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

Vanessa Salete de Paula1, Damião Carlos Moraes dos Santos1,2, Detlef Michel3, Manuela Michel1, Thomas Mertens2, Marcelo Pelajo-Machado4, Luzia Fátima Gonçalves Caputo4, Lucio Filgueiras Pacheco-Moreira1, Jonas Schmidt-Chanasit5,6, and Marcelo Alves Pinto1*
1Fundação Oswaldo Cruz, Laboratório de Desenvolvimento Tecnológico em Virologia, Brasil
2Institut für Virologie, Universitätsklinikum Ulm, Germany
3Centro Estadual de Transplantes, Hospital Estadual da Criança, Brasil
4Fundação Oswaldo Cruz, Laboratório de Patologia, Brasil
5Bernhard Nocht Institute for Tropical Medicine, WHO Collaborating Centre for Arbovirus and Haemorrhagic Fever Reference and Research, Germany
6German Centre for Infection Research (DZIF), Hamburg-Lübeck-Borstel, Germany
7Universidade Estácio de Sá, Brasil

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 hepatotropic or nonhepatotropic viruses may induce severe liver damage, among 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.
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 peristals. 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/mm³), 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 desencludular proliferation and mixed inflammatory infiltrate permeating the walls of hepatic venules terminals. Cholestasis and numerous macrophages phagocytizing 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; Hb: 26.2%; hemoglobin 8.8g/dl, a leucocytes counts 6.700 cells/mm³, lymphocyte counts 2010 cells/mm³; eosinophil counts 67 cells/mm³, and the main laboratorial results were summarized in the (Figure 2). The patient presented the following serological markers: anti-HAV IgM positive and anti-HAV IgG 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 refractory hypotension and multiorgan failure. The HAV RNA load [11], in serum sample was 6,45x10³ 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).

**DISCUSSION**

HCMV infection remains one of the most challenging
The infection by HAV is generally mild and limited in most patients, but some complications mainly ALF may occur 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 mononcytosis and mild symptoms 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 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 laboratory data, between them, C-reactive protein and antibodies for autoimmune, 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 reinfction [34].

In our study, the patient 1 survived after liver transplantation, while patient 2 died during the surgery. Although the absence of some laboratory 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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