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Fulminant hepatitis A infection in second trimester of pregnancy requiring living-donor liver transplantation

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Abstract

We present an 18-year-old pregnant woman who was referred to our emergency clinic as a case of acute hepatic failure and hepatic encephalopathy. Laboratory tests showed abnormal liver function tests and serological workup was consistent with acute hepatitis A infection. Ultrasonography revealed a single live fetus with fetal biometry compatible with 18 gestational weeks. The patient underwent a highly urgent liver transplantation using a right lobe graft from her husband. Histological examination of the explanted liver showed acute, lymphocyte-rich, diffuse necrotizing hepatitis, consistent with acute necrotizing hepatitis A. After the operation her allograft function gradually recovered. Her follow-up obstetrics ultrasound revealed a male fetus with severely decreased amniotic fluid. The patient was informed about the poor prognosis of her pregnancy and the pregnancy was terminated by vaginal misoprostol induction. She has maintained a good general condition and liver function for 4 months postoperatively, up to the present time.

Key words: hepatic encephalopathy, hepatic failure, hepatitis A, liver transplantation, pregnancy.

Introduction

Acute liver failure accompanying pregnancy may be caused by fulminant viral hepatitis, drug-induced hepatic toxicity, or liver diseases unique to gestation, such as the hemolysis, elevated liver functions and low thrombocyte count (HELLP) syndrome and acute fatty liver of pregnancy.[1,2] Depending on the underlying cause, reported maternal mortality of the acute liver failure during pregnancy ranges from 25 to 75% and the perinatal mortality ranges from 10 to 90%.[1,2]

The hepatitis A virus (HAV) is a small RNA virus that belongs to the family of *Picornaviridae*, genus *Hepatovirus* and its infection is a public health problem throughout the world.[3] The infection is generally mild and limited in most patients. The main complications of HAV infection are fulminant hepatitis (FH) and acute liver failure with encephalopathy, which occurs in less than 1% of cases.[3] Factors influencing the severity of viral hepatitis A consist of host and viral factors. For the host factors, chronic liver disease, old age, heavy alcohol drinking, HIV infection and pregnancy are being suggested.[4–6] Signs and symptoms during pregnancy are non-specific, and most cases are anicteric and usually mild, however, more severe courses of viral hepatitis have been observed in pregnant patients with hepatitis A and E infection.[5–7]

We report here a case of an 18-year-old nulliparous woman who underwent a living-donor liver transplantation during the second trimester of her pregnancy due to severe acute liver injury associated with HAV infection.

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Case Report

An 18-year-old, gravida 1, para 0 patient at 18 weeks of gestation was referred to our emergency clinic as a case of acute hepatic failure and hepatic encephalopathy. The patient was unconscious, not able to cooperate and she was in a state of grade 4 hepatic encephalopathy. On clinical examination her blood pressure was 110/60 mmHg, pulse rate was 90 b.p.m. and axillary temperature was 37°C. On abdominal examination, uterine size was appropriate to her gestation and the liver was palpable just under the costal margin, with no physical signs of chronic liver disease. According to information received from the patient's relatives, she suffered from jaundice, which had begun 2 weeks before, accompanied by nausea and edema of the legs. The patient had not been taking any medications aside from multivitamin pills.

Laboratory investigations showed the following: alanine aminotransferase (ALT) concentration, 470 IU/L; aspartate aminotransferase (AST) concentration, 483 IU/L; lactate dehydrogenase (LDH) concentration, 410 U/L; total bilirubin concentration, 24.2 mg/dL; γ-glutamyl transferase (GGT) concentration, 74 IU/L; alkaline phosphatase (ALP) concentration, 143 IU/L; prothrombin time (PT) 41 s; international normalized ratio (INR), 3.7; ammonia concentration, 140 μmol/L; lactate concentration, 32 mg/dL; and creatinine concentration, 0.4 mg/dL. The patient had normal serum glucose and total cholesterol levels.

Serological workup showed that she was positive for anti-HAV immunoglobulin (Ig)M (10.39 IU/mL) anti-HAV IgG (10.86 IU/mL) and antibody to hepatitis B virus surface antigen (anti-HBs) (12.34 IU/mL), but negative for hepatitis B surface antigen, hepatitis B virus (HBV)-DNA probe, and anti- hepatitis C virus (HCV). The patient was serologically negative for Epstein–Barr virus and cytomegalovirus. There was no evidence of hemochromatosis, Wilson's disease, or autoimmune hepatitis.

Doppler ultrasonography and computed tomography (CT) showed that her liver bile ducts and hepatic vessels were normal. Obstetric ultrasonography showed a single live fetus at 18 weeks of gestation with decreased amniotic fluid and normally placed placenta. Written informed consent was obtained from our patient's husband for an urgent liver transplantation. Based on the King's College criteria for liver transplantation, the patient underwent a highly urgent living-donor liver transplantation using a right lobe graft from her husband about 9 h after her admission.[8] Histological examination of the explanted liver showed acute, lymphocyte-rich, diffuse necrotizing hepatitis with canalicular and hepatocellular cholestasis and proliferation, consistent with acute necrotizing hepatitis (Fig. 1). After the operation, the patient was treated with methylprednisolone, tacrolimus, and mycophenolate mofetil. Her allograft function gradually recovered. A CT of the transplanted liver showed normal hepatic artery, hepatic vein and portal vein with minimally periportal edema immediately after transplantation (Fig. 2). The early postoperative course was uneventful except for bilateral vulvar edema, which progressed within days and was managed with needle aspiration. At 4 weeks after the operation, a laboratory evaluation demonstrated elevated white cells count (21 000/mm3) and elevated bilirubin (13.73 mg/dL). A percutaneous transhepatic cholangiography under radio-scope observation was performed, in order to evaluate the biliary tract anatomy. Critical stenosis of the common biliary tract was detected (Fig. 3) and a biliary drainage catheter was placed into the duct, with the tip downstream in the duodenum. Obstetric ultrasound of the patient revealed a growth-restricted male fetus with a biometry

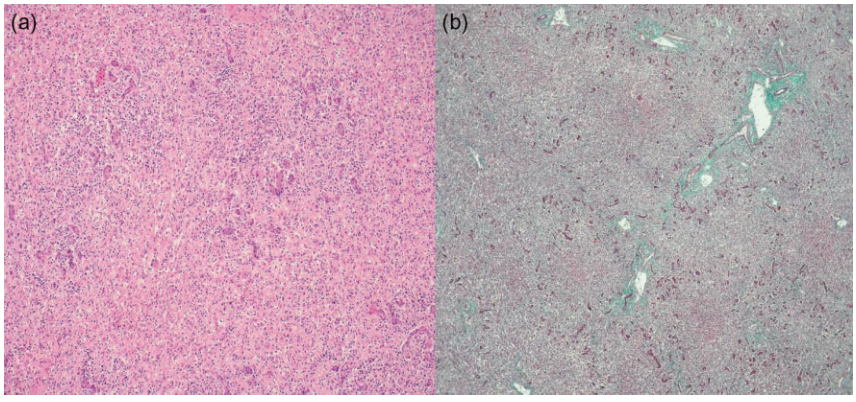

Figure 1 Histological examination of the explanted liver. Lobular disarray with ductal proliferation which is most prominent around periportal areas along with the widespread infiltration of mononuclear cells. (a) Hematoxylin–eosin ×100, (b) Masson's trichrome, connective tissue stain ×100.

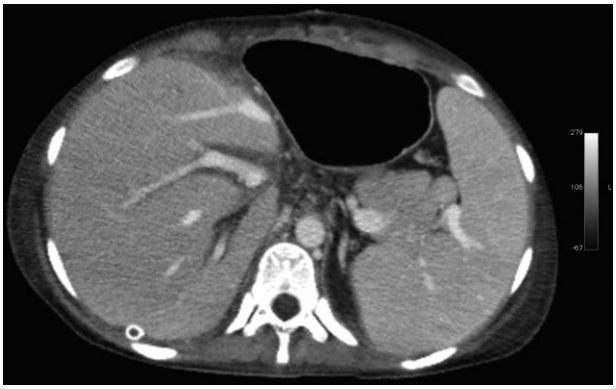

Figure 2 Contrast-enhanced computed tomography scan obtained 9 days after transplantation revealed normal appearance of hepatic vasculature with minimal periportal edema.

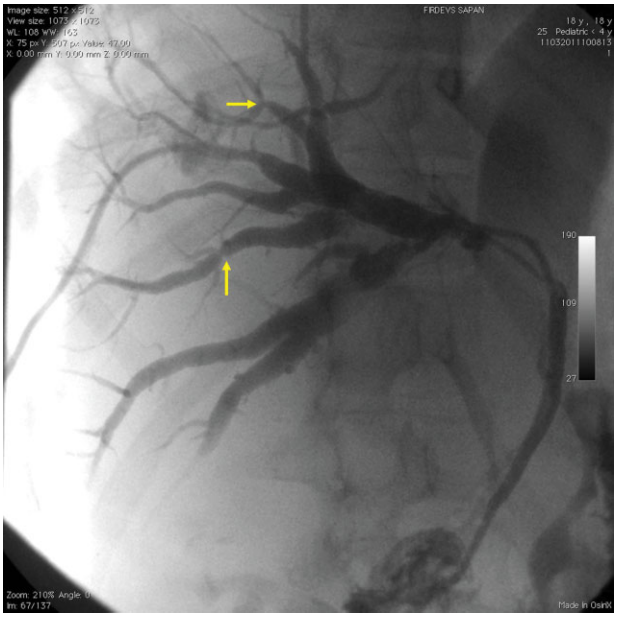

Figure 3 Percutaneous transhepatic cholangiography image of bile ducts. The arrows indicate numerous narrow bile ducts branching, 4 weeks after transplantation.

equivalent to 20 weeks and a diagnosis of severe oligohydramnios. The absorbed radiation dose in the uterus was calculated by physical dosimetry and estimated cumulative radiation dose of the fetus was found to be 6800 mrad. The patient was informed about the poor prognosis of her pregnancy secondary to the early absence of amniotic fluid and the high dose of *in utero* radiation exposure of the fetus. Termination of the pregnancy was offered. The written informed consent of the patient was obtained, and the pregnancy was terminated by vaginal misoprostol induction with a total dose of 800 μg in two divided doses. A male fetus, weighing 280 g, was delivered within 8 h. Consequently, the patient's recovery and further follow up was uneventful with good liver function. On 8 weeks after transplantation the patient was well with normal laboratory investigations, except a slightly elevated LDH concentration of 292 U/L (normal range: 125–243 U/L) and a GGT concentration of 65 IU/L (normal range: 9–64 IU/L). At the 12-week follow up, serum LDH and GGT concentrations of the patient were in normal range (243 U/L and 51 IU/L, respectively). Currently, 4 months postoperatively, the patient has good general condition and normal liver function.

Discussion

Fulminant hepatic failure has been reported at any stage of pregnancy but appears more frequently in the third trimester with serious maternal and fetal consequences. In the present case, however, the cause of fulminant hepatic failure was HAV infection during the second trimester of pregnancy.

In fact, most cases with HAV infection during pregnancy are anicteric and usually mild, and fulminant hepatitis due to HAV was considered rare.[1,6] Previously, it has been reported that fulminant HAV infection accounts for 0.35% of all HAV cases and approximately 3% of patients presenting with acute liver failure.[7] It has been generally accepted that pregnancy itself does not show a negative impact on the course of hepatitis A infection.[1,4] Acute hepatitis A during pregnancy, however, may be associated with a higher risk of maternal complications. A recent series from Israel evaluating the impact of acute HAV infection on pregnancy over consecutive admissions of 79 458 pregnant women over a 25-year period reported an increase in certain obstetrical complications.[5] Thirteen cases of second- and third-trimester HAV infection were found. Nine of the 13 patients (69%) developed gestational complications, including premature contractions ($n = 4$), placental separation ($n = 2$), premature rupture of membranes ($n = 2$), and vaginal bleeding ($n = 1$).[5] Similarly, oligohydramnios and fetal growth restriction were observed during pregnancy follow up of the present case. To the best of our knowledge, this is the first report of acute fulminant HAV infection complicating the second trimester of pregnancy and requiring a liver transplantation.

Early delivery is indicated in such cases if severe liver dysfunction is present at the third trimester of gestation,

which may prevent perinatal mortality.[2,9] On the other hand, when fulminant hepatic failure occurs during the first or second trimester of pregnancy, particularly before the 24th week, the fetus has little possibility of survival after delivery. Thus, liver transplantation, if indicated, must be performed considering the surgical and medical risks to the fetus, including exposure to immunosuppressive drugs, other medications and radiation. Patients that show a worsening in liver function, and/or patients who develop encephalopathy, coagulopathy, hypoglycemia or other features of severe liver dysfunction should be referred early to a specialized liver centre in order to evaluate the possibility of an urgent liver transplantation. Some cases of liver transplantation during the second trimester of pregnancy with successful maternal outcomes have been previously reported, however there is little worldwide experience in liver transplantation in pregnant women.[9–11] Current data indicate that pregnancy itself is not a contraindication to liver transplantation with life-threatening illness. Unfortunately, fetal outcomes in published cases have been poor with a neonatal survival rate of only 27%. Reported causes of perinatal death range from spontaneous and artificial abortion to neonatal death.[10,11] Although no evidence of fetal damage or anomalies was found in the present case, repeated ultrasonographic examinations revealed fetal growth restriction and severely decreased amniotic fluid. Therapeutic abortion was considered as an option because of poor fetal prognosis related with early-onset growth restriction and fetal exposure to potential toxic effects of immunosuppressive drugs or X-ray examinations. In patients who want to continue the pregnancy, however, it should be noted that based on the published evidence, tacrolimus and methylprednisolone are both considered safe immunosuppressive options during pregnancy.[12,13] Human case reports, on the other hand, have suggested that mycophenolate mofetil use during pregnancy is associated with a phenotypic pattern of congenital malformations characterized by orofacial clefts and microtia/anotia.[14] Preterm delivery and low birthweight on the other hand, seem to be persistent problems in all solid-organ transplantation under any form of immunosuppression.[15]

In conclusion, liver transplantation performed during early pregnancy with a successful maternal outcome occurs very rarely. The achievement of this goal involves a multispecialty-team approach, including transplant surgeons, hepatologists and obstetricians, and requires appropriate prenatal management. As in other high-risk pregnancies, close fetal and maternal survey should be carried out during pregnancy and during puerperium. Finally, prenatal counseling including the documentation of maternal and fetal risks from a multispecialty team and ethical advice from an ethical committee may be needed for proper management of pregnant patients with fulminant hepatic failure.[16]

Disclosure

None declared.

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