PATHOLOGY AND IMMUNOPATHOLOGY OF ACUTE AND CHRONIC HEPATITIS B

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In this paper, I will describe the pathologic characteristics of acute and chronic hepatitis B, as derived from our current konwledge of the biology of hepatitis B virus (HBV) (l) and of the immunopathology of the disease (2). Since the exact mechanism of hepatocyte necrosis by HBV is still unknown, some of the information presented here is speculative.

Several lines of evidence indicate that HBV is not directly cytopathic for hepatocytes. First, there is no correlation between the amount of HBV antigens in the serum or liver of patients with hepatitis B and the severity of liver damage(3-6). In fact, the relationship is often inverse (7-10). Second, infected hepatocytes containing HBV or its antigens show only minor, if any degenerative changes at light and electon mic-roskopic levels (ll). Many HBV carriers have normal liver morphology and function, although their hepatocytes frequently express abundant amounts of HBV or its antigens (12-14). Third, there is no cytopathic effect in cultured human hepatoma cells which actively replicate HBV and produce mature infectious Dane particles, as recently reported by several groups of investigators (15-17). In the absence of a direct viropathic effect, it is likely that the immune response of the patient mediates hepatocyte injury in acute and chronic HBV infection. This is supported by the predominance of lymphocytes and macrophages rather than polymorphonuclear leukocytes in the infected liver. In acute hepatitis B, conspicuous numbers of lymphocytes and other mononuclear cells infiltrate portal tracts and sinusoids throughout the hepatic lobules and are often in apposition to hepatocytes. The latter show evidence of cell injury which may present in 2 forms, i.e. ballooning degeneration and cytolysis or coagulative necrosis and formation of acidophilic or apoptotic bodies. Sometimes, lympocytes are seen within the cytoplasm of hepatocytes (emperipolesis) (18). Close contact between lymphocytes and damaged hepatocytes (peripolesis) or acidophilic bodies has been described as a characteristic finding in hepatitis B in contrast to one form of non-A, non-B hepatitis which may be mediated by a direct viropathic mechanism. Regeneration in acute viral hepatitis is reflected in mitoses and bi-or multinucleation of hepatocytes. The combination of these features,i.e. hepatocyte degeneration and regenaration, sinusoidal cell activation, and diffuse inflammation result in the characteristic overall picture of lobular disarray, hepatocyte plemorphism and hypercellularity (19-28).

What is the phenotype, target and effect of the lymphocytes in the liver of patients with hepatitis B ? The life cycle of HBV may shed some light on these questions. Studies of the natural history of hepatitis B suggest that HBV infection proceeds through two stages, an early replicative (permissive) stage and a later non-replicative (non-permissive) stage (29-31). During acute infection and the initial period of chronic infection, the viral DNA is present in episomal (free or extrachromosomal) form and the virus replicates in the hepatocyte with complete transcription of the genome resulting in production of mature infectious virions, HBV, DNA, DNA polymerase, HBsAg, HBcAg and HBeAg. HBV replication appears to occur primarily in the cytoplasm (32) with concamitant expresion of HBcAg or HBeAg on the cell surface (33). This replicative phase of HBV infection is associated with progressive liver disaese (34-37).

Immunohistochemical studies of lymhocyte subsets in liver sections revealed that CD8 positive lymhocytes accumulated in areas of focal necrosis in acute hepatitis B and of piecemeal necrosis in chronic active hepatitis B (38-46). These cells probably represent cytotoxic T lymphocytes which recognize HBcAg or HBeAg on the surface of infected cells in the context of class I HLA antigens (2) A series of cytotoxicity studies of peripheral blood lymphocytes against autologous hepatocytes in patients with chronic HBV infection suggested that T lymphocytes were cytotoxic for hepatocytes with HBcAg or HBeAg, but not for hepatocytes with HBsAg, on the cell surface (47-52). If confirmed, it follows that hepatocytes with active HBV replication and expression of nucleocapsid antigens on the cell surface may be attacked by cytotoxic T lymhocytes. This mechanism may result in the elimination of the virus and termination of the infection. The necrotic debris is phagocytosed by macrophages or Kupffer cells. These phagocytes are recognized by their PAS potive diastase resistant cytoplasm and are seen in the hepatic lobules,often in clusters, and in the portal tracts during the late or residual stage of acute hepatitis B.

It is not known why a small percentage (less than 5 %) ofpatients with acute hepatitis B does not eliminate the virus and develops chronic hepatitis B. It is very difficult for the Pathologist to recognize transition to chronicity in the liver biopsy specimen of a patient with prolonged viral hepatitis B (Table 28) (53-56).

The presence of HBsAg containing groundglass hepatocytes appears to be the only reliable criterion indicating the development of chronicity (53) with the possible exception of piecemeal necrosis in the absence of hepatitis A (55). The extraordinary variations in the course and outcome of chronic hepatitis B may be related to the genetic background of the individual (57-59), modulatory factors such as antibodies to viral antigens or to idiotypes (60-6l), serum-, cell-, or liver-derived immunoregulatory molecules (62) or immunoregulatory cells (63).Environmental factors such as super or coinfection by other viruses may also play a role (see below).For instance, antiviral antibodies such as anti-HBc, can bind to the cell surface and mask HBcAg expression on infected hepatocytes (33) which then may escape immune clearance and support persistence of HBV.Continued active viral replication will result in the development of chronic active

Table 28. Histologic findings which have been suggested to predict transition to chronicity in prolonged viral hepatitis.

HBsAg-containing groundglass hepatocytes
Piecemeal necrosis
Bridging necrosis
Bile duct damage
Plasma cells in portal tracts
Lymphoid follicles in portal tracts

hepatitis B. HBV replication is probably a major cause of active and progressive liver disease (35-37,64) Depending on factors still unknown, HBV DNA will become integrated into the chromosomes of increasing numbers of hepatocytes with conversion to the non-replicative phase of HBV infection (30,31) This period of HBeAg/anti-HBe conversion is often preceded by increased necroinflammatory activity in chronic active hepatitis B (65-68). The morphologic hallmark of this disease represents piecemeal necrosis, (69, 70) i.e. extension of the inflammatory infiltrate from the portal tracts (as the sites of entry) into the surrounding limiting plate with destruction of single or grouped hepatocytes. Hepatocytes at the edge of portal tracts and septa often show peripolesis and emperipolesis by lymphocytes. As decribed above, CD8 positive cytotoxic T lymphocytes predominate among the inflammatory cells, but macrophages, plasma cells and scattered polymorphonuclear leukocytes are also present. The portal tracts are expanded by the periportal zone of piecemeal necrosis, inflammatory infiltration and fibrosis with formation of septa. Increased synthesis of collagen and proliferation of bile ductules are probably secondary phenomena mediated by lympho- or monokines.

The progressive fibrosis extends from the portal tracts to and around the periportal hepatocytes with formation of pseudo-rosettes and septa which eventually connect portal tracts with terminal hepatic venules leading to loss of the normal lobular architecture and to the development of cirrhosis (19-25,73-78). Increased activity may also be reflected in irregular necroinflammatory foci in the hepatic lobules (69) and around the terminal hepatic venules, in the formation of bridging necrosis (70-82) between portal tracts and terminal hepatic venules or in multilobular necrosis and collapse of liver parenchyma (83). These processes, particularly the cincumscribed lobular alterations (31), which may mimic acute hepatitis and may be followed by seroconversion to anti- HBe (65-68), probably hasten the development of cirrhosis and may be precipitated by reactivation of latent HBV infection (or "reversion") (5,89,90,64) or superinfection by other viruses (84-88) (Table 29). Immunohictochemical studies demonstrated that scattered hepatocytes express HBsAg in the cytoplasm and/or along the plasma membrane and HBcAg in the nuclei and/or cytoplasm or plasma membranes (reviewed in 91). The cytoplasmic localization of HBcAg appears to correlate best with increased necroinflammatory activity in chronic active hepatitis B (92).

Tablo 29. Events which may be related to intralobular necroinflammation in chronic active hepatitis B.

Reactivation of HBV replication (" reversion ") (anti - HBe ⟶ HBeAg)
Increased immune elimination of HBV infected hepatocytes (HBeAg ⟶ anti - HBe)
Superinfection by other viruses (HAV, HDV, non - A, non - B, ? HIV)

In the non-replicative phase of HBV infection, the integrated viral genome often shows deletions or rearrangements resulting in incomplete viral gene expression and transcription mainly of the S gene and little or no production of HBcAg., HBeAg, free HBV DNA, DNA polymerase, and complete virus (93). This phase is usually associated with anti-HBe in the serum and remission of disease activity in the liver which may show chronic persistent hepatitis or inactive cirrhosis (31,35, 94- 96). If it is true that HBcAg or HBeAg represent the major target antigens for cytotoxic T lymphocytes, the lack of production of these antigens during the non-replicative phase would explain the decreased activity.

Chronic persistent hepatitis B is characterized by little or no necroinflammatory activity in the hepatic parenchyma and the limiting plate which remains intact (73,74,97) The mononuclear cell infiltrate is confined to the portal tracts which are expanded, but usually do not show significant fibrosis or proliferation of bile ductules. The lobular architecture is preserved and the sinusoidal lining cells are activated to varying degrees. In contrast, chronic septal hepatitis (98) and inactive cirhosis are characterized by fibrosis while inflammation and necrosis are minimal. Histochemical (orcein or Victoria blue) or immunohistochemical stains often reveal large numbers of HBsAg positive groundglass hepatocytes in chronic persistent hepatitis and inactive cirhosis, while no or little HBcAg is demonstrable (91). It should be noted that the separation between chronic active hepatitis and chronic persistent hepatitis and between the two phases of HBV infection is not sharp. i.e. serum HBV DNA and/or intrahepatic HBcAg have been found in a significant number of anti-HBe positive patients with severe chronic active hepatitis B (29, 94, 99-101).

CONCLUSIONS

An attempt has been made to relate the pathologic findings in acute and chronic hepatitis B to our current knowledge of the life cycle and immunobiology of hepatitis B virus. Several lines of evidence support the hypothesis that cytotoxic T lymphocytes which recognize HBeAg on the surface of infected cells, mediate necrosis of hepatocytes with active viral replication. Other immune reactions such as humoral mechanisms (102), antibody dependent cellular cytoxicty, macrophage mediated cytolysis or natural killer cell activity (63, 103) may also play a role. In addition, genetic influences including sex-linked factors (104), hormones, lifestyle and environmental parameters, such as drugs, and superimposed infections by other viruses, such as hepatitis A, D, non-A, non-B viruses (84-88,105) as well as human immunodeficiency virus may influence the type, severity and course of hepatitis B. Lymphocytotoxicity rather than a direct viropathic effect would explain the characteristic histologic finding of close contact between lymhocytes and hepatocytes throughout the lobular parenchyma in acute hepatitis B and in the areas of piecemeal necrosis in chronic active hepatitis B. Histologically, deposition of collagen distinguishes acute from chronic hepatitis B. Chronic persistent hepatitis does not show significant necroinflammatory activity and may occur de novo or during the nonreplicative phase of HBV infection.

Over the last decade,much progress has been made in our knowledge of HBV including recent success in the propagation of the virus in vitro.The mechanism of hepatocyte injury and the pathogenesis of acute and chronic hepatitis B,however, remain major unsolved problems in this world wide disease.

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