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【 CASE REPORT 】

The First Case Report of Acute Symptomatic HEV Genotype 4 Infection in an HIV-positive Patient in Japan

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Abstract:
Hepatitis E virus (HEV) is a common cause of acute hepatitis. Four major genotypes of HEV have been studied, with genotype 4 being the predominant genotype across Asia. We herein describe the case of a 50-year-old man with a history of human immunodeficiency virus (HIV) infection who was admitted with acute transaminitis. Serum anti-HEV-IgA and HEV-RNA were detected at the time of presentation and further testing revealed HEV genotype 4. To the best of our knowledge, this represents the first clinical case report of acute symptomatic HEV genotype 4 infection in an HIV-positive patient in Japan.

Key words: hepatitis E, hepatitis E virus, human immunodeficiency virus, men who have sex with men

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Introduction

Hepatitis E virus (HEV) is a 27- to 34-mm single-stranded RNA virus that was first reported as a non-A non-B hepatitis in the late 1970s following an epidemic in Kashmir (1). HEV has been recognized as a common cause of acute hepatitis around the world, with the second highest number of years of life lost among the hepatitis viruses (18.9 years of life lost per 100,000), after hepatitis B virus (49.4 years of life lost per 100,000) (2). HEV is mainly transmitted through a fecal-oral route, which explains the frequent outbreaks from infected water sources or ingestion from infected animal reservoirs (3). The most common genotypes are genotypes 1 to 4 (3). Genotypes 1 and 2 are prevalent in regions with poor sanitation, whereas genotypes 3 and 4 are prevalent in industrialized countries, where they present as zoonotic or autochthonous infections (3). Genotype 4, in particular, is the most prevalent genotype in Asian countries, including China, Indonesia, and Japan (4, 5).

Case Report

A 50-year-old Japanese man with a three-year history of human immunodeficiency virus (HIV)-1 infection presented to the outpatient clinic with a three-day history of dark-colored urine and increased fatigue. His past medical history included *Pneumocystis jirovecii* pneumonia and disseminated *Mycobacterium avium* complex disease, which were treated concomitantly at the time of HIV and the diagnosis of acquired immunodeficiency syndrome (AIDS) two years prior to presentation. He had since been on tenofovir disoproxil fumarate, emtricitabine, raltegravir, levofloxacin, ethambutol, clarithromycin, and monthly inhaled pentamidine. While managed as an outpatient, his CD4 count had gradually increased from 29 cells/μL to approximately 150-200 cells/μL, with no further increase in the CD4 count over the last one year.

He had no travel history within the past six months and had not eaten any raw/undercooked food. He reported no history of illegal drug use or exposure to wildlife. His last reported sexual activity was with a man was approximately three months prior to his presentation.

The results of physical examination were mostly unremarkable, with the exception of mild jaundice. A basic metabolic panel revealed increased liver enzymes and biliary markers: aspartate aminotransferase (AST), 1,228 U/L; alanine aminotransferase (ALT), 1,866 U/L; and total biliru-

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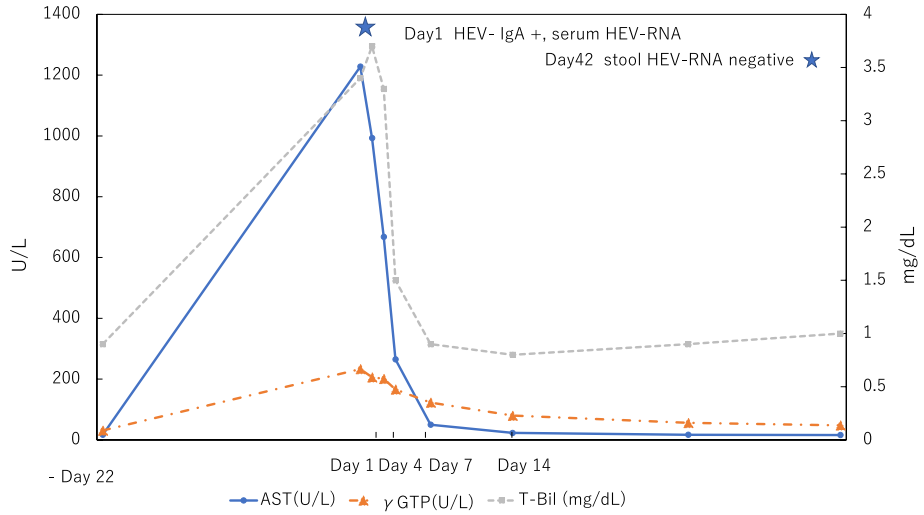

Figure. **Clinical course of the liver enzyme levels.**

Table. **Time Course of the HBs Antigen and HCV Antibody Test Results.**

	two years prior	one year prior	on admisson	after one month	after one year	after two years
HCV Ab	-	-	-	-	-	-
HBs Ag	-	-	-	-	-	-

HCV Ab: hepatitis C virus antibody, HBs Ag: hepatitis B surface antigen

bin, 3.4 mg/dL. The patient was admitted due to acute symptomatic liver injury. His CD4 count and HIV viral load on admission were 148 cells/μL and undetectable, respectively. Abdominal ultrasonography on admission revealed bright liver, indicative of fatty liver.

His transaminase and bilirubin levels began to improve by day 2 after admission with only close observation (Figure). Viral serology for hepatitis A, B, and C, and serological tests for syphilis yielded negative results, while serology for cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and varicella-zoster virus revealed past infections. The patient was discharged at one week after admission due to clinical stability and was followed in an outpatient setting. While the exact diagnosis was unclear, a serum sample obtained during admission returned a positive result for anti-HEV IgA after hospital discharge. A subsequent serum HEV-RNA test on plasma taken during admission returned a positive result, suggesting hepatitis E as the cause of acute liver injury. Further genetic testing revealed genotype 4 HEV as the culprit. HEV-RNA levels in stool was undetectable at one month post-discharge, leading to a final diagnosis of acute HEV infection. Tests for HBs antigen and HCV antibodies have remained negative in the two years since then (Table). The patient has not experienced any other relapses since that time.

Discussion

The seroprevalence of HEV and HIV co-infection varies by region, with Africa and Asia as the most endemic (>40% in most countries), followed by continental European Union countries (10-20%) and finally, countries of the Americas and Oceania (<10%) (6). There are only limited data on seroincidence, which ranges from approximately 2 to 15%, with China reporting the highest incidence (6-9). HIV infection is not viewed as a definite risk factor for HEV infection (6). However, several reports in the literature have described a low CD4 count (<200 cells/μL) as a suspected predisposing factor for the acquisition of HEV infection (10). On the other hand, other studies have reported that higher CD4 counts are associated with a higher HEV seroprevalence (11, 12). Given such divergent results, the risk factors for HEV infection in HIV-positive patients are controversial and no universal consensus has been reached (10).

Apart from asymptomatic and acute hepatitis manifestations, HEV infection may manifest as a chronic infection in immunosuppressed patients, including those with HIV infection (13). In most cases, chronic HEV infection is associated with genotype 3 (14). Conversely, genotype 4 rarely presents as a chronic infection, although one case of chronic infection was described in a patient with acute lymphoblastic leukemia (13, 15). Genotype 4 is usually detected in Asian countries, while genotype 3 is predominant in Europe (16). A nationwide study of HEV prevalence in Japan revealed the predominance of genotype 3 infections (17). However, studies in the Hokkaido region of northern Japan have shown the predominance of genotype 4 infections (up to 85%), suggesting geographical variations within Ja-

pan (18, 19). Studies conducted in Hokkaido have also revealed genotype 4 infection to be associated with higher levels of ALT, a lower prothrombin time, and a longer median hospital stay, suggesting a more severe clinical course in comparison to genotype 3 (20, 21). There are few data on genotype 4 infection and HIV co-infection; however, Lin et al. reported that among 23 patients with HEV seroconversion, 22 patients had detectable HEV genotype 4 viremia (22). The reported 23 patients showed no hepatic or extrahepatic symptoms and only 7 patients showed abnormal results in liver function tests (22). However, the genotype distribution of HEV within Japan and its clinical phenotypes in the HIV-positive populations require further evaluation (20-22).

Although genotype 4 infection is predominant in Asian countries, Hakze-van der Honing et al. detected genotype 4 HEV from swine fecal samples in Belgium (23). Since then, several autochthonous cases have been reported from France, suggesting the emergence of this particular strain in Europe (24-27). The origin and dispersal history of genotype 4 HEV was investigated by a phylogeographical analysis, which suggested migration from Japan or China, which eventually extended to Europe (16). As such, genotype 4 may become a more relevant genotype among Western countries.

HCV infection was included in the differential diagnosis of our case. However, HCV antibody levels remained negative for more than one year, despite a relatively constant CD 4 count of close to 200/mm^3, which suggested that the likelihood of HCV infection was low. In addition, our patient lacked a history of intravenous drug use, which is a strong risk factor for seronegative HCV infection in HIV-positive patients (28, 29). However, testing for HCV RNA would have been a clinical aid to completely rule out seronegative HCV infection. This was one limitation of our report. HEV infection compounded by immune reconstitution inflammatory syndrome (IRIS) was another potential diagnosis, as this entity has been reported in the past (12). In our case, the patient's CD4 count stabilized at 150-200/mm^3 one year prior to the onset of this episode, which does not rule out IRIS, but suggests that it is less likely due to temporal dissociation. In addition, he experienced a relatively prompt spontaneous remission without the addition of immunosuppressant medication. Hence, acute HEV infection seems more compatible in our case, despite difficulty in ruling out IRIS due to absence of prior status on HEV infection.

The incubation period for HEV ranges from two to ten weeks (30). Our patient had not ingested undercooked meat during this period. The clinical presentation was self-limited with no chronicity, similar to the typical symptomatic presentation of HEV genotype 4 infection in the general population (13).

In conclusion, we encountered the first case of acute symptomatic HEV genotype 4 infection in an HIV-positive patient in Japan. A concomitant workup to rule out other causes of hepatitis is crucial when documenting HEV as the cause. Currently, there are few reports on HEV genotype 4 and HIV co-infection and further studies are warranted to compare the epidemiology, risk factors, and clinical characteristics.

The authors state that they have no Conflict of Interest (COI).

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