Case Report

Spontaneous Retroperitoneal Hemorrhage Caused by Idiopathic Acquired Hemophilia A Misdiagnosed as a Delayed Traumatic Hematoma: A Case Report

Seon Hee Kim, Sung Jin Park *, Chan Ik Park, Seon Uoo Choi, Jae Hun Kim

Department of Trauma Surgery, Pusan National University Hospital, Busan, Korea

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*Corresponding Author:

Sung Jin Park
 Department of Trauma Surgery,
 Pusan National University
 Hospital, Busan, Korea
 E-mail: psjtrauma@gmail.com
ORCID
<https://orcid.org/0000-0002-4852-5442>

ABSTRACT

Acquired hemophilia A (AHA) is a rare disease where typically coagulation factor VIII is inhibited by autoantibodies. It occurs in patients with no personal or familial history of bleeding. In this case study a 61-year-old male presented with a huge psoas hematoma. He had no history of bleeding disorders. He was initially diagnosed with delayed traumatic hematoma. Despite conservative and surgical treatments, coagulopathy was not resolved and postoperative bleeding continued. Consequently, coagulation factor tests were performed and showed reduced activity of factor VIII (2.7%). In addition, factor VIII inhibitor was detected. The patient was diagnosed with AHA and administered recombinant factor VIII for 3 days which resulted in the cessation of bleeding. AHA can lead to a life-threatening hemorrhage, and needs to be considered in differential diagnoses in any patients presenting with unexplained and repeated bleeding, where there is no personal or familial history of bleeding disorders.

Keywords: autoantibodies, blood coagulation disorders, factor VIII, hematoma, hemophilia A

Introduction

Acquired hemophilia A (AHA) is a coagulation disorder caused by the development of autoantibodies against circulating coagulation factors, usually factor VIII (FVIII) [1-7]. It is very rare (0.2-4 cases per million per year) but has a high mortality (3.3-42%) rate [1-9]. Mortality is mostly caused by life-threatening bleeding [1,5]. The priority in treatment of AHA is to diagnose quickly and stop the bleeding [8]. However, AHA is rare and diagnosis is difficult and may not be made directly upon admission to emergency or trauma centers (except some specialized hospitals). Without an AHA diagnosis it is difficult to stop the bleeding. In most cases, AHA first presents as acute onset life-threatening hemorrhage following surgery, trauma, or invasive procedures. However, spontaneous bleeding has also been reported [1].

It is often difficult to diagnose AHA because the patient

has no previous history of coagulation disorders or familial history, and the disease is rare [4,7]. In the blood coagulation test the prothrombin time (PT) is usually normal, and isolated prolongation of activated partial thromboplastin time (aPTT) is observed. However, it is more difficult to diagnose AHA if the prothrombin time is not normal.

In this report, a rare case of spontaneous retroperitoneal hemorrhage caused by AHA, which was misdiagnosed as delayed traumatic hematoma in a trauma center in Korea was described.

Case Report

A 61-year-old man was transferred to the Trauma Center of Pusan National University Hospital on November 24th, 2014. On admission his vital signs were measured and his blood pressure

(150/90 mmHg), heart rate (98 beats/min), and respiratory rate (18 breaths/min) were stable. However, he looked anemic and complained of abdominal pain on his left side and had abdominal distension over several days. The initial hemoglobin level was low (6.6 g/dL) and the platelet count ($176 \times 10^3/\mu\text{L}$) was in the normal range. The PT test time (12.9 seconds), international normalized ratio (1.20) and aPTT (68.3 seconds) test time were slightly elevated compared with the normal range. So, transfusions of packed red blood cells and fresh frozen plasma were administered immediately.

He had no personal or familial history of bleeding or clotting disorders. In the patient's past history, his left ribs were fractured due to a blunt trauma sustained in an accident (6 months ago) where he was crushed between a forklift truck and a wall. He was treated conservatively.

For further evaluation, an abdominal computed tomography (CT) scan (contrast enhanced) was performed. The CT scan showed an $18.3 \text{ cm} \times 9.3 \text{ cm}$ -sized left psoas muscle and retroperitoneal hematoma, without active bleeding (Figure 1A). He

was diagnosed with delayed traumatic hematoma and chronic consumptive coagulopathy. The patient was admitted to the intensive care unit and conservative treatment was started. After 48 hours, a follow-up CT scan was performed which showed the hematoma had increased ($20.7 \times 10.4 \text{ cm}$), but there was no sign of active bleeding (Figure 1B). It was decided that an angiographic embolization of left lumbar arteries should be performed prophylactically. The left lumbar arteries were embolized using absorbable Gelfoam powder (Figure 1C), and a pig-tail catheter was inserted to drain the hematoma. After which conservative treatment continued. However, the patient's anemia and coagulopathy had not been corrected by repeated transfusions of packed red blood cells, fresh frozen plasma and cryoprecipitate. Moreover the amount of drainage from the hematoma through the pigtail catheter was not reduced. The patient's condition deteriorated further.

On December 3rd, surgical hemostasis was performed to control the bleeding and coagulopathy. The hematoma was removed ($950 \mu\text{L}$) under general anesthesia, and bleeding

Figure 1. Radiological findings. (A) A computed tomography (CT) scan showed the left psoas muscle ($18.3 \times 9.3 \text{ cm}$) and a retroperitoneal hematoma without active bleeding. (B) A follow-up CT scan the next day showed the size of the hematoma ($20.7 \times 10.4 \text{ cm}$) had increased, but active bleeding was not observed. (C) Although there was no active bleeding, an angiographic embolization of left lumbar arteries was performed prophylactically.

Figure 2. Surgical findings. (A) After failure of non-operative management, the hematoma was removed ($950 \mu\text{L}$) under general anesthesia. The bleeding was controlled, and the wound was packed with gauze and negative suction drainage by the anterior extraperitoneal was applied. (B) Despite repeated surgery for hemostasis, the bleeding did not stop. (C) After administration of recombinant factor VIII, the bleeding completely stopped and the wound was closed successfully.

control and gauze packing with negative suction drainage by anterior extraperitoneal approach, were performed (Figure 2A). Postoperatively, the hemoglobin level increased to > 8.0 g/dL, and there was no evidence of further bleeding. After 3 days, the gauze was removed and the wound was closed with closed suction drainage. However, this procedure caused bleeding at the surgical site. The wound was reopened immediately at the bedside and compression was applied to the bleeding site (Figure 2B). There were 5 more operations under general or local anesthesia, performed for hemostasis but the bleeding continued. This could not be simply explained by chronic consumptive coagulopathy due to a huge hematoma.

On December 15th a blood coagulation factor test was performed to evaluate the presence of other hematological disorders. According to the test, FVIII activity was decreased to 2.7 (70-130%). After administration of 4,500 IU/day of recombinant FVIII (Xyntha, Wyeth, Philadelphia, PA, USA) for 3 days (based on hematology results), the bleeding completely stopped.

Following 5 more operations under local anesthesia for wound management, the wound closed successfully on February 24th, 2015 (Figure 2C). According to follow-up tests on February 6th, the FVIII activity increased to 9.0%. However, FVIII inhibitor was detected leading to the diagnosis of AHA caused by the development of autoantibodies to coagulation factor VIII. The patient was transferred to the Department of Hematology to eradicate the autoantibodies against factor VIII. The patient was discharged from hospital on March 20th, 114 days after admission.

Discussion

AHA is a rare but critical coagulation disorder. It is caused by the development of inhibitors against circulating FVIII. According to the European Acquired Hemophilia Registry, it occurs at an incidence of 1.5 per million population, per year, in people with no personal or familial history of coagulation disorders [1,2,6]. The range of incidences of AHA have been reported to be between 0.2 to 4 cases per million, per year [3-5,8]. Regardless of gender, there is a tendency of AHA to occur in older patients (>60 years). In the case of women, there is a small peak in young adults aged 20 to 30 years because of AHA association with pregnancy [2,4,6,7]. The reported mortality rate in AHA, ranges from 3.3% to 42% [1,2,4,5,7,9]. It may result from life-threatening bleeding, the underlying disease, or the side effects of treatment such as sepsis [1,2,4,5,7,9]. Known risk factors of acquiring AHA include malignancies, autoimmune diseases (systemic lupus erythematosus and rheumatoid arthritis), pregnancy, exposure to drugs, blood transfusions or

infections. However, 50% of the cases of AHA are idiopathic [1-3,6,8]. In this case, there was no personal or familial history of disease or coagulation disorders, indicating that the cause of AHA in this patient was idiopathic.

In patients with congenital FVIII deficiency, hemarthrosis occurs predominantly. However, in patients with acquired FVIII deficiency, hemarthrosis is rare and bleeding usually occurs into the skin, muscles, soft tissues or mucous membranes (e.g., epistaxis, gastrointestinal and urological bleeds, retroperitoneal hematomas, intracerebral hemorrhages, prolonged postpartum bleeding and excessive bleeding following trauma or surgery) [2,4,6].

The early diagnosis of AHA is critical because the bleeding is life-threatening. After an accurate diagnosis, optimal hemostatic therapy and eradication of antibodies should be followed. However, it is difficult to diagnose AHA in a patient with no previous personal or family history of bleeding, and even more difficult to diagnose AHA in general emergency rooms or trauma centers, as most hemophilic patients attend specialized hospitals. In addition, most emergency room physicians, surgeons or intensive care physicians who do not have as much experience hematologists may easily delayed diagnosis and give suboptimal treatment [2].

The initial detection of an isolated prolongation of aPTT may be a diagnostic clue, and the following identification of a reduced FVIII concentration, with evidence of FVIII inhibitor activity confirms AHA [2,4]. In this case, PT and aPTT were prolonged, so it was more difficult to make an early diagnosis of AHA which was compounded by the rarity of the disease. Perhaps the aPTT is only prolonged when bleeding begins. Activation of the coagulation cascade may have occurred as the quantity of bleeding gradually increased. It can be assumed that the change in the test values, was caused by the administration of the coagulation factor. Due to the recurrent bleeding and despite the cause, it was thought that this condition was a coagulation disorder. It was diagnosed as 1 of several coagulation conditions randomly tested for to find the cause. The final diagnosis of AHA required laboratory confirmation of isolated FVIII deficiency and its inhibitor. The presence of FVIII inhibitor was assayed using the Bethesda method [5,10]. However, this assay is not available in all hospital laboratories and may need to be outsourced to another laboratory, as was the case in this study. This leads to time delays until the final test results were confirmed.

There are 2 goals in the treatment of AHA. The first is cessation of acute life-threatening bleeding, and the second is eradication of the autoantibody. Treatment options for cessation of acute bleeding are bypassing agents, agents for raising circulating FVIII, activated prothrombin complex concentrates, and recombinant activated FVII, are all

Table 1. Treatment options for acquired hemophilia A [1,3,5,6,8,10].

Treatment of acute bleeding	Eradication of autoantibodies
Bypass agent	Corticosteroids
aPCC	Corticosteroids+cyclophosphamide
rFVIIa	Rituximab
Agent for raising circulatory FVIII level	Azathioprine
Human FVIII	Vincristine
Porcine FVIII	Mycophenolate
Desmopressin	Cyclosporine

aPCC = activated prothrombin complex concentrate; rFVIIa = recombinant activated FVII; FVIII = factor VIII.

recommended as 1st line therapy. If this is not possible, human or porcine FVIII or desmopressin should be used for 2nd line therapy. After the diagnosis of AHA is confirmed, support from the National Health Insurance in Korea may be given, but it is limited due to the high cost. Before the diagnosis of AHA is reached, an empirical injection of recombinant FVII (NovoSeven; Novo Nordisk, Plainsboro Princeton, NJ, USA) is recommended due to uncontrolled bleeding and coagulopathy despite medical and surgical efforts. In this case, it could not be used because of its high cost. First line treatment options for eradication of autoantibodies is recommended for corticosteroids (+cyclophosphamide), and rituximab, which could be used for 2nd line therapy. The cure of the possible associated diseases is also important as, in some cases, it will lead to the disappearance of the inhibitor (Table 1) [1,3,5,6,8,10]. The first step (cessation of acute bleeding) is more important for an emergency room physician or surgeon, or intensive care physician. Collins et al [2] recommended a patient with suspected or confirmed AHA, with or without bleeding, should consult with a specialist such as a hematologist, or attend a hemophilia center where there is expertise in managing inhibitors, and this should be acted upon as soon as possible. In this case study, the patient was transferred to a hematologist for eradication of the autoantibody after the acute bleeding had stopped.

Although the incidence is very low, AHA can lead to a critical hemorrhage. So, early diagnosis of this disease is critical. However, except for some specialized centers, emergency room physicians, trauma surgeons or intensive care physicians have

very little chance of encountering this disease, so its rapid diagnosis is difficult. Furthermore, diagnosis is more difficult if the isolated prolonged aPTT test characteristic of AHA is not seen. However, both PT and aPTT tests can be increased when accompanied with consumptive coagulopathy due to excessive blood loss. In conclusion, AHA needs to be considered as a diagnosis in any patients presenting unexplained, and recurrent bleeding, without personal or familial history of bleeding tendencies, and characteristic isolated aPTT prolongation.

Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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