

Immunoglobulin G4-related disease mimicking multiple myeloma

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ABSTRACT

Immunoglobulin G4-related disease (IgG4-RD) is a rare, poorly understood immune mediated disorder. It is characterized by a wide clinical spectrum depending on the organs affected. Serum IgG4 may be elevated, but this is not mandatory. Imaging abnormalities are usually detected in the affected organs, which typically show enlarged dimensions. Definitive diagnosis is made upon tissue biopsy demonstrating lymphoplasmacytic infiltration with predominance of polyclonal IgG4-positive plasma cells, storiform fibrosis and obliterative phlebitis. The most common renal manifestations [(IgG4-related kidney disease (IgG4-RKD))] include tubulointerstitial nephritis, membranous glomerulonephritis and pyelitis. There is, usually, good therapeutic response to corticosteroids, but rituximab may be needed in cases of relapsing or resistant disease. A diagnostic challenge, and because its diagnosis needs specific immunohistochemical staining techniques, IgG4-RKD should be contemplated in the differential diagnosis of obscure kidney disease in order not to be missed.

Keywords: Immunoglobulin G4; immunoglobulin G4-related disease; immunoglobulin G4-related kidney disease; lymphoplasmacytic infiltration; storiform fibrosis; tubulointerstitial nephritis.

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a multi-organ immune mediated disorder that mimics malignant, infectious and inflammatory conditions.¹ It is characterized by lymphoplasmacytic tissue infiltration with the predominance of IgG4-positive plasma cells and by the development of fibrosis.

Its incidence and prevalence are poorly understood since it was not recognized as an individual pathological entity until 2003.² One cross-sectional study estimated an incidence of 60:1,000,000 and a prevalence of 8,000/year.³ Unlike the majority of autoimmune disorders, IgG4-RD has a male predominance⁴, with a male to female ratio estimated at 2.8:1.⁵ The mean age at diagnosis is 61.4 years.⁶

It is thought that this disorder has an allergic background with an anomalous immune response where type 2 T

helper cells and regulatory T cells are up regulated.⁷ This incites an inflammatory cascade that culminates with the differentiation of B cells in IgG4 producing plasma cells.⁸ Their expansion leads to infiltration of the organs and their dysfunction. Regulatory T cells are also responsible for activating fibroblasts⁹ and the differentiation of endothelial and epithelial cells into myofibroblasts,¹⁰ resulting in tissue fibrosis. No specific target antigen has yet been identified, and the role of IgG4 antibodies remains obscure.

This newly recognised condition links many autoimmune entities once regarded as isolated (Table I).

The presentation of IgG4-RD is usually subacute and the overall signs and symptoms are dictated by the organs involved.

The gold standard for the diagnosis is tissue biopsy demonstrating the characteristic histopathological

Table 1

Autoimmune Diseases considered Part of the IgG4-RD Spectrum

Eosinophilic angiocentric fibrosis	Orbits and upper respiratory tract
Mikulicz's syndrome	Salivary and lacrimal glands
Küttner's tumor	Submandibular glands
Hypertrophic pachymeningitis	Meninges
Riedel's thyroiditis	Thyroid gland
Multifocal fibrosclerosis	Orbits; thyroid gland; retroperitoneum; mediastinum; others
Inflammatory pseudotumor	Orbits; lungs; kidneys; others
Fibrosing mediastinitis	Mediastinum
Chronic sclerosing aortitis	Aorta
Autoimmune pancreatitis	Pancreas
Sclerosing cholangitis	Biliary tract
Autoimmune hepatitis	Liver
Idiopathic hypocomplementemic TIN with extensive tubulointerstitial deposits	Kidney
Retroperitoneal fibrosis (Ormond's disease)	Retroperitoneum
Sclerosing mesenteritis	Mesentery

findings and immunohistochemical staining: lymphoplasmacytic tissue infiltration with predominance of polyclonal IgG4-positive plasma cells (30 to 50

IgG4-positive cells per high power field in most tissues; 10 IgG4-positive cells per high power field in the kidney) and CD4⁺ T lymphocytes, fibrosis and obliterative phlebitis. The fibrosis in IgG4-RD has a storiform pattern, represented by a cartwheel appearance of the arranged fibroblasts and inflammatory cells.¹¹

IgG4-related kidney disease (IgG4-RKD) may present as tubulointerstitial nephritis, membranous glomerulonephritis and pyelitis.¹²

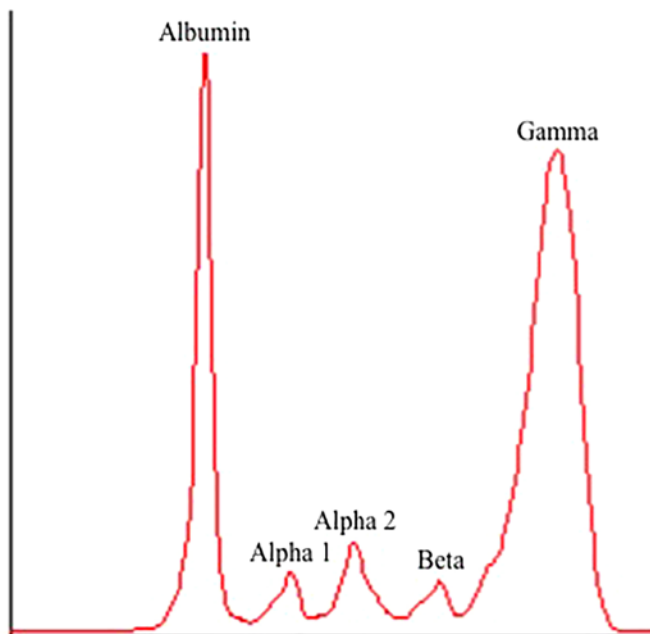
A good therapeutic response to glucocorticoids is characteristic, particularly if excessive tissue fibrosis has not supervened.¹³ In the presence of a corticoreistant disorder, B cell depletion with rituximab is known to induce clinical response in some cases.¹⁴

■ **CASE REPORT**

An 80-year-old man, previously referred to the Hematology department for thrombocytopenia, was assumed to have multiple myeloma (MM) IgG kappa and lambda. He had elevated serum levels of IgG [5838 mg/dL (650 – 1600 mg/dL)], kappa [5230 mg/dL (598 – 1329 mg/dL)]

Figure 1

Migration graphic of serum proteins electrophoresis (left), showing an accentuated gamma peak, with respective total and relative values (right)



	%	g/dL	NORMAL RANGE
Total Proteins	-	10,0	6,6 – 8,7
Albumin	24,8	2,47	4,02 – 4,76
Alpha 1	3,7	0,37	0,21 – 0,35
Alpha 2	7,2	0,72	0,51 – 0,85
Beta	6,6	0,66	0,57 – 0,99
Gamma	57,7	5,75	0,80 – 1,35
Albumin / Globulin Ratio	0,33		

and lambda [3630 mg/dL (280 – 665 mg/dL)] light chains and beta-2-microglobulin [14,5 mg/L (0.8 – 2.2 mg/L)]. Serum protein electrophoresis showed hypergammaglobulinemia (Figure 1) and kappa and lambda monoclonal bands were detected in serum immunofixation electrophoresis (but not in urine). Bone marrow aspiration and biopsy were inconclusive. Renal function was normal.

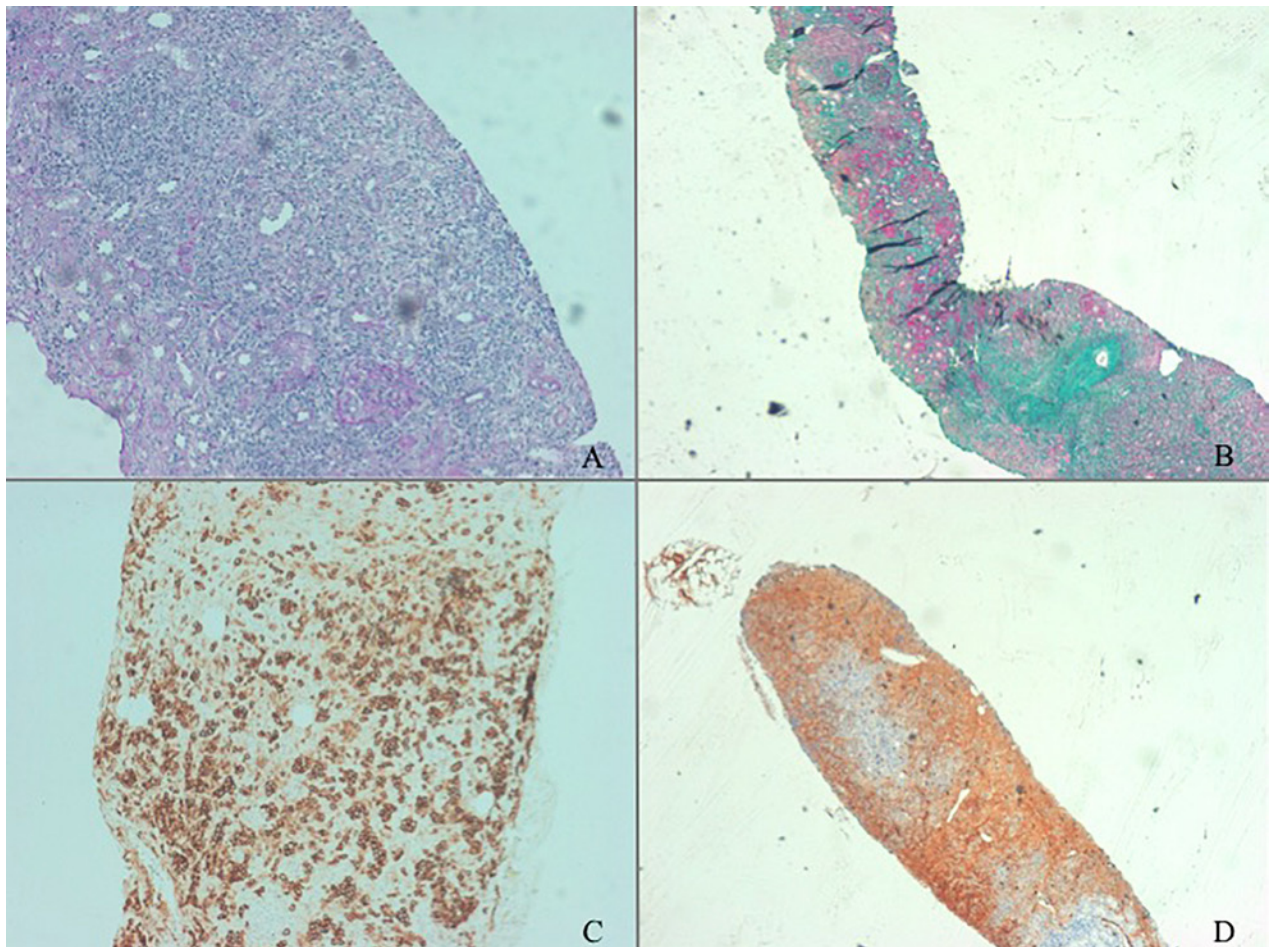
After treatment with prednisolone, cyclophosphamide and talidomid he was considered to be in remission.

The patient was referred to the Nephrology department for elevation in serum creatinine levels three years later. Serum creatinine was 1.8 mg/dL (0.4 – 1.2 mg/dL) with a proteinuria of 510 mg in a 24-hour urine

collection and microscopic hematuria in a spot urine sample (46/uL). He had a polyclonal gammopathy with elevation of total serum IgG (4803 mg/dL), kappa and lambda light chains. Serum free light chains were marginally elevated, with a kappa/lambda ratio of 0.92, and no monoclonal bands were detected in serum or urine immunofixation electrophoresis. Specific IgG subclass measurement showed elevation of IgG1 [36200 mg/L (3150 – 8550 mg/L)] and IgG3 [11300 mg/L (230 – 1960 mg/L)], with a mild rise of IgG4 [1650 mg/L (110 – 1570 mg/L)] and normal IgG2. Serum C4 was markedly reduced [1.3 mg/L (12.0 – 36.0 mg/dL)]. The autoimmunity panel revealed positive antinuclear antibodies (ANA) in a 1/1280 titer with a homogeneous pattern and rheumatoid factor [55.7 UI/mL (< 20.0 UI/mL)]. Virus markers were negative for hepatitis B and C and HIV.

Figure 2

Kidney biopsy showed massive lymphocytic interstitial infiltration [A (PAS 40x)] and extensive fibrosis [B (TVF 10x)], with accentuated immunohistochemical staining for CD138, a marker of mature plasma cells [C (40x)], and for specific IgG4 producing cells [D (10x)].



He had normal sized kidneys on renal ultrasound, with adequate corticomedullary differentiation. Bone marrow aspiration and biopsy revealed 0.6% of mature plasma cells (with polyclonal characteristics) and no signs of neoplastic disease. Kidney biopsy unveiled massive interstitial infiltration of T and B lymphocytes and plasma cells with extensive tubular destruction (70%) due to storiform fibrosis (Figure 2 – A and B). Immunohistochemical staining was diffusely positive for IgG3 and IgG4 (Figure 2 – C and D) with more than 10 IgG4-positive plasma cells per high power field, establishing the diagnosis of tubulointerstitial nephritis (TIN) due to IgG4-RKD.

The patient began prednisolone at a dose of 40 mg/day. In 6 months serum creatinine decreased to 1.5 mg/dL and total IgG to 1476 mg/dL. Proteinuria stabilized at 230 mg/day and microscopic hematuria disappeared. C4 remained markedly low (3.1 mg/dL). Corticotherapy was tapered to a maintenance dose of 10 mg/day and the patient has remained clinically stable since.

DISCUSSION

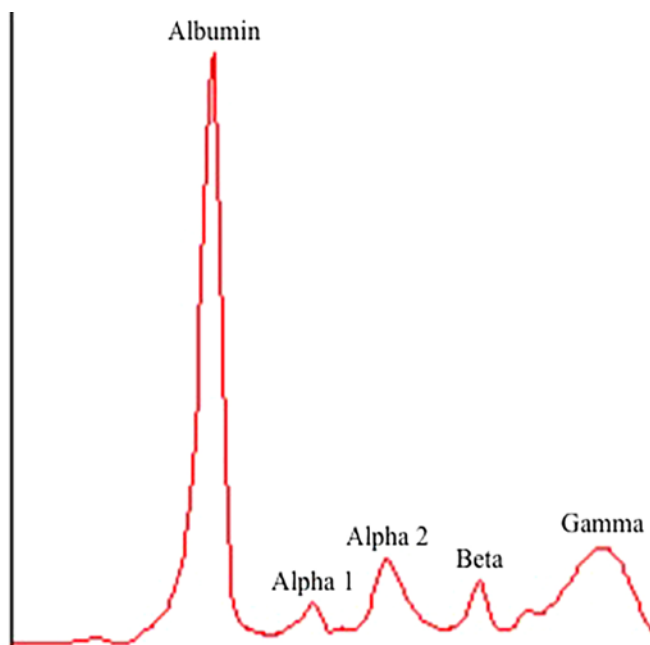
IgG4-RKD has two major clinical presentations: renal dysfunction and imaging oddities. The rise in serum creatinine is usually insidious, but can be rapidly progressive.¹⁵ TIN is the most common renal manifestation of IgG4-RD. Proteinuria and hematuria may be present, but are not usually detected unless there are concomitant glomerular lesions.¹⁶ Nephrotic range proteinuria is rare and its presence is suggestive of membranous glomerulonephritis. Peripheral eosinophilia is detected in about 40% of cases associated with IgG4-RD.¹⁷ The most common radiological findings are diffuse bilateral renal enlargement and multiple hypodense lesions.¹⁸

Umehara *et al.* proposed an algorithm for diagnosing IgG4-RD¹⁹ whereas Kawano *et al.* suggested criteria for specific IgG4-RKD.²⁰ Tissue biopsy with evidence of the characteristic histopathological pattern is mandatory.

Elevated IgG4 levels is a common serological finding in IgG4-RKD. The main functions of the IgG subclasses are opsonization and complement activation. IgG4 is

Figure 3

Migration graphic of serum proteins electrophoresis (left) with respective total and relative values (right) after treatment with prednisolone (2 years after the diagnosis of IgG4-RKD).



	%	g/dL	NORMAL RANGE
Total Proteins	-	6,6	6,6 – 8,7
Albumin	53,4	3,52	4,02 – 4,76
Alpha 1	4,0	0,26	0,21 – 0,35
Alpha 2	12,6	0,83	0,51 – 0,85
Beta	8,3	0,55	0,57 – 0,99
Gamma	21,7	1,43	0,80 – 1,35
Albumin / Globulin Ratio	1,15		

the least expressed IgG subclass, accounting for 1 to 4% of IgG levels in normal settings.²¹ Although an elevated serum concentration is not a diagnostic criterion for IgG4-RD, it is highly suggestive. Carruthers *et al.* estimated that the sensitivity and the negative predictive values of elevated serum IgG4 level (> 180 mg/dL) are 90% and 96%, respectively, with a low specificity and positive predictive values.²² Because of their unique structural and functional characteristics, IgG4 antibodies undergo single Fab exchange, resulting in a hybrid antibody with two different Fab domains that crosslink with two different antigens.²³ The failure to link two identical antigens results in the inability to form immune complexes and, therefore, to initiate cell immunity and activate the complement system.²⁴ Also, in contrast to the other subclasses, IgG4 has a very low affinity for the binding of Fc receptors and C1q, accounting for its unique anti-inflammatory properties.

When quantifying the levels of IgG subclasses, prozone effect should always be eliminated through successive dilution methods, which was done in this case. Despite its low positive predictive value, IgG4 levels are a useful tool in monitoring responsiveness to treatment and in predicting relapses.²⁵

Hypocomplementemia is a distinct feature of IgG4-RD and it seems to be more frequent if the kidney is involved; however only a low proportion of patients present it.²⁶ IgG1 and IgG3 have the highest affinity for C1q binding and complement activation via the classical pathway, which may account for the striking C4 consumption in these cases, as well in the one here described. Complement levels may be used to appraise disease recurrence in IgG4-RKD.²⁷

Our patient presented with circulating ANA, rheumatoid factor and polyclonal hypergammaglobulinemia and many patients with IgG4-RD have been shown to have circulating ANA or rheumatoid factor.

There is still controversy as to whether IgG4-RD is an autoimmune disease. Its association with hypergammaglobulinemia, autoantibody seropositivity and good responsiveness to corticoid therapy has raised this possibility. Some authors defend that the disorder has an allergic background since it is frequently allied with increased serum levels of IgE and eosinophilia.²⁸ However Mattoo *et al.*²⁹ showed that plasmablast-derived antibody clones from patients with IgG4-RD react with autoantigens in the cytosole of Hep-2 cells, supporting the role of a disease-specific autoantibody. Another possibility is that the clonal expansion of

IgG4-positive plasma cells is an induced anti-inflammatory response to another underlying immune condition. Some researchers have reported elevated plasmablast accumulations in the blood of patients with active systemic lupus erythematosus and rheumatoid arthritis.³⁰⁻³¹

When submitted to chemotherapy, the patient went into remission due to treatment with prednisolone and cyclophosphamide. Glucocorticoids are the first line agent for remission induction in all patients with active disease – prednisone 0.6 mg/Kg/day or 30 – 40 mg/day.³² The initial dose is continued for 2 – 4 weeks and then tapered gradually (5 mg every 1 – 2 weeks) to a maintenance dose (5 – 10 mg/day). Additionally, in a prospective cohort study conducted by Yunyun *et al.* treatment with glucocorticoids alone versus glucocorticoids plus cyclophosphamide were shown to be equally effective at the initial stage of the disease, but the latter had a lower relapse rate than monotherapy overtime.³³

Clinical improvement is rapid and a follow-up serological assessment should be made within two weeks.³⁴

When first line therapy fails to control the disorder, the use of steroid-sparing agents, such as rituximab, may be needed.³⁵ However, this and other possible therapeutic agents, such as azathioprine, mycophenolate mofetil, methotrexate, tacrolimus and omalizumab, still require more investigation.³⁶

An international consensus statement has been drawn up by the American College of Rheumatology on the treatment of IgG4-RD.³⁷

In conclusion, IgG4-RD is still a poorly understood disorder and its etiology is not yet established. It appears to have characteristics of both allergic and autoimmune disorders. Elevated levels of serum IgG4 are highly suggestive and tissue proven biopsy is the gold standard for diagnosis. IgG4-RKD usually presents as TIN and treatment response depends on the degree of established fibrosis. Glucocorticoids are the first line treatment and rituximab may be administered in cases of resistant or relapsing disease.

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