Case Report

Herpes Simplex Hepatitis Presenting as Fulminant Hepatic Failure in Pregnancy

Kalyani Parvathy¹, Aravind Reghukumar², Athul Gurudas², Kirankumar V. Sasidharan² and Lakshmi J. Nair¹

Abstract

Herpes simplex hepatitis can progress to fulminant hepatic failure in immunocompromised patients as well as in pregnancy due to alterations in T cell-mediated immunity in these populations. If not identified early, herpes simplex virus (HSV) hepatitis will progress to fulminant hepatic failure requiring liver transplantation. Early identification and treatment with acyclovir can be life-saving as HSV hepatitis in pregnancy has been found to be associated with high mortality rate. We report the case of a 23-year-old woman who developed HSV-induced fulminant hepatic failure in the third trimester of pregnancy.

Keywords

Herpes simplex virus, hepatitis, pregnancy

Introduction

Historically, herpes simplex virus (HSV) infections were first described by Hippocrates, but most of the important findings regarding HSV infection and its treatment were made from the 20th century onward. HSV infections are caused by HSV-1 and HSV-2, and it has been found that HSV-1 causes predominantly orofacial lesions, while HSV-2 is associated with genital lesions. In pregnancy, genital infection due to HSV is mostly caused by HSV-2; however, the prevalence of HSV-1 infection has been increasing. HSV hepatitis is an exceedingly rare complication of HSV during pregnancy, and only around 40 cases have been reported so far worldwide. Early recognition and treatment is crucial as maternal mortality rate due to HSV hepatitis ranging from 20% to 67% with delayed or no treatment. Here, we report a case of HSV-induced fulminant hepatic failure in a pregnant woman in the third trimester, who was managed with acyclovir and termination of pregnancy.

Case Report

A 23-year-old primigravida at 34 weeks of gestation presented with acute flu-like symptoms and persistent vomiting to our tertiary care center in Thiruvananthapuram, Kerala. On examination, she was febrile (temperature: 102°F) and tonsils were congested. No skin lesions were observed. Laboratory evaluation was significant for leukopenia (white blood cells count: 3,500), thrombocytopenia (platelet count: 90,000), and transaminitis (serum glutamic oxalacetic transaminase [SGOT]: 450 IU/L and serum glutamate-pyruvate transaminase [SGPT]: 220 IU/L). Over the next 7 days, SGOT and SGPT increased to 2,700 IU/L and 1,500 IU/L, respectively and international normalized ratio increased from a baseline of 1.1 to 3.2. By the 10th day, patient progressed to fulminant hepatic failure, disseminated intravascular coagulation, and stage 3 hepatic encephalopathy. A suspicion of Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome and acute fatty liver of pregnancy were entertained. Serologies for anti-HCV, HbsAg, anti-HAV, anti-HEV, HIV by ELISA, IgM leptospirosis, IgM dengue, IgM scrub typhus, and Typhi dot IgM were negative. Rapid malaria test was negative. HSV-2 IgM came as positive and IgG negative. HSV-2 serum quantitative polymerase chain reaction (PCR) was positive at 19,500 copies/mL. Patient was started on intravenous acyclovir and lower

¹ Department of Internal Medicine, Government Medical College, Thiruvananthapuram, Kerala, India
² Department of Infectious Diseases, Government Medical College, Thiruvananthapuram, Kerala, India

Corresponding author:
Kalyani Parvathy, Department of Internal Medicine, Government Medical College, Thiruvananthapuram, Kerala, India.
E-mail: kal.parvathy@gmail.com
segment cesarian section (LSCS) was performed. Patient gradually improved. Once the coagulation parameters were corrected, a liver biopsy was performed and reported as resolving hepatitis with areas of parenchymal necrosis. Intranuclear inclusion bodies were not demonstrable as the patient was already on acyclovir (14 days) at the time of biopsy. Antinuclear antibodies profile, cytomegalovirus, and Epstein-Barr virus serologies were later reported as negative. HSV-2 IgM titer increased by 4-fold and IgG became positive after 1 month.

**Discussion**

HSV is a double-stranded, enveloped DNA virus, belonging to the family of Herpesviridae. After gaining entry into the human body, the virus migrates to the nerves, where it persists in a latent state. Traditionally, it has been taught that HSV-1 causes orofacial lesions (infection above the belt), and HSV-2 causes genital lesion (infection below the belt). HSV-1 is usually found latent in the trigeminal ganglia and HSV-2 in the lumbosacral ganglia.3

HSV infection during pregnancy can be a primary HSV infection or a recurrence. Risk factors for acquisition of HSV infection during pregnancy include the coexistence of another sexually transmitted disease and HSV infection in the partner. Symptomatic genital herpes occurs after an incubation period of 2 to 20 days, and can last up to 21 days. It causes blistering and ulceration of the genitalia causing vulval pain and dysuria, and vesicular lesions may be observed over the perineum, inner thighs, and buttocks. HSV can also infect the cervix leading to vaginal discharge and local lymph node enlargement. Clinical manifestations of genital herpes during pregnancy has not been found to differ from those outside pregnancy. Complications related to HSV infection in pregnancy include herpes hepatitis, herpes encephalitis, and preterm delivery. HSV infection during pregnancy can be transmitted to newborns and can cause skin lesions, meningoencephalitis, dissemination infection, and fetal malformations.1,3

Disseminated infection or isolated HSV hepatitis is seen usually in patients who are immunocompromised. This population of patients compromise those who are on immunosuppressive therapy, organ transplant recipients, and those with immunodeficiency disease like HIV. The second group of individuals who are prone for such a severe infection are pregnant women in their second and third trimester, as was observed in our patient.4

In pregnancy, the immediate differentials that are considered when a patient develops acute liver failure include acute fatty liver of pregnancy, HELLP syndrome, and hepatitis E infection. HSV hepatitis accounts for less than 1% of all cases of acute liver failure, and it has been observed that pregnant patients are at a higher risk for this complication. This may be due to the fact that in pregnancy there is an increase in regulatory T cells and a decrease in natural killer cells, which create a state of immune tolerance that permits the growth of the fetus. Since natural killer cells are an important part of the immune response to HSV infection, decrease of their number during pregnancy poses a higher risk of complications when there is a concomitant HSV infection. HSV should be suspected when a patient presents with fever, leukopenia, thrombocytopenia, and respiratory or gastrointestinal symptoms, with lab features suggestive of acute hepatitis. Oral or genital vesicular lesions are absent in up to 50% of patients with HSV hepatitis.5 Our patient presented with fever and was found to have leukopenia, trombocytopenia, elevated liver enzymes, and coagulopathy but she did not have any skin lesions that could have served as a definite pointer to the etiological diagnosis.

Lab detection of HSV infection can be divided broadly into viral detection techniques and antibody detection techniques. Viral detection techniques include viral culture and HSV detection by PCR. Antibody detection involves testing for antibodies to HSV-1 and HSV-2. Sensitivity of HSV viral culture is limited since it can produce false negatives due to improper sampling or transportation of the lab specimen. Detecting HSV by PCR has higher sensitivity than viral culture, and hence PCR is currently recommended over culture for detection of HSV. However, the diagnosis of HSV infection should be confirmed either serologically or with viral cultures.3

Liver biopsy is the gold standard for establishing a diagnosis of herpes hepatitis. Classically described findings include hemorrhagic necrosis, inflammation, and enlarged ground glass nuclei with marginalized chromatin. However, liver biopsy in these patients is a high-risk procedure, due to the associated coagulopathy that poses a risk of significant hemorrhage.3 We performed a liver biopsy relatively late in our patient, owing to the initial coagulopathy. At the time of the biopsy, the patient had completed 14 days of acyclovir therapy, so the classical findings of herpes hepatitis could not be appreciated.

Treatment of genital herpes in pregnancy is using antiviral agents, specifically acyclovir or valacyclovir. Antiviral treatment can be given empirically without awaiting lab results, depending on the clinical status of the patient. Acyclovir is the first choice for treating HSV hepatitis. Prophylaxis is recommended at 36 weeks of gestation until delivery since it reduces the need for Cesarean section because of herpes lesions. When lesions suggestive of herpes are present at the time of labor, a Cesarean delivery is recommended as it reduces the risk of transmission of infection to the neonate. Maternal breastfeeding is not contraindicated unless there are lesions over the nipples. Early recognition of the symptoms and prompt treatment are crucial since maternal mortality from HSV can be as high as 67% with treatment delay.1,2
Conclusion

Fulminant hepatic failure due to HSV usually affects immunocompromised hosts. However, pregnant women especially in the third trimester are susceptible to HSV hepatitis due to the defects in T cell-mediated immunity, which promotes viral dissemination. Any pregnant patient with flu like symptoms, anicteric hepatitis, leukopenia, and thrombocytopenia should be suspected of having HSV hepatitis, and it should be kept in mind that half of these patients would not have any mucocutaneous lesions suggestive of herpes infection. Empirical acyclovir can be life-saving as it may help in preventing progression to fulminant hepatic failure and death.

Author Contributions

KP - Writing the manuscript.
KP, AR, AG, KVS, LJN - Jointly developed the structure of the manuscript and edited the manuscript.
KP, AR, AG, KVS, LJN - Made critical revisions of the manuscript and approved the final manuscript draft.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Patient Consent

Written informed consent for patient information to be published was obtained.

ORCID iDs

Kalyani Parvathy https://orcid.org/0000-0003-0316-1849
Aravind Raghukumar https://orcid.org/0000-0002-5332-0978
Lakshmi J. Nair https://orcid.org/0000-0001-8480-5081

References

1. Sénat M-V, Anselem O, Picone O, et al. Prevention and management of genital herpes simplex infection during pregnancy and delivery: guidelines from the French College of Gynaecologists and Obstetricians (CNGOF). *Eur J Obstet Gynecol Reprod Biol*. 2018;224:93-101.
2. Magawa S, Tanaka H, Furuhashi F, et al. A literature review of herpes simplex virus hepatitis in pregnancy. *J Matern Fetal Neonatal Med*. 2020;33(10):1774-1779.
3. Straface G, Selmin A, Zanardo V, De Santis M, Ercoli A, Scambia G. Herpes simplex virus infection in pregnancy. *Infect Dis Obstet Gynecol*. 2012;2012:385697.
4. Noor A, Panwala A, Forouhar F, Wu GY. Hepatitis caused by herpes viruses: a review. *J Dig Dis*. 2018;19(8):446-455.
5. Holt EW, Guy J, Gordon SM, et al. Acute liver failure caused by herpes simplex virus in a pregnant patient: is there a potential role for therapeutic plasma exchange. *J Clin Apheresis*. 2013;28(6):426-429.