Fatal Myocarditis Associated With HHV-6 Following Immunosuppression in Two Children

Heather E Stefanski, MD, PhD, a Kathryn A Thibert, BS, a Joshua Pritchett, BS, a Bhubesh K Prusty, MD, b John E Wagner, MD, a Troy C Lund, PhD, MDa

aDivision of Pediatric Blood and Marrow Transplant, University of Minnesota, Minneapolis, Minnesota; and
bBiocenter, Chair of Microbiology, University of Würzburg, Würzburg, Germany

Dr Stefanski conceptualized and designed the study, and drafted the initial manuscript; Ms Thibert, Mr Pritchett, and Dr Prusty carried out the initial analyses, and reviewed and revised the manuscript; Drs Wagner and Lund oversaw the data and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: 10.1542/peds.2015-1352

Accepted for publication Sep 15, 2015

Address correspondence to Troy Lund, PhD, MD, FAAP, University of Minnesota, Pediatric Blood and Marrow Transplant Program, MMC 366, 420 Delaware St SE, Minneapolis, MN 55455. E-mail: lundx072@umn.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2016 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This work was supported in part by the NIH/NICHD K12 HD068322 (HES and TCL) and K08HL108998 (TCL) and the St Baldrick’s Foundation (HES and KAT). Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Human herpesvirus 6 (HHV-6) antibodies are found in >90% of adults in the Western Hemisphere, with infection acquired by 3 years of age.1 Moreover, HHV-6 DNA detection in blood via polymerase chain reaction (PCR) (reactivation) can occur in nearly 50% of patients after hematopoietic cell transplantation (HCT).2 HHV-6 reactivation most commonly manifests as viremia within the first 28 days of HCT and can be associated with several complications, including encephalitis, altered mental status, bone marrow suppression, and delayed engraftment.2–5 HHV-6 treatment guidelines are most often practitioner-based.

Viral myocarditis can be seen in the immunocompromised setting and has etiologies including enterovirus, adenovirus, parvovirus B19, and HHV-6 implicated in multiple studies.6,7 The gold standard diagnostic study is endomyocardial biopsy; it typically shows a lymphocytic infiltrate into the cardiac tissue. Recently, PCR of blood DNA has been used in diagnosis, but there are no definitive levels of viral DNA to make an accurate diagnosis. In this report, we show HHV-6 as a cause of myocarditis in 2 immunosuppressed pediatric patients.

CASE 1

A 13-year-old boy presented with priapism and a white blood count of 649,000. He was diagnosed with pre-B cell acute lymphoblastic leukemia based on flow cytometry. He was treated for high-risk acute lymphoblastic leukemia, although at the end of induction still had presence of disease. He underwent a double umbilical cord blood transplant with conditioning consisting of fludarabine, cyclophosphamide, and total body irradiation with graft versus host disease (GvHD) prophylaxis consisting of Cyclosporin A and mycophenylate mofetil.
Peritransplant complications included fevers, mucositis, mild transaminitis, and positive blood culture. Neutrophil engraftment occurred on day +9 and the patient was discharged on day +22. He was readmitted to the hospital on day +25 for fever and a generalized erythroderma with maculopapular features on 75% of his body. At the time of admission, the patient reported nasal congestion and epiphora. He was started on broad-spectrum antibiotics. Viral studies were negative for cytomegalovirus, adenovirus, and respiratory syncytial virus; however, he was positive for HHV-6 with 7600 copies per mL from his blood by PCR. A skin biopsy indicated nonspecific findings but could not exclude GvHD; intravenous methylprednisolone was started at 48 mg/m² for Grade II acute GvHD. The fever began to improve within 48 hours. The rash slightly improved day 5 after initiation of steroids. An echocardiogram showed no evidence of thrombi and an ejection fraction of 60% (similar to the pre-HCT ejection fraction).

On day +34, he had new fevers and antibiotic coverage was broadened, as well developed a new oxygen requirement, persistent tachycardia, hypotension, and decreased urine output. Physical examination revealed fine rales at the right base consistent with an infiltration on chest radiograph. HHV-6 viremia increased to 146,200 copies per mL of blood; at that time ganciclovir was initiated. The following day he developed acute respiratory decompensation with hypoxia and was transferred to the PICU for endotracheal intubation and mechanical ventilation. A repeat echocardiogram revealed an ejection fraction of 24%. The patient received inotropic support with multiple agents and transitioned to oscillatory ventilation for support. On day +36, the patient acutely worsened, requiring initiation of cardiopulmonary resuscitation; the attempts were ultimately unsuccessful and the patient died.

On autopsy, the heart was not grossly abnormal, but did show a pericardial effusion. The lungs showed pulmonary edema and bilateral pleural effusion. The cardiac tissue showed a mild interstitial lymphocytic infiltrate without evidence of fibrosis or viral inclusions on histologic sections; however, HHV-6 PCR was positive from the left ventricle and left lung upper pulmonary lobe. HHV-6A was detected in cardiac tissue by immunofluorescence, implicating viral myocarditis as the cause of death (Fig 1A).

**CASE 2**

A 2-year-old previously healthy girl was evaluated in her primary care physician’s office for a fever and rash. On physical examination, the patient was found to have multiple ecchymoses and petechiae on the lower extremities. The patient’s laboratories showed a white blood cell count of 2400 cells/μL, a neutrophil count of 300 cells/μL, lymphocytes of 1300 cells/μL, hemoglobin of 9.9 g/dL, and platelets of 7000/μL. She had normal electrolytes and a normal chest radiograph. The patient was admitted to the hospital for further workup and started on broad-spectrum antibiotics. On hospital day 2, her white blood cell count decreased to 400 cells/μL, hemoglobin 7.9 g/dL, and platelets were 0. Bone marrow biopsy showed marrow cellularity of 80% to 90% with trilineage hemato poiesis without evidence of malignancy or dysplastic changes and normal flow cytometry. The patient was diagnosed with Evans syndrome and started on prednisone 2 mg/kg per day divided twice a day. The patient continued to have intermittent fevers throughout her hospital course. Blood cultures were negative as were viral PCRs for Epstein-Barr virus and cytomegalovirus. The patient’s hemoglobin stabilized but she continued to have profound thrombocytopenia. On hospital day 6 the patient had decreased urine output, change in mental status, and hypotension and went into shock. Despite cardiopulmonary resuscitation, the patient died. Ultimately, HHV-6 PCR of the blood revealed 64,600 copies/mL. Autopsy results indicated acute lymphocytic myocarditis consistent with viral infection in both the left and right ventricles, and HHV-6A detected the cardiac tissue by immunofluorescence (Fig 1B).

**DISCUSSION**

HHV-6 reactivation is a common complication of HCT. Although...
plasma HHV-6 DNA load dynamics are often indicative of associated disease severity, the virus is highly cell-associated and can become persistent in tissues even at low circulating levels of viremia. Several studies have demonstrated disease states attributable to HHV-6 infection in the heart, brain, and liver tissues in the absence of detectable plasma viremia.\(^8\)\(^9\) Furthermore, HHV-6 infection has been reported to cause fatal myocarditis at very low levels of viremia.\(^9\)\(^-\)\(^14\)

Currently, there is no unified approach for routine monitoring or treatment of HHV-6 in the setting of HCT.\(^15\)\(^-\)\(^17\) There is some evidence that rapid diagnosis and intervention in cases of HHV-6 myocarditis may prevent fatality in these patients. Hakacova et al\(^18\) described the successful treatment of antiviral-resistant HHV-6B myocarditis in a young child with the drug Artesunate, which has shown efficacy against HHV-6 in vitro. More often, foscarnet or ganciclovir is used when HHV-6 is accompanied by symptoms.\(^19\)\(^20\) However, no randomized controlled trials have been conducted to determine which agent is best suited to treat HHV-6.

Endomyocardial biopsy is considered the gold standard for the diagnosis of myocarditis. However, the sensitivity of endomyocardial biopsy is low and myocarditis is confirmed on biopsy in only 20% to 50% of pediatric patients in the United States.\(^21\) In these cases, viral PCR of the tissue is often performed but could be an incidental finding due to the combination of circulating blood cells present in the tissue and the exquisite sensitivity of PCR. Although viral myocarditis usually results in a lymphocytic infiltrate, the immune response in case 1 may have been limited by the patient’s lymphopenia, as well as by steroid administration.

We report 2 cases of HHV-6 reactivation associated with myocarditis in immunosuppressed patients with direct staining of HHV-6 in heart tissue. Commonly, HHV-6 testing is performed only if a suggestive syndrome is present. Furthermore, therapy is often only initiated if high-grade viremia is present. In both cases, our patients initially had low-grade viremia and developed fatal myocarditis. Treatment of myocarditis in the immunocompromised setting warrants further investigation and consideration of early therapy regardless of HHV-6 viral load in the blood. This could be critical in decreasing morbidity and mortality in these patients.

### ABBREVIATIONS

- GvHD: graft versus host disease
- HCT: hematopoietic cell transplantation
- HHV-6: human herpesvirus 6
- PCR: polymerase chain reaction

### REFERENCES

15. Betts BC, Young JA, Ustun C, Cao Q, Weisidor DJ. Human herpesvirus 6 infection after hematopoietic cell transplantation: is routine surveillance...


Fatal Myocarditis Associated With HHV-6 Following Immunosuppression in Two Children
Heather E Stefanski, Kathryn A Thibert, Joshua Pritchett, Bhupesh K Prusty, John E Wagner and Troy C Lund

Pediatrics 2016;137; DOI: 10.1542/peds.2015-1352 originally published online December 17, 2015;
Fatal Myocarditis Associated With HHV-6 Following Immunosuppression in Two Children
Heather E Stefanski, Kathryn A Thibert, Joshua Pritchett, Bhupesh K Prusty, John E Wagner and Troy C Lund
Pediatrics 2016;137;
DOI: 10.1542/peds.2015-1352 originally published online December 17, 2015;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/137/1/e20151352