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From the Clinic

Plasma exchange for concurrent lupus nephritis and antiphospholipid syndrome

Systemic lupus erythematosus (SLE) can be associated with vascular thrombosis due to antiphospholipid antibodies. Accumulating evidence indicates that renal microvascular thrombosis due to lupus anticoagulant is an independent risk factor for poor renal outcome in lupus nephritis [1, 2]. In this report, we present a young woman with diffuse proliferative lupus nephritis and glomerular microthrombosis associated with lupus anticoagulant. Whereas MMF and glucocorticoids failed to induce remission, therapeutic plasma exchange (TPE) led to rapid clinical and immunological recovery.

Case vignette

With an unremarkable past medical history, a 23-year-old woman developed arthralgia and a rash during her second pregnancy. Following a miscarriage during the 19th week of pregnancy, she developed edema, malaise, hair loss and a maculopapular rash. She was found to have hypertension, proteinuria (5.9 g/day), hypocomplementemia and elevated serum creatinine (132.6 μmol/L, 1.5 mg/dL). Serologic tests revealed antibodies to double-stranded DNA and chromatin. A kidney biopsy demonstrated diffuse proliferative lupus glomerulonephritis. She was transferred to our hospital for further management.

The patient was a young Hispanic woman with anasarca. Laboratory data are summarized in Table 1. The serum creatinine concentration was 168 μmol/L (1.9 mg/dL). Urinalysis revealed proteinuria, hematuria and leukocyturia. Proteinuria was estimated to be 8.0 g/day. Fibrin degradation products were increased. Coagulation studies showed lupus anticoagulant and IgM antibodies to cardiolipin. The treatment consisted of intravenous methylprednisolone of 1 g/day for 3 days followed by oral prednisone 60 mg/day, oral MMF 3 g/day and hydroxychloroquine 400 mg/day. Over the ensuing days, serum creatinine was ∼141.4 μmol/L (1.6 mg/dL). On the 12th hospital day, the patient became septic and received intravenous norepinephrine (1 day) and piperacillin/tazobactam. Blood cultures grew *Pseudomonas aeruginosa* sensitive to antibiotics given. In the meantime, renal function deteriorated requiring hemodialysis. Despite rapid resolution of septicemia and hemodynamic instability, the patient continued to require hemodialysis.

Reexamination of a kidney biopsy demonstrated nine glomeruli, none of which were globally sclerosed. There was marked mesangial and endocapillary proliferation (Figure 1A). Intracapillary thrombi were noted in two glomeruli (Figure 1A–C). There was mild interstitial fibrosis and tubular atrophy. There was no evidence of acute

Table 1. Laboratory data

Analyte	Reference range	On admission	Analyte	Reference range	
Sodium (mmol/L)	135–145	144	Fibrin split products (μg/mL)	<5	**5–20**
Potassium (mmol/L)	3.4–4.8	**5.7**	D-Dimer (mg/L FEU)	0.2–0.5	**1.9**
Chloride (mmol/L)	99–109	**113**	Lupus anticoagulant panel	Negative	**Positive**
Carbon dioxide (mmol/L)	21–30	23	DRVVT ratio	<1.2	**1.35**
Urea nitrogen (mg/dL)	7–22	**81**	Hexagonal phospholipid (sec)	<8	**Positive**
Creatinine (μmol/L)	44–80	**133**	Anti-cardiolipin Ab	Negative	**Positive**
Glucose (mg/dL)	65–200	159	IgG (U/mL)	<23	4.4
Calcium (mg/dL)	8.4–10.2	**7.4**	IgA (U/mL)	<22	9.6
Albumin (g/dL)	3.5–5.0	**1.9**	IgM (U/mL)	<11	**13.1**
Lactate dehydrogenase (IU/L)	84–246	**259**	Anti-β_2-glycoprotein I Ab	Negative	Negative
Haptoglobin (mg/dL)	30–200	62	IgG (U/mL)	≤20	<9
Hemoglobin (g/dL)	12.0–16.0	**8.2**	IgA (U/mL)	≤25	<9
Leukocyte count (×10^3/μL)	4.8–10.8	**20.5**	IgM (U/mL)	≤32	<9
Neutrophils (×10^3/μL)	1.5–8.0	**19.6**	Antinuclear antibodies	Negative	**Positive**
Lymphocytes (×10^3/μL)	1.0–7.7	**0.5**	Anti-dsDNA Ab (IU/mL)	<4.9	**>300**
Monocytes (×10^3/μL)	0.0–1.1	0.4	Anti-chromatin Ab (U/mL)	≤0.9	**>8.0**
Eosinophils (×10^3/μL)	0.0–0.5	0.0	Anti-centromere Ab (Au/mL)	≤0.9	≤0.9
Basophils (×10^3/μL)	0.0–0.4	0.0	Anti-Jo-1 IgG (Au/mL)	≤0.9	≤0.9
Platelet count (×10^3/μL)	130–400	355	Anti-Smith Ab (Au/mL)	≤0.9	≤0.9
Urinalysis			Anti-SSA/Ro Ab (U/mL)	≤0.9	≤0.9
Color	Yellow	Yellow	Anti-SSB/La Ab (U/mL)	≤0.9	≤0.9
Turbidity	Clear	Cloudy	C3 (mg/dL)	90–180	**18**
pH	4.6–7.8	6.0	C4 (mg/dL)	15–47	**2**
Specific gravity	1.001–1.035	1.020	ADAMTS13 (%)	>66	100
Blood	Negative	**3+**	Factor V (%)	62–150	140
Protein (mg/dL)	Negative	**100**	Antithrombin III (%)	52–128	122
Leukocyte esterase	Negative	**Trace**	Protein C, Antigen (%)	70–140	106
White blood cells/hpf	0–2	**10–12**	Protein S, total (%)	58–150	84
Red blood cells/hpf	0–2	**15–25**	Protein S, free (%)	56–124	64
Urine protein/creatinine	0.02–0.13	**7.98**	Prothrombin mutation	Negative	Negative

Values out of the reference range are in bold. Ab, antibodies; ADAMTS-13, a disintegrin and metalloprotease with thrombospondin-1-like domains; DRVVT, dilute Russell viper venom time; ds, double stranded; prothrombin mutation, G20210A.

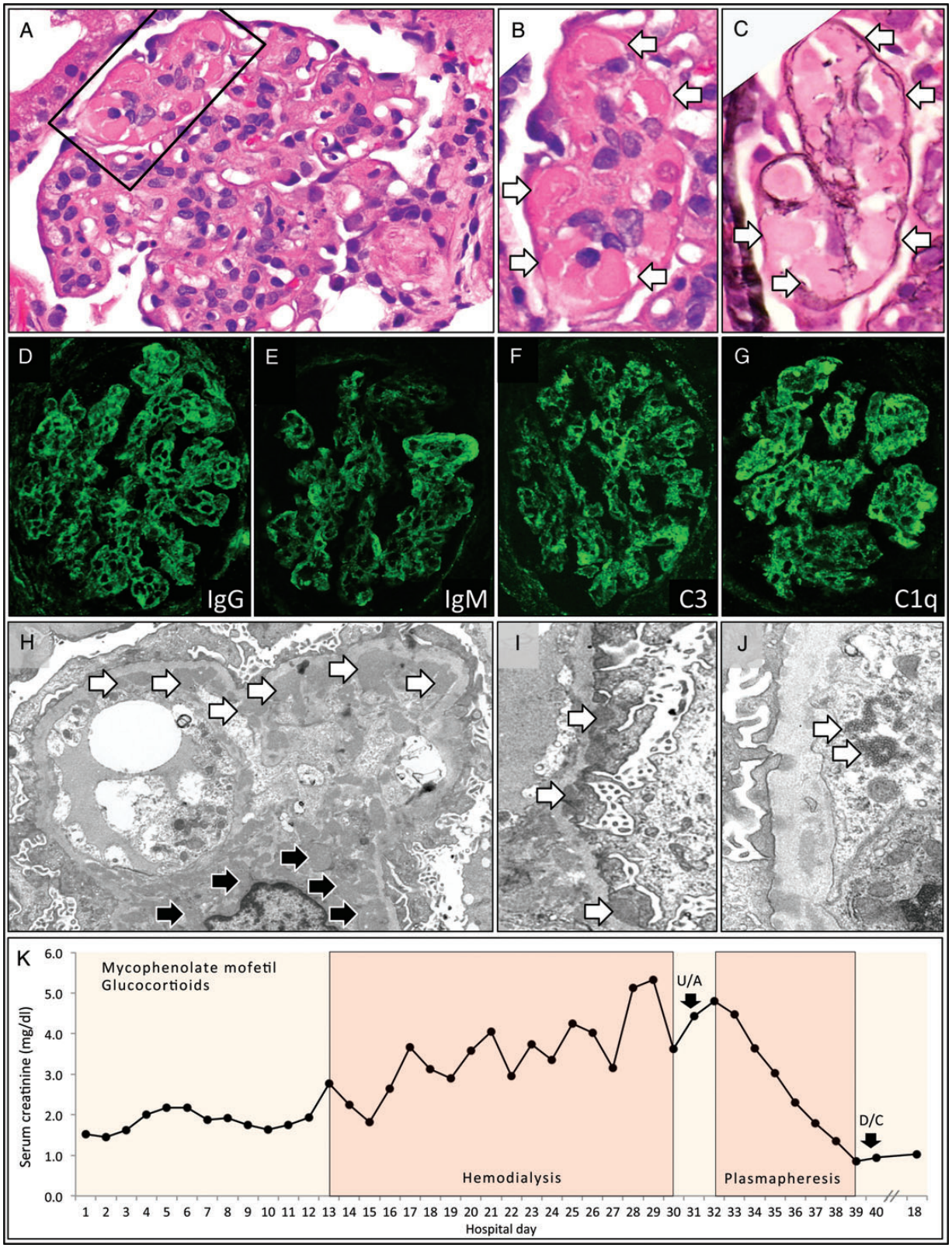

Fig. 1. Proliferative lupus nephritis, glomerular microthrombosis and effects of therapeutic interventions on renal function. A glomerulus demonstrating mesangial and endocapillary proliferation as well as segmental capillary thrombosis (rectangle) (**A**). Higher magnification of the glomerulus in (A) demonstrating capillary microthrombi (white arrows) (**B** and **C**). Immunofluorescence examination revealing strong glomerular staining for IgG, IgM, C3 and C1q (**D**–**G**). Ultrastructural examination demonstrating numerous electron-dense deposits in subendothelial space (white arrows) and mesangium (black arrows) (**H**). Small subepithelial electron-dense deposits (white arrows) are noted (**I**). Tubuloreticular inclusions (arrows) in the cytoplasm of an endothelial cell (**J**). Tissue sections were stained with hematoxylin and eosin (A and B) as well as with Jones' methenamine silver stain (C). Immunofluorescence micrographs (D–G). Electron micrographs (H–J). Effects of therapeutic interventions on renal function (**K**). Colored boxes represent the duration of specific treatments. D/C, discharged home; U/A, repeat urinalysis.

tubular necrosis. Arteries and arterioles were unremarkable. Immunofluorescence examination showed diffuse strong granular staining for IgG, IgA, IgM, C3, C1q, kappa and lambda light chains in the mesangium and capillary walls (Figure 1D–G) corresponding to numerous electron-dense deposits upon ultrastructural examination (Figure 1H and I). Diffuse effacement of podocyte foot processes and tubuloreticular inclusions in occasional endothelial cells were noted (Figure 1J). A pathologic diagnosis of diffuse proliferative lupus nephritis and thrombotic microangiopathy was rendered.

On the 32nd hospital day, despite continued MMF and prednisone, serum creatinine kept rising following a hemodialysis treatment 3 days prior (Figure 1K). Urinalysis revealed proteinuria (300 mg/dL), numerous dysmorphic erythrocytes and erythrocyte casts, but no muddy brown granular casts. TPE was initiated and resulted in rapid renal recovery. One plasma volume was exchanged with fresh frozen plasma every day for 7 days. Following the 5th TPE, lupus anticoagulant was undetectable. At the completion of TPE, serum creatinine was 79.6 μmol/L (0.9 mg/dL) (Figure 1K). The patient was also started on anticoagulant therapy (low-molecular-weight heparin followed by warfarin) 3 days before discharge from the hospital. At the time of discharge, her immunosuppressive regimen consisted of MMF 3.0 g/day and prednisone 30 mg/day. Three weeks later, serum creatinine was 88.4 μmol/L (1.0 mg/dL). The titer of antibodies to double-stranded DNA and chromatin decreased to 17.0 and 0.3 U/mL, respectively. Lupus anticoagulant remained undetectable. Serum C3 and C4 concentrations increased to 87 and 15 mg/dL, respectively. Proteinuria was estimated to be 4.2 g/day.

Discussion

TPE represents an adjunctive therapeutic strategy for antibody-mediated autoimmune diseases by removing pathogenic autoantibodies and circulating immune complexes, altering T-cell functions (favoring type 2 helper T-cell differentiation) and suppressing interleukin 2 and interferon-gamma production. The role of TPE in lupus nephritis is controversial. TPE was reported to be effective in rapidly progressive lupus nephritis associated with high immunologic activity when the rise in serum creatinine was >88.4 μmol/L (1.0 mg/dL) per month or when normal creatinine clearance decreased to <40 mL/min within 1–2 months [3]. In addition, TPE was reported to be effective in patients with lupus nephritis who developed nephrotic syndrome within a year after diagnosis [3]. However, a randomized clinical trial of TPE in lupus nephritis showed no additional benefit beyond a combination therapy consisting of oral cyclophosphamide and glucocorticoids [4]. Therefore, it has been argued that TPE could serve as an adjunct treatment in patients with severe lupus nephritis who do not respond to the conventional therapy or those who demonstrate a rapidly progressive decline in renal function [3].

Our patient fulfilled the diagnostic criteria for the antiphospholipid syndrome (APS), and glomerular microthrombosis was associated with lupus anticoagulant. This raised the question whether concurrent APS can affect the renal outcome in proliferative lupus nephritis, and if so, what the treatment of choice would be. Lupus nephritis was accompanied by APS nephropathy in one-third of patients who underwent a renal biopsy [1]. APS nephropathy was associated with lupus anticoagulant and represented an independent risk factor for hypertension, interstitial fibrosis and diminished renal function. Zheng *et al.* [2] observed glomerular microthrombosis in 20% of renal biopsies demonstrating lupus nephritis. Glomerular microthrombosis directly correlated with systemic lupus activity as well as with the activity and chronicity of lupus nephritis. Furthermore, lupus anticoagulant and antibodies to β_2-glycoprotein I and thrombin were more prevalent in patients with lupus nephritis who demonstrated glomerular microthrombosis.

It could be argued that resolving acute tubular necrosis (due to preceding sepsis) could have been the main reason for the recovery of renal function in our patient. However, shortly before TPE was initiated, an experienced pathologist (A.N.) examined the urine sediment under a microscope and observed numerous dysmorphic erythrocytes and erythrocyte casts, but no muddy brown granular casts to indicate ongoing acute tubular necrosis. In addition, our patient's serum creatinine level continued to rise following the final hemodialysis treatment and before the initiation of TPE. During the recovery phase of severe acute tubular necrosis, before serum creatinine level trends downwards, the degree of daily increase in serum creatinine level lessens followed by a plateau in serum creatinine of variable duration. This was not the case in our patient as rising serum creatinine level acutely fell following the initiation of TPE.

Although long-term anticoagulation has been recommended for patients with recurrent spontaneous thrombotic events secondary to APS, no consensus has been reached for patients with a single or provoked thrombotic event. Similarly, despite accumulating evidence indicating adverse renal outcome, there is no consensus on effective treatment strategies for concurrent lupus nephritis and APS nephropathy. Although little is known about the effects of TPE in APS, it is considered an effective treatment for a rare life-threatening form of APS known as catastrophic APS [5].

In conclusion, this report calls attention to a significant subset of patients with severe lupus nephritis who fail to respond to the conventional therapy, might have concurrent APS nephropathy and could potentially benefit from adjunctive TPE, anticoagulation or both.

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