A patient with acute fatty liver of pregnancy (AFLP) with acute pancreatitis manifestations

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ABSTRACT

Background: Liver disease in pregnancy can be related to the process of pregnancy (liver disease of pregnancy) or not associated with pregnancy (liver disease in pregnancy). Acute fatty liver of pregnancy (AFLP) is a rare but life-threatening cause of jaundice in the third trimester of pregnancy and early postpartum period which in most cases no definitive risk factors are found. In this case report, we report a patient with AFLP with acute pancreatitis manifestations.

Case presentation: A 33-year-old woman referred to the Dr Soetomo General Academic Hospital, Surabaya, Indonesia with diagnosis of day-4 post-section caesarian (SC) accompanied by ileus paralytic, obstructive jaundice, hepatobiliary and liver injury (AKI) with dd acute on chronic kidney disease (ACKD), suspect pneumonia, and sepsis. Indications for SC were premature rupture of membrane (PROM). The patient initially complained of yellow body and eyes 10 days before delivery with additional complaints including tea-colored urine and brown feces. Chest x-ray results showed infiltrates on the right paracardial suggesting pulmonary inflammation. Abdominal x-rays showed normal result. Abdominal ultrasound results suggested acalculi cholecystitis, however, liver, lien, pancreas, kidney right and left, urinary bladder, uterus, adnexa right and left showed no abnormality. The patient was treated with intravenous fluids, nasogastric insertion for nutrition, analgesics and antibiotics and other symptomatic therapy. The patient was discharged after 20 days of treatment.

Conclusion: This case highlights a potentially fatal complication of AFLP case with acute pancreatitis manifestations and the need of rapid diagnosis and comprehensive management to avoid the complication and death.

Keywords: acute fatty liver of pregnancy, acute pancreatitis, Swansea criteria, jaundice, liver disease.

INTRODUCTION

Liver disease in pregnancy can be related to the process of pregnancy (liver disease of pregnancy) or not associated with pregnancy (liver disease on pregnancy). This disease group comprises five conditions: hyperemesis gravidarum, intrahepatic cholestasis of pregnancy (ICP), preeclampsia/eclampsia, HELLP syndrome and acute fatty liver of pregnancy (AFLP).1,3 Management of jaundice during pregnancy, especially in the third trimester, is a dilemma for clinicians because of its varied etiology and unpredictable prognosis. AFLP is a rare but life-threatening cause of jaundice in the third trimester of pregnancy and early postpartum period. This is associated with high maternal and infant mortality rates.4 AFLP is rare, estimated at one case in 13,000 deliveries. In most cases no definitive risk factors are found.5 Until the late 1970s, maternal and fetal mortality was reported to be close to 85%. Kelly calculated 44% of maternal deaths and 47% of fetal deaths.2 A retrospective study from one hospital in India found that of 285 maternal deaths (total 113,755 pregnancies from 1999-2011), 23 (8%) were secondary to pregnancy-related liver disorders and 17 (6%) had AFLP, histologically proven in 7 patients.6

In severe cases, AFLP could involve multiple organs, including acute renal failure, encephalopathy, gastrointestinal bleeding, pancreatitis and coagulopathy.7 The incidence of pancreatitis in AFLP ranges from 16%,8 43.7%9 to 88%.10 In this case report, we discuss a AFLP patient with manifestations of acute pancreatitis and its management.

CASE PRESENTATION

A 33-year-old woman referred to Dr. Soetomo General Academic Hospital, Surabaya, Indonesia on March 3, 2019 with diagnoses with day-4 post-section caesarian (SC) accompanied by ileus paralytic, obstructive jaundice, hepatobiliary and liver injury (AKI) with differential diagnoses of acute on chronic kidney disease (ACKD), suspect pneumonia, and sepsis. Indications for SC were premature rupture of membrane (PROM). This was a second child, and the first was 9 years old.

The patient initially complained of yellow body and eyes 10 days before delivery. Additional complaints include tea-colored urine, brown feces, nausea but no vomiting. The patient had never been like this before. The patient complained of swelling of the feet and hands a week before giving birth, epigastric pain like being stabbed, but no itching. The patient routinely checked by midwife but it was said to be normal. History of diabetes mellitus and hypertension was denied. The
patient gave birth to her second SC at Wates Hospital for indications of premature rupture of membranes. Two days post SC the patient experienced shortness of breath and decreased consciousness and was referred to Dr. Soetojo General Academic Hospital. Cough, phlegm, night sweats and weight loss denied. The patient also complains of fever. Post SC the patient unable to defecate, but able to fart. Diarrhea was denied. The patient had no history of hepatitis, vomiting blood, bloody bowel movements, bleeding, and itching. The patient's child is normal, there are no complaints of jaundice. Child 1 patient aged 9 years.

Physical examination showed weakness with GCS 345. Blood pressure 110/80 mmHg, pulse 100x/min, regular rhythm, lifting strength, normal amplitude. Respiration rate 24x/min, axillary temperature 36.5°C, SpO2 98% with nasal O2, and pain scale 3. The patient's weight and height were 75 kg and 165 cm, respectively. Head and neck examination revealed icterus sclera, no anemic conjunctiva, no cyanosis or dyspnea. There was no increase in jugular venous pressure or enlarged lymph nodes. Thoracic examination found symmetrical movement, no intercostal or supraclavicular retraction was found. Lung margin at ICS 6 midclavicular line dextra. On cardiac examination, single S1 and S2 were found, regular, no heart murmurs, gallop rhythm or pericardial friction sounds were found. On lung examination, vesicular breath sounds were found in both hemithorax, no crackles or wheezing in both lung fields. Abdominal examination found a flat abdomen, no bowel sounds, supple to touch, epigastric tenderness. Liver and spleen not palpable. Extremities were warm dry yellow, capillary refill time less than 2 seconds, found edema in the lower extremities and capillary refill time less than 2 seconds, extremities were warm dry yellow, tenderness. Liver and spleen not palpable. Bowel sounds, supple to touch, epigastric examination found a flat abdomen, no tenderness. Liver and spleen not palpable.

Abdominal ultrasound results suggested asymmetrical movement, no intercostal or supraclavicular retraction was found. Lung margin at ICS 6 midclavicular line dextra. On cardiac examination, single S1 and S2 were found, regular, no heart murmurs, gallop rhythm or pericardial friction sounds were found. On lung examination, vesicular breath sounds were found in both hemithorax, no crackles or wheezing in both lung fields. Abdominal examination found a flat abdomen, no bowel sounds, supple to touch, epigastric tenderness. Liver and spleen not palpable. Extremities were warm dry yellow, capillary refill time less than 2 seconds, found edema in the lower extremities and capillary refill time less than 2 seconds, extremities were warm dry yellow, tenderness. Liver and spleen not palpable. Bowel sounds, supple to touch, epigastric examination found a flat abdomen, no tenderness. Liver and spleen not palpable.

Abdominal x-rays showed no opaque stones along the urinary tract, ground glass appearance projected into the pelvic cavity, suggesting a full bladder. Abdomen ultrasound results suggested acalculi cholecystitis, however, liver, lien, pancreas, kidney right and left, urinary bladder, uterus, adnexa right and left showed no abnormality (Figure 1).

Based on anamnesis, physical examination and laboratory examinations, the patient was diagnosed as a postpartum patient with acalculi cholecystitis, sepsis, multiple organ dysfunction syndrome (MODS) due to reactive hepatitis bilirubinuria) dd acute fatty liver of pregnancy (AFLP), paralytic ileus, and stress-related mucosal disease (SRMD). On the 1st day of treatment. The patient's complaints were shortness of breath, occasional cough, fever for 1-day, abdominal pain, body and yellow eyes, and edema of the lower extremities. The vital sign showed BP 135/80, pulse 110 x/m, temperature 37.6°C, and GCS 456. The patient had 50 cc of hematin installed, a urinary catheter placed with concentrated urine production of 2600 cc/24 hours. Laboratory results showed Hb 11.1 g/dL, RBC 4.12x106/µL, WBC 19x109/µL, platelet (PLT) 196,000/µL, Serum Glutamic Oxaloacetic Transaminase (SGOT) 69, serum glutamic pyruvic transaminase (SGPT) 43, direct bilirubine 16.56, mg/dl, total bilirubine 22.83 mg/dl, c-reactive protein (CRP) 29.64, BUN 55 mg/dl, creatinine 1.87 mg/dl, albumin 2.57 mg/dl, random blood glucose 76 mg/dl, lactate dehydrogenase (LDH) 684 U/L, potassium 5.4 mg/dl, sodium 126 mg/dl and chloride 108 mg/dl. Urine analysis showed glucose (-), bilirubine (3+), ketoine (-), RBC (5+), pH 7.0, protein (-), urobilinogen (3+) nitrites (-), leukocyte (2+), erythrocytes (microscopic) >1/field, leukocytes (microscopic) 20-30/field and epithelial (microscopic) scanty. Blood gas showed pH 7.34, pCO2 24, pO2 83, HCO3 12.9, BE 12.9, SO2 95, AaDO2 37, pO2/FiO2 395,. The patient had non-reactive HBsAg and non-reactive HIV rapid test.

Chest x-ray results showed infiltrates on the right paracardial suggesting pulmonary inflammation, no heart abnormality. Abdominal x-rays showed no opaque stones along the urinary tract, ground glass appearance projected into the pelvic cavity, suggesting a full bladder. Abdomen ultrasound results suggested acalculi cholecystitis + sepsis, MODS, paralytic ileus, SRMD, AKI with differential diagnosis ACKD, suspected urinary tract infection (UTI), P2002 post SC day-5. The patient was treated with temporary fasting, aminofluid infusion (tutofusi 2:1 branch infusion of Dextrose 10%), 10 units of insulin, ceftriaxone 1 gram/12 hours IV, metoclopramide 10 mg/8 hours IV bolus, omeprazole 40 mg/12 hours IV bolus, and vitamin K 10 mg/12 hours IV bolus.

On the 2nd day, occasional fever, shortness of breath, weakness, cough, no nausea, vomiting and abdominal pain were complained. Vital signs showed BP 135/70, heart rate 101 beats per minute, temperature 36.5°C, GCS E4V5M6. The patient had 50 cc of hematin installed, a urinary catheter placed with concentrated urine production of 2600 cc/24 hours. Laboratory results showed Hb 11.1 g/dL, RBC 4.12x106/µL, WBC 22740/µL, PLT 159000/µL, Procalcitonin 9.8, base excess (BE) -14.3, SO2 97, HCO3 11, FiO2 21%, HBsAg non-reactive, anti-HCV non-reactive, fibrinogen 77.8, and Albumin 2.57. The patient was diagnosed with acalculi cholecystitis + sepsis, MODS, paralytic ileus, SRMD, AKI with differential diagnosis ACKD, suspected urinary tract infection (UTI), P2002 post SC day-6. The patient was treated with temporary fasting, aminofluid infusion (tutofusi 2:1 branch infusion of Dextrose 10%), 10 units of insulin, ceftriaxone 1 gram/12 hours IV, metoclopramide 10 mg/8 hours IV bolus, omeprazole 40 mg/12 hours IV bolus, and vitamin K 10 mg/12 hours IV bolus.

On the 3rd day, the fever and cough decreased, no tightness, but urine was still in brownish color. Urin output was 2000 cc/24 hours. Lab results showed amylase 298, lipase 3709, kalium 3.6, sodium 146,
CASE REPORT

Patient had fever and flatulence. Vital signs showed blood pressure 115/70 mmHg, pulse 96, and temperature 37.8°C. Urine output 1500cc/24 hours, there was edema of the lower extremities. Laboratory results showed amylase 380, lipase 3011, albumin 2.2, direct bilirubin 14.76, SGOT 86, SGPT 76, bilirubin total 17.76, kalium 3.9, natrium 131, chloride 97, Hb 9.8 g/dL, WBC 29650/µL, PLT 95, SGPT 78, bilirubin direct 13.2, SGOT 95, SGPT 78, bilirubin total 17.42, GDA 2.2, BUN 39, bilirubin direct 13.2, SGOT 95, SGPT 78, bilirubin total 17.42, GDA 2.2, BUN 40 mg/12 hours IV bolus, omeprazole 40 mg/12 hours IV bolus, and vitamin K 10 mg/8 hours IV bolus.

On the 6th day, the laboratory results showed amylase 685, lipase 5476, albumin 2.2, BUN 39, bilirubin direct 13.2, SGOT 95, SGPT 78, bilirubin total 17.42, GDA 97, Hb 8.0 g/dL, WBC 29650/µL, PLT 143000/µL. The patient was diagnosed with sepsis, acute pancreatitis, AFLP, community-acquired pneumonia (CAP), suspected UTI, P2002 post-SC day-9.

On the 10th day, the patient had fever and flatulence. Vital signs showed blood pressure 115/70 mmHg, pulse 96, and temperature 37.8°C. Urine output 1500cc/24 hours, there was edema of the lower extremities. Laboratory results showed amylase 130, lipase 1031, albumin 2.5, Hb 10 g/dL, HCT 29.1%, WBC 10310/µL. Sepsis diagnosis improved, AFLP, CAP improved, UTI improved, hypoalbumin, anemia post-correction, acute pancreatitis, P2002 post SC day-16.

On the 17th day, the laboratory results showed amylase 290, lipase 2561, albumin 2.3, Hb 9.9 g/dL, HCT 28.6%, and WBC 12140/µL. The patient had a working diagnosis with sepsis improving, AFLP, CAP improving, UTI improving, hypo albumin, anemia post-correction, acute pancreatitis, P2002 post SC day-16.

on the 20th day of treatment, the patient had no complaints. Lab results of amylase 125 and lipase 981. The patient was admitted to outpatient clinic for further follow up.

DISCUSSION

AFLP is a rare and potentially fatal complication that occurs in the third trimester or early postpartum period. The incidence of AFLP is approximately one in 10,000 to 15,000 pregnancies. This condition is more common in primigravidas, multiple pregnancies, and pregnancies containing fetal fatty acid metabolism abnormalities.

Although the exact pathogenesis is unknown, the disease is associated with fetal fatty acid metabolism abnormalities. Several reports have documented a strong association between AFLP and long-chain enzyme 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency in the fetus, a disorder of mitochondrial fatty acid beta-oxidation. LCHAD deficiency is an autosomal disorder that appears (recessive) and often occurs in mothers who have heterozygous gene abnormalities with homozygous fetuses, resulting in excess of toxic metabolites. AFLP is characterized by infiltration of hepatocyte microvesicular fat without inflammation or necrosis. Some medical evidence indicates that disturbances of fatty acid metabolism in maternal mitochondria may cause AFLP.

Another hypothesis supports that above-normal estrogen levels (in pregnancy) potentiate the effects of hormone influences on mitochondria in the third trimester.

On physical examination, the patient usually has fever and jaundice, which occurs in more than 70% of patients with AFLP. The liver is usually small and not palpable. In this patient, yellow body and eyes were complained 10 days before giving birth, nausea but no vomiting, headache, and upper left abdominal pain like stabbing. Urine was reddish like tea; brownish feces were also complained.

To make a diagnosis of liver disease during pregnancy, we need to distinguish whether the disease was related to the pregnancy or not. This patient had no previous history of jaundice or epigastric pain. There was also no history of drinking alcohol. From examination of IgM anti-HAV, anti-HCV and HbsAg virus markers were negative. Abdominal ultrasound of the liver was within normal limits, only acalculi cholecystitis was found. Therefore, it was suspected that the patient had liver disease related to pregnancy (liver disease of pregnancy). This disease group consists of 5 diseases, namely, hyperemesis gravidarum, intrahepatic cholestasis of pregnancy (ICP), preeclampsia/eclampsia, hemolysis-elevated liver enzyme-low platelet (HELLP) syndrome and AFLP.

Hyperemesis gravidarum usually occurs in the 1st trimester and typically begins less than 8 weeks after the last menstrual period, so other diagnoses need to be considered. Preeclampsia was characterized by the presence of new-onset hypertension in pregnant women and proteinuria beyond 20 weeks gestation, which did not occur in these patients. Elevated serum transaminases, increased bilirubin, LDH, and hemolytic anemia and thrombocytopenia characterize HELLP. The Mississippi criteria require increased serum transamination, LDH, and thrombocytopenia. In this patient, there was an increase in SGOT, SGPT, and LDH, but no thrombocytopenia was found. Another differential diagnosis was intrahepatic cholestasis of pregnancy (ICP), usually occurs in the third trimester, but sometimes earlier. The main symptom
of ICP is intense pruritus, mainly on the palms and soles, but can affect other parts of the body which this patient did not complain.17

The diagnosis in this patient was acute fatty liver of pregnancy (AFLP). AFLP is usually diagnosed based on clinical symptoms and typical pathology according to Swansea criteria, without the need for liver biopsy, although PA examination will produce pathognomonic findings and is useful if the obstetrician is unsure about terminating.18 According to Swansea criteria, this patient met clinical criteria in which 10 clinical criteria were obtained (score>6), namely nausea, heartburn, leukocytosis, increased bilirubin, hypoglycemia, increased BUN, increased transaminases, impaired kidney function, and coagulopathy characterized by increased hemostatic physiology. The patient did not undergo liver biopsy examination.

Pancreatic involvement usually occurs only in severe cases after hepatic and renal impairment development. From the results of the study, it was found that in AFLP patients, 91% experienced increased blood lipase levels. Of these, only 67% underwent imaging tests, of which 88% were diagnosed with pancreatitis.19 Until recently, little knowledge was available about how this disease causes pancreatitis. The mechanisms by which pancreatitis may develop as a complication of fatty liver during pregnancy are not well understood because this association is rare. Our hypothesis is that accumulated 3-hydroxyacyl long-chain metabolites are toxic to liver and pancreatic tissue. Thus, the pancreas may be affected when increased concentrations of these metabolites are present, as occurs in cases of severe liver disease. This hypothesis serves as a plausible explanation for the pancreatic disorder featured in this case of liver failure.19

Pathophysiologically, pregnancy creates a series of conditions that can lead to acute pancreatitis, namely: (1) hyperlipidemia, secondary to increased physiological levels of estrogen. The triglyceride level that can induce acute pancreatitis is between 750-1000 mg/dl; (2) high blood progesterone levels cause increased lipase and trypsin secretion. It also causes spasms of the sphincter of oddi and hypotonia of the pancreatic duct; and (3) immunological processes that usually occur during pregnancy are risk factors for acute pancreatitis.15

Management of acute pancreatitis consists of accurate diagnosis, appropriate triage, good supportive therapy, monitoring and treating complications, and prevention of recurrence. Resuscitation fluid recommendations are given within the first 12 to 24 hours after symptom onset and are less useful after 24 hours. Administration of crystalloids is recommended at 200-500 mL per hour, or 5-10 mL/kgBW/hour, approximately 2500-4000 mL in the first 24 hours.20 Most patients with mild acute pancreatitis can be put on a low-fat enteral diet soon after admission, in the absence of severe pain, nausea, vomiting, and ileus. If the complaint is still severe or unable to receive oral nutrition on the fifth day, nutrition with an artificial enteral canal can be performed.20 Prophylactic antibiotics in patients with acute pancreatitis were not found to affect mortality or morbidity, so they are no longer recommended. Antibiotics are only given for acute pancreatitis infected with empiric antibiotics which include gram-negative and positive, aerobic and anaerobic bacteria.21

So far, acinar cells are considered to have a major role in the pathophysiology of acute pancreatitis. Trypsin was found to be prematurely activated in pancreatic acinar cells, which in turn activate various pancreatic digestive enzymes, leading to the use of inhibitors of exocrine pancreatic enzyme secretion such as somatostatin and its analogue, octreotide. Somatostatin reduced APACHE II scores, sepsis complications, MODS, mortality, and the expression of proinflammatory factors such as TNF-α and IL-6 in 306 patients with severe acute pancreatitis.22 The results of animal studies have found positive results, but in humans, various studies have found varying results. This is hypothesized because giving somatostatin is more useful in the early phase of the process of acute pancreatitis for reducing pancreatic exocrine secretion, reducing pro-inflammatory cytokines, and Oddi sphincter tone, whereas these studies did not include the time span between onset and administration of therapy.23,24

This was supported by data that the use of somatostatin and its analogues as prophylaxis was found to prevent complications of pancreatitis in pancreatic surgery and endoscopic retrograde cholangiopancreatography (ERCP).25,26

In this patient, a SC was performed to deliver the baby at the previous hospital. The patient was given antibiotic therapy according to sputum culture, namely moxifloxacin 400 mg/24 hours IV, adequate fluid administration because this patient also had acute pancreatitis, NGT for nutrition but this patient came with suspicion of paralytic ileus and abdominal pain so she was temporarily fasted. Due to reduced complaints, on the third day the patient began to be given a liquid diet orally. The patient was also given somatostatin analog therapy 2 ampoules/24 hours IV and other symptomatic therapy as well as blood transfusion because the patient was anemic. On the 20th day of treatment, there was a decrease in amylase and lipase (125 and 98) in outpatient clinics.

Full clinical recovery in patients with AFLP and pancreatitis usually occurs within weeks without long-term sequelae, although histological changes in the liver may persist for months.2 The patient was sent to polyclinic with education about the disease, awareness about complaints, and symptoms of necrotic pancreatitis.

CONCLUSION

AFLP is a rare and potentially fatal complication that occurs in the third trimester or early postpartum period. We reported a AFLP with acute pancreatitis manifestations and this case highlights the need of rapid diagnosis and comprehensive management to avoid the complicaton and death.

PATIENT CONSENT

The patient signed informed consent prior to the study and agreed that the case will be published in an academic journal without revealing the patient identity.

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