Hepatocellular Carcinoma in Primary Biliary Cirrhosis at an Early Histologic Stage: Coincidental or Causally Related?

**Key words:** Primary biliary cirrhosis

Recent studies have shown that hepatocellular carcinoma (HCC) arises relatively frequently at an advanced, cirrhotic stage of primary biliary cirrhosis (PBC) without evidence of hepatitis viral infection (1–3), though the precise incidence of such association remains unclarified. Shibuya et al reported that most HCC associated with PBC arise at the cirrhotic stage and in males gender and the risk of HCC in patients with late stage PBC is relatively comparable to HCV-related cirrhosis (2). Long-standing hepatocellular damage and regeneration of hepatocytes seem to be causally related to hepatocarcinogenesis at the cirrhotic stage of PBC as speculated in other chronic liver diseases with eventual development of HCC (1, 2). In comparison with HCC in hepatitis virus-related cirrhosis, HCC detected in PBC cases was generally small and HCC itself was not always lethal in these cases (2, 3); rather, the majority of such patients died of hepatic failure due to advanced cirrhosis of PBC. In fact, small HCCs were detected incidentally at autopsy or transplanted livers (3). Shibuya et al reported that superimposition of hepatitis viral infection could be a synergistic factor for HCC development in PBC (2).

Regarding preneoplastic lesions in the development of HCC in cirrhotic PBC, dysplastic nodules which are now proposed as a preneoplastic lesion of HCC in hepatitis virus related chronic liver diseases have also been reported in advanced stages of PBC (4). In fact, foci of classical HCC within dysplastic nodules are reported in cirrhotic PBC livers (4), suggesting that the dysplastic nodule-HCC sequence may be one type of HCC development in advanced PBC.

As for HCC arising in the non-cirrhotic stage of PBC, there have been few cases in the literatures (5). The background liver pathology preceding or related to the occurrence of HCC has not been described in detail. However, according to the literature or based on our experience, the following candidate histologic lesions are considerable for the development of HCC. First, nodular regenerative hyperplasia of the hepatocytes (NRH) can be such a lesion. Occurrence of NRH is established in the non-cirrhotic liver of PBC including stage I (6), and NRH associated with PBC at early histological stages may reflect an active hepatocellular proliferation (6). In non-PBC cases, there have been several studies suggesting that NRH is a preneoplastic lesion of HCC (7).

Particularly, NRH with dysplastic changes can be a lesion associated with HCC development. That is, Nzeako et al reported that liver cell dysplasia occurred in a significantly greater population of patients with NRH and that HCC may develop in the livers with dysplastic foci and NRH (7). Furthermore, irregular and active regeneration of hepatocytes in chronic liver disease related to HCV infection is reportedly likely followed by the development of HCC. In this context, NRH of PBC could also be related to the occurrence of HCC, probably via dysplastic changes. However, the precise significance of NRH in PBC and the long-term follow-up studies of PBC patients with NRH remain to be documented.

Second, small cell changes of hepatocytes resembling small cell dysplasia have been reported in the non-cirrhotic liver of PBC (8). Such small cell dysplasia was reported to be related to the development of HCC in hepatitis virus related liver cirrhosis. While small cell change in non-cirrhotic PBC liver may be a candidate lesion related to HCC development, our previous study showed that proliferative activities of small cell change found in non-cirrhotic stage of PBC was low and reduction of reticulin fibers were not evident in contrast to small cell dysplasia or early HCC found in hepatitis virus-related cirrhosis (8).

To date, the exact relation between these candidate lesions in non-cirrhotic liver of PBC and development of HCC is still controversial or remains unexplored, and the studies of such lesions in more cases of PBC associated with HCC are necessary to resolve these issues.

The occurrence of HCC in an early stage (stage I) of PBC is very rare. Kadokawa et al reported such a case in this issue (9). While they found stage I histologies of PBC in the background liver, they failed to find NRH or small cell dysplasia or other lesions related to HCC development. Therefore, NRH or small cell changes of hepatocytes do not seem to be related to the development of HCC in their case.

Clinical hepatologists and pathologists might have encountered anecdotal case(s) of HCC arising in PBC in individual hospitals or institutions. At the moment, it is still controversial whether HCC in stage I of PBC is a coincidence as speculated by Kadokawa et al (9) or has some causal relations. It is also unsettled whether HCV or HBV or carcinogenic factors may be synergistic in the development of HCC in PBC.
of HCC in PBC or not. A large-scale or nationwide survey of such cases seem mandatory to resolve these issues.

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References