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Case study

Human herpesvirus 6–related fulminant myocarditis and hepatitis in an immunocompetent adult with fatal outcome

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Summary A 59-year-old previously healthy man had flulike symptoms of fever and diarrhea for a week, which worsened despite treatment with antibiotics. After admission, his medical condition rapidly deteriorated with renal failure, heart failure, and a marked increase of aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. The patient died of a cardiac arrhythmia 3 days after the admission. The autopsy showed diffuse myocarditis with a granulocytic and monocytic infiltrate, necrotizing arteritis of the coronary arteries, and fulminant hepatitis, with microvesicular steatosis and necrosis. Cell-free serum showed high copies of human herpesvirus 6 B variant DNA by polymerase chain reaction. Human herpesvirus 6 B was identified in the heart, liver, lung, and spleen by immunohistochemistry. No parvovirus B19 was evident in the heart by immunohistochemistry. Human herpesvirus 6 is increasingly found in association with myocarditis in immunocompromised patients; however, histopathologic features and the clinical severity of this disease have not yet been clearly defined. Only 4 to 5 cases of human herpesvirus 6 fulminant myocarditis have been reported, all in young children or immunosuppressed patients. To the best of our knowledge, this is the first case in the English literature of human herpesvirus 6 fulminant myocarditis and hepatitis in an immunocompetent adult with a fatal outcome. In addition, several pathologic features of our case have not been previously reported.

1. Introduction

Although myocarditis is commonly a chronic disease and may be associated with end-stage cardiac failure, it is well documented that myocarditis may be a major cause of sudden unexpected death in adults [1,2]. When acute viral myocarditis is suspected on the basis of clinical and pathologic findings, the specific etiologic agent is often difficult to detect. So far, viruses are the most common identifiable causes of myocarditis in the United States and European countries. Coxsackie, enterovirus, and adenovirus are known as common pathogens for viral myocarditis. Evidence increasingly suggests that human herpesvirus 6 (HHV-6) is underestimated as an important cause for viral myocarditis in Western countries, and it may have a less favorable prognosis than other known viruses [2-5]. HHV-6 myocarditis is often clinically underestimated in practice, likely because of a lack of clinical awareness. We hope that this report will help to raise awareness for this disease and further improve pathologic diagnosis and patient care in our community.

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2. Case report

A 59-year-old man was admitted to the hospital in February with complaints of fever, diarrhea, abdominal pain, and malaise. His medical history was unremarkable. Four days before the admission, he developed a nonproductive cough, fatigue, fever, and abdominal pain. He took Tamiflu and Levaquin for 1 day, and shortly after, the patient developed rashes with worsening diarrhea and persistent fever. He denied bloody or dark stools or chest pain. Physical examination showed a temperature of 39°C, heart rate of 118/min, blood pressure of 93/41 mm Hg, respiratory rate of 27/min, and dehydration. Chest x-ray suggested early heart failure, with no evidence for pneumonia. Hematologic and chemical tests showed white blood cell count of 18 600/μL with neutrophilia, Hb of 13.5 g/dL, serum urea nitrogen of 32 mg/dL, and creatinine of 2.5 mg/dL. Electrocardiogram revealed nonspecific ST changes and tachycardia. Microbiologic screening tests were negative for *Clostridium difficile* toxin, influenza antigen, and streptococcal antigen. The initial diagnosis was of septic shock syndrome, with multiorgan failure. On day 2, the serum urea nitrogen and creatinine rose to 50 and 4.9 mg/dL, respectively, white blood cell count rose to 20 900/μL, and Hb dropped to 11.8 g/dL. B-type natriuretic peptide was markedly increased to 1100 pg/mL with total creatine kinase in the reference range, increased aspartate aminotransferase of 330 U/L, alanine aminotransferase of 153 U/L, and coagulopathy. Blood culture yielded no bacterial or fungal growth. Fecal cultures for *Escherichia coli* 0157, *Salmonella*, *Yersinia*, and *Campylobacter* were negative. Viral cultures and rapid respiratory viral screen were negative. Viral hepatitis panel showed no evidence of acute viral hepatitis A, B, or C. During his hospital course, the patient was primarily treated with vancomycin and Flagyl for a suspected unidentified bacterial infectious disease. With aggressive supportive therapy and hemodialysis, the creatinine declined to 2.4 on day 2, without overall significant improvement. On day 3, serum aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase rose to 4880, 1320, and 7950 U/L, respectively. He developed a ventricular arrhythmia and died on the same day.

3. Materials and methods

3.1. Immunohistochemistry

To localize HHV-6 B variant (HHV-6B) and parvovirus B19 (B19), we performed immunohistochemistry (IHC) for HHV-6B on the heart, liver, lung, spleen and kidney, and B19 on the heart. We also performed IHC of hepatitis C on the liver. Our protocol has been previously published [1]. We used the Benchmark LT automated system from Ventana Medical Systems, Tucson, AZ. In brief, optimal conditions were determined to be a dilution of 1:250 with pretreatment in protease 1 for 4 minutes. We used primary monoclonal antibody against HHV-6B (MAB 8535; Chemicon, Temecula, CA), the monoclonal antibody against B19 and hepatitis C (Ventana Medical Systems), tested according to the manufacturer's recommendations. The antigen was detected with the Ultraview Universal DAB system from Ventana with a counter stain of hematoxylin. The negative controls included human heart (from a patient who died of an acute myocardial infarction 12 hours before the death) and human liver (from a patient who had hepatitis C–related acute hepatitis).

4. Results

4.1. Histopathologic findings

The heart weights 540 g, with mild left ventricular dilatation. Histologic sections demonstrated diffuse interstitial and intramyocardial fiber inflammation in both left and right ventricles (Fig. 1). The inflammatory infiltrate consisted of numerous granulocytes, mononuclear cells, and scattered eosinophils, and involved the full thickness of the myocardium. Focal myocytolysis and necrosis were noted. No giant cells, granulomas, or old infarction was identified. A mixed inflammatory infiltrate and cellular necrosis were seen in the adventitia and external elastic layers of the medium-sized coronary artery branches, moderate to severe. Similar adventitial inflammation was focally noted in the small muscular arteries of the spleen and kidney. Pathologic changes of endothelial cells in these vessels were unable to

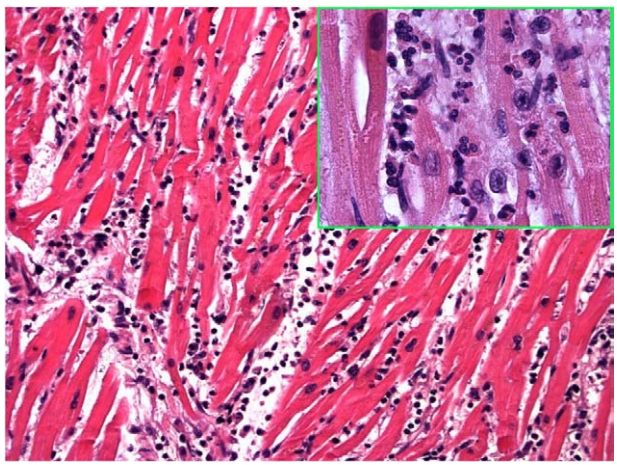

Fig. 1 Fulminant myocarditis shows extensive interstitial and intramyocardial inflammatory infiltrates, composed principally of granulocytes, mononuclear cells, and eosinophils (hematoxylin and eosin stain, original magnification ×100). Inset: granulocytes, lymphocytes, and rare eosinophils with macrophages (hematoxylin and eosin stain, original magnification ×1000).