Eculizumab in Systemic Lupus Erythematosus Complicated with Thrombotic Microangiopathy

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Thrombotic microangiopathy (TMA) is a rare but serious complication of systemic lupus erythematosus (SLE) in children, which is often resistant to different medical treatments. This is the report of a 13 years old female with a newly diagnosed SLE, complicated with a refractory course of SLE-TMA. Eculizumab had an effective therapeutic impact with clinical and laboratory improvement of TMA.

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Case Report

INTRODUCTION

Thrombotic microangiopathy (TMA) is an infrequent complication of systemic lupus erythematosus (SLE) with an incidence of 0.5 to 10% of patients. Multiple thromboses lead to intense cytokine release, with 30% mortality rate.[1-3]

Complement pathway dysregulation has a major role in the pathogenesis of secondary TMA in children with SLE. Therefore, targeting the complement pathway seems necessary for the appropriate management of these patients.[1] Eculizumab is a recombinant humanized IgG2/IgG4 monoclonal antibody, which inhibits terminal complement complex activation and has been introduced as a potential treatment for these patients.[4-6]

Data about the efficacy of eculizumab in children with autoimmune disorders are rare. The present report emphasizes the therapeutic effect of eculizumab in a patient with SLE and positive antiphospholipid antibody (aPL-A), whose condition was complicated by refractory SLE-TMA, and responded successfully to eculizumab treatment.

CASE PRESENTATION

A 13-year-old female was admitted to the Aliasghar Childrens' hospital with a history of fever, generalized arthralgia, skin rash, palmar erythema, oral ulcer, hair loss, limb edema, photophobia, morning stiffness, epistaxis, hand tremors and decreased appetite, since a few months ago. Physical examination revealed high blood pressure (BP = 160/90), leukoplakia, oral aphthous lesions, tongue fasciculation, splenomegaly, arthritis, and cervical adenopathy. The parents were consanguineous. Her father had psoriasis and her mother had a history of rheumatoid arthritis.

Laboratory findings

Laboratory tests showed pancytopenia, microscopic hematuria, proteinuria (1000 mg/24h), increased ESR, fibrinogen and ferritin level. Serologic tests of SLE were remarkable. Serum antiphospholipid antibodies were elevated, with positive lupus anticoagulant and prolonged PTT (Tables 1and 2).

Serologic tests including rheumatoid factor (latex), cytomegalovirus (CMV), Human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), and herpes simplex virus (HSV) PCR were all negative. Serum level of related cluster of differentiation (CD) markers (CD2, CD3, CD4, CD5, CD7, CD8 and CD45 were all low. Antimitochondrial Antibody (AMA) and Anti-Smooth Muscle Antibody (ASMA) were negative. Schistocyte, burr cells, helmet cell, teardrop and fragmented RBCs were identified in peripheral blood smear. Complement inhibitory factors complement factor H (CFH), complement factor I (CFI), membrane cofactor protein (MCP) and ADAMTS-13 levels were normal. Peripheral blood smear showed microangiopathic changes.

Echocardiography showed a dilated and hypertrophied left ventricle with increased left ventricular mass index, mild tricuspid regurgitation, moderate mitral regurgitation, with ejection fraction (EF) value of 55%. Axial cuts of brain MRI showed few scattered high signal foci in bilateral centrum semi-ovale, suggestive of small vessel disease (Figure 1).

Table 1. Laboratory characteristics at admission

Variables	Values at admission	Reference value
WBC (mm^3)	2000	$4\text{-}10\times10^3$
Hgb (g/dl)	6.9	12-16
Platelets (mm^3)	90000	$140\text{-}440\times10^3$
ESR (mm/h)	90	< 20
CRP (mg/L)	70	< 10
BS (mg/dl)	102	< 140
BUN (mg/dl)	81	6-20
Cr (mg/dl)	4.85	0.5-1
LDH (U/L)	1100	< 436
PT (sec)	14	10-14
INR	1.2	0.9-1.0
PTT (sec)	78	28-24
D-Dimer (ng/ml)	3200	< 200
Ferritin (ng/ml)	800	7-140
Fibrinogen (mg/dl)	396	200-400

Table 2. Diagnostic laboratory exams at admission

Variables	Values at admission	Reference Value
C3 (mg/L)	43	62.5-146.8
C4 (mg/L)	8	8.9-41.7
CH50 (mg/L)	11.7	41.6-95.1
Anti ds-DNA (u/ml)	> 300	< 5
APL ab (IgM) GPL/ml	3.5	< 12
APL ab (IgG) GPL/ml	57.8	< 14
Anti CL ab (IgM) u/ml	31.2	< 12
Anti CL (IgG) u/ml	260.3	< 12
$ß_2$ GPAb (IgM) u/ml	94.7	< 12
$ß_2$ GPAb (IgG) u/ml	206.2	< 12
dRVVT (sec)	50	33-46

APL ab. anti phospholipid antibody, Anti CL ab: anti cardiolipin antibody, $ß_2$GPAb: $ß_2$ glycoprotein antibody, dRVVT: Russell viper venom time

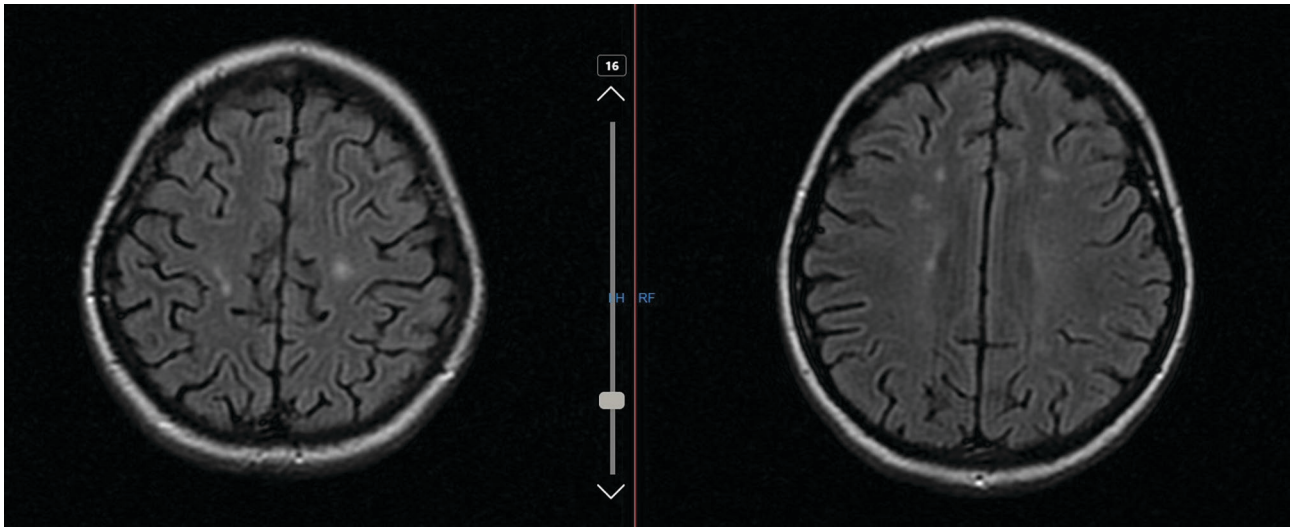

Figure 1. Axial FLAIR MRI brain images showing a few scattered high-signal foci in the bilateral centrum semiovale, suggestive of small vessel disease.

Renal histopathology

Renal biopsy showed glomerular mesangial and endocapillary proliferation with poly morph nuclear (PMN) infiltration. Some glomeruli showed endothelial swelling and mesangiolysis with endocapillary thrombi and focal or total necrosis. The tubulo-interstitium showed intratubular proteinaceous and red blood cell (RBC) casts, with small focus of tubular atrophy, interstitial fibrosis and inflammatory cells in 5-10% of specimen, as focal tubulointerstitial nephritis. In addition, arteriolar thrombi, fibrinoid necrosis and subintimal myxoid edema were noted (Figure 2). Immunofluorescence study showed full-house pattern of antibodies deposition including C1q. According to the clinical and laboratory findings, renal biopsy was suggestive of lupus nephritis class IV-G (A/C) of International Society of Nephrology/ Renal Pathology Society (ISN/RPS) (disease activity index 7/24 and chronicity index 2-3/12), concomitant with TMA.

According to the clinical, laboratory and renal histopathologic findings, SLE-TMA with anti-phospholipid syndrome was suggested as the final diagnosis.

Treatment and clinical course

Initial treatment consisted of methylprednisolone pulse therapy (1g/m^2/d for 4 days), in addition to hydroxychloroquine (200mg/d), aspirin (80mg/d), rituximab (375 mg/m^2, two weeks apart) and antihypertensive medicines. Plasmapheresis was performed every other day for five sessions. As the clinical condition was poor, IVIg (400 mg/kg for five days) was added to the medical treatments. However, there was no improvement in clinical and laboratory findings of lupus nephritis and TMA by the completion of the treatment. Therefore, eculizumab was started with conventional protocol treatment (900 mg/week for four doses), which had good therapeutic effects on thrombocytopenia, serum Cr and hemolysis. However, clinical condition

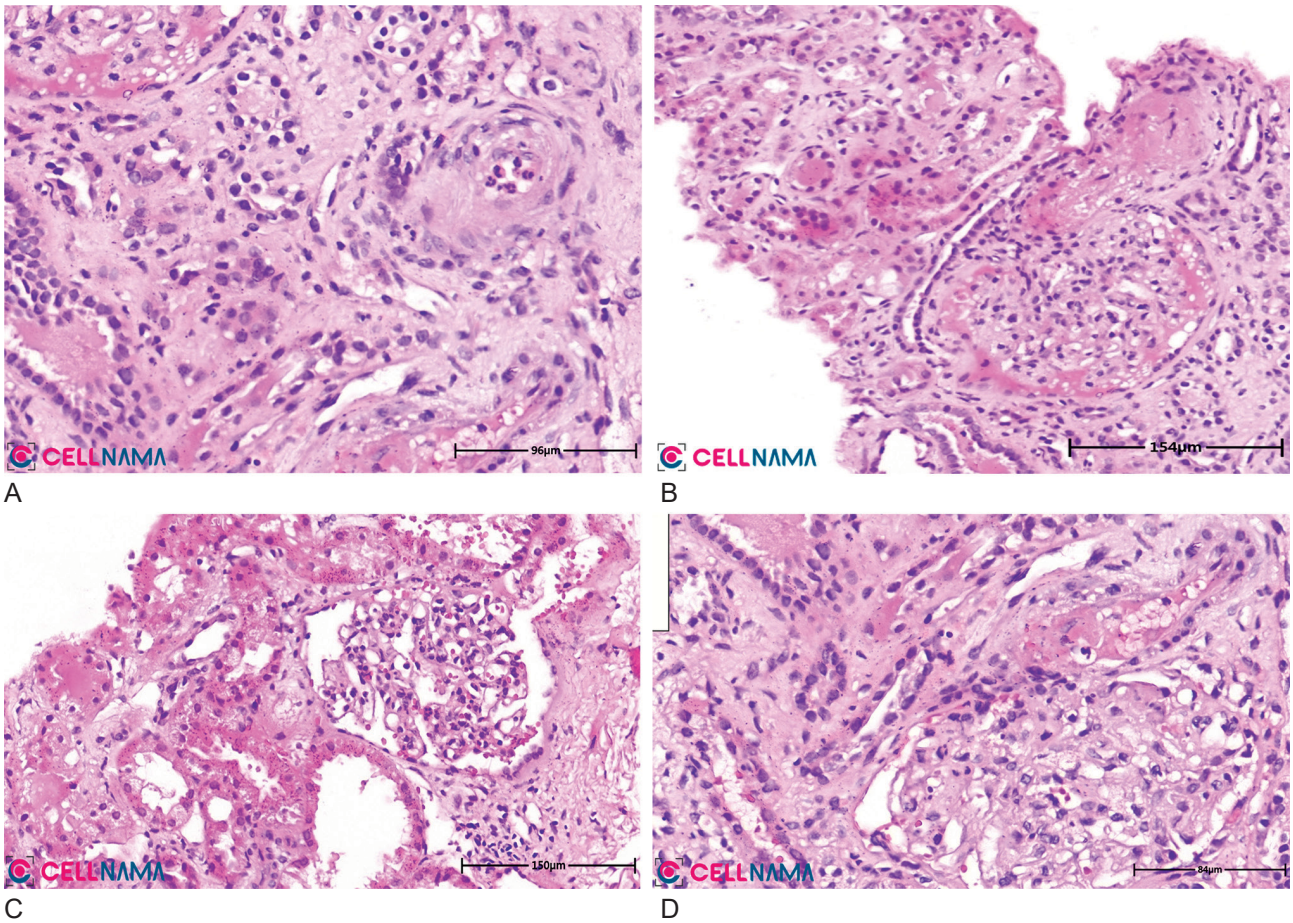

Figure 2. Histopathological findings demonstrating arteriolar thrombi, fibrinoid necrosis, and subintimal myxoid edema.

Table 3. laboratory exams and medical treatments

Variables	Initial treatment*	Pre-Eculizumab	Pre-CPA	At discharge
WBC (mm^3)	2000	7100	7100	14000
Hgb (g/dl)	6.9	7.5	8.5	9
Platelets (mm^3)	90000	68000	172000	192000
BUN (mg/dl)	81	75	50	35
Cr (mg/dl)	4.85	3.5	2	2.7
LDH (U/L)	1100	1800	1500	750

*Initial medical treatment included Methylprednisolone pulses, plasmapheresis, IVIg, rituximab, CPA: Cyclophosphamide

of patient did not improve and cyclophosphamide pulse treatment (500-750 mg/m^2/month for six doses) was started with subsequent improvement. Therapeutic response is shown after each specific medical treatment in Table 3.

During the follow up period, she experienced refractory and resistant hypertension. Selective renal angiography showed normal renal artery with no evidence of renal artery stenosis. TC^{99} DMSA renal scan was normal, with no cortical defect or decreased renal function. Hypertension gradually decreased by lowering steroid dosage. After two years of follow up, the patient has been in clinical and laboratory remission with no significant hypertension or episode of TMA.

DISCUSSION

Secondary TMA in pediatric patients with underlying autoimmune disorders is uncommon. In the study by Alhamoud *et al.*, TMA was reported in approximately 24% of patients with lupus nephritis.[7]

TMA has been reported in class III/IV lupus nephritis associated with aPL-A, mixed connective tissue disease, malignant hypertension, or adverse effects of calcineurin inhibitors,[8] reflecting autoimmunity and inflammatory response in patients with active lupus nephritis. In addition, TMA may occur in patients with genetically dysregulated alternative complement pathway, by increasing serum C5a and C5b-9 levels.[9-11] Without appropriate treatment, SLE-TMA has significant morbidity and mortality. Therefore, early recognition and prompt treatment might reduce its potential complications.[12] It seems that intractable TMA occurred secondary to the presence of aPL-A in our patient, which was resistant to the conventional treatment of lupus nephritis.

Complement activation plays a significant pathogenic role in antiphospholipid antibody (aPLA)–mediated thrombosis in SLE.[13] Blockade of terminal complement activation has emerged as a novel therapeutic strategy in a few cases of refractory aPLA syndrome and SLE associated with complementmediated TMA that are unresponsive to conventional immunosuppressive treatments. Eculizumab, a terminal complement inhibitor, has demonstrated efficacy in aborting and preventing clinical thrombotic events in patients with lupus nephritis.[5,10,11,14,15] Furthermore, studies have reported that eculizumab can induce prompt remission of vasculitis, normalize complement levels, and improve proteinuria, hematuria, thrombocytopenia, and renal function in patients with SLE refractory to conventional immunosuppressive treatment and plasmapheresis.[7] Our patient experienced a refractory course of lupus nephritis complicated by TMA, which showed a dramatic and stable response to eculizumab treatment during a 2year followup period.

CONCLUSION

Eculizumab may represent an optional treatment for refractory TMA secondary to lupus nephritis with positive aPL-A, warranting further confirmation in a larger cohort of pediatric patients.

Informed consent was taken at admission.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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