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An Unusual Cause for a Hepatic Flare in a Chronic HBV Carrier

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Introduction: Hepatitis E is an emerging disease in developed countries with an increasing incidence. In developed countries, HEV genotype 3 prevails as a zoonotic disease carried by wild boars or pigs, which usually causes asymptomatic infection.
Case Presentation: An asymptomatic HBsAg carrier was tested regularly at a German university hospital and showed no signs of chronic hepatitis B (CHB) activity. At a routine visit, elevated aminotransferases were detected while HBV DNA remained low and the patient was clinically asymptomatic. The laboratory signs of acute hepatitis resolved spontaneously. When aminotransferases returned to normal limits, the patient showed a flare of HBV-replication, which resolved spontaneously. In follow-up, further investigations revealed a resolved hepatitis E (HEV) superinfection causing an acute hepatitis before the HBV flare. No potential risk factors for HEV infection were identified.
Conclusions: Elevated aminotransferases in CHB patients are most commonly caused by exacerbation of CHB. Nevertheless, when HBV DNA is not elevated, other reasons should be excluded. Amongst others, superinfection with another hepatotropic virus can be the reason for decompensation of chronic hepatitis B. This case report describes an asymptomatic HEV superinfection followed by a flare in HBV replication in an HBsAg carrier without signs of HBV replication for eight years. In CHB carriers with signs of acute hepatitis, rare causes should be considered as well. HEV should be a part of routine laboratory evaluation for hepatitis flares given the rising number of infections.

*Keywords:*Hepatitis E; Chronic Hepatitis B; Risk Factors; Hepatic Flare; Superinfection

1. Introduction

Hepatitis E virus (HEV) is an RNA virus belonging to the family of Hepeviridae with four known major humanopathogenic genotypes and one serotype. Genotypes 1 and 2 cause waterborne and fecal-orally transmitted epidemic hepatitis, whereas genotypes 3 and 4 are zoonotic. HEV-1 and -2 occur in developing countries. HEV-1 is endemic mainly in Asia, being a major cause of acute hepatitis, especially in India (1), while HEV-2 is endemic in Africa and Mexico. HEV-4 primarily affects South East Asia, although cases of autochthonous infection have been reported in Europe. HEV-3 appears worldwide and is increasingly reported as a cause of acute hepatitis in developed countries (2). In Europe, pigs are a major reservoir for HEV (3), although other species might well play a role in transmission of HEV-3. A high prevalence of HEV in wild boars has been described in Eastern Germany (4). In the state of Brandenburg, seroprevalence of HEV in humans is higher than the average in Germany (5). Risk factors for autochthonous acute HEV infection include consumption of undercooked meat or exposure to pigs (2). In addition, other risk factors for infection are high age or transfusion of blood products (6). After an incubation period of 2-6 weeks, anti-HEV (IgM and IgG) can be detected by various assays with varying accuracy rates. To confirm positive results, immunoblot or molecular techniques are commonly used, which are especially important for detection of HEV in immunocompromised patients such as transplant recipients (7). In most cases, autochthonous hepatitis E infection follows an asymptomatic clinical course and viremia lasts for about six weeks. Complications of autochthonous HEV infection include chronic infection in immunocompromised hosts, acute on chronic liver failure and extrahepatic symptoms such as arthritis, pancreatitis or neurologic disorders (8, 9). Chronic hepatitis E is seen in immunosuppressed patients and can cause cirrhosis (8). Since HEV infection is usually a self-limiting disease in immunocompetent patients, therapeutic strategies are focused on the rare event of chronic HEV. Ribavirin monotherapy as well as pegylated interferon-alpha or the combinations of the two agents have shown therapeutic success in acute hepatitis (10, 11). A vaccine with good efficacy has been developed and recently licensed in China (12).

2. Case Presentation

A 52-year-old male asymptomatic HBsAg carrier (HBeAg negative) presented regularly every three months at the outpatient clinic of the Department of Hepatology and Gastroenterology at Charité University hospital for the last eight years. HBV viremia was assessed regularly and constantly showed negative results or viral loads below

250 IU/mL. Aminotransferase levels remained within the normal range for the last eight years. Fibroscan testing repeatedly showed results below 10 kPa, indicating absence of advanced fibrosis. Ultrasound examinations displayed signs of a mild fibrosis. Based on these findings, no antiviral treatment was considered necessary. In March 2013, the patient attended the outpatient department for a routine visit. He presented without clinical symptoms. At this visit, laboratory findings showed signs of an acute hepatitis with elevated aminotransferases (ALT 1010 U/l, AST 338 U/l, GGT 307 U/l, AP and Bilirubin were within the normal range). Due to the underlying disease, acute hepatitis B re-activation was suspected, and viral load was analyzed. However, the result was not consistent with HBV reactivation given the low viral load (145 IU/mL). Repeated abdominal ultrasound displayed no additional findings. A week later, aminotransferases decreased (ALT 232 U/l, AST 53 U/l), no signs of autoimmune disease or hepatitis D virus (HDV) superinfection were detected (negative anti-HDV (DiaSorin®) and normal results for IgA, IgM, IgG and negative results for ANA, AMA, AMA-M2, anti-SMA and anti-LKM were detected. Hepatitis A infection was unlikely because of preexisting immunity (positive Anti-HAV-IgG). The patient had not taken any new or immunosuppressive medication. On follow-up one month later, he reported clinical signs of fatigue and weakness. Laboratory testing showed normal aminotransferases. An acute HCV-infection was ruled out by HCV-RNA testing. At this visit, HBV-DNA was 23.200 IU/mL. No therapy was initiated since aminotransferases had returned to normal range. Still facing an unclear episode of hepatitis one month earlier, less common causes of acute hepatitis were examined. Laboratory testing showed positive results for hepatitis E virus IgM by ELISA (Mikrogen®) and HEV-IgG Blot by immunoblot. Further tests revealed a questionable result for HEV-IgM by immunoblot and negative results for HEV-RNA. Suspected acute HEV-superinfection as the most probable cause of the undergone hepatitis was confirmed by testing the blood sample from March 2013 for HEV-RNA. HEV-PCR had positive results at 76.400 copies/mL. Retrospective testing of previous blood specimens (from august 2012) showed negative results for HEV serology. During the follow-up visits, the patient had normal aminotransferase levels and HBV-DNA declined to 141 IU/mL, while HEV-RNA remained negative. The patient still had fatigue. Five months after acute HEV infection and four months after the HBV flare, HBV viral load had negative results again, serology remained unchanged (HBs Ag positive). The patient was asked for potential risk factors for acquiring HEV. He did not have contact to pigs or wild animals; he lived in an urban area, did not eat intestines or uncooked meat, did not travel abroad, did not receive transfusions or had contact to HEV-infected patients.

3. Conclusions

Chronic hepatitis B (CHB) is characterized by three phases including an immunotolerant phase, an immune phase and an inactive phase. In the natural course of CHB, spontaneous viral flares and biochemical deterioration may be observed. These reactivations are more frequent in patients with impaired immunological control such as concomitant HIV-infection, during pregnancy or after surgery (13). Immunosuppressed patients infected with HIV often have a coinfection with HBV and are at risk of liver failure (14). Acute liver failure due to reactivation in CHB patients under immunosuppression, chemotherapy or treatment with rituximab among others (15), is associated with a high mortality rate despite treatment. Drug induced CHB exacerbation is often characterized by an unfavorable course and is difficult to treat. Another important cause for elevated aminotransferases in CHB patients is superinfection with another hepatotropic virus leading to unfavorable outcomes in patients with chronic hepatitis B (16). A viral superinfection unique to CHB patients is infection with hepatitis D virus (HDV) usually leading to aggravation of liver disease and acceleration of cirrhosis progression. HDV is a problem not only in regions where hepatitis B is highly endemic, but also in developed countries. The diagnosis is primarily based on serologic testing for anti-HDV; RNA-assays are still somewhat unreliable and have to be further standardized. Superinfection with HEV can cause severe decompensation in patients with chronic liver disease (9, 17), also in autochthonous infections in developed countries (18). Acute HEV superinfection on CHB cirrhosis can even have a lethal course (9). In areas where HBV is endemic, there seems to be an association between HEV and HBV. A survey in Chad found that 20 of 27 patients with acute HEV infection had positive results for HBsAg (19). Two studies analyzed the effect of HEV superinfection in CHB patients (12, 16). A Chinese study compared HAV and HEV superinfection in CHB patients, demonstrating a more severe course in patients with HEV superinfection. Among 136 patients with CHB and HEV infection, 12 were inactive HBsAg carriers. There were no significant differences regarding HBV viral load between HAV and HEV superinfection groups, suggesting that HEV superinfection did not affect HBV DNA replication (16). A retrospective study from India investigated acute exacerbations of previously unrecognized HBV-related chronic liver disease. In 20% of patients, HEV was the reason for acute exacerbation, especially in patients with low HBV-DNA (HBeAg negative). HAV and HEV superinfected HBeAg negative patients did not show significant differences regarding the level of HBV (12). In conclusion, we described an asymptomatic HBsAg carrier who acquired an acute autochthonous HEV superinfection in Germany followed by a transient increase in replication of HBV. The patient was from an area of Germany in which HEV is endemic, but no known risk factor was present. Our patient developed a mild HBV DNA flare without elevation of aminotransferases after superinfection with HEV. The reason for this observation remains unknown. The patient did not achieve HBs seroconversion five months after HEV superinfection. Unlike

other cases of HEV superinfection in CHB or other underlying chronic liver diseases (16, 17), our patient did not have a severe course but had only mild symptoms, likely explained by his low stage of fibrosis. This case illustrates the increasing problem of HEV infection as an emerging zoonotic disease in developed countries. Rising numbers of patients were recently reported from several European countries (2, 6). One reason for this finding could be rising awareness and more frequent testing for an infection, which is usually mild or asymptomatic. Another reason could be an increased prevalence of the virus in animals. Since pigs and wild boars show high seroprevalences in developed countries (4), further investigations of the epidemiology and the routes of transmissions is warranted. Furthermore, investigating other risk factors for the transmission of HEV is necessary. Since there is a vaccine available (20), it should be discussed whether a certain population at risk, such as forestry workers or transplant recipients, should be vaccinated in developed countries as well. To provide them in developed countries, vaccines need to be tested for their efficacy in genotype 3 HEV infection.

Authors' Contributions

Marten Schulz: wrote the case report and reviewed the literature; Eckart Schott: writing and revising the manuscript and reviewing the literature.

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