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Pathologic Diagnosis of Nonalcoholic Fatty Liver Disease

Jinping Lai, MD, PhD; Hanlin L. Wang, MD, PhD; Xuchen Zhang, MD, PhD; Huamin Wang, MD, PhD; Xiuli Liu, MD, PhD

Recent epidemiologic studies have shown that nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease in the US, with an estimated prevalence of 34% in the general population (based on screening using liver proton magnetic resonance spectroscopy). Steatosis and steatohepatitis are the most common morphologic patterns of liver injury in NAFLD patients, which are commonly seen in liver biopsy specimens from patients with obesity, diabetes, hyperlipidemia, hypertension, and use of certain drugs. NAFLD is characterized by hepatic steatosis in the absence of a history of significant alcohol use or other known liver disease. Nonalcoholic steatohepatitis (NASH) is the progressive form of NAFLD. The well-recognized histopathologic features of NASH include hepatocellular steatosis and ballooning, mixed lobular and portal inflammation, and zone 3 perisinusoidal fibrosis. Alcoholic steatohepatitis (ASH) shares histologic similarities with NASH but there are some subtle differences that may suggest one diagnosis or the other. Both ASH and NASH can progress to advanced fibrosis and cirrhosis leading to end-stage liver disease and hepatocellular carcinoma (HCC). In cirrhosis, the characteristic findings of steatosis and ballooning may be lost but epidemiologic studies indicate that NASH is a common cause of cryptogenic cirrhosis. This review covers the histologic spectrum of steatosis and steatohepatitis and discusses their related topics such as cryptogenic cirrhosis, NASH regression, steatohepatitic HCC, anti–programmed death receptor-1 (PD-1) immunotherapy-related steatosis, and coronavirus disease 2019 (COVID-19)–related steatosis.

HISTOLOGY OF STEATOHEPATITIS

The hallmarks of steatohepatitis are steatosis and hepatocyte ballooning. Steatosis is the simplest form of fatty liver disease characterized by the presence of fat droplets in hepatocytes without other abnormal findings. This finding is sometime termed simple steatosis. Often a small amount of inflammation (lobular or portal) accompanies the steatosis. Steatosis is divided into macrovesicular and microvesicular types based on the size of fat droplets in the cytoplasm of hepatocytes. Macrovesicular steatosis is further subdivided into large droplet and small droplet steatosis. In large droplet macrovesicular steatosis, 1 or few large fat droplets in the cytoplasm occupy greater than one half of an individual hepatocyte with or without nuclear displacement. In small droplet steatosis the droplets (usually >1) are smaller than the nucleus and do not push the nucleus to the

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From the Department of Pathology and Laboratory Medicine, Kaiser Permanente Sacramento Medical Center, Sacramento, California (Lai); Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California (HL Wang); Department of Pathology, Yale University School of Medicine, New Haven, Connecticut (Zhang); Departments of Anatomic Pathology and Translational Molecular Pathology, University of Texas MD Anderson Cancer Center, Houston (HWang); and the Department of Pathology, Immunology and Laboratory Medicine, University of Florida College of Medicine, Gainesville (Liu).

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Corresponding author: Jinping Lai, MD, PhD, Department of Pathology and Laboratory Medicine, Kaiser Permanente Sacramento Medical Center, Sacramento, CA 95825 (email: Jinping.X.Lai@kp.org).
periphery, but not as tiny as those of microvesicular steatosis. Small droplet steatosis is frequently seen in combination with large droplet macrovesicular steatosis in fatty liver disease. This mixed pattern is part of the spectrum of macrovesicular steatosis and should not be confused with microvesicular steatosis in which hepatocytes show diffuse replacement of the cytoplasm by extremely tiny fat droplets (usually <1 μm), leading to a foamy appearance. This distinction between small droplet macrovesicular steatosis and diffuse microvesicular steatosis is important because they are caused by different etiologies.5 Based on the NASH Clinical Research Network (CRN) criteria, steatosis is evaluated at low magnification and a visual estimate is made of the proportion of parenchyma involved by macrovesicular steatosis. Steatosis is graded as grade 0, 1, 2, and 3 with macrovesicular steatosis present in less than 5%, 5% to 33%, 34% to 66%, and more than 67% of the hepatocytes, respectively. Only the portion of the biopsy specimen occupied by the hepatocytes (ignoring large bands of fibrosis, portal areas, vein profiles, etc) is considered for the steatosis grading. The steatosis can be mainly in zone 3 (Figure 1, A), zone 1, or may involve all zones equally in a panacinar pattern.5 Steatosis that is irregularly distributed is referred to as azonal. In adults with NAFLD, steatosis usually appears first in zone 3, while in children, zone 1 steatosis is more common. Macrovesicular steatosis could be large droplet-predominant or mixed large and small droplets. Ballooned hepatocytes (Figure 1, B) and lobular inflammation are the other 2 key features to distinguish steatohepatitis from simple steatosis. Like steatosis, ballooning is usually noted first in zone 3, near the central vein. There may be lobular inflammation and perisinusoidal fibrosis in the immediate vicinity. A definitive diagnosis of steatohepatitis (NASH or ASH) requires ballooned hepatocytes in addition to steatosis and lobular inflammation.5 Ballooned hepatocytes are the swollen hepatocytes (>1.5 times of the adjacent normal hepatocytes) with voluminous clear to rarified cytoplasm and small bits of eosinophilic

Figure 1. Steatosis and steatohepatitis. A, Simple steatosis at zone 3 (P, portal tract; C, central zone). B, Steatohepatitis showing steatosis, mild lobular inflammation, and many classic ballooned hepatocytes, some with Mallory-Denk bodies (arrows). C, Acidophilic body (arrow) and nonclassic ballooned hepatocyte (arrowhead). D, Perisinusoidal/pericellular fibrosis (hemoxynin-eosin stain, original magnifications ×100 [A] and ×400 [B and C]; trichrome stain, original magnification ×400 [D]).
Table 1. Nonalcoholic Steatohepatitis Clinical Research Network Nonalcoholic Fatty Liver Disease Activity Scoring System

| Histologic Features                        | Score |
|-------------------------------------------|-------|
| Steatosis                                 |       |
| <5%                                       | 0     |
| 5%–33%                                    | 1     |
| 34%–66%                                   | 2     |
| >67%                                      | 3     |
| Ballooned hepatocytes                      |       |
| None                                      | 0     |
| Few                                       | 1     |
| Many                                      | 2     |
| Lobular inflammation                      |       |
| No foci                                   | 0     |
| <2 foci per 200 × field                   | 1     |
| 2–4 foci per 200 × field                  | 2     |
| >4 foci per 200 × field                   | 3     |
| Fibrosis stage                            |       |
| None                                      | 0     |
| Zone 3, perisinusoidal (seen on trichrome stain) | 1a |
| Zone 3, perisinusoidal (seen on H&E stain) | 1b   |
| Periportal fibrosis                       | 1c    |
| Perisinusoidal and periportal             | 2     |
| Bridging                                  | 3     |
| Cirrhosis                                 | 4     |

Abbreviation: H&E, hematoxylin-eosin.

A Data derived from Kleiner et al.6

Grading of Steatohepatitis

There are 3 histologic scoring systems developed for grading of steatohepatitis including steatosis, activity, and fibrosis (SAP); the Brunt staging system; and the NASH CRN NAFLD activity scoring system.2 The NASH CRN system (Table 1) is modified from the Brunt staging system and is broadly used in pathology practice.5 Based on the NASH CRN criteria, the overall grade of steatohepatitis in this scoring system is expressed as the sum of the steatosis grade, the lobular inflammation grade, and the ballooning grade. The total is referred to as the NAFLD activity score (NAS) and it ranges from 0 to 8, depending on the findings. It should be emphasized, although the diagnosis of steatohepatitis does not depend on the NAS score, it would be helpful to give a number such as most confirmed NAS cases with more than moderate activity have a NAS of 5 or more. The steatosis is scored or graded 0 to 3 as mentioned above. Hepatocyte ballooning is scored or graded 0 with no ballooned hepatocytes identified, grade 1 with few ballooned hepatocytes, and grade 2 with many ballooned hepatocytes. Grade 1 can be limited to cases in which the ballooned cells are isolated and present in only a couple of places in the biopsy specimen, whereas in grade 2 they are easy to find and well-formed. Hepatocyte ballooning is a key yet challenging feature in NAS. It is conventionally defined as enlarged hepatocyte, which is at least 1.5 times the normal hepatocyte diameter and has rarefied or wisp cytoplasm rendering a “spider web” appearance on hematoxylin-eosin stain.5 To further stratify the scoring of ballooned hepatocytes, the NASH CRN pathology committee has proposed a new ballooned hepatocyte scoring system that takes into account the quality of the ballooned cells. Cells which are well-formed and easy to recognize are termed “classic,” while cells that show cytoplasmic features of ballooning but are not enlarged or not easily recognized are termed “nonclassic.” The proposed score includes grade 0 with no ballooned hepatocytes identified, grade 1 with only nonclassic ballooned hepatocytes (Figure 1, C), grade 2 with few classic ballooned hepatocytes, grade 3 with many ballooned hepatocytes, and grade 4 with many classic ballooned hepatocytes present in large clusters that are easily seen at ×4 field.5,13 Lobular inflammation is scored as grade 0 with no lobular inflammation, grade 1 with an average of less than 2 foci per ×20 field, grade 2 with 2 to 4 foci per ×20 field, and grade 3 with more than 4 foci per ×20 field (Table 1). The number of foci should be the average of at least 5 random fields of a core biopsy specimen.5

Although not part of the overall grading, portal inflammation has been shown to be important in disease progression.14 It is generally scored as none, mild, and more than mild, based on both the overall inflammation and the amount of inflammation in most severely affected portal areas. Interface hepatitis may also be seen, but is generally milder than chronic viral or autoimmune hepatitis.

Staging of Fibrosis for Steatohepatitis

In 1999, Brunt et al12 proposed a fibrosis staging system for NAFLD to take into account the unique perisinusoidal and pericellular patterns of fibrosis in the central zone seen in NASH (Figure 1, D). This system was revised in 2005 and incorporated into the NAS stage system with modifications. The modified stage 1 includes stage 1a with mild perisinusoidal fibrosis that requires trichrome stain to recognize, stage 1b with moderate perisinusoidal fibrosis that can be seen on hematoxylin-eosin stain (Figure 1, B), and stage 1c with only portal/pericellular fibrosis (Table 1).6 The system is often applied to all cases of steatosis or steatohepatitis irrespective of alcoholic or nonalcoholic because the etiology is often unknown at the time of case sign out.6,8 The majority of the other fibrosis staging systems developed for chronic viral hepatitis do not take into account the unique fibrosis patterns seen in early stage of steatohepatitis.5

NASH AND METABOLIC DYSFUNCTION/TYPE 2 DIABETES MELLITUS

Parallel to the increasing prevalence of type 2 diabetes mellitus (T2DM) and obesity, NAFLD has become the most common chronic liver disease in the world over the past 30 years, with an estimated prevalence of 10% to 40% worldwide.1-4 For this reason, a new term of metabolic-associated fatty liver disease is recently proposed.15,16 In the setting of T2DM, the prevalence of NAFLD/metabolic-associated fatty liver disease is at least 2-fold higher than in general population, with a range from 57% to 80%, depending on the diagnostic test performed. There is also a consensus that the presence of T2DM is a key factor for the progression of NAFLD to its most severe forms, with worse steatohepatitis, relentless fibrosis, and a higher incidence of...
HCC. Of note, the presence of T2DM has been associated with a faster progression to NASH and advanced fibrosis, supporting the concept that NASH should be considered as a complication of T2DM in most cases. In a report including 698 patients from the NASH CRN, patients with definite NASH were much more likely to have diabetes and insulin resistance than those with milder liver disease. Among 1069 middle-aged patients with NAFLD, diabetes was associated with an adjusted odds ratio of 1.76 for NASH and of 2.57 for fibrosis. The 2 recent large population-based studies have confirmed that approximately 17% of patients with T2DM may have significant hepatic fibrosis.

There are still no approved therapies indicated for NASH patients. As novel agents become available, combination of several agents to treat NASH will likely become a common practice. Promising results from phase 2 and 3 clinical trials have found some benefits, which appeared to halt disease progression with reduction in steatosis and ballooning and regression of fibrosis. Rapid changes in the diagnosis and management of NASH are likely to occur in the near future. More specific screening and treatment recommendations for such patients are needed. A high level of suspicion with accurate diagnosis, grading, and staging of NASH is required for patients with T2DM. Clinicians are at the dawn of a new era of greater awareness about the impact of NASH to overall health and the availability of better treatment options. Prevention of the long-term consequences of NASH will significantly improve the quality of life of many patients whose fatty liver diseases are currently overlooked and undertreated.

**NASH AND CRYPTOGENIC CIRRHOSIS**

Epidemiologic studies indicate that NASH is a common cause of cirrhosis clinically described as “cryptogenic.” To address this from a histologic perspective and to examine the significance of residual histologic findings as a hint of prior NASH, Caldwell et al reviewed the biopsy specimens retrospectively from patients who presented with cirrhosis without sufficient histologic features to diagnose NASH but who had prior histologically confirmed noncirrhotic NASH. They found macrovesicular steatosis, although uniformly present in the precirrhotic NASH specimens, declined in the late-stage cirrhotic NASH specimens and was not useful in the distinction of NASH cirrhosis from cirrhosis secondary to chronic viral hepatitis. However, the presence of ballooned hepatocytes, Mallory-Denk bodies and megamitochondria, and the absence of apoptotic bodies were significantly different in cirrhosis secondary to NASH (so called “cirrhosis with burnt-out NASH”) compared with cirrhosis caused by chronic hepatitis C. We and others also found that histologically advanced NASH presenting as nonspecific or cryptogenic cirrhosis has residual changes (minimal steatosis, rare ballooned hepatocytes with focal perisinusoidal fibrosis) that are consistent with prior steatohepatitis, but differ from cirrhosis caused by hepatitis C. These results provide histologic support for the established epidemiologic associations of NASH with “cryptogenic” cirrhosis and for criteria used in several proposed classifications of cryptogenic cirrhosis. Therefore, a liver biopsy specimen with minimal steatosis, rare ballooned hepatocytes with or without Mallory-Denk bodies, and perisinusoidal fibrosis could be suggestive of burnt-out steatohepatitis as the etiology of cirrhosis.

**REGRESSION OF NASH AND NASH FIBROSIS**

Results from several clinical trials indicate reversibility of NASH. Often, histologic response is defined as decrease in NAS by 2 or more, with no worsening of fibrosis. Features associated with improvement of histology at 72 weeks in the Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment Trial include baseline NAS greater than 5, baseline triglycerides 154 mg/dL or less, baseline international normalized ratio 1 or less, baseline aspartate aminotransferase 49 U/L or less, and decrease in alanine aminotransferase at week 24 by 17 U/L or more. In addition to medication, weight loss by gastric bypass surgery is associated with histologic improvement and resolution of NASH over a mean period of 18 months. Steatosis, hepatocyte ballooning, lobular inflammation, and centrilobular fibrosis improved by gastric bypass surgery—induced weight loss. Although obtaining a follow-up liver biopsy specimen either after treatment or in untreated patients is not a common clinical practice outside clinical trial setting, it would be ideal and clinically important if pathologists can compare with patient’s available prior liver biopsy specimen and comment on the degree of progression or improvement of fatty liver disease. The degree of changes in histology over time may be more important prognostically than the simple histologic findings from a single biopsy specimen.

**DIFFERENTIAL DIAGNOSIS OF NASH**

NASH can be concurrently seen in patients with other types of hepatitis (such as viral hepatitis and autoimmune hepatitis), hepatic neoplasms (including hepatocellular carcinoma and hepatocellular adenoma), Wilson disease, and other liver diseases. Two main differentials, alcoholic fatty liver disease and steatohepatitic HCC, are discussed here.

**Alcoholic Fatty Liver Disease**

As little as 40 g/d of alcohol for men and 20 g/d for women has been reported to increase risk of alcoholic liver disease. Most individuals with excessive consumption of alcohol will develop steatosis, which is reversible after cessation of drinking, but approximately 30% will develop steatohepatitis with an increased risk for fibrosis, cirrhosis, and HCC. The microscopic findings of alcoholic liver fatty disease may show similar histologic features as described for NALFD/NASH, but subtle histologic differences may exist. Although lobular inflammation is commonly composed of mixed inflammatory cells with predominant lymphocytes, neutrophils can be the dominant inflammatory cells in ASH. Rings of neutrophils surrounding ballooned hepatocytes with Mallory-Denk bodies may be present, which has been referred to as neutrophilic satellitosis. Features like bile duct injury with canalicular cholestasis, numerous well-formed Mallory-Denk bodies, acidophilic bodies, sclerosing hyaline necrosis, foamy degeneration, and less cytoplasmic glycogenosis are more commonly seen in ASH as compared with NASH.

**Steatohepatitic HCC**

HCC currently ranks as the fifth most common cancer worldwide and its incidence has steadily increased over the past 3 decades. NAFLD-related cirrhosis is a known risk factor for the development of HCC although the underlying pathogenesis of NAFLD-related HCC remains unclear. The steatohepatitic variant of HCC (SH-HCC)
typically occurs in patients with metabolic risk factors and NAFLD (either cirrhotic or noncirrhotic), and shares many of the histologic features found in NASH. Given their similar morphologic features, distinguishing SH-HCC from background fatty liver can be a diagnostic challenge. Malignant hepatocytes in some SH-HCC cases may show a foamy histiocyte-like appearance and could be mistaken for benign hepatocytes on a core biopsy (Figure 2, A). Typical HCC changes may include unpaired arterioles, loss of reticulin framework, and loss of iron deposition as compared with the adjacent background hepatic parenchyma. In combination with the presence of mitosis, diffuse sinusoidal staining pattern of CD34, diffuse staining pattern of glutamine synthetase and possible positive glypican-3 immunoreactivity, a correct diagnosis of SH-HCC can be made on a biopsy specimen from a liver mass. However, the presence of extensive fatty change may significantly limit the diagnostic value of immunohistochemical and histochemical stains. Because NASH and ASH may show reticulin loss, this can be an important diagnostic pitfall when considering a diagnosis of SH-HCC. Pathologist should be aware of this entity when interpreting a liver biopsy specimen from a liver mass showing features of NASH. Whether the steatotic phenotype of SH-HCC results from the tumor’s adaptive response to an environment rich in fatty acids or from an independent pathogenic pathway remains to be elucidated.

DRUG-INDUCED STEATOSIS AND STEATOHEPATITIS

Although the nondrug etiologies of fatty liver disease, such as T2DM, are very common, drug-induced fatty liver disease is well documented. Caution should be taken before reporting simple steatosis or NASH as drug-induced liver injury in some cases. There are 3 basic patterns of fatty liver disease caused by drugs and other agents as follows: macrovesicular steatosis (with or without inflammation and fibrosis), steatohepatitis, and microvesicular steatosis. In drug-induced macrovesicular steatosis and steatohepatitis, the changes may be very similar to those of NAFLD (Figure 2).
logic patterns of hepatic toxicity induced by anti–PD-1 therapy. Specifically, a steatohepatitic pattern (Figure 2, D) has been reported by our careful and systematic approach.25,26 The initial evaluation challenge to pathologists. The interpretation requires a suspected drug-induced liver injury poses a particular problem.25 Effects, such as weight gain or drug-associated lipodystrophy and steatohepatitis may also result from secondary drug effects. On the other hand, tamoxifen-associated steatosis tends to be periportal rather than perivenular, and necrosis. Specific drugs may cause histologic changes that are subtly different than common NAFLD and NASH. For example, methotrexate can be associated with portal fibrosis and lack the classic ballooning injury of typical NASH, although the degree and character of steatosis, ballooned hepatocytes, inflammation, cholestasis, apoptosis, and necrosis. Specific drugs may cause histologic changes that are subtly different than common NAFLD and NASH. For example, methotrexate can be associated with portal fibrosis and lack the classic ballooning injury of typical NASH, although the typical pattern of steatohepatitis (Figure 2, C) can also be observed. In amiodarone-related injury, the Mallory–Denk bodies tend to be periportal rather than perivenular, and there is often prominent ballooning changes but less degree of steatosis. On the other hand, tamoxifen-associated steatohapatitis is indistinguishable from NASH. Steatosis and steatohepatitis may also result from secondary drug effects, such as weight gain or drug-associated lipodystrophy.

### IMMUNOTHERAPY-INDUCED STEATOSIS AND STEATOHEPATITIS

The anti–PD-1 antibodies, such as nivolumab and pembrolizumab, have been successfully used to treat patients with multiple advanced malignancies.25 The histologic patterns of hepatic toxicity induced by anti–PD-1 treatment have not been well studied.25,27 However, anti–PD-1 therapy-induced steatohepatitis has been reported by our group.28 Specifically, a steatohepatitic pattern (Figure 2, D) of injury was observed in 1 of 8 cases in our study. That patient was obese but his liver function tests were normal before nivolumab treatment. A liver biopsy was performed before treatment, which showed only mild macrovesicular steatosis (15%) without histologic features of steatohepatitis or significant fibrosis. The patient developed steatohepatitis with stage 2 fibrosis 2 months after 5 cycles of nivolumab treatment, suggesting that nivolumab-augmented inflammation may have brought out inflammation and hepatocyte ballooning. Focal bile duct injury with mild cholestasis was also present after nivolumab treatment in that patient. Of note, among our cases with lobular hepatitis, mild simple steatosis was detected in 3 cases.25 However, it is unknown whether the steatosis was induced by anti–PD-1 therapy or present before therapy in these cases.

### COVID-19 AND STEATOSIS AND STEATOHEPATITIS

The current pandemic caused by the novel SARS-CoV-2/COVID-19 has resulted in significant pulmonary injury and mortality. Liver function abnormalities occur in COVID-19 patients and seem to correlate with the severity of pulmonary disease.28,29 A small case series reported the presence of macrovesicular steatosis in hepatocytes.30 A recent autopsy series reported steatosis in 75% (30 of 40) of COVID-19 patients who died of complications of COVID-19.31 The steatosis was macrovesicular in all cases, ranging from mild to severe, restricted to zone 3, zones 2 and 3, or zone 1, and 2 of them had features of steatohepatitis. Mild lobular inflammation and portal inflammation were present in 50% (20 of 40) of cases. SARS-CoV-2 RNA was detected in the liver tissue in 55% (11 of 20) of cases. Thirty-two patients had body mass index (BMI) information and only two of them had a body mass index over 35. There was no correlation between body mass index and percent steatosis. Neither having a history of DM nor treatment with corticosteroids was associated with the percent steatosis or distribution of steatosis.31 Although in some cases steatosis may be due to preexisting NAFLD, in many cases it develops during the course of their COVID-19 illness, likely of multifactorial etiologies including virus-induced hyperinflammatory status, viral cytopathic effect, hypoxia, congestion, malnutrition, and medication. Ultrastructural study

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**Table 2. Pathologists’ View on Liver Biopsy for Patients With Clinical Nonalcoholic Fatty Liver Disease (NAFLD)**

|   |   |
|---|---|
| 1. Routine liver biopsy screening for NAFLD in high-risk groups attending primary care, diabetes, or obesity clinics is not advised |   |
| 2. Liver biopsy screenings should be considered in patients with NAFLD who are at increased risk of having advanced fibrosis (bridging fibrosis or cirrhosis) |   |
| 3. Liver biopsy screenings should be considered in patients with suspected NAFLD in whom competing etiologies for the presence and/or severity of coexisting chronic liver diseases or drug effects cannot be excluded without a liver biopsy procedure |   |
| 4. Clinically useful pathology reporting should include a distinction between steatosis and NASH/ASH. A comment on severity (mild, moderate, or severe) may be useful. Specific scoring systems such as NAS and/or SAF may be used as deemed appropriate |   |
| 5. The presence or absence of fibrosis should be described. If present, a further statement related to location, amount, and parenchymal remodeling is warranted |   |
| 6. Medication such as pioglitazone is reported to improve liver histology in patients with and without T2DM with biopsy specimen–proven NASH. But it should not be used to treat NAFLD patients without biopsy specimen–proven NASH |   |
| 7. Patients with NASH/ASH cirrhosis should be considered for HCC screening. Current evidence does not support routinely repeating a liver biopsy screening in patients with noncirrhotic steatosis or NASH, but this may be considered on a case-by-case basis |   |
| 8. Because of a paucity of evidence, a formal recommendation cannot be made with regard to screening for NAFLD in children with overweight and obesity |   |
| 9. Children with fatty liver who are very young or not overweight should be tested for monogenic causes of chronic liver diseases, such as fatty acid oxidation defects, lysosomal storage diseases, and pentoxyisomal disorders, in addition to those causes considered for adults with NAFLD |   |
| 10. Liver biopsy screenings in children with suspected NAFLD should be performed in those in whom the diagnosis is unclear or in whom there is possibility of multiple diagnoses or before initiating potentially hepatotoxic medical therapy |   |
| 11. A liver biopsy screening to establish a diagnosis of NASH should be obtained before starting children on pharmacologic therapy for NASH |   |
| 12. Pathologists interpreting pediatric liver biopsy specimens should recognize the unique pattern frequently found in children with NAFLD to appropriately characterize pediatric NAFLD |   |

**Abbreviations:** ASH, alcoholic steatohepatitis; HCC, hepatocellular carcinoma; NAS, NAFLD Activity Score; NASH, nonalcoholic steatohepatitis; SAF, steatosis, activity, and fibrosis; T2DM, type 2 diabetes mellitus.
of 2 cases revealed that SARS-CoV-2 virus–infected hepatocytes, leading to mitochondrial swelling, endoplasmic reticulum dilation, and apoptosis in the liver showing steatosis, suggesting an association of viral cytopathic effect and steatosis. Whether similar frequency and degree of steatosis occur in COVID-19 patients with less severe disease remains unknown. The exact mechanism of COVID–19–associated steatosis warrants further investigation.

CONCLUSIONS

Steatosis or steatohepatitis is a common liver injury pattern in patients with fatty liver disease. In NAFLD/ metabolic-associated fatty liver disease, steatosis and steatohepatitis can be seen in patients with metabolic dysfunction/T2DM, and the use of certain drugs including newly developed immune checkpoint inhibitors. Pathologists should be aware that the cause of NAFLD may be multifactorial and genetic. Based on the current clinical practice guidelines, a list of pathologists view on liver biopsy specimens for the patients with NAFLD is included in Table 2. Correlation with clinical information and lab results is important when interpreting liver biopsy specimens showing steatosis or steatohepatitis. NASH is a common cause of cryptogenic cirrhosis and features supporting a steatohepatitic etiology include identification of ballooned hepatocytes and perisinusoidal fibrosis despite the presence of only minimal steatosis. The main differential diagnoses of NASH could include ASH, steatohepatitic HCC, and viral infection such as COVID–19 given the surge of COVID–19 cases. ASH and NASH share similar histologic features, but some changes help favor one over another. Recent clinical trial results for NASH treatment are promising, with reduction of severity of steatosis, ballooning, and fibrosis, but a comprehensive histologic assessment in a liver biopsy specimen is required.

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