CASE REPORT

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N-Acetylcysteine Treatment for Acute Fatty Liver of Pregnancy

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ABSTRACT Acute fatty liver of pregnancy (AFLP) is a life-threatening disease for both mothers and the baby presented with liver failure. Although early recognition and prompt delivery (the best maternal survival rate is when the interval from the occurrence of AFLP to delivery is one week), maternal stabilization in the intensive care setting and supportive therapy is ideal. Still, effective treatment for liver failure is unknown. For AFLP diagnosis, high bilirubin levels, low platelet count, coagulopathy, and renal impairment were used as Swansea criteria. AFLP is usually observed after 30 weeks of gestation. In our case, N-acetylcysteine (NAC) treatment was used for AFLP, and the results are discussed. Maternal stabilization is achieved uneventfully and quickly. NAC treatment is effective to further studies are needed.

Keywords: Hepatic encephalopathy; N-acetylcysteine; steatohepatitis

Pregnant liver diseases are crucial and may require immediate intervention for mother-fetus surveillance. In developed nations, it affects about 3 percent of all pregnancies. Pregnancy disorders and unrelated to pregnancy (preexisting chronic liver disease) disorders are the two groups into which it is divided. Preeclampsia, hemolysis, elevated liver enzymes and low platelets syndrome, hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy (AFLP), and other liver conditions are all linked to pregnancy.

Preeclampsia is the most prevalent kind, while AFLP is rare but fatal. Between 1/7,000 and 1/20,000 pregnancies experience AFLP.[1]

Although it tends to occur in the third trimester between 30 and 38 weeks of gestation, it can also be seen in the postpartum period.[2] In the pathology of AFLP, in zone 3 (centrilobular zone) of the liver, microvesicular steatosis and rapid deterioration of liver function were observed. In addition, liver failure signs such as hypoglycemia, elevated liver enzymes, and coagulopathy might cause maternal intensive supportive care.[3]

During the follow-up of a patient in the third trimester, our goal in this case was to diagnose AFLP, treat the condition, and talk about the use of N-acetylcysteine (NAC) therapy.

CASE REPORT

A 28-year-old, gravida 5, para 4, pregnant woman at 35 weeks of gestation was referred to our tertiary medical center for jaundice and encephalopathy for one week. She was suspected as diagnosis of preeclampsia due to +1 proteinuria, blood pressure of 110/70 mmHg, and elevated aminotransferases of 109/191 U/L, but her creatinine level was 1.6 mg/dL, total bilirubin level was 11.6 mg/dL, direct bilirubin was 10 mg/dL, she had coagulopathy of international normalized ratio 2.46, prothrombin time 47, activated partial thromboplastin time 59, her platelet count was 46x10³/uL, white blood cell count was 25x10³/uL. Hemoglobin was 6.8 g/dL.

Her medical history was standard, and she had no drug usage. However, because of her severe jaundice and encephalopathy, she was diagnosed with AFLP and underwent a cesarean section immediately (Figure 1). She had a live male fetus. After birth, 15

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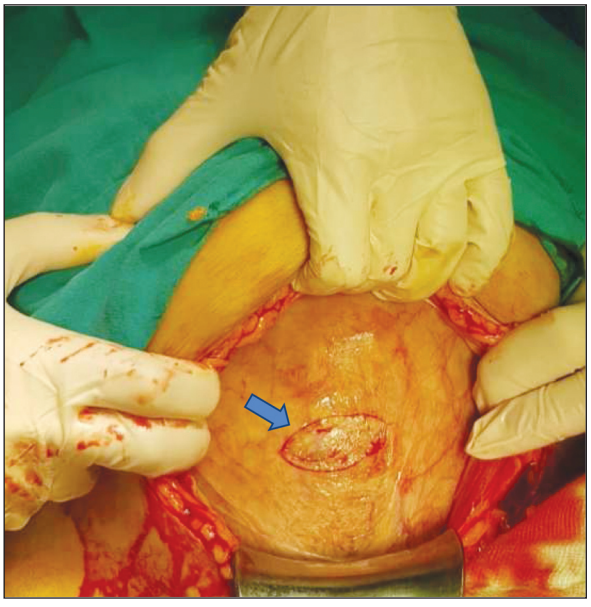

FIGURE 1: Severe jaundice in the uterus (arrow) and skin.

units of erythrocyte, 20 units of fresh frozen plasma, and 19 g of fibrinogen transfusion were performed to stabilize the patient's hemodynamic status.

After gastroenterology consultation, the Model for end-stage liver disease score (2016) was calculated to be 22 (estimated 3-month mortality was 19.6%). The patient was a candidate for liver transplantation. For differential diagnosis, portal venous Doppler and liver ultrasonography were performed and were normal. ELISA tests were negative for viral hepatitis. Anti-mitochondrial antibody, anti-nuclear antibody, and anti-smooth muscle antibody tests were negative, as were tests for autoimmune hepatitis.

Although it was 1 week after the pregnancy was terminated, bilirubin levels did not decrease and the general condition did not improve. We decided to try NAC, which can be beneficial in remission in every disease that goes with liver inflammation, with the recommendation of gastroenterology.

A 150 mg per kilogram intravenous loading dosage of NAC was given for 15 to 60 minutes, then an infusion of 12.5 mg per kilogram per hour for four hours, and then an infusion of 6.25 mg per kilogram per hour for sixteen hours. The patients' liver function tests declined dramatically after NAC treatment and recovered uneventfully.

Permission was taken from the patient to publish the data for the case report and present it on scientific platforms.

DISCUSSION

While diagnosing liver diseases in pregnancy, the primary differential diagnosis is, due to the common incidence, of preeclampsia. In particular, with high bilirubin levels above 6 mg/dL in AFLP, diagnosis of preeclampsia is excluded.[4] Therefore, Swansea criteria are used for diagnosis instead of liver biopsy. In addition, to fulfilling the diagnostic criteria, at least six positives of the 15 criteria are needed (Table 1).[5] In our case only microsteatosis in liver biopsy criteria was negative because we could not get biopsy due to the coagulation abnormalities. Other criterias of Swansea were positive.

Increased accumulation of free fatty acids and 3-hydroxy fatty acyl-CoA leads to oxidative stress, mitochondrial malfunction, and placental lipotoxicity, which are the main contributing factors to the etiology of AFLP. Finally, acute liver failure is brought on by oxidative and nitrosative stress.[6] This syndrome can also occur in fetuses with long-chain 3-hydroxy acyl-CoA dehydrogenase impairment. Mortality rates for mothers and fetuses were 10% and 45%, respectively. It's a kind of inflammation and NAC could improve this.

The best course of action for treating AFLP is early diagnosis, rapid delivery, maternal stabilization in the intensive care unit, and supportive therapy. Supportive treatment options include a low-fat, high-

TABLE 1: Swansea criteria for AFLP diagnosis.[1]

Vomiting	Elevated bilirubin >0.8 mg/dL
Abdominal pain	Hypoglycemia <72 mg/dL
Polydipsia/polyuria	Elevated urea >950 mg/dL
Encephalopathy	Leucocytosis >11×109/L
Nausea	Elevated transaminases AST/ALT>42 U/L
Ascites or bright liver by ultrasound	Elevated ammonia >66 μmol
Renal impairment, creatinine >1.7 mg/dL	Coagulopathy or PT>14 s or aPTT>34 s
Microvesicular steatosis in liver biopsy	

AFLP: Acute fatty liver of pregnancy; AST: Aspartate transaminase; ALT: Alanine transaminase; PT: Prothrombin time; aPTT: Activated partial thromboplastin time.

protein, and high-carbohydrate diet, transfusions and hemodialysis, broad-spectrum antibiotics, rehydration, and electrolyte and acid-base replacement. Usually, 1-4 weeks following delivery, the patient's clinical condition gets better.[7]

Cysteine-derived NAC is a crucial precursor of glutathione synthesis. NAC is an antidote for acetaminophen toxicity and has been discovered as an anti-inflammatory, anti-fibrotic, and remodeling of chromatin.[6]

According to a study by Buhimschi et al., NAC shields the fetus against the negative consequences of inflammation and stillbirth.[7] NAC treatment throughout pregnancy also lowers the chance of newborn morbidity and mortality.[8] The Food and Drug Administration-approved protocol for acetaminophen intoxication was followed for administering the NAC infusion. NAC (Acetadote, Cumberland Pharmaceuticals) is given as a loading dosage of 150 mg/kg over the course of one hour, followed by a four-hour 50 mg/kg continuous infusion, a 16-hour 100 mg/kg infusion, or until delivery if it happens earlier.[8] We offered it to treat inflammatory liver disease in the mother, but it may also be given to improve the survival of the fetus before birth in the future.

In studies about inflammation, NAC plays a direct scavenger role of free radicals. NAC and cysteine can also directly scavenge free radicals and increase the pool of endogenous sulfur-containing species in the mitochondria.[9] In rodents, NAC is used to alleviate lipid-induced oxidative stress during pregnancy. Its category is category B, crosses the placenta, and results in an increase also in fetal glutathione levels too.

In humans, NAC has improved treatment for non-alcoholic fatty liver disease, other fulminant acute hepatitis, and recurrent pregnancy loss. AFLP is caused by inflammation, and a high accumulation of fatty acids causes liver failure. Therefore, NAC treatment might also be used to prevent liver failure and may be used before delivery for fetal and maternal improvement.

In conclusion, NAC treatment improves maternal outcomes in AFLP; further studies are needed for widespread usage of NAC in AFLP.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Alev Esercan;* ***Design:*** *Alev Esercan;* ***Control/Supervision:*** *Emre Ekmekci;* ***Data Collection and/or Processing:****Emre Ekmekci, Alev Esercan;* ***Analysis and/or Interpretation:*** *Ozan Cengiz;* ***Literature Review:*** *Alev Esercan;* ***Writing the Article:*** *Alev Esercan;* ***Critical Review:*** *Alev Esercan;* ***References and Fundings:*** *Emre Ekmekci;* ***Materials:*** *Emre Ekmekci.*

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