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Case Report

Thrombotic Microangiopathy in Systemic Lupus Erythematosus: Efficacy of Eculizumab

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Thrombotic microangiopathy (TMA) is a severe disorder with poor outcomes. The cause is unknown for many patients, although TMA is associated with connective tissue disorders, including systemic lupus erythematosus (SLE). While uncommon, TMA is one of the most serious complications of SLE and in many cases may be resistant to therapy. We report a patient with SLE complicated by TMA that was refractory to standard therapy but responded well to eculizumab, with continued remission after 1 year of follow-up. Eculizumab might be useful in the management of resistant cases of TMA caused by SLE.
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Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP-HUS) is a rare disease characterized by kidney failure associated with microangiopathic hemolytic anemia, thrombocytopenia, and fever, with or without neurologic impairment. Systemic lupus erythematosus (SLE) is one of the rare causes of TTP-HUS. Gharbi et al[1] reported that long-term outcomes are worse in patients with both TTP-HUS and lupus nephritis than in those who have lupus nephritis only.

Eculizumab is a fully humanized monoclonal antibody that acts as a terminal complement inhibitor. It is the first therapy approved to treat paroxysmal nocturnal hemoglobinuria and atypical HUS (aHUS).[2,3] Eculizumab targets the human C5 complement component and prevents formation of the membrane attack complex.[4] Here, we report a patient with SLE and refractory thrombotic microangiopathy (TMA) that responded favorably to eculizumab.

CASE REPORT

A 24-year-old African American woman developed proteinuria approximately 5 years after SLE was diagnosed. At her initial diagnosis, she had tested positive for antinuclear, anti-Smith, anti–double-stranded DNA (dsDNA), anti-SSA, and antiribonucleoprotein antibodies. She began hydroxychloroquine treatment at that time. After her presentation with proteinuria, a kidney biopsy demonstrated class V lupus nephritis and she was initiated on prednisone and mycophenolate mofetil therapy. She developed vulvar and perineal condylomata acuminata secondary to human papilloma virus infection and required multiple resections. Her subsequent course also was complicated by Ramsay Hunt syndrome due to varicella zoster virus.

Eight years after the patient's initial SLE diagnosis, she was admitted with a lupus nephritis flare. Serum C3 and C4 levels were low and tests for antinuclear antibody and anti-dsDNA were positive, whereas those for lupus anticoagulant, immunoglobulin M (IgM), and IgG anticardiolipin antibodies were negative. Repeat kidney biopsy showed class III and V lupus nephritis with cellular crescents (Fig 1). Daily oral prednisone dosage was increased to 60 mg.

Six weeks later, the patient developed anemia, thrombocytopenia, acute kidney injury with worsening proteinuria, and hypertension. Peripheral-blood smears were consistent with microangiopathic hemolytic anemia, and tests for lupus anticoagulant, anti-dsDNA, and anti–Scl 70 were negative. An additional kidney biopsy was performed. By light microscopy, the biopsy specimen demonstrated class III and V lupus nephritis with cellular crescents and mesangiolysis, as well as arteriolar fibrin thrombi and fibrinoid necrosis indicative of TMA (Fig 2). Immunofluorescence showed full-house staining in the mesangium and capillary loops, and electron microscopy demonstrated electron-dense deposits in the mesangial and subepithelial location. Direct antiglobulin test was negative and antiphospholipid antibodies were not detected. There was no evidence of parvovirus B19 DNA by polymerase chain reaction. Glucose-6-phosphate dehydrogenase activity was within the normal range, while ADAMTS13 (von Willebrand factor protease) activity, though below normal, was not consistent with classic TTP. Serum levels of complement factors H and I and levels of membrane cofactor protein on peripheral-blood mononuclear cells were within normal ranges.

A 6-month regimen of monthly cyclophosphamide infusions was initiated to treat the patient's lupus nephritis. Because TTP could not be excluded, plasmapheresis and high-dose intravenous methylprednisolone treatment were started immediately. Plasmapheresis was halted after 8 treatments because there was no noticeable clinical or laboratory response. On hospital day 33, the patient was given the first of 2 doses of the meningococcal conjugate vaccine and subsequently was placed on prophylactic penicillin V therapy. Four days later, she was started on treatment

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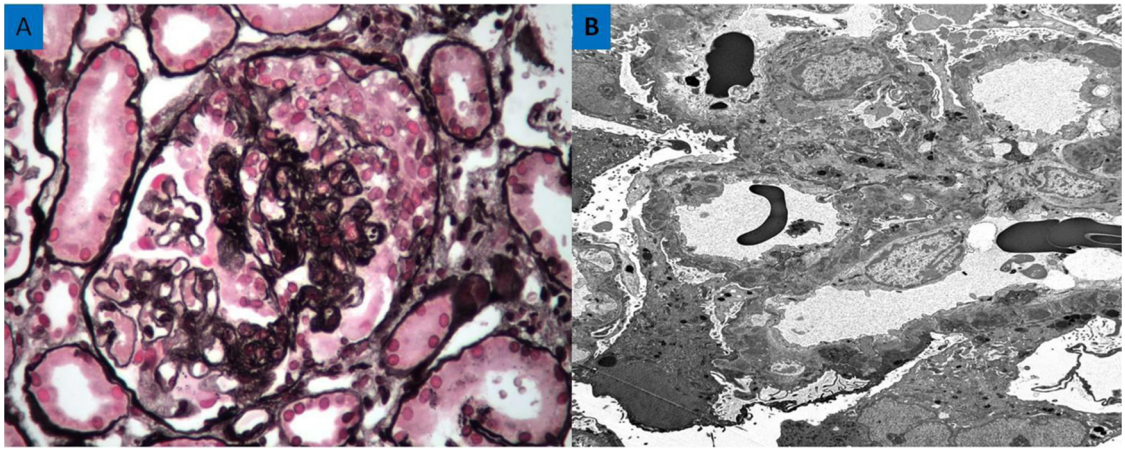

Figure 1. Kidney biopsy specimen. (A) Segmental cellular crescent and glomerular basement membrane fragmentation (Jones silver stain; original magnification, ×40). (B) Subepithelial complex immune deposits (electron microscopy; original magnification, ×1,200).

with 1,200 mg of eculizumab intravenously every 2 weeks. Two weeks following the initiation of eculizumab therapy, the patient's creatinine level decreased from a peak of 4.92 mg/dL to 2.92 mg/dL (corresponding to estimated glomerular filtration rate values of 12 and 24 mL/min/1.73 m^2, respectively), and values for hemoglobin, hematocrit, and platelet count had improved (Table 1). However, by hospital day 62, the patient's creatinine level had increased to 5.07 mg/dL and she developed acute hypoxic respiratory failure, likely due to flash pulmonary edema. She required continuous renal replacement therapy for the next 6 days, followed by intermittent hemodialysis for an additional week.

The patient was discharged on hospital day 79 and was followed up in our clinic. She was readmitted 3 times in the next 10 months. The first readmission, which lasted 5 days, occurred 1 month after discharge and was due to acute pancreatitis; the second readmission was an overnight hospitalization that occurred 3 months after the initial discharge and was attributed to diarrhea; and the third readmission, 4 months later, lasted 3 days and was for pneumonia. She finished 6 months of treatment with eculizumab, 1,200 mg, every 2 weeks, then she was followed up for another 6 months. At the time of writing, the patient's serum creatinine level was 1.6 mg/dL (estimated glomerular filtration rate, 47 mL/min/1.73 m^2), spot urine protein-creatinine ratio was 1.6 mg/mg, and platelet count and hemoglobin level were stable with no evidence of hemolysis. C3 and C4 levels remained within the normal ranges (Table 1).

DISCUSSION

TTP and HUS are part of a pathophysiologically and clinically heterogeneous disorder called TMA.[5] TTP usually is idiopathic but may be secondary to drugs, infections, malignancy, pregnancy, and autoimmune diseases such as SLE.[6] Complement inhibition has growing implications for treatment in many diseases with complement activation, including aHUS.[4] Dysregulation of the alternative complement pathway has been found in up to 70% of patients with aHUS. Eculizumab is a fully humanized monoclonal antibody that blocks formation of the terminal complement complex C5b-9 through binding to the C5 complement component with high specificity and affinity; thus, it inhibits terminal complement-mediated

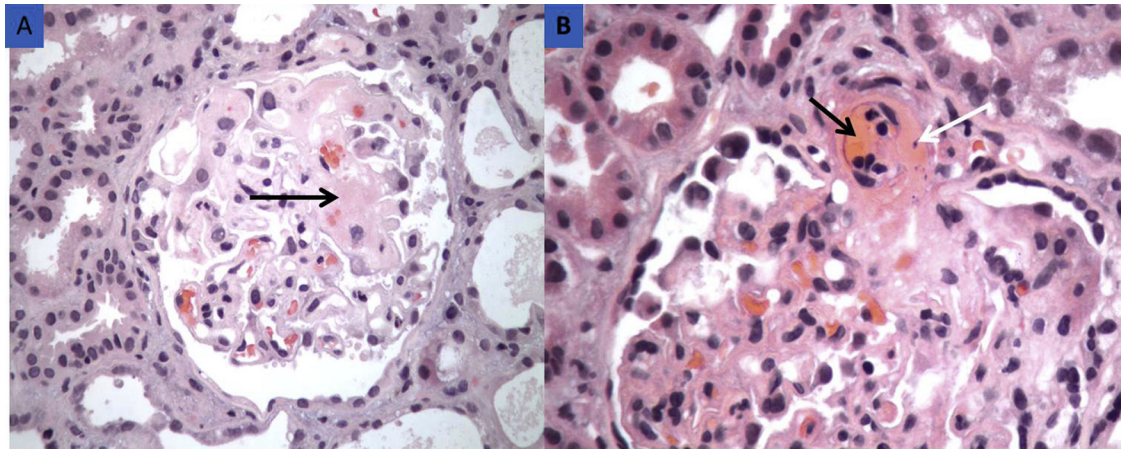

Figure 2. (A) Mesangiolysis (black arrow) (hematoxylin and eosin stain; original magnification, ×20). (B) Fibrin thrombi (black arrow) and fibrinoid necrosis (white arrow) involving the glomerular vascular pole (hematoxylin and eosin stain; original magnification, ×40).