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Concomitant Acute Hepatitis E Infection and Autoimmune Hepatitis

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Abstract: The role of viral infections as precipitants for autoimmune hepatitis (AIH) has been previously suggested, yet the direct link between acute hepatitis E virus (HEV) infection and the onset of AIH remains to be elucidated.

Keywords: autoimmune; hepatitis; autoantibodies; necrosis

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Introduction

Autoimmune hepatitis (AIH) is a chronic hepatic disorder marked by the presence of circulating autoantibodies and distinctive histopathological findings. While the exact etiopathogenesis of AIH is still under investigation, viral etiologies have been implicated as potential initiating factors. This paper discusses a case that suggests an association between acute hepatitis E virus (HEV) infection and the subsequent development of AIH, thereby contributing to the understanding of the complex interplay between viral infections and autoimmune liver diseases.

Case Report

A 21-year-old male with a history of idiopathic bradycardia necessitating pacemaker implantation in 2018 sought medical attention in the emergency department (ED) due to a 2-week period of diminished appetite, nausea, and headaches, accompanied by 6 days of jaundice. The patient reported no fever, chills, diarrhea, or abdominal discomfort. Notably, the patient had traveled to Pakistan and Turkey, returning 2 weeks prior to symptom onset. Upon examination in the ED,

the patient exhibited a low-grade fever of 99.3 °F and visible jaundice, with no other significant findings on physical examination. Laboratory investigations revealed notable abnormalities, including a total bilirubin level of 7.7 mg/dL, AST at 227 U/L, ALT at 1125 U/L, and an albumin level of 3.0 g/dL. A computed tomography scan of the abdomen and pelvis indicated hepatomegaly, with trace pericholecystic fluid or gallbladder wall thickening, and trace fluid accumulation in the right upper quadrant and right paracolic gutter. Further diagnostic efforts, including a toxicology screen and acetaminophen levels, were within normal limits, as were tests for ceruloplasmin, antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), malaria smear, and hemoglobin electrophoresis. However, anti-smooth muscle antibody (anti-SMA) was positive at a titer of 1:80. Serological tests for cytomegalovirus, Epstein-Barr virus, and hepatitis A, B, and C were negative. The diagnosis was clarified with the detection of hepatitis E IgM antibodies and a hepatitis E viral load of 8,830,000 IU/mL through polymerase chain reaction (PCR) testing, suggesting an acute hepatitis E infection.

The initial conservative management of the patient did not halt the progression, as evidenced by the escalating transaminases. Consequently, a liver biopsy was undertaken on the fourth day of hospitalization. The histopathological findings revealed acute cholestatic hepatitis with features suggestive of an autoimmune etiology, alongside a mild duct reaction and patchy single-cell hepatocyte necrosis, without any evidence of fibrosis. Stains specific for viral inclusions yielded negative results.

Given the histological findings indicative of AIH, coupled with the clinical course, the decision was made to initiate corticosteroid therapy. This intervention led to a notable improvement in both the patient's liver function tests and clinical symptoms before his discharge from the hospital.

At a follow-up appointment 3 weeks post-discharge, remarkable progress was noted: the hepatitis E viral load had become undetectable, and liver function tests had normalized.

Discussion

Autoimmune hepatitis (AIH) is a chronic liver disorder mediated by immune responses, characterized by hypergammaglobulinemia and the presence of autoantibodies [1]. The clinical manifestations of AIH are diverse and nonspecific, often including symptoms such as nausea, loss of appetite, and abdominal discomfort. Laboratory findings typically show disproportionate elevations in transaminase levels relative to alkaline phosphatase and bilirubin levels. Additionally, circulating autoantibodies such as ANA, anti-SMA, and antibodies against liver/kidney microsomal type 1 (anti-LKM1) are commonly detected [1]. AIH frequently occurs in individuals who have other autoimmune disorders and shows a higher incidence in females.

The histopathological landscape of AIH is marked by inflammatory infiltrates rich in lymphocytes and plasma cells, portal tract enlargement with moderate to severe inflammatory activity, and lobular lesions exhibiting necroinflammation, sometimes with areas of bridging necrosis [2]. The disease spectrum of AIH can vary widely, from asymptomatic conditions to acute liver failure.

The hepatitis E virus (HEV) is a non-enveloped, single-stranded RNA virus primarily known for causing acute viral hepatitis that is usually self-limiting. However, the disease can manifest more severely in pregnant women or individuals with pre-existing liver conditions, where it may lead to liver failure [3]. Chronic HEV infection tends to occur in individuals with compromised immune systems, such as organ transplant recipients, patients with hematological cancers, or those living with HIV.

The diagnosis of HEV infection relies on the detection of anti-HEV IgM antibodies or the identification of HEV RNA through PCR testing. The viremic phase of HEV typically lasts about 3 weeks following the onset of symptoms [3]. The management of HEV infection is generally supportive, but for severe cases, particularly in chronically infected individuals, antiviral therapy with ribavirin has shown efficacy. In transplant recipients experiencing chronic HEV infection, reducing immunosuppressive therapy can lead to a decrease in viremia in approximately 30% of cases. If this strategy fails, treatment options may include ribavirin alone or in combination with interferon-alpha [3].

The relationship between AIH and HEV infection has been acknowledged in the medical literature, suggesting a potential link in the pathogenesis of AIH. The exact mechanism underlying AIH remains unclear, but it is believed that environmental factors can trigger an immune-mediated response in genetically susceptible individuals, leading to liver inflammation. Various agents, including medications, vaccines, and viruses such as hepatitis A and C, herpes simplex, Epstein–Barr virus, and cytomegalovirus, have been implicated as potential triggers [4]. While there have been case reports of concurrent AIH and HEV infection, the role of HEV as a direct trigger for AIH development remains uncertain [5].

There also appears to be an increased prevalence of AIH-related autoantibodies in patients with HEV [6], as well as an increased prevalence of HEV serology in patients with AIH [4]. A study involving 48 subjects with acute HEV infection revealed that half (50%) of the participants tested positive for at least one autoantibody, with ANA being the most prevalent (33%), followed by anti-SMA at 21% [6]. These data point to a possible immune-mediated reaction associated with acute HEV infection. Additionally, Pischke et al. observed a higher frequency of HEV antibodies in AIH patients compared with healthy controls (7.7% vs 2.0%; $P = .0002$) [4], suggesting several potential explanations such as HEV acting as a trigger for AIH, an elevated risk of HEV infection due to the immunosuppressive state in AIH, or antibody cross-reactivity.

In the presented case, the diagnosis of acute HEV infection was confirmed through the PCR detection of HEV RNA, and the consideration of AIH was supported by a positive anti-SMA test and corroborated by histopathological analysis. While the natural progression of HEV infection might account for the subsequent reduction in viremia and the amelioration of liver function abnormalities, the administration of corticosteroids appears to have expedited this improvement. Utilizing immunosuppressive therapy in the context of HEV infection might initially seem paradoxical, yet the existing literature documents the successful management of acute severe HEV cases with corticosteroids [7,8].

The association between HEV infection and AIH has previously been described in the literature, although the exact relationship is unclear. Although viral infections have been implicated as potential triggers for AIH, acute HEV infection has not been definitively proven to be causative. Patients with AIH have been shown to have a higher prevalence of positive HEV serologic testing, and patients with acute HEV infection also have been described as having an increased incidence of autoantibody detection [6]. The presence of this laboratory data as well as studies demonstrating clinical improvement with steroids suggests that the immunologic response related to HEV infection can be significant.

Diagnosing AIH involves a multifaceted approach that includes clinical assessment, immunological testing, distinctive histological examination, and the ruling out of other hepatic disorders [1]. Considering the documented association between HEV and AIH, it is prudent for clinicians to evaluate for concurrent HEV infection in patients presenting with AIH. This approach not only aids in accurate diagnosis but also informs the therapeutic strategy, potentially including the consideration of immunosuppressive treatment even in the context of viral hepatitis.

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