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

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ABSTRACT

We report a case of massive bleeding due to a coagulation disorder associated with acute fatty liver of pregnancy (AFLP); the patient survived by massive transfusion. She presented at 34 weeks of gestation, met six of the Swansea criteria, and was diagnosed with severe AFLP. We performed an emergency cesarean section because termination of the pregnancy was necessary for the treatment of the AFLP. After the surgery, which led to massive bleeding in the peritoneal cavity due to the coagulation disorder, she underwent two further operations and three transarterial embolizations. She received factor VII and underwent plasma exchange, and hemostasis was achieved on day 10 after hospitalization. The total volume of blood transfused was 772 units (170 units of red cell concentrate, 212 units of fresh frozen plasma, and 390 units of platelet concentrate). To the best of our knowledge, this is the most severe case of non-fatal AFLP reported to date in terms of the transfusion volume.

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. The estimated fetal weight was 2315 g. 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,

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Table 1
Laboratory data at admission.

	This case	Normal range	Swansea criteria
White blood cell count (WBC) (/μL)	9780	3300–8600	
Hemoglobin (Hb) (g/dL)	13.3	11.6–14.8	
Platelet count (PLT) (x10,000/μL)	4.8	15.8–34.8	
Fibrinogen (Fib) (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) - B (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) (IU/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.

hemostasis was achieved postoperatively after administration of platelet concentrate (PC) and FFP. Following cesarean section, 380 U/kg of thrombomodulin was intravenously administered as a disseminated intravascular coagulation (DIC) treatment.

On day 2, abdominal pain and exacerbation of anemia were observed. Abdominal contrast-enhanced computed tomography (CT) revealed 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 procedure. Uterine bleeding was minor at that time; however, considering the risk of possible later uncontrollable uterine bleeding, a total hysterectomy was performed, and hemostasis was achieved using fibrin sealant (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-butyl-2-cianoacrylate (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 observed 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 subsequent bleeding. During the surgery, we did not observe active bleeding. Thin-needle biopsy revealed that the liver had a grayish color and an 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 oxygenation status improved. The patient was extubated on day 13. However, ascites continued, causing severe abdominal pressure. On day 17, an abdominal paracentesis was performed and a drain was inserted, from which 6000 mL of brownish fluid was drawn. The amount of fluid gradually decreased after that, and the drain was removed on day 28. Histological analysis of a liver biopsy showed no sinusoidal fibrin deposition, whereas bile retention and hepatocyte degeneration were observed.

Laboratory tests performed on day 19 to screen for Sheehan syndrome showed free triiodothyronine (FT3) 1.3 (normal range 2.3–4.0) pg/mL, free thyroxine (FT4) 0.7 (normal range 0.9–1.7) ng/dL, and thyroid stimulating hormone (TSH) 2.3 (normal range 0.33–4.05) μU/mL. The patient also showed low TSH levels on testing and she was diagnosed with Sheehan syndrome. The levels of other pituitary hormones were found to be within normal limits. At this time, the surgical wound was separated by about 10 cm and fascial necrosis was found. On day 48, debridement and wound suture were performed. The postoperative course was favorable, and the patient was discharged on day 54.

For this patient, to determine the need for blood transfusion, 86 blood samples were collected from day 1 to day 14 (Fig. 1) (Fig. 2). To save the patient, a total of 772 units of transfused blood (RCC 170 units, FFP 212 units, and PC 390 units) were required (Table 2). Currently, the patient is surviving without any sequelae with continuous administration of levothyroxine sodium 50 μg/day and an estradiol patch 0.72 mg/2 days.

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 required platelet transfusion [6]. The patient reported here required massive 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 HELLP [4]. However, six of the Swansea diagnostic criteria for AFLP were met and so the patient was given that diagnosis (Table 2). Liver biopsy 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 disease had already begun to improve, such histological findings were not observed.

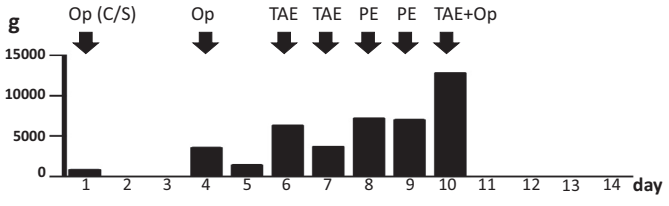

Fig. 1. Summary of clinical course from day 1 to day 14. Amount of hemorrhage including intraoperative bleeding per day. Op; operation. TAE; transarterial embolization, PE; plasma exchange. X axis; day after admission. Y axis; amount of hemorrhage.

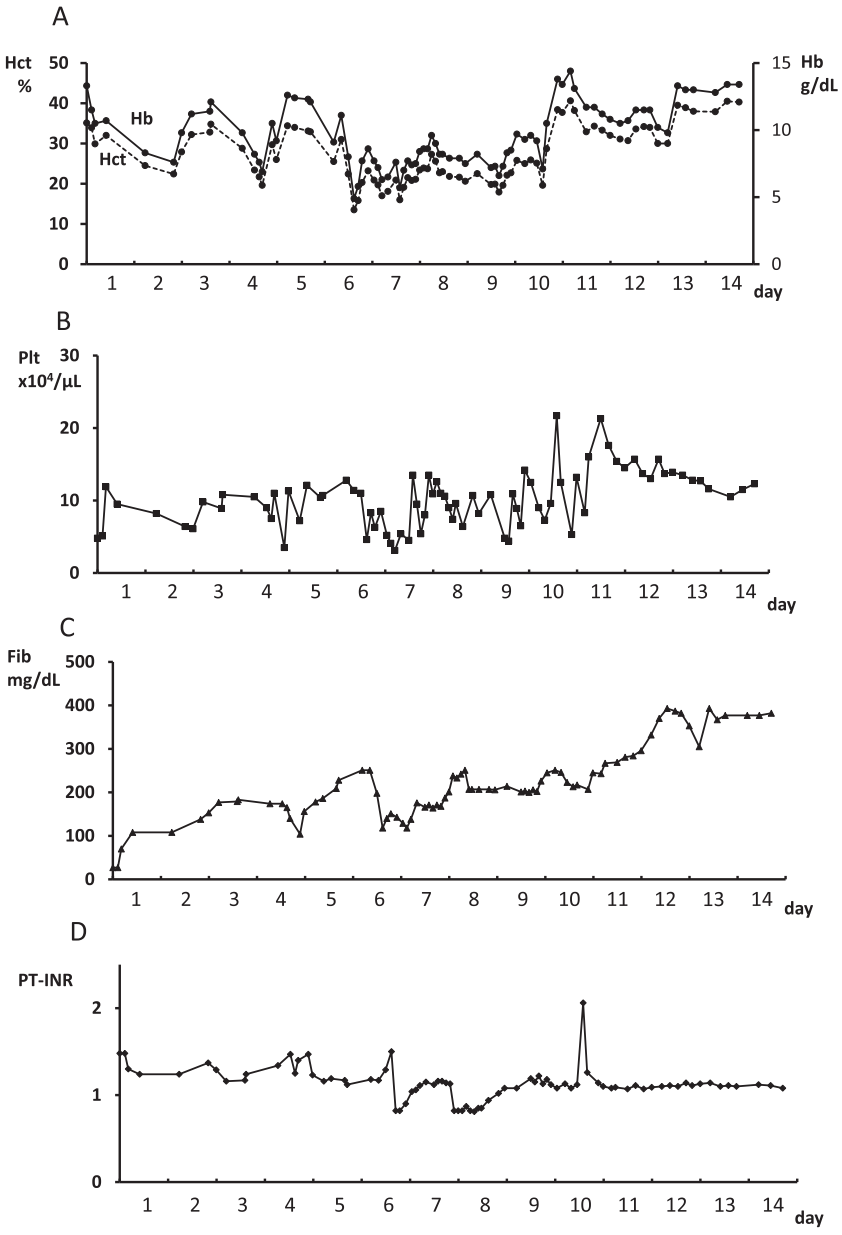

Fig. 2. Change of laboratory data from day 1 to day 14. A) hemoglobin (Hb) and hematocrit (%) levels. B) platelet (Plt) levels. C) fibrinogen (Fib) levels. D) PT-INR levels. X axis; day after admission. Y axis; data level.

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			2	
Fresh frozen plasma (units)	12	4	2	16	10	16	36	48	26	28	10	4		
Platelet concentrates (units)	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)							2	1						
Eptacog-alfa (mg)						5	5	5						
Thrombomodulin-alfa (×100 units)	200	200	200		256	256	256	256	156					
Antithrombin III (×1000 units)	3				3	6	3	3	3	3		3		

(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 drafted 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 Yo 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.

Noriomi 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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