CLINICAL VIGNETTE

Acute Fatty Liver of Pregnancy

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The patient is a 34–year-old Japanese American woman who is gravida 2 para 2. Her first pregnancy was uncomplicated. The patient was at 38 weeks in her second pregnancy when she noticed tactile fevers, body aches, abdominal discomfort (which she attributed to pregnancy contractions), dark urine and yellow eyes. She underwent induction and had an uncomplicated delivery.

Patient delivered a healthy male infant who demonstrated neonatal jaundice, but otherwise developed no other complications.

In the week after delivery, she continued to have increasing fatigue, lethargy, increasing jaundice, darker urine, pruritus and development of lower extremity edema. She denied fevers, but has had occasional episodes of chills and sweats. She had abdominal pain possibly related to meals, but no nausea, vomiting or diarrhea.

The patient had a positive hepatitis A antibody, but hepatitis B, hepatitis C and HIV antigen studies were negative. The patient had no prior history of liver disease or jaundice. She was taking prenatal vitamins and had prior history of tobacco but had quit. She denied alcohol or drug use. She had no known allergies to medications and no family of liver disease.

Her review of systems was notable for profound fatigue and exertional dyspnea. She had no fevers, but possible chills. She denied headache, sore throat. She has had scleral icterus.

She denied cough, but had profound dyspnea on exertion. She denied any chest pain. No significant orthopnea or PND. She had not had any nausea or vomiting. She denied diarrhea or dysuria. She had mild discomfort from her episiotomy. She described diffuse muscle aches which were somewhat improved from several days prior. She had noticed increasing abdominal girth and peripheral edema.

On admission to the hospital, she was in no acute distress, afebrile with normal vital signs. Sclerae were icteric. Her cardiac and pulmonary exams were normal. She had no jugular venous distention. Her abdomen was mildly distended and mildly diffusely tender to palpation. There was no hepatosplenomegaly. She had 3 + pitting edema. Her neurologic exam was nonfocal and she was alert and oriented.

Laboratory Data: Sodium 126, potassium 3.6, chloride 98, creatinine of 0.8, glucose 88. White count of 15.8. Her neutrophils were 75, bands were 7,15 lymphocytes, hemoglobin of 12.9, platelets 302, amylase of 70, AST 84, ALT 367, total bilirubin of 10.2, direct bilirubin of 6.4, alkaline phosphatase of 184. Her INR was 2.2, albumin was 2.2.

Chest x-ray showed no acute disease and no failure. She had a normal echocardiogram. Her ultrasound showed stones in her gallbladder, but no gallbladder wall thickening or biliary dilatation. An abdominal CT scan showed evidence of pericholecystic fluid, some gallbladder wall thickening, gallstones with common duct

measuring 7 mm. The pancreas reportedly appeared boggy without any discrete masses.

She was given vitamin K and started on IV antibiotics. Gastroenterology and general surgery were consulted and the patient underwent ERCP to assess biliary anatomy due to elevated bilirubin. The duodenum was noted to have severe erosions noted throughout and up to the second portion of the duodenum where the ampulla also appeared to be somewhat abnormal with adenomatous-type changes. The common bile duct and the intrahepatic ducts appeared normal. The cystic duct was cannulated and did not opacify, probably secondary to stone within this region. A 1-cm sphincterotomy was performed after which a 12-mm balloon was used to express copious amounts of sludge and small calculi. Balloon occlusion cholangiogram again failed to opacify cystic duct region. The patient subsequently underwent laparoscopic cholecystectomy and liver biopsy. Labs at that time: AST was 52, ALT 105, alkaline phosphatase 153, albumin 2.2, bilirubin total 12.4 and conjugated 7.7.

After the surgery, her total bilirubin continued to rise to a peak of 14.7, conjugated bilirubin rose from 7.7 to 8.4, ALT 136, AST 135, alkaline phosphatase 169. The intraoperative Liver Wedge Biopsy revealed:
- Extensive cholestasis, most consistent with cholestasis of pregnancy.
- Focal hepatocellular dropout.
- Not suggestive of biliary obstruction
Gallbladder (cholecystectomy):
- Cholelithiasis with edema, consistent with acute cholecystitis.
- Mild chronic cholecystitis.

Because of progressive elevation of bilirubin, hepatology consultation was obtained and recommended labs to rule out autoimmune etiologies, Wilson's disease, and hemochromotosis, including TIBC, ferritin, ceruloplasmin, ANA, smooth muscle antibody, and mitochondrial antibody. These were negative and she was felt to have a diagnosis of acute fatty liver of pregnancy based on her symptomatology. She continued to have improvement of her liver function tests and complete resolution at 4-6 weeks post partum and did not require any treatments except Ursodiol for pruritus associated with hyperbilirubinemia. She had no sequelae of her liver dysfunction.

Patient's infant was monitored and had developed no issues related to the patient's condition.

Acute fatty liver of pregnancy was first described in 1934 as "yellow acute atrophy of the liver" and is a rare condition exclusive to pregnancy with onset in the third trimester. Initial symptoms include nausea or vomiting, abdominal pain, anorexia, jaundice, headache and fatigue. Half of patients have signs of preeclampsia[1,2]. The incidence is one in 10,000 to 15,000 pregnancies. Maternal and perinatal mortality have been as high as 75% and 85% respectively in the past. Now with earlier diagnosis and treatment, maternal and perinatal mortality have been reduced to 18% and 23%, respectively. Women have onset of symptoms between 28-40 weeks, and on exam, they may have fever, jaundice, epigastric or right upper quadrant pain. In severe cases, patients can present with acute renal failure, encephalopathy, gastrointestinal bleeding, pancreatitis, coagulopathy, edema and hypertension[3].

Lab values are abnormal with high levels of aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, alkaline phosphatase and ammonia. There

are prothrombin and partial thromboplastin time prolongation and hypoglycemia due to hepatic insufficiency. DIC can occur. Elevated creatinine and high uric acid can also be present. Patients have elevated WBC, normal hemoglobin. Platelets are normal to low[2, 3, 4].

Diagnosis can be challenging since patients can present with nonspecific symptoms and have biochemical derangements that overlap with other conditions. Pre-eclampsia is common in late pregnancy but distinguishes itself from AFLP in that patients do not have hypoglycemia or jaundice and AFLP develops more acutely than pre-eclampsia[3]. Another common condition to rule out is HELLP syndrome, which is characterized by hemolysis, elevated liver enzymes and low platelet count. Hypoglycemia, prothrombin time prolongation and encephalopathy suggests AFLP [2, 4]. Acute viral hepatitis can be ruled out with serology tests and patients with hepatitis have higher levels of serum transaminases (>1000) Intrahepatic cholestasis of pregnancy can also cause jaundice but is not associated with abdominal pain, nausea, vomiting, liver failure or coagulopathy[3].
Ultrasound and computed tomography demonstrate fatty infiltration of the liver but sensitivity and specificity are insufficient to diagnose. Liver biopsy showed microvesicular fatty infiltration of hepatocytes and patchy hepatocellular necrosis but widespread necrosis or inflammation was absent[3].

The primary treatment is early diagnosis and prompt delivery. Complications of AFLP can include hypoglycemia, coagulopathy, hepatic and renal dysfunction. Pancreatitis can develop after the onset of hepatic and renal dysfunction with subsequent pseudocysts or hemorrhagic pancreatitis. For severely ill patients, admission to the intensive care unit for monitoring, glucose infusion for hypoglycemia and blood products to reverse coagulopathy may be needed. Liver tests and coagulopathy usually revert to normal after delivery but there can be transient worsening of liver and renal function during first few days after delivery[2, 3]. In rare cases of patients who continue to have progressive clinical deterioration despite delivery and aggressive support, orthotopic liver transplantation has been performed with correction of the patient's multisystem failure[5].

AFLP can recur in subsequent pregnancies. However, the risk of recurrence is unknown. Women who become pregnant again should be closely observed for signs of acute fatty liver[2, 3].

Acute fatty liver of pregnancy may be due to inherited defects in mitochondrial beta-oxidation of fatty acids. Multiple reports have been published linking mothers who developed AFLP with infants with long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency[4]. Mitochondrial fatty acid beta-oxidation starts with carrier transporters that bring fatty acids to the mitochondrial inner membrane. The fatty acids are then broken down by four enzymes resulting in energy production for the brain, heart, liver and skeletal muscle during fasting. Deficiency of LCHAD causes accumulation of medium and long-chain fatty acids[3]. The human placenta and chorionic villus show high activity of fatty acid oxidation enzymes. It is postulated that the combination of the metabolic stress of the third trimester with maternal reduction in capacity to oxidize long-chain fatty acids causes fatty acid metabolites to accumulate in the maternal circulation as well as metabolites from the fetus are toxic to the

maternal liver and lead to development of AFLP[4].

The effect on the fetus is fatty infiltration of muscle fibers which can affect skeletal and cardiac muscle development. The liver enlarges with lipid deposition and causes jaundice, liver failure, and hypoketotic hypoglycemic encephalopathy. Children can develop severe cardiomyopathy, slowly progressing peripheral neuropathy and skeletal myopathy. Some cases of sudden infant death syndrome were found to have undiagnosed fatty acid oxidation disorders on autopsy. Diet low in long-chain fatty acids supplemented with medium-chain triglycerides is recommended for the newborn[3, 4].

Molecular studies have found an association between AFLP and E474q mutation in the fetus. The E474Q mutation changes glutamate to glutamine at position 474 in the mature mitochondrial trifunctional protein complex alpha subunit. The LCHAD is part of the MTP complex. Newborn screening for E474Q mutation allows for dietary treatment in affected infants and screening of women who developed AFLP allows for genetic counseling and prenatal diagnosis in subsequent pregnancies[6].

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Submitted on March 31, 2011