CLINICAL VIGNETTE

Acute Fatty Liver of Pregnancy – A Case Report

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Case Report

A 25-year-old female G3P0020 with a history of two spontaneous abortions, negative testing for APS, presented to an outside hospital at the request of her obstetrician for induction of labor at 36 weeks for cholestasis of pregnancy. Her induction was complicated by development of a category III fetal heart rate tracing requiring urgent CS under general anesthesia. The fetus was delivered without complication, but upon extubation, she was noticed to have blood in her oropharynx of unknown source and was reintubated.

Pre-operatively, the patient's labs were notable for a WBC 10.7, Hct 31.1, Plt 222, Cr 0.7, AST 75, ALT 125, and INR 1.8. Post-operatively, her labs reflected a WBC 5.5, Hgb 7.5, Plt 84, Anion gap 23, Cr 1.5, ABG 7.17/30/86 with A-a gradient 447, and a random glucose of 20. AST 65, ALT 74, Alk Phos 407, LDH 465, and INR was uptrending to 2.0. Her vitals included a fever of 100.3°F. CXR was unremarkable immediately post reintubation. Abdominal US was notable for increased echogenicity of the liver suggestive of steatosis and gallbladder wall thickening without gallstones. No ascites or free fluid was noted. She was transferred to the ICU for presumed DIC and possible aspiration pneumonia vs. severe sepsis and possible amniotic fluid embolism.

She was given FFP and cryoprecipitate. Given her ultrasound findings and new fever, there was an initial concern for cholecystitis and she was taken to the OR for cholecystostomy with consequent drainage of bloody fluid. She also had a paracentesis of 1.2L. On POD #2, she was transferred to UCLA for further management. Labs were remarkable for WBC 25, Hgb 4.8, Plt 51, Anion Gap 30, Cr 3. AST/ALT had peaked at 2100s/360s, and BNP ~5000. Urinalysis was notable for >1000 RBC. CXR showed asymmetric interstitial and airspace opacities 2/2 edema and possible underlying infection. EKG and TTE demonstrated sinus tachycardia with a preserved EF and no evidence of underlying cardiomyopathy. In light of her hypoglycemia, the MICU team treated her supportively for acute fatty liver of pregnancy, with fluid/electrolyte repletion, maintenance of euglycemia, and transfusion of blood products as necessary to control coagulopathies. Elevated lactate, transaminases, and bilirubin normalized with continued supportive care. Hospital course was complicated by AKI/ATN requiring SCUF, quickly transitioned to CRRT and discontinued with eventual return of her kidney function. Her course was further complicated by cerebral edema and subdural hematoma with clinical aphasia and encephalopathy that largely returned to baseline. She developed an isolated episode of Afib with RVR which was adequately rate controlled with beta blockade followed by eventual conversion to sinus rhythm. Interventional radiology replaced her cholecystostomy tube that was placed at the outside hospital once it was found to be draining hemoperitoneum and fluoroscopy demonstrated contrast extravasation into the abdomen. Repeat abdominal imaging demonstrated a stable hematoma without abscess. She was supported on TPN and eventually transitioned to the floor on POD #18 and discharged POD #21.

Discussion

Acute fatty liver of pregnancy (AFLP) is an uncommon, yet potentially fatal, liver disease typically occurring in the third trimester marked by acute liver synthetic dysfunction. The possibility for severe complications such as DIC and renal failure necessitates a prompt differentiation between it, other pregnancy-specific and non-specific liver disorders, and thrombotic microangiopathies that may present similarly. With appropriate treatment with immediate delivery of the fetus and supportive care, maternal outcomes are generally favorable with near-full to full recovery anticipated within weeks.

Epidemiology

The incidence of AFLP varies in recent epidemiological studies between 1:7,000–1:15,000 pregnancies, making AFLP a relatively uncommon disease. Due to the suspected pathogenesis of AFLP (discussed below), risk factors for AFLP include include multigravid state and previous episodes of AFLP.[1] The contribution of other liver diseases of pregnancy to the risk of AFLP developing remains unclear.

Pathogenesis

Recent evidence continues to strongly suggest a fetal-maternal interaction involving fatty acid metabolism as the suspected root etiology of AFLP. In particular, an inherited fetal deficiency of the enzyme long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) demonstrates the strongest association. Current hypotheses speculate that the enzymatic deficiency in the fetus or placenta leads to increased levels of potentially hepatotoxic long-chain fatty acids introduced into

maternal circulation with subsequent deposition into the liver, leading to impaired hepatic function.[2,3]

Medium-chain acyl-CoA dehydrogenases (MCAD) and short-chain acyl-CoA dehydrogenases (SCAD) have been rarely associated with AFLP, and very long-chain acyl-CoA dehydrogenases (VLCHAD) have not yet been associated with AFLP.[1]

Histology

Liver biopsy demonstrates microvesicular fatty infiltration of hepatocytes without changes in overall hepatic architecture. Fatty infiltration gives hepatocytes a swollen, foamy appearance. Few patients also demonstrate rare, larger fat vacuoles. These infiltrations are not always immediately apparent on H&E stain and thus a specimen should be set aside to evaluate if they stain positive for a fat-specific stain, Oil Red O. There is never massive panlobular hepatocellular necrosis, as is seen in processes such as viral hepatitis. Biopsy, electron microscopy and staining may help to solidify the diagnosis if other imaging modalities such as ultrasound or CT fail to demonstrate findings consistent with steatosis.[4]

Diagnosis

The difficulty in diagnosis of AFLP lies in the similarities in the clinical constellation of findings to other pregnancy-specific liver disorders. Severe preeclampsia (PE), HELLP syndrome, and AFLP have all been described to present with non-specific symptoms, including nausea/vomiting, headache, and RUQ/ epigastric pain in the third trimester. Their severe complications are also nearly identical, including DIC, renal failure, and pulmonary edema. In addition, the possibility of an undiagnosed thrombotic microangiopathies of pregnancy (P-TMAs - i.e. TTP/HUS) that may also present similarly, further clouding the clinical picture. However, the presence of severely elevated transaminases and hepatic dysfunction strongly favors PE/HELLP/AFLP and less so the P-TMAs.

There remains a large clinical overlap between AFLP and PE/HELLP syndrome, and clinical differentiation in an acute setting is difficult, if not impossible. However, the clinical presence of hepatic failure and encephalopathy favor a diagnosis of AFLP. One study of women who developed liver disease during pregnancy found that 70% had acute fatty liver of pregnancy whereas only 15% had HELLP.[5] The presence of severely depressed antithrombin III and hypoglycemia may also help to differentiate between these clinically similar etiologies, as one study noted depressed antithrombin III in 23/23 patients with AFLP. [6-8]

Liver biopsy remains the gold standard in diagnosing AFLP, but it is rarely obtained due to its invasive nature, particularly in the setting of coagulopathy. If a biopsy must be obtained in the setting of coagulopathy, a transjugular liver biopsy carries a lower risk of bleeding compared to a percutaneous liver biopsy.[1] It remains important to consider that disorders not specific to pregnancy, including viral hepatitis, biliary obstruction, Budd-Chiari, and toxic ingestion be concurrently.

The Swansea criteria has been proposed as a diagnostic tool in determining the presence of AFLP, a positive result being defined as having at least 6 of 15 criteria. Though it is 100% sensitive, it is only 57% specific and intended to be used in the absence of other suspected diagnoses of liver dysfunction. No study has demonstrated an earlier time to diagnosis and multiple patients fulfilling the requirements of AFLP by Swansea criteria also fulfill the requirements of HELLP syndrome.[1]

Treatment

Proper identification of the correct underlying process of hepatic insufficiency is crucial to optimizing maternal outcome. Though the delivery of the fetus and supportive care improves maternal clinical outcome in AFLP and HELLP, there is no benefit in patients with P-TMAs, where plasma exchange is the first-line treatment.[8] The acute clinical distinction between PE/HELLP/AFLP remains largely of academic importance, as treatment for these conditions largely involve prompt delivery of the fetus with aggressive supportive care, with the addition of glycemic control with dextrose infusion in AFLP. In the long-term, distinguishing AFLP as the culprit etiology may be helpful as the suspected genetic basis of disease pathophysiology may carry consequences for future pregnancies (discussed below).[8]

Prognosis

Advances in supportive care have resulted in the decline of maternal and fetal deaths. Morbidity and mortality remain higher in developing countries less able to provide necessary supportive care. US maternal mortality rates from AFLP have dropped from ~85% in the 1980s to 10-15% in the 2000s[9,10] largely attributed to greater recognition, prompt delivery of the fetus, and improvement in supportive care. With prompt identification, expected time to improvement is approximately 1-3 weeks, with laboratory evidence of slowing of hepatic necrosis – plateauing/decreasing LFTs – evident within a few days.[11] AKI usually improves in 7-10 days with appropriate supportive care (SCUF, CRRT, HD as necessary).[6,8]

While some liver diseases of pregnancy such as preeclampsia are known to recur and have significant comorbid impact on future gestations, little is known about recurrent cases of AFLP in subsequent pregnancies. More work is required to determine appropriate follow-up and monitoring.

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