Simultaneous Hepatitis E and Paratyphoid Fever

JMAJ 48(9): 468–470, 2005

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Abstract
We recently treated a Japanese man who, upon his return from India, presented with a co-infection of the hepatitis E virus (HEV) and Salmonella Paratyphi A. Our experience with this patient underlined the importance of investigating HEV-RNA and antibodies against HEV in patients recently returned from tropical or subtropical areas who manifest elevated serum aminotransferase levels, even when they are infected with other infectious diseases.

Key words  Hepatitis E virus, Salmonella Paratyphi A, India

Introduction
Hepatitis E caused by infection with the hepatitis E virus (HEV) and paratyphoid fever caused by Salmonella Paratyphi A (S. Paratyphi A) are endemic in tropical and subtropical areas. However, to our knowledge, only 2 cases of the co-existence of these two conditions have been reported in the literature.1,2 We recently treated a Japanese patient who, upon his return from India, presented with hepatitis E complicated with paratyphoid fever. After recounting the details of this patient co-infected with HEV and S. Paratyphi A, this paper discusses the importance of screening for hepatitis E in sickly patients returned from HEV endemic areas even when they are infected with other infectious diseases.

Case Report
A 24-year-old Japanese man traveled in India for 2 months and returned to Japan on August 26, 2003. He visited another hospital on September 13 because of 2 days of fever. In the past, his health had been unremarkable. S. Paratyphi A was cultured in his blood and stool, and he was diagnosed as having paratyphoid fever. Upon his admission to our hospital by referral on September 22, 2003, his only definite abnormality on physical examination was a fever of 39.4°C. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin (T-Bil), and C-reactive protein (CRP) were 116 IU/l, 100 IU/l, 867 IU/l, 375 IU/l, 1.1 mg/dl, and 6.13 mg/dl, respectively. The S. Paratyphi A isolated from the patient was resistant to ofloxacin, so he was treated with cefotaxime from September 22 to October 5. Immunoglobulin G (IgG) class antibodies to cytomegalovirus (CMV) and the Epstein-Barr virus (EBV) were detected, but the patient tested negative for immunoglobulin M (IgM) class antibodies to these viruses. The patient’s hepatitis A, B, and C serology was negative. Ultrasonography revealed no stones in the gall bladder or the bile duct. The patient was defervescent on September 29 and discharged on October 6. The serum laboratory data on October 6 were as follows: AST 56 IU/l, ALT 116 IU/l, LDH 221 IU/l, ALP 424 IU/l, T-Bil 0.7 mg/dl, and CRP 0.19 mg/dl.

Three weeks later, on October 27, 2003, he was readmitted to our hospital because of 4 days of fever and identification of S. Paratyphi A in his
stool and blood. His body temperature was 38.3°C on admittance. The laboratory data on October 27 were as follows: AST 146 IU/l, ALT 148 IU/l, LDH 487 IU/l, ALP 469 IU/l, T-Bil 3.5 mg/dl, and CRP 6.46 mg/dl. He was diagnosed as having relapsed paratyphoid fever and was treated with azithromycin from October 27 to October 30, and then ceftriaxone from October 30 to November 8. His body temperature was 39.9°C on October 29, but he was defervescent on November 5. His serum concentrations on November 7 were as follows: AST 155 IU/l, ALT 208 IU/l, LDH 377 IU/l, ALP 1,369 IU/l, T-Bil 1.4 mg/dl, and CRP 0.59 mg/dl, and he was discharged on November 8, 2003.

Five days later, on November 13, 2003, he was readmitted to our hospital when the following data were obtained at our outpatient clinic: AST 697 IU/l, ALT 588 IU/l, LDH 331 IU/l, ALP 1,473 IU/l, T-Bil 1.4 mg/dl, and CRP 0.59 mg/dl. However, the patient did not complain of fever. His continuous stool cultures revealed no S. Paratyphi A while in this admission. The laboratory data on November 19 were as follows: prothrombin time 77.5%, AST 3,908 IU/l, ALT 2,405 IU/l, LDH 12.3 mg/dl, and T-Bil 12.3 mg/dl, and treatment with glucagon insulin therapy was initiated. PCR revealed HEV-RNA (genotype 1) in his serum obtained on October 27, but not in his serum obtained on November 16, and HEV-IgG antibody was identified in his serum collected on both October 27 and November 16. On these bases, he was diagnosed as having hepatitis E. The HEV-RNA, HEV-IgG antibody tests were performed at the Tokyo Metropolitan Institute of Public Health. The patient recovered and was discharged on November 29. The serum levels of AST, ALT, LDH, and T-Bil are shown in Table 1.

### Discussion

The incubation period of paratyphoid fever ranges from 1 to 3 weeks, while that of hepatitis E ranges from 2 to 10 weeks. Our patient was therefore likely to have been infected with these causative organisms in India, where both diseases are endemic. The genotype of HEV isolated from domestically infected patients has been reported to be type 3 or 4 in Japan. In our patient, the genotype of HEV was type 1, a very common genotype in India. This confirmed that he was likely to have been infected with HEV in India.

Mildly elevated levels of serum AST, ALT, LDH, ALP, and T-Bil are commonly observed with typhoid fever and paratyphoid fever, but these abnormalities are generally improved in patients with good therapeutic effect. If elevated serum levels of AST, ALT, LDH, ALP, and T-Bil persist in patients returned from tropical and subtropical areas and they have no serological markers of ongoing infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), CMV, or EBV, the presence of HEV-RNA or antibody against HEV should be investigated.

In a single volunteer study of HEV transmission, HEV was reported to become positive in stool at the onset of the icteric phase and to remain positive until the ALT activity peaked. In contrast to HBV and HCV, the mode of transmission of both HEV and HAV is fecal-oral. While hepatitis E has an overall mortality rate of only 0.07–0.6%, it can be particularly severe among pregnant women, with mortality rates reaching as high as 25%. The prompt identification of patients with acute hepatitis E and timely and thorough measures to prevent contact

| Table 1 Serum AST, ALT, LDH, and T-Bil concentrations (in 2003) |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Sep. 22 | 116 | 207 | 56 | 146 | 155 | 357 | 697 | 3,545 | 3,908 | 254 | ND | ND |
| Oct. 6 | 100 | 219 | 116 | 148 | 208 | 363 | 588 | 1,949 | 2,405 | 665 | 139 | 66 |
| Nov. 27 | 867 | 441 | 221 | 487 | 377 | 280 | 331 | 863 | 533 | 212 | ND | ND |
| Nov. 11 | 1.1 | 0.7 | 0.7 | 3.5 | 1.4 | 2.8 | 4.3 | 8.9 | 12.3 | 6.3 | 3.1 | 1.6 |

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, T-Bil: total bilirubin, ND: not done
transmission from these patients to others are essential within a hospital. This paper emphasizes the importance of screening for hepatitis E in patients who, upon returning from tropical or subtropical areas, manifest high levels of serum aminotransferase, regardless of whether they suffer from other infectious diseases.

Acknowledgements

We are grateful to the staff of the Division of Virology, Department of Microbiology, Tokyo Metropolitan Institute of Public Health, for measuring HEV-RNA and antibodies against HEV.

References