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Persistent Hepatitis E Virus Genotype 4 Infection in a Child With Acute Lymphoblastic Leukemia

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Introduction: In general, the hepatitis E virus (HEV) causes acute, self-limiting hepatitis. Prolonged and chronic infections caused by HEV genotype 4 have been found in some immunosuppressed patients in developed countries.

Case Presentation: Here we report a Chinese boy with acute lymphoblastic leukemia, who developed hepatitis E during a period of intensive chemotherapy. Twenty months after the initial infection, HEV viremia was reappeared in the patient, with detectable anti-HEV IgM and IgG and modestly elevated serum transaminases. Sequence analysis of the viral RNAs revealed the reactivation of the HEV genotype 4d strain, indicating viral persistence in the patient.

Conclusions: To our knowledge, this is the first chronic case confirmed by the prolonged presence of HEV RNA in china. It is also the first reported persistent hepatitis E infection caused by HEV genotype 4.

Keywords: Hepatitis E virus; Precursor Cell Lymphoblastic Leukemia-Lymphoma; Chronic Hepatitis; Persistent Infection

1. Introduction

Hepatitis E virus (HEV) infection is a major cause of acute hepatitis in developing countries, and is an emerging health problem in industrialized countries. HEV is a non-enveloped virus with a single-stranded, positive-sense RNA genome, of approximately 7.2 kb. HEV belongs to the genus Hepeivirus of the family Hepeviridae, and four genotypes have been recognized to infect humans (1). HEV genotypes 1 and 2 are restricted to humans, and are often associated with large outbreaks and epidemics in developing countries with poor sanitation conditions, whereas HEV genotypes 3 and 4 infect humans, pigs and several other mammalian species, and are responsible for sporadic cases of hepatitis E in both developing and developed countries (1).

HEV infection is generally asymptomatic and most commonly manifests as a self-limiting, acute hepatitis in immunocompetent individuals (2). Chronic hepatitis E in immunosuppressed persons has been reported since 2008 (3). Patients with hematological disorders, HIV infection, or undergoing immunosuppressive therapy after solid organ transplantation, are at risk of developing chronic hepatitis E. Recent evidence suggests that about 50% of the cases of acute hepatitis E in immunocompromised patients progress to chronic hepatitis, with rapid progression to cirrhosis (4). Chronic hepatitis E cases have thus far been reported in France, Germany and other European countries and Canada. However, these chronic infections have all been caused by HEV genotype 3, which occurs as a zoonosis in these areas (1). In China, there is a high frequency of HEV epidemics of acute infections, which occur at about 4% per year, as estimated by the prevalence of anti-HEV IgM and the spontaneous rise of anti-HEV IgG levels (5). HEV genotype 4 has been found to be responsible for most hospitalized HEV cases in the recent years (6). However, to date, no chronic hepatitis E cases have been reported in China. Moreover, chronic HEV infection has been described in immunosuppressed adults, but rarely in children. Here, we report a persistent infection by HEV genotype 4d in a Chinese boy with acute lymphoblastic leukemia.

2. Case Presentation

A four-year-old boy was diagnosed with acute lympho-
Table 1. Transaminases and Markers of HEV Infection in the Patient

<table>
<thead>
<tr>
<th>Serum Collection Date</th>
<th>ALT, U/L</th>
<th>AST, U/L</th>
<th>Anti-HEV IgM</th>
<th>Anti-HEV IgG</th>
<th>HEV-RNA, Geq/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-08-02 b</td>
<td>376</td>
<td>146</td>
<td>Yes a</td>
<td>No a</td>
<td>NA a</td>
</tr>
<tr>
<td>2011-08-10 b</td>
<td>241</td>
<td>150</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>2011-09-14 b</td>
<td>585</td>
<td>263</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>2011-09-21 b</td>
<td>166</td>
<td>60</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2011-10-08</td>
<td>540</td>
<td>259</td>
<td>Yes</td>
<td>Yes</td>
<td>3.2 × 10^2</td>
</tr>
<tr>
<td>2011-10-13</td>
<td>331</td>
<td>135</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2011-10-26</td>
<td>128</td>
<td>95</td>
<td>Yes</td>
<td>Yes</td>
<td>3.2 × 10^2</td>
</tr>
<tr>
<td>2011-11-10</td>
<td>118</td>
<td>94</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2013-05-11 b</td>
<td>184</td>
<td>82</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>2013-05-21</td>
<td>523</td>
<td>822</td>
<td>Yes</td>
<td>Yes</td>
<td>3.5 × 10^6</td>
</tr>
<tr>
<td>2013-06-04</td>
<td>156</td>
<td>117</td>
<td>Yes</td>
<td>Yes</td>
<td>1.1 × 10^4</td>
</tr>
<tr>
<td>2013-07-20</td>
<td>121</td>
<td>84</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

a Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HEV, hepatitis E virus, NA, not available; No, negative; Yes, positive.

The data was extracted from the clinical records transferred with the patient from another hospital.
hepatitis E was associated with immunosuppression. Immunodeficiency due to both leukemia and long periods of chemotherapy exposed the boy at risk of a persistent hepatitis infection.

Chronic hepatitis E cases in immunocompromised patients have also been reported in both European countries and Canada. Such chronic infections have all been related to HEV genotype 3, which is prevalent in these areas. HEV is endemic in China, where HEV infection rates are generally higher than those reported in developed countries. In addition, the dominant HEV strains isolated in the recent years from sporadic human cases and pigs were genotype 4 (5, 11). However, until recently, no chronic hepatitis case was reported in China and no chronic case caused by genotype 4 has been reported in any other area. Phylogenetic analysis showed that the HEV strain detected from this patient belonged to subgenotype 4d.

To our knowledge, this is the first case of a persistent hepatitis E infection caused by genotype 4, and the first chronic case in China confirmed by the prolonged presence of HEV RNA. Since specific antibodies against the infected viruses may be absent or produced with delay in immunocompromised patients, serologic testing for the diagnosis of HEV infection is likely to be unreliable in this context, thus PCR-based detection of hepatitis E viral RNA is essential to make the diagnosis. Currently, clinical diagnosis of hepatitis E is primarily based on anti-HEV IgM detection in most hospitals. Therefore, chronic hepatitis E infection may be overlooked and misdiagnosed in cases where drug-induced liver injury is common in patients receiving chemotherapy or antiviral therapy. The prevalence of persistent hepatitis E infections in China and the effects of chronic hepatitis E in immunocompromised patients should be investigated.

The HEV genotype 4d strain detected in this patient showed high similarities with the genotype 4d strains isolated from humans and pigs in China, for instance the nucleotide similarities to the human strain GS-NJ-10 and swine strain HB-SB (Genbank accession Numbers: JF309217 and FJ461765) were 98.4% and 97%, respectively. However, the virus origin was difficult to clarify. The patient was in hospital for several months before the first HEV infection, thus, it is unlikely that he had been infected with HEV through direct contact with animals. The possibility of transmission via contaminated blood products could not be excluded, because the patient had received blood transfusions and blood products during the chemotherapy. In China, HEV-contaminated blood donations are a challenge for transfusion viral safety, since neither HEV antibodies nor HEV RNA are systematically tested in blood donors, and blood donations are currently not tested for ALF. Conversely, consumption of contaminated pork cannot be excluded completely in this patient, because pork is commonly consumed in China.

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The authors have nothing to declare.

Authors’ Contribution

YCW designed the study; HXZ, WJH, KJG and YSG tested the samples; YCW, YSG, ZL and TJH wrote the manuscript.

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The authors declared that there was no financial disclosure.

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References
