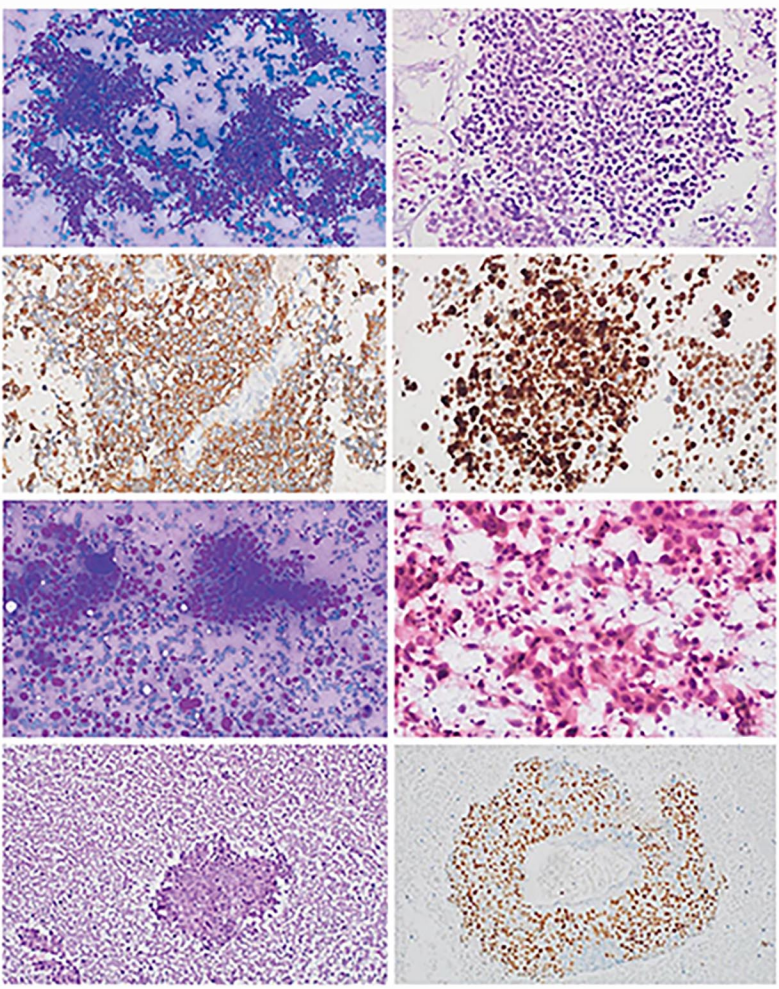
PATHOLOGY

Recent Advances in Pathology-1



Editor
Pranab Dey

JAYPEE

Contents

1

CHAPTER

Updates in Liver Pathology

Suvradeep Mitra

INTRODUCTION

Liver pathology is a growing branch and numerous advances and clarifications in the concept and the criteria have been made in the last decade. This branch of histopathology surpasses the realm of histomorphology alone and encompasses various immunohistochemistry, molecular methods, in silico analysis, and recently artificial intelligence. The advent of different molecular techniques, machine learning, and artificial intelligence caused a paradigm shift from invasive biopsy procedures to relatively noninvasive/minimally invasive techniques. However, histopathological evaluation remains the gold standard. We aim to briefly mention and discuss the salient changes and advances in the current concepts and practices in various branches of liver pathology though a detailed discussion on each topic is beyond the ambit of this chapter. These branches of liver pathology include both non-neoplastic hepatocellular changes as well as hepatic neoplasms. We have retained the older terminology in the subheading for the benefit of the readers especially in situations where a change in the nomenclature is recommended/considered.

UPDATES IN NONALCOHOLIC FATTY LIVER DISEASE

Historically alcoholism is considered to be the major reason behind the accumulation of neutral fat within the hepatocytes. Accumulation of neutral fat within the hepatocytes in causes other than alcoholism is known under the rubric of nonalcoholic fatty liver disease (NAFLD). The classic form of NAFLD is associated with metabolic syndrome and affects nearly a quarter of the population.[1,2] The hepatic fat is not innocuous, as historically perceived and can lead to both reversible and irreversible hepatocellular damage portending to cirrhosis/advanced-stage chronic liver disease (aCLD). Though there are various causes of fatty liver disease other than alcoholism, metabolic syndrome/metabolic dysfunction-associated fatty liver disease needs to be distinguished from all other causes due to its prevalence among the general population including pediatric age groups. Thus, an attempt has been made to change the

nomenclature of NAFLD, an umbrella term encompassing metabolic syndrome, drug/toxin/chemotherapy-associated fatty liver, and miscellaneous other causes. Thus, a consensus panel proposed the terminology of metabolic-associated fatty liver disease (MAFLD) considering metabolic dysfunction to be the critical pivot of this disease rather than an exclusionary terminology of NAFLD.[1,2] Although the absence of significant alcohol intake is considered to be a crucial criterion for the diagnosis of a "pure" MAFLD, the disease is caused by metabolic dysfunction and can coexist with alcoholic liver disease. MAFLD recognizes the primary driving force/association of the disease rather than merely excluding alcoholism as the cause. This consensus statement recognizes the heterogeneity of MAFLD, its association with other CLDs including alcoholism, and recognizes this disease to be a modern epidemic.

A more recent Delphi consensus had further modified the MAFLD terminology to metabolic dysfunction-associated steatotic liver disease (MASLD) as "fatty" was considered to be stigmatizing for individual patients.[3] The reasons for the change in the nomenclature are depicted in **Table 1**.

The diagnostic criteria of MASLD have also been modified **(Table 2)**.

The MAFLD criteria recognize any patient with fatty liver who is obese, has type 2 diabetes mellitus, or has any two of the seven metabolic risk factors. These risk factors include central obesity, hypertension, prediabetes, and four laboratory features including hypertriglyceridemia, low high-density lipoprotein (HDL), elevated high-sensitivity C-reactive protein (hs-CRP), and insulin resistance assessed by homeostatic model assessment for insulin resistance (HOMA-IR).[4,5] The MAFLD criteria in contrast to the latest MASLD criteria had a few drawbacks including (1) failure to identify the cases of lean NAFLD and (2) difficult-to-follow parameters like hs-CRP or HOMA-IR.[4,5] The latest Delphi consensus also redefined and renamed other causes of steatotic liver diseases (SLD) **(Flowchart 1)**.

Broadly, there are five major causes of SLD. This includes alcohol-associated/alcohol-related liver disease (ALD), MASLD, a combination of both where an individual with MASLD has increased alcohol intake (MetALD), specific-etiology SLD, and cryptogenic SLD. Insignificant alcohol intake to diagnose "pure" MASLD requires an average daily alcohol intake of <20 g/day for females and <30 g/day for males [weekly alcohol intake < 140 g/week (females)/

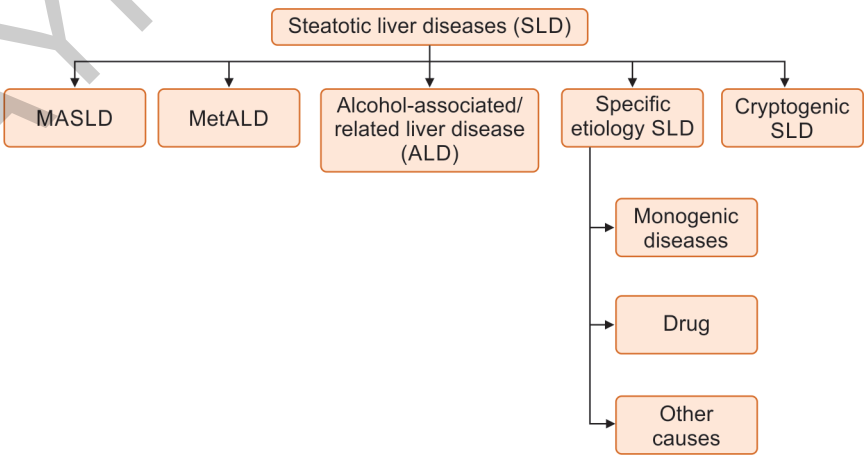
TABLE 1: Reason for the change in nomenclature from nonalcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated steatotic liver disease (MASLD).[3]

Old terminology	New terminology	Reason for change
Nonalcoholic	Metabolic dysfunction-associated	• The nonalcoholic is an exclusionary term and merely states the absence of lack of association of significant alcohol intake. However, it does not highlight the salient background cause in the form of metabolic dysfunction/metabolic syndrome. • New terminology highlights the fundamental pathogenesis of the disease instead of the exclusion of significant alcohol intake
Fatty liver disease	Steatotic liver disease	"Fatty" is believed to be stigmatizing for individuals

TABLE 2: Diagnostic criteria of metabolic dysfunction-associated steatotic liver disease (MASLD).[3]

Diagnostic criteria	• Presence of hepatic steatosis proven by biopsy/imaging • Exclusion of other known causes of hepatic steatosis (alcohol, drug, toxin, and others) • Presence of at least one (out of five) cardiometabolic criteria	
	Adult cardiometabolic criteria	**Pediatric cardiometabolic criteria**
Body mass index (BMI)	BMI ≥ 25 kg/m^2 (23 kg/m^2 for Asians) or waist circumference > 94 cm (male)/80 cm (female) or ethnicity adjusted values	BMI ≥ 85th percentile for age/sex (BMI z-score ≥ +1) or waist circumference > 95th percentile or ethnicity adjusted values
Glucose	Fasting serum glucose ≥ 100 mg/dL OR 2-hour postload glucose level ≥ 140 mg/dL or HbA1c ≥ 5.7% or type 2 diabetes mellitus (without on treatment)	Fasting serum glucose ≥ 100 mg/dL or serum glucose ≥ 200 mg/dL or 2-hour postload glucose level ≥ 140 mg/dL or HbA1c ≥ 5.7% or type 2 diabetes mellitus (without on treatment)
Blood pressure	Blood pressure ≥ 130/85 mm Hg or on antihypertensive treatment	*For ≥13 years*: Blood pressure ≥ 130/85 mm Hg or on antihypertensive treatment *For <13 years*: Blood pressure ≥ 130/85 mm Hg or blood pressure ≥ 95th percentile (whichever is lower)
Plasma triglycerides	Plasma triglycerides ≥ 150 mg/dL or on lipid-lowering agent treatment	*For ≥10 years*: Plasma triglycerides ≥ 150 mg/dL or on lipid-lowering agent treatment *For <10 years*: Plasma triglycerides ≥ 100 mg/dL
Plasma HDL-cholesterol	Plasma HDL-cholesterol ≤ 40 mg/dL (male)/50 mg/dL (female) OR on lipid-lowering agent treatment	Plasma HDL cholesterol ≤ 40 mg/dL or on lipid-lowering agent treatment

Note: Red highlights are differences between the adult and pediatric cardiometabolic criteria.
(HbA1c: glycated hemoglobin; HDL: high-density lipoprotein)



FLOWCHART 1: A schematic diagram depicting different causes of steatotic liver diseases.[3]

<210 g/week (males)]. An average daily alcohol intake of 20–50 g/day for females (140–350 g/week) and 30–60 g/day (210–420 g/week) for males along with metabolic dysfunction qualifies for MetALD, a combination of metabolic dysfunction and ALD. Different specific diseases are responsible for SLD, including many drugs causing drug-induced liver injury (DILI), monogenic diseases such as Wilson disease, liposomal acid lipase deficiency, and other inborn errors of metabolism, and miscellaneous causes such as chronic hepatic C, celiac hepatopathy, and malnutrition. Cryptogenic SLD is the preferred terminology if no specific cause of SLD is identified.[3]

The recent recommendations also highlight the role of genetic testing in the evaluation/management of MASLD. While the single nucleotide polymorphism p.I148M variant (rs738409) in the *PNPLA3* gene is one of the most well-validated drivers of hepatic steatosis, other variants involving *GCKR, TM6SF2, MBOAT7, APOE*, and *GPAM* also affect MASLD. In contrast, a few other genetic variants involving *HSD17B13* and *CIDEB* may be protective for MASLD.[6]

Histologically, NAFLD/MASLD is identified by zonal macrovesicular steatosis in >5% of the liver parenchyma. The macrovesicular steatosis in adult MASLD and a subset of pediatric MASLD affect zone 3 (centrizonal) hepatocytes while pediatric MASLD can also affect zone 1 (periportal) hepatocytes. The steatosis can be associated with lobular inflammation in NAFL/MASL. The diagnosis of steatohepatitis, a more active form of NAFL/MASL requires the unequivocal presence of ballooned hepatocytes in zone 3 (adult/occasional pediatric MASLD) or in zone 1 (subset of pediatric MASLD) with/without the presence of intrahepatocytic Mallory hyaline **(Fig. 1)**.

The identification of nonalcoholic steatohepatitis/metabolic dysfunction-associated steatohepatitis (NASH/MASH) is crucial as this form progresses to aCLD/cirrhosis/hepatocellular carcinoma (HCC). NASH CRN (NASH clinical research network) histologic scoring system/SAF (steatosis, activity, and fibrosis) scores are the reliable histologic scores to assess the activity of NASH/MASH **(Table 3)**.[7,8]

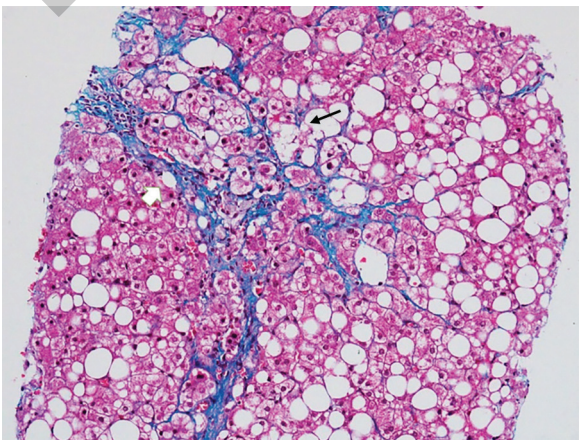


FIG. 1: Histopathology of a case of metabolic dysfunction-associated steatohepatitis with macrovesicular steatosis, ballooned hepatocyte (black arrow), and perivenular/pericellular fibrosis (white arrow) (Masson trichrome stain, 200×).

TABLE 3: A schematic diagram depicting the components of NASH CRN score and SAF score.[7,8]

<table>
<tr><td colspan="4">NASH CRN score: NAS (NAFLD activity score) and fibrosis score</td></tr>
<tr><td>Steatosis:
• 0: <5%
• 1: 5–33%
• 2: 34–66%
• 3: >67%</td><td>Lobular Inflammation:
• 0: None
• 1: <2 foci/20× optical field
• 2: 2–4 foci/20× optical field
• 3: >4 foci/20× optical filed</td><td>Ballooning:
• 0: None
• 1: Mild, few
• 2: Moderate, marked, many</td><td>Fibrosis (F):
• 0: None
• 1a: Mild (delicate) zone 3 perisinusoidal fibrosis
• 1b: Moderate (dense) zone 3 perisinusoidal fibrosis
• 1c: Portal/periportal fibrosis only
• 2: Zone 3 perisinusoidal with portal/periportal fibrosis
• 3: Bridging fibrosis
• 4: Cirrhosis</td></tr>
<tr><td colspan="4">SAF Score: Steatosis, Activity (lobular inflammation and ballooning) and Fibrosis</td></tr>
<tr><td rowspan="2">Steatosis (S): Quantities of large or medium-sized lipid droplets, but not foamy microvesicles:
• S0: <5%
• S1: 5–33%, mild
• S2: 34–66%, moderate
• S3: >67%, marked</td><td colspan="2">Activity (A) (0-4): Unweighted addition of ballooning and lobular inflammation
A1: mild, A2: moderate, A3,4: Severe</td><td rowspan="2">Fibrosis (F):
• Stage 0 (F0): None
• Stage 1 (F1): Zone 3 perisinusoidal (1a or 1b) or portal (1c) fibrosis
• Stage 2 (F2): Perisinusoidal and periportal fibrosis without bridging
• Stage 3 (F3): Bridging fibrosis
• Stage 4 (F4): Cirrhosis</td></tr>
<tr><td>Ballooning:
• 0: Normal hepatocytes with cuboidal shape and pink eosinophilic cytoplasm
• 1: Presence of clusters of hepatocytes with a rounded shape and pale cytoplasm usually reticulated. Size similar to that of normal hepatocytes, shape different
• 2: Same as grade 2 with some enlarged hepatocytes, at least twofold that of normal cells</td><td>Lobular Inflammation: Focus of two or more inflammatory cells within the lobule counted at ×20 magnification:
• 0: None
• 1: 2 foci/×20
• 2: >2 foci/×20</td></tr>
</table>

(CRN: clinical research network; NAFLD: Nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; SAF: steatosis, activity, and fibrosis)

However, these existing staging and grading systems are not without fallacies and though simple and easy to apply in day-to-day practice, these systems do not provide accurate weightage to individual features, are subject to inter- and intraobserver variabilities, and ignore multiple important histopathological parameters.[9-11] Therefore, an expanded NAFLD activity score (NAS) including Mallory Denk bodies, portal inflammation, an alternate calculation of lobular inflammation, and ballooned hepatocytes is proposed.[11]

The fibrosis in MASLD and most other liver diseases is a reliable indicator of disease progression. It is a dynamic process and the existing fibrosis staging system falls short of commenting on the type of fibrosis (progressive or regressive) and quantitating it. Thus, many morphometry-based methods are employed to characterize the type and quantitate the amount of fibrosis in various liver diseases including MASLD. Measurement of collagen proportionate area (CPA), second harmonic generation (SHG) microscopy, two-photon excitation filter (TPEF) microscopy, and automated computational algorithm tools like qFIBS shows reliable results and even outperform hepatopathologists.[12,13] Various noninvasive radiology-based methods are also tested for accurate prediction of the disease activity and disease progression and form the basis of artificial intelligence-based predictions. These methods are operator-independent and algorithm-based and reduce the interobserver and intraobserver variability, reduce the time, and need of skilled/trained pathologists in interpreting the liver biopsies and predict the course of the disease more accurately.[12,13]

The management of MASLD depends on lifestyle changes, dietary modification, exercise, and pharmacotherapy. INASL guidelines recommend the use of vitamin E, pioglitazone, and saroglitazar in MASLD-MASH.[14] Vitamin E and pioglitazone are recommended by various international societies in biopsy-proven NASH/MASH. While vitamin E should be used in individuals without diabetes, pioglitazone can be used in both diabetics and nondiabetics. Saroglitazar is approved by the drug controller general of India for use in NAFLD/MASLD with comorbidities and NASH/MASH with F1-F3 fibrosis.[14] Various other drugs are also under various clinical trials and some of them appear to show promising pharmacotherapeutic results including farnesoid-X-receptor (FXR) agonists such as obeticholic acid and tropifexor, GLP-1 agonist such as semaglutide, and peroxisome proliferation-associated receptor (PPAR) agonist such as elafibranor to name a few.[15] These drugs along with the antioxidants, anti-inflammatory agents, and immunomodulators are expected to unravel a new horizon of effective pharmacotherapy in the near future.[15]

UPDATES IN IDIOPATHIC NONCIRRHOTIC PORTAL HYPERTENSION

Idiopathic noncirrhotic portal hypertension (INCPH) is traditionally characterized by the presence of clinical features of portal hypertension in the absence of cirrhosis of the liver or any underlying CLD that may explain the portal hypertension. The patency of portal and hepatic veins is also required for the

diagnosis of INCPH. INCPH has many monikers including noncirrhotic portal fibrosis (NCPF), idiopathic portal hypertension, hepatoportal sclerosis, and benign intrahepatic portal hypertension to name a few.[16,17] Despite the knowledge and acceptance of the presence of INCPH for more than a few decades, a unified terminology, definition, and descriptions are lacking. Therefore, the clinical as well as histopathological diagnosis of INCPH remains variable and individualistic. Besides, the pathogenesis also remains poorly understood owing to the variability of the definitions.

The vascular liver disease interest group (VALDIG) proposed a novel nomenclature in 2019 to circumvent these issues. Thus, the term porto-sinusoidal vascular disease (PSVD) has been introduced by the VALDIG.[18,19] The VALDIG has recognized several limitations to the previous definition of INCPH—(1) the exclusion of all individuals without portal hypertension also excludes individuals with preportal hypertension/subclinical portal hypertension, (2) the exclusion of all cases of portal venous thrombosis (PVT) also excludes cases of INCPH diagnosed after the development of PVT, as PVT is a complication of INCPH, and (3) the definition of INCPH excludes all causes associated with the development of portal hypertension thereby refuting the possibility of coexisting INCPH with another liver disease.[18,19]

The new term "porto-sinusoidal vascular disease" has been coined to encompass the whole spectrum keeping in mind that all pathology about this entity essentially involves the portal venules and/or the sinusoids. The diagnosis of PSVD does not require portal hypertension, but a characteristic histomorphology in the absence of cirrhosis in a given clinical scenario suffices for the diagnosis. The presence of risk factors for parenchymal liver diseases does not negate a diagnosis of PSVD if the histopathology is supportive. The definition and the diagnostic criteria of PSVD are depicted in **Table 4**.

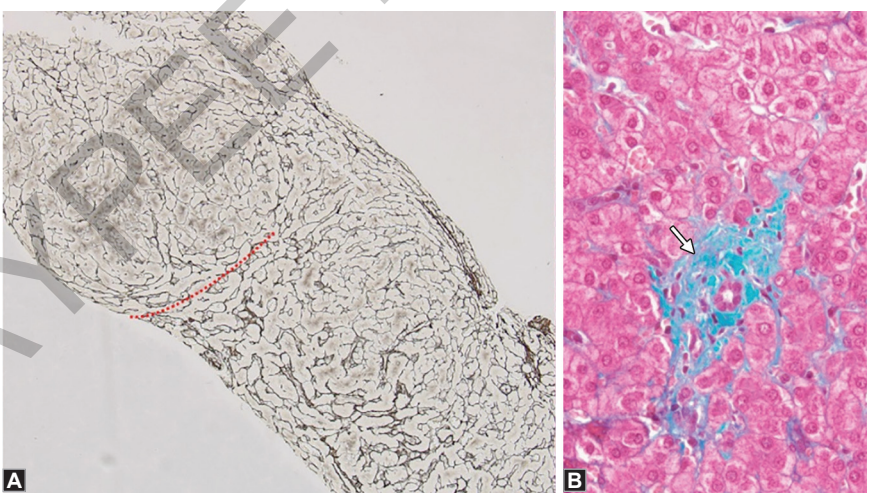
Though inclusive of multiple entities causing CLD, the definition of PSVD excludes various entities such as Budd–Chiari syndrome and other causes of hepatic venous outflow tract obstruction, Abernathy syndrome, hereditary hemorrhagic telangiectasia, history of bone marrow transplantation, cardiac failure, congenital hepatic fibrosis, sarcoidosis, etc.

The detailed discussion of the hepatic histomorphology of the specific and nonspecific features of PSVD is beyond the scope of this chapter. However, obliterative portal venopathy (OPV) is characterized by the thickening of the wall and fibrosis of the portal venous radicles with obliteration and loss of the venous radicles. The nodules of nodular regenerative hyperplasia (NRH) show hyperplastic hepatocytes with the double-cord pattern at the center of the nodule while the periphery of the nodule shows atrophic hepatocytes with reticulin stretching in the absence of any fibrous septa. Delicate fibrous septa emanating from a portal tract and blindly ending into the hepatic lobule without any connection with another portal tract or central vein denote incomplete septal fibrosis/cirrhosis **(Figs. 2A and B)**.

The proposal of PSVD has received many flaks from experts in recent times, despite its simplicity and easy applicability. The too-simplistic approach of PSVD fails to address the complexity and heterogeneity of the disease. Some

TABLE 4: Definition and criteria of porto-sinusoidal vascular disease (PSVD).[18,19]

	Clinical	Histopathological
Specific features	Gastric, esophageal, or ectopic varices	Obliterative portal venopathy
	Portal hypertensive bleeding	Nodular regenerative hyperplasia
	Imaging: Portosystemic collaterals	Incomplete septal fibrosis/cirrhosis
Nonspecific features	Ascites	Architectural changes (irregular distribution of portal tracts and central veins)
	Platelet count < 1,50,000/μL	
	Spleen size ≥ 13 cm in its largest axis	Lobular changes (nonzonal sinusoidal dilatation, megasinusoids, perisinusoidal fibrosis, and central vein abnormalities)
		Portal tract changes (multiplication, arterial dilatation, arterialization of portal veins, periportal shunting vessels, herniated portal vein, aberrant vessels, and portal tract remnant)
Diagnosis of PSVD (requires a liver biopsy ≥ 20 mm without cirrhosis)	• One specific clinical sign • One nonspecific clinical sign	• One specific histopathological feature • One nonspecific histopathological feature



FIGS. 2A AND B: Histopathology highlighting specific histopathological signs of PSVD: (A) Nodules of nodular regenerative hyperplasia (Reticulin stain, 100×) (the margin of a nodule marked with red dotted line); (B) Obliterated portal vein (white arrow) in a portal tract (Masson trichrome stain, 400×).

cases diagnosed as PSVD may be a CLD evolving into a precirrhotic/cirrhotic disease. The specific histopathological signs of PSVD can be associated with "aging", trauma, cholecystectomy, hemochromatosis, dialysis, or various other causes unrelated to INCPH and thus lack in their specificity. A subset of individuals diagnosed based on only histopathological signs of PSVD without any clinical signs of PSVD fail to develop portal hypertension on an extended follow-up period. Thus, the concept of preportal hypertensive phase of PSVD does not appear true for all cases.[18,19] In short, the new moniker "PSVD" appears lucrative in terms of simplicity and increases the sensitivity of diagnosis. However, it lacks specificity, needs to address multiple questions, and requires revision for uniform worldwide acceptance.

UPDATES IN AUTOIMMUNE HEPATITIS

Autoimmune hepatitis (AIH) is a relatively uncommon cause of CLD although it is increasingly recognized globally. A hepatitic form of autoimmune liver disease, AIH is characterized by an immune/inflammatory injury to the hepatocytes dominantly attributed to T cell-mediated injury along with autoantibody production.[20,21] The diagnosis of AIH depends on the clinical features, biochemical parameters (increase in serum transaminases), serology (autoantibody positivity and hypergammaglobulinemia), histopathology, and often response to immunosuppression. However, seronegativity in AIH is seen in early acute, severe, and fulminant forms (10–40% of cases).[22,23] Normal serum gamma globulin can be seen in 25–47% of cases.[22,23] Thus, histopathological evaluation of AIH often becomes crucial in the diagnosis of AIH.

The histopathological features of AIH are portal/periportal-based inflammation/fibroinflammation including interface hepatitis, the inflammatory milieu comprising lymphocytes, and plasma cells. Besides, hepatocellular rosettes and emperipolesis are considered important histopathological features. These traditional histopathological features essentially depict chronic AIH although the portal-based inflammation can be less reliable in acute AIH which may show lobulocentric inflammation. Therefore, consensus criteria using a modified Delphi panel approach were proposed for a uniform histological diagnosis of both acute and chronic AIH.[24] In brief, the consensus recommends histopathology to be the standard of AIH diagnosis.

A portal hepatitis is considered "likely AIH" when portal lymphoplasmacytic infiltrate is associated with (1) more than mild interface activity and/or (2) more than mild lobular inflammation in the absence of histological features of another liver disease. Any lobular hepatitis with/without centrilobular necroinflammation is considered "likely AIH" when more than mild lobular hepatitis (with/without centrilobular necroinflammation) is associated with either (1) portal-based fibrosis, or (2) lymphoplasmacytic infiltrate, or (3) interface hepatitis in the absence of histological features of another liver disease **(Fig. 3)**.[24]

Diagnostic criteria for possible AIH and unlikely AIH had also been proposed **(Table 5)**.[24]

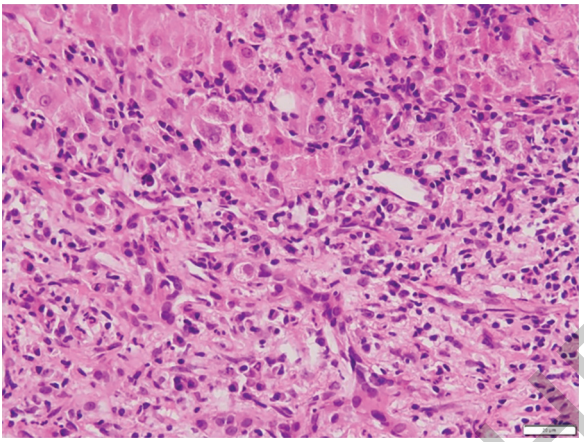


FIG. 3: Histopathology of a case of autoimmune hepatitis depicting moderate portal lymphoplasmacytic inflammation, marked interface activity, and foci of lobular inflammation (Hematoxylin and eosin, 400×) (scale bar attached).

TABLE 5: Diagnostic histopathological criteria for autoimmune hepatitis (AIH).[24]

	Portal hepatitis	Lobular hepatitis
Likely AIH	Portal lymphoplasmacytic infiltrate + one/both of the following: • More than mild interface hepatitis • More than mild lobular inflammation Absence of features of other liver disease	More than mild lobular inflammation ± centrilobular necroinflammation + at least one of the following: • Lymphoplasmacytic infiltrate • Interface hepatitis • Portal-based fibrosis Absence of features of other liver disease
Possible AIH	*Portal lymphoplasmacytic infiltrate*: • Without either of the "likely" features • Absence of features of other liver disease OR • With one/both of the "likely" features • Presence of features of other liver disease	More than mild lobular inflammation ± centrilobular necroinflammation • Without either of the "likely" features • Absence of features of other liver disease OR • With any of the "likely" features • Presence of features of other liver disease
Unlikely AIH	Portal hepatitis • Without either of the "likely" features • Presence of features of other liver disease	Any lobular hepatitis • Without either of the "likely" features • Presence of features of other liver disease

This consensus also disregards emperipolesis or hepatocellular rosettes to be the specific features of AIH.[24] Thus, these features are considered histopathological features of AIH but not pathognomonic of AIH.

The conceptual acceptance and recognition of acute AIH led to the clinical terminologies in relation to AIH causing acute liver failure (ALF).[22,25] Thus, AIH presenting within ≤26 weeks without any evidence of preexisting liver disease is clinically divided into (1) acute icteric AIH (icteric, no coagulopathy, and no encephalopathy), (2) acute severe AIH (AS-AIH) [icteric and coagulopathy (INR ≥ 1.5), no encephalopathy], and (3) AS-AIH with ALF [icteric, coagulopathy (INR ≥ 1.5), and encephalopathy].[22]

UPDATES IN INFECTIOUS HEPATITIS (COVID-19 AND OTHER UNCOMMON INFECTIOUS FORMS)

Various forms of hepatotropic and nonhepatotropic organisms especially viruses affect the hepatic parenchyma manifesting as minor elevations in the serum transaminases to fatal and fulminant hepatic failure. The hepatotropic viruses including hepatitis A, hepatitis E, hepatitis B, hepatitis C, and hepatitis D are well known to cause hepatocellular damage. However, there is growing evidence of hepatic injury caused by the nonhepatotropic viruses. The non-hepatotropic viruses often inflict injury in the immunocompromised individuals although immunocompetent individuals can also be affected.

Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has emerged as a viral agent affecting multiple systems including the liver during COVID-19 (Coronavirus disease 2019) pandemic. Dominantly, it affects the lungs causing diffuse alveolar damage although hepatic manifestations are not uncommon.

The hepatic manifestations of COVID-19 occur through both direct and indirect pathways. Direct hepatotoxicity occurs following the direct entry of the SARS-CoV-2 virus within the cholangiocyte and hepatocyte through the angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) receptors, the cholangiocytes being the primary cells of injury.[26] The indirect modes of hepatic injury occur due to immune overactivation and hypercytokinemia, systemic inflammatory drive, hypoxic ischemic hepatitis with/without reperfusion injury especially in the setting of respiratory failure, endothelial damage due to endothelial dysfunction, DILI, and also vaccine-induced liver injury.[26-28] Direct or indirect viral-mediated injury and vaccine-induced liver injury are often overwhelmingly diagnosed while the possibility of DILI should not be overlooked.[29]

The most common form of derangement in the liver function test occurs in the form of hypoalbuminemia, elevated levels of gamma-glutamyl transferase (GGT), aspartate transaminase (AST), and alanine transaminase (ALT), and hyperbilirubinemia in nearly 61%, 28%, 23%, 23%, and 11% of the individuals.[27] This data was obtained from the meta-analysis of 128 studies. The most common histopathological change in COVID-19 infection is macrovesicular steatosis (75%) followed by mild portal and lobular inflammation (50% each), and variable porto-sinusoidal vascular pathology including dilatation of the portal venous radicles, portal venous and sinusoidal thrombi, focal to multifocal phlebosclerosis, and other minor changes. Portal fibrosis and incomplete fibrous septa, cholestasis, and hepatocellular swelling are also observed **(Fig. 4)**.[26,30-32]

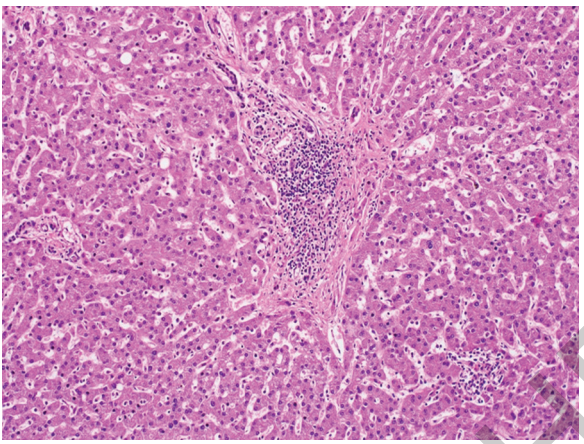


FIG. 4: Histopathology of a case of COVID-19 hepatitis depicting mild portal and periportal fibrosis along with mild lymphocytic porto-lobular inflammation (hematoxylin and eosin, 200×).

Electron microscopy and viral immunostains usually fail to demonstrate the viral particles in the liver though an expansion of the endoplasmic reticulum and edematous mitochondria with disruption of the cristae can be documented by transmission electron microscopy.[31]

Several other uncommon nonhepatotropic viruses have gained recognition for causing hepatic injury in recent times. An epidemic of adenoviral hepatitis has occurred among the pediatric population in 2021–2022 causing significant morbidity and mortality.[33] While the reason for the severity of adenoviral hepatitis, usually a mild disease, is debatable, the histopathology uniformly mimics AIH and is characterized by marked portal mixed inflammatory infiltrate, portal plasmacytosis with/without plasma cell clustering, more than mild interface hepatitis, and milder lobular inflammation.[33] The liver tissue usually does not show any viral inclusion although serological evidence of adenoviral infection remains strong.[33]

Epstein–Barr virus (EBV), a nonhepatotropic virus, causes infectious mononucleosis characterized by fever, diarrhea, lymphadenopathy, and hepatosplenomegaly. Infectious mononucleosis is usually associated with a mild form of hepatitis. EBV-associated ALF comprises 0.21% of all ALF cases according to the US ALF study group.[34] Usually, a disease of immunocompromised individuals, a fatal form of infectious mononucleosis-associated acute hepatitis can affect the immunocompetent individuals.[35] The disease is usually caused by hypercytokinemia where the innocent hepatocytes are killed by the immune insult inflicted by the cytotoxic-T-lymphocytes against the viral-infected B cells as collateral damage. The characteristic histomorphology of EBV-hepatitis includes dense portal-based mixed inflammation comprising of T-lymphocytes and plasma cells along with eosinophils, portal-based lymphoid aggregate/periductal lymphoid cuffing, an intrasinusoidal linear array of lymphocytes in a string-of-beads appearance, and abundant hemophagocytosis, especially erythrophagocytic figures. Endotheliitis, bile duct damage, and epithelioid/fibrin-ring granuloma can also be seen **(Figs. 5A to C)**.[35,36]

Recent Advances in Pathology-1

The book "*Recent Advances in Pathology-1*" highlights the various topics on the cutting edge of pathology. It contains the recent developments in histopathology of the various lesions (lung, liver, pancreaticobiliary, breast, thyroid, neuroendocrine, renal, endometrium, and central nervous system), different molecular techniques, molecular basis of metastasis, micronucleus, cancer stem cell, artificial intelligence, precision medicine, liquid biopsy, and pan-cancer biomarkers. The chapters of this book are written by the eminent pathologists from the various prestigious institutes of India with in-depth knowledge in these fields. These chapters are short, simple, and updated. Each chapter is equipped with multiple tables and figures to illustrate the text. Overall, the book is a helpful guide in the field of frontiers of Pathology.

Pranab Dey is a fellow of the Royal College of Pathologists, UK and enlisted in the top 2% of scientists by SCOPUS for the successive 3 years. He worked for over three decades as a Professor of Cytology at the Postgraduate Institute of Medical Education and Research, Chandigarh, India. He is presently working as a Director of Pathology and Transfusion Medicine at the National Institute of Medical Science, Jaipur, Rajasthan, India. Dr Dey is one of the eminent cytologists in India and is the sole author of 12 books in pathology. He has been actively engaged in teaching and research in Cytology for more than three decades and had more than 500 research works and reviews in various international journals of pathology and cytology.

Printed in India

Available at all medical bookstores or buy online at www.ejaypee.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
EMCA House, 23/23-B, Ansari Road,
Daryaganj, New Delhi - 110 002, INDIA
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers
Follow us on instagram.com/JaypeeMedicalPublishers

Shelving Recommendation
PATHOLOGY

ISBN 978-93-6616-098-6