IgA nephropathy in systemic lupus erythematosus

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Received on July 18, 2006; accepted in revised form on December 5, 2006.

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Key words*:* lupus, lupus nephritis, IgA nephropathy.

Competing interests: none declared.

ABSTRACT

Renal involvement in systemic lupus erythematosus (SLE) is a typical manifestation of the disease. The occurrence of non-lupus nephritis in SLE patients has rarely been reported; we describe the case of a woman suffering from SLE and IgA nephropathy (IgAN). Although IgAN and lupus nephritis share some common physiopathological characteristics, their laboratory and histopathologic findings and the extra-renal clinical manifestations are different and support a different pathogenesis. Our case highlights the importance of renal biopsy in lupus patients with urinary alterations since a correct diagnosis would permit the most appropriate treatment to be started, thus avoiding unnecessary immunosuppressive treatments.

Introduction

Renal involvement in systemic lupus erythematosus (SLE) is one of the most typical aspects of the disease. The histological classes of lupus nephropathy (LN) are currently distinguished using the WHO classification, which is based on the different alterations shown by light microscopy and the immunofluorescence patterns. They are polymorph and can change and evolve over time, switching from moderate glomerular lesions (minimal change nephritis), to more severe lesions, which require more aggressive treatment. In SLE patients the occurrence of non-lupus nephritis has been rarely reported; we describe the case of a woman suffering of SLE and IgA nephropathy (IgAN).

Case report

A 43-year-old Caucasian woman, non-smoker with no previous serious disease, was referred to our clinic due to increased muscle weakness, fever and polyarticular and symmetric arthritis involving the small joints of the hands, wrists and ankles. The patient had intermittent erythema nodosum, localised on the extensor muscle surface of the legs, which had appeared three years previously. On clinical examination there was a skin rash on chest and malar region and arterial hypertension.

Laboratory blood tests revealed an increase of inflammation indices (ESR 92 mm 1st h, RCP 2.5 mg/L) and circulating immune-complexes and a polyclonal hypergammaglobulinaemia. Urine analysis showed a microscopic hematuria of glomerular origin, as indicated by phase contrast Addis count. The presence of high titre (1:180) of antinuclear antibodies with homogeneous pattern, anti-Ro/SSA antibodies and anti-native-DNA antibodies was detected, with a reduction of C3 and C4 fractions of the complement. Renal function tests, full blood cell count, total serum proteins, alkaline phosphatase, and electrolytes were normal.

Clinical and biochemical findings fulfilled the American College of Rheumatology diagnostic criteria for SLE. To better define the type and extent of renal involvement, a needle-biopsy was carried out; histological examination at light microscopy showed a serious vessel sclerosis with regular mononuclear infiltrates and a slight mesangial proliferation. Immunofluorescence staining revealed mesangial deposits of IgA, but no C1q, C3, C4 and IgM deposits (Fig 1A, 1B, 1C). This histological pattern was typical of IgA nephropathy. Treatment with low-dose of prednisone and ACE inhibitors was started, with subsequent improvement of arthritis and cutaneous signs, resolution of arterial hypertension and disappearing of microscopic hematuria.

Discussion

IgAN associated to autoimmune disease has been previously described (1, 2), but at present only 4 cases of association between SLE and IgAN have been reported (2, 3). Despite being two clinically, pathologically and prognostically distinct diseases, they share some common physiopathological characteristics.

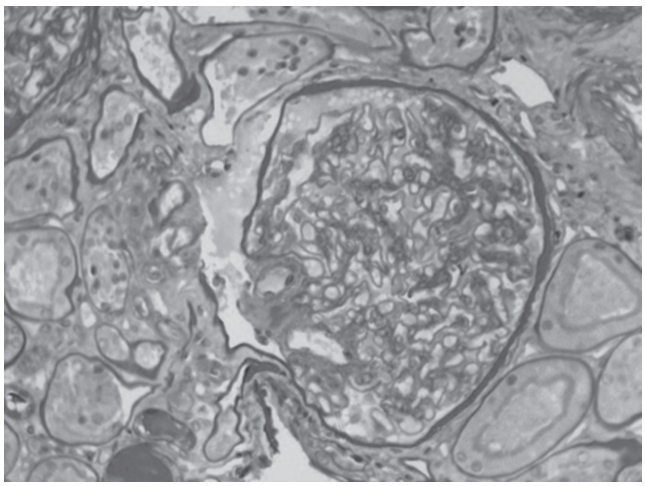
The morphological alterations of LN include vascular, glomerular and tubulo-interstitial lesions deriving from immune-complexes deposition and complement activation. LN is characterised by cellular proliferative lesions, wire-loop lesions and deposits of polyclonal immunoglobulins, (prevalently IgG isotype) and complement fractions (C1q, C3 e C4), which are often local-

ised in the basal membrane of glomerular capillary.

Renal involvement in SLE is characterised by proteinuria (defined as 0.5 g per 24 hours or a dispstick score of > 3+) or the presence of casts (red blood cells, heme, granular or mixed casts) on microscopic analysis of spun urine, and may be manifested by an increased serum creatinine level or by the presence of hematuria and/or pyuria in the absence of infection or menses. Renal biopsy is the most definitive tool to assess the degree of renal involvement as well its activity and damage, so it can guide therapeutic decision (4). LN is often associated with typical extra-renal signs (in the skin, joints and blood), which permit easy differentiation from IgAN. Nevertheless, in IgAN there may also be some extra-renal signs, such as arthralgias, vasculitis type skin lesions and erythema nodosum.

IgAN is the most common glomerulonephritis which evolves to chronic renal failure in only 10% of cases (5). It is characterised by arterial hypertension associated with microscopic hematuria and/or repeated episodes of macroscopic hematuria, whereas proteinuria is not always present. Conversely, proteinuria is constant in LN and it is associated to microscopic hematuria in 80% of patients, whereas the frequency of arterial hypertension in LN patients is comparable to that of lupus patients without renal involvement (6). The immune-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. The absence of C4 and C1q deposits (7), which are present in LN, suggest that the alternative way of complement activation is involved in the pathogenesis of the disease. Experimental observations (8) and glomerular and serological analysis on IgAN affected patients, have suggested the pathogenic role of immune-complexes containing structurally altered IgA. Circulating levels of IgA are increased in more than 50% of IgAN patients and immune-complexes containing IgA have been detected both in serum and in renal glomeruli of these subjects. The lack of common antigens in the immune-complexes from IgAN patients leads to hypothesises that the disease is induced by an excessive synthesis of structurally altered IgA rather than to an abnormal immune response to an antigenic stimulus (9).

An increase of anti-C1q antibodies, whose IgG isotype correlates with class IV WHO LN (proliferative glomerulonephritis) (6) has been detected in IgAN patients (IgA isotype) (10), but their exact role in both diseases is controversial and poorly understood. Furthermore, anti-C1q antibodies have



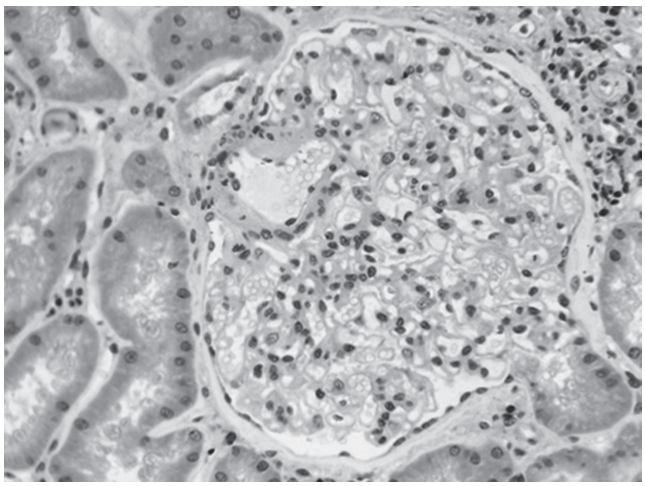


Fig. 1A and 1B. PAS and trichrome staining. Slight irregular mesangial proliferation with some areas of glomerular sclerosis and a fibrous crescent. Serious vessel sclerosis with regular mononuclear infiltrates.

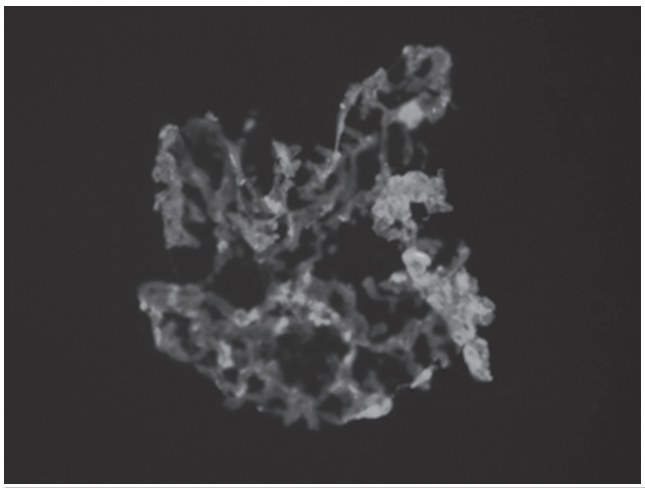


Fig. 1C. Immunofluorescence staining of renal biopsy using FITC-labelled anti-IgG, anti-IgA, anti-IgM, anti-C1q, anti-C3 and anti-C4 antibodies. Staining is observed with anti-IgA antibodies, but not with anti-IgG, anti-IgM, anti-C1q, anti-C3 and anti-C4, indicating the presence of IgA deposits (diffuse granular mesangial and diffuse segmental glomerular pattern of deposition) and the absence of C1q, C3, C4 and IgM deposits.

also been detected in other immunocomplexes-mediated diseases without renal involvement; one possible explanation for their occurrence may be that these antibodies have different specificities, but subclass or titre may also be of importance (10, 11).

The presence of anti-C1q antibodies in both LN and IgAN patients, though of different isotype, suggests that some similar pathogenic mechanisms in these diseases exist, further confirmed by the detection in both diseases of anti-endothelial antibodies (12) (absent in other glomerulonephritis) and the possible existence of hereditary deficit of complement factors, such as C1q, C2, C4 (13, 14). Nevertheless, the laboratory and histopathologic findings of IgAN and LN and their extra-renal clinical manifestations are quite different and support a different pathogenesis.

The occurrence of IgAN during SLE is a rare event and, given the relatively high frequency of IgAN, could be attributable to a casual association, but considering the physiophathological mechanisms of both diseases it assumes pathological and therapeutic interest. Unless IgAN is characterised by a persistent proteinuria ≥ 1g /24h and the support therapies (arterial hypertension control, no smoking) are not achieved, immunosuppressive therapy is not the first choice therapy. Furthermore, IgAN could be an expression of a particular subset of lupus patients with a tendentially less aggressive renal involvement, as shown by the follow-up of reported cases in which slight renal involvement was confirmed over time, according to IgAN, and did not evolve into classic LN. Our case highlights the importance of renal biopsy in lupus patients with urinary alterations since a correct diagnosis would permit the most appropriate treatment to be started, avoiding unnecessary immunosuppressive treatments.

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