Nonalcoholic Steatohepatitis

Histopathology Basics Within a Broader Context

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KEYWORDS

• Fatty liver disease • Hepatocyte ballooning • Diagnosis

Key points

- At least 5% hepatic steatosis is essential for the diagnosis of nonalcoholic fatty liver disease. Steatosis is often in zone 3 in adults and in zone 1 in children.
- Hepatocyte ballooning is an essential element for the diagnosis of adult nonalcoholic steatohepatitis.
- Mild lobular inflammation and mild portal inflammation are common in nonalcoholic steatohepatitis.
- Nonalcoholic steatohepatitis commonly has pericellular "chicken wire" fibrosis.
- Many of these key features can be absent in cirrhosis (often referred to as "burnt out" steatohepatitis).

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is a major health concern and the prevalence continues to increase in many industrialized and developing countries around the world. NAFLD affects adults and children. NAFLD-related cirrhosis is expected to become the top indication for liver transplantation in the near future, and the incidence of NAFLD-related hepatocellular carcinoma is also increasing. Nonalcoholic steatohepatitis is the more severe form of NAFLD. The pathogenesis of NALFD/nonalcoholic steatohepatitis is complex and new concepts continue to evolve. The diagnosis and categorization of nonalcoholic steatohepatitis currently rests on hepatopathologists. Accurate morphologic interpretation is important for therapeutic, prognostic, and investigational purposes.

OVERVIEW

Overweight/obesity and related metabolic conditions are major public health concerns in many parts of the world, including the United States, Europe, the Middle East, Asia, and Latin America.[1] Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome, and by definition occurs in the absence of significant alcohol consumption (eg, <20 g/d for women and <30 g/d for men). Metabolic syndrome describes a systemic disorder with at least 3 of 5 of the following: large waist-to-hip ratio (abdominal obesity), high triglyceride level, low high-density lipoprotein cholesterol level, hypertension, and high fasting blood sugar or diabetes mellitus/insulin resistance. NAFLD encompasses a spectrum of hepatic pathology that ranges from isolated steatosis (nonalcoholic fatty liver [NAFL]) to severe

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hepatocellular injury with steatosis, inflammation, and ballooning (nonalcoholic steatohepatitis [NASH]). NASH is a more severe and progressive form of NAFLD that is import to diagnose because cirrhosis and hepatocellular carcinoma (HCC) can develop. NASH strongly correlates with hepatic fibrosis. Hepatic steatosis can be diagnosed by imaging studies such as ultrasound examination; however, liver biopsy is the gold standard for the diagnosis of NASH. This review focuses on individual histopathologic lesions used for the diagnosis of NASH and aims to provide a diagnostic roadmap within an epidemiologic and pathobiological context.

EPIDEMIOLOGY

On imaging studies, 25% of adults worldwide are estimated to have NAFLD.[1] Figures are even higher in the Middle East (almost 32%) and South America (30%). Approximately 25% of US adults have NAFLD, equating to 64 million Americans. The estimated incidence of NASH in the general population ranges from 1.5% to 6.5%. NASH is now the leading cause of cirrhosis in the United States and is expected to be the leading indication for liver transplantation by 2020. The negative health and societal impacts of NASH are massive, and the economic burden of NASH and its sequela are projected to be more than $100 billion annually in the United States in direct medical costs.[2]

PATHOGENESIS

NASH is a dynamic disorder that can progress to cirrhosis and HCC, smolder along, or regress to NAFL.[3] The "2-hit" hypothesis of NASH pathogenesis is no longer the pervasive view. In fact, hepatic steatosis is now considered an early and beneficial adaptive response to mitigate lipotoxicity; the incoming and de novo free fatty acids are packaged into relatively inert triacylglycerol.[4]

NASH is a complex disease with a strong genetic component in combination with environmental and nutritional factors (eg, increased consumption of saturated fats, cholesterol, sugars, and processed fructose[5]) and decreased energy expenditure. NAFLD is considered a polygenic and heritable disease[6] with marked interpatient variation regarding disease outcome.[7] The 2 most important genetic modifiers are believed to be *PNPLA3* and *TM6SF2* single nucleotide polymorphisms. Furthermore, an allelic variant of *PNPLA3* has been linked to an increased risk of NAFLD-associated HCC.[8] Ethnicity and gender[9] also influence NASH pathogenesis.

Two major underlying components of NAFLD pathogenesis include obesity and insulin resistance. Other key contributions result from ongoing hepatocellular stress (eg, oxidative stress, endoplasmic reticulum stress, and lipotoxicity), hepatic inflammation, cellular damage, and death (eg, hepatocyte ballooning and apoptosis), with resultant fibrogenesis.[4,10,11]

MICROSCOPIC FEATURES

STEATOSIS

Hepatic lipid droplets are not simply static fat storage depots, but are dynamic organelles composed of a central triacylglycerol core and sterol esters encompassed by a monolayer of phospholipid and proteins.[12] Although the major function of lipid droplets is as an energy reserve, an increasing complexity of lipid droplet biology is now recognized. Although steatosis is regarded a hallmark lesion of NAFLD, growing evidence supports the counterintuitive notion that hepatic triglycerides accumulate as a cytoprotective mechanism against the lipotoxic effects of free fatty acids.[13]

The 2 major forms of hepatic steatosis are macrovesicular and microvesicular. Macrovesicular steatosis is the most common type in NAFLD, and it is used as a component in the 2 most common grading systems (**Table 1**). Macrovesicular steatosis comes in 2 main varieties, large droplet and small droplet. Large droplet steatosis expands to fill the hepatocyte cytoplasm and seems to displace the nucleus to the side (**Fig. 1**). Small droplet steatosis is seen as several small cytoplasmic droplets, and the nucleus is often retained centrally (see **Fig. 1**C). Microvesicular steatosis is often first identified on low-power magnification as an indistinct, pale, eosinophilic area or "patch." Higher power evaluation shows "foamy" cytoplasmic changes (see **Fig. 1**D).

Small patches of microvesicular steatosis in a nonzonal distribution can be seen in a small proportion of NAFLD cases, and has been associated with more severe injury and advanced fibrosis.[14] Extensive microvesicular steatosis has not been described in NAFLD, and if present other etiologies (eg, drug toxicity or Reye syndrome) must be considered.

Macrovesicular steatosis is considered pathologic when it involves more than 5% of hepatocytes. The degree of steatosis is usually assessed in a semiquantitative manner using