

Case Report

Severe Acute Fatty Liver of Pregnancy (AFLP) Associated with Unknown Factor VII Deficiency

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Abstract

We present a case of acute fatty liver of pregnancy (AFLP) associated with unknown factor VII deficiency. The final diagnosis for our patient, a 28 year old female, G2P1, has been a challenge and required multiple treatments included a postpartum emergent laparotomy with haemostatic hysterectomy. Multidisciplinary approach with other specialists was crucial for the outcome of this patient who

required a massive amount of resources both diagnostically and therapeutically

Keywords: AFLP; Factor VII deficiency; Obstetrical Emergency; Thromboelastography

1. Introduction

Acute Fatty Liver of Pregnancy (AFLP) is a rare but life-threatening complication of pregnancy, affecting

approximately 1 in 7000 to 1 in 20000 births. This condition is characterized by microvesicular fatty infiltration of hepatocytes during the second half of pregnancy (usually the third trimester) [1]. Gastrointestinal symptoms, including anorexia, vomiting, jaundice and abdominal pain are the most common presenting symptoms and for this reason an early diagnosis is very difficult [2]. In the past it was thought to be universally fatal but nowadays mortality ranges between 0 and 12.5% [3] but AFLP still causes severe maternal morbidity such as Acute Liver Failure (ALF), acute renal failure (ARF), pancreatitis, Disseminated Intravascular Coagulation (DIC) and encephalopathy. Factor VII (fVII) is a vitamin K dependent plasma protein synthesized by the liver, which takes part in the coagulation process in vivo. Its congenital deficiency is a rare autosomal recessive disorder, characterized by a reduction in activity levels of fVII, which ranges from less than 10% in homozygous to 20–60% in heterozygous form. The disorder has an estimated prevalence of 1:300.000–500.000 for severe cases, while heterozygous form is more frequent (1:350). Haemorrhagic events are very variable in severity and weakly correlate with plasma fVII levels [4,5]. Here we present a rare case of AFLP complicated by an unknown deficiency of factor VII of coagulation.

2. Case Presentation

A 28 year-old G2P1 female of Caucasian descent with an Estimated Gestational Age (EGA) of 38 weeks and 1 day presented to our Department with nausea, mild abdominal pain and a single event of vomiting. She had a previous uneventful pregnancy with uncomplicated vaginal delivery. There was no history of diarrhea or flu-like symptoms. She had no history of travels to tropical countries. Virus (HIV) status was negative. Her general physical examination was unremarkable. An Ultrasound (US) scan showed a cephalic,

normally grown foetus with decreased normal amniotic fluid index. Cardiotocography was normal. Blood pressure, pulse and temperature were 130/75 mmHg, 95 bpm and 36.8 degrees Celsius respectively. Respiratory and cardiovascular examinations were normal. The patient's blood samples showed a normal platelet count ($178 \times 10^9/L$) a White Blood Cell Count (WBC) of $11 \times 10^9/L$, and a total blood Hemoglobin (Hb) of 12 g/L. Moreover investigations revealed an elevated uric acid, hypoglycemia (serum glucose 62 mg/dl), renal impairment (serum creatinine 2.11 mg/dl), impaired liver function (serum alanine aminotransferase [ALT] 485 U/L, serum aspartate aminotransferase [AST] 732 U/L, serum LDH 725 U/L, serum total bilirubin 68.4 $\mu\text{mol/L}$, and coagulopathy (thromboplastin time [PTT] 41.1seconds), international normalized ratio [INR] 2.15); with striking low levels of ATIII (2%), fibrinogen 57 mg/dl and D-Dimer (32.3 ug/ml). After adequate correction of coagulation an emergency caesarean section was performed a few hours later; the baby received an Apgar score of 6/8 and birth weight was 3350 gr. The surgery was uneventful and the patient was transferred to the Intensive Care Unit (ICU) for post operative assistance. The first hypothesis of diagnosis was a suspected HELLP syndrome but the normal platelet count associated with coagulation impairment, elevated uric acid levels and hypoglycemia made the hypothesis of AFLP more consistent. The peripheral blood smear was examined by a haematologist, and no signs of haemolysis supported this hypothesis.

During day 1 postpartum the patient was conscious and alert, and did not require ventilator support.

Day 2 postpartum was characterized by progressive anemization associated with a worsening coagulation status.

Clinical examination revealed an enlarged and flaccid uterus accompanied with abdominal pain and peritonism; a Computed Tomography (CT) showed multiple hematomas in the abdominal wall associated with hemoperitoneum. Liver, spleen, pancreas, stomach and bowel presented normal CT features. Subsequently an emergent laparotomy drainage of hematomas and hemoperitoneum associated with a haemostatic hysterectomy were performed. The bilateral ligation of hypogastric arteries was also necessary in order to control the bleeding. The patient returned to the ICU and required mechanical ventilation.

On day 6, after progressive worsening of hepatic, renal, pancreatic and coagulative function despite massive supportive therapies (intravenous fluid and dextrose infusion, multiple units of fresh frozen plasma, multiple units of cryoprecipitate, and multiple units of packed red blood cells), an important bleeding from the surgical drain, from the eyes and mouth was observed. A CT showed the presence of ascites, multiple abdominal hematomas and a liver enlargement with features of steatosis. An angiography was carried out and a session of plasmapheresis was performed without appreciable results. On day 7 postpartum a second emergency laparotomy was necessary; after the drainage of ascites and hematomas, a hepatic biopsy was performed and a Mikulicz compressive surgical drain was applied. This procedure was the only and best action to take in order to ensure an adequate haemostasis. On day 8 a deficiency of factor VII of coagulation was identified (17 % of plasma residual FVII activity). Factor VII deficiency was slowly corrected until the maximum level of 40% was achieved. On day 10 postpartum a third laparotomy was performed to remove Mikulicz drain; the abdominal cavity showed no bleeding, no ascites. The liver only maintained features of steatosis.

On day 11 mechanical ventilation was suspended.

On day 14 the patient was discharged from ICU after progressive improvement of clinical condition and blood tests.

On day 15 the patient developed an entero-vaginal fistula which was treated conservatively with parenteral nutrition.

On day 28 the patient was discharged with hepatic, renal and pancreatic function almost normalized. No neurological or cognitive consequences have been reported. Hepatic biopsy was consistent with AFLP.

3. Discussion

AFLP has been attributed to a defect in mitochondrial β -oxidation of fatty acids, and is characterized by hepatic microvesicular fatty infiltration. The most common gene mutation is a defect in the longchain 3-hydroxyacyl-CoA dehydrogenase/mitochondrial trifunctional protein (LCHAD/MTP) but other associated gene mutations are described; however in many case reports and series, AFLP has not been associated with a detectable gene mutation. At present no pre-existing medical conditions which may predispose to AFLP have been identified. [6,7] This condition can be serious and could represent a very dramatic clinical event with sudden and catastrophic consequences to healthy women. Because of the potential for rapid progression to coma and death, AFLP is considered to be an obstetric emergency. However, some data report that 100% of AFLP cases could survive if they were delivered within a week after onset of the disease, while 30% would die if they were delivered beyond 2 weeks after onset [8,9]. Thus, early diagnosis and prompt delivery are important in order to lower the mortality rate. A well known tool for the recognition AFLP is the Swansea criteria. The use of the Swansea criteria is justified for the presumptive diagnosis of AFLP by high negative predictive

value (100%) in diagnosing microvesicular steatosis, but it is not targeted at early diagnosis [10,11]. Some of its diagnostic terms could only be reached when symptoms and signs have progressed, which might be too late for treatment. Our case clearly presented this problem because despite the few subjective symptoms the seriousness of blood values showed a critical situation with the presence of hepatic and renal damage associated with DIC. The urgency of delivery was immediately recognised and the correct diagnosis was made shortly thereafter. In our opinion identifying AFLP before the worsening of blood test is almost impossible, and for this reason the diagnosis is usually made when the patient is already in a serious condition.

The first and most important step is to carry out the differential diagnosis with other pathologies that cause similar conditions i.e. gastroenteritis, severe viral hepatitis, pre-eclampsia, and HELLP syndrome, which require different management. Blood smear with no sign of hemolysis was very useful to differentiate AFLP from HELLP syndrome. Women with AFLP have proteiform presentation such as impaired liver function with increased bilirubin and transaminase levels, altered leukocyte counts, elevated serum ammonia, prolonged prothrombin times, acute renal failure, hyperuricemia and poor pancreatic function with hypoglycemia. Moreover, the platelet count can be reduced with or without additional signs of Disseminated Intravascular Coagulation (DIC) in conjunction with a significant reduction of antithrombin [12]. The best and first approach is undoubtedly the prompt delivery after maternal stabilization. The data available nowadays demonstrate the absence of a specific treatment for AFLP and underline the need to understand the evolution of the disease and also to adapt the treatment plan

to the patient's status. In the most favourable cases liver function tests begin to normalize after delivery although after the first few days a transient worsening of renal and hepatic function may be observed. In severe cases more days of illness can be observed, requiring supportive treatment in an ICU (such as mechanical ventilation, dialysis, parenteral nutrition) and/or advanced surgery. Our patient required a complex decision making process because the DIC seemed to be irresponsive to infusion of multiple units of fresh frozen plasma, multiple units of cryoprecipitate, and multiple units of packed red blood cells as well as other surgical procedures. According to the consideration that the standard plasmatic coagulation screening tests are weak bleeding predictors in critically ill patients and represent suboptimal tests for monitoring coagulopathy, our guiding hemostatic therapy was thromboelastography. This procedure, unlike the conventional or standard coagulation tests, is able to monitor the entire blood coagulation system and determine the clot strength as well as lytic processes. In current clinical practice it has been used mainly for early prediction of bleeding complications and goal-oriented therapy with specific hemostatic drugs such as coagulation factor concentrates and blood products in different patients, including trauma, sepsis, anesthesia, liver and cardiac surgeries [13]. Moreover, identifying factor VII deficiency was fundamental because after it was corrected a rapid improvement of coagulation was obtained. In presence of negative personal and familiar history of spontaneous bleeding, it is difficult to postulate a congenital factor VII deficit and for this reason the deficiency was at first linked to extreme hepatic damage. After a targeted supplementation, the improvement of clinical conditions made the hypothesis of a congenital Factor VII deficiency more consistent; probably the infusion of fresh frozen

plasma and cryoprecipitate alone was inadequate to balance the extreme impairment of hepatic function (i.e. synthesis of coagulation factors) due to AFLP and the congenital defect of factor VII. Nowadays the patient's value of the activity levels of fVII demonstrate a slight congenital defect of fVII, with a 59 % of plasma residual activity. We believe the unknown cause of deficiency of factor VII plays a pivotal role in this case; a profilaxys during delivery could have been applied (actually controversial in current literature) or prompt correction could have been performed if the cause had been known beforehand [14,15]. The enterovaginal fistula was probably due to repeated surgical procedures associated with angiography and Mikulicz drain that produced an ischemic damage. The small diameter of fistula and the progressive improvement of clinical conditions allowed for conservative management thus avoiding colic surgery. Although most severely ill patients can recover without liver disease consequences, substantial morbidity and even maternal mortality may occur. Some Authors have also described patients who required liver transplantation, which is rarely needed when diagnosis and pregnancy termination are achieved in sufficient time. At present our patient has normal hepatic function and the liver shows normal echographic aspects.

3. Conclusion

To our knowledge, our case is the only one in literature presenting AFLP complicated by an unknown factor VII deficiency. Our clinical approach followed the current recommendations for management of AFLP (immediate diagnosis, prompt delivery and supportive care). We believe that a multidisciplinary approach with other specialists was crucial for the success of this patient who required a massive amounts of resources both diagnostically and therapeutically. Finally we think these kinds of patients

must be referred to a health care Center with an experienced multidisciplinary team. Patient anonymity has been preserved and informed consent was collected from the patient.

Disclosure

None

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