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LIVER FAILURE ASSOCIATED WITH AUTOIMMUNE HEPATITIS IN THE PRESENCE OF ACTIVE INFECTIONS BY EPSTEIN–BARR VIRUS AND CYTOMEGALOVIRUS: A CASE REPORT

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RESUMO

A falência hepática ocorre devido à extensa lesão hepatocelular e pode ser induzida por diversas etiologias, incluindo autoimunidade e infecções por vírus hepatotrópicos e não-hepatotrópicos. Citomegalovírus (CMV) e Epstein–Barr (EBV) são vírus da família Herpesviridae que normalmente causam infecções latentes, porém podem produzir grave doença e disfunção hepática. No presente estudo, relatamos o caso de uma paciente do sexo feminino, de 48 anos de idade, com icterícia, coagulopatia, encefalopatia, hiperbilirrubinemia e marcadores sorológicos de autoimunidade. A paciente foi referida a um hospital público do município do Rio de Janeiro, RJ, Brasil e foi submetida ao transplante hepático. O diagnóstico sorológico e molecular demonstrou infecções ativas por EBV e CMV. A presença de infecções ativas por EBV ou CMV precisa ser investigada em pacientes com falência hepática de etiologia desconhecida, pois pode estar associada com grave hepatite autoimune.

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PALAVRAS-CHAVE: Falência hepática. Herpesvirus. Autoimunidade. Relato de caso.

ABSTRACT

Liver failure occurs due to extensive hepatocellular damage and may be induced by several etiologies, including autoimmunity and hepatotropic and non-hepatotropic viruses. Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) are viruses from the Herpesviridae family that usually cause latent infections but may trigger severe liver disease and dysfunction. Herein, we report a case of a 48-year-old female patient with jaundice, coagulopathy, encephalopathy, hyperbilirubinemia, and autoimmunity marker. The patient was referred to a public hospital in Rio de Janeiro, Brazil, and underwent a liver transplant. Serological and molecular diagnosis showed active infections by EBV and CMV. The presence of latent or active infection by EBV or CMV needs to be investigated in patients with liver failure of unknown etiology, which might trigger severe autoimmune hepatitis.

KEYWORDS: Liver failure. Herpesvirus. Autoimmunity. Case report.

INTRODUCTION

Liver failure may occur due to extensive liver damage, is clinically characterized by encephalopathy and coagulopathy, and has a high mortality rate when liver transplantation is not available. Massive loss of liver parenchyma can develop as acute liver failure (ALF) when no preexisting 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 chronic decompensation of preexisting end-stage liver disease (Ngu *et al*., 2023). Several etiologies may be associated with liver failure, such as viruses and autoimmunity. In most cases, a strong or persistent inflammatory response is related to extensive liver damage (Ichai; Samuel, 2011).

Autoimmune hepatitis (AIH) refers to chronic and progressive inflammation of the liver and, although rarely, may trigger liver failure. AIH may be subdivided into two

major subtypes. AIH type 1 is characterized by antinuclear autoantibodies (ANA) and/or smooth muscle antibodies (SMA). AIH type 2 is characterized by the anti-liver kidney microsomal type 1 (anti-LKM-1) antibody (Terziroli; Mieli-Vergani; Vergani, 2018).

Some hepatotropic or nonhepatotropic viruses may induce severe inflammation and extensive liver damage, including hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis E virus (HEV) and members of the *Herpesviridae* family (Ichai; Samuel, 2008; Kayaalp; Ersan; Yılmaz, 2014). Several cases of acute hepatitis and ALF or ACLF have no determinate etiology, and it has been postulated that previously unidentified viral infections could be related to some cases (Canbay *et al*., 2011). Recently, physicians in the United Kingdom (UK) have diagnosed children with mysterious acute hepatitis that has afflicted at least 197 youngsters in the UK and more than 600 worldwide. Approximately 9% of 180 cases in the United States that presented liver dysfunction required liver transplants. The UK Health Security Agency (UKHSA) suggested the adenovirus 41 hypothesis and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coinfection; however, this hypothesis was not confirmed (Wang; Xie, 2022). On the other hand, a recent study involving cases of acute non-A-E-hepatitis detected the presence of infection by some herpesviruses and the absence of adenoviral infection in patients with acute severe hepatitis (Leiskau *et al*., 2023).

Herpesviridae are a large group of well-characterized double-stranded DNA viruses that include human cytomegalovirus (HCMV) and Epstein–Barr virus (EBV). HCMV usually reactivates in immunocompromised and organ transplant recipients, which may produce pneumonia, myocarditis, encephalitis, cholestatic hepatitis and even ALF (Canbay *et al*., 2011). EBV usually occurs early in childhood and may lead to infectious mononucleosis (IM) in young adults. EBV is extremely prevalent worldwide, infecting more than 98% of the human population by the age of 40 years. Previous studies concluded that EBV hepatitis is an uncommon self-limiting infection, mainly detected among people aged ≥ 60 years (Vine *et al*., 2012). AIH following EBV infection has been described previously in some studies (Cabibi, 2008). Although rarely, EBV may also induce severe liver disease such as acute liver failure (Busch *et al*., 2014; Mellinger *et. al*, 2014). Coinfection with CMV and EBV may also occur occasionally, but the impact on autoimmune hepatitis and liver dysfunction has not

been well established. Previous studies have shown that hepatitis associated with dual infection by EBV and CMV has a favorable prognosis (Leonardsson *et al*., 2017; Li *et al,* 2017).

CASE PRESENTATION

A 48-year-old female patient with severe acute hepatitis and jaundice and prothrombin time test (*PT*) <50% was referred to a public hospital in Rio de Janeiro, Brazil. Despite the support therapy, signals and symptoms of progressive liver dysfunction were confirmed during the hospitalization period that were indicative of a liver transplant. Ethical permission for the collection and testing of samples was provided by the FIOCRUZ Ethical Committee (440.614 and 222/03).

At the time of the liver transplant, the patient presented anorexia, jaundice, flapping, grade II encephalopathy, i*nternational normalized ratio* (INR): 3.6 and total bilirubin of 24.4 The hematological and chemistry analysis revealed leukocytosis (11.300 cells/mm^3), alanine transaminase (ALT) 348 U/L and aspartate transaminase (AST) levels 284 U/L. All enzymes showed values above the reference values. The main laboratory results are summarized in figure 1. The patient presented the following serological viral markers: IgM negative/IgG positive for hepatitis A, anti-HBc IgM/IgG negative, HBsAg negative, anti-HBs negative for hepatitis B, anti-HCV negative for hepatitis C, IgG positive and IgM negative for CMV, and IgM positive/IgG negative for Epstein–Barr virus. Electrophoretic analysis of plasmatic autoantibodies showed that antinuclear antibody (ANA: positive 1:160), smooth muscle antibody (SMA) and liver-kidney microsomal antibody (LKMA) markers were negative, and the plasmatic content of γ-globulin was 40.2%. The patient received the liver from an anti-HBc-positive donor but was anti-CMV negative. Prophylactic therapy with hyperimmune serum anti-HBV and lamivudine was adopted. The patient survived after liver transplantation. The histopathology of the liver explant showed extensive massive necrosis and increased eosinophilic intracytoplasmic inclusion bodies (Fig. 2A). In addition, in the parenchymal infiltrate, it was possible to observe a predominance of mononuclear infiltrates, such as macrophages, lymphocytes and plasmocytes (Fig. 2B), hepatocytes in the process of apoptosis and other binucleated hepatocytes (Fig.

2C), with the presence of bilirubin pigment (Fig. 2D). Ballooned hepatocytes were also observed (Fig. 2E). Close to the lobular center vein, the sinusoids were retracted in proximity to areas with necrosis and accumulation of pigments (Fig. 2F).

Acute hepatitis and liver failure without etiology can also be attributed to the nonhepatotropic virus, as has been recently suggested for mystery hepatitis in UK children (Wang; Xie, 2022). For this reason, viral nucleic acid from samples was extracted, and genus- and family-specific reverse transcription-polymerase chain reaction (RT-PCRs) and polymerase chain reaction (PCRs) for flavi-, rhabdo-, orthobunya-, nairo-, arena-, filo-, alpha, picorna-, paramyxo- and herpesviruses were performed. The panherpesvirus PCR was positive. Direct sequencing of the amplicons (~160 bp) revealed the presence of CMV DNA. CMV infection was confirmed by virus-specific real-time PCR, sequencing of the CMV UL97 gene, and genotype (Sassenscheidt *et al*., 2006).

Figure 1

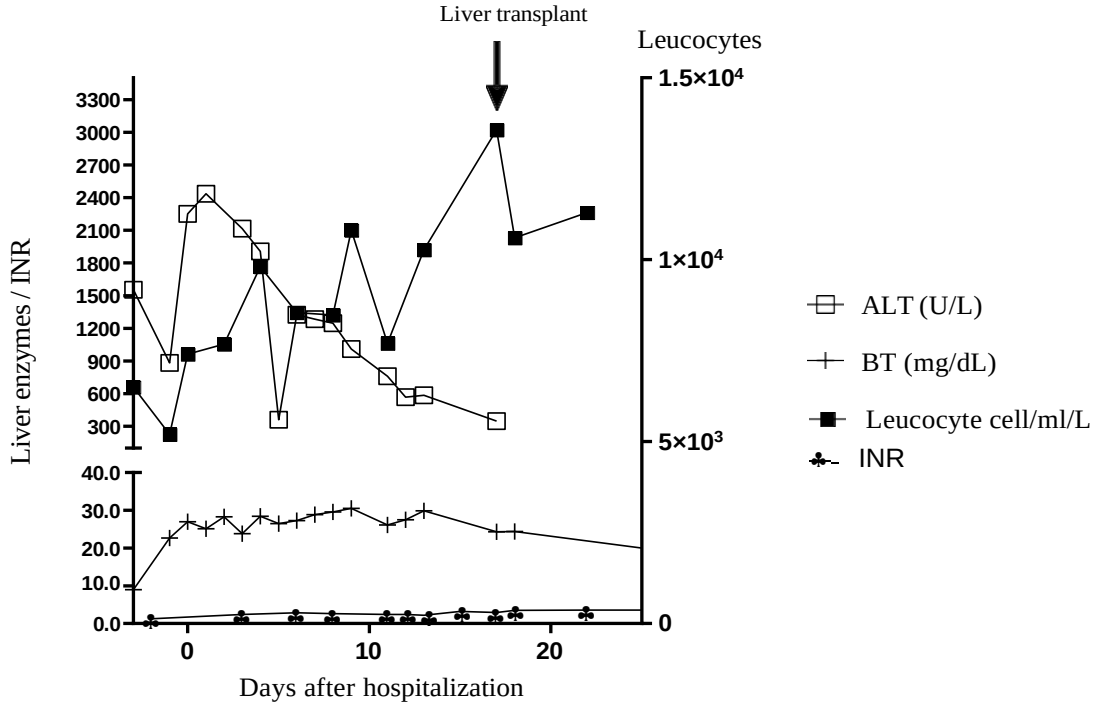


Figure 1. Biochemical and hematological values from patient with liver failure due Epstein–Barr virus and human cytomegalovirus.

Figure 2 A and B: A- Photomicrograph showing hepatic parenchyma with nuclei of hepatocytes in cariopicnose (⟶), karyorrhexis (★) and karyolysis (#), stained with H & E, 80x; B - Photomicrography showing leukocyte inflammatory infiltrate, predominantly mononuclear (★) stained with H & E, 40x.

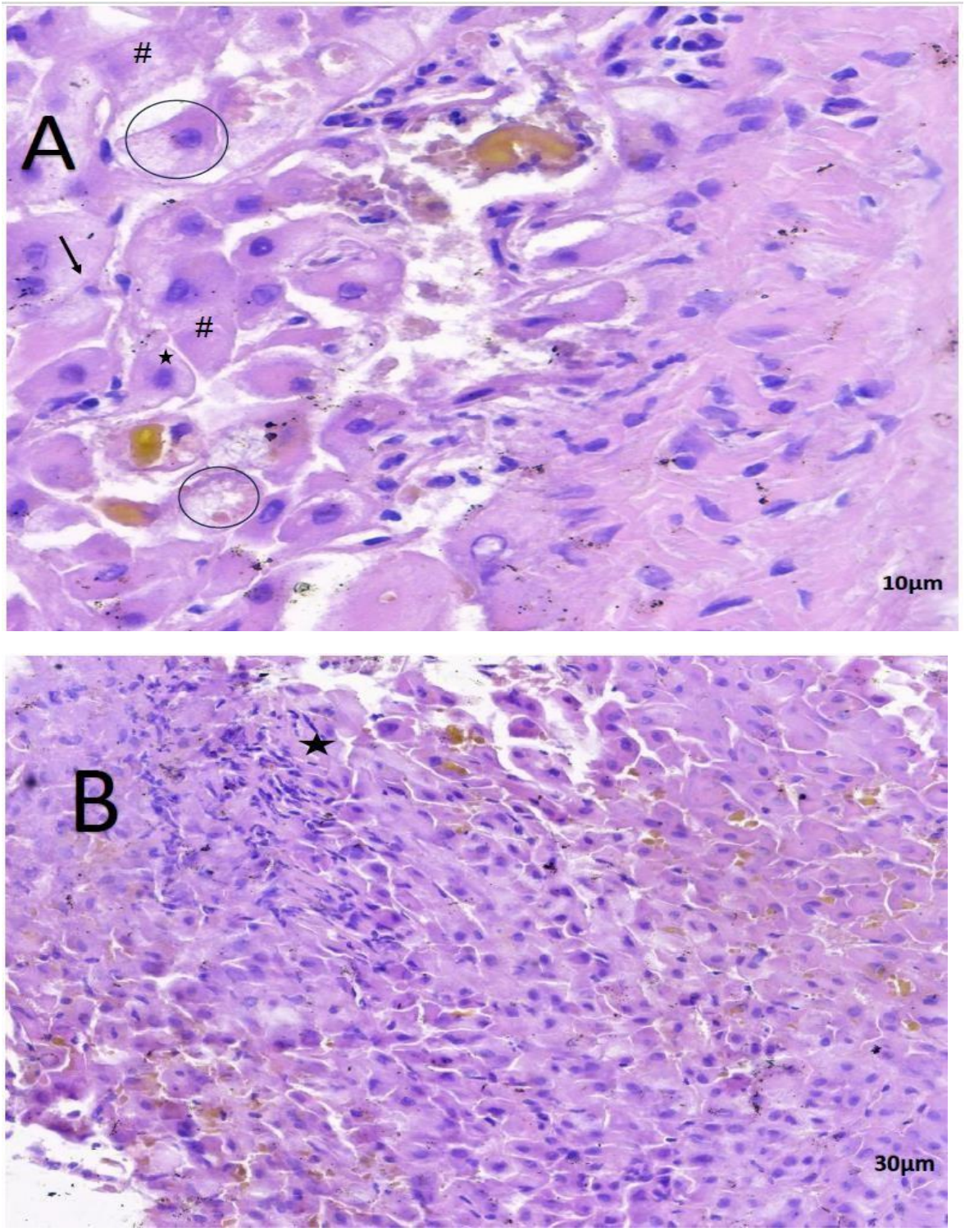


Figure 2 C and D: C - Photomicrograph showing hepatocyte in apoptosis (#) and binucleated (↘) stained with H & E 80x; D - Photomicrograph showing bilirubin accumulation (★) and sinusoidal dilation (&) stained with H & E, 80x.

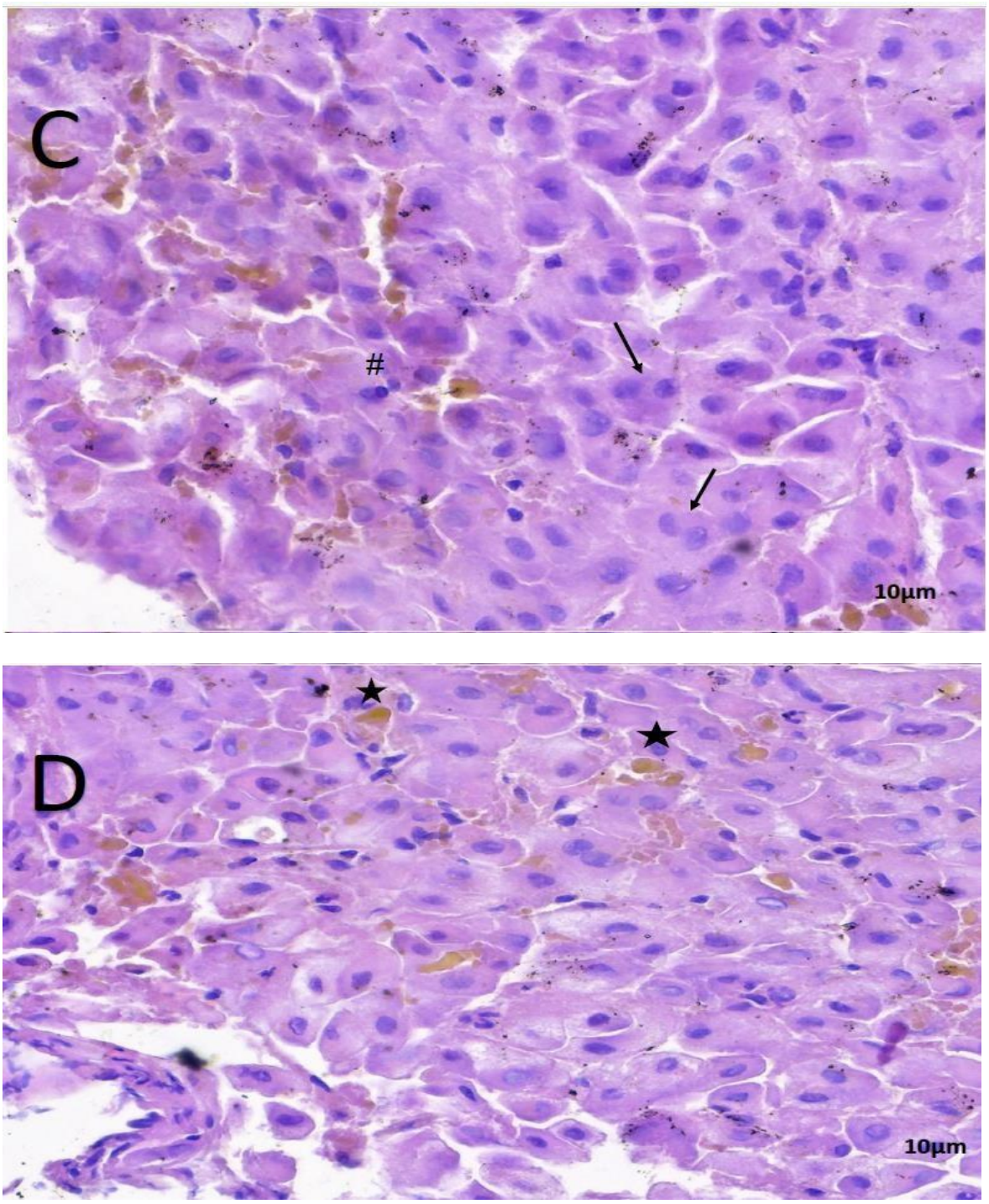
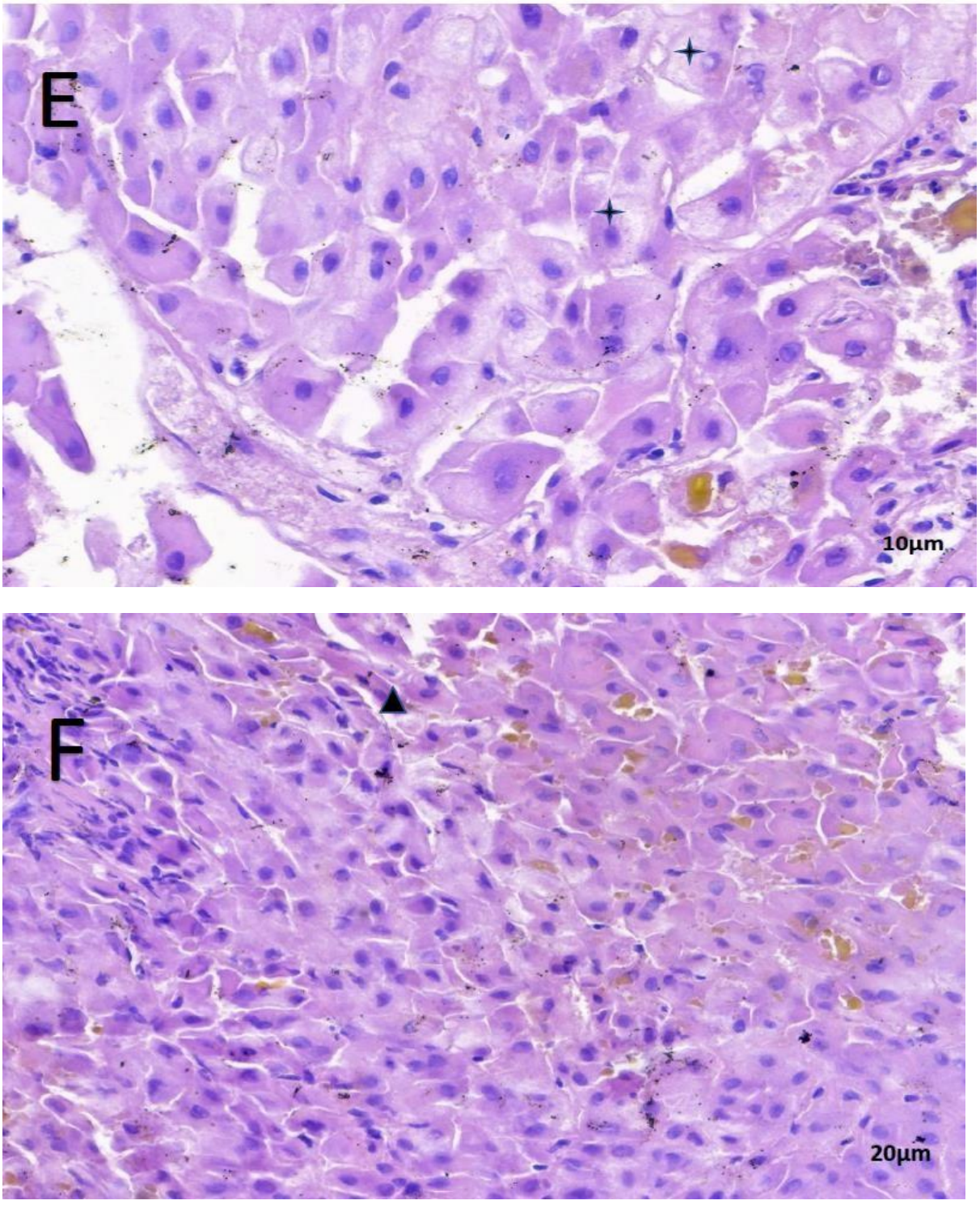


Figure 2 E and F: E - Photomicrograph showing hepatocytes with cytoplasmic swelling (✚), stained with H & E, 80x ; F - Photomicrography with presence of lobular center vein presenting area in necrosis, pigment accumulation and retraction of sinusoidal beds (▲), stained with H & E, 40x.



DISCUSSION

EBV is the primary cause of mononucleosis, and hepatic involvement in infectious mononucleosis is common. Approximately 80-90% of patients with EBV infection exhibit a self-limited and transitory elevation of liver enzymes (Crum, 2006; Gupta *et al*., 2013). Hepatitis by EBV is mainly detected among people aged ≥ 60 years (Vine, 2012), and although primary EBV infection is rarely fatal, fulminant infection may occur (Cabibi, 2008; Mellinger *et al*., 2014). Although liver disease caused by HCMV in immunocompetent patients has rarely been described, there is increasing evidence that HCMV may also trigger liver disease, including ALF, even in patients with no immunodeficiency (Yu *et al*., 2013). Furthermore, in a previous study, triple infection by betaherpesviruses (HCMV, HHV-6 and HHV-7) was associated with one case of ALF (Raposo *et al*., 2021).

AIH is a classical autoimmune liver disease with clinical manifestations, including a female predominance, hypergammaglobulinemia and the presence of autoantibodies (especially anti-nuclear antibody; ANA). AIH may also be induced by viral infections and can result in liver failure due to extensive liver lesions (Sajja *et al*., 2021). In the present case, the severe liver injury justified the liver failure. Necro-inflammatory lesions with lymphohistioplasmocytic infiltrate, the presence of bilirubin pigment in phagocytic cells, hepatocyte swelling and ballooning, and vascular alterations were observed. Hypergammaglobulinemia and autoimmunity markers (ANAs) were associated with AIH. In addition, the presence of IgM to EBV, in addition to the detection of CMV DNA, suggests that active infection by these viruses triggers autoimmunity.

The single association between dual acute infection by EBV and HCMV as a cause of extensive liver damage in the absence of anti-HCMV IgM is controversial. Other authors suggested that coinfection by EBV and HCMV as an etiology of liver failure is not common (Leonardsson *et al*., 2017; Li *et al*., 2017), but the concurrent reactivation of EBV and CMV in older adults has been related to a strong systemic inflammatory response linked to other morbidities (Bennett *et al*., 2012). A single EBV infection has been associated with autoimmune diseases (Balandraud; Roudier, 2018), including Sjögren's syndrome (Suzuki *et al*., 1996). The association between

EBV and AIH has been described, but the favorable outcome differs from the majority of AIH cases (Cabibi, 2008).

In our hypothesis, HCMV infection contributed to autoimmunity, and this condition was exacerbated due to EBV reactivation. Since EBV infects more than 98% of adult individuals, it is not reasonable to suggest an acute infection by EBV (Sajja *et al*., 2021).

Classic hepatotropic viruses, such as hepatitis A and hepatitis C viruses, are associated with autoimmune hepatitis, justified by autoimmunity triggered by molecular mimicry when mutations in hepatitis viral proteins closely resemble human self-epitopes (Huppertz *et al*., 1995; Kammer *et al*., 1999). Some herpesviruses are also considered inducers of autoimmune disorders due to their lifelong persistence and periods of reactivation and latency (Dittfeld *et al*., 2016; Aloisi; Giovannoni; Salvetti, 2023). Despite anti-EBV IgM indicating acute infection, the maintenance of titers may be due to a persistent primary infection or reactivation followed by new mutated epitope exposition in the infection course, as has been demonstrated for EBV and HHV-6 infections (Nystad; Myrmel, 2007). Furthermore, the absence of IgG may be due to a decline in serum titers, since anti-EBV IgG antibodies decrease over time in adult individuals (Balfour *et al*., 2022).

CONCLUSIONS

We assume that active EBV and CMV infection could play a pivotal role in autoimmune hepatitis, triggering autoantibody production. Therefore, the presence of latent infection by EBV or CMV needs to be routinely investigated in patients with liver failure, mainly in the presence of autoimmunity markers.

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