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Rapidly Progressive Lupus Nephritis with Extremely High Levels of Antineutrophil Cytoplasmic Antibodies

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Key Words
Lupus nephritis · MPO-ANCA · Plasma exchange

Abstract
A 43-year-old woman, with a 3-month history of fatigue, anaemia and swollen lymph nodes, underwent biopsy of a lymph node, which revealed reactive lymphadenopathy. Due to an increased serum creatinine concentration and severe proteinuria, a kidney biopsy was performed, which revealed diffuse, segmental, proliferative, immune-complex glomerulonephritis with crescents. Electron microscopy showed tubulo-reticular structures within one endothelial cell. These were a typical clinical presentation and compatible histopathological findings for systemic lupus erythematosus; however, the anti-myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) level was extraordinarily high. In spite of treatment with intravenous cyclophosphamide and methylprednisolone pulse therapy, the patient's kidney function declined. Starting plasma exchange improved her renal function and removed MPO-ANCAs, which were suspected to play the major role in the pathogenesis of glomerulonephritis. These findings indicate that in addition to lupus nephritis, MPO-ANCAs may be involved in the pathogenesis of glomerulonephritis and that the coincidence of systemic lupus erythematosus and ANCA may be responsible for the severe clinical course in our patient.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of multiple autoantibodies against a variety of nuclear antigens. A common and serious complication of SLE is lupus nephritis (LN), which plays a key role in the prognosis of SLE and is a risk factor for the development of end-stage renal failure. LN is a classic immune-mediated renal disease. Excess immune-complexes accumulate in the small vessels of organs, such as the kidney, where they become pathogenic. Accumulated immune-complexes induce inflammation through the local activation of the complement system leading to cellular proliferation. Pauci-immune glomerulonephritis (GN) differs from LN in that glomerular necrosis and crescent formation occur in the absence of significant cellular proliferation and only rarely glomerular immune-complex deposits are observed [1]. Anti-neutrophil cytoplasmic antibodies (ANCAs) are directly implicated in the pathogenesis of this form of glomerular injury and are thought to activate cytokine-primed neutrophils and monocytes, which express the ANCA antigens proteinase 3 and myeloperoxidase (MPO) on their surface [1, 2]. Neutrophils release cytokines, toxic oxygen metabolites and lytic proteinases, leading to endothelial damage with subsequent glomerular basement membrane rupture, necrosis and crescent formation. Although most patients with pauci-immune crescentic GN have ANCAs, pauci-immune necrotizing GN in SLE is rare [1, 3–5]. Therefore, the clinical and pathogenic significance of ANCAs in patients with SLE remains unclear [6, 7]. This report discusses the association of extremely high levels of MPO-ANCAs in a refractory case of LN treated with immunosuppressive therapies. In addition to immune-complex-mediated glomerulopathy, MPO-ANCAs may be the cause of a severe clinical course.

Case Report

A 43-year-old Caucasian woman was admitted to the hospital due to acute renal failure and proteinuria in the nephrotic range. She presented with a 3-month history of fatigue, anaemia and lymphadenopathy. Before admission, a CT scan was performed, which revealed lymphadenopathy of the neck as well as generalized abdominal and mediastinal lymphadenopathy. Lymph node excision showed reactive lymphadenopathy. No history of skin rashes, photosensitivity, joint swelling, hair loss or oral ulcers was identified. On physical examination, the patient's height was 170 cm, her weight 56 kg (BMI 19.4), she was afebrile and her blood pressure was 117/77 mm Hg.

Laboratory examinations revealed (table 1) a white blood cell count of 3.2 × 10^9/l (reference range, 4–10 × 10^9/l), lymphocytes 13.5% (reference range, 10–50%), haemoglobin 102 g/l (reference range, 115–165 g/l), platelets 147 × 10^9/l (reference range, 150–350 × 10^9/l), total protein 71 g/l (reference range, 64–83 g/l), albumin 27 g/l (reference range, 35–50 g/l), lactate dehydrogenase 161 U/l (reference range, <250 U/l), haptoglobulin 1.85 g/l (reference range, 0.3–2.0 g/l), urea 12.6 mmol/l (reference range, 2.7–6.8 mmol/l), creatinine 174 μmol/l (reference range, 45–84 μmol/l), C-reactive protein <5 mg/l (reference range, <5 mg/l) and an increased erythrocyte sedimentation rate of 81 mm/h. Urine analysis showed proteinuria of 6.4 g/day and an active sediment containing dysmorphed red blood cells. Serum complement levels were low with a C3c of 0.2 g/l (reference range, 0.8–1.8 g/l), C4 0.02 g/l (reference range, 0.1–0.4 g/l), and CH50 14 U Eq/ml (reference range, 70–180 U Eq/ml). Antinuclear antibodies were elevated to 1:80 (reference range, <40-fold), anti-double-stranded DNA antibodies were not detectable and anti-C1q was 20 IU/ml (reference range, <15 U/ml). ANCA titres on immunofluorescence were

increased up to 1:640 (reference range <1:20). Using enzyme-linked immunosorbent assay (ELISA), MPO-ANCAs were positive with 3,622 U/ml (reference range, <5 U/ml) and PR3-ANCAs were not detectable. Anti-SS-A/Ro52 were 22 U/ml (reference range, <10 U/ml) and anti-SS-A/Ro60 were >240 U/ml (reference range, <10 U/ml). Cryoglobulines were not detectable. Serologic tests for HIV, hepatitis B/C and cytomegalovirus were all negative. Epstein-Barr-virus IgG was positive, IgM was negative and EBNA1 IgG was positive.

Renal biopsy was performed on day 2, which revealed a diffuse, segmental, proliferative, immune-complex GN with crescents in 4 of 19 glomeruli corresponding to an LN class IV-S (A/C; fig. 1). Immunofluorescence staining showed deposition of IgA, IgM, C1q, C3 and C5–9 in the mesangial area and peripheral capillaries. Electron microscopy revealed mesangial and peripheral electron-dense deposits without obvious structuring. Most of the peripheral deposits were located subendothelially, there were also some subepithelial deposits. Tubuloreticular structures within one endothelial cell were found.

After renal biopsy, methylprednisolone pulses were initiated (500 mg/day for 3 days) followed by oral prednisone 50 mg/day and cyclophosphamide 1 g intravenously. However, the serum concentration of creatinine gradually increased, so that again methylprednisolone pulses (500 mg/day for 2 days) were repeated on day 13, and high volume plasma exchange was started for 5 consecutive days to eliminate MPO-ANCAs (fig. 2). After the plasma exchanges, the MPO-ANCA levels were decreased to 104 U/l and renal function improved so that the patient was discharged on day 39. Cyclophosphamide therapy was continued with 500 mg intravenously every second week for 3 months, so that the patient received a cumulative dose of 3.5 g. The maintenance therapy with azathioprine had to be switched to mycophenolate mofetil due to gastrointestinal side effects. Eighteen months after starting treatment, the patient is still in remission. MPO-ANCAs are not detectable and renal function has recovered completely with a creatinine concentration of 88 μmol/l (reference range, 45–84 μmol/l) and a minimal proteinuria of 0.2 g/day – using a treatment regime consisting of mycophenolate mofetil 2 g, prednisone 7.5 mg and hydroxychloroquine 200 mg per day.

Discussion

Our patient had a biopsy-proven LN IV-S (A/C) with positive antinuclear antibodies (ANAs) so that the current SLICC criteria for SLE were fulfilled [8]. Additionally, complement consumption, positive anti-Ro/SSA and positive anti-C1q further support a diagnosis of SLE. However, her MPO-ANCA level was extraordinarily high. ANCAs have been found in patients with SLE, but the prevalence of ANCAs remains unclear. Using indirect immunofluorescence, the prevalence of ANCAs in SLE patients has been reported to range from 3 to 69% [7, 9, 10]. The major cause of the great difference might be due to the presence of high titres of ANA in the serum of SLE patients and the difficulty to distinguish p-ANCA from ANA by immunofluorescence. Since nearly all lupus patients have positive ANAs, indirect immunofluorescence might not be the appropriate method to screen for ANCAs in SLE patients. ANCA positivity by ELISA in SLE patients is lower than by immunofluorescence [7, 10]. Using ELISA, Galeazzi et al. [7] demonstrated that 9.3% of the SLE patients were MPO-ANCA positive and only 1.7% were proteinase 3-ANCA postitive. Nevertheless, the significance of ANCA seropositivity in SLE patients varies considerably among reports. LN patients have significantly higher positive ANCA rates than patients without nephritis; these are primary MPO-ANCAs [1]. It seems that patients with ANCA-positive LN present with more severe renal involvement, too, since ANCAs are associated with the presence of diffuse proliferative LN [5, 9, 11]. A few cases of refractory LN with crescentic GN, possibly due to MPO-ANCAs, have been reported

[4, 12, 13]. However, in none of these cases were the MPO-ANCA levels so extraordinarily high. Despite recommended induction therapy with methylprednisolone and cyclophosphamide, renal function continuously deteriorated in our case. Since it has been shown that p-ANCA and c-ANCA vasculitis patients with rapidly progressive GN benefit from plasma exchange, we also performed plasma exchanges, which led to the elimination of MPO-ANCAs and finally improved our patient's renal function [14].

In conclusion, we demonstrated a rare case of extremely high MPO-ANCA levels in a patient with LN. These findings indicate that in addition to LN, which usually results from the deposition of circulating immune-complexes, MPO-ANCAs may be involved in the pathogenesis of crescentic GN or ANCA-associated necrotizing and crescentic GN may occur on top of LN. However, the coincidence of SLE and ANCAs may be responsible for the severe clinical course seen in our case.

Disclosure Statement

The authors declare no conflicts of interest.

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Table 1. Laboratory results of the patient

	Reference	At admission	After 3 months' treatment
Haemoglobin, g/l	115–165	102	122
MCV, fl	80–97	87	92
Reticulocytes, %	0.8–1.6	0.5	1.2
WBC, $\times 10^9$/l	4.0–10.0	3.2	6.5
Lymphocytes, %	10–50	13.5	
Platelets, $\times 10^9$/l	150–350	147	275
Creatinine, µmol/l	45–84	174	106
Urea, mmol/l	2.7–6.8	12.6	9.8
CRP, mg/l	<5	<5	<5
Albumin, g/l	35–50	27	40
LDH, U/l	<250	161	193
Haptoglobulin, g/l	0.3–2.0	1.85	
ANA	<1:40	1:80	<1:40
Anti-dsDNA, IU/ml	<10	<10	<10
Anti-SS-A/Ro52, U/ml	<10	22	12
Anti-SS-A/Ro60, U/ml	<10	>240	148
ANCA titre	<1:20	1:640	1:20
Anti-MPO-ANCA, U/ml	<5	3,622	7
C3c, g/l	0.8–1.8	0.2	0.76
C4, g/l	0.1–0.4	0.02	0.17
CH50, U Eq/ml	70–180	14	74
Anti-C1q, U/ml	<15	20	
Anti-phospholipid antibodies		negative	

anti-dsDNA = Anti-double-stranded DNA antibodies; CRP = C-reactive protein; LDH = lactate dehydrogenase; WBC = white blood cell count.

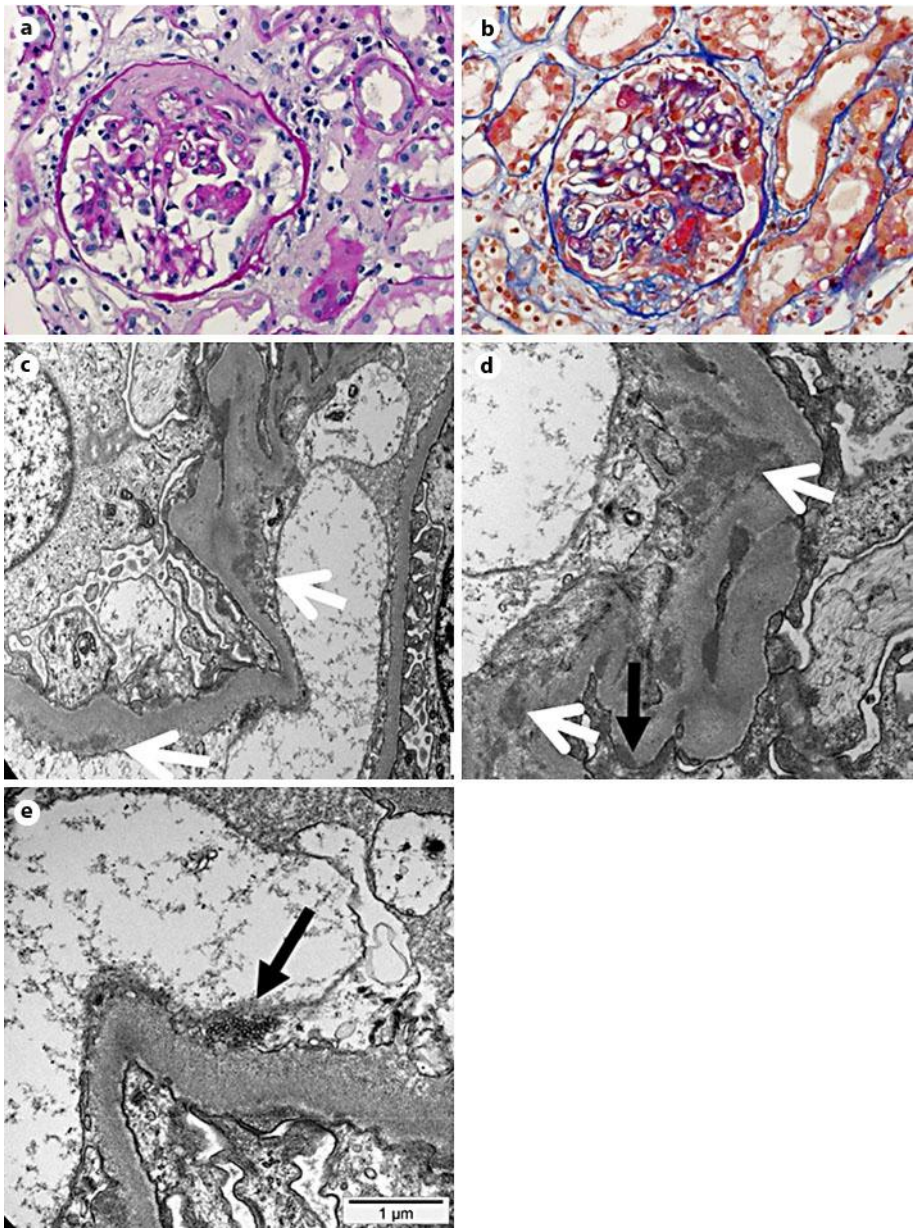

Fig. 1. Kidney biopsy revealed diffuse proliferative LN class IV-S (A/C). Four of 19 glomeruli presented crescent formation. **a** One glomerulus with fibrocellular crescent and widened mesangium (PAS staining, ×400). **b** Capillary loop rupture with formation of a crescent and mesangial protein deposits (trichrome staining, ×400). **c**, **d** Electron microscopy: peripheral capillary loop with subepithelial (black arrow) and subendothelial (white arrows) electron-dense deposits. **e** Tubulo-reticular structure in one endothelial cell (arrow).

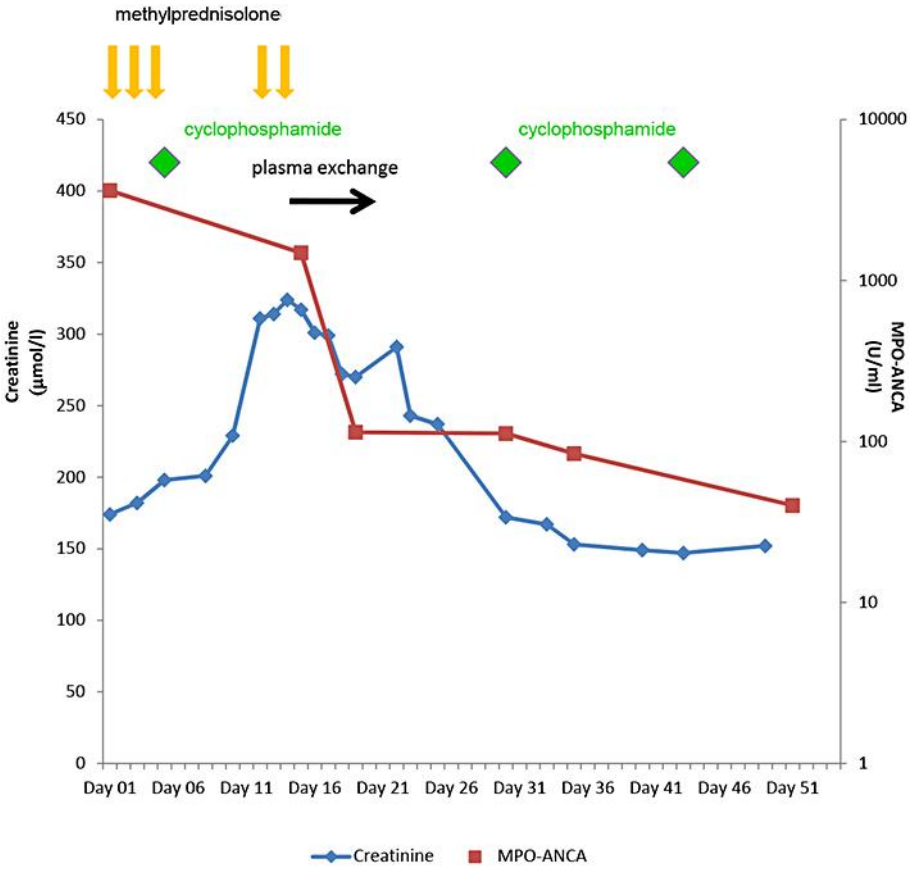

Fig. 2. Clinical course of the patient.