Focal Segmental Glomerulosclerosis in Systemic Lupus Erythematosus: One or Two Glomerular Diseases?

Glomerulosclerose Segmentar e Focal em Lúpus Eritematoso Sistêmico: Uma ou Duas Doenças?

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ABSTRACT

Some patients with clinical and/or laboratory diagnosis of systemic lupus erythematosus (SLE) present with nephritis which from the morphological point of view does not fit in one of the 6 classes described in the WHO classification of lupus nephritis. On the other hand, nonlupus nephritis in patients with confirmed SLE is rarely reported. This condition may not be so uncommon as it seems. The associated glomerular lesions most frequently described are amyloidosis and focal segmental glomerulosclerosis (FSGS). We report on a 46 year-old, caucasian woman, who fulfilled the American College of Rheumatology criteria for SLE diagnosis: arthritis, positive anti-DNA, ANA, anti-Sm antibodies, and cutaneous maculae. During the follow-up, she presented arthralgias, alopecia, vasculitis, lower extremities edema and decreased serum levels of C3 and C4. Proteinuria was initially nephrotic, but reached negative levels. The serum creatinine varied from 0.7 to 3.0 mg/dl. The patient was submitted to the first renal biopsy at admission and to the second one, 3 years later, with diagnosis of minimal change disease and FSGS, respectively. No deposits were demonstrated by immunofluorescence. In the present case, we believe that the patient had SLE and developed an idiopathic disease of the minimal change disease-FSGS spectrum. (J Bras Nefrol 2006; 28(3):171-175)

RESUMO

Alguns pacientes com diagnóstico clínico e/ou laboratorial de lúpus eritematoso sistêmico (LES) apresentam nefrite que, do ponto de vista morfológico, não se enquadrar no um destes 6 classes de nefrite lúpica descritos na classificação da OMS. Por outro lado, nefrites não-lúpicas em pacientes com LES confirmado são raramente relatadas. Essa condição pode não ser tão incomum como parece. As lesões glomerulares associadas mais frequentemente descritas são amiloídes e glomerulosclerose segmentar e focal (GESF). Nos relatamos o caso de uma mulher de 46 anos, branca, que preenchia critérios da Associação Americana de Reumatologia para diagnóstico de LES: artrite, FAN, anti-DNA e anti-Sm positivos, presença de máculas cutâneas. Durante o seguimento, ela apresentou artralgias, alopecia, vasculite, edema de membros inferiores e níveis baixos de C3 e C4 séricos. A proteinúria que inicialamente era nefrótica chegou a negativar. A creatinina sérica variou de 0,7 a 3,0 mg/dl. A paciente foi submetida à sua primeira biópsia renal quando da chegada ao serviço e à segunda, 3 anos mais tarde, com diagnósticos de doença de lesões mínimas e GESF, respectivamente; a imunofluorescência revelou-se negativa. No presente caso, acreditamos que a paciente tinha LES e desenvolveu uma doença idiopática do espectro doença de lesões mínimas-GESF. (J Bras Nefrol 2006; 28(3):171-175)

INTRODUCTION

Renal involvement is frequent in systemic lupus erythematosus (SLE) and lupus nephritis is present in almost all cases of SLE, as documented by biopsies¹.

Although lupus nephritis can selectively involve any renal compartment, glomerulonephritis is the most frequent manifestation² and lupus glomerulonephritis (GN) is divided into 6 distinct morphologic classes according to the World Health Organization (WHO)

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classification: I-normal, II-mesangial proliferative, III-focal proliferative, IV-diffuse proliferative, V-membranous and VI-advanced sclerosing GN.

Beyond these lesions, renal biopsies from patients with SLE may show changes that are pathogenetically and morphologically unrelated to SLE\(^4\), whose occurrence is only identifiable by renal biopsy. Few of these cases have been described, including several distinct renal lesions with predominance of amyloidosis and focal segmental glomerulosclerosis (FSGS). The diagnosis of other nephritis in SLE patients is important as they may have different prognosis and treatment. The morphology, behavior and best therapeutic approach in cases of nonlupus nephritis in patients with SLE are not well known.

**CASE REPORT**

We report on the case of a 46 year-old, non Caucasian woman, who fulfilled the following criteria of the American College of Rheumatology for SLE diagnosis: arthritis, cutaneous maculae, positive antinuclear antibodies (ANA), positive anti-native DNA and anti-Sm.

At admission, she reported a month history of edema of the lower extremities that progressed to anasarca, decrease of urinary volume, headache and dyspnea. Systemic hypertension, nephrotic proteinuria and acute renal insufficiency were observed. At the initial physical examination, it was observed generalized edema, including ascitis, without other abnormalities, but high blood pressure. The first laboratory tests revealed: serum creatinine 3.5 mg/dl, urea 175 mg/dl, sodium 145 mEq/l, potassium 4.6 mEq/l, hemoglobin 14.6 g/l, ESR 61, WBC 7600/mm\(^3\), positive ANA 1:100. Afterwards, she was submitted to a first renal biopsy (figures 1a and 1b), that did not reveal glomerular or tubular lesions by light microscopy and the immunofluorescence was negative for C1q, C3, IgG, IgM and IgA.

At the beginning the patient was treated with oral prednisone and presented serum creatinine normalization and the proteinuria within a year went down to 1.3 g/24 h.

As she was followed in our Service during 20 years, it is not possible to describe in details the entire course of her disease, so only the most important points are shown below.

After 3 years, she presented alopecia, cutaneous maculae and arthritis, positive ANA (titer superior to 1:640). She was maintained with low dosage of corticosteroid (CS), her renal function was normal and proteinuria increased again, up to nephrotic range levels. A second renal biopsy (figures 2a and 2b) was then performed and was compatible with focal segmental glomerulosclerosis (FSGS). The patient was kept on CS in low doses and the 24-hour proteinuria decreased to 0.8 g about 1 year later.

After another year, as proteinuria reached again nephrotic levels, ACE inhibitor was added to the schema of treatment and proteinuria decreased to 0.46 g.

In the eighth year of evolution, the 24-hour proteinuria reached 4.58 g and she received oral prednisone 1 mg/kg/day. Proteinuria increased and decreased independent of the CS dose. During this year and the previous one, she presented poliarthralgias; serum cholesterol and tryglicerides levels were elevated (and the highest levels were 312 mg/dl and 624 mg/dl, respectively).

During the ninth year of evolution, due to a 24-hour proteinuria of 6.22 g after a partial remission with the use of oral prednisone 1mg/kg/day (levels of 4.58g that fell to 0.73 g/24 h), it was administered oral azathioprine 2 mg/kg/day, that was rapidly discontinued as the patient presented symptomatic drug-induced hepatitis, confirmed by high levels of SGOT, SGPT, bilirrubins, with recovery after withdrawn of the drug.

From the tenth to the fourteenth year of follow-up, it was observed frequent variation of the 24-hour proteinuria levels (minimum: 0.32 g; maximum: 7.59 g) and
during these years she received variable doses of CS and ACE inhibitor. At the end of this period, it was diagnosed cataracts.

At the beginning of the fifteenth year of evolution, it was detected elevation of serum creatinine from 0.8 to 2.0 mg/dl. At this moment, pulse therapy with methylprednisolone was administered and, after three courses, serum creatinine returned to 0.8 mg/dl, although proteinuria was still elevated. She was submitted to nine courses of pulse therapy during which oral prednisone 30 mg/day was maintained. The dose of ACE inhibitor was increased with the aim of normalizing blood pressure levels.

During the follow-up, the titers of antinuclear antibodies varied from 1:160 to 1:12800 and sometimes anti-DNA was positive, as well as low levels of C3 and C4 were detected. Except for the leukopenia observed for a short time during the first year of follow-up, blood cell counts were always normal.

At the beginning of the eighteenth year, she still presented normal levels of serum creatinine and serum albumin and no hematuria, proteinuria was of 2.31 mg/dl, serum cholesterol 212 mg/dl and tryglicerides 198 mg/dl, using oral prednisone 5 mg/day, captopril 100 mg/day and simvastatin 20 mg/day.

Her proteinuria became negative without loss of renal function (serum creatinine 0.9 mg/dl) about 2 years later and, since then, immunosuppressive drugs were withdrawn. During the twentieth year of follow-up, these parameters have not changed expressively, there was no relapse and the last serum creatinine was 1.1 mg/dl.

**DISCUSSION**

It is generally assumed that in patients with well-documented SLE, renal abnormalities are caused by lupus nephritis. Thus, renal biopsy in SLE is usually recommended not for diagnostic purposes, but rather to determine the type and extent of renal involvement, as well as to evaluate the activity and chronicity indices. Interestingly, in rare occasions, clinically significant renal diseases unrelated to lupus nephritis have been described in patients with SLE. There are only few reports of this association mostly as isolated cases.

Among approximately 36 reported cases of nonlupus nephritis in patients with SLE, renal amyloidosis was diagnosed in more than half (approximately 20 cases) and it is the most frequent type of nonlupus renal involvement in SLE patients. The other lesions described in decreasing order of frequency were FSGS, minimal change disease, IgA nephropathy, infection-related glomerulonephritis, glomerulocystic kidney disease, necrotizing glomerulitis, sarcoidal tubulointerstitial nephritis and nonsteroidal anti-inflammatory drug-induced tubulointerstitial nephritis.

Baranowska-Daca et al., in 2001, reviewed 252 renal biopsies performed on 224 patients with SLE and identified 13 additional nonlupus nephritis. They were divided in 3 clinically distinct groups, i.e., patients in whom SLE was diagnosed at the time of the renal biopsy who showed: FSGS (3 cases), IgM nephropathy (2 cases) and thin membrane disease (1 case); patients in whom SLE was diagnosed 2 to 9 years prior to the renal biopsies that revealed FSGS (2 cases) and hypertensive nephrosclerosis (1 case); patients in whom SLE was diagnosed 5 to 36 years prior the renal biopsy that showed: amyloidosis (1 case), FSGS (1 case), hypertensive nephrosclerosis (1 case) and acute tubulointerstitial nephritis (1 case).

In 2002, 11 additional SLE patients with nonlupus nephritis from 6 Nephrology Centers were reported by Hertig et al. The patients fulfilled the criteria for SLE and had nephrotic syndrome with the diagnosis of MCD (4 cases) and FSGS (7 cases). These authors believe that in most patients with SLE, lupus has a precipitating role in the appearance of an idiopathic nephrotic syndrome.

Based on their own study, Baranowska et al. consider that nonlupus nephritis, identified in 5% of their SLE patients, is not exceptional. They suggest that renal diseases other than lupus nephritis should be clinically suspected in patients with serologic and clinical remission of lupus activity who nevertheless present with severe renal abnormalities, including heavy proteinuria, markedly decreased renal function and acute renal failure, manifestations observed in 4 of their 13 patients. Although amyloidosis was identified in only 1 patient of this study, it was the most frequent type of nonlupus renal involvement in SLE patients considering all the already reported cases.

Our patient had initially the histological diagnosis of MCD and the second biopsy revealed features of FSGS. These entities are reported to be related glomerular lesions, within a spectrum of a less severe to a more severe form of glomerular epithelial cell damage. In our case, the first biopsy revealed no glomerular or tubular lesions by light and immunofluorescence microscopy. The patient did not respond to immunosuppressive treatment and neither the presentation nor the behavior of the renal abnormalities after treatment were those expected for class I lupus nephritis. After the second biopsy, although treated for FSGS, the patient never experienced a full remission during the course of the disease.

Our patient presented at least four American College of Rheumatology criteria for diagnosis of SLE.
(arthiritis, cutaneous maculae, positive ANA, positive anti-native DNA and anti-Sm,) and other clinical findings consistent with this diagnosis (hypocomplementemia, arthralgia, alopecia, vasculitis and leukopenia).

When the diagnosis of a nonlupus nephritis was raised, she was treated with azathioprine, in addition to corticosteroids for MCD-FSGS, with partial remission and recurrences.

An important differential diagnosis that must be considered is between FSGS and class III lupus nephritis. It might be argued whether the present case could not correspond to a healed focal proliferative lupus GN. This is unlikely, as healed focal proliferative lupus GN is preceded by an active focal proliferative and/or necrotizing lupus GN, which was never demonstrated.

Other possibility in the differential diagnosis would be class VI lupus nephritis, however sclerosing lupus GN usually represents the common final pathway of other forms of lupus GN and is rarely seen in the early course of SLE. It is characterized by predominantly global sclerosis involving most glomeruli, in which residual lupus activity is still recognizable. There are 17 previous reports of FSGS in SLE. Another case of FSGS has been recently described in a transplant kidney of a patient with SLE who presented with nephrotic proteinuria on postoperative day 4, a behavior observed in recurrent FSGS.

All reported patients presented with the nephrotic syndrome, normal or, more frequently, decreased renal function and hypertension. FSGS was preceded 3 to 18 years by renal abnormalities, which were related mostly to a previous lupus GN.

How nonlupus nephritis develops in patients with SLE remains poorly understood. The association between SLE and certain entities such as thin membrane disease, hypertensive nephrosclerosis, IgA nephropathy and infection-related GN is probably fortuitous. On the other hand, the more frequent association with amyloidosis and FSGS may be pathogenetically related to SLE.

The elevated serum amyloid A (SAA) protein levels observed in SLE patients, may potentially deposit in various tissues including kidney and explain the SLE-associated amyloidosis of AA type.

Some authors have suggested that the altered T-lymphocyte function in SLE may generate a glomerular permeability factor involved in the pathogenesis of idiopathic nephrotic syndrome.

A large variety of renal lesions unrelated to lupus nephritis can be observed in SLE patients. Renal biopsy plays a crucial role in identifying the glomerular disease associated with SLE, which may have significant prognostic and therapeutic implications distinct from those of lupus nephritis.

Finally, nonlupus nephritis may occasionally be encountered in SLE patients regardless of clinical or serologic disease activity. These renal lesions display a broad morphologic spectrum in which focal segmental glomerulosclerosis and amyloidosis are most frequently seen. Renal biopsy is an essential tool in the identification of these lesions.

**REFERENCES**


