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Case Report

Patient Diagnosed with Acquired Hemophilia A who Developed Intramuscular Hematoma during Comprehensive Rehabilitation after Stroke: A Case Report

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뇌졸중 이후 포괄적 재활치료 도중 근육 내 혈종이 발생하여 후천성 혈우병 A로 진단된 환자: 증례보고

정연규 · 문현임

분당제생병원 재활의학과

Abstract

Acquired hemophilia A (AHA) is a rare but fatal disease that leads to severe bleeding by autoantibodies to endogenous factor VIII. AHA is more prevalent in elderly patients with underlying comorbidities. Pathophysiology and treatment strategies of AHA are quite different from congenital hemophilia A. AHA is difficult to diagnose early unless the clinician understands and suspects the disease. Delayed diagnosis can have devastating consequences, especially for the elderly. The main goals of the treatment are to control bleeding and eradicate autoantibodies using immunosuppressive agents. We report a case of a 76-years-old patient who bruised easily and developed intramuscular hematoma diagnosed with AHA during comprehensive rehabilitation after subacute stroke. Although intramuscular hematomas or bruises are common during stretching exercise, if intramuscular, mucosal, or submucosal bleeding of unexplained causes persists despite low-intensity rehabilitation treatment in an elderly without a personal or family history of bleeding, AHA should be suspected.

Key Words

Acquired hemophilia A, Intramuscular hematoma, Comprehensive rehabilitation

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Introduction

Acquired hemophilia A (AHA) is a rare but life-threatening disease that leads to severe bleeding and is caused by autoantibodies to endogenous factor VIII (FVIII). It occurs in both men and women without any previous history of bleeding.[1,2] Although most of the cases are idiopathic, AHA is more prevalent in elderly patients with underlying comorbidities such as autoimmune disorders, malignancy, and infection.[1,3] AHA is a disease with high morbidity and mortality rates resulting from underlying comorbidities, bleeding, or complications of treatments.[1,3]

Incidence of AHA has been reported around 1.2-1.48 cases per million people every year but is significantly higher in the elderly, with 14.7% of all patients over 85 years of age.[4,5] In elderly patients undergoing rehabilitation treatment in the subacute phase after stroke, although rare, AHA can be associated with comorbidities. To our knowledge, there have been no reports of cases of AHA being diagnosed during rehabilitation treatment. Here, we present a case of a 76-years-old patient who bruised easily and developed intramuscular hematoma during comprehensive rehabilitation after intracranial hemorrhage (ICH) diagnosed with AHA.

Case Report

A 76-years-old woman with no personal or family history of bleeding was referred to our hospital with sudden onset of left side weakness, and mental change of about 3.8 cm sized acute ICH in the right frontal lobe confirmed by brain computed tomography (CT). She underwent craniotomy and evacuation of ICH by the neurosurgeon on the next day, and after a month, she was transferred to the rehabilitation medicine department and started early comprehensive rehabilitation treatment. On the initial evaluation, her range of motion was a full range in all of bilateral joints, and on the manual muscle test, her muscle strength on the affected side was grade 1, and that on the unaffected side was grade 3. Her Korean Mini-Mental State Examination score was 5/30. She was only able to ambulate by wheelchair, and it was difficult to communicate due to her cognitive impairment. Therefore, rehabilitation treatments were performed with low intensity gentle passive range of motion (ROM) stretching and sitting balance training. Low-intensity active assisted ROM exercise for the left side, and static standing balance training with an assistive device such as a standing frame were performed, and muscle strengthening for the right lower extremity was not excessively performed. Two months later, the swelling was found in her right thigh, and an 11.3 x 7.7 cm sized intramuscular hematoma was confirmed in CT (Fig. 1). During the two-month period, there was no traumatic history, and she had not taken any medications that may increase the risk of bleeding, such as non-steroidal anti-inflammatory drugs, antiplatelet drugs, and anticoagulants. In spite of conservative treatment such as compression using an elastic bandage and application of an ice pack on the hematoma site, hemoglobin (Hb) decreased from

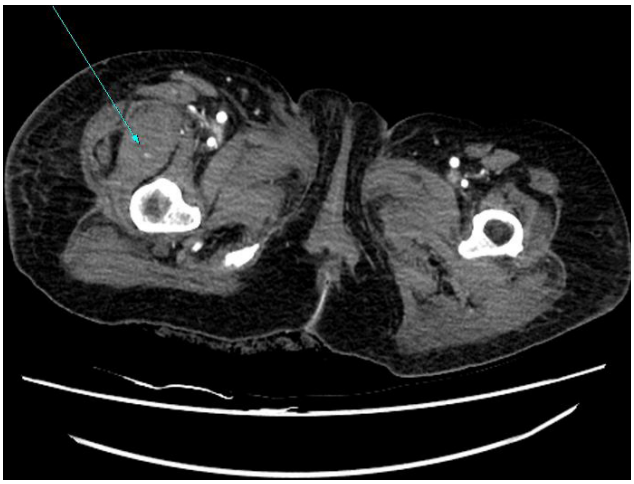

Fig. 1. 11.3 x 7.7 cm sized intramuscular hematoma confirmed in computed tomography.

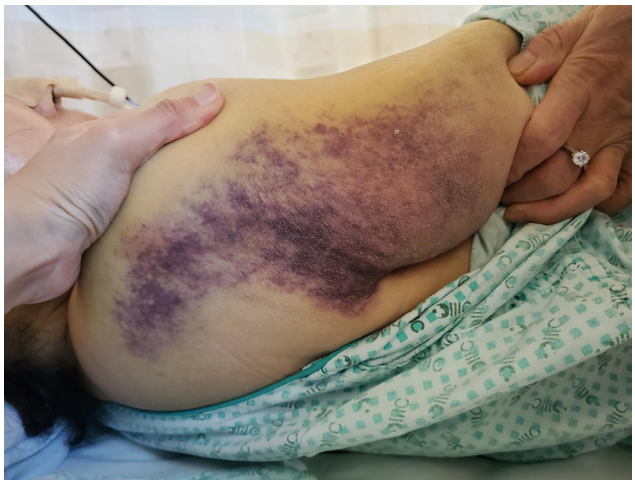

Fig. 2. Multiple bruises found on her limbs.

10.6 to 6.8 g/dL in two days. We performed brain CT and abdominal-pelvic CT to rule out other bleeding focuses, and no other points were found. Despite the transfusion of one pack of packed red blood cells (PRBC) per day, Hb level was consistently found to be between 6.8 and 7.5 g/dL. Even after withholding the rehabilitation treatment, she had multiple bruises on her limbs (Fig. 2). She was referred to a hematologist and underwent coagulation tests. The prothrombin time (PT) was normal, and activated partial thromboplastin time (APTT) was extended to 80 seconds. As APTT prolongation was found, three pints of daily fresh frozen plasma (FFP) transfusion was performed. However, the abnormal findings continued to be Hb 6.8-7.5 g/dL and aPTT 70-80 seconds. She was referred to the Korea Hemophilia Foundation (KHF), and on November 6th, 2021, she was diagnosed with AHA with an elevated FVIII antibody of 5.04 Bethesda unit (BU)/mL and 1.7% of FVIII level. With the diagnosis of AHA, maintenance therapy of factor eight inhibitor bypassing activity (FEIBA) for at least six months and oral prednisone and oral cyclophosphamide for six weeks was recommended, and she was transferred to the other hospital. According to the recommendation of KHA, FEIBA of 50 International units (IU)/kg per every other day, prednisone 50 mg/day, and cyclophosphamide 100 mg/day were applied, and after three days, the dose of FEIBA was increased to 100 IU/kg/dose, two doses/day.

Discussion

AHA is a rare but fatal disease with 20% of mortality rates, as antibodies to endogenous FVIII interfere with normal hemostasis and possibly lead to fatal catastrophic bleeding.[6] Although it is common for Hb reduction of below 7 to persist despite continuous RBC and FFP transfusions due to massive bleeding during or after surgery or delivery, it is rare that such a condition is detected during comprehensive rehabilitation after subacute stroke. In this case, the patients showed symptoms of easy bruising and intramuscular hematoma, and there was no evidence of GI bleeding. Bruises and intramuscular hematomas that occur from passive ROM stretching exercise are quite common, but in most cases, conservative treatment such as compression and cryotherapy on the site of hematoma can improve symptoms, and if necessary, RBC transfusion can normalize Hb levels. However, in this case, Hb decrement persisted in spite of continuous RBC and FFP transfusions. In case of bleeding tendency, family history, traumatic history, and history of taking medications with bleeding risk should be investigated, but none of these were found in our patient. Accordingly, we intuitively realized that it is unusual, and under consultation with a hematologist, FVIII test and FVIII antibody test, which is available at the KHF were performed and diagnosed her with AHA.

AHA is predominant in the elderly (median age 64-78 years), and most of the cases are idiopathic (50%), but AHA is also can be associated with autoimmune disorders (most commonly rheumatoid arthritis), malignancy, pregnancy, medications, dermatologic conditions, and infection.[1,3] However, in our patient, since there was no specific cause as above, it is most likely idiopathic. It is reported that the prevalence of autoantibodies increases significantly in the elderly due to tissue damage and high exposure to apoptotic cells, and these mechanisms appear to be the most probable cause of AHA in our patient.[7]

AHA is difficult to diagnose early, and it is underdiagnosed due to its rarity and the unawareness of the disease. Also, it is underreported because of the severity of AHA with life-threatening bleeding, especially in the elderly which other bleeding disorders may coexist.[8] Thus, AHA is easily overlooked, and delayed diagnosis may worsen the outcomes.[5,8] Additionally, AHA patients mostly do not have any past medical or familial history of bleeding, and the symptoms of AHA also vary across patients, from mild symptoms to severe major bleeding, which makes diagnosis more complicate.[5,8]

AHA is different from congenital hemophilia A (CHA) in many ways. The presence of autoantibodies against FVIII instead of the absence of FVIII is the pathophysiology of AHA different from CHA.[5] Also, the clinical presentation

of AHA is not identical to CHA. Although CHA presents as hemarthrosis, AHA presents as subcutaneous blood extravasations, mucosal hemorrhages, and intramuscular hemorrhages.[4,6,8] Severe bleeding, including gastrointestinal and intracranial bleedings, can also be seen in AHA[6].

Laboratory findings of AHA are prolonged APTT with a normal range of PT, presence of autoantibodies against FVIII, and decreased FVIII levels.[9] The severity of bleeding in AHA does not have any relationship with the level of FVIII and APTT.[10] For diagnosis of AHA, first-line test findings are a prolonged APTT with a normal range of PT. In such a state, Tiede et al.[2] suggested mixing test, analysis of FVIII activity, and analysis of lupus anticoagulant for differential diagnosis, and if AHA is very likely, consultation to expert and special tests such as Bethesda assay or enzyme-linked immunosorbent assay for anti-FVIII antibodies are recommended to confirm AHA. Our patient had a prolonged APTT of more than 80 seconds, and thus, a mixing test was performed. The mixing test involves mixing the patient's plasma and pooled normal plasma in a 1:1 ratio to see whether APTT normalizes, and failure to normalize APTT suggests a possible presence of an inhibitor to FVIII.[10] After that, the confirmation test can be performed by requesting the KHA, and our patient was confirmed with AHA.

The main goals of the treatment of AHA are to control bleeding, avoid procedures that can induce bleeds, and eradicate autoantibodies using immunosuppressive agents.[12] In the first place, if Hb falls below 7, PRBC transfusion should be performed. In addition, once APTT prolongation is found, transfusion of FFP, which contains FVIII can be initiated, but APTT may be seldom corrected in patients with AHA.[12] If AHA is confirmed, hemostatic therapy using bypassing agents should be initiated as soon as possible for acute bleeding episodes. FEIBA is one of the activated prothrombin complex concentrates and has been reported to have a response rate of 76% in severe bleeding and 100% in moderate bleeding.[13] However, major adverse effects such as thromboembolic events, including myocardial infarction, disseminated intravascular coagulation, pulmonary embolism, and ischemic stroke, should be cautioned, especially in elderly patients.[10,13]

Besides, it is recommended that patients with AHA should undergo immediate inhibitor eradication with immunosuppressive therapy. Patients with FVIII antibodies greater than 5 BU/mL, such as our patient, are generally refractory to FVIII replacement therapy, and immunosuppressive therapy is usually started to eradicate the inhibitors.[10] It has been reported that the overall mortality rate without treatment was 41%, but immunosuppressive therapy was able to reduce the mortality rate to 20%.[12] The most common regimen utilizes steroids alone (prednisone 1-2 mg/kg/day for 4-6 weeks) or in combination with cyclophosphamide (1-2 mg/kg per day for 5 weeks), have reported of 70-80% of complete remission rate.[10] But, limited efficacy of immunosuppressive therapy has been reported in patients with FVIII antibody titers of more than 200 BU/mL.[14] Our patient was treated with FEIBA, prednisolone, and cyclophosphamide according to the recommendation of the hematologist of KHA.

In conclusion, this is a rare case in which a patient who bruised easily and developed intramuscular hematoma during comprehensive rehabilitation treatment after ICH was diagnosed with AHA. Although intramuscular hematomas or bruises are common during passive ROM stretching, there is a possibility of AHA in elderly patients with persistent symptoms or severe drop of Hb despite low-intensity rehabilitation treatment. If intramuscular, mucosal, or submucosal bleeding of unexplained causes persists in an elderly without a personal or family history of bleeding, although rare, AHA should be suspected, and a referral to a hematologist is required and proper examination and timely treatment are vital for the patient's prognosis.

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