Pathology of idiopathic non-cirrhotic portal hypertension

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Idiopathic non-cirrhotic portal hypertension (INCPH) represents diseases in which splenomegaly, anemia, and portal hypertension occur but no causative disease, such as liver cirrhosis, occlusion of the extrahepatic portal vein/hepatic vein, blood disease, parasitic disease, granulomatous liver disease, or congenital hepatic fibrosis, can be demonstrated [1, 2].

Regarding the geographical prevalence of INCPH, it was previously high in India and developing countries, but INCPH patients have recently decreased worldwide, probably because of improvement of social and environmental conditions.

The main clinical signs and symptoms of this disease are splenomegaly, anemia, esophageal/gastric varix, and portal hypertensive gastroenteropathy. Hematemesis/melena and anemia are observed in about half of INCPH patients. Ectopic varix and ascites also develop in association with portal hypertension. A hemorrhagic tendency, liver dysfunction, and hepatic encephalopathy may appear. This disease does not usually progress to liver cirrhosis, and although it may be complicated by hepatocellular carcinoma, such cases are very rare [3]. Hepatic atrophy may progress to liver failure.

As to the cause of this disease, many theories have been reported. Theoretically, the etiology of INCPH can be divided into five categories: chronic infections, exposure to medication or toxins, genetic disorders, thrombophilia, and immunologic disorders. Regarding the infection theory, repeat infection of bacteria such as *Escherichia coli* through the gut may cause septic embolization and

subsequent intrahepatic portal vein occlusion. This theory is supported by the high prevalence of INCPH in low socioeconomic areas where the incidence of abdominal infection is high. Exposure to several medications and chemicals has been reported to cause INCPH, especially arsenic. The thrombophilia theory is predicated on the high prevalence of prothrombotic disorders and high incidence of portal vein thrombosis in INCPH patients. The immunologic disorder theory is based on reports that INCPH is characterized by female preponderance, that it is complicated with various autoimmune disorders such as systemic sclerosis and systemic lupus erythematosus, and that various autoantibodies are present in serum. As to the genetic disorder theory, familial clustering of INCPH and association with human leukocyte antigen (HLA)-DR3 and with congenital disorders (e.g., Adams-Oliver syndrome and Turner's disease) suggest a genetic background for INCPH. However, these theories remain speculative because of a lack of supportive data [1, 2].

Possible mechanisms of portal pressure elevation include an increase in portal blood flow resistance induced by occlusion of the intrahepatic portal vein branches and an increase in splenomegaly-associated splenic blood flow [1, 2, 4]. However, it is difficult to explain splenomegaly, which is a characteristic of INCPH, simply in terms of portal pressure elevation-associated congestive spleen. Strong expression of inducible NO (iNOS) and endothelial nitric oxidase synthetase (eNOS) in the sinus-lining cells of the spleen have been demonstrated. Both iNOS and eNOS may cause the dilatation of the splenic sinuses, subsequently contributing to splenomegaly [4]. The main pathology of this disease is present in both the liver and spleen, suggesting that some type of immune reaction plays an important causative role.

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The mechanism of occlusion of the portal branch is unclear. The peripheral portal branch thrombosis theory offers one possible explanation. This states that thrombosis occurs primarily in the peripheral portal vein branches, resulting in their occlusion. However this theory seems questionable since thrombus in the portal branch is very rarely observed in biopsies of INCPH liver.

Regarding the mechanism of peripheral portal vein occlusion, Nakanuma et al. discovered an interesting pathologic finding of INCPH [5]. They pointed out that small portal veins and skin findings are similar between patients with scleroderma and INCPH. They reported that transforming growth factor- β (TGF- β) and connective tissue growth factor, which are fibrosis-related and vascular endothelial growth factors, respectively, increase in serum, skin, and the portal vein and suggested that they could be mechanisms of the portal vein occlusion in INCPH. Recently the endothelial mesenchymal transition (EndMT) theory was proposed by Kitao et al. based on these findings [6]. They hypothesized that vascular endothelial cells of portal venules transform into myofibroblastic cells, as evidenced by reduced expression of vascular endothelial marker CD34 and increased expression of mesenchymal marker S100 and α -SMA. The increase of TGF- β in sera may act as a potent inducer of EndMT.

Pathologic studies over many years have clarified the characteristics of various pathologic changes in the INCPH liver [1–9]. They can be briefly summarized as follows. Macroscopically, the liver surface shows wrinkle-like irregularities. The intermediate-size portal tracts are expanded by fibrosis and get closer to each other or to the hepatic capsule, reflecting parenchymal atrophy in the subcapsular area. The main branch of the intrahepatic portal vein is thickened and dilated. Histologically, the portal tracts show a round-shaped fibrous expansion. Some cases show septal-like fibrosis extending from the portal tracts. In the most peripheral portal tracts, narrowing, collapse, and loss of the portal vein branch are almost always observed. These lesions were often previously referred to as hepatoportal sclerosis, but this nomenclature is no longer used. Obliterative portal venopathy is now considered to be a more appropriate and accurate term. Abnormally dilated thin-walled vessels or aberrant vessels are frequently observed adjacent to portal tracts. Hyperplastic nodules are formed by hyperplasia of hepatocytes, and lesions of nodular regenerative hyperplasia (NRH) and focal nodular hyperplasia-like lesions may be present, probably as compensatory changes related to the parenchymal atrophy [10].

Thus, INCPH liver has various pathologic characteristics including obliterative portal venopathy. On the other hand, histologic findings similar to those in INCPH have been reported in non-INCPH cases [11–14]. Zuo et al.

recently investigated fatty liver histopathologically and reported some interesting findings [11]. They found that histopathologic changes in the INCPH liver also occur in fatty liver cases without portal hypertension. Their study is significant with regard to the pathogenesis and pathophysiology of INCPH, but from another viewpoint, it pointed out again that changes that have been regarded as pathologic characteristics in the liver with INCPH may be nonspecific, i.e., their study pointed out that histopathologic changes in the liver with INCPH appear regardless of the presence of portal hypertension. However, they stated in their discussion that “fatty liver cases with hepatic pathological findings of INCPH may develop portal hypertension in the future even though it is not observed at the time of liver biopsy.” Studies supporting their assumption have been reported. For example, Cazals-Hatem et al. found that portal hypertension developed during the course of some patients with histologic findings of INCPH liver despite no portal hypertension being observed at the time of biopsy [13]. They also reported aggravation of symptoms when portal hypertension was present. Careful long-term follow-up may be necessary to clarify whether cases of portal hypertension develop from the non-INCPH cases with fatty liver investigated by Zuo et al. [11].

It is of interest that findings similar to those of INCPH have been found not only in other diseases but also in autopsy cases of elderly people without disease [14]. In the hepatic subcapsular area in the elderly, collapse of the portal branch and round fibrous expansion of the portal tract very similar to those in INCPH are often seen. Therefore care is needed when making a pathologic diagnosis in case of the hepatic lesions similar to those of INCPH.

Regarding the pathologic diagnosis, liver biopsy is useful to diagnose INCPH because of the characteristic findings. INCPH is diagnosed by exclusion. The most important disease to differentiate from INCPH is liver cirrhosis, and this can be excluded by liver biopsy. However, diagnosis is difficult when the biopsied liver specimen is small. Therefore, to diagnose INCPH, it is very important to obtain a pathologically evaluable liver specimen by needle biopsy, i.e., a long and broad specimen is preferable. I believe it is desirable for at least ten portal tracts to be contained in a liver biopsy specimen. Regarding the evaluation of obliterative portal venopathy in liver biopsy specimens, the usefulness of quantitative assessment using morphometry has been reported [14]; however, it may not be practical.

From the pathologic point of view, there are issues with pathologic changes in INCPH liver that need to be resolved more precisely. We do not dispute the results of studies such as the Zuo et al. report, which showed that histologic

changes similar to those in INCPH can be observed in diseases other than INCPH [11]. However, it is not yet clear whether these similar pathologic changes found under INCPH and non-INCPH conditions are actually the same or not. It seems important to examine this question in more detail. For example, Zuo et al. described thin-walled vessels present in the paraportal area as shunt vessels in their study [11], but it is unclear whether these have the same shunt function in fatty liver as they do in INCPH. This vascular change observed in fatty liver may not be a shunt but simply an expansion of the vasa septalis and inlet venule induced by another cause. Therefore, at present, it may be more appropriate to describe them as aberrant vessels rather than shunt vessels. Furthermore it may also be necessary to clarify which blood vessels these aberrant vessels connect to. We concluded in our previous study that aberrant vessels observed in INCPH end in the parenchymal sinusoid and that they do not form a shunt with the central vein [15]. Ohbu et al. also observed no shunt between aberrant vessels and the central vein [16]. However, Sato et al. recently reported shunt formation in the liver with INCPH [17]. Aberrant vessels in INCPH have been investigated from various viewpoints, as described above, but the pathologic clarification is still insufficient.

Many pathologic points remain to be elucidated with regard to the liver and spleen in INCPH. Proceeding pathologic studies on INCPH will improve our understanding of the cause and pathogenesis.

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