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BRIEF REVIEW

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Pathological Features of Fatty Liver Disease

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Alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) are significant causes of chronic liver disease worldwide. Both are characterized by histological lesions that can include steatosis, and each can lead to cirrhosis. It might be possible for pathologists to identify lesions and patterns of ALD and NAFLD; we review these lesions and propose methods to distinguish between the disorders. Any form of ALD can lead to end-stage liver disease, according to long-term studies of biopsy specimens and patient outcomes. Although steatosis can be a significant cofactor in progression of established chronic liver disease, or even development of hepatocellular carcinoma, only steatohepatitis indicates the presence of progressive liver disease in patients with NAFLD. Pediatric and adolescent NAFLD differ from adult nonalcoholic steatohepatitis and should be recognized as distinct conditions. Benign and malignant liver tumors have been more frequently reported with the increasing prevalence of obesity and diabetes. Histological scoring systems for ALD and NAFLD have been proposed to monitor efficacy in clinical trials and serve as prognostic factors. We review what we have learned from pathological analyses about the development of these disorders and how this information might be used to detect and treat them.

Keywords: NASH; Histology; Diagnosis; Prognosis.

Excess accumulation of triglyceride in the liver can occur in patients with rare genetic disorders characterized by defects in lipid delivery or oxidation or export. However, environmental and lifestyle factors (dietary and exercise), conscious or unconscious, combined with genetic factors, have produced the more common medical problems of alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD), the 2 most common types of fatty liver disease in the world today.[1]

Alcohol abuse is an ancient but thriving disorder restricted only by cultural mores; sadly, NAFLD has increased in incidence with the abundances of modern life.[2,3] Each is likely to continue to plague society for the foreseeable future. Liver biopsy evaluation is required to diagnose the most serious, potentially progressive form of NAFLD, steatohepatitis,[4,5] and to localize the fibrosis associated with these diseases (discussed in Brunt et al[5]). Noninvasive markers, based on imaging and clinical and laboratory tests, can accurately assess the amount of steatosis and collagen; however, no test can replace histopathologic evaluation of fibrosis location and remodeling in the potentially reversible ranges, or histological lesions that distinguish steatohepatitis from steatosis, despite the recognized limitations of liver biopsy.[5,6] We review the histopathologic aspects of these 2 liver diseases, discussing their pathogenesis and areas of controversies in diagnosis.

Diagnosis

Although many histological features of ALD and NAFLD overlap,[7] likely due to similarities in genetic factors that contribute to disease and pathogenic processes,[8] these entities are not always indistinguishable microscopically[9] (Table 1). For instance, steatosis, a necessary, defining lesion for NAFLD and nonalcoholic steatohepatitis (NASH), is not always detected in livers of patients with the severe form of ALD, alcoholic hepatitis (AH). Other lesions found in patients with AH or alcoholic steatohepatitis but not in NASH include the fibro-obliterative lesions of the outflow venules (Figure 1), acute canalicular cholestasis, and marked periportal ductular reaction. In fact, AH is characterized more by the venous outflow lesion and numerous Mallory–Denk bodies than by triglyceride accumulation. The VOD-like lesion correlates with decreased steatosis, increased canalicular cholestasis, and Mallory–Denk bodies.[10]

Liver tissue from patients with alcoholic cirrhosis, unlike those with NAFLD-associated cirrhosis, frequently contains periseptal copper. Foamy degeneration, a clinicopathologic lesion of nearly pure microvesicular steatosis in ALD, has not been detected in livers of patients with NAFLD.[5] Features of pediatric NAFLD (zone 1 accentuation),[11] on the other hand, have not been detected in livers of patients with ALD. The types of inflammation in the lobules and in the portal tracts also differ. Itoh et al described distinct portal and periportal infiltration by neutrophils in patients with ALD that distorted the shape of the portal tract.[12] Extensive neutrophilic infiltration in the hepatic lobules is another histological feature of AH or steatohepatitis that differs from NASH, in which the lobular infiltrates are composed predominantly of lymphocytes and macrophages. The infiltration of neutrophils in AH has been attributed to interleukin

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Abbreviations used in this paper: AH, alcoholic hepatitis; ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; IL, interleukin; K, keratin; MIR, microRNA; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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Table 1. Histologic Features of NAFLD/NASH, ALD/ASH, Cryptogenic Cirrhosis[a]

Lesion	Pre-cirrhotic NAFLD/NASH: adult	Pre-cirrhotic NAFLD: pediatric	Pre-cirrhotic ALD/ASH/AH	Cirrhosis NASH	Cirrhosis ALD/ASH/AH	Cirrhosis Cryptogenic
Steatosis						
Macrovesicular, predominant (this includes large and small droplet steatosis)	Required for NAFLD or NASH; zone 3 is most common location	Required for dx; Zone 1 or panacinar	Not required in alcoholic hepatitis	+/-; zonality is commonly "lost"	+/-; zonality is commonly lost	+/-; uncommon to see $\geq$ 5%
Microvesicular, azonal clusters admixed with macrovesicular	Has been associated with more severe NASH	Not studied	May be associated with worse outcome in "pure" alcoholic steatosis	+/-	+/-	Not described, but likely not present
Microvesicular predominant	Not described; would raise concern of diagnosis	Not described; would raise concern of diagnosis	"Alcoholic Foamy Degeneration"	Not described, unlikely	Not described, unlikely	Not described, unlikely
Lobular inflammation						
Primarily mononuclear infiltrates	Required for NASH dx	Common, not required	Common, not required	Present if active NASH present	+/-	+/-
Clusters of PMN's: "satellitosis" surrounding MDB containing hepatocytes	+/-; not common would raise consideration for alcoholic hepatitis	Not common; would raise concern of AH	Common lesion active alcoholic hepatitis	Would raise consideration of AH	Sign of ongoing active AH	Would re-assign case from "cryptogenic" to AH categorization
Kupffer cell aggregates: microgranulomas with or without a lipid inclusion	Common	+/-	Not studied	Not uncommon	Not studied	Not studied
Large lipogranulomas in perivenular region with associated fibrous bands	Common	+/-	+/-	+/-	Not known	Not studied
Predominant portal inflammation						
Mononuclear; amount relative to to lobular	Most common; usually < lobular; if > lobular, consider concurrent disease or more severe SH; may be seen in resolution	Most common; usually > lobular	May be mononuclear or mixed with PMN's, ductular reaction and periportal fibrosis	May be admixed with ductular reaction and fibrosis	May be admixed with PMNs, ductular reaction and fibrosis	+/-
Portal lipogranulomas	+/-	+/-	Common	+/-	Common	+/-