

Complement Inhibition in the Treatment of SLE-Associated Thrombotic Thrombocytopenic Purpura

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a well-described complication of systemic lupus erythematosus (SLE).¹ Historically, plasma exchange has been the mainstay of treatment for TTP as well as for other thrombotic microangiopathies.² Recently, the complement inhibitor eculizumab has demonstrated efficacy in treating atypical hemolytic uremic syndrome (aHUS).³ Whether eculizumab therapy could be beneficial in the treatment of TTP is unknown. We report a case of pediatric SLE-associated TTP treated with eculizumab, in conjunction with steroids, plasma exchange, and additional immunosuppressant therapies.

Case Report

A 12-year-old, previously healthy, Southeast Asian female presented to the emergency room with a 2-day history of increased menstrual bleeding, mild abdominal pain, and petechial rash. Two days prior to presentation, she had emesis, loose stools, and subjective fever. These symptoms had resolved prior to her arrival at the hospital. Her vital signs revealed a temperature of 38°C, blood pressure 117/69, and normal heart rate. She had petechial lesions over face and trunk. She had no peripheral edema, and her neurologic exam was normal.

Her initial laboratory studies showed severe thrombocytopenia (platelets 11 000/ μ L), hemoglobin 11.1 g/dL, positive direct Coombs test, and normal red blood cell morphology on peripheral blood smear (see Table 1). Urinalysis showed 3+ blood, 3+ protein, >100 red blood cells/hpf, >100 white blood cells/hpf, and hyaline casts. Serum creatinine was elevated at 3.6 mg/dL. Serum C3 and C4 were both below the level detectable by the lab (C3 < 26.3 mg/dL, C4 < 7.9 mg/dL). She had a positive antinuclear antibody with a 1:640 titer. Anti-double stranded DNA antibody was positive. Testing for antiphospholipid antibodies was negative.

The patient was initially treated with 500 mg/m² intravenous cyclophosphamide and daily 1 g methylprednisolone infusions. Her working diagnosis was SLE, manifesting as autoimmune thrombocytopenia and nephritis. Over the course of the next 2 days, her platelet count decreased to 9000/ μ L. Her hemoglobin decreased as well, reaching a nadir of 6.2 g/dL. Serum creatinine rose to 5.7 mg/dL. Hemodialysis treatment was initiated. At this time, her peripheral blood smear revealed new appearance of moderate schistocytes, suggesting thrombotic microangiopathy. These developments led to the initiation of plasma exchange therapy. Due to the severity of microangiopathic disease (requiring platelet and blood transfusions) and the known high risk of morbidity from SLE-related TTP, we decided to treat the patient with eculizumab 900 mg IV, to be followed with a supplemental daily dose of 600 mg after each subsequent plasma exchange.⁴ The patient received 7 consecutive days of plasma exchange (hospital days 3 to 9). The initial dose of eculizumab was administered on hospital day 4, and supplemental dosing was continued until hospital day 7. The patient developed brain magnetic resonance imaging findings and clinical symptoms consistent with posterior reversible encephalopathy syndrome on hospital day 6. This problem resolved promptly with initiation of appropriate blood pressure control and tapering of the methylprednisolone dose. Rituximab treatment was initiated on hospital day 9.

Repeat C3 and C4 testing on hospital day 4 revealed improved serum complement levels, with C3 = 60.5 mg/dL and C4 = 8.3 mg/dL. Testing on hospital day 8 revealed C3 = 70.9 and C4 = 11.4. The patient's

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Table 1. Laboratory Data.

	Reference Values	Initial Laboratory Values	Hospital Day 2
Hemoglobin (g/dL)	11.3-13.4	11.1	6.2
Platelets (thousand/ μ L)	138-345	11	9
Creatinine (mg/dL)	0.5-1.2	3.6	5.7
Red blood cell morphology	Normal	Normal	Moderate schistocytes
C3 (mg/dL)	80-180	<26.3	
C4 (mg/dL)	15-45	<7.9	
Antinuclear antibody	Negative	1:640	
Coombs	Negative	Positive	

ADAMTS13 activity was subsequently found to be <5%, revealing severe deficiency. ADAMTS13 functional inhibitor was not detected, but ADAMTS13 antibody was detected by ELISA assay (55; reference interval <18). After discontinuation of plasma exchange, the patient's hemoglobin and platelet count remained stable, with hemoglobin 9.2 g/dL and platelet count 162 000/L at discharge. Her renal function recovered, with serum creatinine 0.8 mg/dL at discharge. Three weeks after her initial presentation, she was discharged home in good condition. Renal biopsy performed after discharge revealed histologic findings consistent with diffuse proliferative lupus nephritis.

Discussion

TTP and aHUS are thrombotic microangiopathies (TMAs) characterized by microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, and renal disease. TTP is a relatively common complication of SLE, and reported rates of TTP in SLE are 1% to 4%.¹ Mortality rates of 26% to 62% have been reported for SLE-associated TTP.^{1,5} The treatment of TTP in SLE typically involves plasma exchange.¹ Adjunctive immunosuppressive treatment with steroids, cyclophosphamide, and/or rituximab has also been reported.⁶

Pathogenesis of TTP is linked to deficiency or dysfunction of the ADAMTS13 metalloprotease, which cleaves von Willebrand's factor (vWF). Lack of functional ADAMTS13 leads to ultralarge vWF multimers and predisposes to the formation of microvascular thrombi.⁷ Rates of severe deficiency in ADAMTS13 activity in idiopathic acquired TTP are 70.3% to 100%.^{2,5} However, the role of ADAMTS13 in the pathogenesis of SLE-associated TTP is less clear, and in a recent case series only 23.4% of SLE patients with TMA had severe deficiency in ADAMTS13 activity.⁵

More recent studies have revealed the possible role for complement activation in the pathogenesis of TTP.

Sera from TTP patients with severe deficiency of ADAMTS13 has been shown to cause complement deposition on endothelial cells, and this effect has been shown to be mitigated by complement blockade.⁸ Additionally, it has been demonstrated that plasma levels of complement activation markers are higher in patients with TTP than in healthy controls.⁹ A patient with acute TTP and severe ADAMTS13 deficiency who did not respond to conventional treatment with plasma exchange and immunosuppression has been successfully treated with eculizumab, providing further evidence for the role of complement activation in the pathogenesis of TTP, even in the setting of severe ADAMTS13 dysfunction.¹⁰

In contrast to TTP, aHUS is characterized by defective regulation of complement activation, resulting in endothelial damage and formation of microvascular thrombi.² Recently, it has been shown that eculizumab, a terminal complement inhibitor, is effective in treating aHUS.³ This development has led to renewed interest in complement inhibition as a potential treatment modality for other disorders characterized by complement activation, including SLE. However, clinical experience with complement inhibiting therapy in SLE has been limited, and the role of complement inhibiting therapies in SLE treatment is unknown. Our case represents the first reported instance of eculizumab treatment for SLE-associated TTP, used in conjunction with conventional treatment including steroids, plasma exchange, cyclophosphamide, and rituximab. Although it is impossible to assess the precise role of eculizumab in our patient's recovery, her good clinical outcome may provide justification for the use of complement inhibition in other patients with SLE-associated TTP, especially for those patients who have failed to respond to other conventional treatment options. Further study of complement inhibiting therapies in SLE and in TTP will be needed to guide clinicians in the application of these new treatments.

Declaration of Conflicting Interests

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