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What's New in Viral Hepatitis and AIH ?

Introduction

Increased application of modern molecular techniques to the diagnosis of liver diseases necessitated certain adjustments in the interpretation of liver biopsies. This pertains especially to the viral hepatitis and autoimmune liver diseases, where additional forms of hepatitis were defined after application of molecular techniques to paraffin-embedded tissues. We briefly summarize in the following respective developments in the viral hepatitis B, C, D and E with a short comment on Epstein-Barr virus (EBV) hepatitis. In addition, we outline the recently proposed pathologic criteria to identify autoimmune hepatitis.

Hepatitis B (HBV hepatitis)

The natural course of chronic HBV hepatitis with continuously decreasing viral replication leads to a late phase where the viral load in the blood falls below the limits of detectability. Still the patients suffer from chronic hepatitis B identified by Torbenson (2002) as **occult hepatitis B**. Occult hepatitis B, which is currently the focus of intense studies, has major clinical implications as various exogenous factors and immunosuppressive regimen may reactivate the viral disease with a massive, even lethal response. Histopathologic features of occult hepatitis B are quite variable ranging from mild (grade II) hepatitis to overt fibrosis, cirrhosis or even hepatocellular carcinoma with HBx antigen as the only viral marker in the tissue. When occult hepatitis B is suspected in a "sero-viral-negative" patient, HBV genome should be demonstrated in biopsy tissue by PCR (polymerase chain reaction).

Hepatitis C (HCV hepatitis)

Liver lesions by HCV are caused by a) viral replication, b) immune response against the virus, and c) by **metabolic interference**. HCV not only uses fatty microdroplets as a matrix for viral reconstruction, but also interferes with the fat metabolism by its core, E, NS₃ and NS₅ regions. Adiponektin levels in serum are reduced in chronic HCV hepatitis. Especially HCV genotype 3 can cause direct hepatic steatosis. HCV genotypes 1a and 1b also can cause steatosis which then can run a progressive course independent of viral activity (Bedossa P et al., 2007). It has been shown that hepatic steatosis in chronic HCV hepatitis is an independent risk factor for rapid progression and for the development of hepatocellular carcinoma.

In addition, HCV can upregulate the cellular transferrin receptor 2 and block the hepcidin protein, both activities support hepatocellular siderosis. Iron overload in the liver is known clinically to decrease the efficiency of interferon therapy in chronic HCV hepatitis.

Hepatitis D (HDV hepatitis)

Although HDV complicates the course of HBV hepatitis in dual infection, HDV RNA does not correlate with either biochemical parameters or histopathological findings. Thus, HDV does not appear to be directly cytopathic for the hepatocyte. As biochemical parameters do not correlate with stage or grade of chronic HDV hepatitis, liver biopsies and classical histopathological investigations are essential for the classification of the disease (Dienes HP, Drebber U, 2008).

Hepatitis E (HEV hepatitis)

Although more common in tropical and subtropical regions, HEV infections tend to be imported to middle European countries with increasing frequency. HEV, a single stranded naked RNA virus should be diagnosed by RT-PCR, since commercially available assays are not sufficiently sensitive. Clinical features of infection are a classical acute viral hepatitis with preferential periportal distribution and prominent cholestatic component.

EBV Hepatitis

The classical picture of EBV hepatitis is known for many years. However, the typical features may vary in cases of late primary infection or in reactivation of EBV infection. In classical EBV hepatitis, typical diffuse lymphocytic infiltrates (infected B lymphocytes, activated T lymphocytes, NK cells) are found alongside sinusoids with focal apoptoses. In addition, endothelitis, cholangitis may occur, less frequently granulomas and steatosis. EBV infections are reported in 6% of seronegative cases of occult chronic hepatitis.

Autoimmune Hepatitis (AIH)

Hennes EM and collaborators (2008) suggested simplified criteria for the diagnosis of AIH applying to Misdraji's (2004) AIH variants: 1. seronegative AIH, 2. acute or recent onset AIH, and 3. AIH with centrilobular necrosis. These criteria are summarized in the table:

Hennes et al. (2008) Simplified Criteria for the Diagnosis of Autoimmune Hepatitis (AIH)

<u>Diagnostic Parameter</u>	<u>Value</u>	<u>Score</u>
ANA or SMA	1:40	1
ANA or SMA or LKM or SLA	1:80 1:40 positive	2
IgG	above normal	1
	above 1.10 times of upper normal limit	2
Liver microscopy:	compatible with AIH	1
	typical for AIH	2
	no evidence for viral hepatitis	2

Interpretation: score 6 = suggestive AIH; equal or above score 7 = definitive AIH

(abbreviations: ANA antinuclear antibodies; antibodies to SMA smooth muscle antigens; LKM antibodies to liver-kidney membrane antigens; SLA soluble liver antigen; IgG immunoglobulin G)

Typical AIH microscopy shows an **interface hepatitis** with lymphoplasmacytic infiltrates and "rosetting" of hepatocytes. About 50% of lymphocytes are CD4+ T helper cells with nodular (follicular) accumulation of B lymphocytes. Less frequent are cases of acute AIH with ballooning degeneration, centrilobular necroses and band-like regional necroses (bridging necroses).

Additional immunologic parameters include abnormal paraproteins, anti dsDNA, circulating immune complexes (CIC), cryoglobulinemia, HLA B8 & HLA DR3.

(Reported from German Society of Pathology Annual meeting, Berlin, May, 15-18, 2008)

Further references:

- Bedossa P et al.: Evidence for a role of non-alcoholic steatohepatitis in hepatitis C. *Hepatology* 46: 380, 2007
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- Hennes EM et al.: Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 48: 169, 2008
- Misdraji J et al.: Autoimmune hepatitis with centrilobular necrosis. *Am J Surg Pathol* 28: 471, 2004
- Torbenson M & Thomas DL: Occult hepatitis B. *Lancet Infect Dis* 2: 479, 2002

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