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Case Report

Liver Failure Associated to Hepatitis A in the Presence of Infection by Cytomegalovirus: Two Case Reports

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Abstract

Liver failure may occur due to extensive liver damage. Several etiologies may be associated to liver failure, in most cases, inducing strong or persistent inflammatory response, whose outcome is the extensive parenchymal loss. Some hepatotropic or nonhepatotropic viruses may induce severe liver damage, between them hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis E (HEV) and members of the Herpesviridae family. Here, we describe two cases of liver failure due to previous active infection by human cytomegalovirus (HCMV) followed by hepatitis A that occurred in immunocompetent individuals.

ABBREVIATIONS

HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HEV: Hepatitis E Virus; HCMV: Human Cytomegalovirus; ALF: Acute Liver Failure; ACLF: Acute-on-Chronic Liver Failure; ALT: Alanine Aminotransferase; BT: Total Bilirubin; INR: International Normalized Ratio; HAV RNA: Hepatitis A Virus Ribonucleic Acid; Anti-HBc: Hepatitis B Core Antibody; HBsAg: Hepatitis B Virus Surface Antigen; Anti-HBs: HBV Surface Antibody; Anti-EBV: Epstein-Barr Virus (EBV) Antibody; PCR: Polymerase Chain Reaction; RT-PCR: Real Time Polymerase Chain Reaction; qPCR: Quantitative Polymerase Chain Reaction.

INTRODUCTION

Liver failure may occur due to extensive liver damage, being clinically characterized by encephalopathy and coagulopathy and has high mortality rate when liver transplantation is not available. Massive loss of liver parenchyma can develop as acute liver failure (ALF) when none pre-existing liver disease is detected, acute-on-chronic liver failure (ACLF) that combines an acute deterioration in liver function in the presence of previously diagnosed or undiagnosed chronic liver disease, or chronically as a decompensation of pre-existing end-stage liver disease [1]. Several etiologies may be associated to liver failure, in most cases inducing strong or persistent inflammatory response, whose outcome is extensive liver damage. Some hepatotropicornonhepatotropicviruses may induce severe liver damage, among them hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis E (HEV) and members of the *Herpesviridae* [2,3]. On the other hand, several cases of ALF or ACLF have no determinate etiology and have been postulated that previously unidentified viral infection could be related to some cases [4].

In general, HAV infection is limited to an acute benign liver disease, and rarely leads to extensive liver damage. Acute HAV super infection may cause ALF, in patients with underlying chronic liver disease [5]. Human cytomegalovirus (HCMV) is a virus belonging to the *herpesviridae* that usually reactivates in immunocompromised and organ transplant receptors, which may produce pneumonia, myocarditis, encephalitis, cholestatic hepatitis and even ALF [6]. In general, liver diseases associated to HCMV in immunocompetent patients are rare, but there is increasing evidence that HCMV may also trigger liver disease, including ALF [7,8]. In addition, viral coinfections may also

trigger more severe liver damage, including classic hepatotropic viruses, such as HAV and HEV [9], HAV and HBV [10], and non-hepatotropic viruses in association with classical hepatic viruses inducing severe liver disease [11,12].

CASES PRESENTATION

Case 1

The 5-years-old girl was admitted at Unit of Liver Transplant of public Hospital from Rio de Janeiro, Brazil, after to be transferred from other public hospital unit non-specialized in liver transplant. She presented with, jaundice, anorexia, reduction of consciousness, paleness, and dehydrated. At the day of hospitalization, she presented grade IV of encephalopathy and in coagulable peripheral blood, abdominal distensions and presence of peristalsis. Serological investigation revealed anti-HAV IgG and anti-HAV IgM positive (BIOELISA HAV; Barcelona, Spain). Anti-HbcIgM and HBsAg negative. In addition, anti-HCMV-IgG was positive and anti-HCMV-IgM negative (BIOELISA CMV; Barcelona, Spain). Hematological analysis and clinical chemistry revealed a leucocytosis (16.300 cells/mm^3), total and direct bilirubin of 39.2 mg/dl and 20.6 mg/dl respectively, alanine transaminase (ALT) 326 U/l and aspartate transaminase (AST) levels 331 U/l; international normalized ratio (INR): 9 and prothrombin time activity 17 seconds, the laboratorial results were summarized in the (Figure 1). The patient undergone liver graft from an anti-HCMV negative donor and the outcome of the liver transplantation was satisfactory. The HAV RNA load [13], in serum sample was 6,45x103 copies/mL before liver transplantation. Liver explant histology suggested chronic lesions. It was detected a pan lobular necrosis associated to denseductular proliferation and mixed inflammatory infiltrate permeating the walls of hepatic venules terminals. Cholestasis and numerous macrophages phagocyting pigments.

Case 2

The 7-years-old boy presented with liver failure and was admitted at a public Hospital from Rio de Janeiro, Brazil. At the moment of liver transplant the patient presented anorexia, jaundice, flapping, grade II/III of encephalopathy. The hematological and chemistry analysis revealed INR: 2,55 and total bilirubin 13,5; albumin 2,1; ALT: 1562 IU/l; AST: 5611; Ht: 26,2%; hemoglobin 8,8g/dl, a leucocytes counts 6.700 cells/mm^3, lymphocyte counts 2010 cells/mm^3; eosinophil counts 67 cells/mm^3, and the main laboratorial results were summarized in the (Figure 2). The patient presented the following serological markers: anti-HAV IgM positive and anti-HAVIgG negative; anti-HbcIgM and IgG negative; HBsAg negative: anti-HBs negative; anti-HCV negative; anti-HCMV-IgG and IgM positive; anti-EBV IgM and IgG negative. The liver donor was anti-HCMV negative. The patient died six days after liver transplantation due to refractoryhypotensionandmultiorganfailure. The HAV RNA load [11], in serum sample was 1,37x102 copies/mL before liver transplantation. Liver explant histology also suggested chronic lesion. In this case, was observed a general disorganization of liver histological structure, with diffuse hepatocyte dissociation, fibrosis, areas of apparent ductal hyperplasia, focal inflammatory infiltrates with a predominance of macrophages and plasma cells, some large bizarre cells and megakaryocytes possible (Figures 3a and 3b).

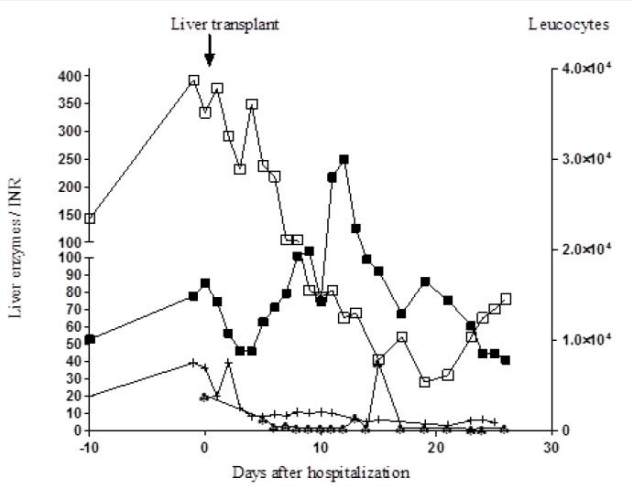

Figure 1 Biochemical and hematological values from a patient with liver failure due to HAV and active HCMV coinfection.
Abbreviations: ALT: Alanine Aminotransferase; BT: Total Bilirubin; INR: International Normalized Ratio

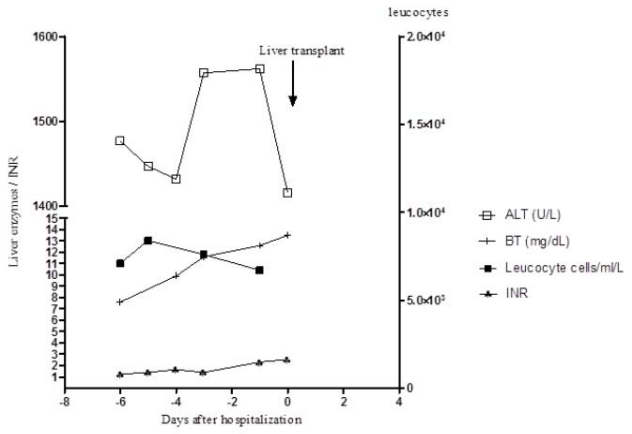

Figure 2 Biochemical and hematological values from patient with liver failure due to HAV and active HCMV coinfection.
Abbreviations: ALT: Alanine Aminotransferase; BT: Total Bilirubin; INR: International Normalized Ratio

Extensive liver lesion can be also attributed to coinfections by non-hepatitis viruses. For this reason, viral nucleic acid from samples of patients 1 and 2 were extracted and genus- and family-specific RT-PCRs and PCRs for flavi-, rhabdo-, orthobunya-, nairo-, arena-, filo-, alpha, picorna-, paramyxo- andherpesviruses were performed [14]. In both patients the pan-herpesvirus PCR was positive. Direct sequencingoftheamplicons (~160 bp) revealed a concomitantactive HCMV infection. The HCMV infection was confirmed by virus-specific real-time PCR and sequencing of the HCMV UL97 gene [15]. The HCMV viral loads in serum samples were 4,15x103 copies/mL and 9,78x104 copies/mL in patient 1 and patient 2 respectively. The results found in qPCR to HAV wereconfirmedbypicorna-PCR.

DISCUSSION

HCMV infection remains one of the most challenging

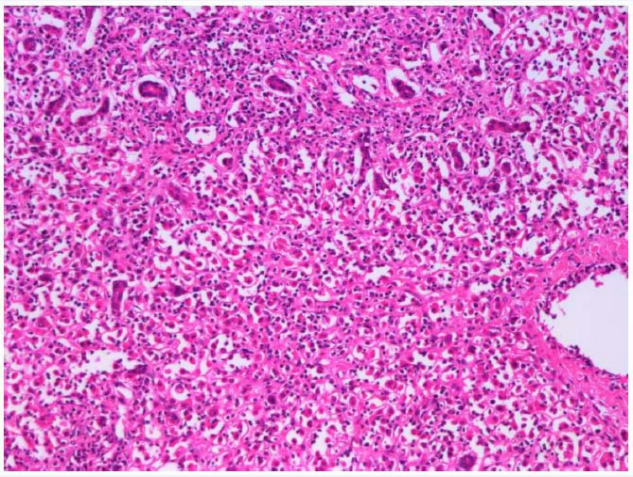

Figure 3a Liver sections stained with hematoxylin and eosin under microscopy analysis - 10X magnification.

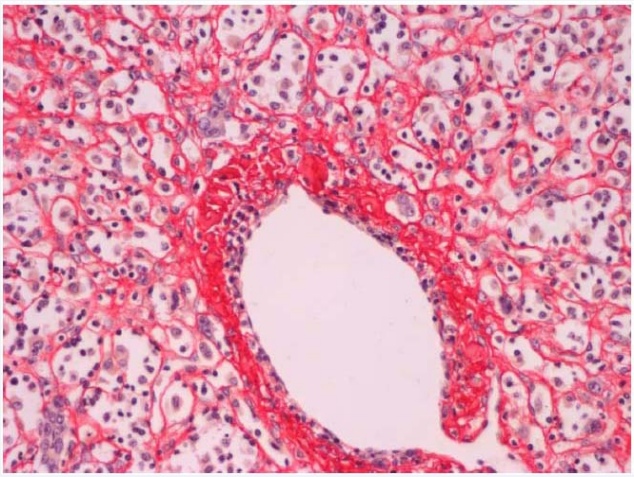

Figure 3b Liver sections stained with picrosirius redunder microscopy analysis - 20X magnification.

infectious complications after transplantation, for this reason the monitoring HCMV infection in transplant recipients is common, and international consensus guidelines on CMV management, that include recommendations as diagnostics, prevention, treatment were developed [16].

Although immunocompetent individuals usually develop subclinical HCMV infections, early findings have associated HCMV infections mild mononucleosis-like syndrome and yet more severe clinical occurrence, between them colitis, meningitis and encephalitis [17]. Despite liver failure due to HCMV in immunocompetent individuals is not common, a rare case of HCMV-associated fulminant hepatitis has been reported [7]. In addition, a recent study related to ALF in childrenshowednonhepatotropicviruses, especially HCMV, as the predominant [18]. Other previous study describing two cases of liver CMV infection/reactivation suggested that CMV may have played a crucial role in precipitating acute hepatic decompensation and ACLF [19].

The infection by HAV is generally mild and limited in most patients, but some complications mainly ALF may occurs in less than 1% of cases [20]. Several factors both associated to host and viral may influence the severity of hepatitis A. Liver injury in hepatitis A may be induced by disrupted host immune response during infection [21]. In addition, the occurrence of concurrent infections may cause worse injury to the liver. This has been observed in relation to reactivation of EBV in children with HAV infection [12].

Hepatitis is a common manifestation of HCMV mononucleosis [22], and is manifested by fever prolonged with lympho monocytosis and mildsymptoms of hepatitis. Most cases of HCMV induced hepatitis occur in adults with severe immune deficiency [23]. Exceptionally cholestatic and prolonged hepatitis can be observed [24,25]. In immunocompromised patients the HCMV hepatitis can be manifested as: HCMV acute viral syndrome with mild hepatitis; hepatitis disseminated and hepatitis after liver transplantation [25]. Severe forms of hepatitis due to HCMV are uncommon presentations, until now few cases were reported [7,23,25,26]. Furthermore, associations between HAV and HCMV infections as causes of liver failure have not been described previously. Thus, previous infection by HCMV it should be tested in patients with liver failure. In this study, the active HCMV infection was confirmed by in both patients by detection, quantification and sequencing of HCMV DNA. The viral load found was 2x104 copies/mL in patient 1 and 3x105 copies/mL in patient 2.

In blood sample obtained at the moment of liver transplantation; patient 1 showed ALT 6,52 folds and AST 9.19 folds higher than normal values (normal value ALT <50U/l and AST <36U/l) and in patient 2 was observed ALT 31,24 folds higher and AST 155,8 folds higher. Liver function abnormalities are frequently encountered in patients with symptomatic HCMV infection. Subclinical elevated transaminases are the most common finding in immunocompetent patients, and elevations of alkaline phosphatase and total bilirubin are less typical [27]. HCMV infections in immunocompetent patients can affect almost every system, even in the liver [17]. In a study included 124 immunocompetent patients who were diagnosed with acute HCMV infection, between them 24% had jaundice [28]. Another study showed that 6% (3/50) of ALF cases were positive for HCMV DNA [29], and severe cholestatic hepatitis was described previously [20]. Incidences of HCMV hepatitis of 2–17 % and even 34 % have been reported [30-32].

In the present cases, the liver fibrosis and ductular proliferation observed in histological analysis suggest hepatic damage for a long period, which may be associated to persistent infection by HCMV. Thus, is possible that in both cases, a previous infection by HCMV have been exacerbated by subsequent infection by HAV.

At the hospital admission timing, the diagnosis of ALF was made for both cases. Hepatic fibrosis was only posteriorly detected in liver explants, when the present study was conducted. The detection of fibrosis excludes the diagnosis of ALF. On the other hand, the definition from both cases as ACLF is difficult; once there are no clear diagnostic criteria for ACLF [33]. In addition, we have no sufficient laboratorial data for this definition. The

fast clinical deterioration, brief clinical management and liver transplantation necessities, besides the presence of HAV IgM antibodies, was the determining factor to suggest HAV infection as inducing agent of liver damage. Thus, some laboratorial data, between them, C-reactive protein and antibodies for autoimmunity, were not investigated in that moment.

Liver cirrhosis associated to systemic inflammation besides the multiorgans failure is usually the hallmark of ACLF. Common precipitants include bacterial and viral infections [1]. Our patients did not develop cirrhosis, and only one patient developed kidney failure. It is not possible to make the exact definition for the clinical syndrome in our patients, but is possible that HAV infection has been a precipitant event that induced liver failure.

In one of our patients, the detection of anti-HCMV IgM, may be justified by possible maintenance of this isotype following persistent primary infection or a virus reactivation due to acute inflammation trigger by HAV infection. These findings are in accordance with previous studies, on which have been described a persistence of specific IgM over time following primary infection in some patients. In addition, HCMV IgM antibodies are also been observed during episodes of reactivation or reinfection [34].

In our study, the patient 1 survived after liver transplantation, while patient 2 died during the surgery. Although the absence of some laboratorial data, such as antibodies for autoimmunity, which could suggest some other possible cause of liver failure, the cases described in this study allow clarify about the possible role of coinfections in liver damage. Here, liver failure due to previous active HCMV infection followed by hepatitis A may have occurred in immunocompetent individuals. Thus, active HCMV infections should be detected in patients with hepatitis A, mainly in severe acute hepatitis A. This may allow that these patients be more effectively accompanied and a better prognosis reached, if a therapy is started early.

CONCLUSION

This study highlights, for the first time, the influence of previous active HCMV infection followed by hepatitis A in liver failure. Our findings suggest that HAV infection in individuals with concomitant active infections by HCMV may produce more severe forms of hepatitis even in immunocompetent patients.

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