Recombinant Human Soluble Thrombomodulin for Treatment of Thrombotic Microangiopathy Associated with Lupus Nephritis

To the Editor:

Thrombotic microangiopathy (TMA) is a rare but frequently life-threatening complication of systemic lupus erythematosus (SLE). TMA is associated with a worse overall prognosis[1,2] and usually requires plasma exchange in addition to immunosuppressive therapy. We treated a 33-year-old woman with SLE who developed TMA and renal dysfunction; she improved remarkably after intravenous (IV) administration of recombinant human soluble thrombomodulin (rTM) in addition to immunosuppressive therapy without plasma exchange.

The patient presented to hospital with a fever with arthralgia, digital and palmar erythema, and alopecia for 2 weeks. Laboratory findings showed pancytopenia, proteinuria with cellular casts, positive antinuclear antibodies, anti-dsDNA antibody, and anticardiolipin antibody. She was diagnosed with SLE. She was initially treated with prednisolone 15 mg/day and aspirin 100 mg/day. After 1 week of treatment, she was admitted to hospital because of severe headache in addition to hypertension (200/110 mm Hg). Her body temperature was 37.4°C; she was conscious and alert. She had neither a stiff neck nor other neurological signs. Moist rales were heard at the lung base. Chest radiography showed cardiomegaly and lung edema.

Laboratory findings on admission are summarized in Table 1, and included proteinuria, hematuria with blood casts, poikilocytes, and elevated urinary fibrin degradation products. Complete blood counts revealed leukocytopenia, normocytic anemia with reticulocytosis, and thrombocytopenia. Other abnormal findings included hypoalbuminemia and elevated D-dimer, and low levels of haptoglobin, C3, and C4. Although direct and indirect Coombs tests were negative, anti-dsDNA IgG and immune complexes were positive. She was diagnosed with nephrosis due to complicated severe lupus nephritis (LN). From the hypertension, headache, thrombocytopenia, and elevated D-dimer, malignant hypertension with possible TMA was considered.

Table 1. Laboratory findings on admission.

Urinalysis	
Protein	6.9 g/day
Occult blood	+
Blood casts	+
Poikilocytes	+
Fibrin degradation products	250 ng/ml
Complete blood counts	
Leukocytes	3200/μl
Erythrocytes	32700/μl
Hemoglobin	9.8 g/dl
Hematocrit	28.0%
Platelets	60,000/μl
Reticulocytes	3.33%
Serum analysis	
Creatinine	0.7 mg/dl
Albumin	3.0 mg/dl
Lactate dehydrogenase	530 IU/ml
C3	51 mg/dl
C4	6 mg/dl
Haptoglobin	< 10 mg/dl
Plasma analysis	
Fibrinogen	275 mg/dl
D-dimer	8.8 μg/ml
Coagulation	
Prothrombin time	98%
Activated partial thromboplastin time	35.7 s
Autoantibodies	
Direct Coombs test	Negative
Indirect Coombs test	Negative
Anti-dsDNA IgG	> 400 IU/ml
Immune complexes (C1q-CIC)	13.4 μg/ml

She was immediately treated with methylprednisolone 1 g pulse therapy for 3 consecutive days, followed by prednisolone 60 mg/day. In addition, she received nifedipine and telmisartan to treat hypertension. Despite improvement of hypertension, her serum creatinine level was further elevated to 1.05 mg/dl and thrombocytopenia progressed to 40,000/μl within 4 days after admission. Moreover, plasma fibrinogen level decreased to 166 mg/dl. Although we speculated that her condition was either lupus-associated TMA or disseminated intravascular coagulation (DIC), a definitive diagnosis of TMA was suspended at this point because we failed to detect red cell fragmentation in the blood smears. Therefore, we started daily IV infusion of rTM 380 U/kg/day on Day 4. Just after the start of rTM, her serum creatinine level improved.

As treatment for LN, IV cyclophosphamide (CYC) was administered at 500 mg/day (0.9 mg/kg body weight) on Day 8. Detection of fragmented red cells on her blood smear on the following day led us to diagnose TMA associated with LN. Because of the negative Coombs test and normal prothrombin time and activated partial thromboplastin time, we excluded autoimmune hemolytic anemia and DIC. During the rTM therapy, we observed improvement of her serum creatinine, lactate dehydrogenase, fibrin degradation products, and platelet counts. Finally, on Day 18, when the disappearance of fragmented red cells was noted, the rTM infusion was discontinued. No adverse effects were noted. The prednisolone dosage was gradually tapered, and IV CYC was repeated intermittently. The proteinuria disappeared and serum creatinine level normalized. She was discharged on Day 56, and has remained in remission for more than 10 months.

The pathogenesis of TMA with SLE has not been fully elucidated. Possible explanations include malignant hypertension, antiphospholipid syndrome, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, diffuse small-vessel vasculitis, and nephritis. One hypothesis is that autoantibodies may result in a decrease in ADAMTS13[3], although some TMA patients with SLE showed normal ADAMTS13 activity[4]. In our case, serum ADAMTS13 was 69.8%, almost within the normal range (reference range 70%~120%).

Current therapy for TMA with LN consists of a combination of immunosuppressive therapy and plasma exchange; there are doubts about the safety of this treatment[5]. Since 2008, rTM has been introduced for the treatment of DIC in Japan, based on a clinical trial[6]. rTM comprises the active extracellular domain of thrombomodulin, and inactivates coagulation by binding to thrombin. In addition, thrombin-rTM complexes activate protein C. The resultant activated protein C inactivates factors VIIIa and V, inhibiting further thrombin formation[7]. Additionally, rTM has been shown to exert antiinflammatory activity by binding to and inactivating high-mobility group box 1 (HMGB1) protein. By this mechanism, rTM has been shown to inhibit endothelial injury[8] and to protect against ischemic damage in the kidney[9,10].

These antiinflammatory and anticoagulant effects of rTM may have contributed to the improvement of TMA with LN in our case. rTM appeared to have a therapeutic potential with fewer adverse effects compared with plasma exchange and to be useful for SLE-associated TMA. Further studies are required to confirm this.

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