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Review Article

IgG4-Related Kidney Disease: An Overview

Círia Sousa[1*], José Francisco[1*], Pedro Reis Pereira[1], Bárbara Rodrigues[1], Mariana Freitas[1], João Borges[1], Beatriz Pereira[1], Marta Costa[1] and Teresa Morgado[1]

[1]Serviço de Nefrologia /Nephrology Department, Centro Hospitalar de Trás-os-Montes e Alto Douro, Portugal

**Co–first authors*

Introduction

IgG4-related disease (IgG4-RD) is an insidious progressive disease characterized by fibrous and inflammatory lesions that can affect almost any tissue or organ. Elevated serum IgG4 may be present, but it is now known that its levels are normal in many patients with a clinical and anatomopathological diagnosis of IgG4-RD [1]. This condition was first recognized in the context of pancreatic disease, and in 2001, Hamano et al. demonstrated that the serum IgG4 level was significantly elevated in patients with sclerosing pancreatitis (now described as autoimmune pancreatitis (AIP) type 1) [2]. However, IgG4-RD was only first recognized as a distinct entity in 2003 after Kamiwasa et al. demonstrated the presence of IgG4-positive plasma cell infiltrates in pancreatic and extra pancreatic lesions [3]. Since then, it has been recognized as a fibro inflammatory and multi-systemic disease, which can virtually affect all organs, and clinical manifestations depend on the organs involved [4].

IgG4-Related Kidney Disease (IgG4-RKD) describes renal involvement. The most common pattern of kidney damage is tubulointerstitial nephritis, but it can also affect the glomerulus, vessels, and even the renal pelvis [5]. This review aims to highlight the main aspects of IgG4-RKD, from pathophysiology to clinical diagnosis and treatment.

Epidemiology

The prevalence of IgG4-RD is unknown, however, the recognition of the disease continues to grow and only a few population-based studies have been performed. Regarding IgG4-RKD, the incidence and prevalence are even more unknown. In 2012, a Japanese study reported a prevalence of approximately 0.28 to 1.08 per 100,000 population, though nowadays the real prevalence is probably underestimated [6]. Most patients are middle-aged men, in opposite to other autoimmune diseases [7]. However, the involvement of the head and neck (sialadenitis, dacryoadenitis, and thyroiditis) varies by gender and is more prevalent in women [8].

Physiopathology

The pathogenesis of IgG4-RD is not fully understood. The most consensual hypothesis is a dysregulation of acquired immunity- and is, therefore, an autoimmune disease [9]. It is characterized by lymphoplasmacytic infiltration (with the predominance of IgG4-positive plasma cells) and the development of fibrosis [10]. It is not clear whether the elevated level of circulating IgG4 is involved in its pathogenesis or if it is just associated with the underlying inflammatory condition [10].

Some initiating mechanisms have been proposed which include genetic factors, bacterial infection, dysregulation of innate immunity and autoimmunity. Genetic factors appear to be associated with IgG4-RD like the serotypes HLA DRB1*0405 and DQB1*0401 in the Japanese population [11]. HLA DQβ1-57 (with substitution of aspartic acid at position 57) in the Korean population [12] and some non-HLA genes like the ones encoding cytotoxic T lymphocyte-associated antigen 4 and Fc receptor-like 3 [13,14]. Bacterial infections have also been hypothesized to induce IgG4-RD through different mechanisms. Helicobacter pylori possess high molecular mimicry with human proteins carbonic anhydrase II and n-recognin 2 (a component of ubiquitin-protein ligase E3 expressed in pancreatic acinar cells [15,16]. Previous authors described an apparent causal link between infection with Mycobacterium tuberculosis and Staphylococcus aureus and IgG4-RD, possibly through an allergic-like mechanism [17,18]. Akitake et al., showed the relationship between bacterial infection and IgG4-RD, with stimulation with toll-like receptor ligands leading to the production of IgG4 and interleukin (IL)-10 from peripheral blood mononuclear cells [19]. Abnormal innate immunity has also been demonstrated in some patients with IgG4-related disease. Watanabe and colleagues reported that activation of nucleotide-binding oligomerization domain-2 and Toll-like receptor ligands on monocytes or basophils in patients with AIP, enhanced the IgG4 response via B-cell activating factor and IL-13 [20]. This antigen-mediated processes can lead to the expansion of B cells and their switch to IgG4 with the help of activated T follicular helper (Tfh) cells, eventually resulting in clonal expansion of IgG4+ blasts and plasma cells [21,22]. Several antigens have been involved, such as galectin-3 [23], laminin-511. [24] annexin A11, [25] carbonic anhydrase II, lactoferrin, pancreatic secretory trypsin inhibitor, and trypsynogen [26,27]. It is likely that more than one antigen can spoil the disease.

IgG4 itself is unlikely to explain the pathogenesis of IgG4-RD. Since an elevation in circulating IgG4 is frequently observed in other diseases characterized by chronic immunological activation, it offers poor specificity for the diagnosis of IgG4-RD [10]. The majority of the research on the effector actions of the IgG4 molecule points

***Corresponding author:** Círia Sousa, Serviço de Nefrologia/Nephrology Department Centro Hospitalar de Trás-os-Montes e Alto Douro Avenida da Noruega Vila Real, Portugal, Tel: +351 259 300 500, E-mail: ciriasousa@msn.com

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to an anti-inflammatory function for this IgG isotype. IgG4 differs from other IgG isotypes in three specific ways that have the potential to have an anti-inflammatory effect: Fab-arm exchange; inferior complement protein C1q fixation; and a diminished ability to bind activating Fc receptors. Altogether, the rise in serum IgG4 concentrations in IgG4-RD may be an ineffective counter-regulatory response in which serum IgG4 concentrations are increased to try and reduce the intensity of the initial immune response [28]. It was demonstrated that when compared to naive and memory B cells from healthy controls, immunoglobulin sequencing of circulating plasmablasts indicated significant somatic hypermutation. This shows that IgG4-expressing plasmablasts are produced as a result of a T-cell-dependent immunological response [22]. Prior research has shown that patients with IgG4-RD exhibit oligoclonal growth of IgG4+ clones among circulating plasmablasts [22]. Additionally, the presence of different plasmablast clones is linked to IgG4-RD recurrence, and the quantity of plasmablasts is directly correlated with disease activity [28,29]. In untreated IgG4-RD patients, an increase in activated B lymphocytes in the peripheral blood is correlated with disease activity [22,28,29]. Although there is extensive descriptive and correlative data regarding B cells in this disease, the demonstrated clinical responsiveness to B cell-depleting therapy finally verifies the postulated pathogenicity of B cells [30].

Helper T cells, cytotoxic T cells, and regulatory T cells are the three main subtypes of T cells. Specialized CD4+ T cells, known as T follicular helper cells, play a key role in the development of a germinal center (GC), which is where B cells grow and antibodies are selected [31]. The expansion of circulating Tfh cells and the presence of many ectopic GCs in the pathological tissues have both been reported in IgG4-RD patients [32,33]. Basic pathogenic events in the development of IgG4-RD are presumed to be GC formation, B cell selection, and IgG4 antibody class-switch via various Tfh cell-produced cytokines [34,35].

Regulatory T cells are CD4+/CD25+ T cells that primarily release IL-10 and the transforming growth factor (TGF-β) to maintain immunological tolerance and immune homeostasis [36] and it is believed that these cells play a major role in the pathogenesis of IgG4-RD [37]. It is possible that IL-10, which is overexpressed in tissues affected by IgG4-RD, plays a function in controlling IgG4 class-switching, making it more likely that T follicular regulatory (Tfr) cells that express IL-10 are relevant to the IgG4 class-switching process in IgG4- RD. A 2019 study showed circulating Tfr cell numbers correlated with serum IgG4 concentrations and with the number of organs involved, but only a small fraction of these circulating cells expressed IL-10 [38]. A sizeable component of the immune cell infiltrates in IgG4-RD are composed of CD4+ T cells. A study verified the proliferation of CD4+ Cytotoxic T Lymphocytes (CTL) in the blood of IgG4-RD patients and showed that the dominant CD4+ CTL clone in the blood was also the most prevalent clone in the patient's afflicted tissue [34].

The quantity of tissue-infiltrating CD4+ CTLs correlates with the degree of organ involvement, and the number of circulating CD4+ CTLs in IgG4-RD declines in response to treatment-induced remission [34]. According to Mattoo et al., peripheral blood levels of proinflammatory substances, such as TGF-β, IL-1b, and IFN-γ, were elevated, pointing to a potential involvement for CD4+ CTL in tissue fibrosis [35]. Activated B cells may also play a role in fibrogenesis by directly promoting fibrosis through the expression of platelet-derived growth factor, a strong fibroblast activator. It's suspected that polarized anti-inflammatory "M2" macrophages also participate in the development of tissue fibrosis [38].

Compared to IgG4-RD, the pathogenesis of IgG4-RKD is less characterized. Many questions remain unanswered, including the specific crosstalk between various types of inflammatory cells in IgG4-RKD and the reasons why some patients have the kidney-specific disease. The majority of studies on the cytokines and lymphocytes involved in IgG4-RD have been conducted in patients without kidney involvement [5].

IgG4-related kidney disease

The kidney is particularly affected by IgG4-RD, with acute and chronic renal failure associated [39, 40]. According to the definition of IgG4-RKD, any pattern of renal injury is called IgG4-Related Kidney Disease [5]. Many presentations could be seen, and the kidney could be affected directly by renal parenchyma damage, and/or indirectly by post-renal obstruction due to urinary tract, prostate or retroperitoneal fibrosis [41]. The kidney is the unique organ that has two histologic subtypes of IgG4-RKD involvement. The most prevalent is Tubulointerstitial Nephritis (TIN), whereas Membranous Nephropathy (MN) linked to IgG4-RD occurs rarely [5,42]. In patients who have IgG4-RD, 15-25% have IgG4-TIN [43]. In a multicenter IgG4-RD cohort, the prevalence of IgG4-RKD was 11.7%, the predominant histological finding was IgG4-TIN (93.3%), and 26.7% of patients had membranous nephropathy. Some patients only present renal disease, but other organs are common involved [44]. Other renal manifestations include IgA nephropathy, membranoproliferative glomerulonephritis, mesangioproliferative immune complex glomerulonephritis, AA amyloidosis, sclerosing pyelitis, IgG4-related plasma cell arteritis, hydronephrosis associated with IgG4-related retroperitoneal fibrosis or ureteral inflammatory pseudotumor [39, 45]. The preponderance of IgG4-RKD symptoms is non-specific. The major clinical features are an insidious renal failure, radiographic mass lesion, or both [46]. Raissian et al. related that mean serum creatinine was lower in patients biopsied for mass lesions compared to those biopsied by renal failure (1.4mg/dL versus 4.2mg/dL) [45]. In a Mayo Clinic cohort with 34 patients whose diagnosis of IgG4-TIN was related, 77% had acute or progressive chronic renal failure [45]. Other authors related moderately impaired renal function at presentation (median creatinine 2,29 mg/dL) [44].

Clinical, laboratory and radiologic features

Patients with IgG4-TIN may have mild proteinuria and microscopic hematuria, sometimes without urinary WBCs or WBC casts, in contrast with other drug-induced acute TIN [45]. If concurrent MN was present, heavy proteinuria or nephrotic syndrome can occur. Some patients can present with obstruction due to retroperitoneal fibrosis or ureteral inflammatory pseudotumor [47]. Frequently bilateral involvement is observed, with multiple lesions areas and cortex extension. Sometimes only a large solitary mass is seen, but could present with small multiple peripheral cortical nodules, nodular or wedge shapes, or diffuse involvement. This lesions may be evident on imaging and are best seen on contrast CT scan or magnetic resonance [48]. On occasions they can be extra-parenchymal and can simulate lymphoma, pyelonephritis, metastatic solid tumors or vasculitis [48]. In approximately 70-80% of patients with IgG4-RKD, hypergammaglobulinemia or elevated serum IgG or IgG4 is present [45,47]. This is not specific because 10% of pancreatic cancer patients and 5% of the general population both had high serum IgG4 levels. Another particularity is in nephrotic syndrome when IgG4 levels remain low because of urinary loss of all IgG. Fifty percent of patients had low complement, CH50, C3 or C4. Curiously, low complement is not low

if the kidney is not involved. Another common finding is high serum IgE and peripheral eosinophilia. Antinuclear antibodies can be positive in some patients (approximately 30%), usually with low titer levels [39, 44].

Pathologic Features

IgG4-RKD can affect all compartments in the kidney, more frequently tubules and interstitium but also the glomeruli and the vessels. Histologic findings are mandatory to achieve the diagnosis [46].

IgG4-TIN

IgG4-TIN is the most common renal presentation of IgG4-RD [39,45]. IgG4-RKD displays a diffuse or multifocal lymphoplasmacytic interstitial infiltrate. There is variability in the ratio of fibrosis to inflammation, which includes acute TIN with minimal fibrosis, an intermediate pattern with some interstitial fibrosis and a marked inflammatory infiltrate, a densely fibrotic, paucicellular pattern with extensive tubular destruction and atrophy [46]. Collagen fibers in the fibrotic interstitium exhibit the hallmark storiform pattern as seen in other involved organs by IgG4-RD [45]. However, this characteristic pattern was seen less commonly in the kidney, but if present is more severe than in other organs [45,46]. Is frequently a moderate to marked interstitial increase in IgG4+ plasma cells and in some cases an increase in mononuclear cells with eosinophils. Focal and mild mononuclear tubulitis is frequently seen, but plasma cell tubulitis is not uncommon and severe tubulitis is rarely present [39,45]. Sometimes, numerous eosinophiles are associated with the lymphoplasmacytic interstitial infiltrate and the possibility of allergic TIN is made [45]. Most of the cases show Tubular Basement Membrane (TBM) immune complex deposits, with focal or diffuse granular staining for IgG. Immunofluorescence staining for IgG subclasses reveals IgG4-dominants. The deposits are also positive for Kappa and lambda light chains without monoclonal restriction, and also C3 with lesser intensity, sometimes C1q. TBM deposits are found more frequently in specimens with interstitial fibrosis and only in areas of the fibroinflammatory process [39,46].

Immunohistochemical staining for IgG4 reveals IgG4+ plasma cells, however IgG4+/IgG+ plasma cell ratio is a more powerful tool than IgG+ plasma cell counts in establishing the diagnosis of IgG4-RD [46]. The amorphous electron-dense deposits detected by electron microscopy match the TBM deposits seen by immunofluorescence [39,46].

IgG4- Related glomerular lesions

MN in the setting of IgG4-RKD is called IgG4-related MN and the main feature is heavy proteinuria with nephrotic syndrome. Glomeruli are normal on light microscopy in majority of cases or have sometimes thickness glomerular capillary loops on hematoxylin and eosin-stained sections. Glomerular Basement Membrane (GBM) spikes may occasionally be seen on silver or PAS (Periodic Acid–Schiff) stains, subepithelial immune complex deposits may at times be seen on a trichrome stain [45-47]. Immunostaining for the phospholipase A2 receptor was negative in all biopsies stained, which supports the secondary etiology [45].

IgG4-MN typically shows segmental or global granular GBM bright staining for IgG, C3, both kappa and lambda chains. Immunofluorescence for IgG subclasses reveals that the glomerular deposits contain predominant IgG4 [39]. IgG4-MN presents subepithelial electron-dense deposits on electronic microscopy [46].

IgG4-related vascular lesions

Vessels are generally normal in IgG4-RKD. Plasma cell-rich renal arteritis has recently been described in a patient with IgG4-TIN [49]. This lesion affected small and medium size arteries on a biopsy, with marked lymphoplasmacytic infiltration of the intima, media and adventitia and many IgG4+ plasma cells in the arterial wall. Neither fibrinoid necrosis of the arteries or rupture of the elastic was seen and neutrophils were not present in the lesions [47].

Diagnosis

Diagnosis of IgG4-RD remains a clinical challenge because there is no simple diagnostic test.(50) ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) classification criteria for IgG4-RD have been developed and validated some criteria that demonstrate specificity of 97.8% achieved at a threshold of ≥20 points and a sensitivity of 82.0% [1]. However, these criteria are not pretended to use in clinical practice as the basis of establishing the diagnosis of IgG4-RD, because it was assumed that broad relevance was in the investigation studies [1].

The gold standard diagnostic criteria for IgG4-RD were published by International Consensus Criteria for IgG4-RD [49]. They preconized that diagnosis is made by the combined presence of the characteristic histopathologic findings and increased numbers of IgG4 plasma cells [49]. Morphologic appearance on biopsy is more important for diagnosis than tissue igG4 counts or IgG4:IgG ratio [50]. The Mayo Clinic has proposed a diagnostic framework for IgG4-TIN based on histologic, immunophenotypic, imaging features, laboratory, and other organ involvement. The patients need to have typical histology of plasma cell-rich infiltrate and increase IgG4 plasma cells and at least one other category including typical imaging, serology (elevated IgG or IgG4) and another organ with an inflammatory process [39].

A working group in the Japanese Society of Nephrology also has a proposal for diagnostic criteria and an algorithm for IgG4-RKD [51]. They classified into three categories: definitive, probable, possible. The combination of kidney injury (abnormal urinalysis or decreased renal function) associated with either elevated serum IgG level, hypocomplementemia or elevated serum IgE could obviate the need for the typical radiographic renal features [52] (table 1). However, these methods are not validated and are required prospective studies to verify the sensitivity and specificity of these criteria.

	Mayo Clinic46	Japanese Society of Nephrology53
Clinical features	None	Clinical or laboratory evidence of kidney injury, including abnormal renal function or abnormal urinalysis with at least one of 3: elevated serum IgG or IgE level or hypocomplementemia
Serology	Elevated serum IgG4 or total IgG level	Elevated serum IgG4 or total IgG level
Histology	Plasma cell-rich TIN with >10 IgG4+ plasma cells/hpf field in the most concentrated field* TBM immune complex deposits by immunofluorescence, immunohistochemistry, and/or electron microscopy ł	a) Dense lymphoplasmacytic infiltrate with >10 IgG4+ plasma cells/hpf and/or IgG4/IgG+ plasma cell ratio of >40% b) Characteristic storiform fibrosis

Imaging	Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvemen; Diffuse marked enlargement of Kidneys	Abnormal radiographic findings: Multiple low-density lesions on enhanced CT; Diffuse kidney enlargement; Hypovascular solitary kidney mass; Hypertrophic lesion of the renal pelvic wall
Other Organ Involvement	Autoimmune pancreatitis, sclerosing cholangitis, inflammatory masses in any organ, sialadenitis, inflammatory aortic aneurysm, lung involvement, retroperitoneal fibrosis	IgG4-RD in other organs. Necessary exclude: systemic lupus erythematosus, systemic vasculitis and cryoglobulinemia. Malignant lymphoma, urinary tract carcinomas, renal infarction and pyelonephritis.
Diagnosis establishment	Diagnosis of IgG-TIN requires the histologic feature of plasma cell-rich TIN with increased IgG4+ plasma cells and at least one other feature from the category of "imaging", "serology", or "other organ involvement". *Mandatory criterion ł Supportive criterion, present in >80% of cases	"Definite" IgG4-RKD occurs with three of the following: clinical features, serology, and histologic features (a and b); imaging, serology, or other organ involvement; or clinical feature, serology, histologic features (a only), organ involvement. "Probable" and "Possible" disease occurs with fewer criteria.

Table 1: Proposal Diagnostic Criteria for Igg4-TIN.

Treatment

Currently, there are no randomized controlled studies to guide the management of IgG4-RD and optimal treatment is still unknown. Glucocorticoids for IgG4-RD and IgG4-RKD are the first line therapy and the most common regimen is prednisolone 0.6-1mg/kg/day to induce remission, with progressive tapered thereafter and maintenance prednisolone in some cases. This regimen was extrapolated from the treatment of type autoimmune pancreatitis from other organ involvement. The maintenance period varies from 1-3 years [53-55].

A typical finding in IgG-RKD is quick responsiveness to corticosteroid therapy, with improved renal dysfunction as well as radiographic and serological abnormalities (increases in complement, normalizes in IgG4 levels, decreased in the ratio and absolute number of IgG4+ plasma cells) [39,45]. Although is responsive, delays in diagnosis and beginning treatment, lead to a risk of irreversible organ damage, which include progression to end-stage kidney disease [39,52]. It was reported by Arai et al. in 4 patients submitted to a re-biopsy after corticosteroid therapy relieves in the stage of fibrosis [56]. A retrospective cohort design including 24 patients who underwent renal biopsy, in most of them the renal function recovery is only partial, suggesting that early treatment is essential [57].

In 2015, an International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease proposed 3 steps:

1. Induction with prednisolone 40mg/d, with the possibility of rituximab (RTX) in patients intolerant or resistant to corticotherapy.
2. Tapered treatment with a duration of 3-6 months.
3. Maintenance treatment with low dose prednisolone associated or not with sparing agents – azathioprine, cyclophosphamide, mycophenolate mofetil or calcineurin inhibitors.

These must be considered in relapses, multiorgan involvement or elevated serum IgG4 [52]. Despite the initial response, high relapse rates occur during tapering or discontinuation [55,58]. A retrospective multicenter study with 166 patents concludes that glucocorticoids are effective in treating IgG4-RKD, however relapses are often observed. They also related those patients treated with a dose of 0.4-0.6mg/kg/day have fewer relapse rates. Fast reduction of the initial dose (> 0.4mg/day) was also associated with a higher relapse rate [58].

Rituximab, which is still under investigation, is an alternative, mainly in cases refractory to steroids and other immunomodulators, or toxic effects. The first randomized, clinical trial on the efficacy of rituximab on IgG4-RD was performed at the Massachusetts General Hospital and Mayo Clinic and conclude that appears to be effective at controlling disease even without concomitant corticoid therapy [30]. A prospective follow-up of 4 years of 5 patients that received rituximab show a significant drop in interstitial plasma cell infiltrates as well as normalization of IgG4+/IgG+ plasma cells on re-biopsy. Both clinical and immunological improvement persisted during the follow-up. The TIN subgroup did not require any maintenance therapy [59]. A French retrospective multicenter study of IgG4-RD patients treated with rituximab conclude that is effective for both induction therapy and treatment of relapses in IgG4-RD, but relapses are frequent. They proposed a maintenance therapy with systematic RTX infusions for longer relapse-free survival [60].

Other steroid-sparing agents are acceptable second choices, to avoid long-term steroid-related side effects because this condition affect middle age to elderly patients who are at major risk of corticoid effects. However, only a limited amount of data suggest their effects and efficacy are not properly assessed on IgG4-RKD [52]. In conclusion, glucocorticoids remain the first approach for most patients in absence of major contra-indications, however the incomplete or relapse observed in many patients indicate that rituximab can be an option [30].

Conclusion

IgG4-RD is a fibro-inflammatory disease that can affect any organ or tissue, including the kidney. The pathogenesis does not appear to be preferentially determined by the serum elevation of IgG4 and it appears that hereditary or acquired abnormalities, as well as B and T lymphocytes and profibrotic factors, are involved in its formation. Despite its potential to cause glomerular and tubulointerstitial disease, the main histologic hallmark is a diffuse or multifocal lymphoplasmacytic interstitial infiltration, with TIN being the most frequent histological finding. The gold standard diagnostic for IgG4-RD is based on histological findings and the rise in IgG4 plasma cells and the two algorithms provided in this article can be helpful even if there isn't an entirely reliable diagnostic procedure or set of criteria at this time. Although the perfect therapy is still being sought, glucocorticoids are still the standard of care. Rituximab or another steroid-sparing medication is another option, particularly for patients who do not respond well to corticosteroids or have frequent relapses. In summary, much is still unknown regarding this disease, both in relation to its pathophysiology and to the ideal diagnosis and treatments.

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