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Abdominal Compartment Syndrome in a Patient with Hemophilia A with a High Titer Inhibitor after a Minor Trauma

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Abstract

Abdominal compartment syndrome (ACS) is a life-threatening condition which can occur in patients with hemophilia although they have trivial traumas. Hemostatic control for bleeding episodes in hemophilia patients with inhibitors is difficult particularly when the availability of bypassing agents, recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (APCC), is constrained. Plasma exchange with continuous infusion of factor concentrate has been reported as a life-saving intervention in these patients. We reported a teenager with severe hemophilia A and a high-titer inhibitor who underwent two surgeries for ACS which developed after a minor trauma. Computerized tomography angiogram (CTA) of abdomen revealed a large pelvic hematoma and a bleeding from the sigmoidal artery. He underwent an abdominal angiography followed by the first surgery to relieve the ACS, and the second surgery for abdominal closure. The patients received plasma exchange with cryo-removed plasma peri-operatively. High-dose factor VIII (FVIII) concentrate (100 U/kg) was started after plasma exchange followed by continuous infusion at the rate 14 units/kg/hour for 7 days. rFVIIa and APCC concomitant with tranexamic acid were used for breakthrough bleeding. He received six times of plasma exchange, three doses of rFVIIa and five doses of APCC. Bleeding was successfully stopped and the titers of inhibitor decreased from the maximum of 4,400 BU to 3,680 BU. Plasma exchange and continuous FVIII infusion can be considered as an option for life-threatening hemorrhage in hemophilia patients with high-titer inhibitors in the countries where an access to bypassing agents is limited.

Keywords: Hemophilia A; Inhibitor; Plasma exchange; Abdominal compartment syndrome; Continuous infusion

Introduction

Factor inhibitor is a serious complication of hemophilia patients. The incidence of factor VIII (FVIII) inhibitors in patients with hemophilia A is approximately 20-30%, while the incidence of factor IX (FIX) inhibitors is much lower as 4-6% in patients with hemophilia B [1-3]. Hemostatic management in life-threatening bleeding episodes in hemophilia patients with inhibitors is challenging, especially in the high-responders who are able to develop high-titer inhibitors more than 5 Bethesda units (BU) within a short period after receiving factor concentrate [1,2]. Although bypassing agents, recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (APCC), are standard treatment of bleeding episodes in these patients, their use is limited in countries with resource constraint. Plasma exchange with continuous infusion has been reported as an option for life-saving procedures during a surgery in hemophilia patients with inhibitors [4-8].

Intra-abdominal hypertension (IAH) and the most severe form, abdominal compartment syndrome (ACS), are critical conditions which are defined by high intra-abdominal pressure (IAP) without and with new organ dysfunction, respectively. These conditions can be found in patients who have abdominal hematomas [9] which increase abdominal content. They can be found in patients with severe bleeding disorders, such as severe hemophilia, who may only have a trivial injury. Unless patients are treated immediately and appropriately, they can suffer from multiple organ dysfunctions and have detrimental outcomes or even succumb from these conditions [10]. We herein reported a case of a patient with hemophilia A and a high titer inhibitor who underwent an abdominal angiography and surgeries due to ACS. The patients received plasma exchange with cryo-removed plasma peri- and post-operatively in combination with continuous FVIII concentrate. rFVIIa and APCC concomitant with antifibrinolytic agent were used for breakthrough hemorrhage.

Case Report

A 14-year-old male teenager who had been diagnosed with severe hemophilia A with high-titer inhibitor presented with abdominal pain and hematuria after a minor trauma. His FVIII gene mutation revealed inversion of intron 22 type I. His previous maximum FVIII inhibitor was 1,200 BU. After the diagnosis of FVIII inhibitor, he received on-demand treatment with prothrombin complex concentrate (PCC) for his bleeding episodes and his activities were restricted. He was not on immune tolerance induction (ITI) as the limited amount of available FVIII concentrate. However, the last FVIII inhibitor prior to the admission was 2 BU. Although APCC is more effective than PCC for bleeding control in hemophilia patients with inhibitors [11], he was prescribed PCC (Profilnine®) for early treatment of acute hemarthrosis regarding the availability of PCC and the non-inferiority of PCC to APCC for treatment of acute hemarthrosis shown by the study of

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Lusher et al. [12]. However, he had not had any bleeding episodes for two years since the last admission.

Two weeks prior to the admission, he had a minor blunt trauma after falling while he was walking. He also had swelling of right wrist. He received PCC 500 International Units (IU) at a local hospital and did not have any abnormal symptoms after treatment. Twelve days later, he suddenly had an abdominal pain and hematuria. At the local hospital, his vital signs were stable but he was markedly pale and had signs of peritonitis. CT of abdomen revealed a large hematoma in midpelvic cavity and lower abdomen. The laboratory investigation results were as follows; low hematocrit (Hct) at 13.5% and prolonged activated partial thromboplastin time (APTT) at 73.9 sec but normal platelet count (Plt) at 310,000/mcL and prothrombin time (PT) at 13.1 sec with international normalized ratio (INR) at 1.25. Before referral, he received PCC 2,000 IU, fresh frozen plasma (FFP) 3 units (U), red blood cell concentrate (RBC) 2 U, vitamin K, tranexamic acid and omeprazole. At first admission at our institute, his vital signs were as follows; high blood pressure (BP) at 156/92 mmHg, increased pulse rate at 112/min but full intensity, rapid respiratory rate at 32/min and normal temperature at 37.6°C. His body weight was 56 kg. Physical examination showed marked distension of abdomen with an abdominal circumference of 90.5 cm. There was no ecchymosis on his abdominal wall. He had generalized tenderness of the abdomen with involuntary guarding. An ill-defined mass at periumbilical area was palpable. He received rFVIIa (Novoseven®) 4,800 mcg (86 mcg/kg) prior to the further investigations as he had a history of FVIII inhibitor and the result of FVIII inhibitor was not reported on the day of procedure.

His laboratory investigation results were as follows; hemoglobin (Hb) 8.9 g/dL, Plt 157,000/mcL, PT 11.2 sec (9.4-14.1), INR 1.05, APTT 59.3 sec (24.1-34.1) and fibrinogen 317 mg/dL. Microscopic hematuria was found (30-50 red blood cells/high power fields). FVIII inhibitor on the first day of admission which came later was less than 0.1 BU. He subsequently received one dose of tranexamic acid 500 mg, 12 bags of cryoprecipitate, 2 U of RBC and 5,000 IU (89 IU/kg) of APCC (FEIBA®) at 3 hours after rFVIIa infusion, before right femoral venous catheter insertion. The bypassing agent was changed to APCC due to the limited available dose of rFVIIa. The CT angiogram of abdomen revealed an active extravasation from sigmoidal branch of inferior mesenteric artery (Figure 1) and a massive hematoma 11 × 12.5 × 17 cm in diameter at pelvic cavity but no intraperitoneal bleeding. The abdominal angiography was done at 20 hours after admission to search for the bleeding site and stop the bleeding. Before intervention, he received rFVIIa 4,800 mcg, cryoprecipitate 10 bags to provide fibrinogen and platelet concentrate (PC) 6 U for bleeding control prior to the procedure. The finding showed no evidence of pseudoaneurysm or extravasation of bilateral iliac arteries and inferior mesenteric artery. The embolization was not pursued as the site of active bleeding was not found.

Because of marked distension of the abdomen, IAP was monitored which showed the maximum pressure of 27.2 mmHg (normal <20 mmHg). He was treated by supportive care by nasogastric tube decompression to relieve abdominal pressure, fluid restriction and O_2 supplementation with nasal cannula 2 L/min. Bleeding was controlled by plasma exchange 1.5 times of total plasma volume (TPV) followed by a bolus dose of recombinant FVIII concentrate (rFVIII; Kogenate FS®) 6,000 IU (107 IU/kg) and subsequent continuous FVIII infusion at the rate 14 units/kg/hour. However, around 30 hours after admission, his IAP did not decrease after supportive treatment. Moreover, he developed worsening dyspnea and desaturation, which need more O_2 supplementation. He was diagnosed with primary ACS due to

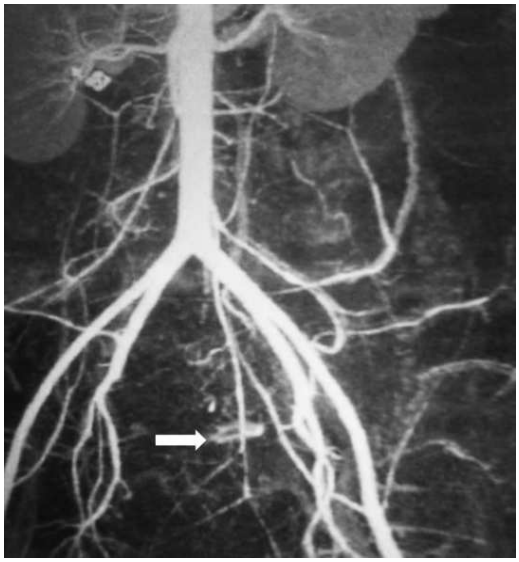

Figure 1: Extravasation from sigmoidal branch of inferior mesenteric artery (arrow).

hemoperitoneum and subsequently underwent the first operation for exploratomy laparotomy to remove blood clots. APCC 5,000 IU and tranexamic acid 500 mg were given prior to the operation. The intra-operative findings showed generalized small and large bowel swelling and huge pelvic hematoma expanding up to umbilical area with oozing from hematoma. An amount of 4,000 ml of old blood was evacuated. His abdomen was packed and left opened for 60 hours. He has also had rectal decompression post-operatively. The IAP and respiratory symptoms markedly improved post-operation. He underwent the second operation to decompress bowel, abdominal toilet and closure. Estimated blood loss was 200 ml. He received total six cycles of plasma exchange followed by continuous FVIII infusion in seven days. During the sixth cycle of plasma exchange, he developed anaphylaxis, so plasma exchange was discontinued. rFVIIa, APCC and RBC transfusion were given intermittently for breakthrough bleeding at intravenous cannulation sites. Adjunct tranexamic acid was also used for hemostatic control after his hematuria resolved on day 10 after admission. He received cryoprecipitate 34 U, leucocyte-depleted RBC 6 U, PC 6 U, FVIII concentrate 114,000 IU (2,035 IU/kg), rFVIIa 20,400 mcg (364 mcg/kg) and APCC 50,000 IU (893 IU/kg) in total (Figure 2). His abdominal wound completely healed on day 13 after admission. The follow-up CT abdomen on day 25 after admission revealed the resolving hematoma in pelvic cavity 10.1 × 9.9 × 11.3 cm in diameter. He was hospitalized for 26 days. He had no thromboembolic events and antibody screening for human immune-deficiency virus (HIV) and hepatitis B and C virus (HBV and HCV) were all negative. He was discharged uneventfully with the FVIII inhibitor at 3,680 BU which later gradually decreased to 30 BU within six months clinic visit after discharge from the hospital.

Discussion

Apart from CT abdomen, angiography is the principle modality for localization of bleeding into abdominal hematoma and non-surgical intervention to stop bleeding by embolization while technetium-99 m red blood cell (TC-99M RBC) scintigraphy is also a sensitive method to localize active hemorrhage with low volume of contrast [13]. However, TC-99M RBC scintigraphy was not performed in this patient as it was not available outside routine hours at our institute. ACS is diagnosed

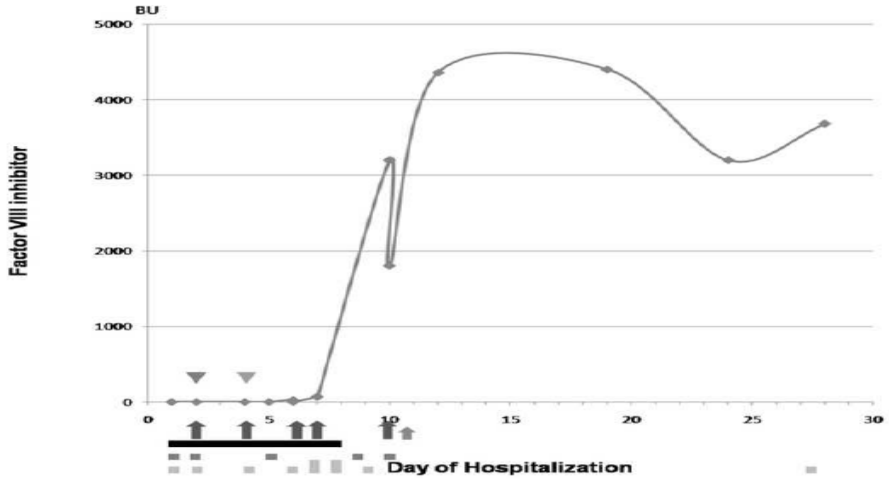

Figure 2: The summary of treatment during the hospitalization and the level of factor VIII inhibitor.

when IAP is higher than 25 mmHg or higher than 20 mmHg with an organ dysfunction [8]. This patient had two risk factors of ACS; hemoperitoneum and bowel ileus [9,10]. The main treatment of ACS is to decrease IAP by supportive treatment and closely monitoring of IAP and fluid balance [10]. However, surgical decompression is needed in patients who develop an organ dysfunction or have persistently high IAP after conservative treatment. As his respiratory distress worsened while was being treated by medical decompression, so this patient was indicated for surgical decompression.

Surgery in hemophlilia patients who are high-responders is difficult. As surgery itself is associated with inhibitor development [14], hemostatic management during emergency surgery is very sophisticated and a guideline is not well established as most evidences are based on case series and case reports. Bypassing agents are the main treatment for hemostatic control in hemophilia patients who are high responders [1]. There is no difference of efficacy of either bypassing agent [15,16]. Around 10-20% of patients would not respond to any bypassing agents [17,18]. The safety and effectiveness of bleeding control by sequential therapy with combined bypassing agents were reported in hemophilia patients with inhibitors [17]. Although an appropriate protocol of bypassing agents was used, the cost of surgery in hemophilia patients with inhibitor is still high [19]. There were a small number of cases of hemophilia patients with inhibitors who were treated with plasma exchange and continuous FVIII infusion with or without concomitant immunosuppressive drugs for bleeding control [4-8]. This therapy is able to remove inhibitors in plasma by 75-85% [20] and allow FVIII to be in the circulation for hemostatic control.

The advantages of continuous FVIII infusion is the steadiness of FVIII level which decrease a risk of re-bleeding and lower dose FVIII usage [21]. Therefore, this patient received continuous FVIII infusion. The development of inhibitors in hemophilia patients who are treated with continuous factor infusion is not higher than intermittent infusion [22]. Moreover, Klintman et al. reported the thrombin generation of bypassing agents combined with FVIII was higher than bypassing agent alone in *in vitro* study [23]. Tranexamic acid is also used in this patient combined with other therapies. Tran et al reported the effect of hemostatic control by using tranexamic acid with bypassing agent in hemophilia patients with inhibitors which showed normal clot stability and no thromboembolic events [24]. However, we waited until his hematuria improved before starting tranexamic acid because it may cause obstructive uropathy [1].

Conclusion

Plasma exchange and continuous FVIII infusion can be considered as treatment option of life-threatening bleeding in hemophilia patients with inhibitors who are high-responders in the setting of constraint bypassing agent usage. Multi-disciplinary collaboration is important for the success of this strategy.

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