Histopathology of Autoimmune Hepatitis: An Update

Despoina Myoteri, MD, PhD, Stratigoula Sakellariou, MD, PhD,† and Dina G. Tiniakos, MD, PhD*‡*

Abstract: Autoimmune hepatitis (AIH) is a rare immune-mediated chronic liver disease that is diagnosed based on a combination of biochemical, immunologic, and histologic features and the exclusion of other causes of liver disease. According to the new consensus criteria of the International Autoimmune Hepatitis Pathology Group (IAIHPG), the likely histologic features include a chronic hepatitis pattern of injury with a lymphoplasmacytic portal infiltrate, interface activity, and portal-based fibrosis. More than mild lobular hepatitis with any of the above features can also be diagnosed as likely AIH in the absence of features of another liver disease. Centrilobular injury with prominent hepatocellular necrosis and mononuclear inflammation may represent an acute-onset disease and indicate possible AIH in the absence of concurrent liver disease. Kupffer cell hyaline bodies and portal lymphocyte apoptosis are significantly associated with AIH, whereas emperipolesis and hepatocellular rosette formation are nonspecific features indicative of disease severity. Liver histology is an integral part of the clinical diagnostic scoring system and is required to confirm or support AIH diagnosis. Substitution of the histologic component of the simplified AIH scoring system with the consensus IAIHPG criteria has been proposed to optimize clinical diagnosis. This review explores the significant role of histopathology in AIH by analyzing its main features and current histologic diagnostic criteria, different AIH presentations, differential diagnosis, assessment of concurrent liver disease, and identification of AIH variants with primary cholangiopathy.

Key Words: autoimmune hepatitis, centrilobular injury, diagnosis, histopathology, liver biopsy, consensus criteria

(*Adv Anat Pathol* 2025;32:414–426)

Autoimmune hepatitis (AIH) is a chronic, progressive, immune-mediated necroinflammatory liver disease of unknown etiology that may affect any person regardless of age, sex, race, or ethnicity and may have acute presentation at onset.[1] AIH has been under clinical notice since 1946 but it was first described in 1950.[2] It is a rare disease with a global incidence of 1.28 cases/100,000 inhabitant-years and global prevalence of 15.65 cases/100,000 inhabitants.[3] In most countries, the incidence and prevalence of AIH is increasing[4] and a recent population-based cohort study showed a 10-year cumulative all-cause mortality and liver-related mortality of 31.9% and 10.5%, respectively, including hepatocellular carcinoma (HCC).[5] The disease is more common in females (female/male ratio 3.6/1) and 30% of the patients are more than 60 years old.[4] The pathogenesis of AIH is complex implicating dysregulated immune mechanisms involving type II natural killer (NK) cells and CD4 T lymphocytes, environmental factors, genetic predisposition, and alterations in the microbiome, among other causes.[6]

In 2025, the diagnosis of AIH remains clinicopathologic and relies on a combination of biochemical and immunologic features, such as increased serum immunoglobulins (total, γ-globulins, or IgG) and high titers of serum autoantibodies [antinuclear antibody (ANA), smooth muscle antibodies (SMA), antiliver kidney microsomal antibody type 1 (anti-LKM-1), antiliver cytosol type 1 (anti-LC-1), antisoluble liver antigens/liver pancreas (anti-SLA/LP), etc.], and portal or lobular hepatitis on liver biopsy.[1] Importantly, the exclusion of other causes of liver disease (viral, drug induced, toxic, metabolic) and response to immunosuppressive therapy play a significant role in AIH diagnosis. Currently, the distinction of AIH subtypes according to autoantibody profile is not considered clinically helpful in adults and, therefore, is not recommended.[1,4]

AIH treatment aims to achieve a complete biochemical response (CBR) with normalization of aminotransferases and IgG levels and histologic remission with first-line induction with predniso(lo)ne combined with azathioprine or mycophenolate mofetil (MMF). MMF is the second-line treatment of choice in patients with intolerance or thiopurine side effects, while in expert centers, tacrolimus, infliximab, rituximab, and belimumab may be used as third-line treatment.[1,4] If left untreated, AIH has a very aggressive course (median survival 3.3 y); therefore, missing the diagnosis has detrimental effects.

This review focuses on the role of histopathology in the management of AIH in adults with updates on the diagnostic histologic features, spectrum of AIH presentations, differential diagnosis, assessment of concurrent liver disease, and evaluation of variants and specific forms of AIH.

ROLE OF LIVER BIOPSY IN AUTOIMMUNE HEPATITIS

The use of noninvasive methods for the evaluation of chronic liver disease has reduced the number of liver biopsies performed. However, in the field of AIH, liver biopsy remains an important tool for patient management, as it is essential for diagnosis and for providing important information for disease remission or progression during treatment. In the absence of positive autoantibodies in repeated tests, liver biopsy is essential to diagnose "autoantibody-negative" AIH, a variant that responds well to

From the *Department of Pathology, Aretaieion Hospital, Medical School; †1st Department of Pathology, Medical School, Laiko General Hospital, National and Kapodistrian University of Athens, Athens, Greece; and ‡Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle Upon Tyne, UK.

D.M. and S.S.: contributed equally for this study (joint first authors).

The authors have no funding or conflicts of interest to disclose.

Reprints: Dina G. Tiniakos, MD, PhD, Department of Pathology, Aretaieion Hospital, National and Kapodistrian University of Athens, 76, Vasilissis Sofias Avenue, Athens 11528, Greece (e-mails: dtiniak@med.uoa.gr; dina.tiniakos@newcastle.ac.uk).

All figures can be viewed online in color at www.anatomicpathology.com.

DOI: 10.1097/PAP.0000000000000500

corticosteroid therapy.[7,8] The identification of cirrhosis on biopsy may guide the selection and dose of immunosuppressants and inform screening for long-term liver complications.[4] Baseline histology is also significant for future therapy decisions because immunosuppressed AIH patients may develop other liver diseases. In addition, histologic findings at presentation can be of prognostic value for the development of progressive fibrosis/cirrhosis and the risk of liver-related death or transplantation and can provide predictive information regarding response in treated patients.[7]

The clinical practice guidelines of the European Association for the Study of the Liver (EASL)[1] and the American Association for the Study of Liver Diseases (AASLD),[9] as well as national guidelines[4] for the management of AIH, agree that liver biopsy is required to establish the diagnosis of AIH. The length and width of the needle liver biopsy sample is important for accurate diagnosis, with a minimum proposed length of 1.5 cm, containing at least 6 to 8 portal tracts and preferably with a 16 G or wider needle.[1] It is advised that, ideally, a specialized hepatopathologist rather than a general pathologist evaluates the specimen.[1] The pathology report should include, in addition to the pattern of inflammation and description of the cardinal histologic findings, grading of necroinflammatory activity according to Ishak's modified Histological Activity Index (mHAI)[10] and staging of fibrosis and architectural remodeling with one of the widely accepted histologic staging systems. The recent EASL clinical practice guidelines strongly recommend classifying the findings as likely, possible, or unlikely AIH.[1]

Besides its diagnostic role, liver biopsy is significant for the differential diagnosis of AIH, sometimes highlighting an alternative etiology for liver injury and may identify concurrent diseases or features indicating a possible variant of AIH with primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). Following the diagnosis of AIH, liver biopsy may be used to monitor response to treatment and, when appropriate, to decide whether to stop or intensify immunosuppressive treatment.[11] However, in clinical practice the need to assess remission by liver biopsy is limited, unless treatment cessation is considered.[1] In this setting, liver biopsy is desirable, since some patients with complete biochemical remission may still have necroinflammation on histology or may have progressed to cirrhosis, and withdrawal of immunosuppression may have detrimental effects.[1] The 2025 EASL clinical practice guidelines indicate that since strong evidence and prospective data are lacking regarding the role of liver biopsy before treatment cessation, patient priorities need to be considered for this decision.[1]

Liver biopsy may be repeated in patients with relapse or inadequate treatment response to monitor inflammatory activity or in the presence of increasing biochemical evidence of cholestasis and suspicion of a variant disorder (AIH/PBC or AIH/PSC).[1]

HISTOPATHOLOGY OF AIH

There is a broad spectrum of histologic manifestations of AIH. Some histologic features have been described as characteristic, but none are pathognomonic, as they can be encountered in other liver diseases. In addition, the histologic features of AIH may change during its clinical course and following treatment.[12,13]

For many years, the combination of interface hepatitis, hepatocellular rosettes and emperipolesis were considered "typical histology" of AIH based on the 2008 International AIH Group (IAIHG) simplified diagnostic criteria.[14] However, these features are not specific for AIH and are rather indicative of liver damage and regeneration of diverse etiology. As the understanding of liver pathology in AIH has evolved, it has been recognized that the typical histologic pattern is that of nonspecific chronic hepatitis with or without lobular activity (Figs. 1–3).[15] According to the recent consensus recommendations of the International AIH Pathology Group (IAIHPG),[16] which will be discussed in detail below, the likelihood of AIH histologic diagnosis in the native liver is based on the pattern and severity of liver injury.

Main Histologic Features

Portal Inflammation

Infiltration of the portal tract by inflammatory cells is a salient feature of AIH and is nearly always present. The severity of portal inflammation varies, and the inflammatory infiltrate consists mainly of lymphocytes, histiocytes, and plasma cells; a few neutrophil or eosinophil polymorphs can also be observed (Fig. 1A).[7,13]

An important feature of AIH is interface hepatitis, which is defined as the extension of portal inflammation beyond the limiting plate and into the periportal liver parenchyma (Fig. 1C). The resulting hepatocellular injury can cause necrosis, which, when severe, may extend to adjacent lobules, either portal tracts or central venules ("bridging necrosis"). While this finding can be observed in other forms of chronic hepatitis, a higher degree of interface hepatitis severity is suggestive of AIH.

Plasma cells have historically been considered a hallmark of AIH and, when prominent, are considered more specific for AIH than for hepatitis of other etiology (Fig. 1C). However, they may be absent in about 30% of liver biopsies from AIH patients, a finding that cannot exclude diagnosis.[7,12] The IAIHPG has proposed the arbitrary definition of "plasma cell clusters" as a group of > 5 plasma cells aiming to increase interobserver agreement for their recognition; however, the optimal cutoff point has not yet been adequately validated.[16] Immunohistochemically, IgG-positive plasma cells predominate in AIH, whereas IgM-positive plasma cells are more common in PBC. The IgG/IgM plasma cell ratio has been proposed as an aid in the differential diagnosis of AIH from PBC when bile duct injury is prominent,[17] but the results of subsequent studies are conflicting.[18–20] IgG predominance is nonspecific for AIH; therefore, it is not helpful for the differential diagnosis of variant syndromes.[13]

Lymphocyte apoptosis in the portal tracts has been proposed as a feature of diagnostic significance in untreated AIH, increasing proportionally to the grade of inflammation.[21]

Lobular Inflammation

Lobular inflammation is a common feature of AIH with variable severity, ranging from scattered necroinflammatory foci ("spotty necrosis") to confluent and bridging necrosis. Hepatocyte injury and subsequent death can result in disruption of normal architecture, causing lobular disarray. Hepatocellular ballooning due to degeneration of injured hepatocytes and/or apoptotic bodies can be

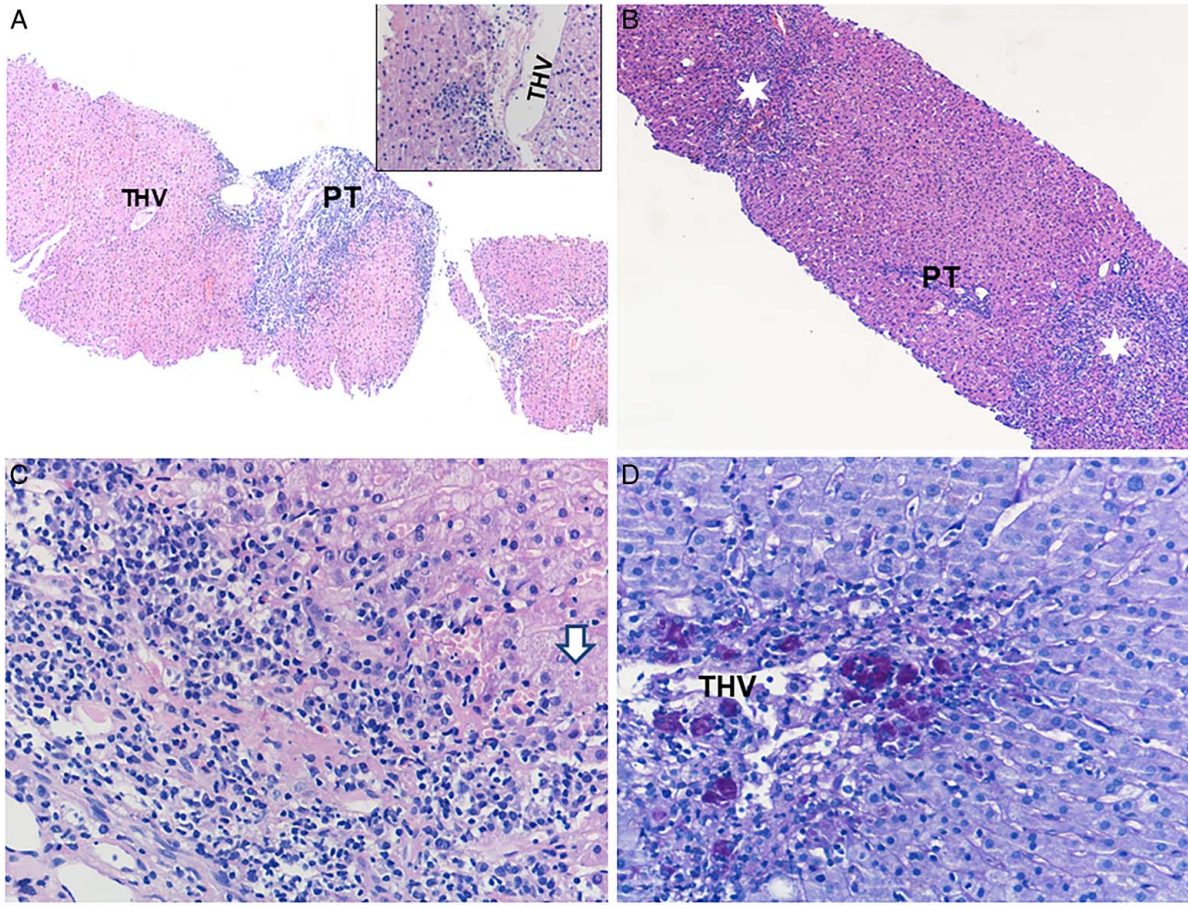

FIGURE 1. Autoimmune hepatitis. A, Portal-based pattern of chronic inflammation with mild lobular inflammation, hematoxylin and eosin (H&E) x40. Inset shows a focus of centrilobular confluent necrosis, H&E x200. B, Lobular hepatitis with mainly centrilobular necrosis (asterisk) and minimal portal inflammation, H&E x40. C, Portal lymphoplasmacytic infiltrate with numerous plasma cells at the portal-parenchyma interface (interface hepatitis). Arrow shows emperipolesis, H&E x200. D, Centrilobular necrosis with PAS-diastase (DPAS)-positive ceroid laden macrophages, H&E ×200. PT indicates portal tract; THV, terminal hepatic venule.

encountered in this setting. In response to hepatocyte injury, features of hepatocellular regeneration with 2-cell thick trabeculae and rosette formation, referring to groups of hepatocytes around a central lumen, are observed (Figs. 2A, B). Like portal/periportal inflammation, these common changes are not specific for AIH.[7,12,13] Similarly, emperipolesis, defined as the presence of an inflammatory cell within the hepatocyte cytoplasm is a nonspecific finding (Figs. 1C, 2A).[22] Emperipolesis, a frequent feature in AIH, encountered in up to 80% of liver biopsies, is related to mechanisms important for the maintenance of immune tolerance.[7] Despite not being considered "typical" features of AIH anymore, reporting them is useful, as their presence correlates with disease severity.[12,15]

Groups of Kupffer cells are frequently observed in the lobules in more severe AIH (Fig. 1D). Kupffer cells containing hyaline globules, a feature more common in pediatric AIH,[23] may have diagnostic significance in adult AIH as they are more frequent compared with chronic hepatitis of other etiology.[15] The hyaline globules originate from excess immunoglobulins secreted by plasma cells that are ingested and stored within Kupffer cells and should be differentiated from the granular lysosomal material frequently seen in their cytoplasm or from erythrophagocytosis.[15]

Additional Features

Centrilobular Injury

Centrilobular injury, also termed central perivenulitis, is defined as the presence of perivenular mononuclear cell inflammation with or without prominent necrosis (Figs. 1B, 2C, D, 3A). It has been reported in 18% to 29% of liver biopsies with AIH, mostly in the presence of portal/periportal inflammation, and is usually associated with an acute disease flare.[24–27] Rarely, it may be the only histologic finding in AIH, reported in 2% to 3% of cases where it may represent an early stage of AIH, before portal inflammation develops.[28] Centrilobular injury is also encountered in other inflammatory settings, like drug-induced liver injury (DILI) and viral hepatitis.[29,30]

Bile Duct Injury

Bile duct injury is a common feature of AIH. It can pose a diagnostic problem when prominent, since its presence must be differentiated from PBC, PSC, or their variant forms. Destruction of interlobular bile ducts can be a focal feature in 12% of AIH cases[31] while lymphocytic cholangitis has been reported in 10% to 83% (Fig. 3B).[31,32] Therefore, these features are not diagnostic of AIH/PBC

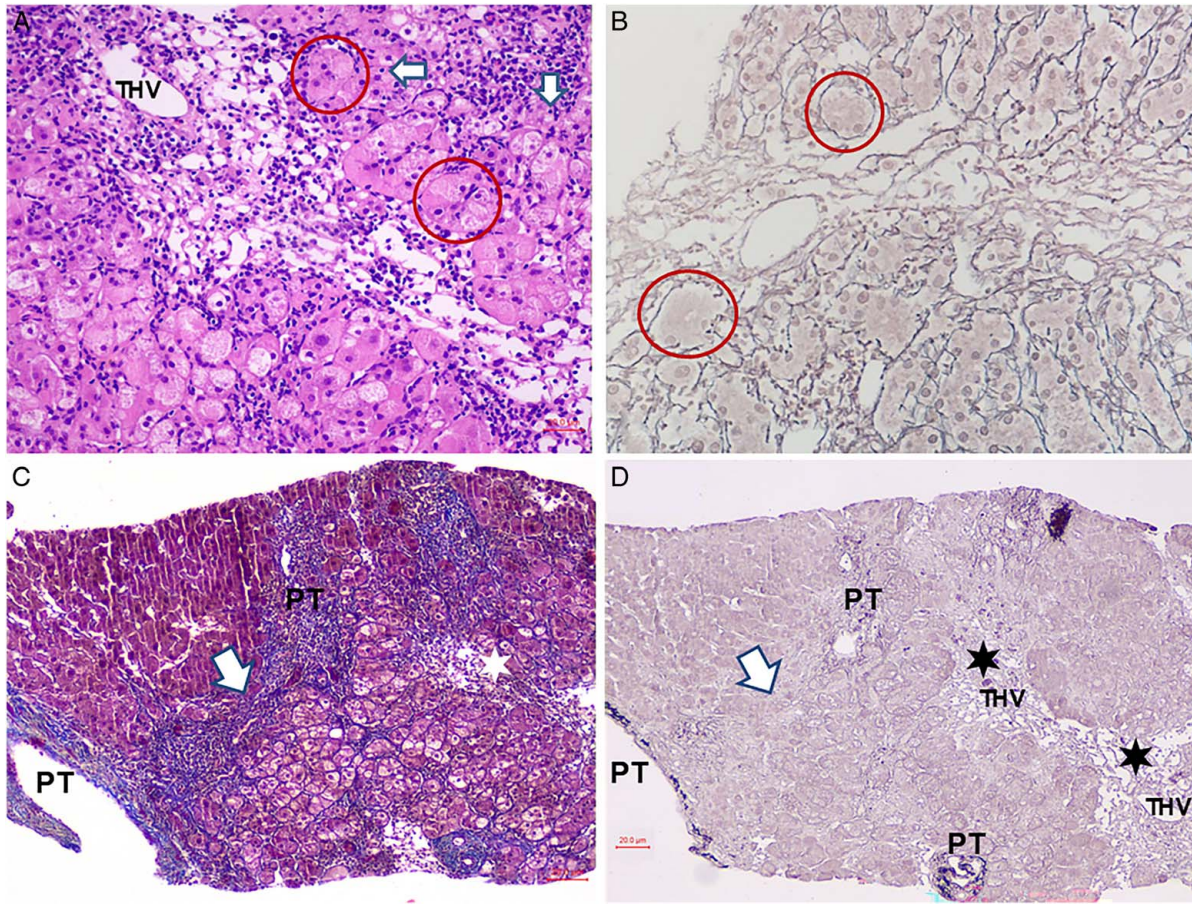

FIGURE 2. Autoimmune hepatitis. A, Prominent hepatocyte rosettes (red circles) and emperipolesis (arrows) close to an area of bridging necrosis. B, Prominent hepatocyte rosette formation (red circle) highlighted by reticulin stain, x200. C, Masson trichrome stain shows features suggestive of portal-portal fibrous bridging (arrow) and centrilobular necrosis (asterisk). D, Orcein stain of the same area as in (C) shows absence of elastic fibers in the collapsed inflamed parenchyma (arrow), indicating that there is no genuine bridging fibrosis, asterisks centrilobular necrosis. PT indicates portal tract; THV, terminal hepatic venule. Please see this image in color online.

variant and, when present, the diagnosis of AIH cannot be excluded.[13,32] Lymphocytic cholangitis is considered the result of collateral injury associated with marked portal inflammation.[33] Patients with AIH with biliary features have similar serology and response to immunosuppression compared with those without.[34]

Ductular reaction, which refers to the periportal proliferation of hepatic progenitor cells forming ductular structures, is also very common in newly diagnosed AIH (Fig. 3C). In one study, it was reported in 71% of conventionally stained and 94% of immunostained liver biopsies.[31] Its presence in AIH correlates with inflammatory features, as well as bile duct injury and fibrosis. Although bile duct injury may resolve following immunosuppression, ductular reaction can persist, indicating that it represents a regenerative response[31] and may contribute to the development of portal/periportal fibrosis.[12]

Cholestasis

Cholestasis is not frequent in AIH but mild hepatocellular and/or canalicular cholestasis may be present in cases with acute presentation and marked lobular inflammatory activity.[7,12] In early stage AIH, features of chronic cholestasis, with periportal copper or copper-associated granule deposition and keratin 7 (K7)-positive "intermediate" hepatocytes, may raise the suspicion of a variant with PBC or PSC. However, in AIH with advanced fibrosis or cirrhosis, this is considered a secondary nonspecific phenomenon (Fig. 3C).[7,12,33]

Granulomas

Approximately 9% to 10% of AIH cases show poorly formed granulomas,[35] while well-formed epithelioid granulomas, classically associated with PBC, are very rarely seen in AIH and are slightly more common in AIH/PBC variant forms.[7] In AIH, microgranulomas, composed of up to 5 macrophages, are associated with lobular inflammation and are more frequent when lobular activity is prominent.

Multinucleated Giant Cells

The formation of multinucleated giant cells in the liver is considered a nonspecific idiosyncratic reaction to various noxious stimuli, although several cases are idiopathic. Giant cell hepatitis is more frequent in neonates, whereas post-infantile giant cell hepatitis (PIGCH) is very rare in adults and has a variable clinical course, with minimal symptoms without clinical relevance to liver failure. AIH is the most frequent etiology of PIGCH (32% to 36%)[36,37] (Fig. 3D) and

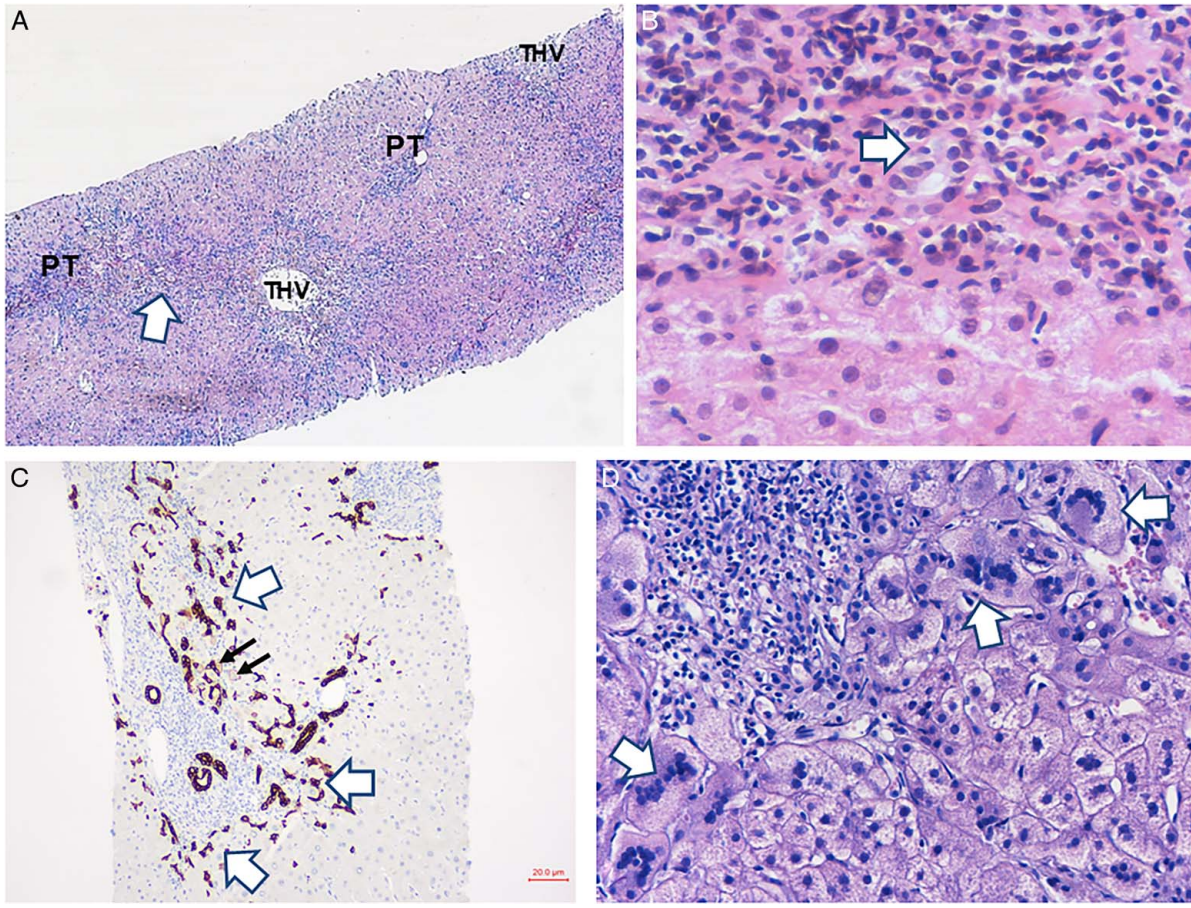

FIGURE 3. Autoimmune hepatitis. A, Portal-central bridging necrosis (white arrow) in severe autoimmune hepatitis, H&E x40. B, Bile duct injury with lymphocytic cholangitis (white arrow) in a severely inflamed portal tract, H&E x400. C, Ductular reaction (white arrows) at the portal-parenchyma interface highlighted by keratin 7 (K7) immunostain. Rare periportal "intermediate" K7-positive hepatocytes indicative of mild chronic cholestasis are also seen (black arrows), K7 immunostain. D, Multinucleated giant hepatocytes (arrows) in the center of the lobule of a biopsy with postinfantile giant cell hepatitis, H&E ×200. PT indicates portal tract; THV, terminal hepatic venule. Please see this image in color online.

has better survival compared with PICGH of other etiology (viral, drug-induced, and, rarely, hematological malignancy).[37] PICGH can recur following liver transplantation,[36] but de novo PIGCH has also been reported.[37]

PRESENTATIONS OF AUTOIMMUNE HEPATITIS

Acute-Onset and Fulminant AIH

AIH may present acutely in ~25% of the cases.[1] However, no strict definition has been established for acute-onset AIH, and inclusion criteria vary in clinical studies. Some patients experience a flare of undiagnosed chronic AIH, while others show features of acute hepatitis without evidence of chronicity, even on histology. In some cases, acute-onset AIH may result from superimposed acute viral or drug/toxin-induced liver injury in the background of chronic AIH.[12] Clinically, if acute AIH is accompanied by jaundice and an international normalized ratio (INR) 1.5 to 2, in the absence of hepatic encephalopathy, the term acute severe AIH is applied. Acute liver failure is ascribed in cases with INR >2 and hepatic encephalopathy.[4] "Fulminant" has been used for severe, potentially lethal, AIH cases with sudden onset and quick escalation within 10 to 30 days.[38]

In the acute-onset setting, differential diagnosis of AIH from DILI or viral hepatitis can be challenging, since helpful autoimmunity markers, such as IgG elevation and positive autoantibody serology, may be missing, while false positivity may occur in non-AIH cases with extensive liver necrosis.[1] ANA or both ANA and SMA may be absent in 27% to 39% and 11% of the acute-onset AIH cases, respectively, while IgG is normal in 14% to 50%.[9,39,40]

Histologically, acute-onset AIH shows more severe lobular inflammation with centrilobular and bridging necrosis (Figs. 2C, D). Portal inflammatory infiltrates and interface hepatitis may or may not be present. Rarely, lobular hepatitis with centrilobular prominence can be the only finding (Fig. 1B). Assessment of fibrosis severity in acute-onset AIH can be challenging due to the possible presence of bridging necrosis and parenchymal collapse with newly formed collagen that may be mistaken as fibrotic septa using common collagen stains, leading to over-staging. This type of immature fibrosis may easily regress with treatment; therefore, in these cases, the absence of elastic fibers by orcein or any other elastic fiber stain will indicate

immature fibrous tissue and help in accurately staging the disease (Figs. 2C, D).[41]

Evidence of fibrosis/cirrhosis indicates unnoticed chronic disease revealed during acute exacerbation. In fulminant AIH, submassive or massive panlobular necrosis with distinctive centrilobular accentuation and lobular disarray is noted.[12,33,42] The revised IAIHG simplified diagnostic criteria are not helpful in the acute setting since they recognize AIH as a predominately portal hepatitis.[30] The new IAIHPG consensus criteria, however, accept a mainly lobular hepatitic pattern as possible AIH (see Section Consensus Diagnostic Criteria for AIH Proposed by International AIH Pathology Group).[16]

Early liver biopsy is proposed in acute-onset AIH, as it may support an autoimmune etiology based on the prominence of plasma cells in the inflammatory infiltrate and evidence of fibrosis. In acute liver failure, needle liver biopsy is not performed routinely because of bleeding risk, although transjugular or minilaparoscopy-guided liver biopsy have been suggested by some in this setting.[25]

AIH Presenting With Cirrhosis

Cirrhosis is present in approximately one-third of patients at the time of AIH diagnosis, probably due to long-standing untreated subclinical disease.[43] Morphologically, AIH-related cirrhosis is macronodular or mixed macronodular and micronodular and usually has no specific features ("burnt-out") to distinguish it from cirrhosis of other etiology.[7,12] Therefore, diagnosis relies on clinical and serological findings but clinical management depends on the presence of inflammatory activity on biopsy requiring prompt immunosuppression.[1] The presence of cirrhosis has prognostic and predictive implications, with worse outcome due to poorer treatment response.[7] Recently, the not-infrequent concurrence of metabolic dysfunction-associated steatotic liver disease (MASLD) with AIH has been identified as an independent risk factor for severe liver fibrosis.[44]

The progression of liver fibrosis is a major prognostic factor and is best assessed histologically. However, since repeat liver biopsies are not recommended to monitor the disease course, serial liver stiffness measurements (LSM) appear to be a safe and reliable alternative after 6 months from the initiation of immunosuppressive therapy and can predict clinical outcomes.[1] The accuracy of earlier LSM may be hampered by inflammatory activity showing falsely higher values.[45] The conventional surrogate serum markers of disease activity, IgG and transaminase levels, are of limited usefulness in monitoring disease activity and/or fibrosis progression.[46,47]

AIH and HCC

AIH carries a risk of HCC development, which is strongly associated with cirrhosis. Nearly all AIH patients have progressed to cirrhosis at the time of HCC diagnosis. However, the incidence (1.44 cases/1000 patient-years) and prevalence (1.7%) of HCC in AIH is lower than that in other chronic liver diseases (average 2 to 4 cases/1000 patient-years).[48] Neither histologic characteristics nor response to treatment appear to confer a higher risk. In contrast, advanced age, obesity, and alcohol intake are independent risk factors for HCC development in patients with AIH. Interestingly, the AIH/PSC variant has been associated with increased HCC risk, further highlighting the prognostic value of histologic examination in AIH.[48,49]

Post-treatment AIH

Post-treatment AIH is a nonspecific chronic hepatitis with fibrosis. Absence of inflammation or mild portal, interface, and/or lobular inflammatory activity may be seen, depending on treatment response.[50] The ultimate treatment goal in AIH is complete histologic remission of inflammation, as any degree of inflammation or plasma cell presence in treated AIH patients is strongly associated with relapse after treatment withdrawal.[33] However, in a recent systematic review of the IAIHG, histologic remission has been defined as mHAI $<4/18$ in an adequate liver tissue sample.[11] Histologic response is usually achieved 3 to 8 months after the improvement of clinical parameters. In almost half of the cases, especially in patients with cirrhosis, post-treatment biopsies show interface activity despite normalization of clinical and laboratory parameters.[1,4]

Relapse is common (in up to 50% of cases), especially in patients with other concurrent autoimmune diseases, and may appear early or even decades after treatment withdrawal. The histologic findings in relapsed AIH are identical to those in patients with pretreated disease.[7,12,13]

Serological Variants of AIH

Autoantibody-Negative AIH

"Autoantibody-negative" AIH patients lack the classic autoantibodies (ANA, SMA, anti-LKM1, and AMA) at initial presentation. The reported frequency of "autoantibody-negative AIH" is 10% to 20% and is overrepresented in severe acute AIH.[7,33] Retest for typical and nontypical autoantibodies with adherence to guidelines, ideally in a reference center, is important as their levels may fluctuate over time. If this procedure is followed, $<5\%$ of AIH cases will remain "autoantibody-negative."[4]

The pathogenesis of autoantibody-negative AIH is obscure, but dysfunction of B lymphocytes has been suggested, especially in patients with concomitant low IgG titers.[51] Liver biopsy is needed to support the diagnosis of AIH and exclude other etiology, while histology and treatment response do not differ from "autoantibody-positive" AIH.[12]

Anti-SLA/LP-Positive AIH

SLA/LP antibodies are highly specific for AIH, but lack sensitivity, as they are found in 15% to 30% of cases. Their presence has been associated with more frequent recurrence after treatment cessation and the need for lifetime immunosuppressive therapy.[4,51]

Anti-AMA Positive AIH

Positive AMA serology is typical for PBC patients. However, 5% of AIH patients show anti-AMA seropositivity without biochemical or histologic findings of cholangiopathy throughout the disease course. It has been postulated that immunosuppressive medication for AIH may have restrained the evolution of an incipient bile duct injury.[7] This AIH subgroup shows similar treatment response and survival to classic AIH patients although histologic features of cholangiopathy at baseline denote a higher frequency of cirrhosis development.[52]

AIH With Normal IgG

Normal serum IgG levels may be found in 10% to 15% of AIH patients. However, this percentage increases in pediatric (up to 50%) and elderly patients, as well as in those

with acute insult (25% to 39%). This subgroup benefits from a longer remission postimmunosuppression.[4,33]

DIAGNOSTIC SCORING SYSTEMS AND HISTOLOGIC GRADING AND STAGING FOR AIH

Historically, histology has always played a significant diagnostic role in AIH, which was reflected in the 1993 criteria of the International AIH Group (IAIHG)[53] and in their 1999 revision,[54] where moderate or severe interface hepatitis was central for AIH diagnosis in combination with clinical and serological parameters. The 2008 simplified criteria of IAIHG[14] included four necessary elements for the "definite" diagnosis of AIH (summative score ≥ 7): increased serum IgG levels, presence of serum autoantibodies (ANA or ASMA or LKM with cutoff $\geq 1{:}40$ or positive SLA), absence of markers for viral hepatitis, and liver biopsy histology "typical" or "compatible" with AIH. A diagnosis of "probable" AIH (score 6) could be made without liver histology by scoring 2 points for each of the first 3 elements. Assignment of histologically "typical AIH" and 2 points in the summative 0 to 8 diagnostic score, required the concurrent presence of lymphocytic or lymphoplasmacytic portal infiltrates with interface hepatitis, hepatocyte rosettes, and emperipolesis, while "compatible AIH" was diagnosed when not all "typical" features were identified giving only 1 point to the simplified score. Histologic evidence of a different diagnosis ("atypical") scored 0 points.

The IAIHG criteria for diagnosing AIH have shown high specificity and sensitivity in many studies.[8,55] However, both the 1999 and 2008 scoring systems have limitations that may lead to underscoring of true AIH cases that present as acute severe hepatitis with mainly centrilobular injury or with concurrent chronic liver diseases such as viral hepatitis or steatotic liver disease (SLD) related to either alcohol use or metabolic dysfunction.[16] In addition, the histologic criteria for diagnosing AIH were based on older, retrospective studies; they had not been prospectively validated, and they lacked international consensus. Hepatocellular rosettes and emperipolesis, which are features necessary for "typical" AIH in the 2008 simplified diagnostic criteria, have limited specificity.

Several clinicopathologic studies have reviewed the simplified IAIHG histologic scoring and proposed modified histologic criteria aiming at preventing AIH underscoring. Balitzer et al[22] showed that scoring based on the severity of inflammatory activity, extent of plasma cells, and results of histochemical stains for copper or K7 immunostaining can increase the histologic score and lead to a "probable" or "definite" AIH diagnosis in 17% of cases that would have otherwise been classified as non-AIH using the simplified score. Gurung et al[15] proposed a modified histologic scoring system based on features significantly associated with AIH, such as prominent plasma cells in the inflammatory infiltrate and Kupffer cell hyaline globules in the absence of another disease process and showed that its application could increase the number of AIH cases diagnosed. Franceschini et al,[21] by adding of 1 point for histology in the simplified IAIHG criteria for ≥ 5 lymphocytic apoptotic bodies per portal tract (mean number of 3 portal hot spots), increased the percentage of first biopsy patients in their series categorized as "definite" AIH from 42% to 68%.

Consensus Diagnostic Criteria for AIH Proposed by International AIH Pathology Group

The IAIHPG, composed of 17 pathologists from Europe, the United States, and Australia with experience and international reputation in AIH histopathology, and 2 hepatologists representing the European Reference Network on Rare Hepatological diseases (ERN RARE-Liver), convened to address the above mentioned limitations and to develop consensus histologic criteria for the diagnosis of AIH and the assessment of disease severity applicable to both acute and chronic presentations in the native liver.[16] The IAIHPG recognized 2 main histologic patterns of liver injury in AIH based on the portal or lobular topography of the hepatitic lesions (Table 1), according to which the diagnosis of likely, possible, or unlikely AIH can be made.

The portal-based pattern of inflammation refers to a mainly portal chronic lymphocytic or lymphoplasmacytic inflammatory infiltrate with or without interface hepatitis. A "likely AIH" diagnosis can be made with the additional presence of more than mild interface hepatitis and/or more than mild lobular hepatitis in the absence of histologic features suggestive of another liver disease, that is, steatotic liver disease or primary cholangiopathy (PBC or PSC) (Table 1). A "possible AIH" diagnosis can be made if there are features suggestive of another liver disease or if there is no more than mild lobular or interface hepatitis (Table 1). However, if there are prominent bile duct and/or cholestatic lesions, primary cholangiopathy may be suspected as the main diagnosis.[16]

The lobular pattern of inflammation refers to the presence of a mainly lobular hepatitis with or without centrilobular injury. A "likely AIH diagnosis, is made when there is more than mild lobular hepatitis and at least one of the following "likely" histologic features: lymphoplasmacytic infiltrates, interface hepatitis, or portal-based fibrosis, in the absence of histologic features suggestive of another liver disease (Table 1). A "possible AIH" diagnosis can be made if there are features of another liver disease or if there is lobular hepatitis of any severity with or without centrilobular necroinflammation but without the likely histologic features in the absence of features of another liver disease (Table 1).[16]

Using the consensus IAIHPG criteria, atypical cases with predominantly centrilobular injury without prominent portal/periportal inflammation or cases with centrilobular necrosis only, which are thought to represent acute-onset AIH,[56] can be diagnosed as possible AIH in the absence of another liver disease and treated with immunosuppression.[1,4,16]

Results of recent retrospective studies show that the application of the IAIHPG criteria can accurately identify AIH with acute-onset,[57] increase the sensitivity and specificity of diagnosing adult AIH[57–59] and more accurately differentiate between genuine AIH and drug-induced-autoimmune-like hepatitis.[60] Therefore, the substitution of the histologic component in the 2008 simplified scoring system[14] with the 2022 IAHPG criteria has been suggested[1] aiming to optimize clinical diagnosis.[61]

Histologic Grading and Staging for AIH

The IAIHPG proposes the use of Ishak's mHAI for the semiquantitative assessment of necroinflammatory activity severity in AIH.[10] The categories A (periportal or periseptal interface hepatitis), B (confluent necrosis), and C (focal/spotty lytic necrosis, apoptosis, and focal inflammation) were considered relevant for predicting fibrosis

TABLE 1. Consensus Histologic Criteria of Likely, Possible, or Unlikely Autoimmune Hepatitis (AIH) by the International AIH Pathology Group

	Portal hepatitis	Lobular hepatitis
Likely AIH	In the absence of histologic features suggestive of another liver disease, presence of portal lymphoplasmacytic infiltrate with one or both of the following characteristics: a. More than mild interface hepatitis b. More than mild lobular inflammation	In the absence of histologic features suggestive of another liver disease, presence of more than mild lobular hepatitis (with or without centrilobular inflammatory activity) with at least one of the following characteristics: a. Lymphoplasmacytic infiltrates b. Interface hepatitis c. Portal-based fibrosis
Possible AIH	Portal lymphoplasmacytic infiltrate Without either of the likely features "a" or "b" above in the absence of histologic features suggestive of another liver disease OR With one or both of likely features above in the presence of histologic features suggestive of another liver disease	Any lobular hepatitis (with or without centrilobular inflammation) Without any of the likely features "a to c" above in the absence of histologic features suggestive of another liver disease OR With any of the likely features above in the presence of histologic features suggestive of another liver disease
Unlikely AIH	Portal hepatitis Without either of the likely features above in the presence of histologic features suggestive of another liver disease	Any lobular hepatitis Without any of the likely features above in the presence of histologic features suggestive of another liver disease

Adapted from Dalekos et al[4] and Lohse et al.[16] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

development, while category D (portal inflammation) was not recommended for grading disease activity as it may not have predictive value in AIH. Mild inflammatory activity was defined as category A ≤ 1, category B $= 0$ and category C ≤ 2. More than mild inflammation was defined as category A ≥ 2, category B ≥ 1, and category C ≥ 3. The mHAI scores are helpful during therapy and follow-up of AIH.[1,16]

Any of the histologic systems developed to assess the extent of fibrosis in chronic viral hepatitis can be used for staging fibrosis in AIH. Simple 5-tiered staging systems, such as Batts-Ludwig,[62] Scheuer,[63] and Metavir[64] are easier to apply routinely and have lower interobserver variability. The more granular 7-tiered Ishak staging system is usually applied for research purposes.[10]

DIFFERENTIAL DIAGNOSIS

From a clinical point of view, nearly every cause of liver injury is included in the differential diagnosis of AIH. Histology proves very helpful in evaluating hepatitis patterns, ruling out other etiologies, and assessing coexisting diseases. A liver biopsy with features of acute hepatitis will prompt the differential diagnosis between acute viral hepatitis, DILI, and acute AIH, whereas a chronic hepatitis pattern will raise the question of autoimmune liver disease, chronic viral hepatitis, or metabolic disorders.

Drug-Induced Liver Injury

Drugs are responsible for almost all patterns of hepatic injury. The relationship between drugs and AIH is complex, as they can imitate an AIH syndrome, but also unmask a quiescent or cause a new genuine AIH. Accurate diagnosis is important for prognosis, as true AIH will most likely relapse after immunosuppression withdrawal, in contrast to DILI.

Differentiating DILI from AIH may not be possible even if all clinical, serological, and histologic data are available. Etiology can be obscured due to a prolonged latent course from drug administration to clinical symptoms that may occur even after cessation of medication.[30] Autoantibodies and high serum globulin titers may be encountered in DILI, whereas some AIH cases are seronegative (see Section Autoantibody-Negative AIH).

More than a decade ago, a group of expert hepatopathologists proposed a model to differentiate DILI from AIH, based on histologic findings. Severe portal plasma cell infiltration, lobular eosinophil-rich inflammation, hepatocellular rosettes, fibrosis stage ≥ 1, and absence of hepatocellular cholestasis were more suggestive of AIH.[65]

The acute presentation of AIH is now well-recognized; however, in the past, it was frequently misinterpreted as DILI on histology due to the presence of lobular hepatitis with centrilobular necrosis. In this setting, only the identification of mature fibrosis on histochemical stains can support the diagnosis of AIH.[16,30]

Drug-induced autoimmune-like hepatitis (DI-ALH) is a DILI phenotype with serological and/or histologic features of AIH lacking specific biomarkers and diagnostic criteria.[29] To date, the only discriminatory factor between DI-ALH and AIH is the prolonged recurrence-free course of the former following cessation of immunosuppression, while AIH patients relapse soon after. DI-ALH cases are immune mediated and often positive for ANA or ASMA, accompanied by high serum immunoglobulin titers. Differential diagnosis based on the type of immunoglobulins (IgM in DI-ALH vs. IgG and IgM and/or polyreactive IgG in AIH) and HLA haplotypes has been proposed, but has not been validated.[29,66]

Liver biopsy is recommended to exclude other entities. Both lobular and portal hepatitis can occur with a wide range of disease activity. Histologic changes imitate AIH and include dense portal inflammatory infiltration, periportal necroinflammation, centrilobular to massive confluent necrosis and plasma cells clusters in various combinations. When present, advanced fibrosis suggests AIH rather than DI-ALH, but no other histopathologic finding is discriminative.[67]

Drugs implicated in DI-ALH include minocycline, nitrofurantoin, hydralazine, methyldopa, diclofenac, and infliximab. However, other pharmaceuticals that interact

with the immune system, such as interferon, methylprednisolone, adalimumab, imatinib, and other kinase inhibitors, as well as dietary supplements, including Tinospora cordifolia (Guduchi/Giloy), black cohosh, Hypericum perforatum (St John's wort) and Khat, can cause DI-ALH. Statins are incriminated for triggering genuine AIH.[68] Immune checkpoint inhibitors (ICIs) that are increasingly utilized in oncological treatment protocols can cause immune-related adverse events (irAEs). Diffuse lobular hepatitis without zone predilection is commonly observed, while central necroinflammation is less frequent. Compared with AIH, hepatic irAEs are characterized by milder confluent necrosis, less frequent eosinophil and plasma cell infiltration, and a significantly elevated CD8+/CD4+ T-cell ratio. Depending on the ICI, bile duct injury or a granulomatous reaction may also be evident.[69,70]

Some DI-ALH cases resolve following drug withdrawal and the remaining are treated with steroids with response rates similar to AIH. Withdrawal of immunosuppressants is feasible without disease relapses, although prolonged surveillance is recommended to monitor for a delayed flare.[71,72] The latter may represent a chronic DI-ALH phenotype or drug-induced genuine AIH.

COVID-19 and Other Vaccine-Related AIH

Many vaccines, including those against measles, mumps, rubella, typhoid, polio, diphtheria/tetanus, influenza, hepatitis A virus (HAV), and COVID-19, have been associated with AIH-like syndrome. Molecular mimicry is the most popular hypothesis regarding the underlying pathophysiology.[73]

Regarding COVID-19, disease may appear on average 15 days postvaccination, more frequently in females (63%),[4] with ANA detected in 56% to 76% and high IgG titers in 35% to 72% of the cases.[73–76] Liver biopsy showed lobular hepatitis in 76% and portal hepatitis in 17% of the cases. Most cases (77%) scored as "probable" or "definite" AIH based on the 2008 simplified IAIHG criteria[74] and depending on the histologic criteria applied, 92% of cases were likely/possible AIH and 82% to 100% typical/compatible with AIH.[73,75,76] Advanced fibrosis was seen in only 3% to 12% indicating acute autoimmune-like hepatitis related to vaccination. Response to treatment was achieved in nearly all patients, but the long-term outcome is largely unknown.[74,76,77]

Viral Hepatitis

Infection with hepatotropic viruses (HAV, hepatitis B-HBV, hepatitis C-HCV, hepatitis D-HDV, and hepatitis E-HEV), Epstein-Barr virus (EBV), and SARS-CoV-2 should be excluded before the diagnosis of AIH. Histology cannot accurately differentiate between viral and AIH patterns of liver injury. For instance, a plasma cell-rich infiltrate is common in liver biopsies from HAV-infected patients and is easily misinterpreted as AIH. Moreover, the presence of autoantibodies cannot rule out viral hepatitis. ANA and SMA can be detected in 1/4 of HBV-infected patients and are even more frequent in HCV-infected,[12] while anti-LKM1 has been reported in 10% of HCV- and anti-LKM3 in 13% of HDV-infected patients.[78] ANA and SMA have been observed in 33% and 21% of HEV-infected patients, respectively.[79] Histologically, prominent portal lymphoid aggregates should raise the suspicion of hepatitis C, while hepatocytes with ground-glass cytoplasm indicate HBV infection.

Approximately 33% of SARS-CoV-2 infected patients presented with acute liver injury within 2 months of infection.[80] Irrespective of the exact mechanism, direct viral effect or immune system activation, a hepatitis pattern with portal or lobular necroinflammation was more commonly seen.[81] Like HBV, HCV, and EBV, SARS-CoV-2 may trigger hepatitis with serology, histology, and steroid response similar to AIH. However, unlike classic AIH, the disease does not recur after steroid withdrawal[82] raising the question of whether it should be considered as genuine AIH.

Metabolic Dysfunction-Associated Steatotic Liver Disease

Patients with MASLD may have laboratory findings that clinically raise the suspicion of AIH. ANA-, SMA-, and/or AMA-positivity can be encountered in 16.9% to 48% of MASLD patients, usually in low titers.[7] In a retrospective study of 923 biopsy-proven MASLD patients, ANA were found in 16.9% without histologic evidence of AIH even after a long follow-up. ANA-positive MASLD cases had a higher prevalence of metabolic dysfunction-associated steatohepatitis (MASH), hepatocyte ballooning, and mild to moderate fibrosis than MASLD patients without ANA.[83]

High IgG is not a common feature of simple MASLD, while increased IgA is observed in 50%.[84] IgG elevation has been reported in 10% to 23% of biopsy-proven MASH patients without evidence of concurrent AIH and was associated with worse prognosis.[85,86] Hence, the simplified IAIHG criteria may not be reliable for the discrimination between MASLD and AIH.[7] In this scenario, biopsy is indispensable for revealing the underlying liver disease with a steatohepatitic pattern prompting the diagnosis of MASLD in the appropriate setting and features of chronic hepatitis without steatosis favoring AIH. In advanced MASH, attention is needed to avoid misinterpreting portal inflammatory infiltration with only mild interface hepatitis as a feature of AIH. However, if portal/periportal inflammation is more prominent than lobular changes, concurrent chronic hepatitis of other etiologies may be suspected. The new consensus IAIHPG histologic criteria are particularly helpful in this regard (see Section Concurrence With Steatohepatitis).[16]

CONCURRENCE OF AIH WITH OTHER CHRONIC LIVER DISEASE

Concurrence With Viral Hepatitis

Exclusion of viral infection is a prerequisite for AIH diagnosis.[14] However, autoimmune and viral hepatitis can coexist, particularly in regions with a high burden of HBV, HCV, and HVD infection. Hepatotropic viruses are also suspected to interfere with immune system tolerance, leading to autoimmune disease initiation in predisposed individuals.[82] Immunosuppressive therapy for AIH may reactivate quiescent viral hepatitis.[87]

Diagnosing concurrent viral hepatitis and AIH is challenging, as autoantibodies and high titers of immunoglobulins can also be present in the former (see Section Viral Hepatitis). Histology alone cannot solve this dilemma, and both serological and clinical data are required.[7] In AIH with proven HBV or HCV infection, interferon-free antiviral therapy should be applied first. Persistent hepatitis with autoimmune features after virus eradication should alert clinicians to the possibility of underlying AIH.[1,88]

Concurrence With Steatohepatitis

As the prevalence of MASLD increases, AIH patients may also be affected. It is important to recognize the coexistence of MASLD and AIH, because this patient group often presents with advanced disease and has a worse prognosis. In a recent study by the IAIHG, MASLD was present in 23% of patients with AIH, reaching the frequency of the general population.[89]

Histologic diagnosis of AIH with concurrent MASH or alcohol-related steatohepatitis is difficult. Awareness of the possible dual nature of hepatic injury, as well as meticulous assessment of pathologic features with the support of histochemical and immunohistochemical stains, help to reach the correct diagnosis. The presence of typical features of steatohepatitis, such as a centrilobular pattern of injury, ballooned hepatocytes with rarefied/reticulated cytoplasm containing Mallory-Denk bodies, pericellular/sinusoidal fibrosis, in addition to a hepatic pattern with any of the "likely features" of the IAIHPG consensus histologic criteria, will support the diagnosis of possible AIH with concurrent steatohepatitis.[16]

Concurrence With Hereditary Metabolic Diseases

Metabolic diseases, including Wilson disease (WD), hereditary hemochromatosis (HH), and alpha1-antitrypsin (α1-AT) deficiency enter the differential diagnosis of AIH, as liver histology may be similar. WD should always be excluded in younger patients with either acute or chronic hepatitis. Liver biopsy with special histochemical stains for copper (rhodanin, rubeanic acid), hemosiderin granules (Perls or Victoria blue) and α1-AT globules (DPAS) in conjunction with disease-specific laboratory tests can lead to the correct diagnosis. However, dual pathology should always be excluded.

Concurrence of AIH with WD is a well-established situation, although WD patients are not susceptible to the development of AIH.[90] In a recent review, 14 patients with mean age 19 years were reported to suffer from both WD and AIH. In 3 cases, the 2 diseases were recognized simultaneously, while in the rest, diagnosis of one preceded the other.[91]

Heterozygosity for the C282Y HH mutation has been reported in 17% of AIH patients. The cellular and subcellular topography of hemosiderin granules helps to clarify the etiology of concurrent iron overload in AIH.[7] A very rare case with simultaneous presence of WD, HH, and AIH has been reported.[92]

AIH/PBC AND AIH/PSC VARIANTS

Patients with autoimmune liver disease can present with overlapping clinical and histologic features. In these patients, the recent EASL clinical practice guidelines recommend initial investigation for PBC-specific autoantibodies, while magnetic resonance cholangiography (MRCP) is advised either at diagnosis or during follow-up if PBC-specific autoantibodies are negative.[1] The features of the 2 diseases may present concurrently or more commonly sequentially, with a primary manifestation of AIH and subsequent development of PBC, although acute AIH-like features may occur in patients with long-standing PBC.[1] Features of AIH/PBC or AIH/PSC may be seen in 7% to 13% and 8% to 17% of adult AIH patients, respectively, while 49% of children with autoimmune disease may have features of AIH-PSC.[93] AIH/PBC and PBC/AIH variants are more common in middle-aged women.[1]

Liver biopsy is essential to confirm the clinical suspicion of these so-called "variant syndromes" (AIH/PBC or AIH/PSC variants, also known as "overlap syndromes"), especially in patients with biochemical cholestasis, to evaluate bile duct injury or loss and to assess the severity of inflammation highlighting the predominant disease and guiding treatment.[7] The diagnosis is clinicopathologic and is based on the rather old "Paris criteria" that rely heavily on serological and biochemical features and less on liver histology, requiring moderate or severe interface hepatitis for AIH and florid bile duct lesions for PBC.[94] However, it has been recognized over the years that bile duct loss and features of chronic cholestasis with copper-associated protein or copper granules or K7-positivity in periportal hepatocytes in early stage disease may also raise the suspicion of an AIH/PBC variant, while severe interface and/or severe lobular hepatitis (according to Ishak mHAI) may indicate a PBC/AIH variant. The differential diagnosis of the latter from PBC with prominent inflammatory interface activity is difficult. A feature that may point towards a PBC/AIH variant is more severe lobular inflammation compared with interface activity, especially if there is centrilobular or bridging necrosis. In advanced stages, chronic cholestasis could be a secondary phenomenon and is not a helpful feature for supporting the suspicion of an AIH/PBC variant.[7,12]

The AIH/PSC variant is more common in children and frequently associated with inflammatory bowel disease. In addition to the biochemical/serological findings of AIH, MRCP imaging may show evidence of bile duct lesions compatible with large duct PSC.[1,4] Liver biopsy may show prominent lobular necroinflammatory activity in combination with typical features of PSC, such as concentric periductal "onion-skin"-like fibrosis, obliterative fibrous cholangitis and/or bile duct loss.[7,12,94] An inherent difficulty in the histologic diagnosis of AIH variant syndromes is that the typical features of primary cholangiopathy are usually randomly distributed and therefore may be absent from a biopsy due to sampling variability.[7]

The management of variant syndromes should be directed at their predominant component. In AIH/PBC, a combination of immunosuppressive therapy with ursodeoxycholic acid (UDCA) is used in patients with moderate or severe hepatitis, while UDCA monotherapy is reserved for those with mild hepatitis, with the possible addition of immunosuppressive therapy if a complete biochemical response is not achieved. Immunosuppressive treatment with or without UDCA is suggested for patients with AIH/PSC.[1,4]

CONCLUSIONS

Histologic evaluation of an adequate liver tissue sample is essential for a firm diagnosis of AIH and provides significant information for prognosis and treatment decisions in AIH, always with the appropriate clinicopathologic correlation that is central for patient management. The new consensus IAIHPG criteria aid the diagnosis and differential diagnosis of AIH in all its different presentations, even in the presence of other concurrent disease, and can identify "likely" or "possible" AIH with high specificity and sensitivity. Predominant or exclusive centrilobular injury that may represent acute-onset disease can be diagnosed as

"possible" AIH in the absence of features of another liver disease, and affected patients can receive life-saving immunosuppression. Therefore, substituting the histologic component of the 2008 simplified scoring system with the consensus IAIHPG criteria may optimize clinical diagnosis and management.

REFERENCES

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of autoimmune hepatitis. *J Hepatol* 2025; in press.
2. Mackay IR. Historical reflections on autoimmune hepatitis. *World J Gastroenterol*. 2008;14:3292–3300.
3. Hahn JW, Yang HR, Moon JS, et al. Global incidence and prevalence of autoimmune hepatitis, 1970–2022: a systematic review and meta-analysis. *EClinicalMedicine*. 2023;65:102280.
4. Dalekos GN, Papatheodoridis GV, Koskinas J, et al.; Hellenic Association for the Study of the Liver. Revised clinical practice guidelines for autoimmune hepatitis. *Ann Gastroenterol*. 2024; 37:623–654.
5. Grønbaek L, Otete H, Ban L, et al. Incidence, prevalence and mortality of autoimmune hepatitis in England 1997-2015. A population-based cohort study. *Liver Int*. 2020;40:1634–1644.
6. Weiler-Normann C, Lohse AW. Autoimmune hepatitis: from immunopathogenesis to diagnostic and therapeutic innovation. *Curr Opin Gastroenterol*. 2021;37:86–90.
7. Tiniakos DG, Brain JG, Bury YA. Role of Histopathology in Autoimmune Hepatitis. *Dig Dis*. 2015;33(suppl 2):53–64.
8. Manns MP, Lohse AW, Vergani D. Autoimmune hepatitis—update 2015. *J Hepatol*. 2015;62(suppl):S100–S111.
9. Mack CL, Adams D, Assis DN, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 Practice guidance and guidelines from the American Association for the Study of Liver Diseases. *Hepatology*. 2020;72:671–722.
10. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *J Hepatol*. 1995;22:696–699.
11. Pape S, Snijders RJALM, Gevers TJG, et al. Systematic review of response criteria and endpoints in autoimmune hepatitis by the International Autoimmune Hepatitis Group. *J Hepatol*. 2022;76:841–849.
12. Zhang X, Jain D. The many faces and pathologic diagnostic challenges of autoimmune hepatitis. *Hum Pathol*. 2023;132: 114–125.
13. Gonzalez RS, Washington K, Lohse AW. Autoimmune hepatitis. Burt A, Ferrell L, Hübscher S, eds. *MacSween's Pathology of the Liver*. Elsevier; 2024:527–555.
14. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatol*. 2008;48: 169–176.
15. Gurung A, Assis DN, McCarty TR, et al. Histologic features of autoimmune hepatitis: a critical appraisal. *Hum Pathol*. 2018; 82:51–60.
16. Lohse AW, Sebode M, Bhathal PS, et al. Consensus recommendations for histological criteria of autoimmune hepatitis from the International AIH Pathology Group. *Liver Int*. 2022;42:1058–1069.
17. Cabibi D, Tarantino G, Barbaria F, et al. Intrahepatic IgG/IgM plasma cells ratio helps in classifying autoimmune liver diseases. *Dig Liver Dis*. 2010;42:585–592.
18. Lee H, Stapp RT, Ormsby AH, et al. The usefulness of IgG and IgM immunostaining of periportal inflammatory cells (plasma cells and lymphocytes) for the distinction of autoimmune hepatitis and primary biliary cirrhosis and their staining pattern in autoimmune hepatitis-primary biliary cirrhosis overlap syndrome. *Am J Clin Pathol*. 2010;133:430–437.
19. Lee BT, Wang Y, Yang A, et al. IgG:IgM Ratios of liver plasma cells reveal similar phenotypes of primary biliary cholangitis with and without features of autoimmune hepatitis. *Clin Gastroenterol Hepatol*. 2021;19:397–399.
20. Hsu M, Ju JY, Pearson MM, et al. IgG and IgM immunohistochemistry in primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH) liver explants. *Am J Clin Pathol*. 2022; 158:770–773.
21. Franceschini T, Vasuri F, Muratori P, et al. A practical histological approach to the diagnosis of autoimmune hepatitis: experience of an Italian tertiary referral center. *Virchows Arch*. 2021;479:937–994.
22. Balitzer D, Shafizadeh N, Peters MG, et al. Autoimmune hepatitis: review of histologic features included in the simplified criteria proposed by the international autoimmune hepatitis group and proposal for new histologic criteria. *Mod Pathol*. 2017;30:773–783.
23. Tucker SM, Jonas MM, Perez-Atayde AR. Hyaline droplets in Kupffer cells: a novel diagnostic clue for autoimmune hepatitis. *Am J Surg Pathol*. 2015;39:772–778.
24. Hofer H, Oesterreicher C, Wrba F, et al. Centrilobular necrosis in autoimmune hepatitis: a histological feature associated with acute clinical presentation. *J Clin Pathol*. 2006;59:246–249.
25. Czaja AJ. Acute and acute severe (fulminant) autoimmune hepatitis. *Dig Dis Sci*. 2013;58:897–914.
26. Nguyen Canh H, Harada K, Ouchi H, et al. Acute presentation of autoimmune hepatitis: a multicentre study with detailed histological evaluation in a large cohort of patients. *J Clin Pathol*. 2017;70:961–969.
27. Shen Y, Lu C, Men R, et al. Clinical and pathological characteristics of autoimmune hepatitis with acute presentation. *Can J Gastroenterol Hepatol*. 2018;2018:3513206.
28. Czaja AJ. Challenges in the diagnosis and management of autoimmune hepatitis. *Can J Gastroenterol*. 2013;27: 531–539.
29. Andrade RJ, Aithal GP, de Boer YS, et al. Nomenclature, diagnosis and management of drug-induced autoimmune-like hepatitis (DI-ALH): An expert opinion meeting report. *J Hepatol*. 2023;79:853–866.
30. Clouston AD, Gouw ASH, Tiniakos D, et al. Severe acute liver disease in adults: Contemporary role of histopathology. *Histopathology*. 2024;85:549–561.
31. Verdonk RC, Lozano MF, van den Berg AP, et al. Bile ductal injury and ductular reaction are frequent phenomena with different significance in autoimmune hepatitis. *Liver Int*. 2016; 36:1362–1369.
32. de Boer YS, van Nieuwkerk CM, Witte BI, et al. Assessment of the histopathological key features in autoimmune hepatitis. *Histopathology*. 2015;66:351–362.
33. Covelli C, Sacchi D, Sarcognato S, et al. Pathology of autoimmune hepatitis. *Pathologica*. 2021;113:185–193.
34. Czaja AJ, Muratori P, Muratori L, et al. Diagnostic and therapeutic implications of bile duct injury in autoimmune hepatitis. *Liver Int*. 2004;24:322-329.
35. Gaspar R, Andrade P, Silva M, et al. Hepatic granulomas: a 17-year single tertiary centre experience. *Histopathology*. 2018; 73:240–246.
36. Matta B, Cabello R, Rabinovitz M, et al. Post-infantile giant cell hepatitis: a single center's experience over 25 years. *World J Hepatol*. 2019;11:752–760.
37. Jiao J, Chezar K, Zhang X, et al. Postinfantile giant cell hepatitis in native and allograft livers: a multi-institutional clinicopathologic study of 70 cases. *Mod Pathol*. 2023;36: 100298.
38. European Association for the Study of the Liver. EASL Clinical practical guidelines on the management of acute (fulminant) liver failure. *J Hepatol*. 2017;66:1047–1081.
39. Aljumah AA, Al-Ashgar H, Fallatah H, et al. Acute onset autoimmune hepatitis: clinical presentation and treatment outcomes. *Ann Hepatol*. 2019;18:439–444.
40. Joshita S, Yoshizawa K, Umemura T, et al. Clinical features of autoimmune hepatitis with acute presentation: a Japanese nationwide survey. *J Gastroenterol*. 2018;53:1079–1088.
41. Myoteri D, Grypari IM, Schina M, et al. An overweight female with a history of allergies and drug-induced liver injury. *J Hepatol*. 2024;81:e93–e95.

42. Stravitz RT, Lefkowitch JH, Fontana RJ, et al. Autoimmune acute liver failure: proposed clinical and histological criteria. *Hepatology*. 2011;53:517–526.
43. Liberal R, Grant CR. Cirrhosis and autoimmune liver disease: current understanding. *World J Hepatol*. 2016;8:1157–1168.
44. Liu K, Feng M, Chi W, et al. Liver fibrosis is closely linked with metabolic-associated diseases in patients with autoimmune hepatitis. *Hepatol Int*. 2024;18:1528–1539.
45. Hartl J, Denzer U, Ehlken H, et al. Transient elastography in autoimmune hepatitis: Timing determines the impact of inflammation and fibrosis. *J Hepatol*. 2016;65:769–775.
46. Putra J, Toor A, Suriawinata AA. The utility of repeat liver biopsy in autoimmune hepatitis: a series of 20 consecutive cases. *Pathology*. 2016;48:449–453.
47. Laschtowitz A, Zachou K, Lygoura V, et al. Histological activity despite normal ALT and IgG serum levels in patients with autoimmune hepatitis and cirrhosis. *JHEP Rep*. 2021;3: 100321.
48. Colapietro F, Maisonneuve P, Lytvyak E, et al. Incidence and predictors of hepatocellular carcinoma in patients with autoimmune hepatitis. *J Hepatol*. 2024;80:53–61.
49. Czaja AJ. Hepatocellular carcinoma and other malignancies in autoimmune hepatitis. *Dig Dis Sci*. 2013;58:1459–1476.
50. Guindi M. Histology of autoimmune hepatitis and its variants. *Clin Liver Dis*. 2010;14:577–590.
51. Bhumi SA, Wu GY. Seronegative autoimmune hepatitis. *J Clin Transl Hepatol*. 2023;11:459–465.
52. Gatselis NK, Zachou K, Loza AJM, et al. Prevalence and significance of antimitochondrial antibodies in autoimmune hepatitis (AIH): results from a large multicentre study of the International AIH Group. *Eur J Intern Med*. 2023;116:43–50.
53. Johnson PJ, McFarlane IG. Meeting report: International Autoimmune Hepatitis Group. *Hepatol*. 1993;18:998–1005.
54. Alvarez F, Berg PA, Bianchi FB, et al. International autoimmune hepatitis group report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol*. 1999;31:929–938.
55. Heneghan MA Lohse AW. Update in clinical science: autoimmune hepatitis. *J Hepatol* 2025. in press. doi: 10.1016/j.jhep.2024.12.041.
56. Zen Y, Notsumata K, Tanaka N, et al. Hepatic centrilobular zonal necrosis with positive antinuclear antibody: a unique subtype or early disease of autoimmune hepatitis? *Hum Pathol*. 2007;38:1669–1675.
57. Colapietro F, Masetti C, Pugliese N, et al. Recommendations for histological criteria of autoimmune hepatitis from the international AIH pathology: validation on a monocentric cohort. *Liver Int*. 2022;42:2583–2584.
58. Ahn S, Jeong SH, Cho EJ, et al. Comparison of four histological scoring systems for autoimmune hepatitis to improve diagnostic sensitivity. *Clin Mol Hepatol*. 2024;30: 37–48.
59. Wang L, Du ZX, Liu HL, et al. IAIH-PG consensus for histological criteria of AIH: multicentre validation with focus on chronic liver diseases in China. *Liver Int*. 2024;44: 2282–2292.
60. Chung Y, Morrison M, Zen Y, et al. Defining characteristics and long-term prognosis of drug-induced autoimmune-like hepatitis: a retrospective cohort study. *United European Gastroenterol J*. 2024;12:66–75.
61. Komori A. Evaluation of the histological scoring systems of autoimmune hepatitis: a significant step towards the optimization of clinical diagnosis. *Clin Mol Hepatol*. 2024;30:157–159.
62. Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. *Am J Surg Pathol*. 1995;19: 1409–1417.
63. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. *J Hepatol*. 1991;13:372–374.
64. Bedossa P, Bioulac-Sage P, Callard P, The French METAVIR cooperative study group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. *Hepatology*. 1994;20:15–20.
65. Suzuki A, Brunt EM, Kleiner DE, et al. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. *Hepatology*. 2011; 54:931–939.
66. Tan CK, Ho D, Wang LM, et al. Drug-induced autoimmune hepatitis: a minireview. *World J Gastroenterol*. 2022;28: 2654–2666.
67. Febres-Aldana CA, Alghamdi S, Krishnamurthy K, et al. Liver fibrosis helps to distinguish autoimmune hepatitis from DILI with autoimmune features: a review of twenty cases. *J Clin Transl Hepatol*. 2019;7:21–26.
68. Björnsson ES, Medina-Caliz I, Andrade RJ, et al. Setting up criteria for drug-induced autoimmune-like hepatitis through a systematic analysis of published reports. *Hepatol Commun*. 2022;6:1895–1909.
69. Zen Y, Yeh MM. Checkpoint inhibitor-induced liver injury: a novel form of liver disease emerging in the era of cancer immunotherapy. *Semin Diagn Pathol*. 2019;36:434–440.
70. Zen Y, Chen YY, Jeng YM, et al. Immune-related adverse reactions in the hepatobiliary system: second-generation checkpoint inhibitors highlight diverse histological changes. *Histopathology*. 2020;76:470–480.
71. García-Cortés M, Ortega-Alonso A, Matilla-Cabello G, et al. Clinical presentation, causative drugs and outcome of patients with autoimmune features in two prospective DILI registries. *Liver Int*. 2023;43:1749–1760.
72. Björnsson E, Davidsdottir L. The long-term follow-up after idiosyncratic drug-induced liver injury with jaundice. *J Hepatol*. 2009;50:511–517.
73. Chow KW, Pham NV, Ibrahim BM, et al. Autoimmune hepatitis-like syndrome following COVID-19 vaccination: a systematic review of the literature. *Dig Dis Sci*. 2022;67: 4574–4580.
74. Efe C, Kulkarni AV, Terziroli Beretta-Piccoli B, et al. Liver injury after SARS-CoV-2 vaccination: features of immune-mediated hepatitis, role of corticosteroid therapy and outcome. *Hepatology*. 2022;76:1576–1586.
75. Trontzas IP, Kyriakoulis KG, Vathiotis IA, et al. Vaccine-related autoimmune hepatitis: emerging association with SARS-Cov-2 vaccination or coincidence? *Vaccines*. 2022;10: 2073.
76. Codoni G, Kirchner T, Engel B, et al. Histological and serological features of acute liver injury after SARS-CoV-2 vaccination. *JHEP Rep*. 2022;5:100605.
77. Ueno M, Takabatake H, Itakura J, et al. Corticosteroid-refractory autoimmune hepatitis after COVID-19 vaccination: a case report and literature review. *Clin J Gastroenterol*. 2023; 16:554–558.
78. Dalekos GN, Gatselis NK. Autoimmune serology testing in clinical practice: an updated roadmap for the diagnosis of autoimmune hepatitis. *Eur J Intern Med*. 2023;108:9–17.
79. Terziroli Beretta-Piccoli B, Ripellino P, Gobbi C, et al. Autoimmune liver disease serology in acute hepatitis E virus infection. *J Autoimmun*. 2018;94:1–6.
80. Wong CKH, Mak LY, Au ICH, et al. Risk of acute liver injury following the mRNA (BNT162b2) and inactivated (CoronaVac) COVID-19 vaccines. *J Hepatol*. 2022;77:1339–1348.
81. Rodriguez-Espada A, Salgado-de la Mora M, Rodriguez-Paniagua BM, et al. Histopathological impact of SARS-CoV-2 on the liver: cellular damage and long-term complications. *World J Gastroenterol*. 2024;30:2866–2880.
82. Fanni D, Gerosa C, Serra G, et al. Autoimmune liver disease triggered by SARS-CoV-2: a case report and review of the literature. *Eur Rev Med Pharmacol Sci*. 2024;28:1632–1638.
83. Younes R, Govaere O, Petta S, et al. Presence of serum antinuclear antibodies does not impact long-term outcomes in nonalcoholic fatty liver disease. *Am J Gastroenterol*. 2020;115: 1289–1292.
84. Dalekos GN, Gatselis NK, Zachou K, et al. NAFLD and autoimmune hepatitis: do not judge a book by its cover. *Eur J Intern Med*. 2020;75:1–9.

85. McPherson S, Henderson E, Burt AD, et al. Serum immunoglobulin levels predict fibrosis in patients with non-alcoholic fatty liver disease. *J Hepatol*. 2014;60:1055–1062.
86. De Roza MA, Lamba M, Goh GB, et al. Immunoglobulin G in non-alcoholic steatohepatitis predicts clinical outcome: a prospective multi-centre cohort study. *World J Gastroenterol*. 2021;27:7563–7571.
87. Anvari S, Tsoi K. Hepatitis B virus reactivation with immunosuppression: a hidden threat? *J Clin Med*. 2024;13:393.
88. Aizawa Y, Hokari A. Autoimmune hepatitis: current challenges and future prospects. *Clin Exp Gastroenterol*. 2017;10:9–18.
89. Zachou K, Azariadis K, Lytvyak E, et al. Treatment responses and outcomes in patients with autoimmune hepatitis and concomitant features of non-alcoholic fatty liver disease. *JHEP Rep*. 2023;5:100778.
90. Gromadzka G, Czerwińska J, Krzemińska E, et al. Wilson's disease-crossroads of genetics, inflammation and immunity/autoimmunity: clinical and molecular issues. *Int J Mol Sci*. 2024;25:9034.
91. Nasri P, Hosseini-Kordkhyli SE, Jafari-Koulaee A, et al. Simultaneous presentation of autoimmune hepatitis and Wilson's disease: a systematic review study. *J Pediatr Rev*. 2021;9:277–292.
92. Fatemi R, Movassagh-Koolankuh S, Mosadeghi N. Simultaneous occurrence of Wilson's disease, autoimmune hepatitis, and hereditary hemochromatosis: a diagnostic challenge. *Middle East J Dig Dis*. 2024;16:64–68.
93. Boberg KM, Chapman RW, Hirschfield GM, et al. International Autoimmune Hepatitis Group. Overlap syndromes: The International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. *J Hepatol*. 2011;54:374–385.
94. Chazouilleres O, Wendum D, Serfaty L, et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. *Hepatol*. 1998;28:296–301.