Kasabach-Merritt syndrome associated with giant liver hemangioma: the effect of combined therapy with danaparoid sodium and tranexamic acid

In patients with Kasabach-Merritt syndrome (KMS), local activation of coagulation commonly results in disseminated intravascular coagulation (DIC). Progress of DIC is associated with 30-40% mortality as a result of uncontrollable hemorrhage. A 39-year-old woman with an enlarging giant liver hemangioma was diagnosed as having KMS with DIC. To control the hemorrhagic diathesis, we commenced combination therapy for DIC with danaparoid (1,250 U×2/day, intravenously (IV)) and tranexamic acid (0.5 g×3/day, perorally (PO)). Rapid improvement of bleeding tendency and coagulopathy occurred in response to this treatment – that is, DIC is controlled without removing giant hemangioma. The therapy did not restrict the behavior of the patient by continuous drip and angiography could be performed without bleeding. Such therapy may be beneficial in chronic DIC with activation of fibrinolysis.

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Kasabach-Merritt syndrome (KMS) was first reported in 1940 in a neonate as the association of thrombocytopenic purpura and rapidly enlarging capillary hemangioma.[1] Not all hemangiomas in this syndrome are cutaneous, and those associated with a more severe phenotype are often visceral. The incidence of hepatic hemangioma in KMS is reported to be about 2%.[2] In patients with this syndrome, local activation of coagulation commonly results in disseminated intravascular coagulation (DIC).[3,4] The incidence of clinically overt DIC is 25% among patients with giant hemangioma.[1,3] However, neither the site nor the size of the hemangioma appears to reliably predict the subsequent development of KMS, which has been associated with 30-40% mortality as a result of uncontrollable hemorrhage.[5]

This report shows the case who have chronic DIC associated with KMS and the management with combination of danaparoid and antifibrinolytics.

Case report

A 39-year-old woman was admitted to our hospital in September 2001 due to abdominal swelling. She had previously undergone surgical ligation of the hepatic artery for giant liver hemangioma in 1994. Although this had resulted in temporary remission, abdominal enlargement had gradually recurred. Physical examination on admission revealed several ecchymoses on the upper extremities and hepatomegaly. Coagulation studies demonstrated the following: platelet count, 90×10^9/L (normal range: 150-300×10^9/L); prothrombin time (PT), 12.5 sec (normal range: 9.4-11.1 sec); activated partial thromboplastin time (APTT), 32.6 sec (normal range: 27.5-42.1 sec); fibrinogen (Fbg), 100 mg/dl (normal range: 206-369 mg/dl); fibrin/fibrinogen degradation product (FDP), 37.8 μg/mL (normal range: <5 μg/mL); and D-dimer, 21.7 μg/mL (normal range: <2.5 μg/mL). In addition, thrombin-antithrombin complex (TAT) level was 29.9 μg/L (normal range: <3.0 μg/L), plasmin-alpha 2 antiplasmin complex (PIC) level was 4.4 μg/mL (normal range: < 0.8 μg/mL), antithrombin (AT) activity was 94% (normal range: 70-130%) and alpha 2 antiplasmin activity was 66% (normal range: 70-130%). As DIC with activation of fibrinolysis was evident from these findings, the patient was diagnosed as having KMS with enlarging giant liver hemangioma (Figure 1).

Figure 1. Enhanced computed tomography. There exists a giant hemangioma (270 x 260 x 165 mm) which replaces the right lobe and is enhanced from outline indistinctly.

Consumption of clotting factors and platelets progressed gradually after admission; however, the patient declined blood transfusion on religious grounds. In order to safely conduct angiography and control the hemorrhagic diathesis, we commenced treatment for DIC using danaparoid (1,250 U×2/day, IV) and tranexamic acid (0.5 g×3/day, PO) combination therapy. Rapid improvement of bleeding tendency and coagulation abnormalities occurred in response to this treatment, making it possible not only to control the hemorrhagic diathesis but also to conduct angiography without excessive bleeding requiring blood transfusion. From the findings of angiography, hepatic irradiation was determined to be the most appropriate treatment. After irradiation, tumor growth was inhibited and DIC was controlled. The patient was discharged without bleeding or coagulopathy in January 2002. The clinical course is shown in Figure 2.

Discussion

DIC is characterized by the widespread activation of coagulation, which results in the intravascular formation of fibrin. Although it is a severe clinical condition that involves considerable activation of both coagulation and fibrinolysis in the circulating blood, the degree to which the fibrinolytic system is activated in DIC varies according to the underlying disease.[3,6,7] In this case of DIC associated with KMS, the data of PIC (above 4 μg/mL) support the existence of activation of fibrinolysis.[7]

The cornerstone of the management of DIC is treatment of the underlying disorder. The replacement of consumed clotting factors with fresh-frozen plasma or platelet concentrate is only indicated when to prevent bleeding.[3] It is known that KMS is a cause of DIC and is reported that a strong local activation and local consumption coagulopathy in hemangioma.[4] The elimination of tumor is needed to control of DIC with KMS. However, no treatment modality has been established as consistently effective.[5] Radiotherapy is rarely considered as first-line therapy because of its known late effects on tumor growth and secondary malignancies. However, it is non-invasive and can be used in extremis as a last

Figure 2. Clinical course. The patient showed bleeding tendency (mainly purpura) because of consumption of clotting factors by DIC. In this case, there was the mild activation of fibrinolysis because the level of PIC was elevated above 4.0 μg/mL accompanying elevation of TAT. To determine the best treatment for the giant hemangioma, we needed to examine the angiogram. However, we could not immediately perform angiography because of bleeding tendency and coagulation abnormalities. Moreover, we were never able to supply the coagulation factors since this patient had requested no blood transfusion for her religion. To control DIC, we selected combined therapy with danaparoid and tranexamic acid. Rapid improvement of DIC occurred in response to this treatment, although about 20 days had passed until increase of fibrinogen level and decrease of fibrinolytic activity to perform safely angiography (9/26-10/24). The continuous treatment of DIC was needed after angiography because of the elevation of FDP and TAT, the existence of thrombin generation (10/25-12/17). From the findings of angiography, hepatic irradiation (total 30 Gy) was determined to be most appropriate treatment for this patient (11/16-11/29). With the time of December 17, the continuous treatment of DIC was needed after liver irradiation because of the elevation of TAT and the existence of clinical symptoms. It might be too early to stop the treatment for DIC in this respect, however, it was needed to stop the treatment for DIC in determining her discharge (12/17-). When the treatment for DIC was stopped, DIC was transiently worsed (12/17-12/28). From this, the combined therapy with danaparoid and tranexamic acid is effective for DIC. The bleeding tendency parallels the degree to fibrinolytic marker. As the effect of irradiation to hemangioma was shown slowly, the state of DIC might be prolonged (12/28-). As a result, tumor growth was inhibited and DIC was finally controlled without bleeding (1/9-). It seems natural to control DIC by treatment of the underlying disease (12/28-1/9). Moreover, she had no bleeding at the discharge and little recurrence of DIC (1/9-10/2).

resort and has occasionally been used as first-line therapy for small inaccessible lesions.[5,8]

It is important to suppress the activated coagulation factor for control of DIC. The oral anticoagulant that can inhibit the activated coagulation factor is not yet commercially available. Warfarin is the only oral anticoagulant at the present time. There were some previous studies that warfarin treatment in chronic DIC associated with aneurysm was effective.[9] Although we discussed in possible warfarin treatment concerning this patient, we had rejected warfarin treatment by two reasons. One reason is that its action is only inhibition of production of vitamin K dependent coagulation factor without suppression of activated coagulation factors, and another is that this patient had mild liver dysfunction due to the giant hemangioma. However, it might be needed adequate discussion whether we had to select warfarin treatment for this chronic DIC.

At present, heparin is commonly used in patients with DIC, being administered in relatively low dose.[3] Low dose heparin has been also used in patients with KMS, however, evidence for its benefit has never been established. As KMS and large aortic aneurysm may both result in local activation of coagulation, coagulopathy in each condition is considered to be similar. Cummins *et al.* reported that long-term treatment with low molecular weight heparin (LMWH) could provide good symptomatic control of chronic DIC associated with abdominal aortic aneurysm.[10] We therefore hypothesized that danaparoid, a kind of heparinoid, might also be able to control DIC occurring in KMS. Danaparoid is heparinoid which is distinct from unfractionated heparin (UFH) and LMWH.[11,12,13] Danaparoid has a longer half life of 20 hours and has a high anti-Xa/anti-IIa ratio (>20 as compared to 1 for heparin and 2 for LMWH). Moreover, as danaparoid also inhibits platelet adherence to a much lesser extent than UFH, its effect on bleeding is less marked[14] In Japan, one double-blind clinical trial in the patients with DIC has shown danaparoid to be equivalent to UFH.[12] In the present patient, danaparoid was selected for the reason, which could inject by bolus and had little risk of hemorrhagic side effects compared with other therapy.

Tranexamic acid has been proposed as a hemostatic agent in many clinical conditions characterized by excessive bleeding, but the use of this agent in patients with DIC is generally not recommended.[3] Moreover, Kario et al. described that monitoring of the TAT/PIC ratio may contribute to decisions regarding the institution and performance of combination therapy for DIC using anticoagulant and antifibrinolytic agents.[15] With regard to this patient, we decide to use the anticoagulant since the level of TAT is elevated. Rodeghiero *et al.* reported 268 consecutive patients with acute promyelocytic leukemia.[16] Patients were separated into three groups (treated with heparin, with antifibrinolytics, and with supportive therapy alone), and no significant difference was detected between these three groups in terms of overall incidence of early hemmorrhagic death.[16] Recently, in a tissue factor induced rat DIC model, we demonstrated that tranexamic acid suppressed the elevation in D-dimer levels and it increased organ dysfunction.[17] It is considered that inhibition of fibrinolysis using tranexamic acid might cause thrombin formation. On the other hand, a case was reported of a patient with aneurysm in which hemorrhage stopped abruptly upon the administration of tranexamic acid.[18] Moreover, tranexamic acid has also been reported to be efficacious in the treatment of severe KMS in the newborn.[19] In the present case, the bleeding tendency improved during the combination therapy described above. When this therapy was transiently discontinued, coagulopathy deteriorated. In this case, from the viewpoint of the characteristics of DIC, danaparoid was useful for inhibiting the activation of coagulation and preventing thrombotic complications. In contrast, tranexamic acid was useful for controlling hemorrhage.

In summary, combined therapy with danaparoid (IV) and tranexamic acid (PO) enabled control of bleeding tendency, and angiography could be performed without limitations in the present patient. Such therapy may be beneficial in chronic DIC with activation of fibrinolysis, in which control of bleeding is required without restricting the behavior of patients by continuous drip.

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