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**Case Report**

# Acquired Hemophilia A with Massive Hemorrhage after Cesarean Section

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*ABSTRACT*

Acquired hemophilia A (AHA) is a rare, but life-threatening disease caused by factor VIII inhibitors. We report on a woman with massive hemorrhage of unknown cause after cesarean section. She was first treated for atonic bleeding. She received a blood transfusion and underwent hysterectomy and laparotomic hemostasis but failed to respond and was, therefore, referred to our hospital on postpartum day 18. Laboratory studies revealed prolonged activated partial thromboplastin time without disseminated intravascular coagulation, suggesting the possibility of a coagulation disorder. The patient was found to have factor VIII inhibitors and was rescued by treatment with recombinant activated factor VII and surgery. Combination drug therapy with prednisolone and cyclosporine A eradicated the inhibitors 5.5 months after the first admission to our hospital. After childbirth, the incidence of atonic bleeding is frequent, and diagnosing acquired hemophilia A is difficult ; thus, AHA can be a critical complication of pregnancy. It is important to take consider the possibility of clotting disorders and to perform coagulation tests. A prolonged activated partial thromboplastin time should not be dismissed. (Jikeikai Med J 2011 ; 58 : 17-21)

Key words : acquired hemophilia A, postpartum, recombinant activated factor VII

## INTRODUCTION

Acquired hemophilia A (AHA) is a rare bleeding disorder caused by the development of autoantibodies against coagulation factor VIII. Its incidence has been estimated to be 0.2 to 1.0 per 1 million persons per year[1,2]. Several clinical situations are associated with acquired hemophilia A, including autoimmune disorders, malignancies, and the postpartum state[1-3]. Postpartum acquired hemophilia A accounts for 7% to 21% of all cases[1-3]. The mechanism by which pregnancy leads to development of factor VIII inhibitors is unclear.

## CASE REPORT

A 39-year-old nulligravida woman with a history of bronchial asthma had a dichorionic twin pregnancy after in vitro fertilization-embryo transfer (IVF-ET). She had no bleeding tendency until she underwent cesarean section in week 37 because of breech presentation. Estimated blood loss was 2,350 mL intraoperatively, and she received 4 units of red blood cells. After being discharged on day 12, she was readmitted with massive vaginal bleeding. Although she underwent hysterectomy with an intraoperative blood loss of 1,730 mL, a large hematoma developed in the abdominal wall (Fig. 1). A second laparotomy was performed for hemostasis, and multiple oozing sites were observed

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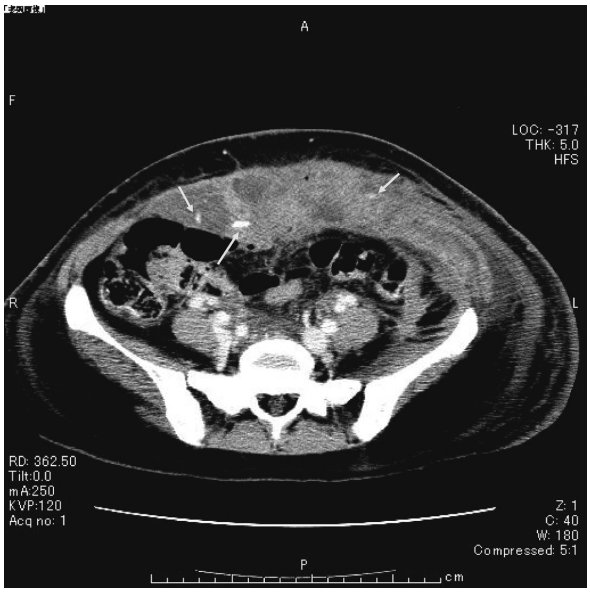


Fig. 1. Abdominal computed tomography with contrast enhancement shows a massive hematoma in the anterior abdominal wall and multiple active bleeding sites (arrowheads). Hematomas were also found throughout the pelvic cavity.

Table 1. Hematological and immunological tests on admission

| | |
|---|---|
| White blood cells | 4,900 /$\mu$L |
| Red blood cells | $242\times10^4$ /$\mu$L |
| Hemoglobin | 7.3 g/dL |
| Hematocrit | 20.4% |
| Platelets | $5.5\times10^4$ /$\mu$L |
| PT | 68% |
| APTT | 71.5 sec |
| Fibrinogen | 333 mg/dL |
| Fibrinogen degradation products | 5 $\mu$g/mL |
| D-dimer | 4.4 $\mu$g/mL |
| antithrombin III | 76% |
| PT-international normalized ratio | 1.3 |
| Rheumatoid factor | 7.1 IU/mL (0-20) |
| antinuclear antibody | 7.6 (0-19.9) |
| anti-DNA antibody | 2.0 IU/mL (0-6.0) |
| anti-ssDNA antibody | 5 U/mL (0-10) |
| anti-RNP antibody | 7 U/mL (0-10) |
| anti-Sm antibody | 7 U/mL (0-10) |
| anti-ssA antibody | 7 U/mL (0-10) |
| anti-ssB antibody | 7 U/mL (0-10) |
| anti-Scl-70 antibody | 7 U/mL (0-10) |
| anti-Jo-1 antibody | 7 U/mL (0-10) |
| lupus anticoagulant | 1.06 (0-1.29) |
| anti-cardiolipin-β2-glycoprotein 1 | 1.7 U/mL (0-3.4) |
| IgG | 1,589 mg/dL (870-1,700) |
| IgA | 287 mg/dL (110-410) |
| IgM | 91 mg/dL (35-220) |
| C3 | 134 mg/dL (65-135) |
| C4 | 33 mg/dL (13-35) |
| CH50 | 56.8 U/mL (30-50) |

around the rectus abdominis muscle ; blood loss was 2,050 mL. Because blood loss from the drainage tube continued to increase, the patient was finally referred to our hospital on day 18. By this time, she had received a total of 34 units of red blood cells, 42 units of fresh frozen plasma, and 10 units of platelets.

On admission of the patient to our intensive care unit, we found marked prolongation of the activated partial thromboplastin time (APTT ; 71.5 seconds) without findings of disseminated intravascular coagulation (DIC) (Table 1). First, we performed pelvic and epigastric artery embolization, but the bleeding continued. Next, we performed a mixing study to rule out a coagulation factor disorder, and the result suggested the presence of a coagulation factor inhibitor. Results of a test for lupus anticoagulant was negative. The patient was found to have coagulation factor VIII inhibitors (6 Bethesda units/mL) and very low levels of coagulation factor VIII (3%). Percentages (of normal) of coagulation factors IX, XI, and XII were 100%, 65%, and 61%, respectively. Accordingly, the final diagnosis was postpartum AHA. We performed a third laparotomic hemostasis with the administration of recombinant activated factor VII (Novoseven, Novo Nordisk A/S, Bagsværd, Denmark) on day 21. There were multiple bleeding sites in the abdominal wall and cavity, with approximately 5,000 mL of blood clots intraperitoneally ; the total blood loss during this surgery was 8,490 mL. She received a total of 82 units of red blood cells and 140 units of fresh frozen plasma from admission to postoperative day 4. To control the factor VIII inhibitor, corticosteroids were administered starting on postoperative day 4. The clinical course is summarized in Fig. 2. Combined therapy with prednisolone and cyclosporine A eradicated the factor VIII inhibitor 5.5 months after admission to our hospital[4].

## DISCUSSION

AHA is caused by polyclonal autoantibodies to factor VIII, usually IgG 1 and 4, directed against the A2 and or C2 domains, but these antibodies are present in 17% of healthy

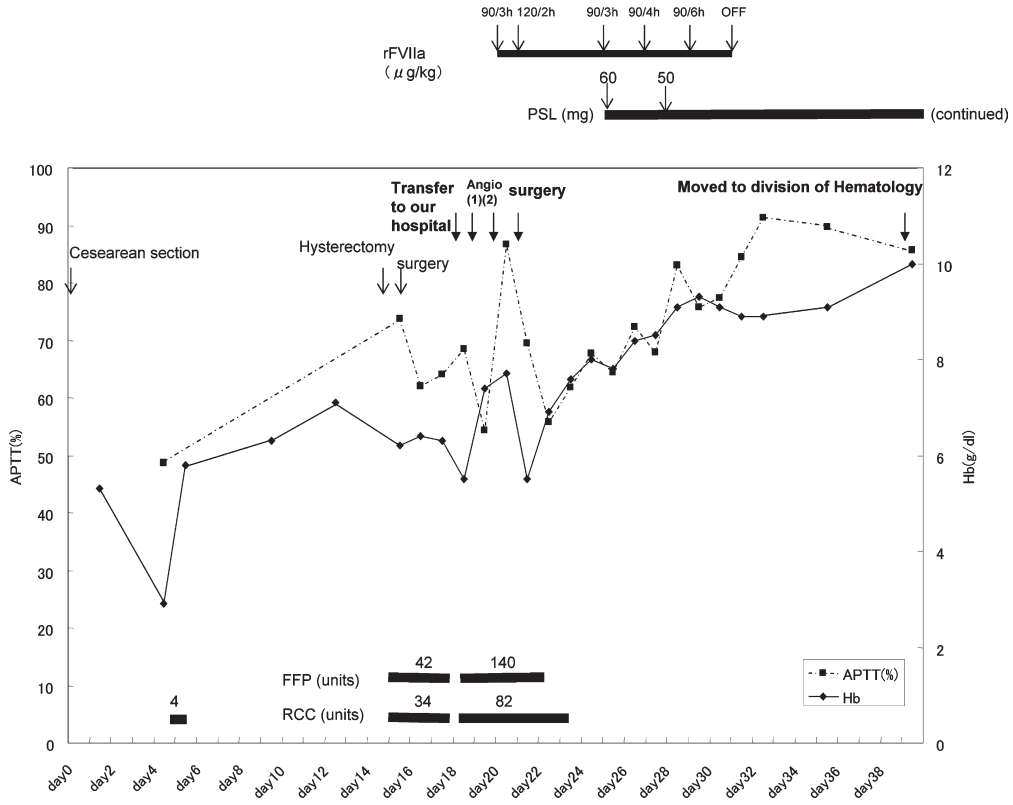


Fig. 2. The patient's treatment course is shown along with the changes in plasma APTT and serum hemoglobin from admission. Abbreviations : FFP ; fresh frozen plasma ; RCC ; red cell concentrate ; rFVIIa ; recombinant activated factor VII ; PSL, predonisolone.

persons, and, accordingly, not all of antibodies are thought to be pathogenic[5]. AHA presents suddenly with subcutaneous bleeding, intramuscular bleeding, or wound hemorrhage in patients who have no personal or family history of bleeding. Bleeding can also lead to compartment syndrome and neurovascular damage[5,6]. The severity of bleeding cannot be predicted, and, despite 25% to 33% of patients not requiring hemostatic therapy, they remain at risk of life-threatening bleeding until the inhibitor is eradicated[5]. The factor VIII level and inhibitor titers are poor predictors of bleeding risk[7].

The diagnosis must be made quickly to minimize the time a patient is at risk for bleeding and to avoid nonessential invasive procedures[5]. Interim data from the European Acquired Hemophilia Registry show a median (5th to 95th percentile) delay of 3 days (range, 0-58 days) between onset of bleeding and diagnosis and median delay of 1 day (range, 0-69 days) between the first abnormal APTT and diagnosis, suggesting a significant delay in a proportion of patients[5].

Typical laboratory findings in AHA are a prolonged APTT with a normal prothrombin time (PT). The diagnosis of AHA is confirmed by a low level of factor VIII and a high inhibitor titer (Bethesda assay).

AHA is a rare complication of pregnancy ; it is estimated to affect 1 in 350,000 births in the United Kingdom[7], and 20 cases were reported in 15 years in a survey of 42 specialist centers in Italy[2]. The pathogenesis of pregnancy-related factor VIII inhibitors remains still poorly understood. One hypothesis is that the mother is exposed to fetal factor VIII during delivery, but in some cases an anamnestic response is absent in subsequent pregnancies[1]. Another hypothesis is that the mother is exposed to paternal alloantigens[8]. Postpartum AHA may occur following any pregnancy but is observed more often in primigravidas[1]. This disease usually arises at the time of delivery or 1 to 4 months after delivery but may occur as late as 1 year afterward[1,4]. The initial symptom of AHA is frequently continuous vaginal bleeding. This disease can be a severe complication of pregnancy if it occurs soon after

delivery. One might think that if AHA had been diagnosed much earlier in the present case, hysterectomy could have been avoided. However, in the postpartum state, the incidence of atonic bleeding or DIC is much greater, and because postpartum AHA is rare, it can be difficult for obstetricians at municipal hospitals to diagnose. It is important to consider the possibility of a clotting disorder and to perform coagulation tests. In particular, in a patient with prolongation of APTT alone, a normal PT, and no evidence of DIC, the presence of coagulation factor inhibitors should be suspected[2].

Only a few cases of AHA after IVF-ET have been reported. Jost et al. have reported on a patient with AHA whose pregnancy was achieved with IVF-ET[9]; AHA developed owing to factor VIII inhibitors, but the patient did not experience a factor VIII inhibitor relapse after a second IVF-ET, which resulted in an uneventful pregnancy and an uncomplicated delivery. Nakauchi-Tanaka et al. have reported a case of factor VIII inhibitor associated with ovarian hyperstimulation syndrome (OHSS)[10]. OHSS is a common complication of IVF-ET and is caused by ovarian hyperstimulation, which is generally performed in IVF cycles. In the patient of Nakauchi-Tanaka et al., severe OHSS developed during the first cycle of IVF-ET and was followed by AHA. After successful treatment with factor VIII inhibitor bypassing activity (FEIBA), levels of the factor VIII inhibitor gradually decreased, and a healthy neonate was born via spontaneous vaginal delivery with no recurrence of AHA. Both these cases have the similar background of IVF-ET and OHSS, but the timing of AHA development differed. Our patient also became pregnant through IVF-ET, but OHSS did not develop. The association between factor VIII inhibitors and IVF-ET or OHSS is not well understood, owing to the small number of reports.

Several reports suggest that AHA in pregnancy has a different natural history and response to inhibitor eradication therapy than does AHA in other settings[11]. Remission reportedly takes longer to achieve in pregnancy-related AHA than in AHA associated with other underlying conditions, but spontaneous remission has also been recognized[2,11]. On the basis of available data, we cannot conclude that outcome is affected by the choice of immunosuppressive agent[5]. Despite the mortality rate of AHA reportedly being as high as 22%[1], the prognosis of postpartum AHA is considered favorable in most cases[3]. Recurrence in subsequent pregnancies is rare[12]. Solymoss reported that AHA recurred in 4 of 6 subsequent pregnancies in 3 patients[12]. In another study, no relapses occurred in 9 subsequent pregnancies[8]. An Italian registry reported no relapses in 4 patients[2]. Maternal IgG antibodies can affect the factor VIII level of the fetus, and this possibility must be considered at the time of delivery[5,13]. These IgG antibodies can cross the placenta into the fetal circulation, but they do not always result in bleeding complications in neonates[13]. Lulla et al. have reported on a second case of newborn with symptomatic bleeding after transplacental transfer of factor VIII inhibitor[13]. The newborn was successfully treated with recombinant activated factor VIIa. A review by Lulla et al. has found that transplacental transfer of the antibody to the neonate is rarely reported; no bleeding was observed in 3 of 4 neonates, but intracranial bleeding was observed in 1 neonate[13]. Unfortunately we could not obtain any information about the neonate in our case.

The management of AHA involves both hemostatic treatment for acute bleeding and immunosuppressive therapy to eradicate the inhibitors[1]. Immunosuppression for inhibitor eradication should be started as soon as the diagnosis of AHA has been made[5,14]. Corticosteroids (alone or in combination with cytotoxic drugs) are the main immunosuppressive agent[1,2,4]. A review by Delgado et al. of data from 20 publications has found that that the use of steroids and cyclophosphamide resulted in more patients achieving CR compared with steroids alone[15]. Rituximab has been used successfully in postpartum AHA[16]. There are no convincing data suggesting that one immunosuppressive regimen is superior to another or that the choice of regimen should be based on the titer of factor VIII inhibitor[5]. The management of bleeding depends on the site and the severity. Bypassing agents are currently the most commonly used first-line treatment, and recombinant activated factor VII (Novoseven) and factor VIII inhibitor bypassing activity (FEIBA) are successfully used to treat AHA[5]. These agents show a hemostatic effect by causing a "thrombin burst," bypassing the need for factor VIII. They lead to the formation of a stable fibrin clot, but monitoring and predicting efficacy is difficult[1,2]. There is no currently validated laboratory technique for monitoring these bypassing agents[5]. Recombinant activated factor VIIa has been reported to be effective or partially effective in 80% to 95% of

cases, but the reports on the efficacy of recombinant activated factor VIIa and that of FEIBA cannot be compared, and no data suggest that either agent has superior hemostatic efficacy[5]. Franchini et al. have stated that they prefer recombinant activated factor VIIa because, as a recombinant product, it has greater viral safety[14]. Both recombinant activated factor VIIa and FEIBA are associated with thrombotic events. Sumner has reported that of 139 patients with AHA treated with recombinant activated factor VIIa, 10 patients had 12 thrombotic events, and 4 of these patients died[17]. The risk of venous thromboembolism associated with bypassing agents in the postpartum period should be considered[5].

Collins et al. have reported that invasive procedures are associated with significant risk and that hemostasis cannot be guaranteed ; thus, only essential procedures should be considered[5]. However, if massive hemorrhage occurs, as in the present case, surgery is also required for hemostasis ; surgery allowed us to avoid abdominal compartment syndrome due to hematoma. Hemostatic options for surgery include the use of bypassing agents.

AHA is rare, but can be encountered in general hospitals. Postpartum bleeding due to AHA may be severe and life-threatening, especially if it is incorrectly diagnosed as atonic bleeding or other conditions. Clotting disorders should be considered, and coagulation tests should be performed. If such tests show prolongation of APTT alone, a normal PT, and no evidence of DIC, the presence of coagulation factor inhibitors should be suspected. We would like to emphasize that the possibility of coagulation disorders should always be considered. Close cooperation among clinical sections, including internal medicine, clinical laboratory, and the intensive care unit, is also extremely important.

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