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Progress in pathology

Recent developments in liver pathology

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Summary Progress in liver histopathology continues to be made, as evidenced by recent publications in all areas of hepatobiliary disease. Multinucleated giant hepatocytes, known to be associated with autoimmune and drug hepatitis, now have been seen in chronic hepatitis C with or without HIV infection and in patients with infection by human herpesvirus-6A. The new term *Mallory-Denk body* (formerly the Mallory body) recognizes the substantial contributions to this field by Professor Helmut Denk of Austria. The problems of fatty liver and hepatic iron overload have been addressed in studies highlighting their complex pathogenesis. Genomic and immunohistochemical analysis of liver tumors provides important diagnostic information, particularly regarding the use of glypican-3 in the diagnosis of hepatocellular carcinoma.

1. Introduction

Since its early days as a specialty area, now some 50 years ago, liver pathology has exemplified the melding of morphologic observations with clinical correlations and basic science investigations. The added ingredient of genomic analysis is already contributing to significant histologic correlations and to issues regarding therapy. The wealth of emerging data continually raises the question of what is important to know. To cite only several recent studies, might it be important for an anatomic pathologist to know that HIV-infected patients may have coexistent autoimmune hepatitis (AIH) [1] or may develop de novo AIH after antiretroviral therapy, that polymerase chain reaction (PCR) of paraffin-embedded liver biopsies showing granulomas may disclose a previously undiagnosed infection by *Bartonella henselae* or *Listeria* [2], or that pure intrahepatic cholestasis and jaundice in pediatric and adult liver may be due to specific mutations in genes encoding bile salt transport pumps located at the bile canaliculus [3,4]? The answer is "yes" because HIV disease, granulomas, and cholestasis are common problems in liver disease. The point was well taken by Dr Elizabeth Brunt in recent editorial comments in the journal *Hepatology* [5] when she wrote that "…careful tissue evaluation can and should continue to serve multiple functions in the multifaceted collective progress in our field…." The present review is a selective overview of recent publications that provide new insights for liver histopathology and for understanding the pathogenesis of diseases of the liver and biliary tree.

2. Viral hepatitis and AIH

Multinucleated giant hepatocytes (giant cell transformation, syncytial giant cell change) are often seen histologically in neonatal liver diseases, including neonatal giant cell hepatitis and cholestatic diseases of various etiologies, but in

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adult liver (Fig. 1), they are uncommon and referred to as postinfantile giant cell transformation (PIGCT). Awareness of the adult entity arose from a case reported by Phillips et al [6] in 1991 with features of paramyxovirus infection. Later studies showed associations of PIGCT with AIH and drug hepatotoxicity [7]. New studies this year offer human herpesvirus-6A (HHV-6A) [8] and hepatitis C virus (HCV) monoinfection or HCV-HIV coinfection [9] as alternative causes. The case of HHV-6A transmission from a donor liver to the transplant recipient was exceptionally well validated, with multiple liver allograft biopsies showing giant cells as well as viral DNA by PCR on formalin-fixed, paraffin-embedded tissue—until both resolved at 1 year after transplantation. Microdissected multinucleated hepatocytes, but not mononuclear hepatocytes, contained HHV-6A DNA on PCR, and the former also stained positively with specific viral antibodies. The authors pointed out that as with paramyxovirus, HHV-6A is reported to cause cell-cell fusion. HHV-6A, the cause of sixth disease of childhood, may be encountered after transplantation as either a new infection or reactivation. Liver biopsies from patients with chronic hepatitis C or HCV-HIV coinfections are the more likely practice setting in which giant cell change may be seen, although this is still relatively rare [10]. Micchelli et al [9] found only 2.6%, representing 22 of 856 HCV-positive cases reviewed histologically, to show these cells. Their study described multinucleated hepatocytes as confined to centrilobular regions, showing peripheral localization of the nuclei in the cell and a glassy gray-pink cytoplasmic appearance similar to that seen with induction of smooth endoplasmic reticulum (ER) (Fig. 1). Why so few cases of HCV infection show giant cell change is currently unknown. Validation studies like those used in the HHV-6A report should be performed for HCV and HCV-HIV cases with PIGCT. The lack of a commercially available and specific antibody for HCV immunohistochemistry is problematic, although a recent study looking at recurrence of HCV after liver transplantation suggested the usefulness of a polyclonal anticore antibody to HCV [11].

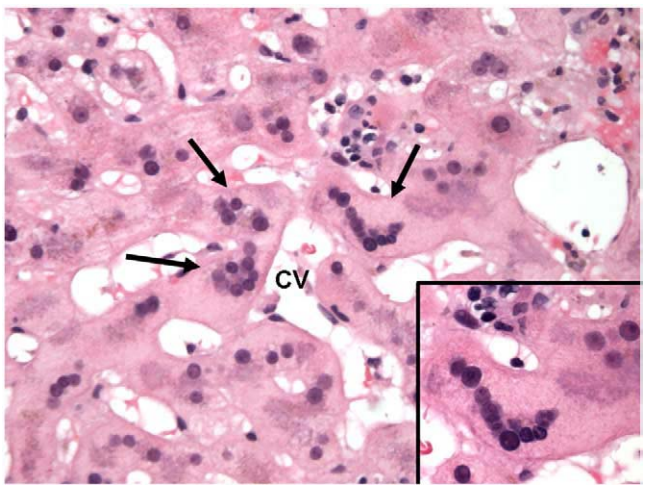

Fig. 1 Multinucleated giant hepatocytes (PIGCT) (arrows) are present near the centrilobular vein (CV) in a liver allograft biopsy from an adult with recurrent HCV infection 9 weeks after liver transplantation. Inset: high power of giant cell (hematoxylin-eosin [H&E] stain; magnification ×200, inset ×400).

Should hepatitis E virus (HEV) be added to the list of currently recognized causes of chronic hepatitis (ie, chronic infection by hepatitis B, C, and D viruses; chronic drug hepatotoxicity; AIH; α-1-antitrypsin deficiency; Wilson disease)? A spate of new reports has suggested as much in liver, kidney, and kidney-pancreas transplant recipients [12-15]. HEV is a small nonenveloped RNA virus with 4 mammalian genotypes with specific geographical distributions [16]. Genotype 1 (Asia, North Africa) and genotype 2 (Mexico, central Africa) are human pathogens incurred through the oral-fecal route. The clinical importance of these genotypes in causing epidemics of acute hepatitis in developing countries, with mortality of approximately 20% in pregnant women [17], has previously been stressed. Genotype 3 (North and South America, several European countries, Japan, several Pacific Rim countries) and genotype 4 (China, Japan, Taiwan, Vietnam) reside in swine in these locations and have resulted in sporadic human hepatitis. Genotypes 3 and 4 residing in swine (where they do not appear to cause disease) and possibly other meat sources (cows, sheep, and goats) provide the zoonotic route of transmission in developed countries. Genotype 3 RNA identified in serum during the chronic course of hepatitis in the transplant patients in recent reports (presumably acquired from infected donor organs) as well as liver allograft biopsy features of chronic hepatitis (with cirrhosis in several cases) served as the basis for suggesting HEV as a new cause of chronic liver disease in the transplant setting. Identification of HEV in liver tissue as well as determination of the mechanism by which viral antigen expression in the liver leads to chronic liver disease are necessary before HEV can be confidently included among the causes of chronic hepatitis [18]. The possibility is nevertheless intriguing, particularly because in 3 cases of "acute" HEV infection reported from the United Kingdom in 2007 (presumed to have been acquired from food sources), liver biopsies showed histologic features of chronic hepatitis (ie, interface hepatitis [IH] and formation of portal lymphoid aggregates) [19].

The histologic features of chronic hepatitis C in children were the subject of a 2008 report, which examined liver biopsies from 121 treatment-naive children with ages 2 to 16 [20]. Most cases showed minimal inflammation (42%), and 56% lacked steatosis, differing considerably from adult chronic hepatitis C. Five cases showed bridging fibrosis, and 2 had cirrhosis. Inflammation was correlated with the duration of infection and fibrosis and obesity with increased fibrosis. Based on the data, the authors suggested that a period of "immune tolerance" similar to that seen in chronic hepatitis B exists in childhood HCV infection and that with time increasing inflammation and comorbid conditions such