

Unusual Initial Manifestation of Acquired Hemophilia A: A Normal Activated Partial Thromboplastin Time, Intramuscular Hematoma and Cerebral Hemorrhage

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Abstract

We herein present a case of acquired hemophilia A with a normal activated partial thromboplastin (aPTT), intramuscular hematoma and cerebral hemorrhage occurring in a 73-year-old man. The patient visited our emergency department with gait disturbance, pain and swelling in his right leg. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed intramuscular hematoma and intracranial hemorrhage. The results of initial coagulation studies were normal, but repeated coagulation studies revealed an isolated prolongation of the aPTT. Additional laboratory tests confirmed the diagnosis of acquired hemophilia A. If the initial aPTT is normal, we should therefore repeat the aPTT and also perform other coagulation studies including a mixing study, factor VIII level and inhibitor, to investigate the underlying diseases in elderly patients with spontaneous hemorrhaging of unknown etiology.

Key words: activated partial thromboplastin time, intramuscular hematoma, cerebral hemorrhage, acquired hemophilia A

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Introduction

Acquired hemophilia A is a rare but potentially life-threatening bleeding disorder that is caused by autoantibodies against factor VIII. Acquired hemophilia A is usually suspected in patients with an isolated prolongation of the activated partial thromboplastin time (aPTT). We herein present a case of acquired hemophilia A with a normal aPTT, intramuscular hematoma and cerebral hemorrhage.

Case Report

A 73-year-old man with a history of hypertension, gastric cancer and abdominal aortic aneurysm visited our emergency department complaining of gait disturbance, pain and swelling in his right leg. His leg had become swollen five days ago and he was not able to walk smoothly. He had not experienced any trauma or fever and had not undergone an

operation in the past month. On examination, his blood pressure was 162/81 mmHg, heart rate was 81 beats per minute and body temperature was 36.4°C. His right thigh demonstrated tender swelling, and the neurological findings revealed a shot-stepped gait without any paralysis or sensory disturbance. Laboratory test results revealed a hemoglobin level of 10.4 g/dL (normal, 13.2-17.2 g/dL), hematocrit of 30.4% (normal, 40.4-51.1%), a von Willebrand factor activity of 203% (normal, 60-170%), elevated fibrinogen of 569 mg/dL (normal, 200-400 mg/dL) and elevated D-dimer level of 1.5 µg/mL (normal, 0.0-1.0 µg/mL). His aPTT level of 34.7 seconds (normal, 26.9-38.1 seconds) was normal, while the prothrombin time international normalized ratio, platelet count and liver function were also within the normal ranges. A computed tomography (CT) scan demonstrated intramuscular hematoma in his right thigh (Fig. 1). The CT also demonstrated no recurrence of gastric cancer, and no new expansion and false lumen enhancement of the abdominal aorta. He had not experienced any previous bleeding epi-

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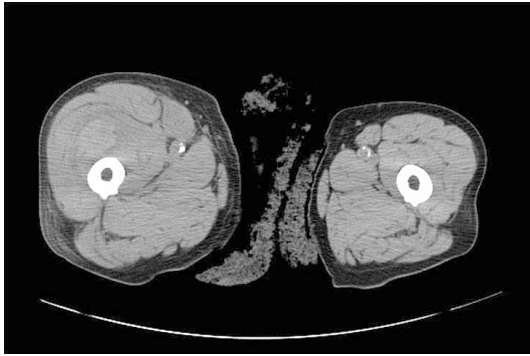


Figure 1. Computed tomography scan showing an intramuscular hematoma in the right thigh.

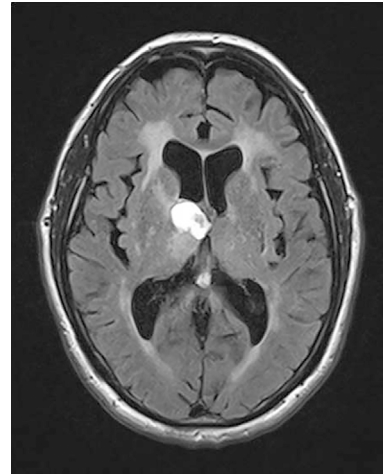


Figure 2. T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI showing a right thalamic hemorrhage.

sodes, even during two previous surgeries (for gastric cancer and for an abdominal aortic aneurysm), and he also had no family history of bleeding.

Four days later, head magnetic resonance imaging (MRI) was performed for further evaluation of his gait disturbance. MRI showed an intracranial hemorrhage, which was responsible for the gait disturbance (Fig. 2). We therefore repeated coagulation studies and detected an isolated prolongation aPTT of 41.4 seconds. Additional laboratory studies including mixing studies, factor VIII and inhibitor titer were ordered. Mixing studies showed no correction by incubating for 2 hours at 37°C patient's plasma with equal volumes of normal plasma. The results of other studies showed a factor VIII antibody with a titer of 1 Bethesda unit/mL (normal, 0 Bethesda units/mL) and decreased factor VIII activity of 22.2% (normal, 50-150%). These results confirmed a diagnosis of acquired hemophilia A. Treatment with 40 mg oral prednisone was initiated without any inhibitor bypassing agents, and no further bleeding episodes occurred. In response to the treatment, the aPTT normalized, while the factor VIII activity was over 100%, and the factor VIII antibody was eradicated according to the level of Bethesda units.

Discussion

The course of the patient indicated two important clinical issues. There is the possibility of a normal aPTT in the initial evaluation in a patient with acquired hemophilia A, and acquired hemophilia A rarely causes life-threatening intracranial hemorrhage.

Regarding the first issue, the diagnostic hallmark of acquired hemophilia A is usually based on the detection of an isolated prolongation of the aPTT. Many algorithms for making a differential diagnosis of acquired hemophilia A start from the isolated prolongation of the aPTT (1, 2). However, a report from a quantitative case-based survey of physicians across multiple specialties suggested that a prolonged aPTT may be overlooked even in actively bleeding patients, especially when the aPTT is only slightly prolonged (3). Acquired hemophilia A with a minimally prolonged aPTT of 41.0 seconds has also been reported (4). In

our patient, the initial aPTT was normal (34.7 seconds) on admission, and a prolonged aPTT was detected for the first time on the 4th day. We speculated that the reason for the normal aPTT at the initial evaluation was due to a low disease level with a titer of 1 for Bethesda units/mL. If we had not repeated the coagulation studies, we might not have diagnosed this potentially life-threatening disorder. This case is the first reported case of acquired hemophilia A with a normal aPTT at the initial evaluation.

Regarding the second clinical issue, most patients with acquired hemophilia A have hemorrhage in the skin, muscles or soft tissues (5), while intracranial hemorrhage is rare (6). However, if it occurs, it sometimes leads to death (7, 8). In our patient, we detected intracranial hemorrhage and made a diagnosis of acquired hemophilia A before any life-threatening events occurred. A delay in establishing a diagnosis for acquired hemophilia A can result in severe bleeding and death, and we should therefore investigate the underlying diseases with spontaneous hemorrhage cases of unknown cause, especially in elderly patients.

In conclusion, in patients with acquired hemophilia A, there is the possibility of demonstrating a normal aPTT at the initial evaluation, and life-threatening intracranial hemorrhage rarely occurs in patients with acquired hemophilia A. If the initial aPTT is normal, we should nevertheless repeat coagulation studies and examine other coagulation studies including a mixing study, factor VIII level and inhibitor to investigate the underlying diseases in elderly patients with a spontaneous hemorrhage of unknown etiology. It is not uncommon to see bleeding symptoms in elderly patients in an emergency department. However, we are prone to attribute these events to anticoagulation therapy, antiplatelet therapy or hepatic disorders. Our case suggested that we should conduct repeated coagulation studies, in order to make a differential diagnosis of bleeding and also carry out adequate consultations with a hematologist.

The authors state that they have no Conflict of Interest (COI).

References

1. Tiede A, Werwitzke S, Scharf RE. Laboratory diagnosis of acquired hemophilia A: limitations, consequences, and challenges. *Semin Thromb Hemost* **40**: 803-811, 2014.
2. Shetty S, Bhave M, Ghosh K. Acquired hemophilia A: diagnosis, aetiology, clinical spectrum and treatment options. *Autoimmun Rev* **10**: 311-316, 2011.
3. Reding MT, Cooper DL. Barriers to effective diagnosis and management of a bleeding patient with undiagnosed bleeding disorder across multiple specialties: results of a quantitative case-based survey. *J Multidiscip Healthc* **5**: 277-287, 2012.
4. Shander A, Walsh C, Bailey H, Cromwell C. Acquired hemophilia presenting as profound hematuria: evaluation, diagnosis, and management of elusive cause of bleeding in the emergency department setting. *J Emerg Med* **45**: e1-e6, 2013.
5. Franchini M, Mannucci PM. Acquired haemophilia A: a 2013 update. *Thromb Haemost* **110**: 1114-1120, 2013.
6. Bonnaud I, Saudeau D, de Toffol B, et al. Recurrence of spontaneous subdural haematoma revealing acquired haemophilia. *Eur Neurol* **49**: 253-254, 2003.
7. Mashiko R, Yamamoto T, Sato M, Noguchi S, Matsumura A. Acquired hemophilia first manifesting as life-threatening intracranial hemorrhage: case report. *Neurol Med Chir (Tokyo)* **49**: 93-95, 2009.
8. Knoebl P, Marco P, Baudo F, et al; EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *J Thromb Haemost* **10**: 622-631, 2012.

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