrate (>30 IgG4+ plasma cells/ hpf). An ALK immunostain was negative. Treatment with steroids for a few months resulted in amelioration of symptoms and shrinkage in overall mass size on MRI.

Another novel concept proposed by Williamson et al. [59] deals with findings observed in a series of urethral caruncle specimens when they investigated these lesions with the goal of attempting to establish a viral, autoimmune or soft tissue myofibroblastic proliferation etiology. Urethral caruncle is a benign, polypoid urethral mass that is seen almost exclusively in postmenopausal women. Surgical pathology material obtained from 38 patients with urethral caruncles was immunostained for IgG and IgG4 to assess for a potential autoimmune etiology. Immunohistochemistry was additionally performed in 9 patients for Epstein-Barr virus (EBV), BK virus, human herpes virus 8 (HHV 8), human papillomavirus (HPV), ALK and adenovirus. Four of these patients (11%) showed

infiltrates of ≥50 IgG4+ plasma cells/hpf, with an IgG4+/ IgG+ plasma cells ratio > 40%. The mean number of IgG4+ plasma cells (14.73 cells/hpf) compared with control benign urethral specimens (mean, 1.19 cells/hpf) was statistically significant ($p<0.01$). One patient with increased counts below this threshold had rheumatoid arthritis. None of the cases exhibited any of the manifestations of systemic IgG4-RD. All of the lesions for the viral and inflammatory myofibroblastic markers tested were negative. The authors suggested the possibility that increased numbers of IgG4+ plasma cells in a subset of urethral caruncle lesions may imply a possible relation to the spectrum of autoimmune IgG4-RD lesions.

PROSTATE GLAND

Prostatic involvement by IgG4-RD is one of the more recently reported manifestations of IgG4-RD. The first case of histologically proven IgG4-related prostatitis was reported by Yoshimura et al. [60] who described a male patient with transurethral prostate resection for benign prostatic hypertrophy, and developed systemic and pancreatobiliary manifestations of IgG4-RD within 6 months. Nishimori et al. [61] reported two additional cases wherein one of the patients was diagnosed 4 years after prostatic resection and had no other evidence of systemic IgG4-RD. The second patient had increased uptake of FDG in the prostate on baseline PET-CT imaging and was also diagnosed with IgG4-related autoimmune pancreatitis (AIP). The patient did not have urinary symptoms and the FDG-avidity resolved after steroid treatment for pancreatitis. Serum IgG levels were elevated in both cases. Histopathologic examination of the prostate gland tissue in both cases showed abundant fibrosis with increased IgG4+ plasma cells akin to the microscopic picture in IgG4-related autoimmune pancreatitis.

Uehara et al. [62] reported the results of a clinicopathologic study conducted to review the features of AIP-associated prostatitis (AIP-P). This study also examined the immunohistochemical expression of the various IgG subclasses (IgG1, IgG2, IgG3, and IgG4) in six AIP-P patients in comparison with 10 control patients who had focal inflammation without malignancy on histological examination of the prostate but appeared suspicious on a clinical basis. All AIP-P patients had the characteristic findings of IgG4-RD along with elevated serum IgG4 levels in each case. Five prostate biopsies and one radical prostatectomy specimen from this group showed IgG4-related prostatitis with dense fibrosis, obliterative phlebitis, scattered eosinophils and a dense lymphoplasmacytic inflammatory infiltrate with increased IgG4+ plasma cells. The lower urinary tract symptoms (LUTS) improved after steroid therapy in this group of patients. In four of five AIP-P patients, digital rectal examination indicated prostate enlargement. Immunohistochemically, the IgG4-positive plasma cell/mononuclear cell ratio was significantly higher in the AIP-P group than in the control group ($P = 0.0011$). All IgG4-related prostatitis patients had marked elevation of serum IgG4 levels. Two of the patients with elevated PSA levels and histological changes of IgG4-related prostatitis had synchronous prostate cancer. One patient had an abnormal PSA with no histopathologic evidence of cancer, with the corollary that IgG4-related prostatitis might be a cause of falsely elevated PSA levels.

More recently, Hart et al. [63] described a similar case of IgG4-related prostatitis in a 55 year old man with a history IgG4-related autoimmune pancreatitis previously treated with steroids. Characteristic storiform fibrosis, stromal lymphoplasmacytic inflammation, multiple foci of obliterative phlebitis and an increased number (>40/hpf) of IgG4+ staining cells with a markedly elevated IgG4+/IgG+ ratio of 80% were recorded. In view of the findings enumerated in the above reports and the fact that IgG4-related prostatitis can occur synchronously with prostatic adenocarcinoma, it is necessary to biopsy the prostate gland with the intent of ruling out a malignancy. The clinical and serological manifestations of IgG4-related prostatitis include an enlarged prostate gland on digital rectal examination and an elevated prostate specific antigen (PSA) level, further stressing the need for biopsy confirmation regarding the nature of the lesion prior to instituting medical or surgical treatment. Urinary symptoms in IgG4-related prostatitis often improve or resolve with steroid therapy and surgical intervention may not be necessary in every case.

TESTIS

Testicular lesions associated with IgG4-RD are rare and may be categorized into paratesticular and primary testicular lesions. Paratesticular fibrous pseudotumor is a rare, benign mass forming condition of uncertain etiology characterized by solitary or multiple intrascrotal nodules composed of dense fibrous tissue with an inflammatory infiltrate of variable severity.

Bösmüller et al. [64] reported their findings in three cases of paratesticular fibrous pseudotumor in a recent study and studied the plasma cell distribution and immunoglobulin isotypes based upon the similarity of these paratesticular lesions to other fibroinflammatory disorders characterized by infiltrates of IgG4+ plasma cells. All three cases showed a significantly increased number of IgG4+ plasma cells with an IgG4+/IgG+ ratio of 44–48%. The fibrous paratesticular fibrous pseudotumors in two of the cases showed strikingly

similar histological features wherein the nodules had a similar morphologic appearance with hyalinized collagenous stroma, sparse residual mesothelial cell nests and a scattered lymphoplasmacytic infiltrate. The lesion in the third case reported as a paratesticular inflammatory pseudotumor was characterized by a dense myofibroblastic proliferation with few mitotic figures. Hyalinized areas with inflammation comprising of plasma cells, lymphocytes, and eosinophils focally aggregating around blood vessels were identified. Small foci of inflammatory necrosis with partial organization were also present along with several vessels demonstrating obliterative phlebitis. The spermatic duct and the epididymis were involved by this inflammatory pseudotumor. The testicular parenchyma showed extensive ischemic necrosis, probably as a consequence of local tumor compression. Based on these findings, the authors of this study suggest that paratesticular fibrous pseudotumor might belong to the expanding list of lesions associated with IgG4-RD. The above mentioned findings were also noted in one case of a paratesticular inflammatory pseudotumor obtained from our case records as represented in Figure 4.

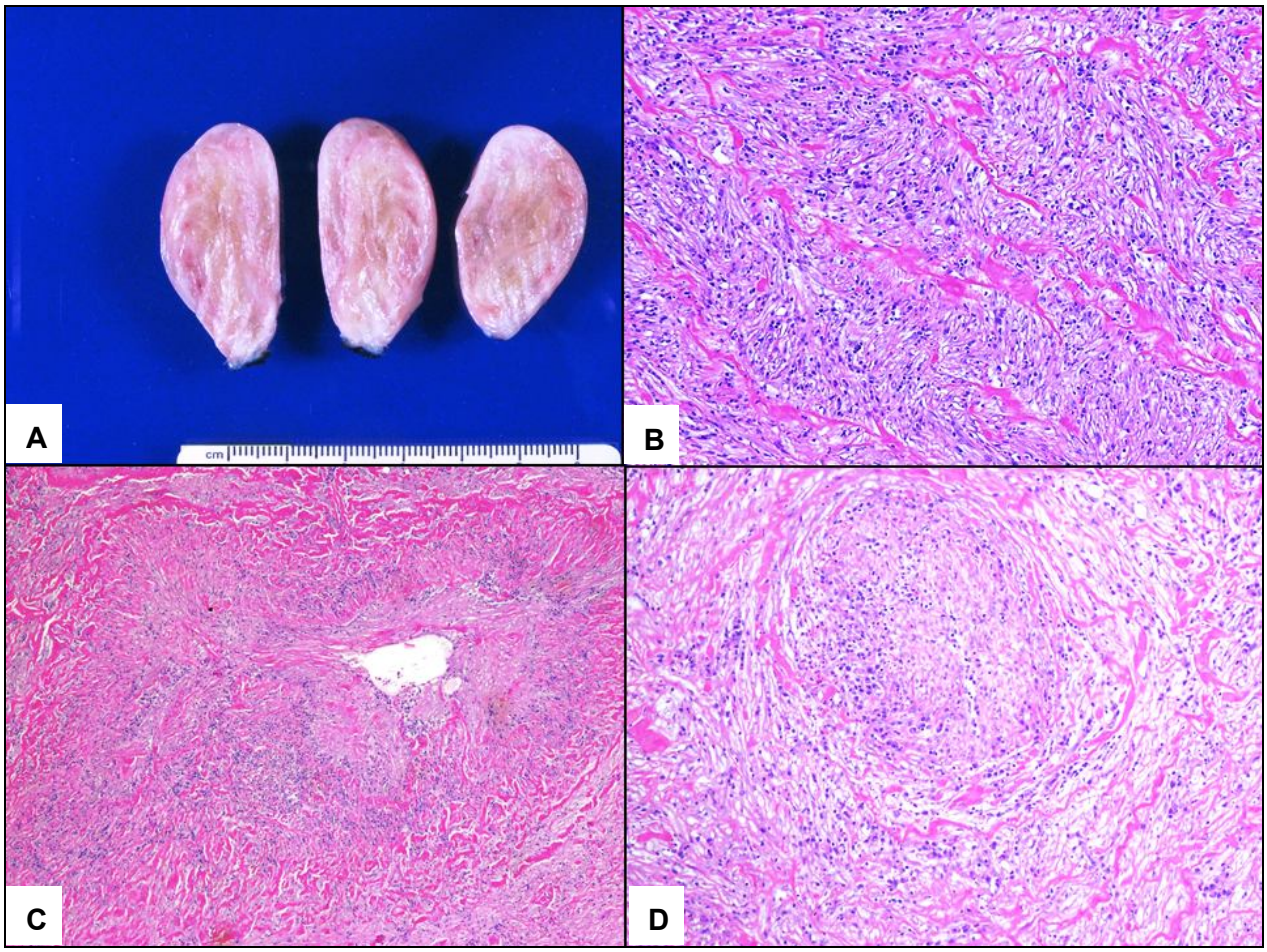

Figure 4: IgG4-related paratesticular inflammatory fibrous pseudotumor. (A) Gross image demonstrating a well circumscribed mass with a tan-pink fibrous cut surface. (B) Microscopic image showing dense fibrosis with sclerotic areas and a prominent inflammatory infiltrate (H&E stain, original magnification x 100). (C) Obliterative thrombophlebitis with partial luminal occlusion and surrounding circumferential sclerosis (H&E stain, original magnification x 100). (D) Obliterative thrombophlebitis with complete luminal occlusion and an inflammatory infiltrate in vessel wall (H&E stain, original magnification x 100).

Hart et al. [65] also reported a case of a patient with an IgG4-related paratesticular pseudotumor and histologically established AIP, who presented with a scrotal mass. Examination of the orchiectomy specimen resulted in the diagnosis of a paratesticular pseudotumor with characteristic histopathologic findings including storiform fibrosis and obliterative phlebitis as well as immunohistochemical results (> 50

IgG4+ plasma cells/hpf in this case) consistent with IgG4-RD.

PENIS

To the best of our knowledge, no substantial evidence based reports of penile involvement by IgG4-RD have been published. However, we cannot exclude the possibility that penile skin may be affected in cases of cutaneous IgG4-RD. In our practice, we have encountered a rare case of plasma cell balanitis (Zoon's balanitis) cases, with increased IgG4+ plasma cells (>50 cells /hpf) and an IgG4+/IgG+ plasma cell ratio > 40% (unpublished data). Although it is uncertain at this point whether this lesion can be included in the spectrum of IgG4-RD or not, additional studies with a sizable number of cases are necessary to investigate this possibility.

SUMMARY

The recognition of IgG4-RD involving various organs of the genitourinary tract provides further evidence that this recently recognized condition spans across a wide range of organ systems. Although the exact pathogenetic mechanism of this condition remains to be described, characteristic histopathologic criteria coupled with increased IgG4+ plasma cells and/or serum IgG4 levels serve as reliable surrogate markers in the proper clinical milieu. The presence of any of the established diagnostic features in isolation does not aid in arriving at a diagnosis of IgG4-RD but requires further validation on a clinical basis. An interactive dialogue between pathologists and other physician members of the treating team is imperative in reaching a consensus for the proper diagnosis and management of this disease condition. A judicious assessment of evidence based diagnostic criteria and clinicopathological correlation are recommended prior to incorporation of newly proposed entities as members of the IgG4-RD disease spectrum. Several organs of the genitourinary system may be associated with either mass forming or other morphologically significant fibroinflammatory lesions as part of the spectrum of IgG4-RD. Recognition of IgG4-RD lesions in the genitourinary tract is decidedly important owing to therapeutic implications following corticosteroid treatment and prevention of surgical intervention whenever feasible.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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