IgA nephropathy in systemic lupus erythematosus

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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-
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-RENNAL SIGNS (IN THE SKIN, JOINTS AND BLOOD), WHICH PERMIT EASY DIFFERENTIATION FROM IgAN. NEVERTHLESS, IN IgAN THERE MAY ALSO BE SOME EXTRA-RENNAL 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 hypotheses 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
also been detected in other immuno-
complexes-mediated diseases without
renal involvement; one possible expla-
nation for their occurrence may be that
these antibodies have different specifici-
cities, 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) (ab-
sent 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 differ-
ent and support a different pathogen-
esis.

The occurrence of IgAN during SLE
is a rare event and, given the relative-
ly high frequency of IgAN, could be
attributable to a casual association,
but considering the physiopathologi-
cal mechanisms of both diseases it as-
sumes pathological and therapeutic
interest. Unless IgAN is characterised
by a persistent proteinuria ≥ 1g /24h
and the support therapies (arterial hy-
pertension control, no smoking) are not
achieved, immunosuppressive therapy
is not the first choice therapy. Further-
more, IgAN could be an expression of a
particular subset of lupus patients with a
tendentially less aggressive renal in-
volvement, 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
during its evolution, it may not evolve
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References
1. HEMMEN T, PEREZ-CANTO A, DISTLER A,
OFFERMANN G, BRAUN J: IgA nephropathy
in a patient with Behçet syndrome - case re-
port and review of literature. Br J Rheumatol
2. MAC-MOUNE LAI F, LI EKM, TANG NLS et al.: IgA nephropathy: a rare lesion in systemic lupus erythematosus. Med Pathol 1995; 8:
5-10.
5. IBELS LS, GYÖRY AZ: IgA nephropathy: analysis of the natural history, important fac-
tors in the progression of renal disease and review of the literature. Medicine 1994; 73:
79-102.
6. CAMERON JS: Lupus nephritis. J Am Soc Ne-
7. MIYAZAKI R, KURODA M, AKIYAMA T
OTANI I, TOFUKU Y, TAKEDA R: Glomerular deposition and serum levels of complement control proteins in patients with IgA neph-
9. MONTEIRO RC, LEROY V, LAUNAY P et al.: Pathogénie de la maladie de Berger. Implications des immunoglobulines A et de leurs re-
cepteurs. Medecine Sciences 2003; 19: 1233-
41.
10. GUNNARSSON I, RONNELID J, LUNDBERG I,
JACOBSON SH: Occurrence of anti-C1q an-
tibodies in IgA nephropathy. Nephrol Dial
11. WISNIESKI JI, JONES SN: Comparison of autoantibodies to the collagen-like region of C1q in hypocomplementemic urticarial vasculitis syndrome and systemic lupus erythematosus. J Immunol 1992; 148: 1396-
403.
12. WANG MX, WALKER RG, KINCAID-SMITH P: Clinicopathologic associations of anti-
endothelial cell antibodies in immunoglobu-
lin A nephropathy and lupus nephritis. Am J
13. TOPALOGLU R, BAKKALOGU A, SLINGSBY
14. BOWNESS P, DAVIES KA, NORSWORTHY PJ et al.: Hereditary C1q deficiency and sys-
87: 455-64.