Causes of Non-B, Non-C Hepatocellular Carcinoma: Is TTV a Causative Agent?

Key words: hepatocellular carcinoma, TTV, non-B, non-C

Hepatitis B virus (HBV), hepatitis C virus (HCV) and alcohol are the major causative agents of liver diseases in the world, while the etiology of approximately 5 to 10% of chronic liver diseases is still unknown. TT virus (TTV) was identified from the serum of a patient with non-B, non-C posttransfusion hepatitis in 1997 (1). The prevalence of this virus has been studied by many investigators. It has been proven that a considerable proportion of patients with various liver diseases such as acute hepatitis, chronic hepatitis and liver cirrhosis with unknown etiology are infected with TTV. However, a similar proportion, or slightly lower proportion of liver diseases with known etiology and healthy controls has been proven to be infected with TTV. TTV is detected in many organs and many types of body fluids (2), which may relate with the high prevalence of TTV in both patients and healthy controls. Some reports have described the possible relation between TTV and liver diseases, while many reports are against this conclusion. Some reports suggest certain genotypes or viral load may be related to liver diseases (3).

In this issue, Toshikuni et al reported a case with hepatocellular carcinoma (HCC) arising from noncirrhotic liver with TTV infection (4).

See also p 1172.

This case implies two important factors; one is the infection of TTV, and the other is HCC from noncirrhotic liver. The prevalence of TTV in patients with HCC has been described in many reports. Some reports favor a relationship and many are against (5–10), which is the same as the studies concerning the relation between TTV and other liver diseases. In addition to the study of the prevalence of TTV, some basic studies have been done concerning a possible role of TTV in carcinogenesis. Integration of TTV-DNA was studied in the liver tissue obtained from serum TTV-positive non-B, non-C HCC, and it has been confirmed that TTV-DNA is not integrated into host hepatocyte DNA (11). Study of TTV gene transgenic mouse has been done, however occurrence of HCC has not been reported to date (12). Some other studies indicate that TTV may have some role in hepatocarcinogenesis in HCV-related liver diseases (13, 14).

However, although the possibility of the etiological relation between TTV and HCC cannot be denied, it is hard to conclude that TTV is a carcinogenic virus from the data in published reports to date.

On the other hand, HCC usually occurs from cirrhotic liver or advanced fibrotic liver in cases with HCV infection. It has been reported that non-B, non-C HCC is more frequently found in cases without liver cirrhosis, which may indicate that the mechanism of hepatocarcinogenesis is different between HCV-related HCC and non-B, non-C HCC (15, 16). In addition to HBV and HCV, aflatoxin, thiorotast, hemochromatosis and Budd-Chiari syndrome are known agents or diseases that cause HCC. It must be noted that a considerable number of patients with many other liver diseases, such as autoimmune hepatitis, primary biliary cirrhosis, primary selerosing cholangitis, alcoholic liver diseases, Wilson’s disease, and non-alcoholic steatohepatitis are complicated with HCC. It used to be believed that the occurrence of HCC was rare in these diseases. However, recent progress of therapy against these diseases has enabled the control of the diseases, and the number of patients who died from liver insufficiency has decreased; patients with these diseases can survive for a longer period than before. This may relate to the increase of patients with HCC in these diseases. The onset of congenital metabolic diseases such as Wilson’s disease is usually in childhood, however, when the degree of metabolic disorder is mild, the age of onset of the disease is sometimes in adults. Therefore, examinations for congenital diseases should be done not only in children but also in adult patients with liver diseases of unknown etiology. For physicians, it is absolutely important to rule out the known liver diseases described above when examining a patient with non-B, non-C HCC. Another important point is to perform careful follow-up and screening of HCC when examining patients with these diseases, as well as HBV- and HCV-related liver diseases. For researchers, further study is needed to clarify the mechanism of hepatocarcinogenesis, including the role of TTV.

Kojiro Michitaka, MD and Morikazu Onji, MD
Third Department of Internal Medicine,
Ehime University School of Medicine,
Shitsukawa, Shigenobu-cho, Onsen-gun, Ehime 791-0295
References


