Acquired hemophilia A

Yoshitomo Maesako^{1*}, Daiki Shimomura², Hitoshi Ohno¹

¹Department of Hematology, Tenri Hospital; ²Department of Clinical Pathology, Tenri Hospital

Received 2013/8/15; accepted 2013/8/28; released online 2013/12/25

Keywords: factor VIII, autoantibody, cross-mixing test, bypassing agents

Figure 1. Top: Pictures of the left forearm (left) and the right thigh (right), showing marked subcutaneous bleeding. Bottom: Transverse (left) and coronal (right) sections of CT scan with contrast material, showing a large hematoma surrounded by the peritoneum, iliacus muscle and psoas major muscle.

An elderly man initially presented with gross hematuria. Five days later, he was admitted to our hospital due to

swelling and subcutaneous bleeding of the left forearm (Figure 1). A computed tomographic (CT) scan suggested that the bleeding occurred within the muscles. His hemoglobin level was 9.7 g/dL, white blood cell count 8,100/ μ L with normal differential, and platelet count

*Correspondence to: Yoshitomo Maesako, MD, PhD
Department of Hematology, Tenri Hospital
200 Mishima, Tenri, Nara 632-8552, Japan
e-mail: maesako@tenriyorozu.jp

$184 \times 10^3/\mu\text{L}$. Blood chemistry data were unremarkable. The titer of anti-nuclear antibody was $\times 160$ (speckled type), while anti-cardiolipin antibodies were negative. He had no personal or family history of bleeding.

Routine tests of blood coagulation showed a prolonged activated partial thromboplastin time (APTT) and a normal

prothrombin time (Table 1), suggesting abnormalities of the intrinsic coagulation pathway. To differentiate between a clotting factor deficiency and an inhibitor directed against the clotting factor, we performed cross-mixing test, in which the patient's plasma was diluted with normal pooled plasma at a 1:1 ratio (5:5 in Figure 2) and the clotting test

Table 1. Results of coagulation tests

Variable	Value	Normal range
Prothrombin time (second)	11.8	10.5-13.3
Activated partial thromboplastin time (second)	109.8	23.0-35.0
Fibrinogen (mg/dL)	399	170-370
Fibrin degradation product ($\mu\text{g/mL}$)	8.0	<5
D-dimer ($\mu\text{g/mL}$)	2.2	<1.0
Activities of clotting factors (%)		
Factor VIII	<1.0	58.0-166.0
Factor IX	106.8	53.0-122.0
Factor XI	86.0	69.0-174.0
Factor XII	46.6	34.0-99.0
Titers of anti-clotting factor inhibitors (BU/mL)		
Factor VIII	36.14	≤ 0.50
Factor IX	0.43	≤ 0.50
Factor XI	0.00	≤ 0.50
Factor XII	0.15	≤ 0.50
Activity of von Willebrand factor (%)	≥ 201	50.0-150.0

BU, Bethesda unit. One BU is defined as the amount of antibody that can block half of the activity of a clotting factor over two hours at 37°C .

Figure 2. Cross-mixing test. After incubation for 2 hours at 37°C , the curve moved upward to show a "convex" appearance, indicating the presence of inhibitors against FVIII.

was repeated. When tested immediately after the dilution, APTT appeared to be corrected. However, when the diluted sample was incubated up to two hours at 37°C, APTT was again prolonged (Figure 2). This slow reaction kinetics is characteristic of factor VIII (FVIII) inhibitors.¹ We finally determined the activities of each clotting factor as well as the titers of inhibitors by the Bethesda assay (Table 1), and established the diagnosis of acquired hemophilia A.

Acquired hemophilia A is a hemorrhagic diathesis caused by the production of autoantibodies (inhibitors) against FVIII. The condition is associated with pregnancy, autoimmune disorders, or malignancy, or can develop with no underlying disorders. Spontaneous subcutaneous, deep muscle, and retroperitoneal bleeds represent the majority of events, while hemarthrosis is uncommon.¹ Bleeding is often severe, constituting a medical emergency. In the present patient, bleeding extended to the lower legs and retroperitoneum (Figure 1), requiring repeated blood transfusions.

The two primary goals of treatment focus on cessation

of bleeding and eradication of the autoantibodies,¹ and in clinical practice, both treatments should be started concurrently. For the former goal, two “bypassing” agents are currently available, namely, activated recombinant factor VII (NovoSeven®) and activated prothrombin complex concentrates (factor eight inhibitor bypassing activity; FEIBA). Both agents are injected intravenously until effective hemostasis is achieved. To eradicate inhibitors, on the other hand, prednisolone alone or in combination with cyclophosphamide is most widely used. Rituximab may be used as a second-line or salvage therapy, although its use is not approved in Japan. The patient presented here was treated with these agents for over 1 month, resulting in resolution of the bleeding; anti-FVIII inhibitors are currently negative and coagulation test results have become normal.

REFERENCES

1. Sborov DW, Rodgers GM. How I manage patients with acquired haemophilia A. *Br J Haematol* 2013;161:157-165.

後天性血友病 A

前迫善智¹, 下村大樹², 大野仁嗣¹

¹ 天理よろづ相談所病院 血液内科

² 天理よろづ相談所病院 臨床検査部