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Acute Myocarditis Secondary to Reactivated Chromosomally-Integrated Human Herpesvirus 6

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To the Editor

Human herpesvirus 6 (HHV-6) encompasses 2 closely related herpesviruses, HHV-6A and HHV-6B, that have combined seroprevalence of >90% in adults.¹ Chromosomally-integrated HHV-6 (ciHHV-6) is a rarer condition in which the complete genome of the virus is integrated into the host germline genome.¹ HHV-6 as a cause of dilated cardiomyopathy has been reported,² however, ciHHV-6 myocarditis is less common, and its diagnosis and management differ. Moreover, the presentations of the 2 are similar, underscoring the importance of a correct diagnosis. In this presentation, we report a case of ciHHV-6 myocarditis successfully treated with the use of antiviral therapy.

Case Report

A 17-year-old man presented with dilated cardiomyopathy, multiple endocrinopathies, and common variable immunodeficiency disorder requiring monthly intravenous immunoglobulin infusions. Three years earlier, he presented with fever, cough, dyspnea, and chest pain. He was intubated for respiratory failure and developed shock, requiring vasopressors and inotropes. Transthoracic echocardiography (TTE) showed a left ventricular ejection fraction (LVEF) of 10%. With aggressive treatment, LVEF improved to 45% and viral myocarditis was presumed without further testing.

On this admission, he presented with fever, chills, confusion, and hypotension (77/40 mm Hg). He had mild leukocytosis of $12.3 \times 10^3/\mu\text{L}$ (23% bands), N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 13,000 pg/mL, and sinus tachycardia. He was intubated for respiratory failure, and dopamine and milrinone were given for mixed septic and cardiogenic shock. Right heart catheterization on these inotropes showed normal intracardiac filling pressures with preserved cardiac index. Quantified LVEF was 27% on TTE. Cardiac magnetic resonance imaging (CMR) showed severely dilated left ventricle, LVEF of 32%, transmural late gadolinium enhancement involving the anterolateral, inferior, and mid-anterior walls, and increased T2 signal indicating inflammation, all strongly suggesting acute myocarditis (Fig. 1). Blood cultures were negative, but HHV-6 polymerase chain reaction (PCR) of whole blood demonstrated a viral load of >2 million copies/mL. Two days after admission, ganciclovir was started for presumed HHV-6 myocarditis. Within 5 days, the patient was extubated, inotropes were weaned, and mentation normalized. TTE 3

weeks later showed improvement of quantified LVEF to 45%. On discharge, NT-proBNP improved to 1000 pg/mL. Endomyocardial biopsy (EMB) performed 6 weeks later demonstrated negative viral PCR.

Despite clinical improvement with ganciclovir, whole-blood HHV-6 PCR titers remained elevated. Suspicion arose for ciHHV-6, thus HHV-6 mRNA levels were obtained. However, by then, he was adequately treated and mRNA levels were undetectable. After discharge, the patient was treated with valganciclovir for 6 months with monitoring of HHV-6 mRNA levels, which remained undetectable, indicating continued resolution of active infection. The patient's brother had blood samples analyzed that also revealed high viral load, further strengthening the diagnosis of ciHHV-6.

Discussion

Chromosomally-integrated HHV-6 is a genetic disorder with mendelian inheritance such that families with 1 carrier have a 50% chance of passing on the condition to each child.³ The true prevalence of ciHHV-6 is unknown, although small studies conducted in Japan and the United Kingdom reported a prevalence of 0.2% to 0.8%, respectively.^{4,5} Furthermore, several small studies show a higher prevalence in immunocompromised patients.¹

Accurately identifying patients with ciHHV-6 is important to avoid unnecessary treatment. Because of complete genomic integration, clinical specimens contain HHV-6 DNA and have characteristically high viral loads.⁶ When ciHHV-6 is suspected, diagnosis is confirmed by means of quantitative PCR using whole blood or isolated peripheral blood mononuclear cells. Individuals with ciHHV-6 have 1 HHV-6 genomic copies per white blood cell, corresponding to >5.5 log₁₀ copies/mL. High levels of viral copies persist over time and are unreliable for following disease activity.^{4,6,7} In a small study evaluating children with congenital HHV-6 infection, those with ciHHV-6 had whole-blood mRNA HHV-6 detected whereas those with transplacental HHV-6 did not.⁷ Measurement of HHV-6 mRNA levels can, therefore, be more accurate for following infection activity.

In a study assessing prevalence and treatment of ciHHV-6, 1656 patients with unexplained symptoms of heart failure underwent EMB to evaluate for presence of HHV-6. HHV-6 was detected in 273 patients (16.5%), and 19 (1.1%) had persistently high HHV-6 viral loads indicative of ciHHV-6. In 6 patients with persistent symptoms and confirmed ciHHV-6, treatment with 900 mg/d valganciclovir for 6 months led to resolution of symptoms.⁸ Serial mRNA levels were followed to monitor infection activity, and a direct correlation was seen between heart failure symptoms and HHV-6 mRNA levels.⁸

Herein, we present a case that demonstrates the complexities in diagnosis and management of patients with ciHHV-6 myocarditis. Although the preceding history of viral myocarditis in our patient was presumed, the similar presentations enhanced our clinical suspicion for recurrence. The elevated titers of HHV-6 according to PCR and CMR imaging suggestive of myocarditis prompted treatment for HHV-6. Despite clinical improvement with treatment, titers remained elevated, urging us to consider reactivated ciHHV-6 as an etiology. Furthermore, the importance of the patient's immunocompromised state should be

emphasized, because these patients have greater potential for ciHHV-6 reactivation¹ and likely require longer durations of treatment.

It must be noted that there is diagnostic ambiguity in our case that centers on the lack of detection of HHV-6 mRNA with ensuing improvement in levels with treatment. In addition, EMB performed during a subsequent hospitalization was negative for viral PCR, but it was done after adequate treatment. Despite this, several features of our case clinch the diagnosis of ci-HHV6: 1) recurrence of viral myocarditis in an immunocompromised patient, 2) persistently high viral load despite treatment and clinical improvement, and 3) high viral load in the patient's asymptomatic brother.

There are several learning points to note from this case. Screening for HHV-6 in acute myocarditis is crucial for prompt diagnosis and treatment. One should consider ci-HHV6 with persistently elevated titers in whole blood, and following mRNA levels is more accurate for following infection activity. Conversely, it is important to recognize that high titers in asymptomatic patients do not require treatment unless mRNA levels indicate active infection. Finally, reactivation of ciHHV-6 is more common in immunocompromised patients, and these patients require longer durations of treatment and close follow-up for symptom recurrence.

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Fig. 1. Myocardial late gadolinium enhancement noted in basal to apical anterolateral and inferior walls.