CASE REPORT

Effective Control of Relapsing Disseminated Intravascular Coagulation in a Patient with Decompensated Liver Cirrhosis by Recombinant Soluble Thrombomodulin

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Abstract

A 70-year-old Japanese man was hospitalized for expanding purpura and chronic disseminated intravascular coagulation (DIC) caused by decompensated liver cirrhosis. As there are no effective treatments for chronic DIC caused by liver cirrhosis, we decided to administer recombinant human soluble thrombomodulin (rhsTM) after he provided informed consent. The DIC was rapidly improved; however, the purpura and coagulopathy recurred after two months, and repeated rhsTM treatments were required. The rhsTM treatment sufficiently controlled the coagulopathy for two years, without any complications, including bleeding. This is the first report demonstrating that rhsTM can be administered safely and repeatedly to a patient with decompensated liver cirrhosis, and that it appears to be associated with a favorable outcome.

Key words: recombinant human soluble thrombomodulin, chronic disseminated intravascular coagulation, liver cirrhosis

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Introduction

Disseminated intravascular coagulation (DIC) is a life-threatening disease that can cause organ failure or bleeding. It is caused by various underlying conditions, such as infection, malignant tumors or leukemia, and treating these diseases is considered to be the cornerstone of DIC treatment (1). In contrast, chronic DIC is often associated with an aortic aneurysm or malignant tumors (2). Moreover, chronic DIC is a late-stage complication of decompensated cirrhosis; however, no effective methods of controlling or curing this type of chronic DIC have been reported, because liver dysfunction strongly affects the coagulation state of these patients.

Recombinant human soluble thrombomodulin (rhsTM) is a promising product, that can significantly improve DIC and alleviate bleeding symptoms, as compared with generic heparin therapy (3, 4). Recent reports demonstrated that rhsTM is effective for treating the DIC caused by infections, malignant tumors and leukemia; however, treatment of chronic DIC caused by decompensated liver cirrhosis using rhsTM has not been reported. We herein present the case of a patient with chronic DIC caused by decompensated liver cirrhosis who was successfully treated with rhsTM.

Case Report

A 70-year-old Japanese man with liver cirrhosis due to hepatitis C was hospitalized with a tendency for bleeding. Interferon treatment had not been previously administered because of thrombocytopenia (approximately 65×10³/L) caused by the liver cirrhosis. Since 2007, the patient’s hepatic edema had been treated with spironolactone. In 2008, gastroscopy revealed mild esophageal varices. Subsequently, in February 2009, expanding purpura appeared with no apparent causes, such as infection, trauma or skin infarction, and the patient was referred to our hospital. A physical ex-
right arm and some portions of both legs (Fig. 1). The laboratory investigation revealed that the purpura appeared on his entire body. The patient's platelet count had decreased to 31×10⁹/L, whereas the prothrombin time-international normalized ratio (PT-INR; 2.7) and levels of fibrin degradation products (FDP; 102.2 μg/mL) (Table). The diagnosis of DIC was made according to the criteria established by the Japanese Ministry of Health and Welfare (5), and the patient was hospitalized for treatment.

Because the patient had widespread and expanding purpura, anticoagulation therapies, including heparin or similar agents which could worsen his bleeding tendency, were not used. Considering its low potential to cause bleeding (4), we decided to administer rhsTM at a dose of 25,600 U/day (approximately 380 U/kg/day) for seven days. Within a week, the patient’s platelet count had recovered to 112×10⁹/L, his PT-INR to 1.35 and the FDP levels to 12.6 μg/mL (Fig. 2), thus indicating that this treatment modality was highly effective for his DIC. The purpura had gradually improved and exhibited near-complete resolution within two weeks, and the patient could be discharged. However, five weeks after discharge, another area of purpura appeared on his left lateral chest, and computed tomography (CT) revealed a hematoma within the muscle of the same side (Fig. 3). Moreover, his platelet count had decreased to 31×10⁹/L, whereas the PT-INR and FDP levels had increased to 2.24 and 93.3 μg/mL, respectively. Because these findings indicated a recurrence of DIC, he was administered rhsTM treatment again; continuing this treatment for a week significantly improved the hematologic abnormalities (Fig. 2) and the hematoma on the left lateral chest (Fig. 3).

There was no evidence of any of the major causes of DIC, including infection, malignancy and trauma. Laboratory data revealed no deficiency of antithrombin III (AT III) or protein C activity, and the serum anticardiolipin antibody level was 3.0 IU/mL (normal 0.0-9.9 IU/mL) (Table). In addition, the CT image did not show any portal thrombosis or aortic aneurysms. Consequently, liver cirrhosis was diagnosed to be the cause of the chronic DIC.

Six months after the second discharge from the hospital, the purpura and coagulopathy gradually developed again, necessitating another round of treatment for the DIC. The patient was hospitalized and treated with rhsTM for one
Table. Laboratory Data of First Admission

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<tr>
<td>WBC</td>
<td>4190 /μL</td>
<td>T.P.</td>
<td>6.7 g/dL</td>
<td>HBs-Ag</td>
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<td>RBC</td>
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<td>Alb</td>
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<tr>
<td>Ht</td>
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<td>D.Bil</td>
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<tr>
<td>PLT</td>
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<td>AST</td>
<td>69 IU/L</td>
<td>PIVKA-II</td>
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<td></td>
<td></td>
<td>ALT</td>
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<td>PIVKA-II</td>
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<td>PT%</td>
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<td>ALP</td>
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<tr>
<td>PT-INR</td>
<td>2.7</td>
<td>LDH</td>
<td>397 IU/L</td>
<td>β₂GPI</td>
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<td>APTT</td>
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<td>γGTP</td>
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<tr>
<td>Fibrinogen</td>
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<td>ChE</td>
<td>84 IU/L</td>
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<td>FDP</td>
<td>102.2 μg/mL</td>
<td>BUN</td>
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<tr>
<td>AT-III</td>
<td>53 %</td>
<td>Cr</td>
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<td>PCA</td>
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<tr>
<td>PIC</td>
<td>6.1 μg/mL</td>
<td>Cl</td>
<td>105 mEq/L</td>
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</table>

RBC, red blood cell count; Ht, hematocrit; PLT, platelet count; PT%, prothrombin time; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; FDP, fibrin degradation products; AT-III antithrombin III activity; PCA, protein C activity; TAT, thrombin antithrombin complex; PIC, plasmin α₂-plasmin inhibitor complex; T.P, total protein; Alb, Albumin; T. Bil, total bilirubin; D. Bil, direct bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; γGTP, γ-glutamyl transpeptidase; ChE, cholinesterase; BUN, blood urea nitrogen; Cr, creatinine; HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; AFP, α-fetoprotein; PIVKA-II, protein induced by Vitamin K absence or antagonists-II; aCL, antiphospholipid antibody; β₂GPI, anti-β₂ glycoprotein I.

week. Following a brief remission of a couple of weeks, the patient experienced another purpura relapse along with a decrease in the platelet count (45x10^9/L) and an increase in the PT-INR and FDP levels (2.05 and 78.8 μg/mL, respectively), which necessitated treatment for the DIC. We attempted outpatient maintenance therapy for coagulopathy using danaparoid (1,250 U/day), but this resulted in the worsening of the hematological parameters for four months. Because of the gradual expansion of purpuric lesions, discontinuation of danaparoid and the administration of rhsTM were necessary.

The patient eventually died of hepatic failure. However, for two years from the onset of his first bleeding episode, he received 11 courses of rhsTM, which were highly effective and did not worsen bleeding tendency.

Discussion

We herein described the treatment of a patient with liver cirrhosis who had recurrent DIC using rhsTM. To the best of our knowledge, this is the first case in which rhsTM was repeatedly administered, and which resulted in remarkable improvement of the chronic DIC caused by severe liver cirrhosis. Coagulopathy frequently occurs in patients with chronic liver disease, particularly in those with end-stage liver cirrhosis; this can be attributed to the fragile nature of the coagulation system, which results from the reduction of procoagulants and anticoagulants (6). As the Child-Pugh score of patients with cirrhosis becomes greater, the levels of anticoagulants such as protein C decrease, and those of procoagulants, such as factor VIII, increase (7, 8). However, recent studies have revealed that increased thrombin generation contributes to the coagulopathy in patients with chronic liver disease (7, 9). Thrombomodulin is a protein that activates protein C, and the activated protein C inhibits the activated forms of factor VIII, and this consequently inhibits the thrombin formation (10). Patients with liver cirrhosis usually demonstrate prolonged PT-INR and decreased AT III. The anticoagulant effect of rhsTM is not influenced by the plasma level of AT III (11). This patient showed a prolonged PT-INR and decreased AT III (approximately 50% of normal), but rhsTM was effective without requiring the administration of fresh-frozen plasma and AT III concentrate. The plasma level of TM is sometimes increased due to damage to the sinusoidal endothelial cells in patients with liver cirrhosis. However, this increased plasma level of TM has low activity. The activity of TM on endothelial cells is decreased due to dysfunction of endothelial cells in patients with liver cirrhosis. Therefore, it is reasonable to administer rhsTM, which has the same activity as native TM, to patients with liver cirrhosis. Because the plasma activity of AT III is usually decreased in patients with liver cirrhosis and liver failure, treatment with anticoagulant agents such as heparin, whose effect is dependent on AT III, may cause a further decrease in the plasma activity of AT III and worsen the DIC (12). Therefore, anticoagulant agents such as rhsTM and recombinant tissue factor pathway inhibitor (TFPI), whose effects are independent of the activity of AT III, should be used to treat patients with DIC caused by liver cirrhosis and failure. Of note, only minimal expressions of TM and TFPI are observed in hepatic sinusoidal endothelial cells compared with those in endothelial cells of other
organs (13). The expression levels of TM and TFPI increase due to the capillarization in the hepatic sinusoid in the cirrhotic liver. However, these changes in expression in the cirrhotic liver are smaller than those that occur in other organs (14). In addition, rhsTM has anti-inflammatory activity via the activation of protein C, which inhibits high mobility group box 1 (15) and lipopolysaccharide [LPS (16)]. The plasma level of LPS has been reported to increase in patients with liver cirrhosis (17). Therefore, it is reasonable to use rhsTM to treat DIC caused by liver cirrhosis. The Child-Pugh score of our patient before the appearance of the initial bleeding symptoms was grade B; however, after the purpura relapse, it became grade C because of the worsening of his bilirubin or albumin levels due to the deterioration of his hepatic functional reserve. However, repeated treatments with rhsTM were effective, and antibodies against rhsTM were not detected, indicating that, regardless of the Child-Pugh score, rhsTM can be an effective and safe treatment for DIC in patients with liver cirrhosis. The anticoagulant effect of rhsTM is influenced by the plasma level of protein C (being especially effective when the level is >10% of the normal level) (11). The plasma level of protein C in this patient decreased to 19-32% before the initiation of the administration of rhsTM, and the administration of rhsTM improved the DIC without the need for additional administration of fresh-frozen plasma. In patients with severe renal failure or hemodialysis due to renal excretion of rhsTM, it is advisable to decrease the dose administered by one-third. In this case, a full dose of rhsTM was regularly administered, because there was no evidence of renal dysfunction due to hepatorenal syndrome or multiple organ failure due to DIC before or during the administration of rhsTM.

In a phase III clinical trial, no pharmacokinetic difference in rhsTM was observed in patients with hepatic dysfunction (4). However, one should be careful while administering rhsTM to these patients, because their general condition could easily worsen. We administered 11 courses of rhsTM (85 days) to our patient under sufficient informed consent, and no side effects such as worsening of the bleeding, hematuria or proteinuria were observed.

Taken together, our case findings suggest that rhsTM can be repeatedly and safely administered to patients with liver cirrhosis. Repeated administration of rhsTM did not exacerbate the bleeding symptoms, nor did it negatively affect the renal functions or cause other organ dysfunctions. These may be considered as positive prognostic factors for a patient. Therefore, it is especially promising that during the treatment of DIC using rhsTM, we could control the bleeding symptoms in a patient with severely reduced hepatic reserve for two years without any apparent side effects.

Our case suggests that rhsTM treatment can sufficiently control the chronic DIC caused by coagulopathy in patients with end-stage liver cirrhosis, and that it may also be able to serve as a bridge to subsequent liver transplantation. However, further studies in a large number of patients with cirrhosis are required.

The authors state that they have no Conflict of Interest (COI).

References
1. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diag-


