Fulminant herpes hepatitis in an immunocompetent pregnant woman and review of differential diagnosis

İmmün bağışık bir gebede gelişen fulminan herpes hepatiti ve ayırıcı tanıya yaklaşım

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Abstract
In this paper, we report the case of an 8-weeks pregnant, 21-year-old immunocompetent woman with chronic hepatitis B infection. She initially presented to another hospital with a 1-week history of progressive fatigue, jaundice, fever, and confusion. The patient subsequently was admitted to our hospital with signs of fulminant hepatic failure. Soon after admission, the pregnancy was terminated because of vaginal bleeding. High-titer type 1 as well as 2 HSV-IgM antibodies were identified. The patient died soon after treatment of the HSV infection began. Pregnant women are predisposed to herpes hepatitis, but because of its infrequency in immunocompetent adults, its diagnosis in pregnant women may not occur or be delayed. Early diagnosis of herpes hepatitis is of paramount importance because of the frequent need for treatment with antiviral agents and for supportive care, which can be lifesaving. Early diagnosis usually requires a liver biopsy.
Key words: pregnancy; herpes simplex virus; fulminant hepatitis

Özet
Bu makalede 21 yaşında immünbağışık kronik hepatit B enfeksiyonu bulunan 8 haftalık gebe bir bayanda gelişen fulminan hepatit vakasını rapor etmekteyiz. Bu hasta hastanemize başvurmadan önce başka bir merkeze bir haftadır devam eden halsizlik, ateş ve konfüzyon şikayetleri ile başvurmuş. Hastanemize fulminan hepatit yetmezlik bulguları ile yatırıldı. Yatışının hemen sonrasında vajinal kanama nedeniyle gebelik sonlandırıldı. Hastada yuksek titrede HSV-IgM tip 1 ve 2 antikorları saptandi. HSV tedavisi başlandıktan kısa bir süre sonra hasta kaybedildi. Gebe bayanlar herpes hepatitine yatkındırlar ancak immün-bagışık erişkinlerde sıklığının az olmasi nedeniyle gebe bayanlarda bu hastalığın tanısı gecikebilmekte veya konulamamaktadır. Anti-viral ilaçlarla tedaviye ihtiyaç göstemesi ve destek tedavisi bakımından Herpes hepatitinin erken tanısı oldukça önemlidi, çünkü erken tedavi hayat kurtarıcı olabilmektedir. Bunun yanısıra erken tedavi genellikle karaciğer biyopsisi yapılmasını gerektirmektedir.
Anahtar kelimeler: gebelik-herpes simpleks-fulminan hepatit-

Introduction

The liver diseases that occur during pregnancy can be categorized into three groups. The first group includes intra-hepatic cholestasis, acute fatty liver, and pre-eclampsia. The second group includes conditions exacerbated by pregnancy, and the third group consists of liver diseases existing prior to pregnancy.

Even though rather rare, fulminant hepatic failure (FHF) can develop in immunocompetent patients as the result of primary or recurrent infection by the herpes simplex virus (HSV). The diagnosis is frequently unclear in the absence of mucocutaneous involvement, but elevated transaminase levels, leukopenia, and a relatively low bilirubin level may provide clues. The herpes simplex virus is one of the few causes of FHF for which potentially effective therapy is available.

Viral hepatitis may also occur during pregnancy and lead to fulminant hepatic failure. Symptoms usually include fever, nausea, right upper quadrant pain, and markedly elevated transaminases (usually above 1000 IU/L). Like the standard viruses, herpes simplex virus can cause severe hepatitis and should be suspected if there are vesicular lesions in the skin. Early diagnosis of herpes hepatitis, which usually requires a liver biopsy (1, 2), is of paramount importance, because the often recommended treatment with antiviral agents accompanied by supportive care can be lifesaving.

Case report

A 21-year-old, immunocompetent woman who was 8-weeks pregnant and had previously been diagnosed with chronic hepatitis B was admitted to our hospital because of a one-week history of persistent, progressive fatigue, jaundice, fever, and confusion. These symptoms had not resolved following stay in another hospital. After our initial evaluation, the medical records from the previous center led us to diagnose the patient as having fulminant hepatitis, and we

immediately admitted her to the intensive care unit (ICU).

On physical examination, the patient was afebrile, jaundiced, mildly confused, and agitated. The results of the head and neck examination were normal, and no mucosal lesions could be found. The chest and cardiac examinations were unremarkable. The abdominal examination and abdominal USG were normal, and the pelvic USG was consistent with an 8-week pregnancy. However, the initial examination revealed markedly elevated transaminases, bilirubin, prothrombin time, and leukocytosis.

On the first hospital day, the patient was confused and agitated. On the second day, she became unconscious, and she was intubated to maintain her airway. A cranial CT revealed diffuse cerebral edema, and intravenous mannitol was administered. Topiramate was added when focal seizures involving the left side of the patient's face were observed. On the third day, the pregnancy spontaneously aborted because of a vaginal hemorrhage that likely was caused by the elevated INR (7.4).

The main laboratory findings were as follows: white blood cells, 15,000 cell/mm3 (4.3–10.3); hemoglobin, 12.1 g/dl (12–14); platelet count, 222.000 cell/mm3 (150–450); total protein, 5.63 g/dl (6.2–8.7); albumin, 3.3 g/dl (3.4–5.5); ALT, 2542 U/L (7–52); AST, 1847 U/L (9–30); alkaline phosphatase, 156 U/L (40-129); total bilirubin, 29.83 mmol/l (0.2–1.2); prothrombin time, 59.1 sn (10.5–14.9); INR, 5.65 sn (0.9–1.1); HBV DNA: negative; HBsAg: positive; anti–HBs: negative; HBeAg: negative; A-HBc Ig M/G: negative; anti-delta: negative; anti–HEV Ig M/G: negative; anti–HCV: negative. Types 1 and 2 HSV–IgM were positive with ELISA. No HSV IgG was detected. In addition, peripheral blood smear was unremarkable and serum haptoglobulin was normal.

On subsequent days, the patient's prothrombin time continued to exceed 45 seconds, and the total biluribin levels were between 24 and 27 mmol/L. Transaminase levels declined dramatically (ALT, 175 U/L; AST, 213 U/L) as did the platelet count (81.000 cells/mm3). N–acetylcysteine, daily vitamin K, and fresh frozen plasma were added to her treatment regimen as necessary.

Unfortunately, the ELISA results identifying HSV were not available until the 10th hospital day, and the patient died two days after treatment (acyclovir 750 mg q8h) began.

Discussion

Hepatic disorders during pregnancy commonly include viral hepatitis (due to HSV, cytomegalovirus, Ebstein Barr virus, or varicella–zoster virus) or pregnancy–specific liver diseases, such as intrahepatic cholestasis, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, and acute fatty liver. Additionally, sarcoidosis, as well as chronic hepatitis B and C, can be encountered.

In such cases a reasonable differential diagnosis list is critical, and we thus considered the common hepatic disorders of pregnancy mentioned above. Intrahepatic cholestasis of pregnancy (ICP) tends to occur later in a pregnancy, usually in the second or third trimester; its diagnosis is based on complaints of pruritus, in combination with elevated serum bile acids and/or aminotransferases, and on the absence of other diseases that might produce similar symptoms (3). The pruritus typically preceding the onset of ICP may be intolerable. Pruritus can occur anywhere on the body, but it is most common on the palms and soles of the feet. It is worse at night, and it may be present before abnormalities appear in the laboratory tests (4). The physical examination is nonspecific, but patients may exhibit excoriations due to scratching. Jaundice occurs in about 10 percent of patients, typically after the onset of itching. Jaundice without pruritus is rare and should prompt an investigation of other possible causes. Total serum bile-acid concentrations increase with ICP, and these may be the first or only laboratory abnormality. Serum aminotransferases also may reach values exceeding 1000 U/L, making it essential to distinguish ICP from viral hepatitis. The prothrombin time is usually normal. Being the cardinal feature of ICP, pruritus helps to distinguish ICP from other types of liver disease associated with similar laboratory results (e.g., early HELLP syndrome, pre-eclampsia) (4). Ultrasound examination reveals no biliary-duct dilation, and the hepatic parenchyma appears normal. A liver biopsy is rarely necessary to establish a diagnosis of ICP. When performed, the histopathology is characterized by cholestasis without inflammation (5).

A second diagnostic possibility is HELLP syndrome. It occurs in approximately 10 to 20 percent of women with severe pre-eclampsia or eclampsia. The majority of patients are diagnosed between 28 and 36 weeks of gestation. The diagnosis is referenced against the laboratory findings characteristic of other patients of the same gestational age. These characteristic findings include a microangiopathic hemolytic anemia, with typical schistocytes on the blood smear. Other signs suggestive of HELLP include an elevated indirect bilirubin and a low serum haptoglobin concentration (

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