Severe fatty liver of pregnancy requiring an extremely large amount of blood transfusion, surgery and transarterial embolization: A case report

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1. Introduction

Acute fatty liver of pregnancy (AFLP) is a potentially fatal condition with a frequency of 1 in 7000 to 15,000 births; it rapidly progresses to liver failure, renal failure, and coagulopathy. The pathogenesis of AFLP is not well understood, but previous reports suggest that it may be caused by mitochondrial dysfunction in both the mother and fetus. AFLP has been linked to mutations in the enzymes required for fatty acid oxidation, specifically in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD). Defects in fatty acid metabolism during pregnancy lead to the development of liver dysfunction and coagulation disorders [1,2]. We report the case of a patient who suffered massive bleeding due to coagulopathy associated with AFLP following cesarean section. The patient survived after a massive transfusion.

2. Case

The patient was a 35-year-old woman (gravidity 3, parity 1) with a history of a vaginal delivery. She received continuous, routine prenatal care at a local obstetrics and gynecology clinic and was under diet therapy for gestational diabetes mellitus. During the course of pregnancy, her blood pressure was normal and urine protein tested negative; furthermore, no abnormalities were observed in fetal growth. At 33 weeks of gestation, she began to experience general malaise, loss of appetite, and nausea. At 34 weeks and 5 days of gestation, she sought medical care for vomiting, yellow discoloration of the skin, pruritus, pale stools, and pedal edema. AFLP was suspected, and the patient was transported to a university hospital.

During presentation at the university hospital (day 1), her mental status was good, blood pressure was 125/81 mmHg, heart rate was 57 bpm, and body temperature was 36.4 °C. She also exhibited marked generalized yellow discoloration of the skin, pruritus, pale stools, and pedal edema. AFLP was suspected, and the patient was transported to a university hospital. A non-stress test showed good fetal status; although she was experiencing uterine contractions every 2–4 min, her cervical os was closed. At presentation, laboratory tests revealed marked hyperbilirubinemia, thrombocytopenia, coagulopathy, liver dysfunction, and renal dysfunction (Table 1). Six of the Swansea criteria [1] were fulfilled; along with the symptom of vomiting, she was diagnosed with AFLP. On the basis of a total bilirubin (T-bil) value of 10.9 mg/dL and a prothrombin time-international normalized ratio (PT-INR) of 1.48, her condition was considered severe and associated with a high mortality rate [3].

Immediately after admission, two units of fresh frozen plasma (FFP) and 3000 units of antithrombin III were administered, and an emergency cesarean section was performed under general anesthesia. The surgery lasted 1 h 2 min; blood loss totaled 796 mL; and the infant weighed 2389 g, with Apgar scores of 8 at 1 min and 9 at 5 min. The placenta weighed 600 g and showed no macroscopic abnormalities. During surgery, oozing due to coagulopathy was observed; however,
Thick-needle biopsy revealed that the liver had a grayish color and an
quent bleeding. During the surgery, we did not observe active bleeding.
removed because they were considered to be responsible for the subse-
served at several sites in the intraperitoneal cavity, complete hemostasis
retention of a blood clot in the peritoneal cavity; therefore, laparotomy
was discussed with the patient, and she agreed to undergo the proce-
general anesthesia on day 4. Before the laparotomy, total hysterectomy
worsen; hence, the decision was made to perform laparotomy under
revealed a large hematoma in the Retzius space, and she was transfused
factor VII) was intravenously administered for 3 days. In addition,
poor oxygenation observed on the same day due to pleural effusion
flow from the drain continued. This patient was diagnosed with Sheehan
hemostasis was achieved using fibrin sealant (Beriplast® P) spray. Intraoperative blood loss was 3384 mL, which
not detected on contrast-enhanced CT images on day 6, to control
was performed using NBCA. While blood out

3. Discussion
AFLP is a severe condition caused by accumulation of toxic metabolic
intermediates in the placenta and maternal liver cells [1]. Nelson et al.
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intermediates in the placenta and maternal liver cells [1]. Nelson et al.

| Table 1  | Laboratory data at admission. |
|---------|-----------------------------|
|         | This case | Normal range | Swansea criteria |
| White blood cell count (WBC) (×10³/L) | 9780 | 3300–8600 |
| Hemoglobin (Hb) (g/dL) | 13.3 | 11.6–14.8 |
| Platelet count (PLT) (×10³/µL) | 4.8 | 15.8–34.8 |
| Fibrinogen (Fb) (mg/dL) | 27 | 150–340 |
| Antithrombin III (AT-III) (%) | 19 | 80–125 |
| Activated partial thromboplastin time (APTT) (sec) | 70.8 | 26–35 |
| Prothrombin time (PT) (sec) | 17.9 | 11–13 |
| PT-international normalized ratio (PT-INR) | 1.48 | 0.8–1.2 |
| Fibrin degradation products (FDP) (µg/mL) | 49.2 | 0–8 |
| Total bilirubin (T-bil) (mg/dL) | 10.9 | 0.4–1.5 |
| Aspartate transaminase (AST) (U/L) | 50 | 13–30 |
| Alanine transaminase (ALT) (U/L) | 41 | 7–23 |
| Lactate dehydrogenase (LDH) (U/L) | 297 | 124–222 |
| Creatinine (CRE) (mg/dL) | 1.84 | 0.46–0.79 |
| Uric acid (UA) (mg/dL) | 7.2 | 2.6–5.5 |
| Glucose (GLU) (mg/dL) | 153 | 73–109 |

○: Data met the Swansea criteria; †: The patient had vomiting, which is one of the Swansea criteria.

irregular surface. Because the risks associated with drain insertion
were considered to exceed the benefits, the surgery was ended without
placement of a peritoneal drain. Intraoperative blood loss totaled
9294 mL, most of which was the blood retained in the intraperitoneal
cavity. Anemia did not progress after the surgery, and the patient’s oxygen-

on day 2, abdominal pain and exacerbation of anemia were ob-
served. Abdominal contrast-enhanced computed tomography (CT) re-
vealed a large hematoma in the Retzius space, and she was transfused
with red cell concentrate (RCC) and FFP. Her anemia continued to
worsen; hence, the decision was made to perform laparotomy under
general anesthesia on day 4. Before the laparotomy, total hysterectomy
was discussed with the patient, and she agreed to undergo the proce-
dure. Uterine bleeding was minor at that time; however, considering the
risk of possible later uncontrollable uterine bleeding, a total hyster-
tomy was performed, and hemostasis was achieved using fibrin seal-
ant (Beriplast® P) spray. Intraoperative blood loss was 3384 mL, which
included the retained hematoma. An intraperitoneal drainage tube was
inserted before closure.

Following surgery, there was an outflow of blood from the drain
inserted in the peritoneal cavity, and massive transfusion was continued
with a potassium-free RCC preparation. Although active bleeding was not
detected on contrast-enhanced CT images on day 6, to control bleeding by reducing the pelvic blood flow bilateral internal iliac
artery embolization with a gelatin sponge was performed. Because the arteries reopened on day 7, a repeat embolization was performed using n-butylicl
c-(c-nitrosoacrylic acid (NBCA). Endotracheal incubation was performed for
poor oxygenation observed on the same day due to pleural effusion
and pleural edema. Starting on day 7, 5 mg of eptacog-alfa (recombinant
factor VII) was intravenously administered for 3 days. In addition,
plasma exchanges were performed on days 8 and 9, after consultation with
a hematologist. However, blood retention in the abdominal cavity as well as outflow of blood from the drain continued.

On day 10, arterial bleeding was observed from the skin incision for
the drain. A contrast-enhanced CT scan confirmed leakage of the
contrast medium from the right inferior epigastric artery, and embolization was performed using NBCA. While blood outflow from drain was minor, the management of respiration and circulation became difficult due
to retention of a blood clot in the peritoneal cavity; therefore, laparotomy
was performed to remove the hematoma. Although oozing was ob-
served at several sites in the intraperitoneal cavity, complete hemostasis
was achieved by applying pressure for about 20 min. Both ovaries were
removed because they were considered to be responsible for the subse-
quent bleeding. During the surgery, we did not observe active bleeding.
Thin-needle biopsy revealed that the liver had a grayish color and an

3. Discussion
AFLP is a severe condition caused by accumulation of toxic metabolic
intermediates in the placenta and maternal liver cells [1]. Nelson et al.
reported that more than half of 51 patients with AFLP required blood
transfusion; one-third of these received over 10 units, and a quarter re-
quired platelet transfusion [6]. The patient reported here required mas-
sive blood transfusion (772 units of RCC, PC, and FFP). To the best of our
knowledge, this case is the most severe non-fatal reported case of AFLP
in terms of the hemorrhage and blood transfusion volume.

When diagnosing AFLP, it is necessary to differentiate it from HELLP syndrome. The present patient had laboratory values, including LDH and AST levels of 297 and 50 IU/L, respectively, which did not suggest
HELPP [4]. However, six of the Swansea diagnostic criteria for AFLP
were met and so the patient was given that diagnosis (Table 2). Liver bi-
opsy was performed on day 10, during the third laparotomy, when coagulopathy was already improving. Biopsy results failed to reveal microangiopathy, which is a characteristic feature of HELLP syndrome, or microvesicular hepatic steatosis or microvesicular fatty infiltration
[5], both of which are characteristic of AFLP. Probably because her dis-
 ease had already begun to improve, such histological findings were
not observed.

![Fig. 1. Summary of clinical course from day 1 to day 14. Amount of hemorrhage including intraoperative bleeding per day. Op: operation. TAE: transarterial embolization, PE: plasma exchange. X axis: day after admission. Y axis: amount of hemorrhage.](image-url)
In the treatment of AFLP, it is important to terminate pregnancy as early as possible to reduce the risk of severe maternal complications such as liver failure, multiple organ failure, and DIC, and increase the survival rate [1]. In the present case, although emergency cesarean section was performed immediately after the patient arrived at hospital, her condition continued to worsen. According to patient interview, onset of symptoms was 10 days prior to presentation, suggesting that the duration from onset to treatment was long. This might explain the severity of the case. Murali et al. created a scoring system to identify potentially lethal AFLP based on the laboratory values before delivery.

Table 2
Blood transfusion, albumin, and anti-DIC therapy from day 1 to day 14.

| Day | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  | 14  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Red cell concentrates (units) | 6   | 4   | 18  | 4   | 20  | 30  | 20  | 44  | 22  | 4   |
| Fresh frozen plasma (units)  | 12  | 4   | 2   | 16  | 10  | 16  | 36  | 48  | 26  | 28  | 10  | 4   | 2   |
| Platelet concentrates (units) | 20  | 20  | 20  | 20  | 35  | 20  | 60  | 40  | 60  | 55  | 40  | 20  |
| Cell saver autotransfusion (mL) | 400 |
| Albumin (g)                  | 38  | 25  | 25  | 25  | 25  | 25  | 38  |
| Fibrinogen (g)               | 3   | 2   | 1   | 25  |
| Eptacog-alfa (mg)            | 200 | 200 | 200 | 256 | 256 | 256 | 256 | 156 |
| Thrombomodulin-alfa (×100 units) | 5   | 5   | 5   | 3   | 3   | 3   | 3   | 3   |
| Antithrombin III (×1000 units) | 3   | 3   | 3   | 3   | 3   | 3   | 3   | 3   |

Fig. 2. Change of laboratory data from day 1 to day 14. A) hemoglobin (Hb) and hematocrit (%) levels. B) platelet (Plt) levels. C) fibrinogen (Fib) levels. D) PT-INR levels. X axis; day after admission. Y axis; data level.
(1.17 · T-bil + 2.09 · PT-INR) and reported that when the value is ≥ 12.9, a fatal outcome is predicted with a sensitivity of 81% and a specificity of 77% [3]. According to this formula, the score of the present patient was 15.8, which can be considered as high risk for mortality. Additionally, among the 43 pre-delivery blood sample values, abnormal values for five factors (platelet count, prothrombin time, fibrinogen, total bilirubin, and creatinine) are correlated with the number of days required for recovery [7]. The present patient had abnormal values for all five factors, which is consistent with the severity of her AFLP. Effective communication and comprehensive antenatal care may improve maternal help-seeking behavior by encouraging early return to a health facility when a mother is ill [8].

In general, liver failure and coagulopathy due to AFLP improve in 1–3 weeks, and survival in severe cases depends on the avoidance of irreversible lethal organ failure, while maintaining respiration and circulation for this period of time [9]. Our patient may have survived because of the frequent collection of blood samples and continuous potassium-free blood transfusion to maintain blood pressure. Additional interventions included surgery, arterial embolization, factor VII administration, and plasma exchange. Plasma exchange reportedly improves AFLP [10]. When managing lethal and severe AFLP, continuous active intervention is most important, given that the condition will likely improve if a week or more passes.

In conclusion, we describe a severe case of AFLP, in which massive bleeding occurred due to marked coagulopathy. For severe cases of AFLP, continuation of active treatments such as massive blood transfusion, plasma exchange, and surgery are important.

Contributors

Kiko Yamamoto was involved in the clinical care of the patient and wrote the draft of the case report.

Ayako Suzuki was involved in the clinical care of the patient and contributed to the conception, drafting, review and revision of the case report.

Masao Shimaoka was involved in the clinical care of the patient and contributed to the conception and drafting of the case report.

Yoshie Yoji was involved in the clinical care of the patient and contributed to the conception and drafting of the case report.

Masaki Mandai was involved in the clinical care of the patient and contributed to the conception and drafting of the case report.

Norioi Matsumura contributed to the conception, drafting, review and revision of this case report.

All authors saw and approved the final version of the manuscript and take full responsibility for the work.

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Patient Consent

Written informed consent was obtained from the patient for publication of the case report and accompanying images.

Provenance and Peer Review

This case report was peer reviewed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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