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An old disease, a new diagnosis; A 49 year-old man with nephrotic syndrome

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ABSTRACT

Background: IgG4-related disease (IgG4-RD) is a systemic immune-mediated disease that typically manifests as fibro-inflammatory masses that can affect nearly any organ system.
Case Report: We present here a case of a 49-year old man with forgotten old disease (Mikulicz disease) with membranous nephropathy (MN).
Conclusions: This entity is currently included within the spectrum of IgG4-related disease. The development of renal disease shortly after the suspension of rituximab suggests another probable pathway involved. To our knowledge the transforming growth factor may be responsible for existing pattern of fibrosis in this disease. The lack of response or at least partial response to rituximab can be explained by greater involvement of regulatory T lymphocyte in the pathophysiology of this entity.

Case Report

Implication for health policy/practice/research/medical education:
According to the criteria of IgG4-RD, it is probable that some of the patients diagnosed formerly as Sjogren's syndrome actually match with this old disease known as Mikulicz's disease and called IgG4-related sialoadenitis in the modern era.
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1. Background

IgG4-related disease (IgG4-RD) is a systemic immune-mediated disease that typically manifests as fibro-inflammatory masses that can affect nearly any organ system. Renal involvement by IgG4-RD usually takes the form of IgG4-related tubulointerstitial nephritis, but cases of membranous glomerulonephritis (MGN) have also been described. Here is a particular case of a patient who for 10 years was diagnosed with Sjögren's syndrome (SS) and was referred to our clinic by proteinuria, having developed proteinuria when he was being treated with rituximab. Mikulicz's disease is considered a subtype of Sjogren although it is now known that there are two different entities (1,2). Inside of the spectrum of involvement of IgG4-RD is the involvement of the salivary glands as described by Mikolicz. A key role has been attributed to B lymphocyte but also greater regulatory T cell activity described. The response to depletion of B cells would be useful in those predominant B cell hyperactivity (1,2).

2. Case Report

A 49–year-old man who was referred to our renal outpatient clinic with clinical and biochemical picture of nephrotic syndrome. He was diagnosed by Sjogren's syndrome 10 years ago. He had mediastinal lymphadenitis, primary sclerosing cholangitis and casual findings on CT scan of enlargement of prostate and low attenuation image on both kidneys. He had been on long-term rituximab 375 mg/m^2 weekly for 7 consecutive weeks that was suspended 14 months prior to our evaluation due to polyneuropathy predominantly in lower limbs. He was not on any other medication. He denied hematuria, rash, arthralgia and weight loss. At the time of presentation in clinic, he had massive proteinuria (7.5 g/24 h), serum creatinine (Cr) was 0.6 mg/dL (eGFR > 60 ml/min/1.73 m^2), albumin; 1.4 g/dl, hemoglobin; 12.7 g/dL, eosinophilia; (12 %), C-reactive protein (CRP) of 0.1 mg/dL and low complement levels (C3; 40 mg/dL and C4 2 mg/dL). He also had a striking hypergammaglobulinemia (IgG; 2220

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mg/dL). Additionally, ANA, anti-DNA, anti-SS-A/ SS-B, RF were negative. On examination, blood pressure was 127/80 mm Hg, heart sounds were normal, lungs were clear and the abdomen was soft and nontender. He had edema in limbs and bilateral symmetrical enlargement of parotid glands. Regarding, proteinuria, an angiotensin-converting enzyme (ACE) inhibitor was introduced at this point. Subsequently, urine culture, anti-glomerular basement membrane antibodies, myeloma screen, hepatitis B and C serology and human immunodeficiency virus were all negative. The ultrasonography showed normal kidneys, since the right kidney measured 12.5 cm and the left, 12 cm in length.

A renal biopsy was performed which revealed thickening of glomerular capillaries without mesangial proliferation, with slight tubulointerstitial fibrosis and granular deposits of IgG on the wall of the capillaries in immunofluorescence (IF) study corresponding to diagnosis of membranous nephropathy (MN) (Figure 1). In addition, serum anti-phospholipase-A2-receptor (PLA2R) was negative, while an increased level of IgG4 (1920 mg/dL) was detected. Secondary causes of MN were sought.

With the atypical presentation of Sjogren's syndrome (persistent gland swelling, mild keratoconjunctivitis Sicca, negative antibodies, unresponsive to rituximab, high levels of IgG4, a differential diagnosis with IgG4-related disease was proposed since both entities are related as secondary cause of MN. Salivary gland biopsy made some years ago, which showed lymphocytes with numerous plasma cells infiltration and abundant IgG4-positive cells and high IgG4-to-IgG ratio (Figure 2).

Therefore, prednisone at 1 mg/kg/d was added to ACE-inhibitor with a significative decrease in proteinuria and improvement of inflammatory parameters 3 months after initiating of treatment (Figure 3).

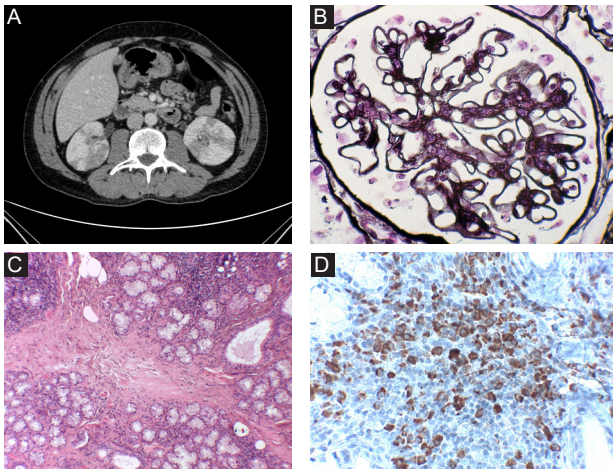

Figure 1. (a) Abdominal CT showing low attenuation image of both kidneys. (b) Kidney biopsy showing a thickening of capillaries (Silver stain ×40), (c) Lymphatic node with extensive zone of fibrosis. (d) Immunohistochemistry of salivary gland showing numerous IgG4 positive plasma cells with diagnostic criteria for IgG4-RD.

3. Discussion

This is a case report of a 49-year old man with MN in the context of IgG4-related disease. Good response to steroids with partial remission of proteinuria and improvement of inflammatory markers strongly suggests the leading role of steroids in the management of this entity (1). Typically when the doses of corticosteroids are diminishing, it can be seen a worsening of inflammatory parameters and clinical recurrence (2). To our knowledge, there is literature evidence for a rapid response to corticosteroids in the tubulo-interstitial disease associated with IgG4-related disease but not in cases with glomerular involvement (3-5). One immunologic characteristic of IgG4- related disease is regulatory T (Treg) lymphocyte activation (1) in contrasts to classic autoimmune conditions, in which the function of Treg cells is impaired. Cytokines produced by the regulatory T lymphocyte such as interleukin 10 or transforming growth factor β (TGF β) are overexpressed in this disease while, the latter seems to have a key role in the genesis of the predominant pattern of fibrosis. The fact that the patient developed renal involvement few months after stopping of treatment with rituximab suggests a

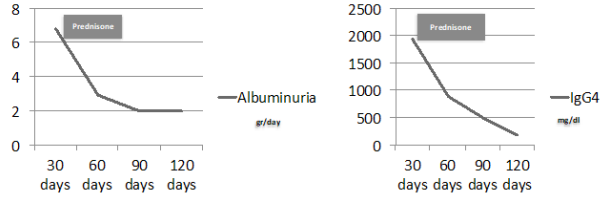

Figure 2. Clinical evolution of the patient during 120 days. We represent the timing of the biochemical parameters; albuminuria of 24 hours, and IgG4. Our patient showed significant improvement after initionation of prednisone in both parameters (inflammatory and albuminuria).

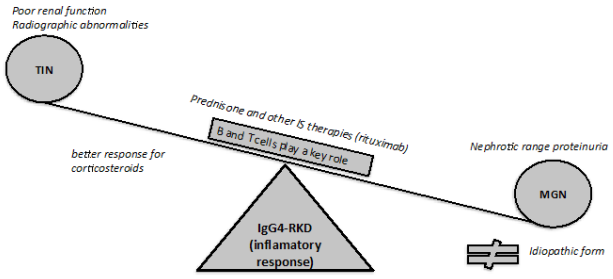

Figure 3. Clinical spectrum of IgG4- related kidney disease; dichotomous pattern of kidney injury. TIN; tubulointerstitial nephritis. MGN; membranous glomerulonephritis. IS; immunosuppressive therapy .

relationship not fully understood with B lymphocyte yet (1,4). The descending concentrations of IgG4 in response to rituximab that often precedes the clinical improvement reinforces this theory (6-8). The lack of response to rituximab or at least a partial response could be explained by a greater involvement of regulatory T lymphocyte.

MGN is a pattern of glomerular injury that may be primary ('idiopathic') or secondary. Most of the patients with primary MGN have antibodies against a podocyte antigen, M-type PLA2R. MGN may also be secondary to a variety of etiologic factors, including autoimmune diseases, infections, neoplasms, and drugs. Autoimmune disorders associated with MGN include systemic lupus erythematosus, rheumatoid arthritis, and Sjogren syndrome (7-9).

The case illustrates a typical presentation of a forgotten old disease. The patient has clinical data described as Mikulicz's disease; male predominance, 40-60 years old, negative anti-SS-A/SS-B antibodies, negative ANA, persistent gland swelling, an excellent response with rituximab and an increased IgG4 (3,9-14).

Currently this disease is considered in the clinical spectrum of IgG4 related disease (IgG4-RD) which also have other systemic manifestations, such as; sclerosing cholangitis, lymphadenopathies, kidney disease, pancreatitis (AIP) but could affect any organ in the human economy (4,5,12).

This disease with pseudotumoral behavior has distinctive histopathological features; dense lymphoplasmacytic inflammation and fibrosis, as we see in Figure 2C. Immunohistochemistry is necessary to demonstrate IgG4-positive plasma cells (>10 cells in HPF, >40-50% IgG4/IgG ratio) which along with the clinical picture allows the diagnosis (Figure 2D) (4-6,11,15).

In the kidney, the most dominant feature associated with IgG4-RD is plasma cell rich tubulointerstitial nephritis (TIN) with increased IgG4positive plasma cells and fibrosis (as is described above). MN is the most frequent pattern of the glomerular disease and is occasionally reported concurrent with TIN (4,5). IgG4 associated MN could be coexisting with TIN or associated to an extra-renal affectation (Figure 3) (5,10).

The gold standard for the diagnosis would be the demonstration of IgG4-positive plasma cells, unfortunately these are not always observed due to the small sample of the renal biopsy and the focal pattern of the fibrosis. However, the CT scan can be used for the diagnosis according with the clinical features (4,5).

In this case the extrarenal involvement was documented with the histopathology criteria in salivary glands and lymphatic nodes. It is noteworthy than the pattern of renal disease on the scanner is compatible with TIN.

The glomerular involvement in form of MN produces less fibro-inflammatory damage than TIN and consequently the response to steroids is less significant (4).

Our patient have been treated with prednisone therapy (60 mg/day) for one month, the proteinuria decreased to 3.5 g/day and the inflammatory markers (IgG4; 1090, C3; 80.4 and C4; 22.4 mg/dl) improved.

According to the criteria of IgG4-RD it is probable that some of the patients diagnosed formerly as Sjogren's syndrome actually match with these old disease known as Mikulicz's disease and called IgG4-related sialoadenitis in the modern era. Both diseases can affect the kidney and it's important to differentiate them due to a possible good response to steroid/rituximab in the case of IgG4-RD.

4. Conclusions

In summary, we report a patient with MN secondary to IgG4-related disease with a previous diagnosis of Sjogren's syndrome in which predominated pseudotumoral behavior with acceptable response to steroids both proteinuria and inflammatory parameters. The lack of response or at least partial response to rituximab reinforces the idea that regulatory T cell is intrinsically involved in this pathology.

Authors' contribution

All authors contributed to the writing , editing and revising the paper equally.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors. The patients gave his consent to publish as a case report.

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