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REVIEW

Immunoglobulin G4-related kidney diseases: An updated review

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Abstract

This review will encompass definition, pathogenesis, renal clinical manifestations and treatment of immunoglobulin G4-related diseases (IgG4-RDs). IgG4-RD is a recently recognized clinical entity that often involves multiple organs and is characterized by high levels of serum immunoglobulins G4, dense infiltration of $IgG4^+$ cells and storiform fibrosis. Cellular immunity, particularly T-cell mediated immunity, has been implicated in the pathogenesis of IgG4-RDs. The most frequent renal manifestations of IgG4-RD are IgG4-related tubulointerstitial nephritis, membranous glomerulopathy and obstructive nephropathy secondary to urinary tract obstruction due to IgG4-related retroperitoneal fibrosis. IgG4-RD diagnosis should be based on specific histopathological findings, confirmed by tissue immunostaining, typical radiological findings and an appropriate clinical context. The first line treatment is the steroids with two warnings: Steroid resistance and relapse after discontinuation. In the case of steroid resistance, B cell depleting agents as rituximab represent the second-line treatment. In the case of relapse after discontinuation, steroid treatment may be associated with steroid sparing agents. Since the disease has been only recently identified, more prospective, long-term studies are needed to an improved understanding and a more correct and safe treatment.

Key words: Immunoglobulin G4-related disease; Storiform fibrosis; Lymphoplasmacytic infiltration; Tubulointerstitial nephritis; Steroid treatment; B cell depleting agents

Core tip: Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized clinical entity that often involves

multiple organs; it is characterized by high levels of serum immunoglobulin G4, dense infiltration of IgG4+ cells, and storiform fibrosis. Cellular immunity, particularly T cell-mediated immunity, has been implicated in the pathogenesis of IgG4-RD. The most frequent renal manifestations of IgG4-RD are IgG4-related tubulointerstitial nephritis, membranous glomerulonephropathy and obstructive nephropathy secondary to urinary tract obstruction due to IgG4-related retroperitoneal fibrosis. In IgG4-membranous glomerulopathy, proteinuria can be in the nephrotic range. Steroid treatment is the first-line therapy. For relapsing or refractory cases, immunosuppressants could be combined with steroids.

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INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a recently identified systemic fibroinflammatory condition that mimics several autoimmune, malignant and rheumatologic diseases. IgG4-RDs may affect several organs as recognized since the 1st international symposium held in Boston in 2011[1] (Table 1). To date the diagnosis of IgG4-RDs unifies several pathologic conditions previously considered well-defined and distinct disorders and now recognized as organ manifestations of IgG4-RD[2-4] (Table 2). Other diseases merely mimic IgG4-RD and hence should be considered and classified separately because they represent diseases with distinct features (Table 3).

Consequently, the classification is rather confusing; hence the American College of Rheumatology recently recommended a revised nomenclature of IgG4-RD and its individual organ system manifestations[5].

Basing on clinical presentation per site of involvement IgG4-RD may be classified as in Table 4.

In this review, following the description of the hallmarks characteristic of IgG4-RD, its epidemiology and its pathophysiology, we principally highlight the so-called IgG4-related kidney disease (IgG4-RKD), its clinical and histological manifestations, the diagnostic criteria and treatment.

RESEARCH METHODOLOGY

We have analyzed the available papers on IgG4-RD pathogenesis, IgG4-RKD clinical and diagnosis and IgG4-RD therapy by a review of the currently available papers. A literature search was performed using PubMed (NCBI/NIH) with the search words "IgG4-RD pathogenesis", "IgG4-RKD clinical and diagnosis", "IgG4-RD treatment", "IgG4-RD classification". As first line research the papers published in the last three years were examined. Paper selection has been made according the relevance of the journal, the authors, and the dimension of the study and the novelty of the findings. So doing 40 papers recently published have been selected, then we proceeded in a backward way and studies previously published have also been included.

HISTOLOGICAL ASPECTS OF IgG4-RD

The major histopathological features associated with IgG4-RD are represented in Table 5.

Pathological features of IgG4-RD may vary according to the organ involved. Obliterative arteritis and neutrophilic infiltration rarely occurs. When present they are characteristic of lung lesions and occur in the alveolar spaces[6]. Absence of storiform fibrosis and lack of obliterative phlebitis may be observed in diseases involving the salivary glands, lymph nodes and kidney[7].

Hallmarks of the diseases are a lymphoplasmacytic infiltrate enriched with IgG4 plasma cells, a storiform pattern of fibrosis and obliterative phlebitis[3,8]. The pattern is often similar to a cartwheel with the bands of fibrosis emanating from the center representing the spokes of the wheel. Immunoperoxidase staining revealed that nearly all plasma cells are strongly positive for IgG4, whereas the small lymphocytes are negative. A total obliteration of venous channels (obliterative phlebitis) may be present. Eosinophils and fibroblasts are present as well[9,10].

Several caveats must be considered in the interpretations of tissue lesions and particularly IgG4 positive plasma cells: (1) IgG4 positive plasma cells are generally present in the lesions, but focal aggregations of IgG4-positive cells are atypical; (2) The absolute number of IgG4 positive plasma cells should be interpreted according to the specific tissue[8]; (3) The ratio of IgG4 to IgG positive plasma cells must be at least 40%; and (4) IgG4-RD cannot be diagnosed on the basis of infiltration by IgG4-positive plasma cells alone because these cells may also be present in other inflammatory or neoplastic disorders[11].

EPIDEMIOLOGY

IgG4-RD was first recognized as a systemic entity in the early 2000s, when autoimmune pancreatitis (AIP) type I patients demonstrated similar conglomerations of fibroinflammatory tissue in other organs or lesions, such as retroperitoneal and mediastinal fibrosis, inflammatory pseudo tumor of lung and liver as well as interstitial nephritis[12-14]. Due to the relatively recent discovery, minimal epidemiological data exist. The majority of the patients reported in the literature are from Japan[15]; however, to date it is not clear whether this higher prevalence is due to genetic or environmental causes or simply because the disease was specifically investigated within this population. The average age of disease onset is between 61 and 70 years and there is a clear male

Table 1 Representative organ manifestations in IgG4-related disease

Organs adopted at the 1st International symposium in Boston in 2011	
Pancreas	Lymphoplasmacytic sclerosing pancreatitis
Eye/orbit/lacrimal glands	Dacryadenitis/orbital inflammation/pseudotumour
Salivary glands	Sialoadenitis/Mikulicz disease/Kuttner's tumor
Aorta/arteries	Aortitis/periaortitis/arteritis
Mediastinum/retroperitoneum	Mediastinitis/retroperitoneal fibrosis/mesenteritis
Kidney	Tubulointerstitial nephritis/renal pyelitis
Pachimeninges/hypophysis	Pachimeningitis/hypophysitis
Lung	Lung disease/inflammatory pseudotumor
Pleura/pericardium	Pleuritis/pericarditis
Breast	Mastitis
Bile ducts/gall bladder/ liver	Sclerosing cholangitis/cholecystitis/hepatopathy
Prostate	Prostatitis
Skin	Skin disease/pseudolymphoma
Limph node	Lymphadenopathy
Organs newly recognized after the Boston meeting	
Nerve	Infraorbital nerve swelling
Paranasal sinus	Chronic rhinosinusitis
Testis/paratestis	Paratesticular pseudotumour
Ureter	Ureteritis
Urethra	Urethritis
Urinary bladder	Interstitial cystitis

Table 2 Conditions once regarded as individual disorders now recognized to be part of IgG4-related disease

Autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis)
Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
Fibrosing mediastinitis
Hypertrophic pachymeningitis
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
Inflammatory pseudotumour (affecting the orbits, lungs, kidneys, and other organs)
Küttner's tumor (affecting the submandibular glands)
Mikulicz's disease (affecting the salivary and lacrimal glands)
Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)
Periaortitis and periarteritis
Inflammatory aortic aneurysm
Retroperitoneal fibrosis (Ormond's disease)
Riedel's thyroiditis
Sclerosing mesenteritis

Table 3 Mimickers of immunoglobulin G4-related disease

Autoimmune	Malignancy	Other
Antineutrophil cytoplasmic antibody-associated vasculitis	Adenocarcinoma and squamous cell carcinoma	Castleman's disease
Granulomatosis with polyangiitis	Extranodal marginal zone lymphoma	Cutaneous plasmocytosis
Eosinophilic granulomatosis with polyangiitis	Inflammatory myofibroblastic tumor	Erdheim-Chester disease
Microscopic polyangiitis	Lymphoplasmacytic lymphoma	Inflammatory bowel disease
Sarcoidosis	Lymphoproliferative disease	Perforating collagenosis
Sjogren's disease	Follicular lymphoma	Primary sclerosing cholangitis
		Rhinosinusitis
		Rosai-Dorfman disease
		Splenic sclerosing angiomatoid nodular transformation
		Xanthogranuloma

predilection with the exception of the forms involving the head and neck[16,17].

PATHOPHYSIOLOGY

Several immune-mediated mechanisms are involved in the pathophysiology of IgG4-RD. They are divided into: (1) Initiating mechanisms; and (2) specific disease pathways.

Potential initiating mechanisms

Genetic background: In Japanese populations, the

Table 4 Clinical presentation of immunoglobulin G4-related disease per site of involvement

Organ system	Nomenclature	Clinical features
Orbit	IgG4-related ophthalmic disease IgG4-related orbital inflammatory pseudo-tumor IgG4-related pan-orbital inflammation IgG4-related orbital myositis	Swelling of orbital tissue and proptosis
Lacrimal gland	IgG4-related dacryadenitis	Bilateral swelling of the glands and impaired production of secretion
Salivary gland	IgG4-related sialoadenitis IgG4-related parotitis IgG4-related submandibular gland disease	Bilateral swelling of the glands and impaired production of secretion
Thyroid	IgG4-related thyroid disease	Hypothyroidism, neck pain, dysphagia, dyspnea
Liver	IgG4-related hepatopathy	Jaundice, right upper quadrant mass
Biliary tract and gall bladder	IgG4-related sclerosing cholangitis IgG4-related cholecystitis	Jaundice, pruritus, cholestasis
Blood vessels	IgG4-related aortitis/periaortitis IgG4-related periarteritis	Chest pain, dyspnea
Retroperitoneal fibrosis	IgG4-related retroperitoneal fibrosis	Flank pain, obstructive symptoms, peripheral edema
Kidneys	IgG4-related kidney disease Tubulo-interstitial nephritis secondary to IgG4-related disease	Hematuria, proteinuria, hypocomplementemia, chronic renal failure
Skin	IgG4-related skin disease	Papulonodular lesions, plaques, purpura

Table 5 Major histopathological features associated with immunoglobulin G4-related disease

Dense lymphoplasmacytic infiltrate
Fibrosis, arranged at least focally in a storiform pattern
Obliterative phlebitis
Phlebitis without obliteration of the lumen
Increased number of eosinophils

frequencies of human leukocyte antigen (HLA) serotypes DRB1*0404 and DRB1*0401 are significantly higher in patients with AIP, a common manifestation of IgG4-RD[18].

Non-HLA genes with single nucleotide polymorphisms (SNPs) are also involved in the expression of disease encoding proteins, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), tumor necrosis factor alpha (TNFα) and Fc receptor like 3, expressed on B cells (FCRL3)[19-21] .

Bacterial infection and molecular mimicry: Homologies existing between human carbonic anhydrase Ⅱ and the alpha carbonic anhydrase of *Helicobacter pylori* (*H. pylori*), as well as between the plasminogen binding protein of *H. pylori* and the ubiquitin-protein ligase E3 component n-recognin 2 expressed on pancreatic cells have raised the question of a possible pathogenetic role of molecular mimicry involving *H. pylori*[22,23]. The contribution of the innate immune response to IgG4-RD is highlighted by the fact that various species of bacteria may induce the stimulation of toll-like receptor ligand in the production of IgG4 and interleukin-10 (IL-10) from peripheral blood mononuclear cells (PBMCs)[24].

Autoimmunity: The involvement of autoimmunity in activating Th cells in IgG4-RD is suspected because of the presence of auto antibodies against carbonic anydrases, lactoferrin, pancreatic secretory trypsin inhibitors and trypsinogens[25-27]. In addition, electron-dense deposits have been observed in the renal tubular membrane and pancreatic ducts of patients affected by IgG4-RD[28].

Specific disease pathways

Th cells and regulatory immune reaction: T cells may ultimately be implicated in the pathogenesis of IgG4-RD. Potential triggers, such as foreign pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) may be recognized by Toll-like receptors (TLR), which may induce the production of IgG4 by $CD19^{+}$[29]. More importantly these triggers by activating the innate immune system, may determine the state of polarization of T helper cells in IgG4-RD. Treg cells are also activated, as indicated by the high expression levels of forkhead box P3 (FOXP3) mRNA in the tissue[30].

Activated T helper cells and Treg cells may produce inflammatory cytokines, including interferon gamma (IFNγ), IL-4, IL-10, IL-5 and IL-13. IL-4 and IL-10, possibly produced by T follicular helper cells, and may cause class switching of auto reactive B cells to IgG4 and IgE and induce differentiation and expansion of IgG4 plasma cells[31,32]. IL-5, IL-13 and tumor growth factor beta (TGFβ) may lead to the recruitment of eosinophils and the activation of fibroblasts[4,33]. IFNγ may also contribute to the activation of macrophages that induce fibrosis[4] and induce a dense storiform fibrosis. On the other hand, B cells that recognize self antigens are capable of efficient antigen presentation to auto reactive T cells, thereby mediating a vicious cycle between T and B lymphocytes[34].

Role of IgG4 antibodies: It is likely that IgG4 per se have a poor role in generating IgG4-RD. The IgG4 antibodies bind weakly to complement C1q and Fcγ receptors. As a consequence, they are not involved

in antibody-dependent cell-mediated cytotoxicity[35]. Additionally, IgG4 form half antibodies through the process of Fab arm exchange[35]. The consequence is a reduced ability to bind to the antigen and to generate immune complexes. Moreover, IgG4 antibodies seem to be stronger suppressors than inducers of inflammation[33].

All the aforementioned mechanisms and pathways are summarized in fig. 1, which unifies all the different mechanisms. Auto-antibodies may drive the Th2-cell response. Molecular mimicry as well as microbial components may also act as triggers for IgG4-RD, wherein they may stimulate innate immune mechanisms by activating nucleotide-activating factors belonging to the tumor necrosis factor (TNF) family (NODR) and the toll-like receptor 2 (TLR2) to produce B cell activating factor (BAFF) and a proliferative-inducing ligand (APRIL), which leads to B cell modifications in a T cell-independent manner. An expansion in Treg cells may contribute to both B-cell Ig class switching and fibrosis. A treatment sensitive expansion in circulatory plasma blasts is present in the active disease.

IgG4-KIDNEY RELATED DISEASES

The kidney may be affected by different histopathologic lesions in the course of IgG4-KRD. This fact represents a peculiarity with respect to other organs that may be affected by IgG4-RD.

The kidney may be affected directly by histopathologic lesions affecting the parenchyma or indirectly as in the case of retroperitoneal fibrosis, which causes renal function impairment because of the obstruction of the urinary tract.

IgG4-related tubulointerstitial nephritis (TIN) represents the parenchymal lesions more often affecting the kidney. The other more frequent lesion is represented by membranous glomerulopathy, in which lymphoplasmacytic infiltrate and storiform fibrosis, typical of IgG4-RD are not present. Other types of glomerular lesions, such as Schonlein Henoch purpura nephritis, may be infrequently observed during the course of IgG4-RD. When present, it is often associated with TIN[36,37]. IgA nephropathy, membrano-proliferative glomerulonephritis and minimal change disease have also been described[38]. Recently, a case of AA Amyloidosis affecting the kidney in the course of IgG4-RD has been reported[39]. Altogether, renal involvement in the course of IgG4-RD occurs in approximately 15% of patients.

IgG4 RELATED TIN

As mentioned above, IgG4-TIN is the most common renal manifestation of IgG4-RD, and the majority of data concerning this lesion come from two series of biopsies: A Japanese cohort[40] and an American cohort[41].

IgG4-related TIN is often diagnosed in the setting of already known extra renal disease. The most common associated manifestations are sialoadenitis, lymphadenopathy, type I AIP and dacryadenitis. When IgG4-KRD with TIN is the only manifestation, the diagnosis is made by a renal biopsy performed because of acute or progressive renal failure.

The Japanese Society of Nephrology proposed a useful algorithm for the diagnosis of IgG4-related TIN[42]. According to the algorithm, in the case of abnormal renal function, principally when associated with high serum IgG or serum IgE, after exclusion of secondary diseases, such as lupus, vasculitis, *etc.,* and with serum IgG4 higher than 135 mg/dl, characteristic radiologic findings, such as multiple low density lesions, diffuse kidney enlargement and/or solitary hypovascular mass should be looked for and renal histology should be performed.

Laboratory findings

In addition to signs of renal dysfunction, nearly all patients with IgG4-related TIN have elevated serum concentrations of IgG and IgG4. Sixty percent of the patients have hypocomplementemia. Peripheral eosinophilia is observed in approximately 40% of the patients and positive antinuclear auto antibodies (ANA) are observed in 32%[43,44].

Radiologic features

Multiple hypodense lesions are the most common observation[40,41]. Such lesions were present in 69.6% of the Japanese cohort and in 78.3% of the Mayo Clinic cohort. Using diffusion-weighted magnetic resonance imaging (MRI), a recent study reported 100% sensitivity with respect to computed tomography (CT)[45]. However, a caveat is that when a solid mass is observed, it may be misdiagnosed as a malignant neoplasm and lead to an unnecessary nephrectomy[46,47].

Histopathological features

Plasma cell-rich TIN with fibrosis and often infiltrating eosinophils represent the typical histopathologic appearance[8,48]. This aspect represents the gold standard for diagnosis and allows for filtering out malignancies and other mimicking diseases[49] (Figure 1). Fibrosis often has a storiform pattern. In IgG4-TIN, fibrosis is generally more severe than the fibrosis observed in other forms of TIN[1]. Obliterative phlebitis, a critical pathological feature of IgG4-RD is rarely observed in IgG4-TIN, probably because of the lack of veins in the biopsy specimen[8,41]. Other histopathological features are represented by the fact that affected and unaffected areas are clearly demarcated[50]. Additionally, sometimes the lesions infiltrate the renal capsule and beyond[51].

Overall there is a spectrum of microscopic appearances, which includes TIN with minimal fibrosis, interstitial fibrosis with marked inflammatory infiltrate and an extensive tubular destruction and atrophy[41,52]. More recently, according to the Mayo Clinic series, 3 histological patterns of IgG4-TIN were described: (1) Acute TIN with minimal interstitial fibrosis; (2) chronic TIN with expansive interstitial fibrosis; and (3)

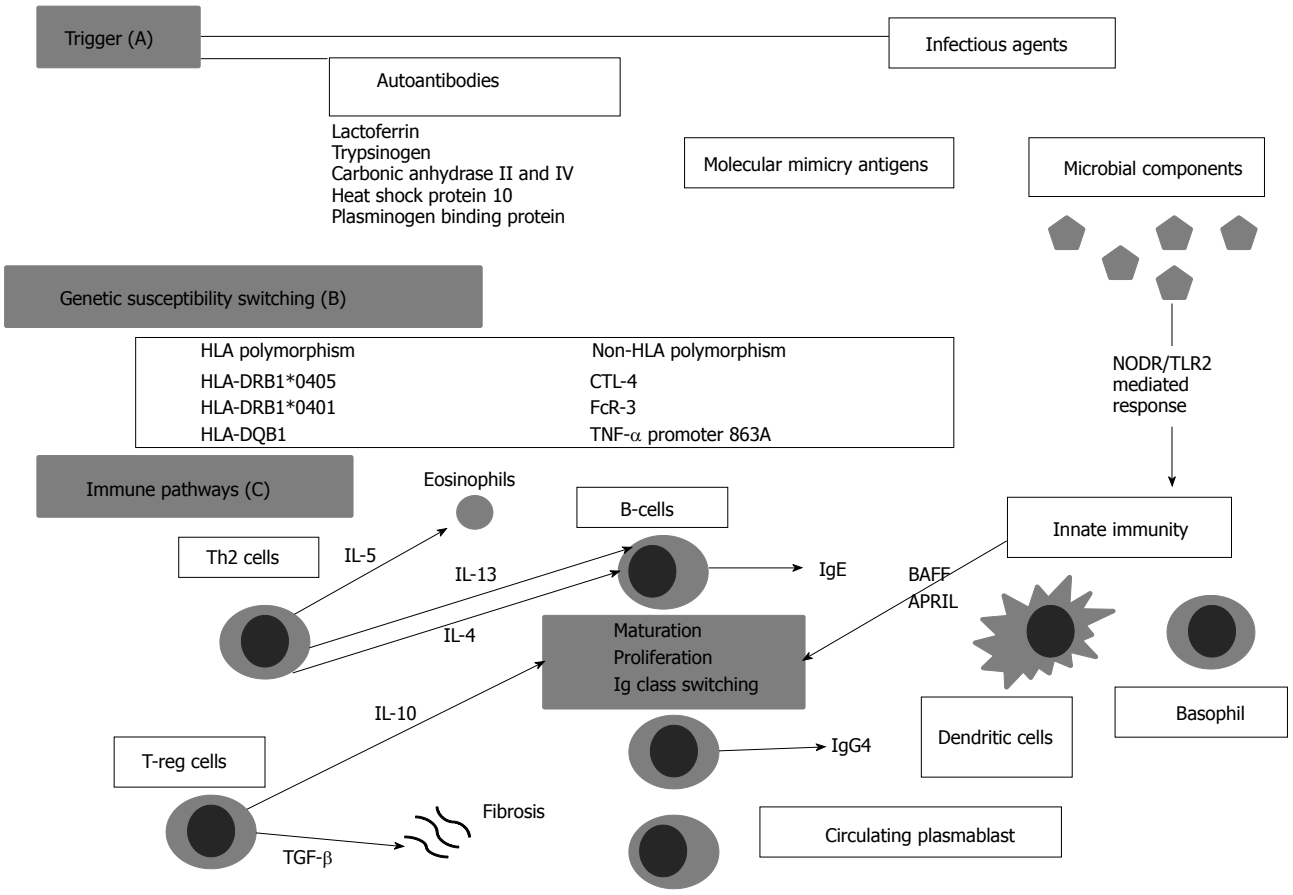

Figure 1 Pathogenesis of immunoglobulin G4-related disease. CTL-4: Cytotoxic T-lymphocyte-associated antigen 4; FcR-3: Fc receptor like 3; TNFα: Tumor necrosis factor alpha; NODR: Nucleotide-activating factor belonging to the tumor necrosis factor (TNF) family; TLR2: Toll-like receptor 2; BAFF: B cell activating factor; APRIL: A proliferative-inducing ligand; TGFβ: Tumor growth factor beta.

advanced sclerosing pattern[43].

Immunohistochemical staining for IgG4 reveals IgG4$^+$ plasma cells, even if the increased number of interstitial IgG4$^+$ plasma cells is not specific for IgG4-TIN and 80% of patients have granular IgG and C3 deposits along the tubular basement membrane (TBM)[41]. Deposits of immune complexes have been observed as electron dense deposits in the TBM[41,53]. Because IgG4 cannot activate the complement system, other subclasses, such as IgG1, may play a role in activating complement and forming immune complexes.

Diagnosis and differential diagnosis

In order to diagnose IgG4-TIN, two sets of diagnostic criteria have been proposed as shown in Table 6. The criteria proposed by Raissian[41] require a TIN with > 10 IgG4$^+$ plasma cells per high-power field (HPF) in addition to either elevated serum IgG4 or evidence of extra renal IgG4-RD. Moreover, Kawano[54] classified patients with features of IgG4-TIN into three categories: Definite, probable and possible.

Contrasted enhanced computed tomography (CT) is widely used to identify radiographic abnormalities in IgG4-TIN[55], even though MRI has a higher sensitivity[45] The most common finding in CT are bilateral, hypodense lesions often multiple that involve the renal cortex and may have the aspect of small peripheral cortical nodules, well or poorly defined round lesions and diffuse patchy lesions[55].

Differential diagnosis of IgG4-TIN includes distinction from allergic TIN, chronic pyelonephritis, granulomatosis with polyangiitis, Castleman disease and other autoimmune TINs. Allergic TIN does not have storiform fibrosis and does not have as many plasma cells in the infiltrate.

Chronic pyelonephritis has several neutrophils in the infiltrate and a typical radiographic pattern. Granulomatosis with polyangiitis has necrotizing vasculitis or granuloma. Moreover, ANCA antibodies in the serum are not present in IgG4-TIN.

Differential diagnosis with Castleman disease may be difficult, and recently, two cases of Castleman disease with kidney involvement closely mimicking IgG4-TIN have been reported[56]. Finally, TIN due to other autoimmune diseases demonstrates clinical and laboratoristic signs of the autoimmune disease, such as lupus or Sjogren syndrome[41].

GLOMERULAR NEPHROPATHIES RELATED TO IgG4-RD

The most important and frequent glomerular lesion is membranous glomerular nephropathy (MGN), which

Table 6 Two proposed criteria for IgG4-TIN by the Mayo Clinic and the Japanese Society of Nephrology

Criterion	The Mayo Clinic criteria	JSN criteria
Histology	Plasma cell-rich TIN with > 10 IgG4+ plasma cells/HPF in the most concentrated field (mandatory criterion) TBM immune complex deposits by immunofluorescence, immunochemistry, and/or electron microscopy	Dense lymphoplasmacytic infiltrate with > 10 IgG4+ plasma cells/HPF and/or IgG4/IgG+ plasma cell ratio of > 40%; Characteristic storiform fibrosis
Imaging	Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement	Multiple low-density lesions or enhanced CT, diffuse kidney enlargement, hypovascular solitary nodule, hypertrophic lesion of the renal pelvic wall
Serology	Elevated serum IgG4 or total IgG level	Elevated serum IgG4 or total IgG level
Clinical features	None	Clinical or laboratory evidence of kidney damage
Other organ involvement	Characteristic findings of IgG4-RD in other organs	Characteristic findings of IgG4-RD in other organs
Definite IgG4-TIN	The histologic feature and at least one other feature from imaging, serology or other organ involvement	The histologic feature (a and b) and at least two of other features from imaging, serology or other organ involvement

IgG4-RD: Immunoglobulin G4-related disease; IgG4-TIN: Immunoglobulin G4-related tubulointerstitial nephritis; CT: Computed tomography.

represents 7% of all IgG4-RKD cases according to the two largest biopsy series[40,41]. Other rare glomerular lesions are classified into two subgroups according to the prevalence of a Th2 response. Henoch Schonlein purpura nephritis and minimal change syndrome are associated with a prevailing Th2 response[38,57], whereas IgA nephropathy and membrano proliferative glomerulonephritis are associated with a poor Th2 response[58,59].

Clinical and laboratory features

IgG4-related MGN occurs principally in males. Other extra renal manifestations of IgG4-RD are often present[60]. Heavy proteinuria with nephritic syndrome is the principal clinical feature. Half of the patients have concomitant TIN. In these patients, TIN is probably the cause of renal dysfunction[61].

Renal histopathology

All patients exhibit sub-epithelial deposits in a membranous pattern. Immunofluorescence demonstrated IgG4 to be the prevailing immunoglobulin. No anti phospholipase A2 receptor (PLA2r) antibody has been observed in IgG4-MGN. Some patients affected by IgG4-MGN also had mesangial and sub-epithelial deposits[41]. Whether the target antigen in IgG4-MGN is located in the podocytes, as in idiopathic MGN, is not known.

RENAL AMYLOIDOSIS RELATED TO IgG4-RD

To date only one case of renal AA amyloidosis associated with extra-renal IgG4-RD has been described[39].

Clinical features

The patient suffered from a mesenteric IgG4-RD with involvement of the lymph nodes. AA amyloidosis developed after 16 years; however, whether or not the treatment of IgG4-RD caused a delay in the development of AA amyloidosis, is not known.

RETROPERITONEAL FIBROSIS

Compared to the described renal diseases, wherein renal dysfunction is caused by parenchymal lesions, retroperitoneal fibrosis causes renal dysfunction by obstruction of the urinary tract.

Pathogenesis

Development of retroperitoneal fibrosis in the periaortic and periiliac retroperitoneum results in hydronephrosis and inflammatory abdominal aortic aneurysm[62,63].

Hydronephrosis is caused by the diffusion of the periaortic inflammation to the ureter, resulting in its obstruction. Involvement of both kidneys may result in end-stage renal failure.

TREATMENT

The optimal treatment for IgG4-RD is unknown. Indeed, to date, there have been no randomized clinical trials that have evaluated and compared the effectiveness of different treatment regimens[33]. Although some patients affected by IgG4-RD may have spontaneous remission and do not require treatment[64], a prompt treatment is generally recommended to avoid deleterious complications and consequences of the evolving disease.

Glucocorticoids are currently the first line treatment for IgG4-RD[65,66] and IgG4-RKD[33,42]. An alternative are the B depleting agents as rituximab (RTX), which is still under investigation in clinical trials[67,68]. An international panel of experts developed recommendations for the management of IgG4-RD and recommended steroids as first line agents for remission induction, while there was low agreement on the use of RTX[49].

IgG4-RD may affect several organs. Recently, Della Torre *et al*[69] categorized six principal clinical phenotypes.

In all the phenotypes the authors confirmed the efficacy of a 4- to 6-mo course of glucocorticosteroids. In the case of steroid toxic effects or steroid resistance, steroid sparing agents or RTX may be considered. According to the aforementioned international consensus[49] IgG4-RD treatment should comprise the following three steps[70]: (1) Induction treatment (prednisolone 40 mg/d). Consider B cells depletion therapy if patient is resistant or intolerant to glucocorticosteroids; (2) Tapering treatment with a

duration of 3-6 mo; and (3) Maintenance treatment (low dose prednisolone associated or not with azathioprine or other agents, such as cyclophosphamide, mycophenolate mofetil or calcineurin inhibitors). Maintenance is necessary only in multiorgan disease, elevated serum IgG4, and relapse).

A prompt response to corticosteroid therapy is characteristic of IgG4-RD and renal involvement is not an exception[41]. In patients with renal dysfunction, a recovery of renal function after glucocorticoid therapy has been documented[71]. Data on the use of steroids in IgG4-TIN are principally reported by the Japanese and the Mayo Clinic series[41]. Data on long-term outcomes of IgG4-TIN treated with steroids are available from a retrospective analysis of 40 patients[72]. These data confirm the beneficial effects of corticosteroids in a majority of the patients. However, 60% of the patients who underwent CT imaging during follow up exhibited evidence of a notable renal atrophy. For these disappointing results, a multicenter phase Ⅱ prospective clinical trial of glucocorticoid for patients with untreated IgG4-RD is to date ongoing[73].

Data on IgG4-MGN are limited to a retrospective analysis of seven patients[60]. Steroid treatment seems to be effective in these patients; however, the retrospective study has several limitations: Some patients had a concomitant IgG4-TIN and other patients received other immunosuppressants in addition to steroids.

AA renal amyloidosis merits few comments. Only one patient has been reported[39], and because of the long-standing IgG4-RD, the authors argue that the treatment of IgG4-RD with steroids not only ameliorated the symptoms but also modulated inflammatory effects and delayed secondary amyloidosis.

Retroperitoneal fibrosis is also treated successfully with steroids, but with a relevant warning. Hydronephrosis is often associated with aortic aneurysm. The latter represents a critical contraindication to steroid treatment because it may cause aneurysm rupture.

Altogether, steroid treatment of IgG4-RD has the limitation that needs a long-term course and has unavoidable side effects. Additionally, a number of patients are steroid-resistant or steroid-relapsing.

For such patients other immunosuppressants, such as azathioprine, mycophenolate mofetil (MMF) should be considered; however, their effectiveness and safety remains to be established[65].

International consensus is to take a pragmatic approach: Start to taper the drug after two to four weeks of induction dosing and aim to stop treatment within three to six months[74]. In the case of relapse, depletion of B cells by RTX should be attempted. In the early phase, two trials have been demonstrated to be highly effective[49,68] . RTX may dramatically decrease the circulating plasma blasts that represent an index if IgG4-responders[75].

In the case of IgG4-RKD, particularly TIN, renal atrophy developed in a number of patients treated with steroids, principally in cases where treatment was started late. Relapse of renal dysfunction following steroid tapering or withdrawal is also frequently observed among patients with IgG4-TIN.

In patients with IgG4-TIN, B cell depletion with RTX may provide a durable response; however, this hypothesis requires confirmation in controlled trials[72].

The first suggestions on the efficacy of RTX in patients affected by IgG4-RD have been reported in patients affected by IgG4-associated cholangitis, AIP, and ocular involvement resistant to steroids[76].

The first, randomized, clinical trial on the efficacy of RTX on IgG-RD was performed at the Massachusetts General Hospital and the Mayo Clinic (Clinical Trials.gov identifier NCT01584388)[68]. Disease response occurred in 97% of the patients and overall, RTX appeared to be an effective treatment for IgG4-RD. Unfortunately, only 4 patients were affected by IgG4-TIN. Recently, McMahon *et al*[77] reported successful treatment with RTX in one patient affected by IgG4-TIN who was steroid resistant.

Beneficial effects of B cell depletion were observed by other investigators confirming its significant role in this condition[78]. In clinical practice RTX is usually considered the first steroid sparing agent after relapse in patients treated with steroids.

Other biologic agents, such as Bortezomib, Abatacept and Infliximab have been used in IgG4-RD refractory to steroids and with a particular disease severity[79-81]. To date their use in IgG4-TIN is not recommended, based on clinical experience.

CONCLUSION

IgG4-RDs have only been recently recognized, and several features, principally concerning nomenclature, pathophysiology and treatment still remain to be completely defined.

Nomenclature

To better recognize which diseases should be included under the umbrella of IgG4-RDs, a consensus statement was held in Boston in 2011, which provided a set of guidelines for the diagnosis of IgG4-RDs[8]. As the spectrum of this group of diseases is continuously expanding, the committee advocated the use of strict criteria for accepting newly proposed entities as components of the group.

As a consequence, in 2015[1] (Table 1), new organs affected by the disease were recognized in addition to the organs identified in the Boston consensus conference. Additionally, pathologic conditions previously considered as well-defined disorders are now recognized as organ manifestations of IgG4-RD[3] (Table 2).

On the other hand, several conditions have been identified, which only mimic IgG4-RDs but should be classified separately because they represent diseases with distinct and different features[49] (Table 3). This point is principally relevant for IgG4-related TIN because a number of TINs have been observed, which are

not related to IgG4-RDs[82]. The American College of Rheumatology recently[5] edited the recommendations for an improved nomenclature of IgG4-RDs.

Pathogenesis

Pathogenesis of IgG4-RD is poorly understood and controversial. IgG4 antibodies do not seem to be pathogenetic in this disease; rather they mediate a down-regulatory response to other processes[4]. In addition, IgG4s are only half-antibodies and are unable to bind the complement proteins. Several findings concerning IgG4-RD pathogenesis are consistent with both an autoimmune disorder[83,84] and an allergic disease[85].

Autoimmunity is principally evident in patients with type 1 AIP[83]. Auto antibodies have been described in IgG4-RDs but an evidence for an autoimmune disease is lacking. Cytokines and increased IgE have been described in affected tissues[85]; however, recent studies[10,57] have documented that circulating Th2 in IgG4-RDs are restricted to a subset of patients affected by atopy.

An improvement in the understanding of the physiopathology of IgG4-RD is represented by the identification of a cytotoxic CD4 T cell. These cells may produce granzyme B and perforin as well as IL-1 and TGF-β, which are important mediators of fibrosis. Moreover, these T cells are continuously stimulated by the antigen presentation by B cells and plasma blasts[10], and this fact highlights the importance of a cross-talk between innate and acquired immunity in the pathogenesis of IgG4-RD[86].

Treatment

The optimal treatment for IgG4-RD has not yet been established. Indeed, to date, there have been no randomized clinical trials that have evaluated and compared the effectiveness of different treatment regimens[33]. An international consensus among experts[49] recommended steroids as first line treatment. Due to some disappointing results with the long-term use of corticosteroids, a multicenter phase Ⅱ prospective clinical trial with steroids is currently ongoing[73].

Steroid treatment has several drawbacks: (1) Steroid resistance or relapse at discontinuation; and (2) Long-term undesirable steroid side effects. In the case of steroid resistant patients or frequently relapsing patients, B cell depleting agents may represent an effective treatment. RTX is the most used agent and a clinical trial on the use of RTX has been conducted in the United States[68].

To avoid long-term steroid related side effects, other steroid sparing agents, such as azathioprine, MMF and cyclophosphamide, are reasonable choices for second-line agents; however, once again, their effects have not yet been adequately evaluated in IgG4-RD.

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