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CASE REPORT

# Therapeutic application of C1 esterase inhibitor concentrate for clinical amniotic fluid embolism: a case report

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### Key Clinical Message

We present the successful application of C1 esterase inhibitor (C1INH) concentrate to a patient with clinical amniotic fluid embolism (AFE).

### Keywords

Amniotic fluid embolism, C1 esterase inhibitor, disseminated intravascular coagulopathy, kallikrein, uterine atony.

## Introduction

Amniotic fluid embolism (AFE) is one of the most serious causes of maternal death [1]. AFE is recognized as a syndrome characterized by the abrupt onset of hypoxia, hypotension, disseminated intravascular coagulopathy (DIC), and uterine atony due to mechanical obstruction of the maternal pulmonary artery or anaphylactic reaction to amniotic fluid [2].

In Japan, AFE was defined based on the Japan consensus criteria for the diagnosis of AFE based on the United States of America and the United Kingdom criteria as shown in Fig. 1 [3, 4]. A pathological diagnosis was determined when fetal debris was found in the maternal pulmonary arteries. On the other hand, the diagnosis of clinical AFE depended on clinical manifestations and was done when factors B1–B3 were all present, but more than one of the signs and symptoms listed in B1 needed to be present.

Previously, we reported that C1 esterase inhibitor (C1INH) activity levels were significantly low in clinical AFE patients. On performing lifesaving treatment for patients with AFE, C1INH activity levels were increased after the administration of fresh frozen plasma [5]. Therefore, we hypothesized that the administration of C1INH concentrate could be effective for patients with AFE. We describe the first reported case of C1INH treatment for a patient clinically diagnosed AFE. The Ethics Committee of Hamamatsu University School of Medicine approved all the procedures in this study (No. 25-107).

## Case

The patient was a 36-year-old Japanese woman, eight Gravida, three parous (3 × normal vaginal deliveries, 1 × stillbirth, 4 × spontaneous abortions). The family histories showed nothing of note. She had no allergy to food or drugs. She became pregnant spontaneously, and the pregnancy course was normal before the third trimester. At the 28th week of gestation, vaginal spotting appeared, and placental previa was diagnosed on ultrasound examination. At the 31st week of gestation, a moderate amount of vaginal bleeding occurred. She was admitted for bed rest and tocolysis. At 36 weeks and 1 day, she underwent uneventful cesarean section. The operation time was 86 min, and blood loss was 770 g.

A. Pathological confirmation; A diagnosis is made on the basis of clinical presentation after excluding differential diagnosis and at autopsy in the event of death of the parturient. The diagnosis is confirmed by histochemical studies.
B. Clinical manifestation; The patient has the hallmark clinical manifestations of AFE following 1, 2, and 3:
1. Signs and symptoms: Cardiac arrest/Respiratory arrest/Consumptive coagulopathy/Post partum hemorrhage more than 1,500 ml of unknown etiology within 2 h after delivery
2. Onset of all of the signs and symptoms during pregnancy, labor, or cesarean section or within 12 hours of delivery.
3. Absence of other illness that could explain the signs and symptoms described above.

**Figure 1.** The Japan consensus criteria for the diagnosis of AFE.

About 400 mL of autologous blood was transfused. When the operation was completed, the levels of hemoglobin and hematocrit were 9.5 g/dL and 31%, respectively. Massive vaginal bleeding and hypotension occurred suddenly just after the operation. We increased the transfusion and administrated oxytocin and prostaglandin F2$\alpha$ intravenously. We also conducted Bakri balloon tamponade for hemostasis. She was refractory to these treatments, and uterine bleeding continued. At 2.0 h after the operation, the total bleeding amount reached 2100 mL and the blood pressure decreased to 76/38 mmHg with fainting. The size of the uterus was large; the fundus of the uterus was over 3 fingers above the umbilicus and the myometrium was very soft. Severe atonic uterus was observed. Clot formation was not observed in vaginal blood. At this point, the levels hemoglobin and hematocrit were 8.7 g/dL and 27%, respectively, however, the fibrinogen concentration was 67 mg/dL. The level of FDP was over the normal range (more than 300 $\mu$g/dL). The complement C3 was 59 mg/dL and C4 was 7 mg/dL, which were both very low levels. From this quite unusual condition, we diagnosed her with clinical amniotic fluid embolism according to the Japanese criteria, as the patient developed marked hemorrhage of more than 1500 mL with DIC within 2 h after delivery and there were no other medical explanations for the clinical course. We administered 1000 units of C1INH (Berinert R) intravenously at 2.5 h after the operation. After administration of C1INH, uterine contraction rapidly improved and uterine bleeding decreased. Thirty minutes after treatment with C1INH, not only uterine bleeding had almost stopped, but also vital signs and the consciousness level had markedly improved. At 3.5 h after the operation (1 h after C1INH administration), we started to give fresh frozen plasma (FFP) and red blood cell concentrates (RBCs) to restore the blood coagulation factor levels. At 4.5 h after the operation, uterine bleeding had stopped completely. The total bleeding amount was 2800 mL and total amount of FFP and RBCs required were 12 U (1680 mL) and 16 U (1920 mL), respectively.

The plasma C1INH activity was 29% at onset, increased to 72% at 30 min after the administration of C1INH. The levels of blood fibrinogen and antithrombin were 67 mg/dL and 38% at the onset of AFE and 72 mg/mL and 52% at 30 min after C1INH administration, respectively. She was discharged 8 days after the operation/delivery without any side effects.

## Discussion

We describe the first case of the clinical application of C1INH to a patient with AFE. The present case demonstrated that C1INH concentrate was sufficient to prevent the aggravation of symptoms with shock vitals, a bleeding tendency, and an atonic uterus. Particularly in the present case, we did not apply any anti-DIC agents such as fibrinogen, antithrombin or FFP before the administration of C1INH concentrate, however, the levels of blood fibrinogen and antithrombin showed marginal change and increased, suggesting the independent effect of C1INH to cease the progression of DIC from AFE.

Recently, AFE has been generally characterized by a rapidly progressive clinical course with dyspnea, hypoxemia, hypotension, and fetal bradycardia with subsequent and acute cardiorespiratory collapse, DIC, neurological compromise, and maternal and fetal death [6]. Mechanical obstructions of the maternal pulmonary artery and an anaphylactic reaction to amniotic fluid have been suggested as pathological causes of AFE [2]. Although there are no universal diagnostic criteria to confirm AFE other than autopsy, the United States of America, the United Kingdom and Japan have similar clinical diagnostic criteria and national registries [7]. In the present case, massive hemorrhage developed of more than 1500 mL with DIC within 2 h after delivery and there were no other medical explanations for the clinical course, meeting the clinical criteria for AFE in Japan.

As for the treatment of AFE, there have been only palliative treatments such as airway management, vascular management, fluid replacement, blood transfusion, and the administration of anti-shock and anti-DIC agents. C1INH, a major inhibitor of C1 esterase, FXIIa, and kallikrein, is capable of not only inhibiting the complement system but also modulating the coagulo-fibrinolytic and

kallikrein-kinin systems [8]. We previously reported that mean C1INH activity level in clinical AFE cases was 30.0 ± 1.8%, which was significantly lower than those of normal postpartum women with 62.0 ± 2.0%, suggesting that C1INH administration would be effective for AFE [5]. As we expected, the present patient's uterus quickly contracted, resulting in the stopping of uterine bleeding, and DIC conditions were gradually alleviated after the administration of C1INH. Although the mechanism of the downregulation of C1INH activity in AFE is not clear, this observation paradoxically suggests that an abnormal uterine hemorrhagic type of AFE is a kind of syndrome of disorders in complement, coagulo-fibrinolytic, and kallikrein-kinin systems due to a decrease in C1INH activity.

Clinically, the use of 500–1500 units of human plasma-derived C1INH concentrates can reverse hereditary angioedema (HAE) in C1INH-deficient patients [9]. Since the present case of AFE showed a significantly lower level of C1INH activity, similar to C1INH deficiency, we administrated 1000 units of C1INH. We must consider the amount and number of administrations of C1INH in further studies.

Our experience is limited and further cases are required; however, in conclusion, we suggest that the administration of C1INH in the early phase of AFE may be very effective for uterine atony with DIC, subsequently preventing the deterioration of conditions associated with AFE.

## Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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## Conflict of Interest

None declared.

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