

Recurrent podocytopathy in a patient with systemic lupus erythematosus

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Abstract

Podocytopathy in systemic lupus erythematosus is characterised by diffuse foot process effacement without significant peripheral capillary wall immune deposits as seen on electron microscopy. Lupus podocytopathy falls outside the scope of the current International Society of Nephrology and the Renal Pathology Society classification of lupus nephritis. We present a case of relapsing podocytopathy with nephrotic syndrome occurring simultaneously with two extra-renal and serological disease flares, which makes it likely that podocytopathy was related to systemic lupus erythematosus activity. This case adds to the growing body of evidence that lupus podocytopathy must be considered in the differential diagnosis of systemic lupus erythematosus patients presenting with nephrotic syndrome.

Keywords

Systemic lupus erythematosus, podocytopathy, nephrotic syndrome

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Introduction

A 22-year-old female student was referred by her general practitioner (GP) to rheumatology with a 3-week history of widespread symmetrical joint pain, swelling and stiffness involving the small and large joints (hands, wrist, shoulders, knees and feet). There was no history of antecedent illness, travel, exposure to medications or bites. She had no features to suggest psoriasis or connective tissue disease. She reported a background of well-controlled asthma with Hashimoto's thyroiditis being the only significant family history.

On review, she was normotensive and weighted 81 kg. Cardiovascular, respiratory and abdominal examinations were all unremarkable. There was mild livedo reticularis over the lower legs and a symmetrical polyarthritis affecting the proximal interphalangeal and metacarpophalangeal joints, wrists, shoulders, knees, ankles and metatarsophalangeal joints.

Her initial blood work showed normal haematology, renal and liver function. Abnormal results include erythrocyte sedimentation rate (ESR): 38 mm/h (normal: 1–20 mm/h), C-reactive protein (CRP): 61 mg/L (normal: <5.0 mg/L), c3: 0.71 g/L (normal: 0.88–1.98 g/L), c4: 0.09 g/L (0.16–0.52 g/L), Immunofluorescence ANA test (F-ANA): >30 (normal: <7 IU/mL), Anti-dsDNA Ab: 62 (normal: <7 IU/mL) and urine protein to creatinine ratio (PCR) of 41 (normal:

<13 mg/mmol). With a differential diagnosis of viral or auto-immune polyarthritis, she was continued on Ibuprofen 400 mg twice a day for symptom control, awaiting further results.

Four days later, the patient was admitted with ongoing polyarthritis and new manifestations of malar rash, pleuritic chest pain, dependent oedema, anaemia, leukopenia and oliguric renal impairment. Pulmonary embolism was ruled out on a ventilation perfusion scan and her electrocardiogram and echocardiogram were normal. Further blood and urine analysis showed urine PCR: 699 mg/mmol, ESR: 83 mm/h, CRP: 11 mg/L, c3: 0.65 g/L, c4: 0.04 g/L, serum creatinine: 211 (normal: 45–90 µmol/L) and serum albumin of

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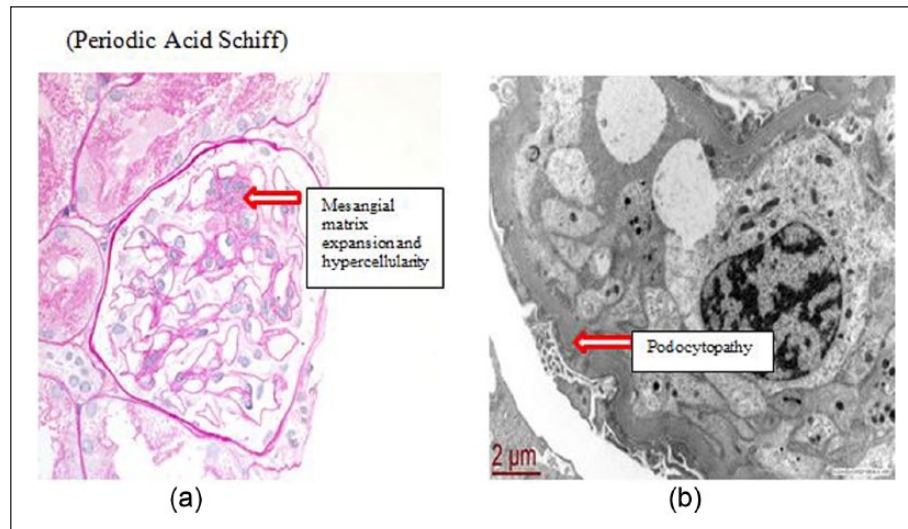


Figure 1. (a) Light microscopy (LM) and (b) electron microscopy (EM).

22 (normal: 34–50 g/L). Urine analysis showed 3+ protein and RBC of $>100 \times 10^6$. Ibuprofen was stopped.

Systemic lupus erythematosus (SLE) was diagnosed with a SLE Disease Activity Index (SLEDAI) score of 22. Given the renal insufficiency, haemoproteinuria and serology, rapidly progressive lupus glomerulonephritis was considered a likely cause for the nephrotic syndrome (NS). A renal biopsy was performed to determine extent and severity (Figure 1(a) and (b)). Light microscopy (LM) showed variable segmental mesangial matrix expansion and mild mesangial hypercellularity. In a single glomerulus, there was evidence of minor endocapillary proliferation in an isolated capillary loop. The capillary loops were otherwise patent. There was no established segmental or global glomerulosclerosis and no basement membrane spikes. There was a moderate tubulointerstitial inflammatory infiltrate composed of lymphocytes and histiocytes with isolated loose granulomas raising the possibility of tubulointerstitial nephritis. Blood vessels were normal without vasculitis. Immunofluorescence (IF) showed moderate to bright mesangial IgG, IgM and C1q with weak mesangial C3 and weak capillary loop IgA. Electron microscopy (EM) revealed the presence of mesangial matrix expansion and mesangial cell hypercellularity, associated with discrete coarsely granular dense deposits in the paracapillary and deep mesangium. Of note was the presence of extensive/subtotal effacement of the podocytic foot processes. Tubuloreticular inclusions were noted within some endothelial cells. There were no dense deposits along the capillary walls. Overall, the features were consistent with mesangiopathic (International Society of Nephrology and the Renal Pathology Society (ISN/RPS) Class II) lupus nephritis (LN) with podocytopathy and negligible evidence of focal proliferative LN (ISN/RPS Class III).

Treatment was started with methylprednisolone 1 g IV for 3 days followed by prednisolone 80 mg daily PO daily with

a planned taper, mycophenolate (MMF) 500 mg bd and hydroxychloroquine (HCQ) 200 mg. She showed a prompt clinical response with the introduction of steroids and immunosuppression, but required two haemodialysis sessions to manage hyperkalemia in the setting of oliguria. On discharge from hospital, she had good symptom control and normal renal function with minimal proteinuria.

Over the following year, while renal function and urine findings remained unremarkable, methotrexate (MTX) was added to her treatment regimen for extra-renal flares involving skin and joints and corticosteroid dependency. One year after the initial presentation following an episode with bullous lupus, she represented with sudden onset of severe NS (oedema, weight gain and proteinuria) with a PCR of 754. The anti-dsDNA Ab level was 10 IU/mL, c3: 0.75 g/L, c4: 0.13 g/L, ESR: 56 mm/h, CRP: 4.2 mg/L and urine analysis which showed haemoproteinuria. Concern about LN class transformation prompted a second biopsy, which again showed the exact same findings as the first biopsy, that is, mesangiopathic (ISN/RPS Class II) LN with minor focal proliferative changes and extensive effacement of podocytic foot processes. This now was in the absence of any non-steroidal anti-inflammatory drugs (NSAIDs) use for a year.

High-dose steroids (1 mg/kg) followed by B-cell depletion therapy (2×1 g rituximab) was commenced due to the relapsing course of renal, extra-renal and serological disease with ongoing steroid dependency. Now 14 months post rituximab, she remains in clinical and serological remission, off corticosteroids but on steroid-sparing agents.

Discussion

Podocytopathy occurring twice in the setting of extra-renal and serological disease activity in the same patient makes it likely

Table 1. Abbreviated International Society of Nephrology and the Renal Pathology Society (ISN/RPS) 2003.

Class	Pathology
I	Minimal mesangial lupus nephritis
II	Mesangial proliferative lupus nephritis
III	Focal proliferative lupus nephritis ^{a,b}
IV	Diffuse segmental (IV-S) or global (IV-G) proliferative lupus nephritis ^{a,b}
V	Membranous lupus nephritis ^c
VI	Advanced sclerosing lupus nephritis

^aIndicates the proportion of glomeruli with active and with sclerotic lesions.

^bIndicates the proportion of glomeruli with fibrinoid necrosis and with cellular crescents.

^cClass V may occur in combination with iii and iv in which case both will be diagnosed. Indicates grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis, or other vascular lesions.

that it is related to SLE. SLE is a multisystem autoimmune disorder with a broad spectrum of clinical presentations, which are not all, captured by classification or activity criteria. Podocytopathy represents a rare and thus far little recognised finding in SLE.¹ In 2003, the ISN/RPS re-classified LN into six categories (Table 1) where NS usually is related to proliferative or membranous glomerulonephritis.²

NSAID can induce glomerular lesions similar to idiopathic podocytopathy and/or cause acute interstitial nephritis with influx of polyclonal T and B cells.³ While the first biopsy in our case did show evidence of interstitial nephropathy, the patient has stopped all NSAID use since which thus cannot explain similar findings on the second biopsy.

Lupus podocytopathy manifests with sudden onset NS, often accompanied by acute kidney injury (AKI) and can appear throughout the disease course. One study found that the probability of podocytopathy in SLE was higher than the overall prevalence data in their population of <1 per 10,000.⁴

Except for immune deposits in the mesangial region, patients with lupus podocytopathy share most histological characteristics with minimal change disease (MCD).¹ Immune deposits were present only in the mesangium of our patient as is found in most SLE patients. There were no capillary wall deposits on EM and podocyte foot process effacement was extensive/subtotal. While proliferative and membranous LN occurs mostly in the context of glomerular deposition of IgG and complement, the absence of immune complexes in lupus podocytopathy suggests that soluble inflammatory mediators cause direct damage to the podocytes. A recent study demonstrated that IgG derived from patients with LN could enter podocytes by way of the Fc receptor (FcRn), which results in an increase in calcium/calmodulin-dependent protein kinase IV (CaMKIV) and expression of gene involved in podocyte damage and T-cell activation.⁵ Another study found that

soluble plasma urokinase-type plasminogen activator receptor (suPAR) levels were increased in LN and could mediate podocyte injury.⁶

Despite failing to meet end points in two large trials, there is accumulating clinical evidence to suggest that RTX has also been useful in patients with non-renal lupus and LN.⁷ Rituximab (RTX) has also been useful in patients with steroid dependent or refractory idiopathic MCD.⁸ While our patient had a good clinical response to RTX, as add on therapy with resolution of proteinuria, arthritis and rash, this is not always the case.⁹

Conclusion

We present a rare case of relapsing podocytopathy in an SLE patient during extra-renal disease activity with podocyte effacement confirmed on EM twice.¹⁰ This case adds to the growing body of evidence that lupus podocytopathy (effacement of podocyte foot processes without peripheral capillary wall immune deposits and glomerular proliferation) must be considered in patients with SLE presenting with NS.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent was obtained from a legally authorised representative(s) for anonymised patient information to be published in this article. Verbal informed consent was obtained from the patient(s) for their anonymised information to be published in this article.

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