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Hemophagocytic Lymphohistiocytosis Due to Primary HHV-8 Infection in a Liver Transplant Recipient

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Abstract: Human herpesvirus-8 (HHV-8) remains best known as an oncogenic virus, but nonneoplastic disease manifestations, such as bone marrow failure or hemophagocytic lymphohistiocytosis (HLH) have gained greater recognition in recent years. In organ transplantation, HHV-8 infection commonly occurs with reactivation of latent virus among recipients from endemic regions of the world or due to transmission from the organ donor. We describe a case of HHV-8–associated HLH in a liver transplant recipient at increased risk for primary infection. Our case highlights the risk of non–donor-derived, posttransplant primary HHV-8 infection, and demonstrates that HLH can be a life-threatening complication of this infection.

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Human herpesvirus 8 (HHV-8) is a DNA virus that belongs to the gammaherpesvirus subfamily.[1] Human herpesvirus 8 infection occurs all over the world but regions of highest prevalence include Africa, the Mediterranean, and Middle East.[2-4] In the United States, higher rates of HHV-8 seropositivity are found among individuals with human immunodeficiency virus (HIV), including 90% of men who have sex with men[5] and 15% of organ transplant recipients.[6] In low seroprevalence areas, posttransplant HHV-8 can occur due to reactivation of latent virus; however, the role of primary infection acquired through blood transfusion, sexual contact, or from the organ donor is increasingly recognized.[2,6-8] Similar to persons with acquired immune deficiency syndrome, Kaposi's sarcoma (KS) is the most common manifestation of HHV-8 in organ transplant recipients.[9] Other well recognized but rare HHV-8–related malignancies include primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD).[2] Although the oncogenic properties of HHV-8 have been well described, little is known about the less-common nonneoplastic disease manifestations, such as bone marrow failure and hemophagocytic lymphohistiocytosis (HLH).

We describe a case of HHV-8–associated HLH in a liver transplant recipient at increased risk for primary infection. Our case highlights the risk of non–donor-derived posttransplant primary HHV-8 through sexual transmission and demonstrates that HLH can be a life-threatening complication of this infection.

CASE DESCRIPTION

Our patient was a 31-year-old liver transplant recipient presenting with fevers, right upper quadrant abdominal pain, and hematochezia for several weeks. He underwent deceased donor orthotopic liver transplantation 4 years prior, after developing fulminant liver failure from drug-induced liver injury, which was presumed to be due to use of an herbal supplement. He had stable allograft function and was on maintenance immunosuppression with tacrolimus alone. He was born in Northern Africa and lived in West Africa for most of his life. He had immigrated to the United States 5 years prior. He was a daily smoker and denied illicit drug use. He

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IRB: This study was exempt from approval from an ethics board as it was a case study.

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identified as a gay male and was sexually active with multiple male partners. In the past few months, he had been repeatedly prescribed nonoccupational HIV postexposure prophylaxis due to condomless sex.

On arrival, his vitals were notable for a temperature of 102°F, blood pressure of 94/51 mm Hg, heart rate of 110 beats/min, respiratory rate of 18 breaths/min with an oxygen saturation of 99% on room air. On physical examination, he had generalized lymphadenopathy, right upper quadrant tenderness, and hepatosplenomegaly. Laboratories demonstrated leukopenia (white blood cell count of 4.1×10^3 cells/μL with 64% neutrophils and 14% monocytes), normocytic anemia (hemoglobin, 8.2 mg/dL from a baseline of 12.5 mg/dL weeks prior), and thrombocytopenia (platelets 79×10^3 cells/μL from a baseline of 178 weeks prior). He had mild acute renal failure (Cr, 1.59 mg/dL), elevated liver enzymes (aspartate aminotransferase, 44 U/L; range, 1-45; alanine aminotransferase, 81 U/L; range, 1-35), low albumin at 2.4 g/dL and coagulopathy with prolonged prothrombin time (17.4 seconds), partial thromboplastin time (38.5 seconds), and international normalized ratio (1.4). Further work-up revealed anemia of chronic inflammation (iron, 22 μg/dL; total iron binding capacity, 163 μg/dL; ferritin, 947 ng/mL), normal haptoglobin (165 mg/dL), and LDH (196 U/L). His initial chest X-ray showed a small left-sided pleural effusion without consolidation.

Given his fevers and new-onset pancytopenia, the initial work-up focused on viral etiologies, including cytomegalovirus (CMV), Epstein–Barr virus, Parvovirus B-19, and HIV, which were all negative by serum polymerase chain reaction (PCR). On hospital day 5, his human-herpesvirus 6 PCR was positive at 78200 copies/mL which was treated with intravenous ganciclovir; however, his clinical status continued to decline. Daily high-grade fevers over the next 2 weeks led to an extensive infectious and hematologic work-up. Serum, urine, sputum, and stool cultures were negative. Respiratory PCR panel was negative for community-acquired pathogens. Urine, pharyngeal, and rectal specimens were negative by PCR for gonorrhea and chlamydia. Fungal markers were negative, including serum cryptococcal antigen, 1-3 beta-D-glucan, aspergillus galactomannan antigen, and histoplasma antigen. Other work-up was notable for a negative buffy coat, negative thin and thick smears for parasites, and negative serologies for toxoplasmosis, leptospirosis, and leishmaniasis.

On hospital day 13, a hematology consult was placed given his fevers, worsening pancytopenia and rising ferritin (1978 ng/mL). Peripheral flow cytometry was negative for malignancy. A bone marrow biopsy was nondiagnostic due to insufficient bone marrow core. On hospital day 21, serum HHV-8 PCR returned at 6.6 million copies/mL with a negative HHV-8 IgG by immunofluorescence. Reference laboratory HHV-8 IgM testing was not available at our clinical center. Given his hematochezia, a flexible sigmoidoscopy was performed which revealed an area of hyperemia and nodularity that on histopathology demonstrated nonspecific proctitis without evidence of KS and immunohistochemical stains for CMV, Epstein-Barr virus–encoded RNA (EBER) and HHV-8 were negative. A repeat bone marrow biopsy was then performed that demonstrated HLH with negative immunostains for CMV, HHV-6, EBER, and HHV-8 (Figure 1). Consistent with diagnosis of HLH, the interleukin-2 receptor level was also elevated (32500 pg/mL). His tacrolimus dose was reduced, and sirolimus was added given the potential role of mammalian target of rapamycin inhibitors in HHV-8 infection.[10]

On hospital day 22, he developed multiorgan failure requiring admission to the intensive care unit. He was started on mechanical ventilation, renal replacement therapy, and systemic pressors. Despite treatment with IVIG and dexamethasone for the management of HLH, his total bilirubin, ferritin, and HHV-8 PCR continued to rise peaking at 24 mg/dL, 116200 ng/mL, and 63 million copies/mL, respectively (Figure 2). HHV-6 PCR also rose, peaking at 173000 copies/mL. He was not given etoposide given his liver failure and tenuous hemodynamics. He received 2 doses of rituximab and a dose of monoclonal anti–IL-6R antibody (tocilizumab), which has been used in cases of refractory MCD.[10] His course was complicated by cardiac tamponade requiring an emergent pericardiocentesis. Ultimately, he and his family decided to transition his care to focus on comfort only, and he died on hospital day 49.

DISCUSSION

This case highlights many unique aspects of HHV-8 infection after organ transplantation. Although the global seroprevalence of HHV-8 remains uneven, it is important to recognize risk factors for infection in low-prevalence areas. In addition to the

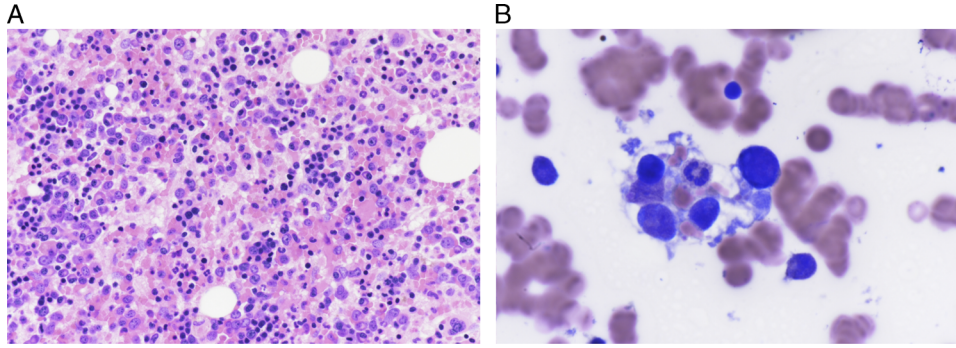

FIGURE 1. A, Bone marrow biopsy shows histiocytes with hemophagocytic activity, normocellular marrow (70-80%) for age with trilineage hematopoiesis and full maturation. Megakaryocytes are normal to mildly increased in number with normal to adequate morphology. Plasma cells/lymphocytes present. No granulomas. EBER1 in situ hybridization and immunohistochemistry (IHC) for HHV-8 latency-associated nuclear antigen were negative. Image was taken at 40× objective with a Nikon DS-Ri2 camera and Nikon Eclipse Ci microscope and image software NIS-Elements D 4.40.00 (courtesy Julie Teruya-Feldstein, MD). B, Bone marrow smear shows histiocytes with hemophagocytic activity. Image was taken at 100x high dry objective with a Nikon DS-Ri2 camera and Nikon Eclipse Ci microscope and image software NIS-Elements D 4.40.00 (courtesy Julie Teruya-Feldstein, MD).

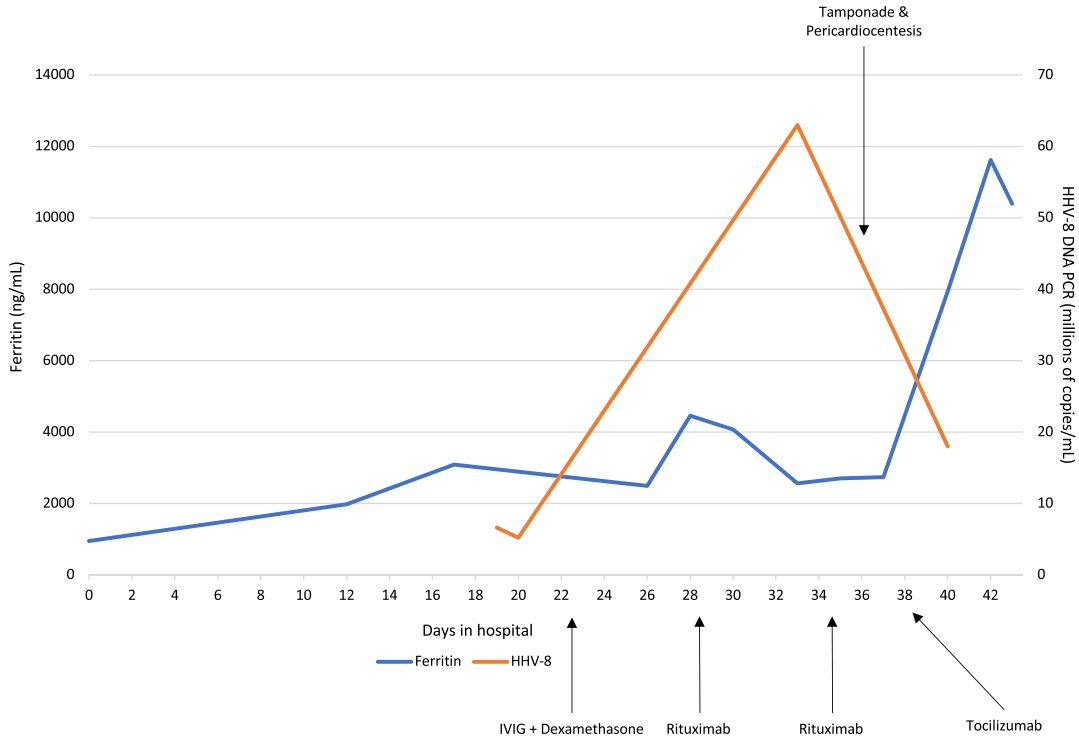

FIGURE 2. Change in ferritin (blue line, in ng/mL) and HHV-8 DNA PCR (orange line, in millions of copies/mL) during patient's hospitalization. Timing of notable medical interventions is indicated with straight arrows.

known risk among people with HIV and men who have sex with men in the United States, higher HHV-8 seroprevalence has also been documented among organ transplant recipients.[6] Furthermore, it has been shown that after organ transplantation, a significant increase in HHV-8 seropositivity occurs,[6] suggesting that primary infection is occurring posttransplant. This is in contrast to high-seroprevelance regions, where posttransplant HHV-8 is felt to be largely due to reactivation of latent infection. Certainly, the occurrence of posttransplant KS among immigrants from endemic areas supports this pathogenesis.[11] However, because most organ transplant recipients in low risk areas, such as the United States, are seronegative for HHV-8, it is plausible that primary infection plays a more significant role in this patient population.

Donor-derived primary HHV-8 is well described and similar to other herpesviruses; seronegative recipients who receive a donor from a seropositive donor are at highest risk of acquiring posttransplant infection.[7,8] In addition to infection from the organ donor, primary HHV-8 also occurs with other exposures. In the cohort published by Jenkins et al,[6] none of the patients who seroconverted posttransplant were found to have a seropositive donor, which supports the risk of primary infection from exposures, such as sexual transmission or blood transfusions. The exact risk posed by these nondonor mechanisms of HHV-8 transmission is not clearly understood. However, it is important to recognize these as potential sources of HHV-8 infection in the immunosuppressed host and counsel patients with behaviors that may increase their risk. It is likely that the patient reported herein acquired primary infection posttransplant through sexual transmission. Certainly, without knowledge of the patient's pretransplant HHV-8 serostatus, we are unable to conclusively rule out the possibility of reactivation or past infection. However, occurrence of HHV-8 infection in the late posttransplant period, negative HHV-8 serology, and very high serum PCR are supportive of recently acquired primary infection independent of the donor.

Human herpesvirus 8 remains best recognized as the etiology of KS, MCD, and PEL and published data are mainly focused on posttransplant KS. Although causality is at times less firmly established, there are several reports of nonneoplastic manifestations associated with HHV-8 in transplant recipients.[12-15] The clinical syndrome of fever, splenomegaly and bone marrow suppression with or without HLH has been reported with primary and most often, donor-derived HHV-8 manifesting in the early posttransplant period.[12-14] Multiple HHV-8–associated manifestations can also occur concomitantly with autopsy showing evidence of KS, MCD, and HLH all in the same patient.[15]

The diagnosis of HHV-8 after transplantation remains challenging due to lack of standardized methodologies. Serologic testing is based on detection of latent and lytic HHV-8 antigens, which have limited sensitivity and specificity especially during acute infection.[2,16] PCR is the diagnostic modality of choice and has been shown to have good correlation with KS,[17] as well as PEL and MCD.[18] Immunohistochemistry or in situ hybridization for latent and lytic protein antigens is often used on bone marrow in cases of suspected HHV-8–associated HLH with variable test characteristics.[2,12-15] We used immunohistochemical staining for the latency-associated nuclear antigen on the bone marrow which was negative. Since bone marrow staining did not show presence of the latent antigen, we were unable to more conclusively establish HHV-8 as the etiology of HLH. Although a lymph node biopsy could have substantiated a diagnosis, we were unable to perform this procedure due to the patient's critical illness.

In addition, repeat convalescent HHV-8 serologies were not obtained because the patient did not survive the hospitalization. Given that HHV-6 titers also increased for this patient, various attempts were made to exclude HHV-6 as a pathogenic entity. Serum HHV-6 IgM and bone marrow HHV-6 immunohistochemical stains were negative. Further supporting HHV-8 as the culprit virus was the fact that HHV-8 viremia was 2 orders of magnitude higher than HHV-6 viremia. Lastly, the patient had a plasmocytic B cell proliferation on his peripheral flow cytometry (7%) and his bone marrow biopsy (12%), a finding that has been well described for HHV-8; the same phenomenon is not associated with HHV-6 infection.[10] Despite these diagnostic limitations, we believe HHV-8 was the most likely etiology of HLH in this individual due to his known risk for primary infection, a very high plasma viral load indicative of lytic/actively replicating virus as well as the absence of another clear etiology.

CONCLUSIONS

This case report highlights the continued risk of community-acquired HHV-8 in the transplant recipient and the need to consider HHV-8 as a pathogen in cases of acute febrile illness with bone marrow suppression and/or HLH.

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REFERENCES

1. Edelman DC. Human herpesvirus 8—a novel human pathogen. *Virol J*. 2005;2:78.
2. Ariza-Heredia EJ, Razonable RR. Human herpes virus 8 in solid organ transplantation. *Transplantation*. 2011;92:837–844.
3. Butler LM, Were WA, Balinandi S, et al. Human herpesvirus 8 infection in children and adults in a population-based study in rural Uganda. *J Infect Dis*. 2011;203:625–634.
4. Calabro ML, Sheldon J, Favero A, et al. Seroprevalence of Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 in several regions of Italy. *J Hum Virol*. 1998;1:207–213.
5. Lennette ET, Blackbourn DJ, Levy JA. Antibodies to human herpesvirus type 8 in the general population and in Kaposi's sarcoma patients. *Lancet*. 1996;348:858–861.
6. Jenkins FJ, Hoffman LJ, Liegey-Dougall A. Reactivation of and primary infection with human herpesvirus 8 among solid-organ transplant recipients. *J Infect Dis*. 2002;185:1238–1243.
7. Pietrosi G, Vizzini G, Pipitone L, et al. Primary and reactivated HHV8 infection and disease after liver transplantation: a prospective study. *Am J Transplant*. 2011;11:2715–2723.
8. Regamey N, Tamm M, Wernli M, et al. Transmission of human herpesvirus 8 infection from renal-transplant donors to recipients. *N Engl J Med*. 1998; 339:1358–1363.
9. Engels EA, Pfeiffer RM, Fraumeni JF Jr., et al. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA*. 2011;306: 1891–1901.
10. Riva G, Luppi M, Barozzi P, et al. How I treat HHV8/KSHV-related diseases in posttransplant patients. *Blood*. 2012;120:4150–4159.
11. Mbulaiteye SM, Engels EA. Kaposi's sarcoma risk among transplant recipients in the United States (1993-2003). *Int J Cancer*. 2006;119: 2685–2691.
12. Karras A, Thervet E, Legendre C. Hemophagocytic syndrome in renal transplant recipients: report of 17 cases and review of literature. *Transplantation*. 2004;77:238–243.
13. Luppi M, Barozzi P, Rasini V, et al. Severe pancytopenia and hemophagocytosis after HHV-8 primary infection in a renal transplant patient successfully treated with foscarnet. *Transplantation*. 2002;74:131–132.
14. Luppi M, Barozzi P, Schulz TF, et al. Bone marrow failure associated with human herpesvirus 8 infection after transplantation. *N Engl J Med*. 2000; 343:1378–1385.
15. Vijgen S, Wyss C, Meylan P, et al. Fatal outcome of multiple clinical presentations of human herpesvirus 8-related disease after solid organ transplantation. *Transplantation*. 2016;100:134–140.
16. Corchero JL, Mar EC, Spira TJ, et al. Comparison of serologic assays for detection of antibodies against human herpesvirus 8. *Clin Diagn Lab Immunol*. 2001;8:913–921.
17. Pellet C, Chevret S, Frances C, et al. Prognostic value of quantitative Kaposi sarcoma-associated herpesvirus load in posttransplantation Kaposi sarcoma. *J Infect Dis*. 2002;186:110–113.
18. Tedeschi R, Marus A, Bidoli E, et al. Human herpesvirus 8 DNA quantification in matched plasma and PBMCs samples of patients with HHV8-related lymphoproliferative diseases. *J Clin Virol*. 2008;43:255–259.