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Pathology of nonalcoholic steatohepatitis

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Summary

To date, histologic evaluation, most commonly in the form of liver biopsy, remains the gold standard in evaluation of nonalcoholic fatty liver disease (NAFLD). Histologic evaluation was fundamental to the initial studies that introduced and defined the concept of fatty liver as a liver disease. Currently, liver biopsy in NAFLD serves multiple roles: confirmation (or exclusion) of the diagnosis; distinction of steatohepatitis from "simple steatosis"; assessment of extent of necroinflammatory activity, fibrosis, and architectural alterations. Histopathologic studies have underscored the fact that not all obese and/or diabetic individuals with elevated liver tests have fatty liver disease; for example, hepatic glycogenosis and hepatosclerosis have been described in diabetics, and other significant liver diseases have been documented. Likewise biopsy studies have documented lesions of steatosis or steatohepatitis in unusual patient groups or clinical settings, such as lean individuals, individuals with normal liver tests, patients taking certain medications, patients with co-existent serologically-diagnosed liver disease, and pediatric patients. Biopsy studies have shown that the lesions of NASH may or may not persist in cirrhosis; prior evidence of NASH on liver biopsy serves as a benchmark for the concept that many cases of otherwise cryptogenic cirrhosis developed from NAFLD/NASH. Liver biopsy remains a significant feature of studies delineating long-term outcome of NAFLD, some of which have shown that "simple steatosis" is not always non-progressive and benign. Finally, investigators have noted correlations of proposed pathophysiologic processes in NASH with particular histologic features.

Therapeutic trials for NASH rely on histologic evaluation as the most sensitive analysis to document effects of treatment. Treatment trials afford an opportunity to evaluate histologic features of resolution, and these trials have also provided an opportunity for correlations of particular histologic lesions with clinical and laboratory features in well-characterized patient populations. These kinds of studies are currently relatively few, but results of a recent study have reinforced the concept of necessary criteria for diagnosis.

Current discussions in pathology include identification of lesions of concern for progression, reproducible methods of diagnosis and semiquantification of lesions, and appropriate nomenclature. Matteoni et al. proposed NAFLD types 1–4 based on long-term outcome studies; Brunt et al. proposed a system of grading and staging for NASH that follows methods of separate assessment for necroinflammatory lesions (grade) and fibrosis (stage) accepted in other forms of non-biliary chronic liver disease. Recently, the Pathology Committee of the NIDDK NASH Clinical Research Network has proposed a system of evaluation that encompasses the entire spectrum of NAFLD from steatosis to steatohepatitis with fibrosis for use in upcoming treatment trials. And, just as the clinician cannot distinguish steatosis and steatohepatitis, the pathologist cannot discern if alcohol abuse may be an underlying cause of the lesions. Proposed nomenclature to align with either extant terminology in other forms of chronic liver disease, or to align with our knowledge of underlying cause(s) (such as metabolic syndrome) will be discussed.

Keywords: Non-alcoholic steatohepatitis; Pathology; Steatosis; Ballooning; Mallory's hyaline; Perisinusoidal fibrosis; Grading; Staging

1. Introduction

For 30 years prior to this publication in 1980 by Ludwig et al. [1] there were several papers in the literature relating to the liver disease in obesity and in obesity in diabetes. However, it was the paper by Ludwig et al. that codified the term nonalcoholic steatohepatitis into the lexicon of hepatology. The Ludwig paper was based on a search of the Mayo Clinic files for liver biopsies with alcohol-like features, but in patients who clearly were not alcoholic. We can recognize not only the histologic findings, but also several of the clinical associations with which we are familiar today.

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Currently our working definition of nonalcoholic steatohepatitis remains a clinicopathologic entity. Clinical features may be suggestive. However, there remain challenges in deciding which patients to include or exclude with current definitions [2–4]. More troublesome, there are no diagnostic laboratory or imaging tests to positively diagnose this entity. Therefore, liver biopsy evaluation remains the gold standard in this disease [2–5]. Biopsy findings are useful for diagnosis, for distinguishing steatosis from steatohepatitis, and to assess ongoing necroinflammatory injury, or activity, and fibrosis and architectural change, or stage.

2. Value of liver biopsy in NAFLD and NASH

Liver biopsy has been used extensively in the last 20 years with natural history studies [6,7], in the studies to predict fibrosis [8,9] to determine which patient would benefit from biopsy [10], to associate with the clinical associations of metabolic syndromes [11–16], certain drugs [17], and to document the concurrence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis with other forms of chronic liver disease such as hepatitis C [17–20]. Certainly liver biopsy remains useful in investigations into pathogenesis and will become even more useful as a measure of efficacy in ongoing treatment trials [2].

Skelly et al. [21] studied biopsies from 354 patients for otherwise unexplained liver test abnormalities; the result was 66% of the patients had fatty liver, half of whom also had fibrosis. But interestingly 6% were normal, almost 10% remained cryptogenic and the remaining 13% actually were able to have a clinical diagnosis made based on the liver biopsy and then re-evaluation/re-examination of the patient. Therefore, it is really not correct to assume without biopsy proof that all otherwise unexplained liver test abnormalities are steatohepatitis or fatty liver disease.

3. Histologic features of NAFLD and NASH

How do we differentiate simple steatosis from the constellations of lesions known as steatohepatitis? If we return to the original paper of Ludwig et al. [1], we note the lesions that he described—steatosis, ballooning, lobular inflammation, Mallory's hyaline, perisinusoidal fibrosis; currently, all of these are very familiar to those of us working in this field. Interestingly, also in the last 20 years with investigation into the pathogenesis of NASH, as shown in this thorough review by Professor Day and Saksena [22], many of the known or putative mechanisms for injury in NASH have histologic counterparts.

One of the first, most important findings in nonalcoholic steatohepatitis is the fact that this lesion is predominantly initially in zone 3. Certainly zone 3 of the acinus is different metabolically, enzymatically, and has different oxygen tension. Likewise studies have shown, as Dr. Seiki will be presenting, studies for lipid peroxidation products and DNA damage predominate also in zone 3, as does the increased expression of CYP-2E1 [23,24].

Liver cell injury in the form of ballooning is also a significant feature in nonalcoholic steatohepatitis and, as can be seen from the well known study of Matteoni et al. [25] in which they provided clinical correlations with types 1–4, assessed by histologic features, and showed increased incidence of cirrhosis in types 3 and 4, compared with type 1. The distinguishing lesion between type 3 and types 1 and 2 was the presence of ballooning.

Lobular inflammation in nonalcoholic steatohepatitis is typically quite mild. However, it is also typically mixed and includes a small number of lymphocytes, a small number of macrophages, Kupffer cells, but also a small number of polymorphonuclear leukocytes. Portal inflammation is either non-existent or very mild.

Mallory's hyaline is a lesion that may or may not be seen. Many pathologists, including the author, do not require it for the diagnosis [26]. When present, MH is typically referred to as "poorly formed", as it lacks the dense ropy quality of Mallory's hyaline seen in alcoholic hepatitis or chronic cholestasis.

Apoptosis is another form of liver cell injury that has gained attention recently [27]. Other lesions seen in nonalcoholic steatohepatitis include fatty cysts and lipogranulomas. Glycogenated nuclei are common in nonalcoholic steatohepatitis. Megamitochondria have gained significant attention in this disease [28–30]. A recent study from Caldwell's group looked at the distribution and morphology of megamitochondria by ultra-structural analysis [31]. Iron is actually not often discussed or looked for in nonalcoholic steatohepatitis [32], but typically there may be very mild hepatocellular iron present or iron present in the reticuloendothelial or sinusoidal lining cells [32]. A recent study published from Japan from Yamauchi et al. showed a very high proportion of patients with NASH with hepatocellular iron [33].

Fibrosis begins in the perisinusoidal regions of zone 3, typically as a very delicate strand of collagen spreading throughout the sinusoids; fibrosis can be present in zone 3 and the portal tract not be involved. With time more extensive damage and fibrosis occurs and bridging fibrosis may be seen. Ultimately, of course, cirrhosis may result. Some cases of cirrhosis related to NASH may actually retain the histologic lesions of active nonalcoholic steatohepatitis [34]. There is growing recognition of the concept mentioned in a series by Powell et al. [6] and substantiated by Caldwell et al. [35] that with progression the histologic lesions, the active lesions may actually burn out and leave a type of cirrhosis that gives absolutely no histologic clue as to the initiating events. Based on series of biopsies such as reported by Abelmalek et al. [36], the concept that cryptogenic cirrhosis may actually derive in a large percent from NASH has developed.