CASE REPORT

Severe crescentic lupus nephritis treated with plasma exchange and modified dose of immunosuppressive therapy

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SUMMARY

Lupus nephritis (LN) is one of the major life-threatening systemic organ involvements in systemic lupus erythematosus. The prognosis and outcome of LN vary depending on its clinical presentation and histopathological classification. Crescentic LN occurs commonly in severe diffuse proliferative LN, often manifests as acute kidney injury requiring intensive immunosuppressive therapy and probable need for renal replacement therapy (RRT) and this is associated with poor renal outcome. We report a case of severe crescentic LN in a young girl who needed RRT while on the induction phase of immunosuppressive therapy with our modified induction regime and managed to discontinue after 5 months with significant kidney recovery.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, characterised by inflammation of different systemic organs with immunologic abnormalities. The natural course of the disease varies from mild mucocutaneous and musculoskeletal manifestation to life-threatening kidney, hematologic and central nervous system involvement – leading to fulminant organ failure and death. Early disease recognition, with judicious therapy and prompt treatment of complications, may improve the prognosis and outcome.

Lupus nephritis (LN) is one of the renal manifestations in SLE, and its presentation can be varying from asymptomatic microscopic haematuria and proteinuria to nephrotic or nephritic syndrome or a combination of both. Crescentic LN is the most severe manifestation of LN, presenting as rapidly progressive glomerulonephritis (RPGN) with hypertension, acute kidney injury and oliguria. The standard acute management of crescentic LN includes high-dose corticosteroids, induction therapy with immunosuppressive agent and probable need of renal replacement therapy (RRT) if indicated. The outcome of crescentic LN is usually poor, resulting in end-stage renal disease requiring long-term RRT.

CASE PRESENTATION

A 16-year-old girl presented with an 1-month history of bilateral lower limbs swelling, associated with facial puffiness, dyspnoea and reduced urine output for 1 week prior to presentation. Other systematic review was not significant and no other symptoms to suggest connective tissue disorder. She has no known medical illness and no significant family history of autoimmune diseases. Upon arrival at the hospital, she had four episodes of seizures and she regained consciousness in between episodes. Initial assessment revealed a young girl with anasarca, however, no stigmata of connective tissue disorder. She appeared pink, not in respiratory distress, and her blood pressure was 189/101mmHg on presentation. Her neurological examination was unremarkable. She was anuric on presentation despite on optimal dose of diuretics. She was stabilised with anti-seizure medication and antihypertensive. Immediate brain computed tomography (CT) was suggestive of posterior reversible encephalopathy syndrome (PRES), which was later confirmed by a brain magnetic resonance imaging, and no evidence of cerebral lupus.

Her blood investigations revealed acute kidney injury with a serum urea of 38 mmol/L and creatinine of 895 µmol/L with an estimated glomerular filtration rate (eGFR) of 5.1 ml/min/1.73 m^2 on presentation. There was hyperkalaemia with a serum potassium of 6.8 mmol/L, and metabolic acidosis with a pH of 7.22 and bicarbonate of 14.4 mmol/L. Her full blood count showed a normocytic normochromic anaemia with haemoglobin 8.8 g/L, total white cell count 7.2 × 10^9/L and platelet count 291 × 10^9/L. There was no evidence of haemolysis in peripheral blood film and coomb's test was negative. Her serum albumin was 14 g/L. Other laboratory investigations include urinalysis of protein 3+ and blood 3+ and urine protein: creatinine index (PCI) of 0.53 g/mmol creatinine. An ultrasound of kidney ureter bladder with renal doppler showed normal kidney size bilaterally with no evidence of renal vein thrombosis. Her workup for autoimmune disease revealed a positive antinuclear antibody with titre of 1:1280, positive double-stranded DNA, and low complement C3/C4 level of 24/5 mg/dL, respectively. Her screening for hepatitis B, C and HIV was non-reactive.

With a clinical diagnosis of crescentic LN, she was given a 3-day course of intravenous (IV) methylprednisolone 250 mg daily, followed by a maintenance of 50 mg (1 mg/kg) daily. Renal biopsy was performed and showed three cores of renal

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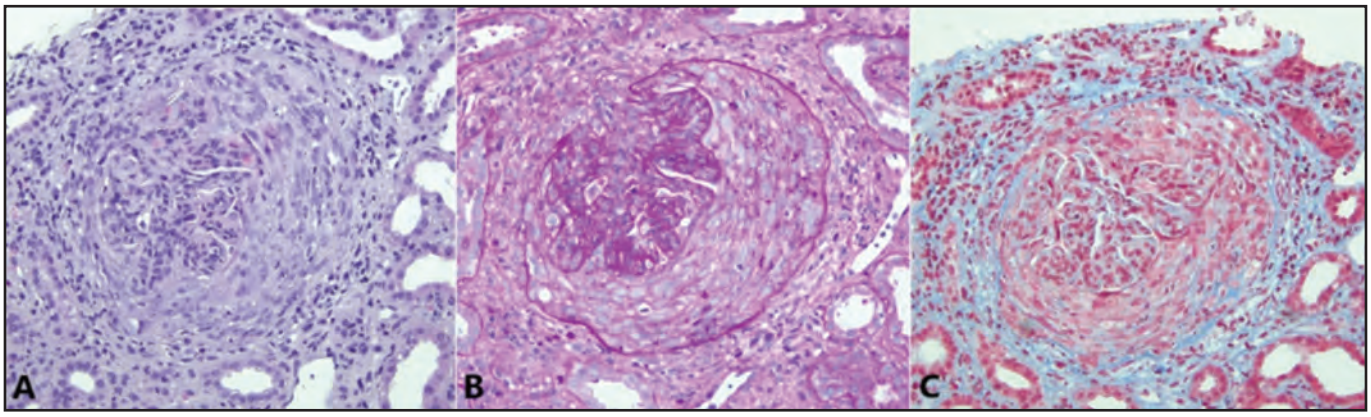

Fig. 1: Cellular crescent with endocapillary and mesangial hypercellularity in haematoxylin and eosin (H&E) stain (A), periodic acid-Schiff reaction (B) and Masson's trichrome stain (C)

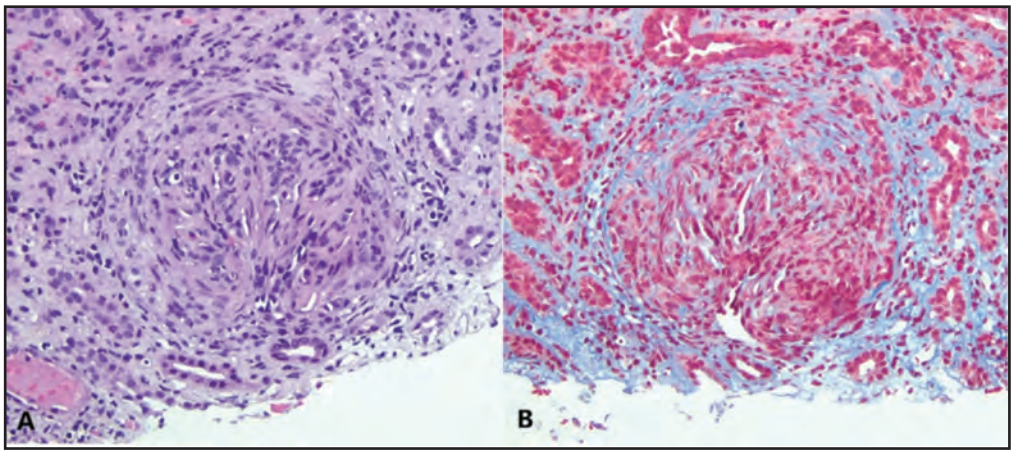

Fig. 2: Fibrocellular crescent in H&E stain (A) and Masson's trichrome stain (B)

cortical tissue comprising of a total of 35 glomeruli. There was a widespread crescents with 50% cellular crescents (Figure 1) and 50% fibrocellular crescents (Figure 2) seen. Eight glomeruli showed segmental sclerosis with adhesions and most of the glomeruli displayed endocapillary and mesangial hypercellularity with karyorrhexis and thickening of basal membrane with double contouring and subendothelial deposit. Pseudothrombi were seen in a few glomeruli. Presence of acute tubular injury with moderate infiltration of neutrophils, lymphocytes, plasma cells and scattered eosinophils within interstitium with 45% tubular atrophy and interstitial fibrosis. An interlobular artery showed evidence of vasculitis with fibrinoid necrosis. The immunofluorescence (IF) study revealed a full-house immunocomplex deposition with 3+ granular positivity for C3, C4, IgM and IgA and 1+ granular positivity for IgG at the mesangium and capillary loops.

The diagnosis of crescentic LN was established, and she was treated with six cycles of plasma exchange. In the ward, her platelet counts dropped further to the lowest reading of 57 × 10^9/L with no other cause to explain. Hence, she was treated as immune-mediated thrombocytopenic purpura and started on intravenous immunoglobulin (IVIg) for 5 days followed by a modified induction therapy regime with 2 weekly intravenous cyclophosphamide. Initial dose of 300 mg IV cyclophosphomide was given fortnightly for first 2 months followed by 250 mg fortnightly for another 4 months concurrent with a tapering dose of oral prednisolone 5 mg fortnightly until 25 mg (0.5 mg/kg) daily then tapered further by 5 mg monthly to maintain at 10 mg daily dose. She remained anuric throughout the admission and was initiated on haemodialysis then later converted to peritoneal dialysis, a month after. She was doing well with her continuous ambulatory peritoneal dialysis (CAPD), and her urine output and renal profiles improved significantly at 3 months of induction therapy. The need for her CAPD able to taper down slowly from daily to 3 days per week, and subsequently discontinued at 4 months of induction therapy with a serum creatinine of 161.2 µmol/L and eGFR of 40 ml/min/1.73m^2. Table I summarises her disease progress with treatment. She was planned for a total 6 months of 2-weekly intravenous cyclophosphamide followed by a maintenance therapy with mycophenolate mofetil (MMF) with regular follow-up in nephrology clinic.

Table I: Clinical course of the disease with treatment

Duration from presentation (Weeks)	Treatment			RRT	Creatinine µmol/L	UPCI g/mmol	Albumin g/L
	Corticosteroids	Cyc	Others				
1	IV MP 250 mg OD for 3 days then IV MP 50 mg OD for 6 cycles (total 12 days)	-	PLEX EOD				
		HD	895.5	0.53	14		
2	IV MP 50 mg OD	-		HD	455.3		31
3	Pred 50 mg OD	-	IVIg OD for 5 days	HD	428.9		29
4	Pred 50 mg OD	-	-	HD	525.0		26
5	Pred 45 mg OD	300 mg	-	HD	688.0		30
7	Pred 40 mg OD	300 mg	-	HD/PD	563.5		32
9	Pred 35 mg OD	300 mg	-	PD	453.1	0.54	29
11	Pred 30 mg OD	300 mg	-	PD	290.3	0.25	32
13	Pred 25 mg OD	250 mg	-	PD	289.1	0.29	29
15	Pred 25 mg OD	250 mg	-	dPD	339.0	0.13	35
17	Pred 20 mg OD	250 mg	-	dPD	245.3	0.25	31
19	Pred 20 mg OD	250 mg	-	dPD	195.5	0.66	30
21	Pred 15 mg OD	250 mg	-	Stopped	185.5	0.81	29
23	Pred 15 mg OD	250 mg	-	-	161.2	0.83	29

Cyc = cyclophosphamide, RRT = renal replacement therapy, UPCI = urine protein: creatinine ratio, IV = intravenous, MP = methylprednisolone, OD = daily, PLEX = plasma exchange, EOD = every other day, HD = haemodialysis, Pred = prednisolone, IVIg = intravenous immunoglobulin, PD = peritoneal dialysis, dPD = decremental peritoneal dialysis 3 days per week

DISCUSSION

Globally, the prevalence of SLE varies widely in different geographical regions, depending on the ethnicity, environmental exposures, and socio-economic status of the population. Its prevalence is low in the White population, with only 29 cases per 100,000 population in Malta of Europe, as compared to the Black population, which can be as high as 7,700 cases per 100,000 population in Senegal of Africa region.[1] A 38% of SLE has renal involvement with LN as the initial presentation, with higher overall morbidity and mortality as compared to those without renal involvement. In Malaysia, the estimated prevalence of SLE is 43 cases per 100,000 population, predominantly in the Chinese ethnic group.[2] The incidence of LN is higher in Malaysia as compared to global data, affecting 74% of SLE patients.[2]

LN can be classified into six classes based on its histopathological findings in the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification for LN. Class I (minimal mesangial) and class II (mesangial proliferative) are considered as non-proliferative LN, whereas class III (focal proliferative and sclerosing) and class IV (diffuse proliferative and sclerosing) are considered as proliferative LN which require aggressive immunosuppressive therapy. Class V (membranous) LN commonly manifests as nephrotic syndrome and class VI (advanced sclerosis) LN is end-stage LN with a terminal prognosis. The natural course of LN is characterised by intervals of active disease and remission. Recurrent relapses of LN especially proliferative LN (class III and IV ISN/RPS) lead to cumulative insults to the kidneys, leading to progression to chronic renal failure and end-stage renal disease. Class V (ISN/RPS) LN has lower risk of renal failure; however, recurrent nephrotic syndrome can increase the risk of cardiovascular events. Thus, properly tailored immunosuppressive therapy is important to maintain disease remission and prevent progression to renal failure.

Crescentic LN has been observed in more than 50% of biopsy-proven RPGN, and around 10% of biopsy-proven LN with higher prevalence (21.7%) in class IV (ISN/RPS) LN.[3] It is one of the most challenging causes of RPGN as it is associated with poor treatment response and high risk of progression to end-stage renal failure especially in those with high serum creatinine upon presentation. Our case presented with acute onset and short disease duration of renal failure with a serum creatinine of 895 µmol/L requiring RRT, and her renal biopsy showed class IV (ISN/RPS) LN with widespread cellular and fibrocellular crescents, with high activity and chronicity indices and 45% of chronic tubule-interstitial damage. These characteristics indicate a poor prognosis and low renal survival rate.

The recommended induction therapy of proliferative LN according to Kidney Disease Improving Global Outcomes (KDIGO) in 2021 includes the use of intravenous methylprednisolone of 250–500 mg daily for 3 days, followed by oral prednisolone of 0.6–1 mg/kg daily to taper to less than 7.5 mg daily by the end of 3 months, with the addition of another immunosuppressive agent which is either intravenous cyclophosphamide 500 mg 2 weekly for total six doses (Euro Lupus Nephritis Trial Protocol) or oral MMF 2–3 g daily for 6 months (Aspreva Lupus Management Study).[4] National Institute of Health (NIH) protocol on the other hand uses high dose intravenous cyclophosphamide of 0.5–1 g/m^2 monthly for 6 months. In our centre, the induction therapy for proliferative LN consists of a lower dose of corticosteroids with intravenous methylprednisolone 250 mg daily for 3 days followed by oral prednisolone 0.5 mg/kg daily with a tapering dose of 5 mg per month to maintain at 10 mg daily. The intravenous cyclophosphamide protocol for induction therapy is 400–500 mg/dose 2 weekly for four doses in 2 months followed by 10–12 mg/kg/dose monthly for 4 months which is a combination of Euro Lupus Nephritis Trial Protocol and NIH protocol. Our treatment protocol utilises an overall

lower dose of immunosuppressive therapy with a lower risk of infection but is able to achieve a comparable long-term renal outcome as compared to world data.[5]

Our present case was treated with plasma exchange for six cycles followed by IVIg for 5 days which are not stated in any standard guidelines for the treatment of crescentic LN. She was then given an induction therapy with a lower dose of intravenous methylprednisolone followed by a standard dose of tapering oral prednisolone. The intravenous cyclophosphamide given was a modified regime of 2 weekly doses of 250–300 mg for a total of 6 months which is a much lower dose as compared to the standard treatment recommended by KDIGO in 2021. She was able to recover and discontinue her RRT after 4 months of treatment without any complications with infection.

CONCLUSION

Our treatment protocol utilise an overall lower dose of immunosuppressive therapy and adjunctive therapy of plasma exchange with lower risk of infection but able to achieve a comparable long-term renal outcome as compared to world data.[5]

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