

The First Case of Postpartum Acquired Hemophilia A in Korea

Ji Hyun Lee¹, Dong-Hwan Kim²,
Kiyoung Yoo³, Yongmook Choi³,
Sun-Hee Kim¹ and Hee-Jin Kim¹

Departments of ¹Laboratory Medicine & Genetics
and ²Medicine, Samsung Medical Center,
Sungkyunkwan University School of Medicine,
Seoul; ³Korea Hemophilia Foundation, Seoul, Korea

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Address for Correspondence:
Hee-Jin Kim, MD

Department of Laboratory Medicine & Genetics, Samsung
Medical Center, Sungkyunkwan University School of Medicine,
81 Ilwon-ro, Gangnam-gu, Seoul 135-710, Korea
Tel: +82.2-3410-2710, Fax: +82.2-3410-2719
E-mail: heejin@skku.edu

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Acquired hemophilia A (AHA) is a rare coagulopathy caused by autoantibodies to coagulation factor VIII (FVIII). Most patients with AHA have been previously healthy; however, a variety of morbidities have been associated with the condition including pregnancy. A 40-yr-old woman visited our institution with extensive hematoma on the right hip area. Her medical history revealed no personal or familial history of bleeding diathesis. Her coagulation tests showed markedly prolonged aPTT (117 sec), markedly decreased level of FVIII activity (0.4%) and high-titer FVIII inhibitor (77 BU). Collectively, she was diagnosed as having postpartum AHA and was treated with bypassing agents and corticosteroids. Her aPTT was normalized on the 174th postpartum day and FVIII inhibitor showed negative conversion on the 224th postpartum day. This is the first case of postpartum AHA with high-titer FVIII inhibitor in Korea. Timely diagnosis and management can reduce morbidity and mortality of this potentially life-threatening condition.

Key Words: Acquired hemophilia A; Postpartum; Factor VIII inhibitor; Korea

INTRODUCTION

Acquired hemophilia A (AHA) is a rare acquired coagulopathy caused by autoantibodies to coagulation factor VIII (FVIII) (1, 2). Although the estimated incidence of AHA is 0.2-1.0 case per one million population per year, cases with a low titer antibodies may be underestimated unless diagnostic coagulation tests are performed in suspected individuals (3). Most of the affected patients have been previously healthy, with idiopathic AHA accounting for approximately 50% of cases (4). Immunologic disorders (such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis and graft-versus-host disease after allogeneic bone marrow transplant), dermatological disorders, malignancy, old age and pregnancy have been known to be associated with the development of autoantibodies to factor VIII (1). Postpartum AHA constitutes 7% to 11% of patients with acquired FVIII inhibitors and is observed more often in primigravidas (1, 5) and has rarely been detected during pregnancy or labor (6). In most cases, the onset of symptoms is usually within a few days to 4 months postpartum, but it may occur as late as 1 yr afterwards. Suspicion of the condition in unexplained postpartum bleeding with prolonged aPTT and timely diagnosis and prompt management including bleeding control and eradication of the inhibitor by immunosuppressive therapy are important to improve the prognosis.

Here we report a case of AHA developed shortly after preg-

nancy and successfully treated with immunosuppressive treatment and corticosteroids. To the best of our knowledge, this is the first report of postpartum AHA in Korea.

CASE DESCRIPTION

A 40-yr-old woman visited our hospital, on November, 9, 2009, with an extensive hematoma on right hip area. She had delivered a full-term baby from her second pregnancy uneventfully 65 days before by Cesarean section at an outside institution. Five days after delivery, she presented with vaginal bleeding and high fever up to 40°C. She was transfused with packed red blood cells for anemia (Hb 6.0 g/dL) and received uterine arterial embolization therapy via femoral artery to control the vaginal bleeding. Swelling and pain on right femoral area where the arterial embolization had been performed exacerbated and progressed to hematoma. Initial coagulation studies at our institution showed markedly prolonged aPTT (117 sec) (reference range, 29.1-41.9 sec), which was not corrected on an immediate 1:1 mixing study with normal plasma (53.6 sec). The mixing test results by prolonged incubation for 1 and 2 hr at 37°C showed further prolongation (73.7 and 96.7 sec, respectively), compatible with the pattern of delayed-acting inhibitor. Factor assays revealed a markedly decreased level of FVIII activity at 0.4% (severe), while other factor activities were within normal ranges. Anti-FVIII Ab assay revealed a high-titer FVIII inhibitor at 77 Bethesda units (BU).

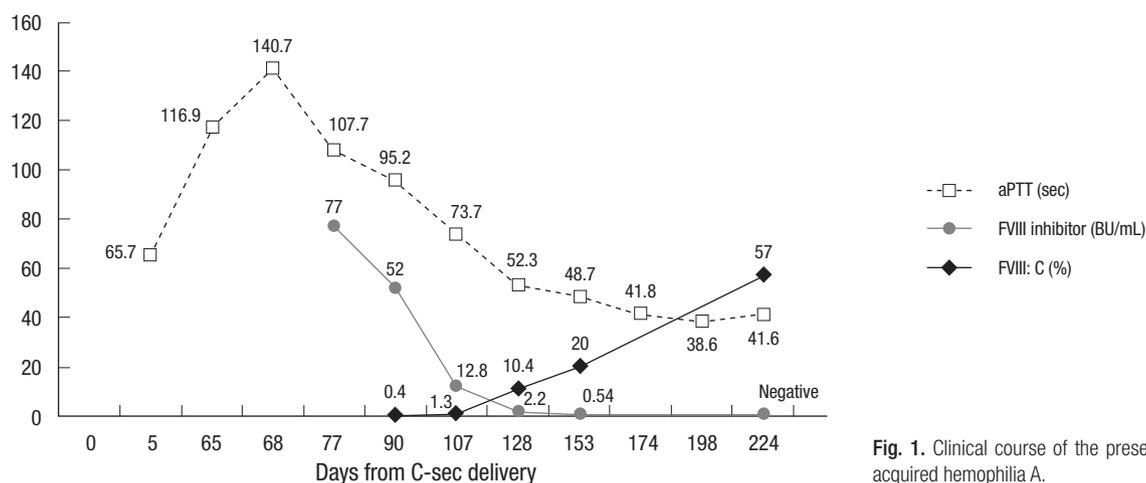


Fig. 1. Clinical course of the present case of postpartum acquired hemophilia A.

Tests for anti-phospholipid Ab revealed negative results for anti-cardiolipin Abs and anti-beta 2 glycoprotein I Abs, while lupus anticoagulant (LA) tests were positive (PTT-LA 138.1 sec and Staclot LA 20.4 sec). Her medical history revealed that she did not have any significant medical history and familial history of coagulopathy. She had a history of induced abortion 2 yr previously, and the coagulation times on that occasion was reported to be within reference ranges (aPTT 26.1 sec and PT 0.91 INR). Collectively, she diagnosed with postpartum AHA with high-titer FVIII inhibitor.

Based on the diagnosis, she was treated with factor eight inhibitor bypassing activity (FEIBA, Baxter, Westlake Village, CA, USA), recombinant activated factor VII (NovoSeven, Novo Nordisk, Princeton, NJ, USA), and corticosteroids. She gradually recovered from hematoma with a progressive improvement of coagulation tests. Her aPTT was normalized (41.8 sec) on the 174th postpartum day, and FVIII inhibitor showed negative conversion on the 224th postpartum day (Fig. 1). Along with the normalization of aPTT, tests for LA also demonstrated negative results. She is currently on routine follow-up without any oral prednisone or hemorrhagic manifestations.

DISCUSSION

AHA is a condition of potentially life-threatening bleeding diathesis caused by autoantibodies against FVIII. While FVIII alloantibodies can occur in 20%-30% of patients with severe form of hereditary hemophilia, FVIII autoantibodies can be acquired spontaneously in postpartum women, in patients with immunologic disorders or with other conditions such as malignancy who previously had normal levels of FVIII, or in old age (7). The patient described in the present report was relatively young and did not have a past medical history relevant to the development of AHA. Taking the clinical course of the occurrence of inhibitor following pregnancy, the diagnosis of post-partum AHA was clinically established. The presence of non-specific inhibitor was

not likely based on the findings of negative solid-phased Abs (anti-cardiolipin and anti-beta2 glycoprotein I). The screening and confirm tests for LA were initially positive; however, positive LA tests by the Staclot LA reagent along with negative solid-phase tests could be considered to be due to the interference of anti-FVIII Ab with phospholipid-dependent coagulation test rather than true presence of LA (8). Indeed, the LA tests revealed negative values along with the normalization of aPTT after treatment. Unfortunately, extensive laboratory workup to search for other underlying conditions was not performed due to the emergent situation of the patient. Risk factors and pathogenesis of pregnancy-related FVIII autoantibodies still remain unclear (9). As these inhibitors develop more frequently during the postpartum period, it was hypothesized that the mother developed antibodies when exposed to fetal FVIII during the delivery (10). However, this theory does not explain the absence of an anamnestic response in subsequent pregnancies. A review of the literature revealed that there were no recurrences on second pregnancies in 8 patients with postpartum FVIII inhibitors whose inhibitors had disappeared (11). In our case, the patient presented the initial symptom 5 days after her second delivery. However, the appropriate management was not instituted until postpartum day 77 due to delayed diagnosis. Patients with acquired inhibitors typically do not have a personal or family history of bleeding episodes, which could lead to increased morbidity and mortality from uncontrolled hemorrhage because of the delay of diagnosis. In addition, pregnancy itself is a blood-losing event and could be accompanied by changes in the coagulation system (6). Although postpartum AHA is known to have a favorable outcome with a high percentage of spontaneous remissions, the mortality due to hemorrhage has been reported between 12% and 22% (2, 3, 12). In particular, the prognosis is worse in patients with a high-inhibitor titer, low FVIII plasma activity, and high transfusional requirements. Therefore, recognition of this condition, clinical suspicion, and timely diagnosis by appropriate coagulation workup are important to reduce morbidity and mor-

tality of postpartum AHA. In our case, the patient had high-titer FVIII inhibitor (76.8 BU), which persisted until postpartum day 224 despite the treatment with bypassing agent and corticosteroids. This is in line with the previous observation that high-titer inhibitors (> 10 BU) do not easily disappear spontaneously and may be resistant to treatment with immunosuppressive therapy. On the other hand, if the inhibitor titer is low (< 5 BU), the inhibitors generally disappear spontaneously and do not recur on subsequent pregnancies (13).

The first aim of the management of postpartum AHA is to control acute bleeding, while the final aim is to accelerate eradication of the inhibitors (14). Bypassing agents are currently the most widely used first-line treatment, and both rFVIIa and FEI-BA have been shown to be effective for bleeding control. When a large amount of activated factor VII is infused, tissue factor is not required and the factor VIIa directly activates factor X on the surface of activated platelets, bypassing FVIII and FIX and thus circumventing the actions of inhibitory antibodies developed (15). For the eradication of FVIII inhibitor, immunosuppressive therapy with corticosteroids and cytotoxic drugs, alone or in combination, has been the mainstay of therapy for the enduring remission. Also, it has been recently reported that rituximab (anti-CD20 monoclonal antibody) and the extracorporeal removal of the autoantibody by plasmapheresis were effective especially in cases with very high-titer inhibitors (16-18).

There have been a couple of published reports on AHA in Korea, in associated with *Mycoplasma pneumoniae* infection and Cobra toxin intake (19, 20). However, this is the first report on postpartum AHA in Korea. Suspicion of postpartum AHA and timely diagnosis and management are critical to reduce morbidity and mortality in this rare but potentially life-threatening condition.

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