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CLINICAL REPORT

A case of acquired hemophilia A with massive hemothorax

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Abstract Acquired hemophilia A (AHA) is an uncommon but potentially life-threatening hemorrhagic disorder caused by the development of an inhibitor against coagulation factor VIII (FVIII). AHA is very rare, affecting approximately 1 in 1 million individuals. However, the incidence may actually be higher, because diagnosis is difficult and the disease can be overlooked. We report a case of an 80-year-old man who presented with sudden onset of severe hemothorax. The patient was diagnosed with presumed AHA based on acute onset of bleeding symptoms and unexplained isolated prolonged activated partial thromboplastin time. Diagnosis was definitely established by demonstrating a decrease in FVIII activity, presence of FVIII inhibitor activity, and normal von Willebrand factor. The patient was successfully treated with recombinant activated coagulation factor VII and transcatheter artery embolization of the intercostal arteries.

Keywords Acquired hemophilia A · Hemothorax · Coagulation factor VIII inhibitor · Recombinant activated blood coagulation factor VII

Introduction

Acquired hemophilia A (AHA) is an uncommon but potentially life-threatening hemorrhagic disorder caused by the development of inhibitor against coagulation factor VIII (FVIII) [1]. The principal manifestations are bleeding into the skin and soft tissues [1, 2] and, on rare occasions, bleeding into the thoracic cavity [3]. Treatment of AHA involves establishment of hemostasis and institution of immunosuppressive therapy to suppress production of the FVIII inhibitor [4].

The present report describes the case of an elderly male patient who presented with sudden onset of massive hemothorax. A presumed diagnosis of AHA was made based on acute onset of bleeding symptoms and unexplained isolated prolonged activated partial thromboplastin time (APTT), and definitive diagnosis was based on demonstration of decreased FVIII activity, presence of FVIII inhibitor activity, and normal von Willebrand factor activity. The patient was successfully treated with recombinant activated coagulation factor VII (FVIIa) and transcatheter artery embolization (TAE) of the intercostal arteries.

Case report

An 80-year-old man (height 155 cm, weight 50 kg) with a history of dementia, cerebral infarction, thoracic aortic aneurysm, chronic renal failure, chronic heart failure, and brain contusion was admitted to an outside hospital for treatment of aspiration pneumonia. At that time, he was treated with cefmetazole and cefepime. He had no prior history of coagulation disorder but developed anemia following admission to the hospital. Chest X-ray showed pleural effusion and multiple rib fractures, but the patient was unclear as to whether he had sustained recent trauma. Chest drainage was performed with return of bloody pleural fluid. Despite conservative medical treatment,

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bleeding continued, and he was transferred to our hospital for further evaluation and treatment.

On arrival at our hospital, a physical examination showed evidence of bleeding into the skin on the arms, chest wall, and lower legs. Systolic blood pressure was less than 100 mmHg, heart rate was greater than 100 beats/min, and oxygen saturation was 93–95%. He was admitted to the intensive care unit (ICU). The patient was intubated because of respiratory difficulty and shock, and mechanical ventilation was initiated. Bleeding from the chest tube continued, and systolic blood pressure persisted below 100 mmHg despite rapid transfusion. Chest X-ray showed a massive right pleural effusion (Fig. 1). Angiography was conducted to isolate the bleeding point and revealed extravasation in the right chest wall from the seventh and eighth right intercostal arteries. TAE of the seventh and eighth intercostal arteries was performed with micro-coils, resulting in resolution of extravasation and some clearing of blood from the chest tube drainage.

Laboratory tests showed prolongation of both APTT (93.4 s) and prothrombin time (PT, 18.3 s) and a decreased platelet count (9×10^4/μl). Fresh frozen plasma (FFP) and gabexate mesilate were administered for treatment of presumed disseminated intravascular coagulation and consumptive thrombocytopenia. Twenty units of FFP were administered over 9 days, and 1,500 mg/day gabexate mesilate was administered for 11 days. Bleeding from the chest tube decreased on day 2 but increased again on day 3. Repeat TAE of the intercostal arteries was elected in response to ongoing need for blood transfusions. The 6th, 9th, 10th, and 11th intercostal arteries underwent TAE, resulting in some decrease in bleeding, but transfusion was still required to maintain hemoglobin concentration and blood pressure. Further testing revealed normal PT (14.6 s) but prolonged APTT (110.9 s), leading to a presumed diagnosis of AHA. FVIIa 4.8 mg (96 μg/kg) was subsequently administered every 3 h with 40 mg/day prednisolone. With these measures, chest tube drainage became less bloody.

Although the hemorrhage had nearly resolved by day 11, retained clots within the thoracic cavity interfered with respiration. Thoracoscopic evacuation was performed just after administration of 4.8 mg FVIIa, showing multilocular hematoma. Hematoma removal was attempted and achieved to some extent, but chest wall and diaphragmatic hemorrhage occurred, requiring administration of 9.6 mg FVIIa and tranexamic acid. After the operation, bleeding gradually decreased, and translucency of the lung increased (Fig. 1). Hemoglobin concentration was maintained at 8.1 g/dl without transfusion on day 14. FVIIa was tapered with discontinuation on day 16. The patient's respiratory status improved gradually, and mechanical ventilation was discontinued on day 17. The patient was then transferred back to the original admitting hospital.

Discussion

AHA can present as a sudden onset of serious bleeding in patients without prior history of coagulation disorder. It arises in response to anti-FVIII antibody and occurs in approximately 1 in 1 million individuals [1], although the incidence of this disease may be increasing [2]. AHA is associated with autoimmune diseases, malignant tumors, diabetes, and the postpartum state, but some patients with AHA do not have any of these underlying conditions [1–3]. Other reports describe cases of AHA perhaps arising from exposure to medications, including antibiotics [1–3]. This patient was treated with cefmetazole and cefepime, but there are no previous reports describing an association between cephalosporins and AHA. AHA manifests with early muscle and subcutaneous bleeding in 70% of cases, although intra-auricular bleeding (as occurs with congenital hemophilia) is rare. This patient had evidence of

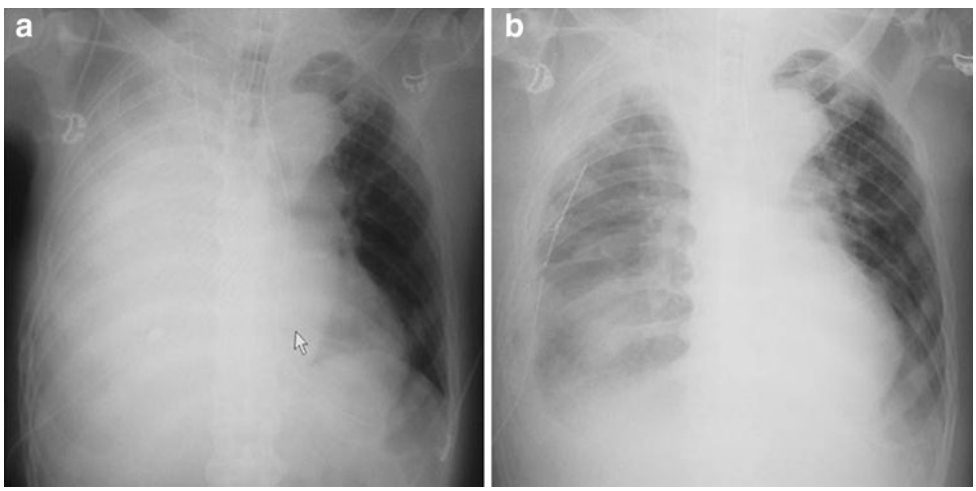

Fig. 1 Chest X-rays. **a** Chest X-ray showed opacification of the right hemithorax. **b** Translucency of the lung increased after the operation

subcutaneous bleeding on the arms when he arrived at our hospital. Recognition of early symptoms of AHA may have been confounded by the patient's dementia. Severe hemorrhage, including retroperitoneal hemorrhage, can also occur, but it is relatively rare (7% of cases) [1–3]. Bleeding from other sites has been reported elsewhere. A case presenting as spontaneous bleeding into the scrotum without any other bleeding has been described, and that report discussed the risk of misdiagnosis [5]. Hemothorax, such as that seen in the present case, is also very rare (1% of cases) [1–3] but is life threatening. Thus, a diagnosis of AHA should be considered when elderly patients develop any type of sudden hemorrhagic episode; such a clinical scenario should prompt coagulation testing. Isolated prolongation of APTT is shown in AHA [4]. In this case, the prolongation of APTT was greater than that of PT, and thrombocytopenia was present. Diagnosis of AHA is based on predominant prolongation of APTT, decrease of FVIII activity, presence of FVIII inhibitor, and normal von Willebrand factor activity [4]. In this case, coagulation testing showed low FVIII activity (2% of normal), 15 Bethesda unit (BU)/ml FVIII inhibitor (which is above the reference range for healthy patients), and increased von Willebrand factor activity (211% of normal). However, this type of testing requires several days and is therefore not helpful for diagnosis in the emergency setting. Coagulation of plasma from healthy persons is strongly inhibited when mixed with a small amount of plasma from patients with AHA because of FVIII inhibitor [1]. This type of plasma mixing study can be done in hospital laboratories with rapid turnaround time. In this case, treatment was initiated before diagnosis, before the availability of results from definitive testing.

Treatment of acquired hemophilia requires hemostasis to address hemorrhage and immunosuppressive therapy to suppress production of the FVIII inhibitor [4]. Because FVIII is inactivated by FVIII inhibitor, FVIII preparations and FFP have no effect on bleeding, especially when inhibitor levels are high (as in the present case: 15 BU/ml). Therapies that activate other coagulation systems [e.g., recombinant activated FVII or the active form of prothrombin complex concentrates (aPCC) derived from human plasma] are effective [4]. Although there has been no head-to-head comparison of FVIIa versus aPCC, aPCC has the advantage of therapeutic efficacy with twice to three times daily administration, but the disadvantages include possible transmission of infectious diseases and the induction of increased FVIII inhibitor development because it contains a small amount of FVIII. By contrast, FVIIa has a relatively short half-life (approximately 2.5 h), and thus requires frequent administration, but it does not carry the risk of transmissible diseases or FVIII inhibitor induction. A dose of 90–120 μg/kg FVIIa is usually administered every 3 h until bleeding is suppressed. Downward titration is recommended according to the guidelines for the treatment of congenital hemophilia A with FVIII inhibitor [6]. Administration for 2–3 weeks is sometimes required. Thrombosis can occur with either agent.

In the present case, FVIIa was very effective in controlling bleeding, especially after operative removal of the massive hematoma. FVIIa therapy was terminated 5 days after hematoma removal. Further, TAE was effective in reducing bleeding from the intercostal arteries and should be considered when medical treatment alone does not terminate bleeding.

In summary, the present report described a case of AHA that presented with massive hemothorax. AHA is a serious bleeding disorder that arises because of inhibitors against FVIII. A diagnosis of AHA should be considered in any elderly patient with sudden onset of bleeding and prolongation of APTT without a prior history of bleeding disorders. Diagnosis of AHA is based on a decrease in FVIII activity, presence of FVIII inhibitor, and normal von Willebrand factor activity. Plasma mixing studies may be helpful in supporting a diagnosis of AHA. Treatment is via exploitation of alternative coagulation pathways with aPCC or FVIIa, and TAE may also be effective.

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