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Hepatitis due to human herpesvirus 6B after hematopoietic cell transplantation and a review of the literature

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Abstract

Human herpesvirus 6B (HHV-6B) is an opportunistic pathogen associated with a growing number of complications in immunocompromised patients. Multiple reports of HHV-6B-associated hepatitis following primary HHV-6 infection and liver transplantation have appeared, but this has only been well documented in 1 patient after hematopoietic cell transplantation (HCT). This report describes a case of acute hepatitis likely caused by HHV-6B in an HCT recipient who was successfully treated with ganciclovir. HHV-6B DNA was demonstrated in plasma and hepatic tissue using quantitative polymerase chain reaction and immunohistochemical stains. Chromosomal integration was ruled out. We review the literature reporting HHV-6B-associated hepatitis, which may be an underappreciated cause of liver disease after HCT.

Keywords

herpesvirus; HHV-6B; HHV6B; hepatitis; liver; transplant

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Human herpesvirus 6 (HHV-6) is a recently identified member of the HHV family, and approximately 95% of adults have serologic evidence of past infection (1). HHV-6 occurs as 2 closely related species, types A and B; HHV-6B accounts for the majority of HHV-6-associated disease. HHV-6B primary infection occurs in early childhood, classically causing exanthema subitum (roseola) (2). HHV-6 chronically infects and establishes latency in a wide variety of cells with intermittent reactivation that usually occurs during periods of immunosuppression (3).

HHV-6B is an opportunistic pathogen in patients undergoing solid organ transplantation (SOT) and hematopoietic cell transplantation (HCT), and it reactivates in approximately 30–80% of these patients around 2–6 weeks after transplantation (4, 5). HHV-6B viremia in SOT and HCT patients has been associated with numerous complications including graft (organ or stem cell) rejection, acute graft-versus-host disease (aGVHD), dysfunction of most organ systems, and increased all-cause mortality. Multiple reports of HHV-6B-associated hepatitis following primary HHV-6 infection and liver transplantation have appeared, but this has only been well documented in 1 patient after HCT (6). We describe a case of hepatitis likely caused by HHV-6B in an allogeneic HCT recipient successfully treated with intravenous (IV) ganciclovir.

Methods

DNA was extracted from plasma samples utilizing the MagnaPure LC DNA Isolation Kit I with the 0.2 mL protocol (Roche, Basel, Switzerland). Detection of HHV-6 DNA was performed using a sensitive high-throughput quantitative real-time TaqMan (Life Technologies, Grand Island, New York, USA) fluorescent probe polymerase chain reaction (PCR) assay used as previously described (7), with the exception of a single base change to primer 5R(A) GTT AGG ATA TAC CGA TGT GCG TGA T. The 95% reproducibility cutoff of the assay is 250 copies/mL or 10 copies/reaction. The HHV-6 primers and probes are specific for HHV-6 DNA and do not amplify or detect DNA from other herpesviruses. A highly conserved region of the U94 gene in HHV-6A and HHV-6B is amplified and used to distinguish species. DNA extracts from white blood cells were tested for HHV-6 and human ribonuclease P (RPP30, a ribonuclease reference gene for cell count) DNA by droplet digital PCR to rule out HHV-6 chromosomal integration (ciHHV-6). Chromosomal integration is excluded if the ratio of HHV-6 DNA to cell genome equivalents (2 RPP30/cell) falls outside the range of 1 ± 0.07 (8).

Immunohistochemistry (IHC) was performed after deparaffinization using anti-mouse monoclonal immunoglobulin (Ig) G1 antibodies to detect HHV-6 early antigen (EA) p41 (an early protein product of cellular transcription of new virus), viral capsid antigen (VCA) p140, and envelope glycoprotein (EG) gH (the viral ligand that binds to CD46 to enter cells) (1, 9) (Bioworld Consulting Laboratories, Mt. Airy, Maryland, USA). Anti-HHV-6 antibodies were diluted to 1.0 µg/mL in buffer and then 25 µL was added to slides incubated for 10 min at room temperature. The slides were covered with 1 drop of labeled anti-mouse IgG using the Immpress anti-mouse Ig Polymer detection kit and developed according to the manufacturer's recommendation (Vector Laboratories, Burlingame, California, USA). Images were obtained using a Nikon Optiphot microscope with a 20× planapochromat

objective and a Leica DFC295 camera. FireCam v. 3.1.4 software was used, with automatic adjustments intrinsic to the software. No photographic manipulation was performed.

Case report

A 23-year-old cytomegalovirus (CMV)-positive man with severe sickle cell (homozygous hemoglobin SS) disease underwent a matched-related myeloablative HCT using cells from his older sister. His conditioning regimen consisted of alemtuzumab, cyclophosphamide, fludarabine, and total body irradiation. Engraftment occurred on day (D) +21. His early post-transplant course was notable for CMV reactivation treated with IV ganciclovir and foscarnet, as well as grade 2A gastrointestinal aGVHD treated with systemic steroids. On D +94, he was started on oral voriconazole for oropharyngeal candidiasis and pulmonary nodules of unclear etiology. He was admitted on D +98 for evaluation of acute-on-chronic epigastric abdominal and lower sternal pain. He described the pain as sharp and constant in character with intermittent radiation to his back, ranking the intensity as 6–8/10 (10 being the most severe). He had associated nausea without emesis, mild constipation, and stable anorexia. A full review of systems was otherwise unremarkable.

The patient's medical history was also notable for multiple complications from his sickle cell disease including iron overload, multiple vaso-occlusive crises, restrictive pulmonary disease, chronic pain, adrenal insufficiency, cleared hepatitis B virus (HBV) infection, malaria, and microfilariasis. Immunizations were up to date and outpatient medications included voriconazole 300 mg twice a day (BID), valaciclovir 500 mg BID, dapsone 50 mg daily, penicillin V potassium 750 mg BID, mycophenolate mofetil 750 mg BID, sirolimus 0.25 mg daily, and prednisone 30 mg tapering by 5 mg daily.

The patient was born and raised in Uganda and lived in the United States for the past 7 years. He had not returned to Africa since emigrating. He was attending university and denied alcohol, tobacco, or other recreational drug use. He had no unusual exposures.

Examination revealed an ill-appearing young man with normal vital signs, except for mild tachycardia, and was primarily notable for a slightly distended abdomen with tenderness to palpation in the epigastrium without hepatosplenomegaly. Basic laboratory studies on admission were notable for stable, mild transaminitis with aspartate aminotransferase (AST) 56 international units (IU)/mL (normal 5–41), alanine aminotransferase (ALT) 81 IU/mL (normal 6–40), and alkaline phosphatase (AP) 275 IU/mL (normal 50–136) (Fig. 1). A basic metabolic panel and complete blood count were normal except for mild anemia. Total bilirubin, lipase, and amylase were within normal limits. Abdominal ultrasound revealed cholelithiasis without cholecystitis and interval increase in the common bile duct diameter from 4.9 mm to 7.5 mm without obvious choledocholithiasis.

Esophagogastroduodenoscopy and flexible sigmoidoscopy were notable for mild inflammatory changes in the stomach and rectum, confirmed again to be aGVHD by histopathology. Because of ongoing abdominal discomfort and ultrasonographic findings, he underwent uncomplicated laparoscopic cholecystectomy on hospital day (HD) 5. An intraoperative cholangiogram was unremarkable.

His pain persisted, and he developed new right upper quadrant tenderness with concurrent new transaminitis that progressively worsened after surgery. Total bilirubin remained normal. He also had new low-grade fevers for 4 days prompting empiric treatment with meropenem. Quantitative PCR assays for CMV, Epstein–Barr virus, herpes simplex virus 1 and 2, adenovirus, and HBV DNA were negative. Plasma HHV-6 PCR was positive for type B, with a viral load (VL) of 170,000 copies/mL on HD 10 (Fig. 1). CiHHV-6 testing of white blood cell (buffy coat) by droplet digital PCR was negative, based on a ratio of HHV-6 to cell genome equivalents of 0.03 (where a ratio of ~ 1 is suggestive of integration) (8). In addition, a serum sample from the donor was negative for HHV-6 DNA. The patient had not been tested for HHV-6 previously. A lumbar puncture was unremarkable, and PCR of cerebrospinal fluid did not detect HHV-6 DNA. Multiple blood cultures were negative. Computed tomography scans of his head, chest, abdomen, and pelvis revealed stable pulmonary nodules.

Because of concern for infection of his liver with HHV-6B, the patient was started on IV ganciclovir 5 mg/kg every 12 h on HD 10. In addition, he was transitioned from voriconazole to micafungin for possible drug-related hepatotoxicity. A percutaneous liver biopsy was performed on HD 15 (D +112 post HCT) followed by empiric initiation of methylprednisolone 1 mg/kg IV daily to treat possible liver GVHD.

Liver biopsy demonstrated slight abnormalities of the bile ductules and proliferation of the larger bile ducts. Occasional neutrophilic aggregates were seen, indicative of lobular hepatitis. Very rare apoptotic hepatocytes were present. The trichrome stain showed no evidence of sinusoidal obstruction syndrome. PCR and/or IHC of biopsy samples were negative for CMV, Epstein–Barr virus, adenovirus, HHV-7, and HBV. PCR was positive for HHV-6B with 180,000 copies/reaction. Hepatocytes and Kupffer cells from the liver biopsy sample stained with antibodies against HHV-6 EA p41, VCA p140, and EG gH (Fig. 2). The EA p41 primarily stained Kupffer cells and relatively few hepatocytes, whereas the VCA p140 and EG gH diffusely stained Kupffer cells as well as hepatocytes. Although diffuse background staining occurred, with darker areas sometimes similar to the distribution of iron in the cells, a control specimen with comparable levels of iron deposition did not take up the stains.

Serum transaminases peaked at AST 719 IU/mL, ALT 814 IU/mL, and AP 378 IU/mL on HD 14 and returned to baseline over the next 10 days (Fig. 1). The HHV-6 VL steadily decreased to <5000 copies/mL 7 days after starting ganciclovir (HD 17). His albumin reached a nadir of 2.8 g/dL (normal 3.8–5.4) 17 days after admission, and he had normal coagulation parameters throughout monitoring.

He began a steroid taper and was transitioned to oral valganciclovir on HD 25. He continued to have similar, although improved, abdominal pain at discharge a few days later. HHV-6 DNA remained detectable at low levels (<5000 copies/mL) for months.

Discussion

We report a case of likely HHV-6B-associated hepatitis in an allogeneic HCT recipient who was successfully treated with ganciclovir. Determining the cause of organ dysfunction after HCT is often challenging, with many possible etiologies, and HHV-6-associated hepatitis may be underappreciated. The combination of identification of HHV-6B DNA in the plasma and liver, IHC staining of HHV-6 antigens in hepatic cells consistent with active infection, and the patient's response to HHV-6-targeted therapy strongly implicated HHV-6B as the cause of his hepatitis (9).

The patient described herein developed progressive transaminitis after an uncomplicated cholecystectomy with negative intraoperative cholangiogram and normal bilirubin, making a retained stone unlikely. He began taking voriconazole approximately 10 days before the development of liver dysfunction, and voriconazole-associated hepatitis typically occurs after a longer duration of therapy and with less severe transaminitis (10). Furthermore, his transaminases initially worsened off voriconazole. Extensive workup for other hepatotoxic infections was negative; varicella zoster virus was not tested for in any clinical samples but would be very unusual in the setting of appropriate antiviral prophylaxis with valacyclovir and lack of a rash. It remains unclear whether the patient's systemic HHV-6 reactivation and associated hepatitis contributed to his initial symptoms of acute-on-chronic epigastric abdominal and lower sternal pain.

The most likely alternative diagnosis would be GVHD. The liver is the second most commonly involved organ in aGVHD, which typically occurs concomitantly with skin GVHD, laboratory evidence of cholestasis, and pathologic signs of bile duct damage (11). A rare hepatic variant of chronic GVHD can present as acute hepatitis with marked elevation of transaminases and pathologic features of lobular hepatitis with bile duct changes (12, 13). The slight bile ductule abnormalities in this patient's biopsy could be seen in GVHD, but no other evidence supported this diagnosis. The proliferative bile ducts are nonspecific and may be a result of the patient's prior HBV infection or cholestasis, among other possible causes. The lobular hepatitis is also nonspecific. With only rare apoptotic hepatocytes and no portal infiltrate, no evidence was seen for the hepatitic variant of GVHD. Although the patient was empirically treated for GVHD with methylprednisolone in addition to ganciclovir, we think GVHD was an unlikely cause of his hepatitis, considering the atypical laboratory and pathologic findings and presence of another etiology.

In vitro studies have demonstrated that HHV-6 can infect and replicate in human liver cells and may have direct cytopathic effects (14, 15). Liver disease is an unusual complication of HHV-6 infection and has been described mainly in the setting of HHV-6B primary infection. A study of 89 infants with primary HHV-6B infection showed that 4% developed transient transaminitis (16). A number of case reports in immunocompetent infants and adults describe liver damage ranging from mild transaminitis to fatal fulminant hepatitis after initial infection (17–25). A retrospective review of patients with acute liver failure of known and unknown etiology demonstrated an association with HHV-6 antigen detection in explanted livers without other explanation of failure (26). Although these reports suggest an

etiologic role for HHV-6 in hepatitis, most did not demonstrate definitive evidence of viral infection of liver cells.

Hepatic dysfunction in association with HHV-6 infection is a significant concern after liver transplantation. HHV-6 infection of transplanted livers may cause increased adhesion molecule expression on vascular endothelial cells resulting in lymphocyte infiltration (27). Primary infection with HHV-6 in infants after liver transplantation has been associated with hepatitis and graft rejection (28, 29). A prospective study in liver transplant patients concluded that HHV-6 detection in serum by PCR is independently correlated with biopsyproven graft rejection (30). Another study described HHV-6 as a cause of acute hepatitis with periportal confluent necrosis in liver allografts, often without detection in the blood (31).

Hepatitis due to HHV-6 infection in HCT recipients has been well documented in only 1 case after a myeloablative matched-related HCT for chronic myeloid leukemia (6). This patient was admitted on D +189 for medication-related leukoencephalopathy and started on high-dose steroids. Moderate transaminitis developed 10 days later, and specimens from liver biopsy were positive for HHV-6B by PCR and IHC; blood samples were not tested. His liver dysfunction resolved with ganciclovir treatment. Another possible case was described after HCT (HCT details not reported) in a patient who developed transaminitis and concurrent HHV-6 (not typed) viremia 3 weeks after transplantation, with 120,000 gene copies in a peripheral blood lymphocyte sample (32). He was treated with foscarnet and had improvement of liver function with clearance of viremia. He died from intracerebral aspergillosis, and liver specimens from autopsy had detectable HHV-6 DNA by PCR and histopathologic findings consistent with viral hepatitis. IHC was not performed.

Evaluating for ciHHV-6, a condition present in about 1% of people in which latent HHV-6 is present in every nucleated cell (33), is important to consider when HHV-6 is detected. HHV-6 DNA levels $>5.5 \log_{10}$ copies/mL of whole blood are suggestive of ciHHV-6. Patients with ciHHV-6 usually have detectable HHV-6 in all cellular and some acellular clinical samples, irrespective of active HHV-6 replication or disease.

Treatment for HHV-6-associated diseases includes ganciclovir, foscarnet, or cidofovir, which demonstrate good *in vitro* and *in vivo* activity against HHV-6 and have been used successfully in clinical settings (4, 34). However, the US Food and Drug Administration has not approved any antiviral drugs for this purpose. Preemptive and prophylactic treatment strategies are being explored and may improve outcomes and reduce the incidence HHV-6-associated diseases. The few published studies have not been conclusive, perhaps because of the dynamic kinetics of HHV-6 viremia and limitations of study design (35–37).

We report one of the few documented cases of HHV-6B-associated hepatitis after allogeneic HCT, which may be an underappreciated cause of liver disease in this population. Prompt testing and initiation of treatment for HHV-6 after appropriate evaluation resulted in a good outcome for the patient. It is reasonable to consider treating HHV-6 in the setting of viremia and hepatitis while diagnostic workup is underway. Large-scale formal clinical studies

should be performed to further explore the epidemiology and characteristics of hepatitis in immunocompromised patients with evidence of HHV-6 infection.

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Fig. 1. Quantitative plasma human herpesvirus 6 (HHV-6) viral loads (VL) and liver enzyme trends during hospitalization. ALT, alanine aminotransferase; AP, alkaline phosphatase.

Fig. 2. Immunohistochemical staining (brown) of a number of human herpesvirus 6 proteins. (A) Early antigen (EA) p41 staining in the cytoplasm of hepatocytes (open arrows) and Kupffer cells (solid arrows) (20 × objective). Inset shows positively staining bodies in the cytoplasm of hepatocytes (60 × objective; bar = 100 μM). (B) EA p41 staining of control liver specimen with hemosiderosis showing light background staining in hepatocytes but not in Kupffer cells. (C) Viral capsid antigen (VCA) p140 staining in Kupffer cell cytoplasm (solid arrows), and in a punctate distribution in hepatocyte cytoplasm (open arrow), both with a patchy distribution. (D) VCA stained control with hemosiderosis showing minimal background staining. (E) Envelope glycoprotein gH stains similarly to VCA with an identical patchy distribution. (F) CD68 staining of the subject liver demonstrating Kupffer cells (solid arrow).