Hepatitis B and C Virus Infection is a Risk Factor for the Development of Cholangiocarcinoma

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Abstract

Objective: Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection may be involved in the development of cholangiocarcinoma. The prevalence of HBV and HCV infection was examined in patients with intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC).

Methods: The levels of HBV surface antigens (HBsAg), antibodies against HBV core antigens (HBcAb) and hepatitis C virus antibodies (HCV-Ab) were determined in sera obtained from 145 consecutive patients (50 patients with ICC, 95 patients with ECC).

Results: The seroprevalence of HBsAg was 10% in the ICC patients and 4.2% in the ECC patients. The prevalence of HCV-Ab was 20% in the ICC patients and 7.4% in the ECC patients.

Conclusion: The prevalence of HBsAg and HCV-Ab is 0.8-2.2% and 1-2%, respectively, in the Japanese population living in the Tottori area. Furthermore, HBV and HCV infection is a possible risk factor for the development of cholangiocarcinoma. Therefore, the surveillance of ICC and ECC is needed in HBV and HCV carriers.

Key words: hepatitis B virus, hepatitis C virus, cholangiocarcinoma

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Introduction

Cholangiocarcinoma is relatively rare in most parts of the world, although high rates of the disease have been reported in populations in various geographic locations, including China, Japan, Korea, India, Eastern Europe and Latin America (1). However, the etiology of cholangiocarcinoma remains poorly understood. Obesity, inflammatory conditions of the biliary tract, ulcerative colitis, an abnormal choledocho-pancreatic junction, Caroli’s disease, exposure to the radiopaque medium thorium dioxide (Thorotrast) and choledochal cysts have been suggested to be risk factors (1, 2). In addition, chronic infection with Salmonella typhi, Helicobacter species and the liver flukes Clonorchis sinensis and Opisthorchis viverrini has been implicated (1, 3-5). Palmer and Patel (6) and Zhou et al. (7) previously reported that hepatitis B virus (HBV) and hepatitis C virus (HCV) infection is associated with an increased risk of intrahepatic cholangiocarcinoma (ICC). Recent studies from China, where the prevalence of the HBV carrier state is very high, have shown that HBV DNA and HCV RNA are detected in the tissue specimens of patients with ICC and extrahepatic cholangiocarcinoma (ECC) (8, 9). In contrast, one recent U.S. study, where the prevalence of HBV chronic infection is very low (0.4%), did not find an association between hepatitis B surface antigen (HBsAg) and ECC (10). In the Tottori area and among Japanese individuals ≥20 years of age, the HBV and HCV infection rates are 0.8-2.2% and 1-2%, respectively (11, 12). In this study, we examined the associa-
Table. Biliary Tract Cancer in Relation to HBV and HCV Infection

<table>
<thead>
<tr>
<th>HBV/HCV</th>
<th>ICC* (%)</th>
<th>ECC** (%)</th>
<th>Gallbladder (%)</th>
<th>Extrahepatic bile duct (%)</th>
<th>Ampulla of Vater (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>total</td>
<td>145</td>
<td>50</td>
<td>95</td>
<td>37</td>
<td>53</td>
</tr>
<tr>
<td>HBsAg/ HBcAb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative, negative</td>
<td>116</td>
<td>34 (68)</td>
<td>82 (86.3)</td>
<td>31 (83.8)</td>
<td>47 (88.7)</td>
</tr>
<tr>
<td>Negative, positive</td>
<td>20</td>
<td>11 (22)</td>
<td>9 (9.5)</td>
<td>4 (10.8)</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>Positive, positive</td>
<td>9</td>
<td>5 (10)</td>
<td>4 (4.2)</td>
<td>2 (5.4)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>128</td>
<td>40 (80)</td>
<td>88 (92.6)</td>
<td>35 (94.6)</td>
<td>49 (92.5)</td>
</tr>
<tr>
<td>Positive</td>
<td>17</td>
<td>10 (20)</td>
<td>7 (7.4)</td>
<td>2 (5.4)</td>
<td>4 (7.5)</td>
</tr>
</tbody>
</table>

* ICC: intrahepatic cholangiocarcinoma
** ECC: extrahepatic cholangiocarcinoma

Table shows the prevalence of HBV and HCV infection in the patients with cholangiocarcinoma. The prevalence in the general population in the Tottori area of Japan is ≤2.2% for HBsAg, 19.7% for HBcAb and <2% for HCV-Ab (11, 12). In this study, the prevalence of HBsAg was markedly higher in the patients with ICC (10%), gallbladder cancer (5.4%) and extrahepatic bile duct cancer (3.8%) than that observed in the Tottori area and in the Japanese population.

Similarly, the prevalence of HCV-Ab was markedly higher in the patients with ICC (20%) and ECC (7.4%) (extrahepatic bile duct cancer (7.5%), gallbladder cancer (5.4%) and ampulla of Vater cancer (20%)) than in the Tottori area and the Japanese population.

We herein present two typical cases of ECC that developed during the follow-up of chronic hepatitis B and C infection. Case 1: A 70-year-old man underwent routine abdominal computed tomography (CT) and echography as part of chronic hepatitis C management from 59 years of age. He was found to have obstructive jaundice and a 10-mm mass in the distal bile duct. Extrahepatic bile duct resection was performed, and well-differentiated adenocarcinoma was detected (Fig. 1). Case 2: A 64-year-old man underwent routine abdominal CT and echography as part of chronic hepato-
titis B management from 40 years of age. He was found to have obstructive jaundice and a 7-mm mass in the left hepatic duct. Extrahepatic bile duct resection was performed, and moderately differentiated adenocarcinoma was detected (Fig. 2).

Discussion

In this study, there was a high prevalence of HBV and HCV infection in the patients with ICC and ECC. These data suggest that HBV and HCV infection are possible risk factors for the development of cholangiocarcinoma.

Previous studies have shown that both HBV infection (13, 14) and HCV infection (14) are linked to ICC. Recent studies from Japan and Italy have also reported an association between HCV and ICC (5, 13). Yin et al. reported that HCV RNA was isolated from ICC tissue using real-time polymerase chain reaction (RT-PCR) (8), which suggests a relationship between HCV infection and the development of ICC.

Previous studies have reported detecting HCV RNA in tissue specimens obtained from patients with ICC (8, 9). Torbenson et al. (15) reported that dysplasia can be found within the intrahepatic bile ducts in chronic HCV cirrhosis patients.

Previous studies have also shown that HCV infection, but not HBV infection (16-20), is linked to ECC. Wu (16) reported that, in both univariate and multivariate analyses, ethanol (p<0.001), ethanol + HCV (p<0.001) and HCV cirrhosis (p<0.001) were significant predictors of the grade of biliary intraepithelial neoplasia. Moreover, hepatitis C virus core proteins exert effects on the modulation of cellular proliferation and apoptosis in hilar cholangiocarcinoma tissues (17, 18), while HCV RNA sequences have been detected in ECC samples (19). Taking these findings into account, HCV infection appears to induce the development of cholangiocarcinoma. In contrast, the mechanisms by which HBV infection induces the development of ICC and ECC are unclear.

In summary, the present study examined the associations between extrahepatic bile duct cancer and HBV and HCV infection. HBV and HCV infection are potential risk factors for the development of cholangiocarcinoma. Therefore, the surveillance of ICC and ECC is needed in HBV and HCV carriers. Although the incidence of cholangiocarcinoma is low in most populations, the high fatality rate of the disease intensifies the need for further studies to clarify its association with HBV and HCV infection.

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

References


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