CASE REPORT

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IgA nephropathy in systemic lupus erythematosus: a purely coincidental association?

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ABSTRACT

Renal involvement in systemic lupus erythematosus is one of the most typical aspects of the disease. Non-lupus nephritis has rarely been reported in these patients.

Although IgA nephropathy and lupus nephritis share some common physiopathological characteristics, their laboratory, histopathology and extra-renal clinical findings are different, and support a different pathogenesis.

We present the case of a female patient with a well established clinical diagnosis of systemic lupus erythematosus in whom the renal biopsy unexpectedly revealed IgA nephropathy, without any superimposed features of lupus nephritis.

Key-Words:
Anti-Ro/SSA antibodies, autoimmunity, IgA nephropathy, lupus nephritis, renal biopsy, systemic lupus erythematosus.

INTRODUCTION

Renal involvement in systemic lupus erythematosus (SLE) is one of the most typical aspects of the disease. Immune depositions are found in nearly all renal biopsies of SLE patients, reflecting the high prevalence of renal involvement, even in the absence of overt clinical manifestations[1].

The morphology of lupus nephritis spans a wide spectrum in different patients as well as in serial biopsies of the same patient and even among different glomeruli of the same biopsy[1,2].

Lupus nephropathy (LN) is currently classified using the new International Society of Nephrology (ISN) / Renal Pathology Society (RPS) classification, based on glomerular alterations on light microscopy integrated with immunofluorescence and electron microscopy patterns[3]. Histology findings are polymorphic and can change and evolve over time. Serial biopsy specimens show that transformation of histology class is frequent[4].

Typically LN presents polyclonal immunoglobulin immune deposits with predominance of IgG, widespread, heavy, distribution of complement factors C1q, C3 and C4 with "fingerprint" immune dense deposits, haematoxylin bodies, "wire-loop" lesions and frequent immune deposits identified in the capillary basement membrane[2-4].

IgA nephropathy (IgAN) is the most common primary glomerulonephritis, characterised by mesangial proliferation and diffuse mesangial IgA deposits[5].

Since the first description of Berger *et al.* (1967), IgA nephropathy has been found typically in association with liver diseases and Henoch-Schönlein purpura, but in the past few years other associations have been reported, mainly with systemic disorders, such as rheumatic diseases (ankylosing spondylitis, rheumatoid arthritis, Reiter syndrome, uveitis, Behcet's syndrome, sicca syndrome), cryoglobulinaemia, and with other illness involving skin and upper respiratory and gastrointestinal tract, among other organs[5]. Some of these associations have been reported only in isolated cases, suggesting that they may be purely coincidental.

Several diseases may be accompanied by a dysregulation of the IgA immune system, implying the presence of increased serum polymeric IgA or of circulating IgA immune complexes, and consequent deposition within the kidney[5].

The superimposition and occurrence of other non-lupus glomerulopathies is rare in SLE patients. Reports include glomerular lesions associated with hepatitis B virus[6], *Escherichia Coli* bacteraemia and human immunodeficiency virus[7]. To the best of our knowledge, at present only five cases of SLE and IgAN association have been reported[1,8,9].

Renal biopsy plays a crucial role in identifying these glomerulopathies, which may have prognostic and therapeutic implications distinctive from those of lupus nephritis.

CASE REPORT

A 28-year-old, non-smoking Caucasian woman with no previous serious illnesses was referred to our clinic in October 2005 with a recent (one month) history of increased muscle weakness, fever, photosensitivity and symmetric polyarthritis involving the small joints of the hands and wrists. Clinical examination revealed oral ulcers and a skin rash on the malar region that had appeared in the previous 3 months, with no other significant findings.

Laboratory blood tests revealed an increase of the erythrocyte sedimentation rate (ESR 72 mm/1st h) and leucopaenia (white cell count 3.20×10^3 / µL). Renal and liver function tests, total serum proteins, alkaline phosphatase, electrolytes and thyroid function tests were normal. The urine analysis was negative for protein and blood. Blood and urine cultures were negative.

Immunological studies revealed strongly positive Anti-Ro / SSA antibodies, with negative results for antinuclear (ANA), ds DNA, anti-Sm, anti-RNP and antiphospholipid antibodies and ANCA. Serum complement C3 and C4 levels were both decreased to 450 mg/l and 5 mg/l respectively (normal ranges 900-1800 and 100-400 respectively).

The serum IgG level was slightly elevated at 19.9 g/l (normal range 7.0–15.0); serum IgM and IgA levels were normal. Rheumatoid factor and laboratory tests for syphilis and hepatitis B surface antigen (HBsAg) were negative. The clinical and biochemical findings met the American College of Rheumatology diagnostic criteria for SLE, and taken together allowed its diagnosis. At that time there was no evidence of renal disease.

Treatment with prednisolone (10 mg per day) and hydroxychloroquine (400 mg per day) was started, with subsequent improvement of the arthritis and cutaneous signs, and normalisation of laboratory blood tests (ESR, white cells count, serum C3 and C4). Renal function tests and urine analysis remained normal.

In July 2007 (approximately 2 years later), a routine urine analysis showed proteinuria and microscopic haematuria. Urine microscopy showed 10 erythrocytes and 2-4 granular casts per high-power field. 24-hour urine protein excretion was 1.2 g.

A percutaneous needle kidney biopsy was performed.

Histological examination at light microscopy showed sclerosis in 6 of the 9 glomeruli, modest mesangial proliferation, tubular atrophy and diffuse interstitial fibrosis (Fig. 1).

Immunofluorescence staining of 6 glomeruli revealed mesangial deposits of IgA and C3 with absence of IgG, IgM, C1q, C4 and fibrinogen (Fig. 2). There were no findings suggestive of lupus nephritis and the diagnosis of IgAN was established.

Previous therapy was maintained and treatment with ramipril 5 mg per day was started, with a decrease

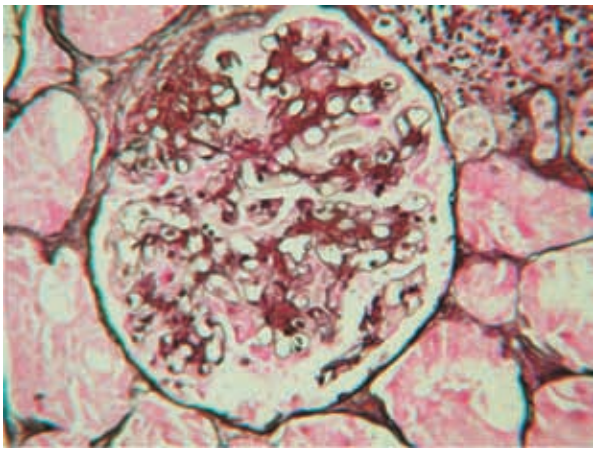

Figure 1

PASx400: Glomerular sclerosis and mesangial proliferation.

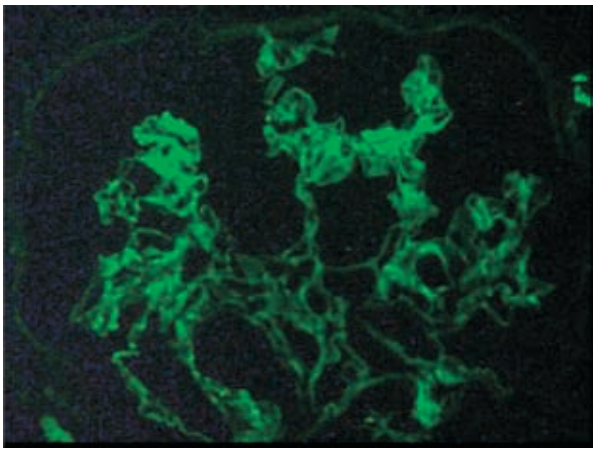

Figure 2

IFx400: IgA mesangial deposits.

in 24-hour urine protein excretion to 0.8 g and disappearance of haematuria 3 months after kidney biopsy. Renal function remained normal. At that time it was decided to add losartan 25 mg per day.

Presently, 12 months after the kidney biopsy, the patient remains asymptomatic, with normal blood pressure. Renal function is normal and 24-hour urine protein excretion has decreased to 0.3 g. White cell count, ESR and serum complement C3 and C4 fractions are normal, ANA titres are undetectable, serum IgG, IgA and IgM levels are normal and anti-Ro/SSA antibodies remain strongly positive.

DISCUSSION

IgAN has previously been described in association with various autoimmune diseases, but to the best of our knowledge, only 5 previous cases of IgAN associated with SLE have been reported[1,8,9]. Despite being distinct diseases, with different clinical and pathological findings, and with different prognosis, they share some common physiopathological characteristics[1,8,9].

The pathogenesis of lupus nephritis remains incompletely understood. Several immune regulation mechanisms are altered[10]. Dysregulated autoreactive T-cell and autonomous B-cell hyperactivity lead to excessive production of heterogeneous auto-antibodies[10].

No specific aetiology has been identified, but lupus nephritis is regarded as the prototype of chronic immune complex glomerulonephritis[8,10].

Morphological findings on LN include vascular, glomerular and tubulo-interstitial lesions deriving from immune-complexes deposition and complement activation. LN is characterised by cellular proliferative lesions, "wire-loop" lesions and deposits of polyclonal immunoglobulin (prevalently IgG isotype) and complement fractions (C1q, C3 and C4)[9].

Renal involvement in SLE is characterised by variable grades of proteinuria, urinary sediment changes with micro-haematuria and erythrocyte casts, hypertension and progressive renal dysfunction.

Typical extra-renal signs in the skin, joints and blood are often associated with LN, which usually permit easy differentiation from IgAN. Nevertheless, in IgAN there may also be some extra-renal features, such as arthralgia, vasculitic skin lesions and erythema nodosum that might result in confusion with SLE[9].

IgAN is the most common cause of idiopathic glomerulonephritis in the world[11]. Although this disorder was initially thought to have a benign course, it is now recognised that slow progression to end-stage renal disease occurs in up to 50 percent of affected patients[11]. The pathogenesis of IgAN is uncertain and its aetiology is unknown. Abnormal immune regulation results in formation of IgA containing

immune complexes characterised by their high affinity for the mesangium.

The factors that lead to the development of the disease are poorly understood, but are thought to include aberrant synthesis and metabolism of IgA resulting in IgA immune complexes with characteristics that favour mesangial deposits, and this mesangial IgA accumulation subsequently leads to cell reaction and proliferation[5].

The lack of antigens in the immune-complexes from IgAN patients leads to the hypothesis that the disease is induced by an excessive synthesis of structurally altered IgA rather than an abnormal immune response to an antigenic stimulus[5].

The role of glomerular immune aggregates in renal injury is believed to be minor, and it appears that in both lupus or IgAN, host factors, activation of complement, lymphokine-derived cell recruitment, and defective clearance by the monocyte-phagocyte system are more important factors[5,10].

SLE is clearly an autoimmune disease; attempts to relate IgAN to autoimmunity have failed due to a lack of significant auto-antibodies in IgAN[12].

The immuno-histological aspects of IgAN are characterised by mesangial proliferation and mesangial deposits of IgA1 (usually absent in lupus nephritis), C3 fraction of complement and occasionally IgG and IgM, which are responsible for complement activation with the consequential release of inflammatory mediators[5]. The absence of C1q and C4 deposits, present in LN, suggest that the alternative pathway of complement activation is involved in the pathogenesis of disease.

The classic presentation of IgAN is with frank haematuria, often recurrent, following an upper respiratory infection. However, the majority of patients are diagnosed following an evaluation for asymptomatic microscopic haematuria and / or mild proteinuria[5].

Although the clinical picture can be highly suggestive, the diagnosis can only be confirmed by a kidney biopsy.

Our patient had characteristic clinical features of SLE, with five diagnostic criteria of the American College of Rheumatology. To the best of our knowledge, our patient had no family history suggestive of an inherited condition such as immunodeficiency.

Two years after the clinical diagnosis of SLE, renal involvement (mild proteinuria and microscopic haematuria with a well-preserved renal function) was detected, and the patient underwent renal biopsy.

In our case the kidney biopsy showed no typical histological findings of SLE. Histology examination at light microscopy showed mesangial proliferation, tubular atrophy and diffuse interstitial fibrosis, that might be classified as LN class II. However immunofluorescence staining only revealed mesangial deposits of IgA and C3, with the absence of IgG, IgM, C1q, C4 and fibrinogen, not supporting the diagnosis of lupus nephritis.

The histological diagnosis of IgAN was straightforward in that glomerular lesions consisted exclusively of mesangial IgA and C3 immune deposits, with modest hypercellularity and sclerosis.

One may argue that the predominance of mesangial IgA immune complexes is a morphological subtype of lupus nephritis. However, the absence of other immunoglobulins, in particular IgG, and of complement fractions of the classical pathway, such as C1q and C4, are strongly against this diagnosis.

Without the clinical history, the histological diagnosis of lupus nephritis would not have been considered, and even with established clinical SLE, the histological findings do not justify a diagnosis of lupus nephritis even of an atypical form.

In our patient the absence of any recognised aetiology justifies the classification of primary or idiopathic IgAN. Considering the pathophysiology of both diseases, the occurrence of IgAN in SLE patients assumes pathological and therapeutic interest. Given the high frequency of IgAN these association could be merely casual.

However this patient may represent a subset of SLE with uncertain host factors that make LN development less probable, or type of immune response resistant to the expression of lupus nephritis; analogous factors may be operative in SLE patients with clinically limited and silent renal disease[1,8].

Another interesting point is that our patient presented with positive anti-Ro / SSA antibodies and

persistently tested negative for ANA. The association between anti-Ro and renal disease in SLE remains controversial. There have been suggestions that renal disease in SLE patients may be inversely associated with the presence of this serological factor[13]. In fact, anti-Ro / SSA antibodies are primarily found in patients with SLE and Sjögren's syndrome[14]. Anti-Ro / SSA antibodies are found in approximately 10 – 60 percent of patients with SLE, and the prevalence depends upon the methodology employed[14]. These antibodies have been associated with photosensitivity, a rash known as subacute cutaneous lupus, cutaneous vasculitis, interstitial lung disease, neonatal disease and congenital heart block[14].

There is a strong linkage between the production of anti-Ro antibodies, and a genetic deficiency in the production of C4 complement and the HLA-DR3 genotype[14].

In the 1970s, there were several reports of patients who met the American College of Rheumatology criteria for SLE, but were persistently negative for ANA. Although not recognised at the time, this consistently negative finding occurred because sera were tested using mouse and not human tissue as substrate. By comparison, anti-Ro / SSA antibodies were found in most of these patients when a human cell line extract was used as the substrate for the Ro antigens[14].

The substitution of Hep2 cells (a human cell line) for a mouse tissue sections in the ANA test has resulted in only a small number of SLE patients who test persistently negative for ANA[14]. Nevertheless, on rare occasions, the anti-Ro / SSA antibody test may be useful in suggesting a diagnosis of systemic autoimmune disease in face of a negative ANA[14].

In spite of their fascinating biological implications and obvious clinical significance, non-lupus nephritides seen in patients with SLE remain poorly understood and limited to isolated case reports[15]. The cases reported in the literature[1,8,9] and our own suggest that renal diseases other than lupus nephritis should be clinically suspected in patients with serological and clinical remission of lupus activity who are found to have renal abnormalities,

Our case highlights the importance of renal biopsy in lupus patients, since a correct diagnosis will permit the most appropriate treatment to be used, avoiding unnecessary immunosuppressive regimens.

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Conflict of interest statement. None declared.

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