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Case(s) Report
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Acute fatty liver of pregnancy: a case report and review of the literature

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Abstract

Objective: Acute fatty liver of pregnancy (AFLP) is potentially life-threatening obstetric complication. It is most frequent cause of acute liver failure during pregnancy.

Case(s): We describe 23 year-old pregnant with AFLP. She went to emergency department with complaints of nausea, vomiting, epigastric pain, according to last menstrual period at 32+3 weeks. She was referred to our hospital upon detecting ALT:227,AST:539,GGT:79,total bilirubin:1,45,direct bilirubin:0,82. On admission to our hospital, ALT:243,AST:601,GGT:98,LDH:1188,platelet:98x10^3,urine protein test:2+,total bilirubin:3,4,direct bilirubin:2,37. Patient was hospitalized with diagnoses of HELLP syndrome and acute fatty liver of pregnancy, and underwent cesarean section resulting from spontaneous decelerations on NST.

Conclusion: When a patient has persistent nausea, vomiting, epigastric pain and elevated levels of AST,ALT,GGT,direct bilirubin, physicians should also consider AFLP in differential diagnosis.

Keywords: AFLP, HELLP syndrome, preeclampsia

Introduction

Acute fatty liver of pregnancy (AFLP) is a potentially life-threatening obstetric complication characterized by acute hepatic failure. Its prevalence is estimated to be 1 to 3 cases per 10,000 deliveries.[1] It has important maternal morbidity and mortality due to complications such as disseminated intravascular coagulation (DIC) and haemorrhage, sepsis, aspiration, acute kidney injury, fulminant hepatic failure, encephalopathy, hypoglycaemia, pancreatitis, gastrointestinal bleeding and multiorgan dysfunction.[3-5] The maternal mortality rate for AFLP is approximately 2%. Rate of perinatal mortality is approximately 10 to 20%. Perinatal morbidity is principally related to prematurity and fetal acidosis.[1] Risk factors for AFLP include multiple gestations, male fetuses, nulliparity, fatty acid oxidation disorders, and previous history of AFLP.[1,5] The majority of cases are present during the third trimester (mean gestational age of 37 weeks) although there are also cases reported during second trimester or postpartum period.[1,2,5] The pathogenesis of AFLP has been attributed to a defect in recessively inherited mitochondrial beta-oxidation of fatty acids in some cases in both the mother and the fetus.[2,3,5] The most common gene mutation is defects in long-chain 3-hydroxyacyl-CoA dehydrogenase /mitochondrial trifunctional protein enzyme complex (LCHAD/MTP), which is caused by the G1528C and E474Q mutations of the gene on chromosome 2 (homozygous in the fetus, heterozygous in the mother). Maybe 20% of AFLP could be associated with this. Other associated gene mutations

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include fetal deficiency of carnitine palmitoyl transferase I (CPT 1), and medium chain acyl-CoA dehydrogenase (MCAD).[5,6] AFLP is pathologically characterized by microvesicular fatty infiltration of the liver.[1,5] It is usually a diagnosis of exclusion and requires a strong index of suspicion.[2] Distinguishing AFLP from preeclampsia and HELPP syndrome can be difficult due to overlapping features such as hypertension, elevated serum transaminase and creatinine levels, thrombocytopenia, acute kidney injury.[5,6] Sensitive diagnostic tools such as Swansea criteria have been developed.[5] Management consists of urgent delivery of the fetus and supportive maternal care for complications.[3,5] Fatty liver recurring in subsequent pregnancy is rare .[5]

Case(s)

The patient was 23-year old primigravid. Double tests were performed when she was pregnant for 12+2 weeks according to her last menstrual period (LMP). Results were PAPP-A: 0.79 Mom; free-beta HCG: 0.24 Mom; combined trisomy 21 risk: 1:5084; and trisomy 18/13 risk: 1:18481. Detailed anatomic screening was performed when she was pregnant for 20+4 weeks according to her LMP. Biometric measurements were consistent with her pregnancy period and there was no fetal anomaly. Oral glucose tolerance test was performed when she was pregnant for 25+2 weeks according to her LMP. Gestational diabetes mellitus was detected and diet was applied. Blood glucose values were regulated based on the diet. She went to emergency clinic with complaints of nausea, vomiting, and epigastric pain when she was pregnant for 32+3 weeks according to her LMP. She was referred to our university upon detecting increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), Gamma-glutamyltransferase (GGT), total and direct bilirubin, and C-reactive protein (CRP). At the time when she was admitted to our hospital, haemoglobin (Hb), haematocrit (Htc), blood glucose, blood urea nitrogen (BUN), creatinine (Cr), alkaline phosphatase, uric acid, total and low density cholesterol (LDL), triglyceride, amylase, lipase, electrolytes (sodium, potassium, chloride), fibrinogen, and coagulation tests (prothrombin time-PT, activated partial thromboplastin time-APTT, international normalized ratio-INR) were all normal. Hepatitis markers (HbsAg, anti-HCV) were negative. AST, ALT, GGT, lactic dehydrogenase (LDH), total and direct bilirubin, CRP, and white blood cell (WBC) were all elevated. Thrombocytopenia and 2+ proteinuria in spot urine were present. The patient was hospitalized to Obstetrics and Gynaecology clinic with provisional diagnosis of HELLP (haemolysis, elevated liver, low platelet) syndrome and acute fatty liver arising out of pregnancy. She had no complaints of pruritus, headache, and visual impairment and had no history of travel or ingestion of drugs or medicinal herbs. On the physical examination, the patient seemed icteric. Blood pressure measurements were normal. Blood glucose was followed hourly and complete blood count (CBC) and biochemistry tests were performed with the intervals of 6 hours. 12 mg betamethasone ampoule was administered to the patient intramuscularly. Non-stress test (NST) monitorization was done. In the blood test results, the values were between the following ranges: platelet: 83-98x10^3, WBC: 11.9-14.9x10^2, AST: 296-601 U/L, ALT: 174-243 U/L, LDH: 556-1188 U/L, GGT: 98-130 U/L, total bilirubin: 3.4-8.8 mg/dl. Abdominal ultrasonography (USG) was performed to the patient. Abdominal USG revealed the liver with a slight increase in size and increased echogenicity of the right lobe, suggesting steatosis, however ascites was not detected. Acute viral hepatitis and intrahepatic cholestasis were excluded as the patient had no pruritus and she had no hepatitis indicators. The patient had six of Swansea criteria. Thus, diagnosis of acute fatty liver was made. The patient underwent urgent caesarean section resulting from non-reactive NST and spontaneous decelerations on NST. The healthy male infant was 1560 grams in weight with an Apgar score of five at the first minute and seven at the fifth minute. After her caesarean section, the patient was transferred to the intensive care unit (ICU) where she stayed for just one day. AST, ALT, GGT, and total and direct bilirubin values decreased postoperatively during first day in a progressive manner, and all returned to normal in third day. Coagulation tests were normal. Complications did not develop. Computed tomography (CT) was performed postoperatively on the 2nd day. Density of liver was low, suggesting steatosis and wall of gallbladder was enhancing and contracted and gallstones was present, but intra-extrahepatic bile ducts were normal.

Discussion

AFLP is a potentially life-threatening obstetric emergency.[1,2] It is the most frequent cause of acute liver failure during pregnancy.[5] It is also called acute fatty metamorphosis or acute yellow atrophy.[5] It was described by Sheehan in 1940.[2] It has a prevalence in the range of 1: 7,000 to 1:20,000).[2] It has maternal mortality rate up to 12.5%-18%.[1,3,4] The diagnosis of AFLP is determined based on both clinical features and laboratory findings, including : a) symptoms of persistent nausea, and vomiting, malaise, fatigue, anorexia, epigastric pain, and progressive jaundice; b) elevated ALT and AST, bilirubin and serum creatinine levels, leucocytosis, prolonged prothrombin time, reduced fibrinojen and hypoglycaemia; c) ultrasonography images or computed tomography

(CT) examination showing fatty liver; and d) liver biopsy sample with microvesicular fatty change.[4,5] Swansea criteria for the diagnosis of AFLP is showed in Table 1. The presence of more than 5 Swansea criteria represents a validated method for supporting the clinical diagnosis of AFLP.[4] Management of AFLP require a combination of maternal stabilization and promptly delivery of the fetus regardless of gestational age.[7] In our case, (vomiting, abdominal pain, elevated bilirubin, leucocytosis, elevated transaminases, liver hyperechogenicity on USG) six of Swansea criteria were present. Liver biopsy was not performed. Ammnoia was not able to be studied.

Table 1: Laboratory test results

	On admission	6 hr after admission	PO 4th hr	PO 16th hr	PO 24th hr	PO 2nd day	PO 3rd day
Plt	98x10³	83x10³	90x10³	90x10³		128 x10³	170 x10³
Wbc	14.930	14.500	18.710				
AST	601	544	163	119	68	37	38
ALT	243	220	118	97	66	45	34
GGT	98	130	81	112	65	65	49
LDH	1188	1041					
Total bilirubin	3.4	8.89	2.24	1.29	0.76		
Direkt bilirubin	2.37	8.35	2.26	1.09	0.49		
CRP	14,9						
Urine test **(proteinüri)**	++						

PO: postoperative hr: hour

Conditions unique to pregnancy that cause liver dysfunction include intrahepatic cholestasis of pregnancy, preeclampsia, Haemolysis Elevated Liver enzymes Low Platelet count (HELLP) syndrome and AFLP.[2]

In a multicenter retrospective study of Gao Q. and coworkers, in total, 133 patients were clinically diagnosed with AFLP. 9.8% of them were diagnosed in the post partum period. Abdominal ultrasonography had 57.1% positive results. Biopsy was not done for any patients. 46.8% of patients were primigravid and had male fetus in 57.4%. The mean maternal age of the patients was 27.1 and mean gestational age was 36.1 weeks.. Age of the patient in our case was 23 and were delivered in 32+3 weeks according to her LMP. In their study, anorexia in 50.4%,, nausea in 42.9%, vomiting in 36.1%, abdominal pain in 30.8%, jaundice in 47.4%, ascites in 45.1% of patients were present. AST in 91.7%, ALT in 78.9%, total bilirubin in 93.2%, serum creatinine in 60.9%, WBC in 77.4% elevated, and PT(s), in 69.2%, aPTT(s) in 78.2% prolonged. Total protein in 89.5%, albumin in 80.5%, blood glucose in 57.1%, platelet in 42.1% of patients reduced. In our case, AST,ALT, and total bilirubin elevated, and leucocytosis, thrombocytopenia were present, but BUN, Cr, PT, and aPTT were normal. In their study, DIC in 20.3%, acute kidney injury in 55.6%, hypoglycemia in 57.1%, encephalopathy in 28.6%, multiple organ system failure in 6.8%, pancreatitis, in 6.8%, gastrointestinal bleeding in 7.5%, postpartum hemorrhagea in 12.8% of patients developed. Major reasons for maternal death in their study were multiple organ system failure, disseminated intravascular coagulation (DIC) and shock. In our case, none of the complications mentioned above did occur.[4]

Gaspar A, and colleagues published a case report. The patient was 34-year old woman. She presented with complaints of nausea, vomiting, jaundice and prostration when she was 37+2 weeks pregnant. On admission, the patient was uncooperative, icteric apyretic and normotensive. She had elevated AST, ALT ,LDH, ALP, total bilirubin, creatinine and WBC with neutrophilia, prolonged PT and aPTT, hypoglycemia and hypoalbuminemia. Thrombocytopenia was absent. Hepatitis serology was negative. Abdominal USG revealed the liver with a diffuse heterogeneity and a slight increase in size and increased echogenicity of the right lobe, suggesting diffuse steatosis. Presumptive clinical diagnosis of AFLP was made. The patient underwent emergency cesarean section due to fetal distress. The male infant was delivered weighing 2810 grams, had an Apgar score of 3 at the first minute and 5 at the fifth minute, requiring resuscitation. The postoperative period was complicated by DIC, acute hepatic and renal failure, and pancreatitis (on postoperative

7th day). The patient was transferred to the intensive care unite and stabilized here. She was discharged on the postnatal 22nd day.[9] In our case, the patient was presented when she was 32+3 weeks with same clinical complaints and laboratory findings, but was delivered preterm due to fetal distress and coagulopathy (DIC), acute renal failure, hypoglycemia, and pancreatitis did not happen.

Ronen J, et al reported a case. The patient was 23-year old primiparous woman at 38 weeks gestational age. She presented with complaints of nausea, protracted vomiting, and poor oral intake for five days and had new-onset headache refractory to analgesic medications and lasted for four hours. On admission, the patient was icteric, tachycardic, tachypneic and hypertensive. USG was unremarkable except for a slightly echogenic left kidney. No other imaging studies were performed. She had elevated AST, ALT, ALP, LDH, total bilirubin and creatinine, prolonged PT and aPTT, reduced glucose and fibrinogen. After a careful analysis of clinical and laboratory findings to rule out preeclampsia and HELLP syndrome, the diagnosis of AFLP was made. She underwent cesarean section as she had unfavorable cervix. The patient gave birth to a 2820 grams female infant with an Apgar score of seven at first minute and eight at fifth minute. Due to the patient's significant coagulopathic state, she was administered a total seven units of fresh frozen plasma (FFP), two units of cryoprecipitate during pre-, peri, and postoperative course. The patient experienced a rapid resolution of her symptoms and normalization of her laboratory tests during her 4th-day postpartum.[7] In our case, the patient was the same age as in this case, but she was primigravid, and presented when 32+3 weeks pregnant with similar complaints as in this case, except for headache and was normotensive. The laboratory findings were similar to this case, except the absence of coagulopathy. The diagnosis of AFLP was done clinically as in this case.

Masoodi I, and coworkers published a case report. The patient was 32-year old woman. She had a complaint of icterus for 1-week. She denied any fever, pruritus, or clay colored stools, any viral prodrom, intake of any offending drug or herbal medication. Apart from elevated bilirubin levels with an elevated direct fraction, all her investigations were normal. She was icteric. Her systemic examination was unremarkable. She underwent cesarean section due to intrauterine death at 37 weeks of gestation. During the postoperative period, the patient had a history of high-grade fever, and jaundice lasting for two weeks following the cesarean section. USG showed gallstone with no intrahepatic biliary obstruction. Magnetic resonance cholangiopancreatography (MRCP) was done and biliary obstruction was ruled out. All viral markers were negative. Abdominopelvic CT showed no abnormality. Apart from elevated bilirubin levels (10 mg/dl) with an elevated direct fraction, and), slightly elevated AST/ALT (52 and 48 IU/L) all her investigations were normal . A liver biopsy was done, which revealed microvesicular steatosis consistent with AFLP.[10]

One of the strenghts of our case is that the patient exhibited six of the Swansea criteria for diagnosing AFLP, along with thrombocytopenia, elevated GGT, LDH, direct hyperbilirubinemia, and proteinuria. Furthermore, all of the patient's clinical and laboratory findings showed regression during the postoperative period . Limitations of our case , the patient was not undergone liver biopsy and, serum ammonia levels could not be able to be studied.

Table 2. Swansea criteria for the diagnosis of AFLP

Parameters	Finding
Vomiting	Positive
Abdominal pain	Positive
Polydipsia and polyuria	Positive
Encephalopathy	Positive
Bilirubin	14 > μmol/L
Hypoglycaemia	< 4 mmol/L
Uric acid	> 340 μmol/L
Leucocytosis	> $11x10^9$L
Liver ultrasonography	Ascites or bright
AST and ALT	> 42 IU/L
Ammonia	47 > μmol/L
Creatinine	> 150 μmol/L
Coagulopathy	
PT	> 14 s
APTT	> 34 s
Liver biopsy	Microvesicular steatosis

s: second

Table 3. Clinical and Laboratory Findings with Acute Liver Diseases in Pregnancy

	Incidence	Symptoms and Signs	Laboratoy findings	Complications
Intrahepatic cholestasis	0.1% to 0.2%	Pruritus, jaundice	ALT/AST <500 U/L, markedly elevated ALP and GGT, elevated bilirubin (1 -4 mg/dl), increased bile acids,	Maternal: Predisposed to cholestasis on subsequent pregnancies Fetal: Stillbirth, Prematurity
Acute Fatty liver of pregnancy	0.01%	Malaise, Nausea& Vomiting, Upper abdominal pain ± Hypertension, liver failure, encephalopathy	ALT < 500 U/L, AST 200-800 U/L, Hyperbilirubinemia (4- 1 0 mg/dl), elevated ammonia, Leucocytosis, thrombocytopenia, DIC, Prolonged PT/aPTT, Hypofibrinogenemia	
Preeclampsia	5% to 11%	Nausea&Vomiting, Epigastric and right upper quadrant pain, edema, Hypertension, Headache, Blurred vision, Mental status change, jaundice	ALT/AST < 500 U/L, proteinuria, elevated bilirubin (1-4 mg/dl), DIC	Maternal: Renal impairment, hepatic rupture/infarct, neurological (seizures, cerebrovascular disease) Fetal: Abruptio placentae, prematurity, IUGR, perinatal morbidity and mortality
HELLP	0.1%	Symptoms of preeclampsia	Hemolysis, ALT<500 U/L, Platelets< $100x10^3$/L, elevated LDH, DIC	Same as preeclampsia
Viral hepatitis	Same as genel population	Nausea&Vomiting, Fever, Jaundice	ALT/AST greatly elevated (>500 U/L), elevated bilirubin (5 -20 mg/dl), positive serology tests	Maternal: Increased mortality with hepatitis E

Conclusion

When a patient has a history of nausea, vomiting, epigastric or right upper quadrant pain, jaundice, and elevatated levels of AST, ALT, GGT, total and direct bilirubin, as well as deteriorating BUN, creatinine, hyperammonemia, hyperuricemia, hypoglycemia, thrombocytopenia, leucocytosis and coagulopathy, physicians should consider a diagnosis of AFLP. Delivery should be performed promptly due to the risk of maternal and fetal mortality.

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