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An Unusual Cause of Acute Isolated Hepatitis in a Cancer Patient Post-COVID Pneumonia: HSV-2

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ABSTRACT

Herpes simplex virus is a rare cause of hepatitis in immunosuppressed and immunocompetent individuals. It can cause clinical pictures in patients ranging from an asymptomatic course to fatal acute fulminant hepatitis. Early diagnosis and treatment may be delayed if it is not suspected because of the patients' nonspecific clinic. This study presents a case of isolated HSV-2 hepatitis in a patient with a history of cancer chemotherapy and a recent diagnosis of COVID-19 who received steroid therapy.

Keywords: herpes simplex virus infections, herpes simplex virus-2, hepatitis, COVID-19

INTRODUCTION

Herpes simplex virus (HSV) is a double-stranded DNA alphaherpesvirus. HSV-1 is a common human pathogen infecting more than 60% of the world's population, and HSV-2 infects about 11% of the population (1, 2). HSV rarely causes visceral organ infections. However, some of these disseminated infections are life-threatening (3). Hepatitis due to HSV is a rare manifestation. It has been reported that 25% of cases of HSV hepatitis occur in patients with immune-competent. It can cause mild, self-limiting clinical pictures that can progress to fatal acute fulminant hepatitis in immunocompromised patients (4).

Clinical suspicion, early diagnosis, and prompt treatment are factors that increase patient survival in HSV-2 hepatitis (4). This study presents a case of HSV-2 hepatitis that followed COVID-19 and was treated early.

CASE PRESENTATION

A 52-year-old female patient was admitted to our clinic with complaints of loss of appetite, extreme weakness, fatigue, and muscle pain in the legs for ten days. The patient's

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history revealed that she had been diagnosed with stage 1 breast cancer and had received the last dose of adriablastine + cyclophosphamide (4 doses every 21 days) five months ago. She was treated with paclitaxel + trastuzumab (12 doses every week) 45 days ago and continued treatment with letrozole. It was learned that the patient was hospitalized in an external hospital for ten days due to PCR-positive, hypoxic COVID-19 pneumonia and received IV dexamethasone (6 mg/day) treatment a month ago. The patient reported that she had three doses of vaccine for COVID-19 (the first two doses of CoronaVac [Sinovac Life Sciences, Beijing, China], the third dose of BioNTech [Pfizer Inc., New York, USA]), and she had her last vaccination one month before the diagnosis of COVID-19. The patient attributed her complaints to COVID-19. The last tests at discharge from the previous hospital showed an alanine aminotransferase (ALT) of 101 U/L (normal <41), an aspartate aminotransferase (AST) of 42 U/L (normal <41), a gamma-glutamyl transferase (GGT) of 131 U/L, (normal <56), a fibrinogen of 379 mg/dL (normal <350), a CRP of 8.05 mg/L (normal < 6), a blood sedimentation rate of 66 (normal < 20). There was no pathological finding in the physical examination of the patient who applied to our clinic with her current complaints. In her investigations, ALT, AST, GGT, and LDH were found to be 888, 277, 494, 325 IU/L, respectively. Blood sedimentation was 41 mm/h, and CRP was 10.08 mg/L. HBsAg, anti-HCV and anti-HIV were negative, anti-HBs was 85.82 mIU/mL, and anti-HAV IgG was positive. Cytomegalovirus (CMV), Epstein-Barr virus (EBV), HSV-1 serology were not compatible with an acute condition, while HSV-2 IgM antibody test resulted in positive, and IgG was negative. (HERPES SIMPLEX 1+2 ELISA IgG/IgM [Vircell Microbiologists, Granada, Spain] refer: antibody index for IgM and IgG ≤ 9 negative, =9-11 equivocal, >11 positive). It was noted that the patient had not taken any other herbal products or medications recently or favipiravir for COVID-19. Letrozole treatment was interrupted with the recommendation of gastroenterology and oncology. She had no history of alcohol or drugs. Toxic hepatitis was not considered in the patient. In the blood PCR analysis requested at the same time as the serological tests, CMV, EBV, parvovirus, HSV-1 DNA, autoimmune tests were negative, and HSV-2 DNA was positive (by artus® HSV1/2 QS-RGQ kit [QIAGEN, Hilden, Germany]). Quantitative PCR was not available. HSV serology was not tested before chemotherapy. The patient stated that she was married and monogamous. Serological information of the patient's spouse could not be reached. There was no history of oral or genital ulcers. The patient did not accept liver biopsy because it was an invasive procedure. Treatment with IV acyclovir was given at 5 mg/kg/dose every eight hours for ten days. Treatment was discontinued when aminotransferases returned to normal. After 30 days, control values for blood count, blood sedimentation, fibrinogen, ALT, AST, GGT, LDH, and CRP were within normal range; HSV-2 DNA and HSV-2 IgM were negative, and HSV-2 IgG was positive. The patient was discharged and followed up in the outpatient clinic.

When enzyme levels remained normal, letrozole treatment was started first, and trastuzumab was added to the treatment one month later. Again, no enzyme elevation and mucocutaneous lesion were observed in the follow-ups.

DISCUSSION

Fatal encephalitis and hepatitis cases due to primary or reactivated HSV-2 are rare (3, 4). In reviewing the literature, no hepatitis cases due to HSV-2 were found during or after the course of COVID-19.

In this case, who presented with nonspecific clinical symptoms, an increase in serum aminotransferase levels was observed with no change in bilirubin levels. Besides, multiple factors such as chemotherapy history, COVID-19 history, and steroid use were thought to be among the reasons that facilitate the development of hepatitis due to primary HSV-2 infection.

In immunocompromised patients, especially those with impaired cellular immune responses, primary and reactivated HSV can cause visceral organ involvement (3). Isolated involvement of the esophagus (5), lungs (6), and liver (7) due to HSV has been reported in the literature. One study revealed that 58% of cases of HSV hepatitis were initially diagnosed at autopsy, and only 23% were clinically suspected before tissue confirmation (4).

Paclitaxel has been indicated to have a bone marrow suppressive side effect and cause an immunosuppressive state by potent type 2 helper T cells (Th-2), as shown by high IL10 levels after acute administration (8). In the present case, it is known that paclitaxel was taken 45 days ago, and the white blood cell count was normal.

Case reports have pointed out that COVID-19 predisposes bacterial, fungal, and viral pneumonia (9) and reactivation of herpes zoster (10). In the study by Le Balc'h et al. (11), it was reported that 47% of COVID-19 patients receiving mechanical ventilation developed at least one viral pulmonary reactivation because of HSV and CMV. Several mechanisms explained the reason for the increase in herpes reactivation during COVID-19. The first one is the immunosuppression that develops during COVID-19 infection. A decrease in absolute lymphocyte count (especially CD4+ CD8+, NK cell cytopenias) and the persistence and severity of stimulation by inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α have been held responsible for immunosuppression (12). The second is the direct effect of COVID-19 on neurons. It has been reported that COVID-19 has a potential neurotropic mechanism and may play a role in primary or reactivated HSV infections (13). Another reason is the steroid therapy used in COVID-19 patients. Franceschini et al. (14) mentioned that they detected HSV-1 viremia in 30% of 70 COVID-19 patients treated in the ICU, including two cases of hepatitis, and that the viremia was related to steroid use. The case we presented had a history of steroid use for the treatment of COVID-19, too. Given this case, it was suggested that HSV-2 should also be investigated in hepatitis cases of unexplained etiology receiving steroid therapy.

The diagnosis of primary HSV-2 in our case was based on blood PCR and IgM positivity. In our case, IgG specific for HSV-2 was positive after four weeks. Acute-phase and convalescent-phase serum can be useful in demonstrating seroconversion during primary HSV infection. However, only 5% of the comparison of acute and convalescent period sera from reactivated HSV cases showed a four-fold or higher increase in antibody titer. In addition, it has been reported that IgM detection for HSV-1 or HSV-2 is not sufficient to identify recent or past acquisition and that IgM antibodies may be positive during reactivated herpes attacks. In the case presented here, IgG antibodies specific for HSV-2 were positive in blood analyzed four weeks after infection. In HSV infections, type-specific antibodies develop in the first few weeks and persist indefinitely. Therefore, we accepted this case as a primary HSV-2 infection because of its serology and lack of history of recurrent infection. However, since IgM positivity can be seen in reactivated HSV infections, it is difficult to distinguish between primary and reactivated HSV infections.

Serologic testing is commonly done but carries a high rate of false results and, therefore, should be used in conjunction with confirmatory PCR testing. In recent years, PCR of blood and cerebrospinal fluid (CSF) has been recommended as the primary test for diagnosing visceral HSV infection, particularly in the central nervous system (CNS) and adrenal glands, liver, bone marrow, and gastrointestinal tracts. This method is 3-4 times more sensitive than tissue culture and provides rapid results (4,15). In addition, the requested HSV PCR allowed early diagnosis if suspected.

The biopsy is the gold standard in HSV organ involvement. However, it is not always possible to take tissue samples. This case did not accept liver biopsy because it was an invasive procedure. The literature has reported that PCR positivity and concomitant increase in aminotransferases support the diagnosis in patients without a liver biopsy. In patients with >500 U/L aminotransferases, fever, coagulopathy, leukopenia, thrombocytopenia encephalopathy, and renal failure, it is recommended to start antiviral treatment with HSV PCR positivity (4).

Hepatitis is a rare manifestation of widespread infection. Without genital or skin lesions, HSV hepatitis cases may have an anicteric course. HSV hepatitis is associated with fulminant liver failure and high mortality (25%). Therefore, HSV-2 should be considered in the differential diagnosis among hepatitis etiologies. It is recommended to start HSV hepatitis treatment with IV acyclovir, and when clinical improvement is achieved, switching to oral valacyclovir therapy is recommended (4,15).

CONCLUSION

The risk and incidence of HSV-2 superinfection, coinfection, and reactivation in COVID-19 cases are not well known. In cases of SARS-CoV-2 infection, it should be kept in mind that the risk of HSV-2 infection may be increased in conjunction with the use of steroids and immunomodulatory drugs.

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