Short Communication

Successful treatment of sepsis-induced disseminated intravascular coagulation in a patient with idiopathic thrombocytopenic purpura using recombinant human soluble thrombomodulin

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Running Head: Efficacy of recombinant sTM in DIC with ITP

Abstract

Disseminated intravascular coagulation (DIC) may complicate a variety of disorders that contribute to mortality, particularly those related to bleeding. It is therefore very difficult to manage DIC in patients with known bleeding disorders. We treated a 62-year-old woman with idiopathic thrombocytopenic purpura (ITP) complicated with sepsis-induced DIC. She had been diagnosed with ITP 8 months prior to admission. Laboratory tests showed an elevation of d-dimer and endotoxin, while pyelonephritis was shown by abdominal computed tomography. Escherichia coli was detected by blood culture. Based on these findings, the patient was diagnosed with sepsis-induced DIC due to urinary tract infection. Thrombocytopenia was refractory despite the use of antibiotics and platelet transfusion, but it was promptly improved in response to recombinant human soluble thrombomodulin (rTM). We suggest that rTM provides a new therapeutic strategy for DIC patients with high hemorrhagic risk.

Keyword: Disseminated intravascular coagulation, Sepsis, Idiopathic thrombocytopenic purpura, recombinant human soluble thrombomodulin

Introduction

Disseminated intravascular coagulation (DIC) frequently complicates infections such as sepsis [1-3]. In such patients, coagulation activation, inhibition of fibrinolysis, and consumption of coagulation inhibitors leads to a hypercoagulable state resulting in fibrin deposition in microvessels and inflammatory reactions. Treatment is generally supportive, with platelet and clotting factor replacement therapy usually being utilized.

The administration of heparin or other anticoagulants to interrupt the underlying coagulopathy in DIC would appear to be a logical therapeutic approach. However, in some cases, these treatments may increase the risk of bleeding tendency and thrombotic complications.

Recombinant human soluble thrombomodulin (rTM) comprises the active, extracelluer domain of thrombomodulin and inactivates coagulation by binding to thrombin [4]. A recent phase III trial comparing the efficacy and safety of rTM to those of low-dose heparin showed that rTM significantly improves DIC associated with hematological malignancies or infections compared with low-dose heparin [5]. Use of rTM for the treatment of DIC has recently been approved in Japan. In addition, previous studies have shown that rTM also possesses anti inflammatory activities [6, 7].

In the present case, successful treatment was achieved by using rTM in a patient

with ITP complicated by acute sepsis-induced DIC, which put her at particularly high risk for coagulation abnormalities and bleeding tendency with high inflammatory reactions.

Case report

A 62-year-old Japanese female, who had been diagnosed with idiopathic thrombocytopenic purpura (ITP) 8 months earlier, complained of fever with chill. The levels of platelet count before this episode was around 50000/μL and she had been followed closely without treatment for ITP. Laboratory tests showed severe thrombopenia, and she was admitted to our hospital for further evaluation of elevated CRP and pyuria.

On admission, the patient's body temperature was 38.7°C, heart rate was 101 beats /min, and the respiratory rate was 28 breaths /min. These findings indicated systemic inflammatory response syndrome. On physical examination, she had nothing remarkable except tenderness and knocking pain over the left costovertebral angle.

Laboratory investigations revealed the following: hemoglobin (Hb) 7.9 g/dL, white blood cell count 6.3 × 10^3/μL (neutrophils 92%, lymphocytes 3%, and eosinophils 5%), platelet count (PLT) 1.0 × 10^3/μL, C-reactive protein (CRP) 32.34 mg/dl (323.4 mg/L), total protein 6.3 g/dL (63 g/L), albumin 2.4 g/dL (24 g/L), total bilirubin 1.3 mg/dL (22.2 μmol/L), lactate dehydrogenase (LDH) 218 IU/L, alkaline phosphatase 202 U/L, aspirate aminotransferase (AST) 21 IU/L, alanine aminotransferase (ALT) 31 IU/L, γGTP 94 IU/L, blood urea nitrogen (BUN) 30.8 mg/dL (11.0 mmol/L), and creatinine

1.2 mg/dL (106.1 μmol/L).

Coagulation tests indicated the following: prothrombin time international normalized ratio (PTINR) 1.27 (normal 0.85-1.22), activated partial thromboplastin time (APTT) 43.3 sec (normal 25.2-34.4 sec), fibrinogen 567 mg/dL (16.7 mmol/L), FDP 29.0 mg/mL, D-dimer 10.0 μg/mL (normal < 1.0 μg/mL), and protein C 75 % (normal 65-135 %).

Immunological studies showed the following: antinuclear antibody 1:320 (homogenous), anti-dsDNA antibody 3.4 IU/mL, anti-Sm antibody 4.5 U/mL, anti-SS-A antibody 105 U/mL, anti-SS-B antibody 14 U/mL, IgG 2120 mg/dL (21200 g/L), platelet-associated IgG (PAIgG) 53.2ng/10^7cells, and IgM 217 mg/dL (2170 g/L). Lupus anticoagulant activity, anticardiolipin antibodies, and anti-2-glycoprotein I antibody were all negative. Blood culture revealed the presence of Escherichia coli.

An abdominal contrast-enhanced CT scan demonstrated renal enlargement, thickening of Gerota's fascia, bridging septa of the peri-nephric fat, and a wedge-shaped zone of poor enhancement consistent with pyelonephritis (Fig. 1A).

DIC was diagnosed according to the diagnostic criteria established by Japanese Ministry of Health and Welfare (JMHW) [8]. Based on the above findings, she was diagnosed with sepsis-induced DIC due to pyelonephritis occurring in a patient with ITP.

We showed the clinical course of the present patient (Fig. 1B). Meropenem, which is a broad spectrum injectable antibiotic, was administered for pyelonephritis. Severe thrombocytopenia was not improved by platelet transfusion or intravenous infusions of gamma globulin. Finally we decided to introduce the rTM (380U/kg/day) for 5 consecutive days, which enabled the patient to promptly recover from severe thrombocytopenia and DIC. She was successfully discharged on hospital day 12.

Discussion

We experienced a rare case of sepsis-induced DIC in a patient with ITP. The platelet levels in this case were fatally decreased, and immediate treatments should have been required. In Japan, clinical use of rTM was approved in 2009, and other successful examples of the use of rTM have been reported in cases such as transplantation-associated thrombotic microangiopathy or sinusoidal obstructive syndrome after hematopoietic stem cell transplantation [9, 10]. Choice of rTM in these cases would be due to the presence of severe hematologic problems.

Sepsis-induced DIC commonly develops due to suppression of the fibrinolytic system, and bleeding is less frequent than that in end-stage cancer or leukemia. However, in the present case, since the patient had suffered from ITP, severe thrombocytopenia was one of the most important problems and we needed to carry out a treatment plan without any bleeding complications. It was previously reported that the incidence of bleeding-related adverse events within the first 7 days were lower in a rTM-treated group than in a heparin-treated group [5]. We therefore selected rTM as the best treatment option, and excellent efficacy was achieved.

Recent studies have found that rTM possesses anti-inflammatory activity through both protein C-dependent and -independent pathways. The N-terminal domain

of TM binds to and inactivates high-mobility group box l (HMGB1) protein, which has recently been found to act as a potent proinflammatory cytokine during infection responses [11]. A growing number of studies have demonstrated HMGB1 to be a cytokine that can mediate inflammation and to be a potential therapeutic target in experimental models of sepsis [12, 13]. This rTM-induced anti-inflammatory effect might also have been favorable in our present case.

It is also clear that, in this case, Meropenem contributed to improving DIC. In addition, the lower risk of bleeding-related adverse events with anti-inflammatory activities of rTM were presumably profitable. Although our experience is limited to one patient, rTM may be an appropriate treatment therapeutic regimen for DIC with high hemorrhagic risk such as ITP.

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Figure legends

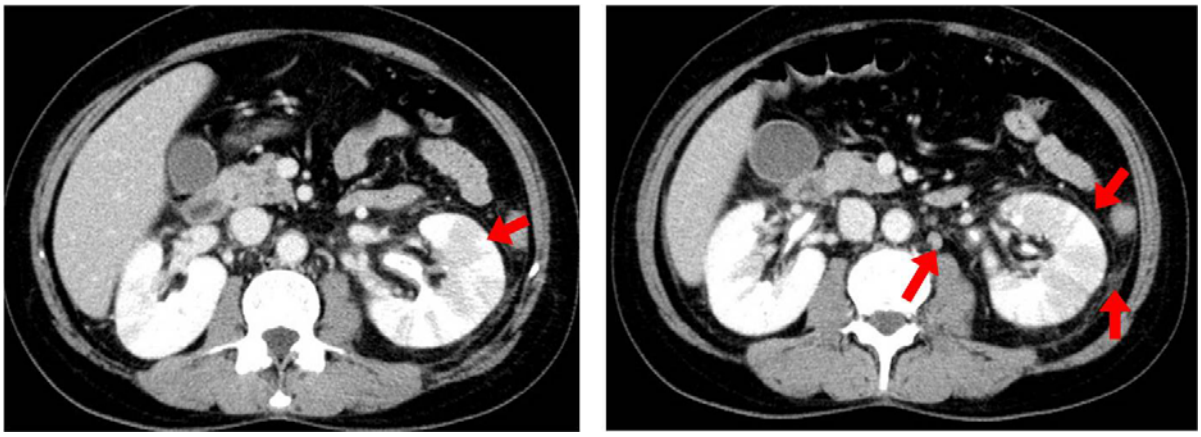

Figure 1 Abdominal CT scan showing renal enlargement, thickening of Gerota's fascia, bridging septa of the peri-nephric fat, and a wedge-shaped zone of poor enhancement consistent with pyelonephritis (arrows).

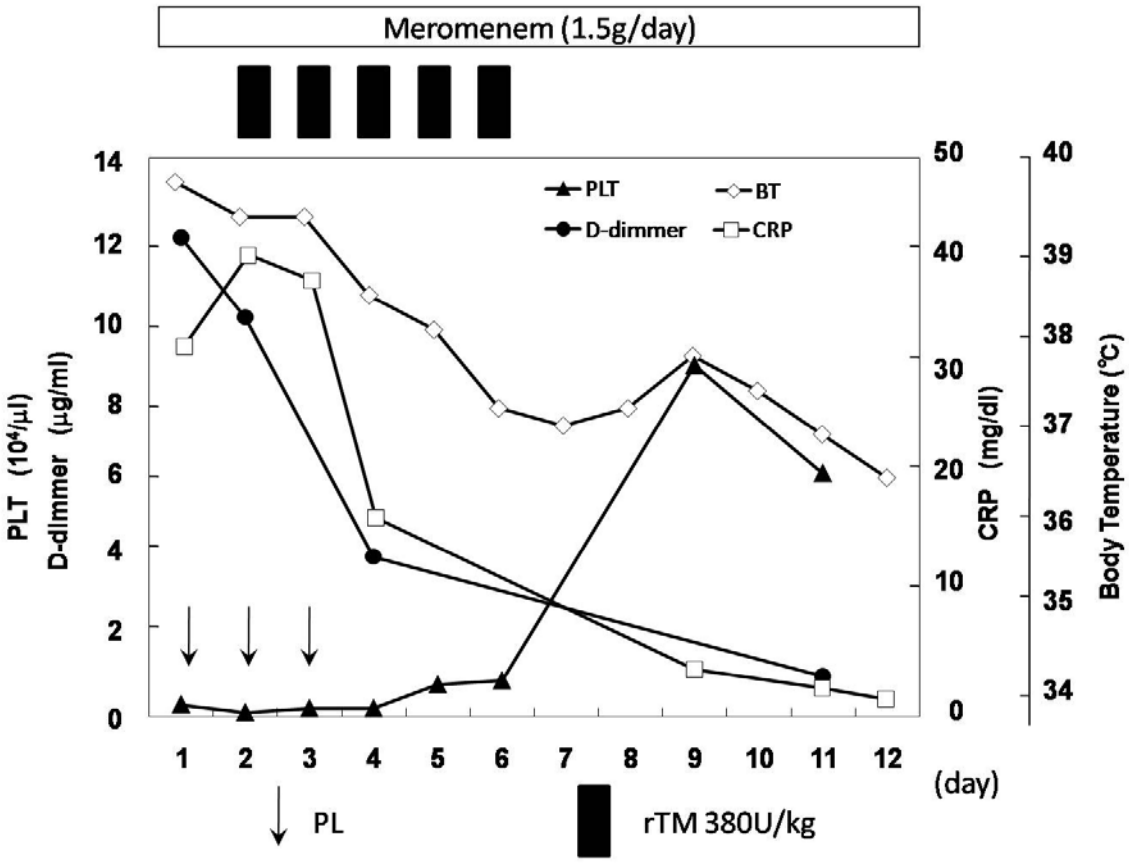

Figure 2 The clinical course of the present patient. The graphs display platelets, D-dimer, CRP, and body temperature, and the treatment interventions during the hospital course. (PL: platelet transfusion rTM: Recombinant human soluble thrombomodulin)