Urological manifestations of the disease related to immunoglobulin G4

Manifestaciones urológicas de la enfermedad relacionada con la inmunoglobulina G4

Luis Daniel Carrillo-Córdova^{1*}, Carlos Alberto Carrillo-Córdova¹, Johnatan Vitar-Sandoval¹,
Jorge Jaspersen-Álvarez², Elba Luz Villena-López³ and Raúl Carrillo-Esper⁴

¹Department of Urology, Hospital General de México Dr. Eduardo Liceaga; ²Faculty of Medicine, Universidad Nacional Autónoma de México;

³Department of Internal Medicine, Hospital Ángeles del Pedregal; ⁴Critical Areas Division CENIAQ, Instituto Nacional de Rehabilitación. Mexico City. Mexico

Abstract

Immunoglobulin G4 related disease (IgG4-RD) is a fibro-inflammatory disease of unknown etiology, characterized by lesions in the form of tumors, elevated serum IgG4 levels, plasma cells with significant IgG4 infiltration, accompanied by phlebitis obliterans and fibrosis. This disease usually has multiorgan disease, including pancreas, biliary tract, salivary glands, peri orbital tissues, kidneys, lungs, lymph nodes and retro peritoneum. IgG4-RD mainly affects men with a predominance of age by young adults until old age. The clinical manifestations of IgG4-RD, depend mainly on the organs affected and the response to steroids. His forecast is not yet clear. Within the affected urogenital organs can be observed kidney, retroperitoneum, ureter, bladder, urachus, testis/epididymis, paratesticular region, prostate and urethra.

KEY WORDS: IgG4-related disease. Retroperitoneal fibrosis. Urology.

Resumen

La enfermedad relacionada con la inmunoglobulina G4 (ER-IgG4) es una enfermedad fibroinflamatoria de etiología desconocida, la cual se caracteriza por presentar lesiones en forma de tumoraciones, concentraciones séricas aumentadas de IgG4 y células plasmáticas con una infiltración importante de IgG4, junto con flebitis obliterante y fibrosis. Esta enfermedad suele tener afección multiorgánica, incluyendo el páncreas, el tracto biliar, las glándulas salivares, los tejidos periorbitarios, los riñones, los pulmones, los ganglios linfáticos y el retroperitoneo. La ER-IgG4 afecta principalmente a hombres, con un predominio de edad por los adultos jóvenes y hasta la vejez. Las manifestaciones clínicas de la ER-IgG4 dependen principalmente de los órganos afectados y de la respuesta a los esteroides. Su pronóstico aún no es del todo claro. Dentro de los órganos urogenitales afectados pueden incluirse el riñón, el retroperitoneo, el uréter, la vejiga, el uraco, el testículo/epidídimo, la región paratesticular, la próstata y la uretra.

PALABRAS CLAVE: Enfermedad por IgG4. Fibrosis retroperitoneal. Urología.

Correspondence:

*Luis Daniel Carrillo-Córdova

Cerro Teponaxtle, 109

Col. Campestre Churubusco, Del. Coyoacán

C.P. 04200, Ciudad de México, México

E-mail: Carrillocor@gmail.com

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a chronic fibrotic inflammation, characterized by the presence of tissue lymphocytic infiltration, IgG4-positive plasma cells, development of fibrosis and sometimes increased serum IgG4 concentrations^{1,2}. This disease usually affects multiple organs. Early diagnosis is very difficult to establish owing to the asymptomatic evolution of the disease at early stages and, when symptoms are present, these are vague and unspecific. The main manifestation is usually secondary to inflammation or fibrosis of a specific organ, causing direct damage to it. It can also be incidentally found during the diagnostic workup of a tumor when taking a biopsy. At all its stages, this disease usually responds well to steroid therapy^{3,4}.

The kidney is one of the most commonly affected organs in IgG4-RD, and renal lesions are encompassed in a spectrum called IgG4-RD-associated kidney disease⁴⁻⁸. As in some diseases that affect other organs, patients are asymptomatic or have vague and unspecific symptoms. However, approximately half of these patients will progress to kidney failure⁹. This shows the need to establish an early diagnosis, in order to initiate treatment in a timely manner. Renal lesions are distributed from the renal parenchyma to the pelvis and ureter^{3,9-16}.

The most representative lesion among renal parenchymal lesions is tubulointerstitial nephritis rich in plasma cells, accompanied by infiltrates of IgG4-rich plasma cells and fibrosis, similar to that observed in the retroperitoneum^{7,9}.

Pathophysiology

The disease is believed to have an allergic background and is mediated by the immune system, with abnormal immune responses being found. Adequate response to steroid therapy supports the immune etiology of this disease. Approximately 30-50% of patients have a history of allergies, eosinophilia or IgE increased serum levels^{17,18}.

Patients with IgG4-RD have up-regulated responses to Th2 (interleukin [IL] 4, IL-5, IL-13 and IL-21) and regulatory T cells (IL-10 and tumor growth factor B1). The Th2 response induces an allergic response mediated by the immune system with eosinophilia and elevated IgE¹⁹⁻²². Activated mast cells, highly positive for IgE, promote the differentiation of naïve T-cells into

Figure 1. Pathophysiology of IgG4-related disease. Diagram showing the immune cells and interleukins involved. 1: eosinophils; 2: IgE; 3: activated mast cells; 4: naïve T-cell; 5: regulatory T-cell; 6: B-cell; 7: plasma cells; 8: IL-10; 9: IgG4; 10: lymphoid follicle; 11: plasmablast.

regulatory T-cells. IL-10 promotes B-cell differentiation into plasma cells, with subsequent IgG4 production. IL-4 activates macrophages to produce high amounts of IL-10. IL-21, produced by follicular Th2 and T cells, is important for the formation of germinal centers and stimulates the production of IgG4 and plasma cells infiltration into tissues^{23,24}. Monocytes cause massive infiltration of affected tissues, forming lymphoid follicles and producing the enlargement and deformation of affected tissues, which leads to their dysfunction; this infiltrate can give the appearance of a tumor in the kidney, renal pelvis or ureter²⁵.

Antigen-induced circulating plasma cells have the phenotypes CD38+, CD27+, CD19+, CD20- and CD22- (short-lived plasmablasts). IgG4-RD is associated with an elevated plasmablast blood concentration, even in patients with normal serum IgG4. The plasmablast count is higher than that of IgG4 serum concentration as a biomarker for the diagnosis of IgG4-RD, and is useful for monitoring the disease and for predicting relapses²⁶⁻²⁸ (Fig. 1).

Epidemiology

In Japan, prevalence is estimated at 0.8 cases per 100,000 population, and the estimated incidence is

Figure 2. IgG4-related disease diagnostic algorithm. The diagnostic approach proposed by Umehara et al.³⁶ is shown.

0.28 to 1.08/100,000, with 336-1300 patients diagnosed every year and 6700-26,000 patients who developed IgG4-RD in the past 20 years²⁹. Another study estimated that the prevalence is 6/100,000 population³⁰. This disease mainly affects males (73-80%); with the only exception of manifestations in the head and neck, average age of presentation ranges from 50 to 60 years^{31,32}. There are some cases in the literature where this disease has been diagnosed in children³³⁻³⁵. There are no articles in Latin America studying the epidemiology of the disease.

Diagnosis

IgG4-RD diagnosis is established by integrating clinical findings, laboratory tests, typical histopathology and radiology, as several authors have proposed³⁶⁻³⁸ (Fig. 2).

One third of patients have a history of atopic disease, including asthma, allergic rhinitis, nasal polyps and

atopic dermatitis; non-atopic patients may exhibit peripheral blood eosinophilia or elevated IgE³⁹. Patients with IgG4-RD have often presented with allergies (up to 57% in a cohort)⁴⁰.

Patients usually do not exhibit general symptoms, such as fever, weight loss, night sweats or general malaise. Malignant tumors have been reported in 7.4% of patients with IgG4-RD. Extranodal marginal B-cell lymphoma can occur in ocular adnexa, salivary glands or dura mater within 5 years after the IgG4-RD diagnosis⁴¹⁻⁴³.

Laboratory tests are usually normal, in some cases with elevated C-reactive protein, increased erythrocyte sedimentation rate, anemia, thrombocytosis, and eosinophilia. Serology may reveal elevated IgE, polyclonal hypergammaglobulinemia, hypocomplementemia (21% of cases, especially when there is renal involvement owing to the disease), presence of antinuclear antibodies (16-50%) and rheumatoid factor (20%). An elevated IgG4 can help to establish the

diagnosis; a cut-off value > 1.35 g/L has shown sensitivity of 97% and specificity of 79.6% to diagnose IgG4-RD. However, 30-50% of patients with IgG4-RD will have normal IgG4 serum values⁴⁴⁻⁴⁷.

Radiological studies can reveal renal, ureteral and pyelic pseudo-tumors, secondary to organ infiltration by lymphocytes and monocytes. These lesions show soft tissue attenuation and well-defined borders on tomography and, on magnetic resonance imaging, these lesions vary from isointense to hypointense at T2, with homogeneous enhancement, which reflects increased cellularity and fibrosis; in case of extrinsic compression of the ureter by retroperitoneal fibrosis (RPF), or intrinsic by a ureteral or pelvic pseudotumor, hydronephrosis may be present⁴⁸.

Positron-emission tomography (PET) with 18F-fluorodeoxyglucose allows carrying out a mapping of sites with inflammation by marking areas with hypermetabolic activity, which helps to assess the extent of disease and monitor its response to treatment⁴⁹.

Currently, the standard method for IgG4-RD diagnosis consists of characteristic histology and immunohistochemistry identification, which is the same regardless of the affected organ. At late stages of the disease, fibrosis is the predominating feature, which makes the diagnosis more difficult⁵⁰.

IgG4-RD three major features are: 1) dense lymphoplasmacytic infiltrates; 2) storiform fibrosis or in an irregular spiral pattern, similar to a straw mat; and 3) obliterating phlebitis. Sometimes, formation of germinal centers and infiltration by eosinophils in affected tissues is observed⁵⁰. Immunohistochemistry for IgG4 shows plasma cell-rich infiltration; a number greater than 50 cells with positive IgG4 staining under a high power field is regarded as highly specific, but some other cut-off points have been proposed⁵⁰. At more advanced stages of the disease, inflammation may have passed and fibrosis be predominant; in these cases, staining must be carried out for IgG-rich plasma cells. The IgG4/IgG ratio must be higher than 0.4 and is mandatory for IgG4-RD diagnosis⁵⁰.

Urological manifestations

Renal pseudo-tumor

Renal pseudo-tumor is a lesion that mimics a renal carcinoma and is a very unusual form of presentation of the disease, with less than five cases reported in the literature to date⁵¹. It is difficult to differentiate between a renal pseudo-tumor

secondary to IgG4-RD and a malignant lesion based only on imaging studies⁵². Renal ultrasound may show hypoechoic lesions or edema of the renal parenchyma, and tomography with intravenous contrast medium may reveal low-density single or multiple lesions⁵³.

Magnetic resonance imaging can show isointense or hypointense renal tumors at T1, and hypointense images at T2, and show homogenous enhancement after contrast medium administration⁵³. Definitive differential diagnosis will be provided by a biopsy, and treatment will be based on corticosteroids, by means of which the lesion will significantly improve, thus increasing renal function and decreasing circulating IgG4 concentration⁵¹.

Pseudo-tumors of the renal pelvis and ureter

IgG4-RD can occur as a single lesion in the renal pelvis or the ureter, causing filling defects and mimicking an urothelial carcinoma. There are only four cases reported in the literature⁵⁴⁻⁵⁷. Most cases that have reported renal or ureteral lesions are accompanied by synchronous or metachronous lesions in other organs⁵⁶. Urinalysis in these patients usually shows moderate abnormalities. The appearance of these lesions in imaging studies is the same as that of renal pseudo-tumors, but in case the pseudotumor causes obstruction of the urinary tract, there will be renoureteral colic and hydronephrosis.

Tomographic findings reported for pseudo-tumors of the renal pelvis and ureter include hydronephrosis, ureteropelvic junction tumor and ureteral tumor. T1 isointense lesions and T2 hypointense lesions have been reported in magnetic resonance imaging. PET has shown an elevated glucose metabolism^{54,55,57}. Management of these lesions is based on steroids, although due to their similarity to urothelial carcinoma, it is common for nephroureterectomy to be performed with a bladder swab, with the IgG4-RD diagnosis being established when the surgical specimen is examined^{54,57}.

There is one case of ureteral pseudo-tumor reported in the literature⁵⁸, which manifested itself with hydronephrosis, thickening of the ureteral wall and renal function deterioration. Nephroureterectomy was performed and final diagnosis was provided by analysis of the pathological specimen. Subsequent management with steroids was given and an important improvement in renal function was achieved.

Retroperitoneal fibrosis

RPF clinical presentation can occur with vague abdominal and lower back pain, accompanied by nonspecific symptoms such as fever, myalgia, anorexia and weight loss. However, half the patients remain asymptomatic and, as the disease progresses, extrinsic compression of the ureter can lead to renal function loss, as well as to hydronephrosis; ureteral obstruction is found in 60-80% of patients with RPF secondary to IgG4-RD^{59,60}.

RPF diagnosis is based on radiological findings and biopsy. IgG4 serum concentrations may or may not be elevated. Kidney ultrasound can provide valuable information about the degree of obstruction in the ureter and kidneys. Computed tomography and magnetic resonance imaging can provide useful information on the extent of disease.

Some authors have proposed to classify RPF in IgG4-RD as: 1) RPF; 2) inflammatory aneurysm of the abdominal aorta; 3) a combination of RPF and aneurysm; and 4) thoracic aortitis⁶¹⁻⁶³.

The management of RPF includes urgent obstruction relief by means of nephrostomy or ureteral stent. Patients with urinary tract mild obstruction can be closely monitored while on steroid therapy. Definitive management of this condition is with the use of steroids^{62,63}.

Vesical pseudo-tumors

There are only three cases of vesical pseudo-tumor documented in the literature, and in one of them, an inflammatory pseudo tumor of the bladder related to IgG4-RD was reported. Clinical presentation included asymptomatic gross hematuria, anemia and elevated serum IgG. Urinalysis revealed bacteriuria, hematuria, fecaluria and proteinuria. A tomography showed a tumor dependent on the bladder lateral wall with adhesion to the colon. The patient underwent partial cystectomy with resection of the affected part of the colon, with histopathologic finding of IgG4-RD. Definitive treatment was with steroid-based therapy⁶⁴⁻⁶⁶.

IgG4-RD localization in the urachus

There is one case reported in the literature of urachal disease due to IgG4-RD, which mimicked an urachal adenocarcinoma, managed with partial cystectomy. The histopathology report confirmed the IgG4-RD diagnosis by showing dense lymphoplasmacytic infiltration with IgG4-positive cells, fibrosis

Table 1. Urogenital tract organs involvement and number of reported cases

Affected organ	N
Kidney	76
Retroperitoneum	19
Ureter	7
Bladder	3
Urachus	1
Testicle/epididymis	2
Paratesticular region	6
Prostate	22
Urethra	5

and phlebitis obliterans. IgG4 serum values were 227 mg/dL⁶⁷.

Pseudo-tumor of the urethra

In 2012, the first case of IgG4-RD with presentation in the urethra was reported, which was found by tomography in a female patient with acute abdominal pain. A biopsy of the lesion was obtained, which revealed IgG4-RD. Patient history included an autoimmune pancreatitis diagnosis 17 years earlier. Treatment with steroids was given, with an important improvement of the condition being achieved.⁶⁸

Another study reported an IgG4-RD prevalence of 11% in patients with urethral polyp diagnosis⁶⁹.

IgG4-RD-associated orchiepididymitis

There have been reports of bilateral orchiepididymitis, accompanied by salivary glands involvement, with left testicle increased volume. Radical orchiectomy was performed owing to the suspicion of mycobacterial infection, with IgG4-RD being found during anatomicopathological study. Serum IgG4 was 505 mg/dL, with testicular and epididymal positive staining for IgG4, and with an IgG4/IgG ratio greater than 85%⁷⁰.

Another author⁷¹ reported a patient with orchitis complicated with testicular abscess, which was treated with radical orchiectomy, with pathological diagnosis confirming IgG4-RD.

Paratesticular pseudo-tumors

Some cases of IgG4-RD-related paratesticular pseudo-tumors have been reported in patients aged 19 to 52 years. On ultrasound, the appearance is the same as that of a paratesticular tumor, and diagnosis is suggested by patient history and steroid treatment response, or by surgical specimen results after definitive treatment⁷²⁻⁷⁴.

Table 2. Diagnostic criteria for tubulointerstitial nephritis due to IgG4-related disease

Histology	Tubulointerstitial nephritis rich in plasma cells with more than 10 IgG4+ per high power field* Deposit of immune complexes in the tubular basement membrane by immunohistochemistry or electron microscopy†
Imaging	Small peripheral cortical nodules, round or wedge-shaped lesions, or diffuse and irregular involvement
Serology	IgG4 or total IgG elevation, hypergammaglobulinemia, eosinophilia
Other organs involvement	Autoimmune pancreatitis, sclerosing cholangitis, inflammatory masses in any organ, aortic aneurysm, lung involvement, retroperitoneal fibrosis

*Mandatory criterion.

†Support criterion in more than 80% of cases.

IgG4-RD-related prostatitis

Numerous cases of IgG4-RD-associated prostatitis have been reported and, in most of them, it is accompanied by lower urinary tract symptoms, in patients within an age range of 55-73 years⁷⁵. These patients have also been reported to usually have increased IgG4 serum levels (499-1550 mg/dL)⁷⁵⁻⁷⁷ and significant lymphoplasmacytic infiltration of the prostate. Definitive diagnosis is by means of prostate biopsy.

It is important for the urologist to know this etiology in order to avoid giving patients unnecessary treatments. An excellent response has been observed after treatment with steroids, although some patients have shown great symptom improvement after transurethral resection of the prostate⁷⁵⁻⁸¹.

Tubulointerstitial nephritis

Kidney lesion clinical manifestation can be variable, either with the appearance of pseudo-tumors, acute or chronic kidney injury or proteinuria associated with glomerular disease. The causes of tubulointerstitial nephritis are determined by biopsy together with patient clinical history, physical examination, serum markers and imaging studies. Tubulointerstitial nephritis secondary to IgG4-RD is reported as an autoimmune tubulointerstitial nephritis. It is IgG4-RD most common renal manifestation. Eighty-five percent of patients show radiographic abnormalities, in 81% with elevated IgG or IgG4 serum concentrations, and 28% with eosinophilia. It is more common to find acute or chronic kidney lesion than the appearance of pseudo-tumors. Eighty-four percent of these patients have autoimmune complexes deposits in the tubular basement membrane, where there is also a granular pattern for IgG, C3, and kappa and lambda light chains.

Table 1 summarizes all urological manifestations and the number of cases thus far reported. IgG4-RD diagnostic criteria are listed in table 2^{82,83}.

Treatment

Recently, a guideline for the management of patients with IgG4-RD was created, but, even so, there is no definitive treatment, and it varies according to each patient.

Strategies that can be resorted to include:

- Watchful waiting strategy: it is the strategy of choice in asymptomatic patients. In case of kidney, ureter or bladder involvement, if this strategy is adopted, it is necessary for renal function to be frequently monitored and to perform serial ultrasounds in order to assess the morphology of the urinary tract.^{22,84}
- Glucocorticoids: the response to low-dose steroids is distinctive IgG4-RD, although, interestingly, up to 30% of patients with IgG4-RD have spontaneous resolution and a similar percentage is refractory or experiences relapses.
- Other therapies: for those patients in whom steroid therapy does not work or, if relapse occurs, B-cell depletion therapy with rituximab is generally adequate. We can also use methotrexate, mycophenolic acid and azathioprine. There is evidence that treatment modifies the natural course of disease, both to normalize organ function and to avoid fibrosis⁸⁵⁻⁸⁷.

Conclusion

IgG4-RD urological manifestations are many and can affect any genitourinary tract organ. It is important for the urologist to have knowledge of this disease, as well as of its clinical manifestations, its diagnostic criteria and its treatment, in order to offer better care to patients.

Ethical responsibilities

Protection of people and animals. The authors declare that no experiments have been conducted in humans or animals for this research.

Confidentiality of data. The authors declare to have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflict of interests

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