Diagnosis and treatment of acquired factor VIII deficiency: a case report and literature review

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Abstract

Acquired haemophilia A (AHA) is a rare haemorrhagic disease characterized by spontaneous extensive subcutaneous haemorrhage and soft tissue haematoma. The activated partial thromboplastin time is significantly prolonged and cannot be corrected by normal plasma. Approximately 50% of AHA patients lack a specific aetiology, so this can easily result in a misdiagnosis. This current case report describes a 27-year-old male that presented with gingival bleeding, haematuria and haematochezia with no obvious cause. At first, it was thought that he might have experienced anticoagulant rodenticide poisoning, but the subsequent anticoagulant rodenticide test was negative. At the same time, the patient was screened for mutations associated with bleeding and coagulation diseases. Two mutations were identified: a p.Y471H mutation the plasminogen activator, tissue type (PLAT) gene; and a p.Y244Y mutation the serpin family E member 1 (SERPINE1) gene. It should be noted that patient had no previous history of thrombosis or haemorrhagic disease, which confused the diagnosis. A professional haemophilia research centre provided clarification of the diagnosis when anti-factor VIII antibodies were detected. The patient was treated with 30 mg/day prednisone orally. Multiple follow-up examinations showed continuous complete remission. No factor VIII antibodies were detected in his blood and coagulation factor VIII increased significantly.

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**Introduction**

Acquired haemophilia A (AHA) is an autoimmune disease that causes serious and even fatal bleeding due to the production of autoantibodies against coagulation factors in the body. Among them, acquired haemophilia A caused by autoantibodies to coagulation factor VIII (FVIII) is the most common. Most AHA are associated with skin ecchymosis, thoracic and abdominal haematoma and deep muscle bleeding. Some patients have life-threatening bleeding, with a mortality of >20%, and there are often patients that fail to heal. Treatment focuses on the use of bypassing drugs to control bleeding and the use of immunosuppressants to clear antibodies. Because early mortality in patients with AHA is high, early diagnosis and timely treatment are the key to the success of AHA treatment.

This current case report describes the diagnosis and treatment of a patient with acquired FVIII deficiency and summarises the relevant literature.

**Case report**

On 17 March 2017, a 27-year-old male that had been experiencing gingival bleeding, haematuria and haematochezia for 6 days was admitted to the emergency department of Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province, China. The patient had no obvious cause for the gingival bleeding 6 days before admission, followed by haematuria, haematochezia, pain in the right lower abdomen, swelling, numbness and weakness of the left lower limb. No dizziness, fever, cough, expectoration, chest tightness and palpitation, so he went to a local hospital for treatment. Laboratory examinations showed the following: white blood cell count (WBC) $23.36 \times 10^9/\text{l}$ (normal range, $3.5–9.5 \times 10^9/\text{l}$); neutrophil percentage 68.1% (normal range, 40–75%); haemoglobin (Hb) 110 g/l (normal range, 130–175 g/l); platelet count $276 \times 10^9/\text{l}$ (normal range, 125–350 $\times 10^9/\text{l}$). Routine urinalysis showed the following: urinary protein 3+, urinary occult blood 3+. There was occult blood in the stool (+). Coagulation tests showed the following: activated partial thromboplastin clotting time (APTT) 85.4 s (normal range, 28–45 s) and prothrombin time 16.6 s (normal range, 11–14.5 s). Liver and kidney function tests showed the following: alanine transaminase 86 U/l (normal range, 9–50 U/l); albumin 35 g/l (normal range, 40–55 g/l); creatinine 65 $\mu$mol/l (normal range, 62–115 $\mu$mol/l); blood glucose 7.1 mmol/l (normal range, 3.9–6.1 mmol/l). The patient received anti-infection, haemostasis and other symptomatic treatments. As a consequence of these findings, he was admitted to the intensive care unit of a local hospital on 16 March 2017. Abdominal computed tomography (CT) showed the following: (i) the density of the bilateral renal pelvis had increased slightly, the bilateral perirenal fascia had thickened, the fat density around the bilateral ureteral walking area was increased and the pelvic fascia had thickened; (ii) liver morphology was...
irregular and liver cirrhosis was not excluded. The patient received the following: gastrointestinal decompression, enema, crystal and colloidal liquid replenishment, volume expansion, blood transfusion, haemostasis, anti-infection, nutrition and symptomatic support. Subsequent laboratory examination showed the following: WBC 34.24 × 10^9/l; Hb 66 g/l; APTT 130 s. The patient was transferred to the emergency department of Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province, China on 17 March 2017. His past medical history included being positive for hepatitis B virus (HBV) surface markers for 5 years. He did not report a history of drug or food allergy, trauma, surgery and blood transfusion. His personal history included the following: lived in the place where he was born; no history of contact with contaminated water; smoking history of 10 years, at 20 cigarettes/day, but had stopped smoking for 3 weeks. His family history was as follows: his father suffers from diabetes mellitus and hypertension. There was no reported history of family genetic diseases and infections.

Upon admission, a physical examination showed the following: body temperature 36.8°C; heart rate 146 beats/min; respiration rate 22 breaths/min; blood pressure 94/66 mmHg; saturation of peripheral oxygen 98%; poor spirit, with drowsiness and an anaemic appearance. The sclera were yellow stained, the bilateral pupils were equal in size and circular with a diameter of 3 mm and were sensitive to light reflection. There was bleeding at the right subclavian vein catheterization. The respiratory sounds of both lungs were thick, but no dry and wet rales were heard. The heart rate was 146 beats/min, the rhythm was uniform and no pathological murmurs were heard in each valve area. The abdomen was bulging, without muscle tension, there were large areas of ecchymosis on both sides of the waist, and the skin around the umbilicus was blue-purple. The left lower abdomen and the right lower abdomen were tender without rebound pain. A hard mass was palpable in the left lower abdomen. The liver and spleen were not felt under the costal margin. The groin circumference of the left lower limb was 72 cm compared with a groin circumference of the right lower limb of 62 cm (Figure 1). Bilateral Babinski signs were negative.

The results of laboratory tests at the time of admission on 17 March 2017 and during treatment are shown in Tables 1 and 2. The values of coagulation factors were as follows on 17 March 2017: coagulation factor V 54% (normal range, 70–120%); coagulation factor VII 28% (normal range, 55–170%); coagulation factor VIII 1% (normal range, 60–150%); coagulation factor IX 85% (normal range, 60–150%). Chest and abdominal CT showed double lung inflammation, pleural, abdominal and pelvic effusion, peritoneal and omental thickness, abdominal and pelvic wall oedema, bilateral femoral muscle space and subcutaneous fat and soft tissue oedema (Figure 2). The preliminary diagnosis was as follows: septic shock, hypovolaemic shock, anaemia to be investigated; coagulation dysfunction, gastrointestinal bleeding, urinary tract bleeding, chronic HBV. The treatment was as follows: diet prohibition, meropenem anti-infection treatment, vitamin K1, phenolsulfonamethyamine, aminometrinic acid, batroxobin haemostatic, omeprazole acid suppression, octreotide to inhibit pancreatin secretion, magnesium isoglycyrrhizin, reduced glutathione liver protection, entecavir to inhibit HBV replication, plasma supplements, cold precipitation, infusion of red blood cells, nutrition and symptomatic support treatment. After inquiring about the medical history, he may have eaten roast goose that was contaminated with anticoagulant rodenticide before developing haematuria, so anticoagulant rodenticide poisoning.
could not be excluded, so he was transferred to the Department of Poisoning and Occupational Diseases, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province, China for further treatment. On the 3rd day after admission, the patient still had black stools. The results of the laboratory tests are shown in Tables 1 and 2. Red blood cells and plasma were infused again. On the 5th day after admission, the following test results were obtained: glucose water test (–); acidified serum haemolysis test (–); plasma free Hb 41.9 mg/l (normal range 10–50 mg/l); direct antiglobulin test (–). Anticoagulant rodenticide was not detected. On the 7th day after admission, the patient’s black stools gradually decreased without special discomfort. The colour of the skin ecchymosis deepened further (Figure 3). The laboratory test results are shown in Tables 1 and 2. Blood cultures showed the following: no anaerobic growth, no bacterial growth. The values of coagulation factors were as follows: coagulation factor V 89% (normal range, 70–120%); coagulation factor VII 85% (normal range, 55–170%); coagulation factor VIII 1% (normal range, 60–150%); coagulation factor IX 92% (normal range, 60–150%).

Tumour markers were detected 12 days after admission: ferritin 709 ng/ml (normal range, 13–400 ng/ml); carbohydrate antigen (CA) 19-9 294.3 U/ml (normal range, 0–39 U/ml); CA 125 306.1 U/ml (normal range, 0–35 U/ml); neuron specific enolase 27.27 ng/ml (normal range, 0–20 ng/ml). No obvious abnormality was found upon examination of the immune system and systemic lupus erythematosus was excluded. Bone marrow puncture showed no obvious abnormality in the morphology of each department of the myelogram. On admission day 14, abdominal CT showed cholecystitis. There were multiple swollen lymph nodes in the retroperitoneal area, multiple strip-like low-density shadows in the abdomen and pelvis, slightly blurred around the pancreas, peritoneal thickening and soft tissue swelling in the left chest and abdominal wall.

On the 21st day after admission, the laboratory indices of the patient were further improved (Tables 1 and 2). The blood was sent to the Haemophilia Diagnosis and
Table 1. Routine blood, liver and kidney function test results over the course of treatment of a 27-year-old male that presented with gingival bleeding, haematuria and haematochezia with no obvious cause.

| Date of examination | WBC, $\times 10^9$/l (3.5–9.5) | Hb, g/l (130–175) | PLT, $\times 10^9$/l (125–350) | ALT, U/l (9–50) | AST, U/l (15–40) | BUN, μmol/l (2.3–7.8) | Cr, μmol/l (62–115) | TBIL, μmol/l (5–21) | DBIL, μmol/l (<6.0) | IBIL, μmol/l (2–15) |
|---------------------|--------------------------------|-------------------|-------------------------------|----------------|------------------|----------------------|----------------|-------------------|-----------------|---------------|
| 17 March 2017       | 59                            | 64                | 196                           | 46             | 32               | 13.3                 | 144            | 26                | 0               | 21             |
| 19 March 2017       | 65.7                          | 67                | 134                           | 31             | 185              | 29.4                 | 158            | 62.5              | 36              | 26.5           |
| 20 March 2017       | 56.74                         | 70                | 106                           | 85             | 397              | 27.8                 | 89             | 101               | 34              | 55             |
| 21 March 2017       | 28.85                         | 59                | 73                            | 64             | 243              | 22.89                | 89             | 101.2             | 58.7            | 42.5           |
| 23 March 2017       | 13.44                         | 81                | 89                            | 53             | 123              | 11.81                | 63             | 129.9             | 73.3            | 56.6           |
| 30 March 2017       | 13.98                         | 98                | 240                           | 47             | 63               | 3.96                 | 46             | 74.4              | 34.8            | 39.6           |
| 6 April 2017        | 10.29                         | 104               | 224                           | 21             | 25               | 5.28                 | 41             | 44.3              | 19.3            | 25             |
| 15 May 2017         | 11.05                         | 160               | 236                           | 40             | 40               | 5.83                 | 51             | 8.8               | 3.0             | 5.8            |
| 15 June 2017        | 9.51                          | 164               | 214                           | 63             | 42               | 4.39                 | 52             | 11.3              | 3.3             | 8.0            |

*aNormal range for each laboratory parameter shown in parentheses.

WBC, white blood cells; Hb, haemoglobin; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; TBIL, total bilirubin; DBIL, conjugated bilirubin; IBIL, indirect bilirubin.
Table 2. Routine coagulation function, coagulation factor and coagulation factor antibody test results over the course of treatment of a 27-year-old male that presented with gingival bleeding, haematuria and haematochezia with no obvious cause.

| Date of examination | APTT, s (28–45) | PT, s (11–14.5) | INR (0.8–1.2) | FIB, g/antibody (2–4) | D-dimer, µg/ml (<0.5) | FDP, µg/ml (<5.0) | Factor V, % (70–120) | Factor VII, % (55–170) | Factor VIII, % (60–150) | Factor IX, % (60–150) | Factor VIII antibody, BU (0–0.6) |
|---------------------|-----------------|-----------------|---------------|----------------------|-----------------------|-------------------|---------------------|------------------------|-------------------------|-------------------------|---------------------|
| 17 March 2017       | 84              | 16.6            | 1.34          | 2.24                 | >20                   | 68.14             | 54                  | 28                     | 1                       | 85                      |
| 19 March 2017       | 105.4           | 17.1            | 1.39          | 1.45                 | 3.08                  |                   |                     |                        |                         |                         |
| 20 March 2017       | 88.7            | 16.7            | 1.35          | 1.1                  | 12.58                 |                   |                     |                        |                         |                         |
| 21 March 2017       | 77.5            | 13.7            | 1.3           | 1                    | 4.37                  |                   |                     |                        |                         |                         |
| 23 March 2017       | 90.2            | 14.1            | 1.09          | 2.02                 | 8.24                  | 34.01             | 89                  | 85                     | 1                       | 92                      |
| 26 March 2017       | 79.9            | 14.1            | 1.09          | 3.91                 | 9.96                  |                   |                     |                        |                         |                         |
| 30 March 2017       | 67.8            | 11.1            | 1.06          | 3.27                 | 1.61                  |                   |                     |                        |                         |                         |
| 6 April 2017        | 80.2            | 11.8            | 1.12          | 4.0                  | 1.82                  |                   |                     |                        |                         | 5.2                     |
| 15 May 2017         | 45.2            | 10.4            | 0.99          | 3.48                 | 0.13                  | 102               | 124                 | 19                     | 101                     |                         |
| 15 June 2017        | 41.1            | 10.8            | 1.03          | 3.44                 | 0.13                  | 41                |                     |                        |                         | 0                       |

*aNormal range for each laboratory parameter shown in parentheses.

APTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; FDP, fibrin degradation products; BU, Bethesda units.
Coagulation factor VIII was 5.2% (normal range, 50–150%) and factor VIII inhibitor was 1.5 Bethesda units (BU) (normal range, 0–0.6 BU). Gene mutation screening and detection of bleeding and coagulation diseases showed the following: (i) a p.Y471H mutation was found in the coding sequence of the plasminogen activator, tissue type (PLAT) gene (SIFT database and Polyphen2 database sequencing). This mutation site may affect protein function. It is known that PLAT gene mutation is related to tissue plasminogen activator (tPA) deficiency and this is an autosomal genetic disease. Patients may have repeated thrombosis and abnormal fibrinolysis. Generally, the release of tPA in plasma is abnormal and the level is usually reduced; (ii) a p.Y244Y mutation was found in the coding sequence of the serpin family E member 1 (SERPINE1) gene. The change of nucleotide does not change the encoded amino acid. SERPINE1 gene mutations are known to be associated with plasminogen activator inhibitor 1 (PAI-1) deficiency. PAI-1 deficiency is an autosomal recessive or dominant genetic disease. Its clinical manifestations are lifelong trauma, postoperative bleeding and haematoma. Patients generally have normal coagulation.

Figure 2. Computed tomography imaging of the lungs and abdomen of a 27-year-old male that presented with gingival bleeding, haematuria and haematochezia with no obvious cause showed double lung inflammation with bilateral pleural effusion and adjacent lung tissue insufflation (a); abdominal and pelvic effusion, thick peritoneum and omentum, and abdominal and pelvic wall oedema (b); bilateral femoral muscle space and subcutaneous fat and soft tissue oedema (obvious on the left) (c).

Figure 3. A physical examination of a 27-year-old male that presented with gingival bleeding, haematuria and haematochezia with no obvious cause showed large areas of ecchymosis on the trunk, arms and tops of the thighs. The colour version of this figure is available at: http://imr.sagepub.com.
screening test results and platelet function, shortened euglobulin dissolution time and abnormal PAI-1 activity and antigen in the plasma.\(^4\)

Considering the clinical characteristics of the patient (no previous bleeding history or family history), a prolonged APTT (normal prothrombin time, fibrinogen level and platelet count), decreased coagulation factor VIII and positive for inhibitor of coagulation factor VIII antibody, the patient was diagnosed as having acquired FVIII deficiency. His treatment was changed to 30 mg prednisone orally once a day and he was transferred to the Department of Haematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province, China to continue treatment with 30 mg prednisone orally once a day and 10 U cryoprecipitate via intravenous drip. After 2 days, the patient’s symptoms and laboratory examination results were further improved and he was discharged for observation. Follow-up examinations were undertaken at 1 and 2 months after hospital discharge. The patient did not have bleeding, the level of coagulation factor VIII was higher than before and the antibody to coagulation factor VIII was negative (Tables 1 and 2). A follow-up CT of the hip joints showed swelling of the left iliopsoas muscle, so bleeding cannot be excluded (Figure 4).

Standard care was provided to the current case so ethical approval was not applicable. Written informed consent was obtained from the patient for publication of this case report. The reporting of this case conforms to the CARE guidelines.\(^5\)

Discussion

Acquired haemophilia A is a rare disease caused by factor VIII autoantibody.\(^1\) It is usually associated with autoimmune diseases, pregnancy, certain drugs, skin diseases and malignant tumours; and it has an incidence rate of approximately 1.48/million/year.\(^6,7\) AHA presents with a biphasic age distribution, with a small peak at the age of 20–30 years and a large peak at the age of \(\geq\) 60 years.\(^8\) The majority of patients aged between 20 and 30 years are women because AHA in this age group is associated with pregnancy and autoimmune diseases.\(^9\) Approximately 50% of patients in whom anti-factor VIII autoantibodies have been detected have no known cause, which is known as idiopathic AHA. In approximately 35–40% of cases,

Figure 4. Computed tomography imaging of the hip joints of a 27-year-old male that presented with gingival bleeding, haematuria and haematochezia with no obvious cause showed swelling of the left iliopsoas muscle, so bleeding could not be excluded.
AHA is associated with autoimmune diseases, solid malignancies, blood tumours, allergic diseases or drug exposure. The remaining 10–15% of AHA cases were found in young women within 12 months after delivery of a baby.9–12

The most common bleeding observed in AHA is extensive subcutaneous bleeding (45%), mucosal bleeding (43%), intramuscular haematoma or retroperitoneal bleeding (33%), followed by gastrointestinal bleeding, urogenital bleeding and other parts.13 Intracranial haemorrhage is rare but can be fatal.12,14 Compared with congenital haemophilia A, there is generally no joint bleeding and deformity, and the degree of bleeding has nothing to do with the antibody titre level.1

An important principle of haemorrhagic diseases is to prevent bleeding. Minor injuries such as intramuscular injection, intrarterial blood collection and any invasive procedures should be avoided. Aspirin or nonsteroidal anti-inflammatory drugs should also be avoided. At present, there is no unified treatment standard, but the basic principles are as follows: (i) bleeding control, especially for patients with high titre inhibitors. The best treatment is to use bypass agents, i.e. recombinant activated factor VII or activated prothrombin complex concentrate (APCC) containing factors II (prothrombin), VII, IX and X.15,16 However, in the elderly with risk factors of venous thromboembolism and/or arterial thromboembolism, attention should be paid to the risk of thrombosis. Infusion of fresh frozen plasma, human FVIII products and desmopressin has limited therapeutic effect and is ineffective in patients with high titre inhibitors. The high homology between human FVIII and porcine FVIII (pFVIII) means that pFVIII is able to play a haemostatic role in the human body. The key epitope recognized by human FVIII autoantibody is different to that of pFVIII, so that a high level of circulating FVIII can be obtained after infusion of pFVIII products.12,17 Antifibrinolytic drugs, such as aminomethylbenzoic acid, are used as adjuvant therapy for patients with mouth, nose, local wound bleeding or menorrhagia. Antifibrinolytic therapy can be combined with drugs other than APCC, which has the risk of thrombosis; (ii) antibody clearance using immunosuppressants, immunoglobulins, rituximab, plasma exchange and immunosorbents. Glucocorticoids are the first choice for immunosuppressants. The most common is oral prednisone/prednisolone at a dose of 1 mg/kg per day. Sometimes prednisone/prednisolone is used in combination with cyclophosphamide from the beginning of treatment, but the latter should not be used in patients of childbearing age. As a second-line drug, rituximab is often used in combination with glucocorticoids and is not recommended to be used alone. Immunoglobulin can inhibit the synthesis of antibody. The mechanism of intravenous human blood gamma globulin is mainly due to the combination of anti-individual genotype antibody and autoantibody in human blood gamma globulin products to inhibit its activity. In addition, human serum gamma globulin preparation inhibits antibody synthesis. In the case of severe bleeding associated with high titre inhibitors, plasma exchange and immunosorbent therapy can be used when antibodies must be removed quickly, especially in patients with severe bleeding (Figure 5).1,9,12

This patient was a young male with no previous history of haemorrhagic diseases and no family history, no history of anticoagulant or antiplatelet drug use, sudden spontaneous bleeding that was difficult to stop and routine haemostatic treatment was ineffective. Laboratory examination showed that Hb had decreased and APTT was prolonged. However, different from simple acquired factor VIII deficiency, the patient also had decreased coagulation
factors V and VII, so the plasma prothrombin time was prolonged. Initially, the patient was asked about his suspected history of anticoagulant rodenticide exposure, but after testing, no anticoagulant rodenticide component was detected in his blood. After treatment, the levels of coagulation factors V and VII returned to normal, and only coagulation factor VIII remained decreased. At the same time, the patient also had abnormal liver function, which does not rule out the possibility that a disorder of liver synthesis of coagulation factors may affect coagulation function. Genetic screening for bleeding and coagulation diseases identified two mutations in this current case: (i) a p.Y471H mutation the PLAT gene, which is associated with repeated thrombosis and abnormal fibrinolysis; (ii) a p.Y244Y mutation the SERPINE1 gene, which is associated with lifelong trauma, postoperative bleeding and haematoma. However, the patient had no previous history of thrombosis or haemorrhagic disease. This made the current diagnosis more unclear. Further clarification of the diagnosis was not achieved until the patient’s blood was sent to a professional haemophilia research centre, which detected anti-factor VIII antibodies. The patient’s laboratory examination excluded lupus disease, but the tumour markers were increased. Tumours were excluded by CT examination and the levels of tumour markers gradually decreased. Therefore, the reason for the formation of anti-factor VIII antibodies in the patient remains unclear. Because the patient’s factor VIII inhibitor titre was low (≤5 BU), the symptoms were gradually controlled after glucocorticoid treatment. Multiple follow-up examinations showed continuous complete remission. No factor VIII antibody was detected in his blood and coagulation factor VIII increased significantly.

In conclusion, AHA is a rare haemorrhagic disease characterized by spontaneous extensive subcutaneous haemorrhage and soft tissue haematoma. In this current case,
APTT was significantly prolonged, but prothrombin time, fibrinogen level and platelet counts were in the normal range. When lupus antibodies and other diseases that cause abnormal coagulation have been excluded, then if the APTT cannot be corrected when using a mixture of equal volumes of test plasma and normal plasma, it can be inferred that there is an antibody to a clotting factor present in the patient’s blood. When such patients are encountered clinically, they should be tested for coagulation factors and coagulation factor antibodies. This should enable early diagnosis and timely appropriate treatment. This should also help to avoid misdiagnosis, missed diagnosis, delayed diagnosis and aggravation of the disease.9

Author contributions
Xiangdong Jian conceived of the case report; Yingli Ren and Tianzi Jian contributed significantly to the data analysis and manuscript preparation; Guangcai Yu and Siqi Cui interpreted the data. All authors read and approved the final manuscript.

Declaration of conflicting interests
The authors declare that there are no conflicts of interest.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The present case report was supported by grants from the Shandong Key Research and Development Plan Project (no. 2015GSF118038 and no. 2016GSF201041).

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