Acute liver failure in an immunocompetent patient

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Case presentation

A 14-year-old immunocompetent female showed clinical signs of severe hepatitis. The diagnosis of hepatic encephalopathy was by clinical signs and symptoms: reduction of consciousness, mental confusion, and hepatomegaly, edema in upper and lower limbs during physical examination. Clinical chemistry revealed total and direct bilirubin of 49.9 mg/dl (normal 0.1–1.2 mg/dl) and 31 (<0.4 mg/dl) respectively, alanine transaminase (ALT) levels of 1393 U/L (<50 U/L) and aspartate transaminase (AST) levels of 1773 U/L (<36 U/L), and severe diminished prothrombin activity. There was no evidence for an acute or chronic infection due to HIV, CMV, hepatitis A, B, C and E. The case was classified as fulminate hepatic failure (FHF) grade III according to King's College Criteria. Three days after hospitalization the patient received a transplanted liver. This was due to the rapidly progressive nature of the liver damage (Fig. 1). Analysis of inflammatory cytokines levels demonstrated elevation of interleukin 8 (IL-8): 3631 pg/ml (normal value: <16 pg/ml); IL-10: 8976 pg/ml (normal value: 3.96 pg/ml) and IL-6: 733.08 pg/ml (normal value: 30.2 pg/ml); interferon gamma (IFN-γ): 41 pg/ml (normal value: 3.53 pg/ml); and tumoral necrosis factor alfa (TNF-α): 5263 pg/ml (normal value: 1056 pg/ml). The
Fig. 1. Summary of laboratorial and clinical finds detected in a patient with autoimmune hepatitis that evolves to fulminant liver failure with the presence of HHV-6B.

Histopathological analysis of liver samples demonstrated subcapsular hemorrhage, changes in acinar structure associated with ductal proliferation in zone 1, 2 and 3 associated with changes in the reticular network of the liver. Clusters of residual hepatocytes presented tumefaction with poor macro- and microvesicular fatty changes, moderate lymphoplasmocytic infiltration in parenchyma and portal tract, and severe intrahepatic cholestasis and fibrosis (Fig. 2).

Which are the diagnostic possibilities in this case?

See evidence-based opinion overleaf.

Fig. 2. Acute liver failure associated with HHV6 subtype B infection. (A) Enlarged intra-hepatic septum and hepatocytes proliferation. (B) Mononuclear cells infiltrated in portal tract (Zeiss Axio Observer Z1, camera Axiocam MRc5).
Virology Question and Answer Scheme (VIROQAS)

Evidence-based opinion

Which are the diagnostic possibilities in this case?

These findings were compatible with submassive liver necrosis, suggesting autoimmune hepatitis (AIH). However, the serology was negative for AIH. Autoimmune hepatitis has a variable clinical phenotype, and the absence of conventional autoantibodies does not preclude its diagnosis. The frequency is autoimmune hepatitis in patients with acute and acute severe presentations is <7% [1]. In order to further elucidate the etiology of the fulminate hepatitis, the nucleic acid from serum and liver transplantation was extracted using the RTP DNA/RNA Virus Mini kit II. Genus- and family-specific RT-PCRs and PCRs for flavi-, rhabdo-, orthobunya-, nairo-, arenav-, filo-, alpha, picorna-, paramyxo- and herpesviruses were performed. All reactions were negative except the pan-herpesvirus consensus PCR [2]. Direct sequencing of DNA polymerase gene confirmed the presence of HHV-6 and a type specific PCR for HHV-6 [3] followed by sequencing confirmed the presence of HHV-6B in serum and liver samples. Additionally, the HHV-6B DNA was quantitated [4] and showed 1 × 10⁵ genomes/ml.

Active HHV-6B infections are associated with primary infections, reactivations or exogenous reinfections. The HHV-6 integrates into the human genome and can reactivate as an active infection. The expression of clinical symptoms is variable among immunocompromised patients but can be extremely severe [5]. AIH affects both adults and children and may induce acute or chronic hepatitis, cirrhosis and finally liver failure, unless immunosuppressive treatment is started promptly. For those with advanced-stage disease and complications, consideration of liver transplantation is appropriate [6]. Hepatitis associated with HHV-6 infection was already described previously [7,8]. In the current case, a portal lymphoplasmocytic infiltration and fibrosis was demonstrated in the liver explant despite the absence of reactivity to auto antibodies. These are common histopathological findings in autoimmune hepatitis [9]. Thus, the observed active HHV-6B infection may be considered as a co-factor of the AIH that led to FHF. The patient died 20 days after liver transplantation due to severe sepsis and septic shock. HHV-6B infection can contribute to severe liver inflammation and decompensation of chronic liver disease [10]. The inflammatory status was marked by excessive production of inflammatory cytokines with TNF-α (14X); IL-8 (2X); IL-6 (10X), IFN-γ (3.8X) IL-10 (22X). The increase of cytokines has been described in other FHF patients [11]. Autoimmune hepatitis is rare in children but it represents a serious cause of chronic hepatic disease that can lead to cirrhosis and hepatic failure. The pathogenic mechanisms that lead to AIH remain obscure [12]. Onset of the disease may be acute with features of liver failure at the time of presentation. Several viruses have been considered to be triggers of autoimmunity and auto-antibody formation. The virus specific evasion mechanism called “molecular mimicry” has been noted in AIH and the interactions of viruses with the immune system serve as an accelerating factor of disease pathogenesis [6,12]. HHV-6B can contribute to acute liver dysfunction and induce FHF in patients with an autoimmune hepatitis. HHV-6 screening should be included in the diagnosis of patients with liver failure.

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Competing interests

None.

Ethical approval

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