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Systemic lupus erythematosus – the discrepancy between renal impairment and clinical and immunological manifestations

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ABSTRACT

Systemic lupus erythematosus (SLE) is the prototype of autoimmune diseases with multiorgan involvement, most commonly targeting the skin, joints and kidneys. The existence and type of renal involvement influence the prognosis and this information may be crucial when it comes to establishing the optimal therapy.

We present the case of a patient with SLE with skin involvement (vasculitis), joint manifestations and immunological markers remitted under synthetic remissive treatment but with severe renal damage diagnosed at the renal biopsy as a glomerulosclerosis type focal segmental podocytopathy (FSGS) collapsing variant associated with a possible ultrastructural defect of the glomerular basement membrane in the context of the disease with a severe prognosis.

Keywords: systemic lupus erythematosus, focal and segmental glomerulosclerosis, lupus podocytopathy

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown cause that can affect virtually any organ, characterized by the production of antinuclear antibodies (ANA), which although not specific to this disease, are a prominent feature of the disease. The clinical features are extremely polymorphic, being characteristic of multiorgan damage, the evolution with periods of exacerbations and remissions, from non-life-threatening clinical forms, such as skin or joint damage, to potentially severe forms as seen in renal or neurological involvement [1].

Kidney disease is typically detected in most patients with SLE by an abnormal urinalysis with or without an elevated plasma creatinine concentration. The most frequently observed abnormality in patients with lupus nephritis (LN) is proteinuria [2–5]. Other common clinical manifestations include microscopic hematuria with or without red cell casts, kidney function impairment, nephrotic-range proteinuria or nephrotic syndrome, and arterial hypertension [2]. As a result, all patients with SLE should be routinely monitored for kidney disease.

CASE PRESENTATION

We present the case of a 55-year-old woman evaluated at the "Dr. Ion Stoia" Clinical Center for Rheumatic Diseases in Bucharest for SLE with skin, joint, and kidney involvement.

The disease onset occurred in 2021 manifested by an episode of non-pruritic diffuse skin rash following sun exposure which remitted spontaneously.

In June 2022, the episode repeated with erythematous, pruritic skin lesions, this time being more extensive on the thighs, buttocks, thorax and lower limbs (Figure 1).

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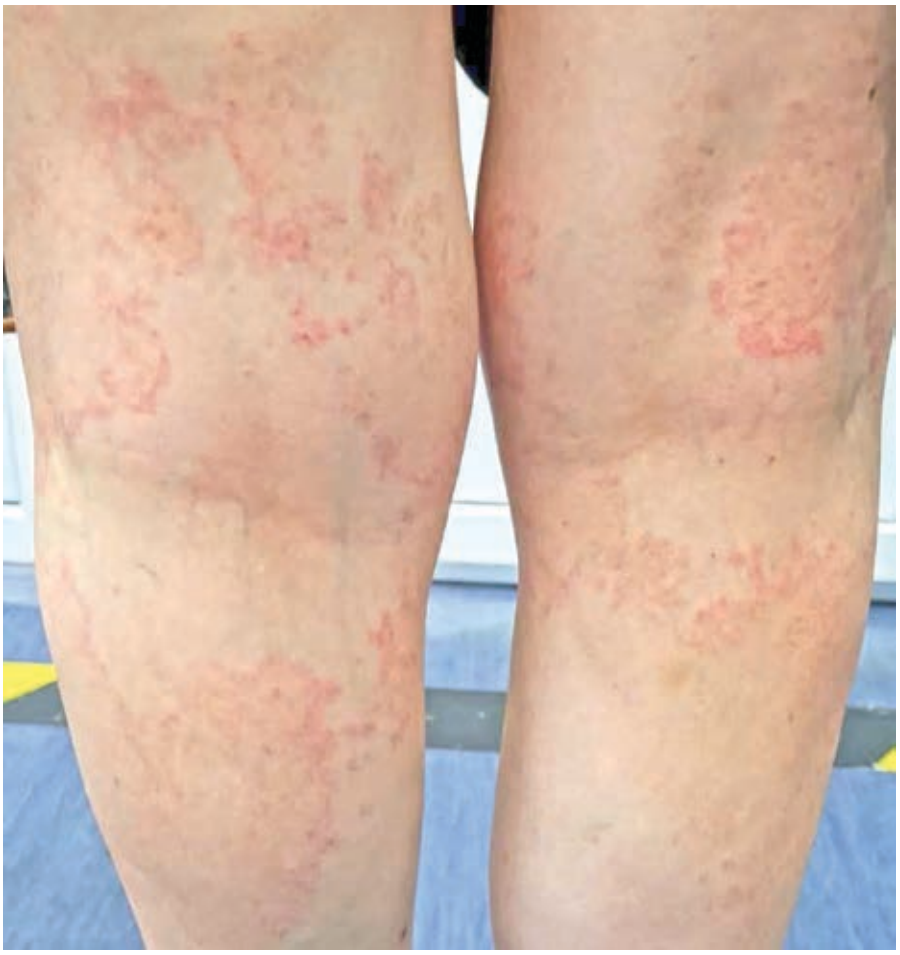

FIGURE 1. - Erythematous plaques with well-defined edges and smooth surfaces, pale pink in the center and more pronounced in the periphery, located on the posterior side of the lower limbs respecting the popliteal fossae

A skin biopsy was performed in the dermatology department revealing cutaneous fragments with mostly uninjured epidermis, with rare necrotic keratinocytes, keratinocytic vacuolization and moderate superficial and deep dermal infiltrate, perivascular, peri-annexal and interstitial, consisting of lymphocytes and rare plasma cells, sometimes with aspects of chronic lymphocytic vasculitis and interstitial hematic extravasations. Discrete interstitial accumulation of mucins in the dermis is observed. Histopathological changes indicated cutaneous lupus erythematosus (subacute) and treatment with hydroxychloroquine 200 mg twice daily (exceeding the dose of 5 mg/kg/day, the patient's weight is 71 kg with 3 kg above the ideal weight) and oral systemic glucocorticoids (prednisone, 15 mg/day) was initiated.

The investigations were completed with a set of tests revealing positive antinuclear antibodies by enzyme-linked immunosorbent assay (ELISA), negative anti-dsDNA, anti-SS-A (Ro), anti-SS-B (La), anti-Sm antibodies and antiphospholipid antibodies and 24-hour proteinuria of 500 mg.

In August 2022, she was evaluated for the first time at our department at the "Dr. Ion Stoia" Clinical Center for Rheumatic Diseases presenting ameliorated skin lesions and intermittent arthritis in the small joints of the hands and left knee and having already received the above doses of hydroxychloroquine and glucocorticoids.

Laboratory tests revealed normal C3 and C4 serum complement, negative ANA by ELISA and immunofluorescence on HEp-2 cells, negative anti-dsDNA, anti-SS-A (Ro), anti-SS-B (La) and anti-Sm antibodies, negative rheumatoid factor, persistent 24-hour proteinuria of 1000 mg and urinalysis with microhematuria. Azathioprine 100 mg/day was added to the treatment and oral systemic glucocorticoids therapy was tapered to 15 mg/day.

The patient returned 4 months later with no clinical complaints but a 24-hour proteinuria of 1697 mg and persistent microhematuria. We decided to refer her to the nephrology department for a renal biopsy because skin and joints were inactive, immunological C3, C4 and anti-dsDNA antibodies were negative, but the proteinuria persisted despite azathioprine treatment. Also, ANA by ELISA became negative.

Renal biopsy showed morpho-pathological findings suggestive of rare lupus lesion i.e., a glomerulosclerosis type focal segmental podocytopathy collapsing variant associated with a possible ultrastructural defect of the glomerular basement membrane (Figures 2-5).

In February 2023 we decided with the nephrologist to start cyclosporine 200 mg/day associated with angiotensin-converting enzyme inhibitors (perindopril, 5 mg/day) and statin therapy (atorvastatin, 20 mg/day) and continue treatment with hydroxychloroquine 400 mg/day and prednisone 15 mg/day with dose reduction over one month to 10 mg/day with a follow-up at 3 months.

DISCUSSIONS

The patient had been referred to our department 2 months after the initiation of high-dose glucocorticoids initially 30 mg/day for one month then tapered to 15 mg/day and hydroxychloroquine 200 mg/day. In this case, we based our diagnosis mainly on skin bi-

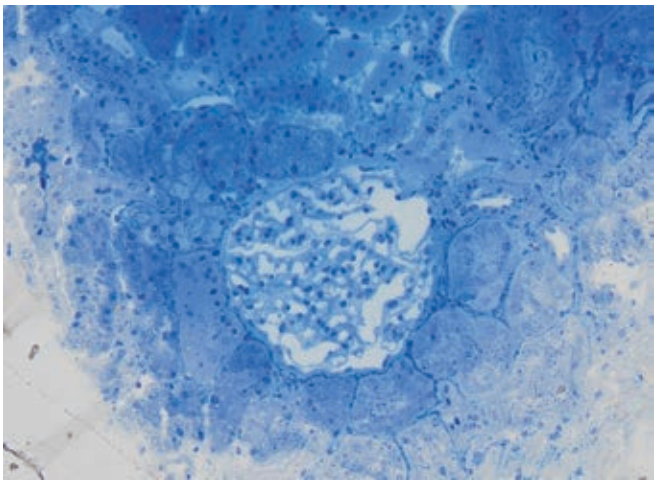

FIGURE 2. - Toluidine blue, 20X, glomerulus with optical appearance within normal limits

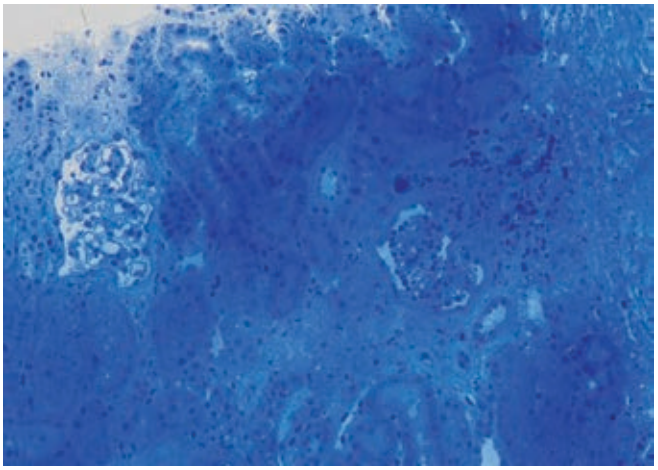

FIGURE 3. - Toluidine blue, 20X, glomerulus with collapsed capillary loops, hyperplasia and hypertrophy of visceral epithelial cells, with palisade appearance; tubular atrophy and focal interstitial fibrosis, with reduced chronic inflammatory infiltrate

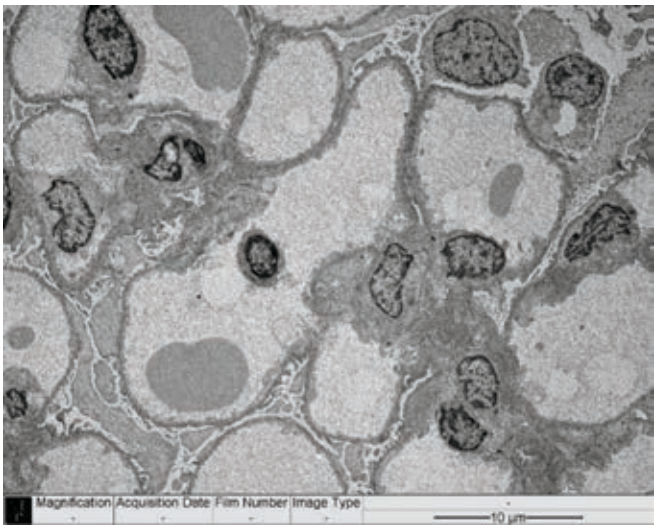

FIGURE 4. - EM, 3000X, permeable capillary loops, with extensively flattened or removed pedicles, no dense deposits present

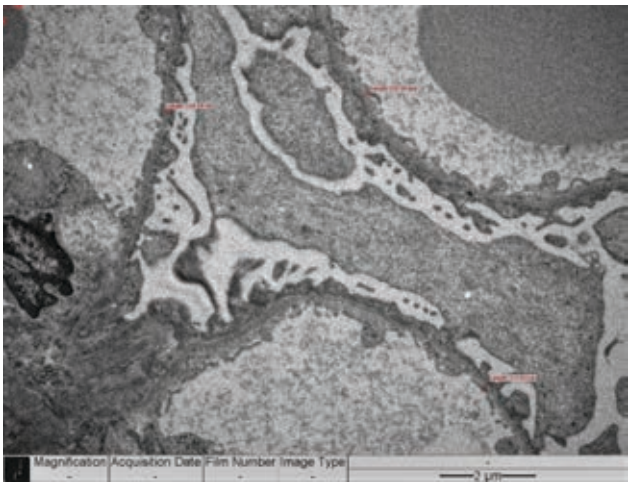

FIGURE 5. - EM, 7000X permeable capillary loops, MBG thinner than 200 nm, with deleted or flattened pedicles

opsy, arthritis and ANA positivity as the skin lesions were significantly improved at that moment.

Lupus podocytopathy is a distinct entity and can be subdivided based on light microscopy and immunofluorescence findings as minimal change disease (MCD) - what we expect to receive as a result, focal segmental glomerulosclerosis (FSGS), including the morphologic subtypes: not-otherwise-specified, perihilar, cellular, tip, or collapsing variant – what was revealed and mesangio-proliferative LN (class I or II LN with concomitant podocytopathy) [6]. The prevalence of lupus podocytopathy represents approximately 1% of LN biopsies [7].

A cohort study of 3750 SLE patients revealed fifty (1.33%) cases as lupus podocytopathy and included minimal change in 13 cases, mesangial proliferation in 28 cases, and FSGS in 9 cases [7]. All patients demonstrated nephrotic syndrome which highlights the particularity of our case, namely that the patient has nephritic syndrome.

In lupus podocytopathy, the most common extrarenal clinical manifestation is malar rash, affecting practically one-half of the cases (46%). Microscopic hematuria and hypertension are also rare in lupus podocytopathy (18%) and may help distinguish from other forms of LN. Regarding serological markers of SLE, all patients reported had positive ANA by ELISA. Low C3 is frequently noted (68%) while low C4 is less common (28%). The FSGS subtype is more frequently (78%) associated with acute kidney injury than the MCD subtype [7].

In our case, the patient presented diffuse skin rash on the thighs, buttocks, thorax and upper limbs and mild arthralgias and paraclinical positive ANA, microhematuria and nephritic rank proteinuria, suggesting an incomplete presentation compared to the patients in the study.

Lupus podocytopathy FSGS collapsing variant is speculated to have pathogenesis associated with local interferons [8] also present in SLE patients. Inter-

feron-α can be a central regulatory cytokine in SLE and especially in LN and may promote the development of autoreactive plasma cells, helper and memory T cells, and several proinflammatory cytokines [9]. A number of cases of lupus podocytopathy have been associated with nonsteroidal anti-inflammatory drug use in patients with SLE [7,10,11]. The pathogenesis of lupus podocytopathy is not well understood and requires future research.

There are few studies related to FSGS lupus podocytopathy, studies have been done predominantly for primary FSGS. Treatment recommendations for this pathology are high-dose glucocorticoids, steroid-sparing agents as calcineurin inhibitors - cyclosporine, mycophenolate mofetil, cyclophosphamide, rituximab and renin angiotensin system inhibitors and plasmapheresis.

Lupus podocytopathy is a glucocorticoid-sensitive entity. FSGS forms have a worse response to steroids than MCD, and the collapsing variant is more aggressive and may require more immunosuppression [12,13].

A few small studies have tested the hypothesis that calcineurin inhibitors prevent or treat FSGS recurrence by inhibiting T cells. Cyclosporine has antiproteinuric effect [14]. In a prospective cohort study, 17 patients with FSGS were treated with intravenous cyclosporine (3 mg/kg/day, converting to the oral route in 3–4 weeks to maintain through levels between 250 and 350 ng/mL). Fourteen patients had a prompt remission of proteinuria that, in some cases, persisted for years [15]. In LN patients with severe podocyte effacement, CNI may have better remission rates and better long-term renal outcomes than those treated with other regimens [16], suggesting that therapies that facilitate podocyte stability may be beneficial in this subgroup of patients [17].

The efficacy of rituximab was explained by mechanisms of depletion of a circulating autoantibody or interference with B-cell antigen presentation. Recent evidence has been provided that rituximab can directly bind to molecules other than CD20, such as SMPDL-3b (a protein implicated in actin remodeling), expressed in human podocytes. Interestingly, in vitro exposure of podocytes to sera from FSGS patients reduces SMPDL-3b, which can be prevented by rituximab [18].

A recent systematic review of the 39 reported cases (19 pediatric) of FSGS recurrence treated with rituximab showed that complete or partial remission occurred in 64% of patients [19].

Only a few cases of the use of renin-angiotensin system inhibitors (RAS) in patients with FSGS relapse have been reported. Retrospective studies have shown a beneficial effect of RAS inhibitors in reducing proteinuria and improving graft or patient survival in subjects with chronic rejection. Evidence of nephroprotective effects of RAS inhibitors should therefore encourage their wider use in transplant patients with proteinuria, including those with nephrotic syndrome associated with FSGS relapse [20].

Although good controlled studies are lacking, plasmapheresis is still widely used to treat recurrent FSGS in kidney transplant patients. Considering the limited evidence on the role of permeability factors in the pathogenesis of FSGS, this treatment should probably be more carefully examined [21].

For our case we chose cyclosporine associated with angiotensin-converting enzyme inhibitors class II and statin therapy, with a good tolerance for the beginning but too soon to have notable results.

FSGS-associated abnormalities and the pathophysiology of progressive podocyte loss open new avenues for identifying novel hypothesis-driven therapies. Stronger and more selective therapies are needed for patients with FSGS.

CONCLUSIONS

Apparently mild manifestations of SLE and few immunological findings can hide severe kidney damage, so all SLE patients may require further investigation for a clear diagnosis and in order to detect multiple organ damage depending on the specific scenario. LN manifested as lupus podocytopathy FSGS collapsing variant is one of the rare and atypical cases and has a poor prognosis. Subtypes of FSGS with lupus podocytopathy, which are less responsive to glucocorticoids, may benefit from initial induction treatment with glucocorticoids and an agent such as calcineurin inhibitors. FSGS-associated abnormalities and the pathophysiology of progressive podocyte loss open new pathways for identifying novel hypothesis-driven therapies. Stronger and more selective therapies are needed for these patients.

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