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Clinical Case Study

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Acute Liver Failure and Human Herpesvirus 6 Infection: Reactivation in Immunoparesis?

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Keywords
Acute liver failure · Human herpesvirus 6 · Malnutrition · Immunoparesis

Abstract

Introduction: HHV-6 infection is usually asymptomatic or self-limited, although in certain populations, particularly in immunocompromised patients, it can cause serious infections. Hepatic involvement, previously described in immunocompromised and occasionally in immunocompetent adults, can lead to acute liver failure (ALF). ***Case Presentation:*** We report a case of a 20-year-old female with no known liver disease, who presented with a 4-day history of diffuse abdominal pain, vomiting, and fever on the first day. She reported an influenza-like syndrome the previous week and undetermined weight loss over the last 2 months, associated with a behavior compatible with a purging eating disorder. She had a binge drinking pattern of alcohol consumption, followed by paracetamol intake for veisalgia, and occasional cannabinoid use. The patient denied other exposures. She developed grade 1 hepatic encephalopathy and was diagnosed with ALF. Further workup for underlying etiology detected HHV-6B, both in peripheral blood and liver tissue. ***Discussion:*** This ALF has a viral cause due to a possible reactivation of HHV-6 in the context of immunoparesis secondary to malnutrition and binge drinking, though we cannot exclude a contribution from a toxic cause due to paracetamol overuse, facilitated by these same susceptibility factors. HHV-6 should be included in the differential diagnosis of ALF of undetermined cause, particularly in immunocompromised and seriously ill patients.

Falência Hepática Aguda e Infeção por Herpes Vírus 6: Reativação em contexto de Imunoparesia?

Palavras Chave
Falência hepática aguda · Vírus herpes humano tipo 6 · Malnutrição · Imunoparesia

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Resumo

Introdução: A infeção pelo HHV-6 é geralmente assintomática ou autolimitada, embora em certas populações, particularmente em doentes imunocomprometidos, possa causar infeções graves. O envolvimento hepático, já descrito em imunocomprometidos e ocasionalmente em adultos imunocompetentes, pode conduzir a falência hepática aguda (ALF). ***Apresentação do caso:*** Descrevemos o caso de uma mulher de 20 anos, sem doença hepática conhecida, que apresentou dor abdominal difusa e vómitos com 4 dias de evolução e febre no primeiro dia. Referiu síndrome gripal na semana anterior e perda ponderal indeterminada nos últimos 2 meses, associada a comportamento compatível com um distúrbio alimentar purgativo. Tinha consumo alcoólico em padrão de *binge drinking*, seguido da ingestão de paracetamol na veisalgia, e consumo ocasional de canabinóides. Sem outras exposições de risco. A doente desenvolveu encefalopatia hepática de grau 1 e foi diagnosticada com ALF. O estudo etiológico identificou HHV-6B no sangue periférico e tecido hepático. ***Discussão:*** Esta ALF tem uma causa vírica devido a uma possível reativação de HHV-6 em contexto de imunoparesia secundária a malnutrição e *binge drinking*, embora não se possa excluir a eventual contribuição de uma causa tóxica, por toma mantida de paracetamol, facilitada pelos mesmos fatores de suscetibilidade. A pesquisa de HHV-6 deve ser incluída no diagnóstico diferencial de falência hepática aguda de causa indeterminada, principalmente em doentes imunocomprometidos ou com infeção grave.

Introduction

Acute liver failure (ALF) is an uncommon and often heterogeneous presentation of severe liver dysfunction in a patient with otherwise no pre-existing liver disease [1]. Common causes of ALF include viral infection, drug toxicity, and vascular disorders. Approximately 15% are of unknown cause in adults [2].

Human herpesvirus 6 (HHV-6) is a beta-herpesvirus with a wide cell tropism in vivo [3, 4]. It refers to the two identified species, HHV-6A and HHV-6B [4, 5], the latter being more common [4–6]. Serological prevalence in the adult population is more than 90% in developed countries [4].

HHV-6 infection is usually asymptomatic or self-limited, although in certain populations, particularly in immunocompromised patients, it can cause serious infections [3–5]. Primary infection is the cause of *exanthema subitum* in infants and a mononucleosis-like syndrome in older children and adults [4–6]. Primary infection in the adult is rare [4–6]. Other clinical manifestations associated with HHV-6 have been described, such as encephalitis, pneumonitis, and hepatitis [4–6]. ALF due to HHV-6 has been reported, sometimes with a fatal outcome [3, 6–9], and rarely in immunocompetent adults [3, 8, 10]. Like other herpesviruses, HHV-6 can remain latent and reactivate later throughout the host's lifespan [4–6]. It is believed that primary HHV-6B infection occurs first and is frequently symptomatic, whereas HHV-6A is acquired later, through asymptomatic infection [4, 5]. However, given the possibility of reactivation of the virus in the setting of ALF, the pathogenic role of HHV-6 as a causative agent is still difficult to demonstrate [3, 4]. According to current consensus, fulminant hepatitis is the direct result of marked apoptosis of hepatocytes induced by overproduction of cytokines and free radicals, which are released in response to viral infection [11].

Case Report

A 20-year-old female presented to the emergency department with diffuse abdominal pain and vomiting in the last 4 days, with a temperature of 38.4°C on the first day. She described choluria without acholia. She had taken paracetamol for symptom relief. One week before, she had an influenza-like syndrome. She also complained of undetermined weight loss over the last 2 months but described habits that raised the suspicion of a purging eating disorder.

Her past medical history consisted of a depressive episode and self-injurious behaviors. The patient reported occasional cannabinoid use, alcohol consumption in a binge drinking pattern, followed by the intake of 3 g of paracetamol per day, three times a week, in the context of veisalgia. Her history was negative for other medications, supplements, herbal products, mushrooms, recent travel, or risky sexual behaviors.

On physical examination, the patient was vigil and oriented, underweight (body mass index 16.2 kg/m^2), with skin pallor, scleral icterus, and traces of gum hemorrhage. Her abdominal exam was remarkable for tenderness in the right upper quadrant and hepatomegaly with the liver edge palpable approximately 2 cm below the right costal margin. She developed grade 1 hepatic encephalopathy, namely, with mild change in behavior, alternation of sleep-wake rhythm, and drowsiness.

Pertinent blood tests (Table 1) included aspartate aminotransferase (AST) of 1,431 U/L, alanine aminotransferase

Table 1. Laboratory data

Parameter	Admission	Maximum/minimum value	Reference range
Complete blood count			
White blood cell count	6.6 G/L	Minimum of 3.8 G/L	3.6–10.5 G/L
Hemoglobin	13.7 g/dL	Minimum of 10.4 g/dL	11.8–15.8 g/dL
Platelet count	292 G/L	Minimum of 129 G/L	150–400 G/L
Blood chemistry			
AST	1,431 U/L	Maximum of 7,053 U/L (202× ULN)	<35 U/L
ALT	1,527 U/L	Maximum of 5,685 U/L (126× ULN)	<45 U/L
Lactate dehydrogenase	1,288 U/L	7,913 U/L	<247 U/L
Alkaline phosphatase	59 U/L	64 U/L	30–120 U/L
γ-Glutamyl transpeptidase	63 U/L	504 U/L	<55 U/L
Albumin	4.7 g/dL	Minimum of 2.8 g/dL	3.5–5.2 g/dL
Ammonia	139 μmol/L	Maximum of 231 μmol/L	18–72 μmol/L
Total bilirubin	2.0 mg/dL	2.2 mg/dL	0.2–1.2 mg/dL
Conjugated bilirubin	1.1 mg/dL	1.4 mg/dL	<0.5 mg/dL
C-reactive protein	1.03 mg/dL	1.22 mg/dL	<0.5 mg/dL
Coagulation			
INR	>1.5 (2.95)	Maximum of 3.31	–
Factor V	13%	Minimum of 8.4%	50–150%
Factor VII	5.3%	Minimum of 5.3%	50–150%

ULN, upper limit of normal.

(ALT) of 1,527 U/L, alkaline phosphatase of 59 U/L, total bilirubin of 2.0 mg/dL, conjugated bilirubin of 1.1 mg/dL, normal albumin, and international normalized ratio (INR) of 2.95 (above 1.5). Renal function and electrolytes were normal. Arterial blood gas analysis showed a discrete acute respiratory alkalosis and a lactate level of 2.76 mmol/L. She progressed with worsening liver chemistries. Liver cytolysis reached 202 times the upper limit of normal (ULN) for AST and 126 times the ULN for ALT. She developed hypoalbuminemia, pancytopenia, and worsened coagulopathy and hyperammonemia.

The diagnosis of ALF of yet undetermined cause was established. Etiological laboratory workup (Table 2) included paracetamol level upon admission of 19.28 μg/mL, considered in a safe range for a non-risk population. The remaining results were negative except for HHV-6B quantitative real time polymerase chain reaction (PCR) that was 1,054 copies/mL.

Abdominal ultrasound showed thickening of the gallbladder wall and a small amount of perihepatic fluid, aspects suggestive of acute hepatitis. Computed tomography of the chest and abdomen with intravenous (IV) contrast injection (shown in Fig. 1) revealed a globular liver, with dimensions at the ULN and regular contours, along with a marked, diffuse, and spontaneous reduction in parenchymal density, consistent with severe steatotic infiltration. Discrete and diffuse heterogeneous enhancement with signs of periportal edema was also shown, as well as marked edematous thickening of vesicular wall. The described aspects support acute hepatitis phenomena.

Considering ALF, the patient's case was signaled and discussed with the liver transplant unit. IV infusion of N-acetylcysteine (NAC) was initiated to enhance recovery, and the patient was admitted to a medical intermediate care unit. During hospitalization, she was submitted to ophthalmological evaluation that did not observe Kayser-Fleischer rings, nor other signs of copper deposition. A transjugular liver biopsy was performed using a 19-gauge needle, yielding two fragments with a total length of 20 mm. Histological evaluation (shown in Fig. 2) reveals seven portal tracts with mild mixed inflammatory infiltrate. There is significant lobular disarray due to confluent necrosis affecting acinar zones 3 and 2, with centro-central lobular bridging and mild associated mononuclear inflammatory infiltrate. Preserved hepatocytes exhibit hepatocanalicular cholestasis and mild macrovesicular steatosis. Frequent mitoses and karyorrhexis are observed. No viral inclusions were identified. Immunohistochemical analysis for HSV-1 and HSV-2 was negative, and PCR analysis detected HHV-6B in the liver specimen (viral load quantification was not possible as the tissue had already been processed).

Table 2. Etiological study

Infectious causes	
Blood and urine cultures	Negative
HAV, HBV, HCV, HEV, HSV 1/2, EBV, CMV, enterovirus, adenovirus, parvovirus, HIV 1/2, *Coxiella burnetii*, *Leptospira, Borrelia burgdorferi, Rickettsia conorii*, *Brucella*, rubella, *Toxoplasma*, and syphilis serologies	Negative
HHV-6 DNA in the blood (by quantitative real-time PCR)	HHV-6B with 1,054 copies/mL
Toxic causes	
Paracetamol at admission	19.28 µg/mL
Hereditary/metabolic causes	
Alpha-1 antitrypsin	1.73 g/L (N: 0.90–2.00)
Serum ceruloplasmin	0.26 g/L (N: 0.20–0.60)
Urinary copper	0.146 mg in 24 h (N: <0.1)
Autoimmune causes	
Antinuclear, anti-ds-DNA, and antineutrophil cytoplasmic antibodies	Negative
Antimitochondrial, anti-smooth muscle, liver-kidney microsome, anti-soluble liver antigen, and anti-liver cytosol antibodies	Negative
Immunoglobulin M	Normal

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HHV-6, human herpesvirus 6; HIV 1/2, human immunodeficiency virus 1 and 2; HSV 1/2, herpes simplex virus 1 and 2.

Given the beneficial effects of NAC that do not seem to be unique to paracetamol hepatotoxicity [12], she completed a 10-day course of IV infusion of NAC. The patient had, then, a favorable clinical and analytical evolution, with nearly normalized liver enzymes at discharge. Antiviral drugs active against HHV-6 were not started due not only to the risk of drug toxicity but also to the late viral detection, when a significant decrease in cytolysis markers had been reached.

The patient was also evaluated by psychiatry, and the suspected diagnosis of purging-type anorexia nervosa was confirmed, along with alcohol and paracetamol overuse, without exclusion of self-harm intention. She was urgently referred for follow-up with psychology and psychiatry specialized in eating disorders.

Discussion

This case report describes the case of a young adult patient who developed ALF that was facilitated by a context of immunoparesis. This patient's malnutrition and alcohol consumption are susceptibility factors to infection and to liver toxicity. Malnutrition influences the immune system through epigenetic changes, impaired T-cell function, and disruption of the gut microbiota. These effects lead to a compromised immune system, increasing individuals' vulnerability to infections and other diseases [13]. Additionally, binge drinking increases the risk of infection [14].

Since we have detected HHV-6B in peripheral blood and in liver tissue, this infection was considered the possible cause of the ALF. This patient's fever, thrombocytopenia, leukopenia, anemia, and hepatitis are manifestations consistently associated with HHV-6 infections [4]. The temporal association between the acute phase of illness and the evidence of viremia by PCR supports an active infection by HHV-6B. Viral loads above 1,000 copies per mL of whole blood correspond to active infections [4]. However, one must exclude chromosomally integrated HHV-6 (ciHHV-6; found in 0.2–1% of the adult population), which is usually associated with viremia exceeding 1 million copies per mL [4]. Although this patient's viral load was not in this range of values, we did not test for the presence of ciHHV-6, and this can be a limitation of our case. Immunosuppression is the major factor promoting endogenous HHV-6 reactivations, with possible hepatic injury [4]. However, we cannot determine if this is a primary infection (though unlikely given the patient's age), an endogenous reactivation, or an exogenous reinfection. Also, the unavailability of HHV-6 antibody testing at our center did not help us in this issue.

Therefore, the patient's immunoparesis in the context of malnutrition and binge drinking, the chronology of clinical symptoms associated with an HHV-6B viral load

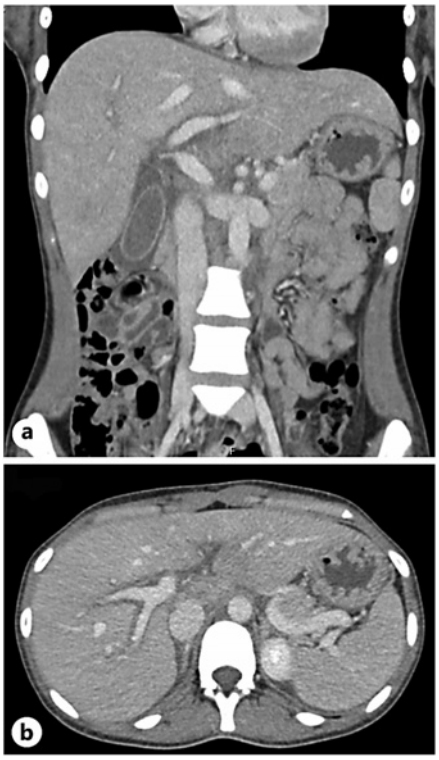

Fig. 1. Abdominal CT with IV contrast injection showing a globular liver, with dimensions at the ULN, along with a marked and diffuse reduction in parenchymal density, as well as discrete and diffuse heterogeneous enhancement with signs of periportal edema and marked edematous thickening of vesicular wall. **a** Coronal view. **b** Axial view.

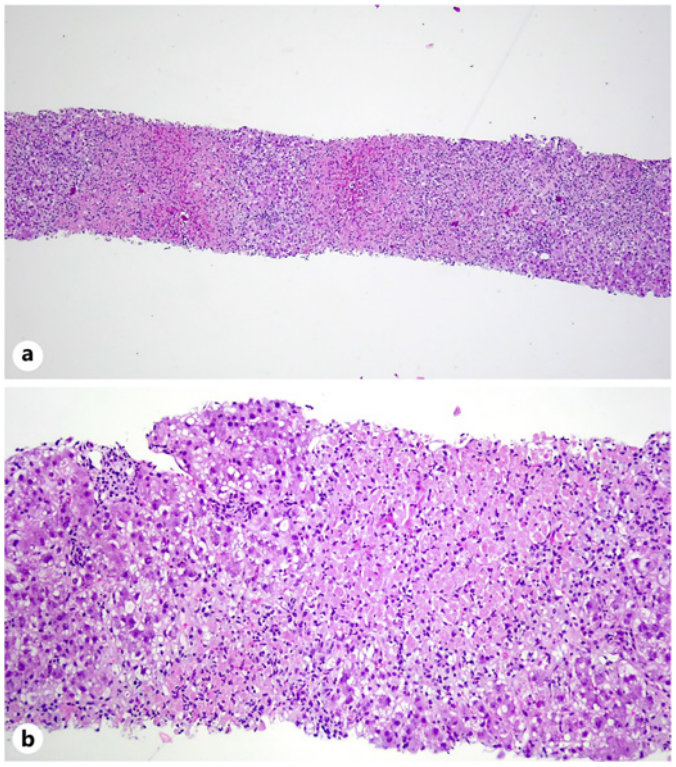

Fig. 2. Transjugular liver biopsy (hematoxylin and eosin). **a** Diffuse centrilobular confluent necrosis affecting acinar zones 3 and 2 with mild inflammation, mainly lymphocytes and histiocytes and normal portal tracts (×4). **b** Viable hepatocytes with diffuse reactive changes and cytoplasmatic swelling and mild macrovesicular steatosis (×10).

compatible with active infection, the correspondence between the nature of symptoms and the known tropism of the virus for liver tissue, the association between active infection and disease in comparable contexts, and the absence of other causative pathogens all support a causative relationship between HHV-6B and the ALF. However, there is a recognized difficulty in ascribing causality to HHV-6 in clinical manifestations concomitant with active infections. In this case, in particular, we must not oversee the other factors implicated and facilitating this ALF. Also, we cannot rule out a synergistic pathogenic role.

This patient took paracetamol shortly before presenting to the ED, and her usual dose was 3 g, three times a week. Although asymptomatic elevations of aminotransferase levels are sometimes seen with chronic use at the maximum recommended daily dose of 4 g, these elevations are typically less than three times the ULN [12]. However, our patient was in greater risk of hepatotoxicity due to malnutrition and excessive alcohol consumption [12, 15, 16]. For at-risk patients, the threshold for referral for further evaluation is lower than for patients without risk factors and is advised for ingestion of more than 4 g or 100 mg/kg within 24 h, whichever is less [12, 15]. Accordingly, this patient's limit to further clinical evaluation would be 3.9 g within 24 h, slightly more than her usual 3 g. Even so, we decided to initiate NAC, given the highly increased transaminases, a paracetamol level exceeding 10 μg/mL (the recommended threshold for management of repeated supratherapeutic ingestion [12]) and its benefits in patients with hepatotoxicity.

Supportive treatment for ALF and cessation of hepatic offending agents (malnutrition, alcohol, paracetamol) were decisive in the patient's outcome. As previously mentioned, in this case antiviral drugs active against HHV-6 were not started also due to an already favorable evolution when the virus was identified. Since the infections by HHV-6 are rare, an unambiguous causative role is frequently difficult to establish, and active HHV-6 infections are often spontaneously controlled, it remains

unclear in which circumstances an antiviral treatment should be started [4, 9]. However, it is essential to reverse immunosuppression, when it is present and can be medically modulated [4].

The most common culprits for the histologic pattern described in this case are medications, illicit drugs, herbal products, and viruses. Regarding the suspicion of paracetamol, it fits in this pattern when taken in high doses, often in cases of attempted suicide, which is not compatible with the patient's reported history. As mentioned, viruses can also be responsible for this pattern [2, 3, 17], in particular HSV (although the negative immunohistochemistry does not favor), adenovirus, and HHV-6. However, the pattern of necrosis of the first two is nonzonal, while in HHV-6, it is centrilobular [18], as observed in our case. All of these were tested, and only HHV-6 was detected. In a recent paper by Wang et al. [18], 5 patients with HHV-6-associated liver injury were studied, and they presented centrilobular necroinflammation, likely due to an immune-mediated process triggered by the virus. Acute graft hepatitis with a periportal pattern of confluent necrosis can be caused by HHV-6 reactivation in immunosuppressed liver transplant recipients [2]. In a study by Härmä et al. [6] on HHV-6 infection and ALF, the predominant histologic findings included hepatocyte necrosis and moderate to severe portal lymphocytic infiltration. In a report of 2 cases of ALF and HHV-6 by Cacheux et al. [3], histology revealed submassive hepatic necrosis and moderate inflammatory cell reaction in 1 case, while the other showed acute hepatitis with bridging necrosis, spotty necrosis, and minimal cholestasis. Charnot-Katsikas et al. [8] described a case in which liver biopsy revealed massive necrosis with a plasma cell infiltrate in the portal areas and no viral inclusions. The liver biopsy of the case reported by Szewc et al. [11] described hepatic necrosis and a marked inflammatory infiltrate. Both HHV-6 and paracetamol can be associated with a scant inflammatory infiltrate [2]. The presence of associated steatosis is described in paracetamol, although other concurrent etiologies cannot be excluded, such as malnutrition and alcohol. The diagnosis in this case report probably results from an ALF of viral cause due to a possible reactivation of HHV-6 in the context of immunoparesis secondary to malnutrition and binge drinking, though we cannot exclude a contribution from a toxic cause due to paracetamol overuse, facilitated by these same susceptibility factors.

Although the pathology of HHV-6 is not fully understood, this virus is associated with ALF in adults, with potentially serious prognosis and should be included in the differential diagnosis of ALF of undetermined cause, particularly in immunocompromised patients. In cases of ALF of unclear etiology, monitoring and supportive treatment should not be delayed, as organ failures may progress rapidly, and patients should be prepared for potential liver transplantation. With this case report, we alert to the possibility of a causative role of HHV-6 in ALF, even in apparently immunocompetent adults, who may harbor an underlying state of immunoparesis, possible to identify after a careful evaluation.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of her medical case and any accompanying images. Ethical approval by Ethical Committee was not required for this manuscript due to national/local laws.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors managed the patient. Isabel Marques Correia and Ana Isabel Rodrigues drafted the paper and performed the literature review. M. Augusta Cipriano made the histological diagnosis and selected and described the liver biopsy images. All authors critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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