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Case Report

Use of Recombinant Human Soluble Thrombomodulin in a Patient with Disseminated Intravascular Coagulation Associated with Abdominal Aortic Aneurysm: A Case Report

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We herein present a case involving an 86-year-old man with abdominal aortic aneurysm complicated by symptomatic disseminated intravascular coagulation (DIC). The patient received preoperative treatment for DIC using recombinant human soluble thrombomodulin (rTM) followed by open surgical repair of the aneurysm. The patient's coagulopathy cleared quickly after the start of rTM, and the intraoperative and postoperative course went smoothly. The patient was followed without anticoagulant medication, and there was no recurrence of DIC during 14 months of follow-up. The preoperative administration of rTM can be a useful choice to assist safe treatment of aortic aneurysm complicated by aneurysm-related DIC.

Keywords: abdominal aortic aneurysm, disseminated intravascular coagulation, thrombomodulin

Introduction

The definitive treatment of disseminated intravascular coagulation (DIC) associated with an aortic aneurysm is surgical repair of the aneurysm. However, surgical intervention in patients with DIC is extremely invasive and carries a high risk of fatal consequences. Therefore, for some patients, supportive treatment is thought to help their coagulopathy. We herein provide the case of a patient with an abdominal aortic aneurysm (AAA) exacerbated by symptomatic DIC, in which preoperative therapy of DIC using recombinant human soluble thrombomodulin (rTM) facilitated the safe open surgical repair of the aneurysm.

Case Report

An 86-year-old man presented with hematuria and upper limb purpura. He had been diagnosed with an AAA 4 years prior and followed up with imaging examinations every 6–12 months. The patient was a current smoker, and his relevant medical history included hypertension, dyslipidemia, and previous myocardial infarction. Laboratory results (**Table 1**) upon admission showed a wide range of abnormalities, including a decreased circulating fibrinogen level (96 mg/dL) with an increased fibrin/fibrinogen degradation products (FDP) level (232 μg/mL). The diagnosis of DIC was made according to the diagnostic criteria for DIC from the Japanese Society on Thrombosis and Hemostasis[1] (seven points). Contrast-enhanced computed tomography with preventive intravenous hydration detected a 55 mm AAA with diffuse aortic atherosclerosis and irregular mural thrombus but no other abnormalities (**Figs. 1A** and **1B**). In the absence of other obvious reasons of DIC, we hypothesized that the DIC in this patient was associated with AAA. After discussing the potential treatment options, we began treating DIC by intravenous administration of 380 units/kg/day of rTM (Recomodulin, Asahi Kasei Pharma, Japan). As the patient was discovered to have lower levels of factor XIII (19%), the intravenous administration of factor XIII concentrate (Fibrogammin P IV Injection, CSL Behring K.K., Tokyo, Japan) was also added (**Fig. 2**). His clinical symptoms of coagulopathy resolved shortly following the start of rTM. On the sixth day of treatment, the DIC score increased to two points,

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Table 1 Serial changes in laboratory findings of the patient

Valuables	Reference range	On admission	Treatment day 6	One month after surgery
White blood cell count (/μL)	3300–8600	7430	6760	5820
Hemoglobin (g/dL)	13.5–17.0	8.5	8.6	10.8
Platelet count (10^4/μL)	15.0–35.0	10.8	18.3	20.6
Serum creatinine (mg/dL)	0.65–1.07	2.62	2.53	1.45
Lactate dehydrogenase (U/L)	124–222	219	153	326
C-reactive protein (mg/dL)	<0.15	0.09	0.14	1.72
Prothrombin time (seconds)	11.0–13.0	13.0	12.0	11.9
Fibrinogen (mg/dL)	200–400	96	292	400
FDP (μg/mL)	<5.0	232	23.1	32.0
D-dimer (μg/mL)	<1.0	76.3	NA	NA
Antithrombin III (%)	80–130	92	89	NA
TAT (ng/mL)	<4.0	91.6	5.9	NA
PIC (μg/mL)	<0.8	13.9	1.6	NA
Factor XIII (%)	70–140	19	148	NA

FDP: fibrin/fibrinogen degradation products; TAT: thrombin–antithrombin III complex; PIC: plasmin–α2 plasmin inhibitor complex; NA: not available

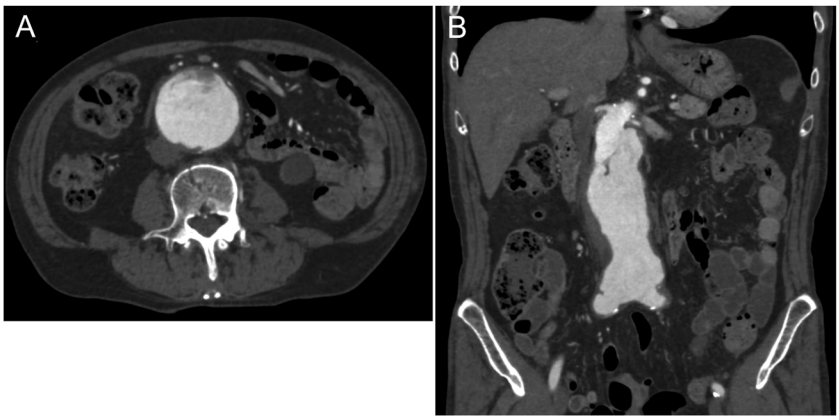

Fig. 1 (**A**) Axial and (**B**) coronal computed tomography images showing an abdominal aortic aneurysm with irregular mural thrombus.

which indicated recovery from DIC. A laboratory investigation at this point revealed a circulating fibrinogen level of 292 mg/dL and an FDP level of 23.1 μg/mL. Seven days following admission, the patient received open surgical repair of the AAA. Despite the patient's old age, we chose open repair because the patient had unfavorable infrarenal neck anatomy for endovascular treatment. The intraoperative findings after longitudinal aortotomy of the aneurysm sac showed diffuse atherosclerotic changes in the aneurysm wall and infrarenal neck area. The patient received 8 units of red blood cells and 12 units of fresh frozen plasma during the procedure before coagulopathy developed, based on the amount of blood loss and intraoperative laboratory results. The intraoperative estimated blood loss was 1325 mL, and hemostasis was successfully achieved. There were no clinical or laboratory signs suggestive of coagulopathy after surgery. The postoperative course was uneventful, and the patient was discharged on the 21st postoperative day. He was monitored without anticoagulant treatment. There was no recurrence of DIC at the 14-month follow-up examination.

Discussion

DIC linked to aortic aneurysm was first published by Fine et al. in 1967.[2] A clinically overt bleeding tendency due to aneurysm-related DIC is a rare but difficult entity, occurring in about 0.5%–1% of patients with aortic aneurysm.[3]

The cornerstone of treatment for DIC is management of the underlying condition. Therefore, the effective treatment of DIC associated with an aortic aneurysm is surgical correction of the aneurysm. However, surgical treatment in patients with DIC is highly intrusive and carries a substantial risk of fatal hemorrhage and mortality. Endovascular aneurysm repair has become the less

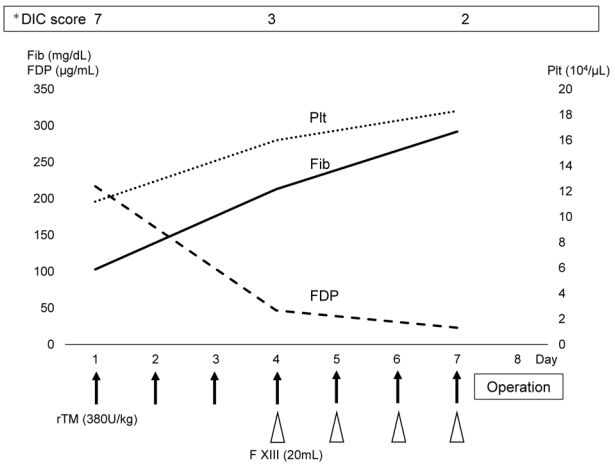

Fig. 2 Preoperative treatment course and changes in DIC related data.
DIC: disseminated intravascular coagulation; Fib: fibrinogen; FDP: fibrin/fibrinogen degradation products; Plt: platelet count; rTM: recombinant human soluble thrombomodulin; F XIII: factor XIII concentrate
*The diagnostic criteria for DIC from the Japanese Society on Thrombosis and Hemostasis.

invasive alternative to open repair, particularly in elderly patients with concurrent conditions, but it is not always the best choice for individuals with DIC. The cause is that DIC might not be resolved even after the successful exclusion of an aneurysm.[4] Moreover, thrombus development or postoperative endoleak can worsen the preexisting DIC.[5] Therefore, in certain patients, supportive treatment is thought to manage the coagulopathy.

Supportive treatment of DIC includes the administration of anticoagulants such as heparin or direct oral anticoagulants with or without antifibrinolytics and replacement therapy with blood components.[6] To date, there is little evidence to support their use.

In the present case, we used rTM to manage DIC. rTM comprises the active extracellular domain of thrombomodulin. Thrombomodulin is an integral membrane protein expressed on the surface of endothelial cells, which binds to thrombin to form a complex that activates protein C. Activated protein C controls thrombin production through the inactivation of factor Va and factor VIIIa. Additionally, thrombomodulin itself inactivates the coagulant activity of thrombin.[6]

rTM is believed to be more successful at controlling DIC and associated with a decreased risk of bleeding problems in comparison with heparin, the anticoagulant most frequently used in the treatment of DIC.[7]

There have been three case reports documenting the management of aneurysm-related DIC with the preoperative use of rTM and subsequent aneurysm repair in the pertinent English literature.[4,8,9]

Tanigawa et al.[4] described the preoperative single administration of rTM in a patient with symptomatic DIC associated with thoracic aortic aneurysm. They stated that the patient's bleeding tendency and DIC score recovered within a week, but the patient's condition was hampered by postoperative bleeding issues. Hoshina et al. reported the preoperative use of rTM in combination with nafamostat mesilate[8] or gabexate mesilate[9] in patients with subclinical DIC associated with AAA. The successive open surgical repairs performed in these patients were uneventful.

It is interesting that our patient had not only DIC diagnosed by the scoring system but also had a clinically overt bleeding tendency, both of which significantly improved soon after the start of rTM. In addition, we measured factor XIII and administered factor XIII concentrate—despite the fact that the patient's clinical symptoms of coagulopathy disappeared following the start of rTM—because surgical treatment was planned. To our knowledge, this is the first report describing combination therapy with rTM and factor XIII concentrate for aneurysm-related DIC. An investigation for factor XIII may be helpful for DIC patients exhibiting indications of clinical bleeding.[10]

Although the use of rTM has not been proven to lower all-cause mortality in patients with DIC,[7] its rapid effect on DIC, as reported in the current case, is advantageous for patients who need interventional treatment for the underlying cause of DIC. There is still a need for large clinical studies to verify the effectiveness and safety of rTM in patients with DIC related to aortic aneurysm.

Conclusion

The preoperative administration of rTM can be a useful option for easing the safe surgical treatment of an aortic aneurysm complicated by aneurysm-related DIC.

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None.

Statement of Patient Consent

The patient provided written, explicit approval for the publication of this case report and any related images.

Disclosure Statement

All authors have no competing interest.

Author Contributions

Study conception: all authors
Data collection: YY, MO

Writing: YY, HU
Critical review and revision: all authors
Final approval of the article: all authors
Accountability for all aspects of the work: all authors

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