



## Urologic manifestations of IgG4-related disease

### Manifestaciones urológicas de la enfermedad relacionada a IgG4

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#### Abstract

IgG4-related disease (IgG4-RD) is a clinical entity characterized by elevated serum IgG4 and tumor-like inflammation, with tissue infiltration by IgG4 and plasma cells. IgG4-RD is rare, but clinically significant, and its urologic manifestations have been reported in the literature. The present review covers a broad spectrum, describing the pathologies related to the area of urology.

In 2003, Terumi Kamisawa was the first to recognize IgG4-RD, characterized by multiorgan lesions in patients with autoimmune pancreatitis and classified as an inflammatory and fibrotic entity with a dense lymphoplasmacytic infiltrate, positive for IgG4.<sup>(1-3)</sup> It presents in middle-aged patients, between 59-68 years of age, with no clear distribution by sex,<sup>(4-6)</sup> and has different clinical presentations. The main urologic manifestations are inflammatory pseudotumors and lower urinary tract symptoms. The present article offers a clear, general overview of the disease, encompassing its pathophysiology, diagnosis, and treatment, from the perspective of urology.

#### Keywords:

Pseudotumor,  
IgG4, Urology,  
Autoimmune disease.

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## Resumen

La enfermedad relacionada con IgG4 (ER-IgG4) es una entidad clínica caracterizada por una concentración sérica elevada e inflamación similar a un tumor con infiltración de tejido por IgG4 y células plasmáticas. Aunque la ER-IgG4 es rara pero clínicamente significativa, sus manifestaciones urológicas se han reportado en la literatura. Esta revisión ofrece un panorama completo que explica las patologías relacionadas en el área urológica.

Desde que Terumi Kamisawa reconoció por primera vez la ER-IgG4 en el año 2003, caracterizada por lesiones multiorgánicas en pacientes con pancreatitis autoinmune, clasificada como una entidad inflamatoria y fibrótica con tumores e infiltración linfoplasmocítica densa, positiva a IgG4.<sup>(1-3)</sup> Presentada en población de mediana edad, entre 59-68 años, sin una distribución clara del sexo,<sup>(4-6)</sup> se presenta con diversas manifestaciones clínicas y como manifestación urológica principal tumores pseudoinflamatorios y sintomatología de tracto urinario bajo. Esta revisión ofrece una visión general y clara de la enfermedad desde la fisiopatología, el diagnóstico y el tratamiento desde un punto de vista urológico

### Palabras clave:

Pseudotumor, IgG4, Urología, Autoinmune.

## Introduction

IgG4 is an antibody with a unique structure and function and makes up less than 5% of the total IgG in healthy individuals. In contrast to IgG1, 2, and 3, serum IgG4 concentrations in healthy persons vary by a factor of more than 100 (reference values from 0.01 to 1.4 mg/dl) but IgG4 values do not generally fluctuate in individual persons.<sup>(1)</sup>

IgG4 binds weakly to the complement component (C1) and Fc receptors and does not play an active role in immune activation.

The diagnostic criteria were proposed by the Japanese study group and validated for the worldwide population.

**Table 1. Diagnostic criteria validated in a Japanese population (Japanese Health Ministry guidelines).<sup>(7)</sup> Adapted from Umehara H. *et al.***

Clinical criteria	Local or diffuse inflammation in one or multiple organs
Serologic criteria	IgG4 concentration >135 mg/dl (1.35 g/dl)
Histopathologic criteria	Extensive lymphocytic infiltration, plasma cells, and tissue fibrosis with IgG4:IgG ratio over 40%, and IgG4 ≥ 10 plasma cells per each IgG4/HPF

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<i>Clinical criteria</i>	<i>Local or diffuse inflammation in one or multiple organs</i>
Conditions	<b>Definitive disease:</b> fulfilling all criteria <b>Probable disease:</b> fulfilling clinical and histopathologic criteria <b>Possible:</b> fulfilling clinical and serologic criteria only
Differential diagnosis	Malignant tumors, such as lymphoma or cancer Sjögren's syndrome Primary sclerosing cholangitis Castleman's disease Secondary retroperitoneal fibrosis Granulomatosis with polyangiitis (Wegener's granulomatosis) Sarcoidosis Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).

## Pathogenesis

Two patterns have been described in IgG4-RD: autoimmune and allergic. IgG4 plays a role in allergen tolerance and the response to infectious agents.

The physiologic function of IgG4 is not well understood, nor how it acts as an autoantigen or antibody.

An elevated serum level is not exclusive of IgG4-RD, given that it is also elevated in Castleman's multicentric disease, allergies, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).<sup>(8,9)</sup>

In relation to autoimmunity, the best example is autoimmune pancreatitis, the prototypical disorder for IgG-RD. Antinuclear antibodies have been identified in some cases, as have antibodies against lactoferrin and carbonic anhydrase II, but there is no conclusive evidence that it is an autoimmune disease.<sup>(7)</sup>

The physiologic response of IgG4 may occur due to chronic and repeated antigen exposure. Its production is similar to the values of IgE controlled by Th2 and cytokines, such as interleukin (Il) 4 and 13, that stimulate the both IgG4 and IgE production. Contrastingly, Il-10, 12, and 21, maintain a balance between

them and when it is lost, disease tends to present.<sup>(1)</sup>

## Pathology

Histopathologic biopsy study is the cornerstone of the IgG4-RD diagnosis. Serum IgG4 levels may be useful in guiding toward the diagnosis, but no specific serum marker has been identified.

The morphologic hallmark in the disease is described as a dense lymphoplasmacytic infiltrate organized in a storiform manner, phlebitis obliterans, and eosinophilic infiltrate. In glandular organs, the infiltrate tends to aggregate around ductal structures and the inflammatory lesion frequently forms a tumor-like mass that destroys the affected organ.

Immunohistochemistry is required for its identification because there is disagreement on certain points for making the diagnosis (10 to 50 affected cells/HPF).

Clinical experience is needed to identify early-stage disease because its characteristic fibrosis presents in the advanced stages (e.g., retroperitoneal involvement). Another important criterion is identifying a difference of at least 50% or more in the IgG4/IgG ratio.<sup>(7,10)</sup>

Histopathologically, lymphoma is the disease that most resembles IgG4-RD, and clonality studies are needed to differentiate them. The characteristic difference between lymphomas and IgG4-RD is B-cell infiltration and T-cell infiltration respectively.<sup>(2)</sup>

### Pathophysiology

#### Genetic risk factors

HLA serotypes have been identified in a Japanese population with IgG4-RD:

- DRB1\*0405
- DQB1\*0401

The presence of these serotypes has been reported to possibly raise the likelihood of presenting with the disease. HLA DQ $\beta$ 1-57, without aspartic acid, was observed in a Korean population.<sup>(3)</sup>

Single nucleotide variants in non-HLA-related genes and a nucleotide have been identified as recurrence and susceptibility factors, which translate to proteins, such as antigen 4, that are associated with cytotoxic T lymphocytes, TNF-alpha, and the constant fraction of the type 3 receptor.<sup>(2)</sup>

Some non-HLA risk genes for extrapancreatic lesions have been proposed by Ishikawa and Terao, such as:<sup>(11)</sup>

- CXCR3
- MLL3
- TNF- $\alpha$  promoter

### Bacterial infection

Homology has been described between human carbonic anhydrase and the alpha carbonic anhydrase of *Helicobacter pylori* and their homo-

logous segments join to the HLA DRB1\*0405, activating the immune system. A connection exists between the plasminogen protein-ligand of *Helicobacter pylori* and ubiquitin ligase E with the n-recognin 2 component that pancreatic acinar cells express, showing a correlation between an infectious agent and the development of autoimmune pancreatitis. No other bacteria are associated with the development of the disease.<sup>(1)</sup>

### Autoimmunity

Serum IgG4 in patients with IgG4-RD attaches to the pancreatic, biliary, and salivary ductal epithelium, also affecting the retroperitoneum, testes, and prostate, among many others. Autoantigens against carbonic anhydrase, lactoferrin, and pancreatic secretory trypsinogen inhibitors that express antibodies against different exocrine organs, have been identified in those organs and are related to the clinical manifestations mentioned in the following section.

An autoantigen (protein 13.1-kD) was identified in a proteomic analysis of 28 patients with IgG4-RD, but no direct correlation has been established with the disease.<sup>(12)</sup>

### Clinical manifestations

IgG4 has diverse clinical manifestations in 60-90% of patients, due to its multiorgan involvement. It generally manifests as tumor-like masses in the affected organs. For example, renal lesions resemble carcinomas, pulmonary involvement produces nodular lesions, and pancreatic lesions have diffuse growth. Lymphadenopathy and asthma or allergy symptoms

are present in approximately 40% of cases, without systemic inflammatory response or constitutional symptoms.<sup>(2)</sup>

Many disorders have been identified that can be associated with the IgG4-RD spectrum:<sup>(2)</sup>

**Table 2 Urologic manifestations of IgG4-related disease**

<i>Clinical condition</i>	<i>Organ or glands involved</i>
Mikulicz syndrome and Küttner's tumor	Salivary glands
Riedel's thyroiditis and Hashimoto's thyroiditis	Thyroid
Eosinophilic angiocentric fibrosis	Paranasal sinuses, lacrimal glands, and lower respiratory tract
Multifocal fibroelastosis	Lungs, pleura, and heart valves
Inflammatory pseudotumor	Kidney, ureter, bladder, prostate, testes
Mediastinal fibrosis	Mediastinum
Retroperitoneal fibrosis (Ormond's disease)	Retroperitoneum
Sclerosing periaortitis and periarteritis	Aorta and its main branches
Inflammatory aortic aneurysm	Aorta
Hypocomplementemic tubulointerstitial nephritis with idiopathic tubulointerstitial deposits	Kidney
Hypopituitarism	Pituitary
Pachymeningitis	Meninges
Constrictive pericarditis	Pericardium

## Kidneys

The most common renal manifestation is tubulointerstitial nephritis.<sup>(5)</sup> When severity is

moderate, it is clinically silent and always focal. Contrasted computed tomography (CT) reveals increased kidney size and areas with poor contrast uptake.<sup>(6)</sup> Nevertheless, it is important to differentiate those lesions from renal carcinoma, especially papillary cell carcinoma and metastasis.

In some cases, lesions associated with IgG4-RD are found in the renal hilum, where the blood vessels, nerves, and ureters enter or exit the kidney. Fifty percent of patients can develop secondary hydronephrosis.<sup>(13)</sup>

Few case series have been reported with renal involvement. In 2007, Saeki et al.<sup>(14)</sup> presented 7 cases documented within the time frame of 1996 to 2006. All the patients were male, with elevated serum IgG4. Three isolated renal patterns were observed: extraparenchymal hydronephrosis associated with retroperitoneal lesions, tubulointerstitial nephritis, and a lymphoplasmacytic lesion in the renal interstitium.

Interstitial nephritis was confirmed in 4 cases, two of which showed diffuse inflammation on the CT scan and elevated levels of serum  $\beta$ 2 microglobulin and N-acetyl- $\beta$ -D-glucosaminidase, common in diffuse interstitial nephritis. Dense and focal lesions were found in another case. Scintigraphy studies with Gallium 67 showed accumulation in both kidneys and there was a decline in renal function after the study.

Murashima et al.<sup>(15)</sup> reported two cases of tubulointerstitial nephritis with multiple renal nodules, whose histopathology studies showed lymphocytes and plasma cells with fibrosis. Rudmik described autoimmune pancreatitis with renal lesions that resembled metastasis.<sup>(16)</sup>

Most cases with renal involvement had a history of pancreatic disease, but isolated di-

sease has also been reported and may or may not be associated with renal insufficiency.<sup>(17)</sup>

### *Retroperitoneal fibrosis*

Some small case series have reported retroperitoneal fibrosis as a manifestation of IgG4-RD.

Before considering IgG4-RD diagnosis, drug-related adverse effects should be ruled out, (e.g., bromocriptine, ergotamine, propranolol, timolol, aspirin, acetaminophen, haloperidol, and sulfonyleureas). In isolated disease or that accompanying other classic manifestations (e.g., autoimmune pancreatitis, periaortitis), the most commonly compromised regions in the retroperitoneum are the thoracic and lumbar areas, affecting the abdominal aorta and its main branches and ureters.<sup>(18)</sup>

Initial clinical manifestations are progressive, colicky lumbar pain that decreases with nonsteroidal anti-inflammatory drugs (NSAIDs). Uremia presents in advanced stages.<sup>(19,20)</sup>

Elevated inflammatory markers, such as the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and anemia of chronic disease have been found, as isolated data. In advanced stages, 60% of patients present with antinuclear antibodies. Periaortitis can progress to aortic aneurysms or hydronephrosis, usually bilateral, as late manifestations of the disease.<sup>(21,22)</sup>

### *Ureters*

Very few cases have been reported with compromised ureters. Terms such as inflammatory pseudotumor or idiopathic segmental urethritis were used in the past to refer to IgG4-RD.

<sup>(23,24)</sup> In 2013, Marando et al.<sup>(25)</sup> reviewed two cases with pseudotumors in ureters consistent with IgG4-RD due to its histologic and serologic characteristics, in addition to carrying out a retrospective analysis of the other 40 cases in the literature that could have been cases of IgG4-RD, before it was described as a disease. Those authors reclassified the cases that had complete medical records and fulfilled all the diagnostic criteria.

### *Bladder*

In a study by Crumley et al.,<sup>(26)</sup> they analyzed a subgroup of 44 cases of interstitial cystitis with IgG4 plasma cells affecting bladder tissue, but only 4 cases fulfilled all the criteria for IgG4-RD.

Interstitial nephritis tends to be more frequent in women, but a study showed that men with positive IgG4 were more commonly affected, at 26%, with an average age of 60, whereas 8% of men with negative IgG4 and a mean age of 41.1, presented with the disease. The association with age, but not sex, was statistically significant. A decrease in bladder capacity under anesthesia was more common in patients with IgG4-positive cells, 33% vs. 0%, establishing IgG4-associated fibrosis. By highlighting the positive cases with higher inflammation, storiform fibrosis, more than 30 plasma cells/HPF, and a IgG4/IgG ratio over 50%, those authors concluded that the presence of IgG4 plays an important role in interstitial nephritis. The disadvantages in that study were its small size, no case-control design, and the fact that only 4 cases fulfilled the diagnostic criteria, but it paves the way for further research on that renal pathology.<sup>(27)</sup>

### Prostate

Patients with prostatic involvement commonly present with symptoms of benign prostatic hyperplasia (BPH), incomplete voiding, increased frequency, intermittency, urinary urgency, nocturia, and a weak urinary stream, and are commonly diagnosed with chronic prostatitis.<sup>(28-30)</sup> Reported cases include manifestations of lower urinary tract symptoms with normal prostate-specific antigen (PSA) levels.

There is limited data on the involvement of the lower urinary tract. Most studies are on Asian populations. Symptoms and age of presentation of BPH are the same as for IgG4-RD, thus multiorgan involvement, especially of the pancreas, should raise diagnostic suspicion.<sup>(31)</sup>

### Urethra

In the study by Williamson *et al.*,<sup>(32)</sup> 38 urethral caruncle biopsies were analyzed to understand the etiology and determine a possible treatment for that disorder. Immunohistochemistry was carried out to evaluate different types of etiology, including viral and autoimmune causes. Four patients (11%) had more than 50 cells/HPF that were positive for IgG4 and an IgG4/IgG ratio over 50%, whereas the other patients presented with few or no IgG4-positive cell infiltrate (<10). A comparison was made with another analysis, composed of 21 case-control studies, in which no inflammatory infiltration was observed, and the diagnostic criteria were not fulfilled for IgG4-RD. Stromal fibrosis and chronic inflammation were found in the four cases of the Williamson study, but none of them presented with any clinical manifesta-

tions of the disease or a viral etiology. Therefore, some cases of urethral caruncle could be related to IgG4-RD, and it should be considered a diagnostic option with the abovementioned clinical manifestations.

### Testes

In 2012, Hart *et al.*<sup>(33)</sup> carried out the first case report of testicular pseudotumor in IgG4-RD, describing a patient in the Mayo Clinic. He had a history of autoimmune pancreatitis, was diabetic with difficult glycemic control, and presented with retroperitoneal fibrosis and hydronephrosis. Adequate clinical control was achieved utilizing prednisone. After those events, the patient presented with the rapid growth of a painful, right testicular mass and no related urinary symptoms. An ultrasound study revealed a multi-septated, fluid-filled mass, measuring 5x5x5.1 cm. Upon resection, its testicular origin was observed. The histologic study reported the classic findings of IgG4-RD. Few related cases have since been reported. Maillet *et al.*<sup>(34)</sup> presented a patient with a similar history, first presenting with a left testicular mass that was managed through orchiectomy. One month later he presented with a right testicular mass with the same characteristics, that was managed in exactly the same way. The manifestation of testicular masses with the presence or history of autoimmune pancreatitis or other characteristics of IgG4-RD should raise high suspicion of the disease.<sup>(35)</sup> The only treatment reported in those cases was resection and no therapeutic trials with anti-inflammatory drugs were carried out due to the high suspicion of malignancy.<sup>(36)</sup>

## Conclusion

The present literature review offers key elements to nephrologists, urologists, and pathologists, that can aid in the early diagnosis of this new and emerging disease in the area of urology, describing its pathophysiology, important clinical data, and appropriate treatment.

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