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Human Herpesvirus 6 Reactivation: A Rare Case of Acute Liver Failure and Literature Review

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Abstract

Acute hepatitis is a frequent cause of admission to intensive care unit (ICU). The differential diagnosis is broad and determining the etiology can be challenging. We report a 68-year-old immunocompromised patient who developed acute liver failure associated with pericardial effusion who was diagnosed with human herpesvirus 6 (HHV-6) reactivation. The diagnosis was made by a positive real-time PCR (rPCR). After an extensive hepatitis workup with viral, toxic and autoimmune investigations and after exclusion of an inherited chromosomally integrated HHV-6 by rPCR of the fingernails, no convincing alternative diagnosis was found. The evolution of transaminases and viremia monitoring by quantitative PCR under antiviral treatment is described. Although HHV-6 reactivation is a very rare cause of acute hepatitis and is difficult to diagnose, fulminant hepatitis is one of the most common complications of HHV-6 reactivation. Since acute liver failure can lead to specific medical interventions, to liver transplantation, or can be fatal, the diagnosis of HHV-6 should be systematically considered, and early detection can lead to a better prognosis.

Keywords: HHV-6 Reactivation; Hepatitis; Immunocompromised; Pericardial Effusion

Background

Acute hepatitis is a frequent cause of admission to intensive care unit (ICU). The differential etiologic diagnosis of acute hepatitis is wide, and pinpointing the actual cause can be challenging. Classical causes of acute hepatitis are viral infections, drugs, alcohol and immune diseases [1]. HHV-6 is a rare but sometimes severe cause of acute hepatitis, and is observed mainly either in young children in the setting of primary infection, or in immunosuppressed pediatric and adult patients following uncontrolled viral reactivation. While some antiviral treatments have been proposed for HHV-6 hepatitis management, the optimal therapy is not well defined. We present here a case of acute HHV-6 hepatitis in a patient on immunosuppressive treatment with a review of the literature on this topic.

Case Presentation

A 68 year-old man with a history of seronegative polyarthritis was admitted to the emergency room with dyspnea, nausea, vomiting and diarrhea for two days. His medical treatment consisted of prednisone 30 mg daily (tapering regimen) and of recently introduced methotrexate 15 mg daily. His vital signs showed tachycardia of 100 beats per minute, normal blood pressure and temperature, and decreased oxygen saturation requiring oxygen

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therapy (4l/min via nasal cannulae). Clinical examination revealed lower limb edema and disseminated skin rash. Blood tests revealed leukocytosis (22.6 G/l), thrombocytopenia (68 G/l), elevated C-reactive protein (CRP, 132mg/l), acute renal failure (KDIGO3, creatinine 223umol/l, eGFR 23ml/min/m^2), elevated liver enzymes (ASAT > 7000U/l, ALAT 5121 U/l, GGT 340U/l) and normal bilirubin. Coagulation tests indicated reduced factor V levels (12%), increased INR (2.59), low Quick (24%), and prolonged PTT (47,7 seconds). The arterial blood gas analysis showed metabolic acidosis (pH 7.28, lactates 8 mmol/l). Abdominal ultrasound showed signs of a congestive liver with hyperechogenic hepatomegaly, modulated portal vein flow and reflux into the suprahepatic veins. The CT-scan also showed an enlarged liver with discrete heterogeneous parenchyma, periportal edema and vesicular wall infiltration (Figure 1). It also revealed a circumferential pericardial effusion up to 14 mm thick around the left ventricle and a moderate pleural effusion. A subsequent echocardiography was performed, which confirmed the pericardial effusion of 15 mm, without signs of compression of the right heart cavities and a normal biventricular function (Figure 2). A diagnosis of acute liver failure (ALF) of yet undetermined origin was retained. A broad ALF investigation workup including virological, autoimmune and toxic tests was performed. The differential diagnosis of hypoxic hepatitis was also considered. N-acetyl-cysteine and empirical IV acyclovir treatment (10mg/kg twice daily) were initiated and the patient was admitted to the ICU. He rapidly developed multi-organ failure with impaired consciousness requiring orotracheal intubation and mechanical ventilation, anuria with hypervolemia treated with continuous veno-venous hemofiltration, and arterial hypotension requiring vasopressor medication. 24 hours after admission, an echocardiography showed an increase of the pericardial effusion with compression of the right cavities. A pericardial drainage allowed the release of 60 ml of serum. The results of the biological examination revealed a positive HHV-6 real-time PCR (rPCR) (quantified at 44000 copies/ml). HHV-6 serology was positive for IgG and negative for IgM, indicating past infection. The rPCR of HHV-6 from a serum sample taken 28 days earlier was negative, as was the HHV-6 rPCR performed on the patient's fingernails, thus ruling out inherited chromosomally integrated HHV-6 (iciHHV-6). HHV-6 detection by rPCR in the hemorrhagic pericardial fluid was positive (CT value 39.3). Investigations for other causes of viral hepatitis as well as paracetamolemia and the autoimmune workup were negative. HHV-6 reactivation associated with the newly introduced immunosuppressive drug (i.e. methotrexate) in addition to ongoing corticosteroid therapy leading to ALF, was retained. Antiviral treatment was changed to ganciclovir 2,5mg/kg/12h (dosage adapted to renal function), and the methotrexate treatment was interrupted. The clinical and biological evolution was excellent within five days of starting ganciclovir therapy (Figure 3). Indeed, the patient regained consciousness, allowing extubation, and liver enzymes, coagulation parameters and kidney function returned to normal. The total duration of treatment was three weeks. The rheumatologists suggested reducing prednisone therapy in view of this infectious event and recommended starting anti-IL-6 therapy six weeks after this acute event.

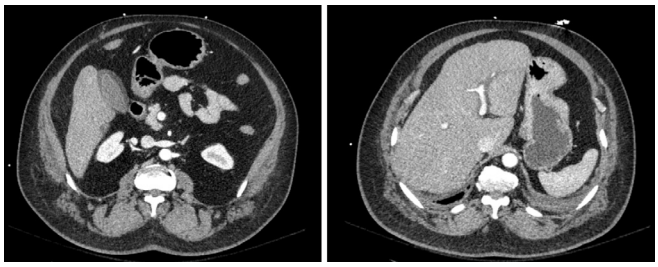

Figure 1: CT-scan with IV contrast injection showing an enlarged liver with discretely heterogeneous parenchyma, periportal edema and vesicular wall infiltration.

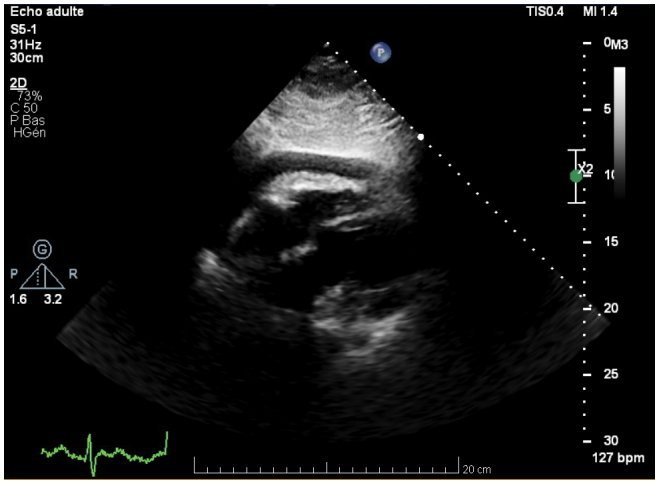

Figure 2: Transthoracic echocardiography-subcostal four-chamber view: pericardial effusion of 14 mm, without signs of compression of the right heart cavities and normal biventricular function.

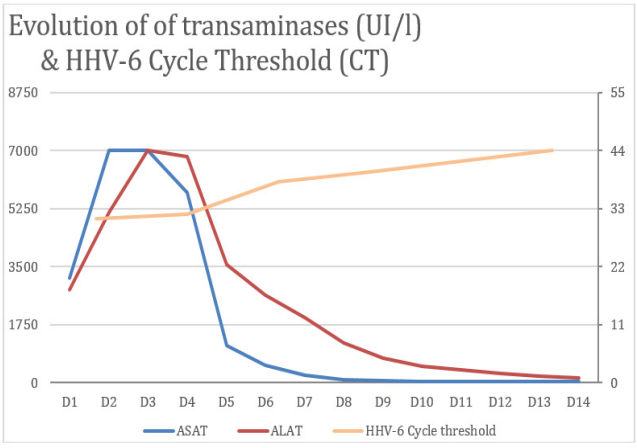

Figure 3: HHV-6 viral load assessed by rPCR CT values and liver tests over time. Ganciclovir treatment was started on day 1 (D1).

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Discussion

In this paper, we describe the case of a patient who developed ALF in the context of the introduction of immunosuppressive therapy with methotrexate. This case illustrates how difficult it is to make a clear diagnosis in some cases of ALF, as the cause is sometimes due to several mechanisms. The definitive diagnosis in our case report probably results from a mixed origin: on the one hand, a viral hepatitis component following reactivation of HHV-6 in the context of immunosuppression and, on the other hand a hypoxic hepatitis component as a consequence of the pericardial effusion. There are only a few case descriptions of HHV-6 ALF in the literature [2]. The present case is unique in that it is the only one to describe the association of ALF with concomitant pericardial effusion and to show the evolution of viremia under treatment. HHV-6 belongs to the *Herpesviridiae* family and the *Betaherpesviriniae* subfamily, to the *Roseolovirus* genus, and is divided into two distinct species, HHV-6A and HHV-6B. It shares a lot of genomic and phenotypic similarities with CMV [3]. HHV-6 is worldwide prevalent and is mainly acquired in early childhood. Studies report rates of more than 90% in children over 2 years of age [4,5]. The exact mode of transmission is not yet fully understood, but close contact, saliva and urine are supposed to be part of the spreading [5]. Primary infection in children is usually asymptomatic or causes only mild disease (Roseola infantum, or sixth disease) [3]. The virus infects various cells, such as brain and liver tissue, salivary glands, endothelium, T cells and macrophages [6]. The virus subsequently persists lifelong in a latent form, as do herpesviruses in general [3]. Viral reactivations are usually controlled by cellular immunity, but can manifest clinically in various forms in the context of immunosuppression [6,7]. Current literature describes cases of encephalitis, retinitis, temporal lobe epilepsy or neurocognitive disorders in the context of HHV6 reactivation [8,9]. Cases of myocarditis [10,11] have also been described, as well as gastro-intestinal disorders, hepatitis [12,13], gastroenteritis [7)] or colitis. Some patients developed pneumonitis or drug-induced hypersensitivity syndrome [14]. All these presentations can be fatal [6]. Importantly, these severe courses occur mainly in severely immunosuppressed patients, typically hematopoietic transplant and solid organ recipients. The severity of HHV-6 reactivation in this case of an apparently moderately immunosuppressed patient (methotrexate and prednisone therapy) is therefore surprising. In the case of a positive HHV-6 PCR result that is not due to a primary infection, it must be first determined whether or not it is explained by inherited chromosomally integrated HHV-6 (iciHHV-6). In fact, HHV-6 is capable of chromosomal integration into the telomeric region of a germline host cell, resulting in the Mendelian inheritance of the viral DNA, of which at least one copy is present in all nucleated cells [15,16]. Fingernails or hair follicles can be tested by qualitative polymerase chain reaction (PCR) to identify iciHHV-6 as direct expression of host germ cell DNA [3,15,17]. When iciHHV-6 has been ruled out, it is then necessary yet sometimes tricky to assess the causality between HHV-6 replication and the patient's clinical picture. In our case, the patient's hepatitis has been linked to HHV-6 reactivation, since this virus is known to cause hepatic injury in the context of immunosuppression, and because no convincing alternative cause was identified despite an extensive etiologic work-up. Regarding antiviral therapy, because of the similarity with the CMV, antivirals with a similar spectrum of activity are usually used [3]. There are three molecules which have been studied to treat HHV-6 active infections: cidofovir, ganciclovir and foscarnet [3,6]. Considering their safety profile and *in vitro* activity, foscarnet 90 mg/kg IV every 12 hours and ganciclovir 5 mg/kg IV every 12 hours for three to four weeks, which must be adapted to renal function, are the first-line treatments chosen in Switzerland [3,19,20]. This treatment options have been used for HHV-6 reactivation mainly in transplanted patients, and there is little literature on non-transplant patients. Since these infections are rare and a final causality by HHV-6 is often difficult to establish, it remains unclear when and how an antiviral treatment against HHV-6 should be started. In a recent literature review [3] the authors suggest initiating treatment when 1) viral load is high and ici-HHV-6 is not present, 2) there is a context of immunosuppression, 3) HHV-6 appears to be the cause of the observed clinical findings, and 4) there is no other more likely cause. In addition to clinical response, monitoring viral load by quantitative PCR allows to confirm the antiviral's efficacy, or on the contrary to suspect antiviral resistance [3]. In addition to antiviral treatment, immunosuppressive therapy should be reduced whenever possible [3].

Conclusion

Although reactivation of HHV-6 is a rare cause of acute liver failure, it should be considered as a cause in immunocompromised patients with acute liver failure of undetermined origin. There is little literature on the most appropriate antiviral treatment for HHV-6-induced ALF. This case illustrates the potential usefulness of ganciclovir for a favorable clinical outcome.

Disclosure Statement

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