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Herpes Simplex Hepatitis in an Immune-Competent Adult: A Case Report

İmmünkompetan Erişkin Bir Herpes Simpleks Hepatiti Olgusu

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SUMMARY

Hepatitis due to herpes simplex virus is a rare complication of primary or secondary herpes simplex virus infection in immunocompetent adults. A case of herpes simplex virus hepatitis in a healthy adult is presented in this report. The case recovered without progression of fulminant hepatitis.

Key Words: *Herpes simplex, Hepatitis*

ÖZET

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Hepatit immünkompetan erişkinlerde herpes simpleks virüse bağlı primer veya sekonder infeksiyonun nadir bir komplikasyonudur. Bu yazıda sağlıklı bir erişkinde gelişen herpes simpleks virüsü hepatiti olgusu sunulmuştur. Olgu fulminant hepatite ilerleme göstermeden iyileşmiştir.

Anahtar Kelimeler: *Herpes simpleks, Hepatit*

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INTRODUCTION

Hepatitis due to herpes simplex virus (HSV) is a rare complication of primary or secondary HSV infection. HSV hepatitis has been reported generally in patients with immune deficiency[1]. A search of the literature revealed only a few cases of HSV hepatitis reported in immunocompetent adults[2-5]. A case of HSV hepatitis in a healthy adult is presented in this report.

CASE REPORT

A 28-year-old male was admitted to the hospital with a two-week history of fatigue, chills and sweating. He had a history of receiving azithromycin and anti-histaminic treatment with a diagnosis of upper respiratory tract infection. Four days after initiation of this therapy, icterus, vomiting, nausea, and epistaxis had developed. Two days after onset of these symptoms, he was hospitalized in our clinic with the pre-diagnosis of acute viral hepatitis and toxic hepatitis.

There was no underlying disease in the patient's medical history. He had complaints of headache, dizziness, cough, epistaxis, epigastric pain, and nausea and vomiting. On admission, his body temperature was 36°C, pulse rate 76/minute, blood pressure 80/40 mmHg, and respiratory rate 20/minute. The patient's clinical condition was good, with good orientation and cooperation. Icterus and bilateral conjunctival hemorrhage were detected in his physical examination. Results of laboratory examinations were as follows: hemoglobin (Hb): 12.6 g/dL, white blood cells (WBC): 5800/mm^3, platelets (Plt): 77.000/mm^3, blood urea nitrogen (BUN): 52 mg/dL, creatinine: 0.6 mg/dL, glucose: 86 mg/dL, aspartate aminotransferase (AST): 479 IU/L, alanine aminotransferase (ALT): 660 IU/L, lactate dehydrogenase (LDH): 344 IU/L, alkaline phosphatase (ALP): 333 IU/L, gamma-glutamyl transpeptidase (GGT): 380 IU/L, total bilirubin: 16.3 g (direct bilirubin: 6.1, indirect bilirubin: 10.2), and C-reactive protein (CRP): 8.32 mg/dL (0-5). Bilirubin was positive in the urine. Hemostatic parameters were as follows: activated partial thromboplastin time (aPTT): 50 seconds and international normalized ratio (INR): 1.4. There was no remarkable finding on abdominal ultrasound except a 12 mm lymphadenopathy localized in the hilar region of the liver.

The patient was consulted to ophthalmologists. The cornea and anterior and posterior segments were found normal. No ocular infection was detected.

Test results for viral hepatitis etiology were as follows: HBsAg (-), anti-HBc IgM (-), anti-HCV (-), anti-HAV IgM (-), anti-HAV IgG (+), Toxoplasma IgM (-) and IgG (-), Rubella IgM (-), Rubella IgG (+), cytomegalovirus (CMV) IgM (-), CMV IgG (+), Epstein-Barr virus (EBV) VCA IgG (+), and HEV IgM (-). On admission, serum HSV IgM and IgG were found negative whereas herpes simplex type-1 polymerase chain reaction (PCR) was reported as positive. A liver biopsy was planned but the patient declined. One week after the admission, serological tests were repeated and HSV type-1 IgM was found positive.

According to the test results, the patient was diagnosed as primary HSV type-1 hepatitis. The clinical condition of the patient recovered during the follow-up. Nausea and vomiting resolved, icterus disappeared, and liver enzyme levels declined over time. The patient was discharged on the 11^{th} day of hospitalization. During his follow-up, liver enzymes, bilirubin and platelet levels normalized.

DISCUSSION

Herpes simplex is a double-stranded DNA virus and Alphaherpesvirinae subfamily of the herpes virus family[6]. HSV-1 and HSV-2 are the main serotypes. HSV infections are very common and can be diagnosed in all ages[7]. HSV-1 is acquired earlier than HSV-2. More than 90% of adults have antibodies to HSV-1 by the fifth decade of life[6]. HSV-2 infection generally appears in young adults[6]. Hepatitis is a rare complication of HSV infection[2,7,8]. The mortality rate was reported as 80-90% without treatment[9,10]. HSV represents less than 1% of all acute liver failure cases[5,11]. Both HSV types 1 and 2 have been known to cause fulminant necrotizing hepatitis[10]. Primary and recurrent HSV infections can result in disseminated herpes leading to fulminant hepatic failure[12].

Impaired immunity and pregnancy are the main risk factors. The incidence of HSV hepatitis is very rare in healthy adults and is presented as case reports in the literature. A few hypotheses have been proposed for HSV hepatitis in healthy adults. Undiagnosed impaired cellular immunity may result in high replication and dissemination of HSV[13,14]. Other possible

mechanisms responsible for dissemination are impaired macrophage function, large HSV inocula at initial infection, enhanced virulence at the time of reactivation, and super infection with a second HSV[15]. Selective hepato-virulence is proposed as another possible mechanism[14,15]. In our case, there was no underlying condition.

Clinical presentation is similar to that of other viral hepatitis cases. Symptoms are reported in a wide range from non-specific symptoms like fever, loss of appetite, vomiting, nausea, and abdominal pain to severe symptoms like unconsciousness and coagulopathy. Fever, abdominal pain and nonspecific flu-like symptoms may appear. In the severe cases, rapid progression, hepatic failure, coma, and death can occur[14-18]. In HSV hepatitis, there are no specific clinical or laboratory findings[14]. Mucosal or cutaneous lesions may not be detected in 30% of patients[19]. In our case, mucocutaneous lesions were not detected, but he had subconjunctival hemorrhage.

Icterus was not detected in most of the cases. Despite elevated liver enzymes in 90% of the HSV cases, bilirubin levels were low or minimally elevated. AST levels were generally significantly higher than ALT levels[14]. Icterus was detected in our case, and AST levels were higher than ALT levels.

Thrombocytopenia and coagulopathy are reported in some HSV case series[15,20]. In the presented case, the platelet count was also low and coagulation parameters were longer than normal. The coagulopathy might lead to epistaxis and conjunctival hemorrhagia.

The diagnosis is confirmed by liver biopsy. The pathological findings are hemorrhagic necrosis, intranuclear inclusion bodies (Cowdry A), cytopathic effect, and HSV reactivity with immunochemical stain [15]. Detection of HSV-DNA by PCR is a reliable method for diagnosis[21]. Discrimination of primary and secondary HSV infection cannot be made by PCR. We could not perform pathological investigation because the patient refused the liver biopsy.

Serological investigation has limited value in the early diagnosis, but positivity supports HSV infection[21-23]. IgM may be found as positive in recurrent infections. When IgG in the serological investigation is negative, IgM positivity implies acute primary infection. Primary HSV infections can be documented by using any serologic method to show seroconversion with paired sera. In this case, seroconversion was shown. IgM was found as negative and HSV type 1 PCR was found as positive in the first sera sample. IgM positivity developed in the second sample of the sera after one week.

Toxic hepatitis was also included in the differential diagnosis in our case, but IgG negativity and IgM positivity of the second serum sample implied acute primary herpes infection. Pre-diagnosis of primary HSV infection was supported by this finding.

Acyclovir 3 x 10 mg/kg is recommended for treatment of HSV hepatitis despite no published randomized study regarding its efficacy[24]. Smaller doses have been found effective, but it was concluded that this situation may represent the rare minority of patients who recover spontaneously[24]. Duration of therapy is 10-14 days. The mortality rate was reported as 80-90% in untreated patients. It was reported that AST levels were higher in fatal patients than in survivors[14,25]. Prognosis is better in pregnant patients than in patients with other comorbid factors[26]. Early initiation of acyclovir treatment was found to be significantly associated with survival. In our case, levels of bilirubin and liver enzymes decreased spontaneously and the clinical condition of the patient improved. It was considered that the patient was recovering spontaneously and thus acyclovir was not administered.

In conclusion, it is important to consider HSV in the differential diagnosis of fever and hepatitis of unknown etiology even in the absence of mucocutaneous herpetic lesions[5]. Similar to other systemic viral infections, mildly elevated liver enzymes may be detected in primary HSV infection without progression to fulminant hepatitis[7]. Several measurements of liver enzymes will show a consistent increase when hepatic damage is severe, and should prompt immediate intervention[7]. Use of acyclovir treatment should be evaluated individually.

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