PBC–AIH variant syndrome: emerging new terminology and a new approach to diagnosis and management

Marcial Sebode[a] *and Alessio Gerussi*[b,c]

Purpose of review
This review summarizes the recent developments of one of the most controversial entities in hepatology, variant syndromes of primary biliary cholangitis (PBC) with characteristics of autoimmune hepatitis (AIH).

Recent findings
Recently a consensus process was initiated to find agreement on the terminology, diagnostic criteria and treatment recommendations for patients with PBC–AIH variant syndromes. The concept and terminology of a variant syndrome, with one component of either AIH or PBC dominating over the other, is currently preferred. No single test can establish the diagnosis of a variant syndrome, only a combination of biochemical, serological and/or histological tests can support the diagnosis. If classical PBC is dominating, histology is mandatory for the diagnosis of a PBC–AIH variant syndrome. Treatment of PBC–AIH variants is based on a combination of ursodeoxycholic acid and immunosuppression. Since the prognosis of a PBC–AIH variant syndrome seems to be worse than the prognosis of classical PBC, the diagnosis of PBC–AIH must not be missed.

Summary
The recent consensus process on PBC–AIH variant syndromes does not provide answers to all questions regarding this entity. Rather, it serves as a starting point for future studies to confirm or even challenge the current consensus.

Keywords
autoimmune hepatitis, overlap syndrome, primary biliary cholangitis, variant syndrome

INTRODUCTION

The autoimmune cholangiopathies primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) can show biochemical, serological and/or histological characteristics of autoimmune hepatitis (AIH). In the past, terms such as "overlap syndrome" or "variant syndrome" have been applied to describe these cases. Particularly for PBC and AIH, a relatively clear cut between diagnostic hallmarks is not easy to make: a certain degree of bile duct inflammation can be found in classical AIH and a certain degree of hepatic inflammatory activity expanding from the bile ducts can be part of classical PBC. Definitions and clinical guidance for PBC–AIH variants syndromes are challenging to provide because of uncertainties on diagnostic criteria, treatment and prognosis. These unclear areas are even reinforced by very heterogenous opinions in the field about the pathomechanistic concepts and the terminology that try to explain and describe what is clinically observed. In the past, diagnostic criteria, the so-called "Paris Criteria" and "Zhang Criteria", with clear thresholds for its criteria have been proposed for PBC–AIH variants, in line with the concept of an overlap syndrome [1▪,2]. More recently, the concept of a variant syndrome arose, supporting the idea that one entity is dominant over the other [3]. As a consequence, a variant syndrome includes less stringent thresholds for diagnostic criteria than an overlap

[a]I. Department of Medicine, University Medical Centre Hamburg-Eppendorf, European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Hamburg, Germany, [b]Department of Medicine and Surgery, University of Milano-Bicocca and [c]Centre for Autoimmune Liver Diseases & Division of Gastroenterology, European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy

Correspondence to Marcial Sebode, I. Department of Medicine, University Medical Centre Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany. Tel: +49 40 7410 53910; fax: +40 40 7410 58531; e-mail: m.sebode@uke.de

Curr Opin Gastroenterol 2026, 42:68–74

DOI:10.1097/MOG.0000000000001149

KEY POINTS

- Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) may exhibit features characteristic of the other condition.
- In such cases, the pathomechanistic concept of a *variant syndrome* – in which one disease predominates over the other – is favored over the concept of an overlap.
- A variant syndrome should be considered in AIH patients who present with PBC-specific autoantibodies and a disproportionate elevation of cholestatic liver enzymes.
- Conversely, in PBC patients, the presence of AIH-specific autoantibodies combined with disproportionately increased transaminase levels should raise suspicion of a variant syndrome, which must be confirmed by liver biopsy.
- Diagnosing a variant syndrome primarily leads to a change in treatment: AIH patients receive additional ursodeoxycholic acid therapy, while PBC require immunosuppressive treatment.

syndrome. The dominating component needs to be identified and treatment should be primarily directed to that component.

Recently, an international multisociety effort, on behalf of the European Reference Network on Hepatological Diseases (ERN RARE-LIVER), the Global PBC Study Group and the International Autoimmune Hepatitis Group (IAIHG), started a consensus process including hepatologists and pathologists to address these uncertainties related to PBC–AIH variants. The results of this endeavor are expected to be published soon. Here, we provide an overview on the current concepts on PBC–AIH variants.

DEFINITION AND TERMINOLOGY

It is remarkable that shared characteristics between AIH and PBC have been described since their first descriptions. Doniach and Walker proposed in 1969 that both conditions might stem from a common autoimmune mechanism, with the clinical phenotype determined by whether the immune response predominantly affects hepatocytes or biliary epithelium [4]. The first definition was provided by Chazouillères in 1998, who introduced the term PBC–AIH overlap syndrome and provided clear thresholds for diagnostic criteria [1▪]. However, a more recent position statement by the IAIHG favors the concept of a variant syndrome, being a variant of the "classical" disease [3].

Despite recent efforts toward standardization, notable discrepancies persist among international guidelines. The EASL guidelines endorse the term variant [5,6], whereas the AASLD guidelines continue to favor the term overlap syndrome [7,8]. It must be pointed out that the distinction is not only terminological, but that different terminology reflects different underlying pathomechanistic concepts: the term "overlap" implies that a patient simultaneously fulfills diagnostic criteria for two separate diseases while preserving distinct disease boundaries. In contrast, the term "variant" refers to a disease subtype in which one condition predominates while the classical disease exhibits atypical features.

CLINICAL PRESENTATION

The shared features of PBC–AIH variant syndromes can manifest at different levels – including liver biochemistry, immunoglobulin profile, presence of autoantibodies, and liver histology. Various combinations of these diagnostic elements account for the marked heterogeneity of this entity.

PBC may present with moderate to severe interface hepatitis on histology, the presence of autoantibodies such as anti-SMA or antisoluble liver antigen/liver–pancreas (SLA/LP) antibodies, elevated immunoglobulin G levels, and/or markedly increased transaminases (3–5 × upper limit of normal, ULN), even after adequate cholestasis control with ursodeoxycholic acid. Conversely, AIH may exhibit biliary abnormalities on histology [9▪] – sometimes resolving with immunosuppression – together with the presence of antimitochondrial antibodies (AMA), a finding long debated under the concept of AMA-positive AIH [10,11]. Such patients may also show raised Alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) values, despite the absence of large-duct cholangiopathy or other cholestatic etiologies.

These presentations, which do not fulfill all of the "Paris Criteria", are increasingly recognized as part of the broader phenotypic spectrum of PBC–AIH variant syndromes (Table 1).

SUSPICION OF PBC–AIH IN PATIENTS WITH PBC

About 10% of PBC patients demonstrate features characteristic of AIH, which usually present simultaneously [1▪]. However, even years after the diagnosis of PBC, hepatitic activity may appear. A PBC–AIH variant should be suspected in a PBC patient if a disproportionate elevation of transaminases and/or an increased immunoglobulin G (IgG)-level is present. The threshold for a marked or disproportionate elevation of transaminases is a very controversial matter of debate. In

Table 1. When to suspect a PBC–AIH variant syndrome in a PBC patient?

Liver function tests	Serology	Histology
Disproportionate elevation of transaminases (AST, ALT)	Selective elevation of IgG	Patterns associated with AIH such as severe interface hepatitis and in acute manifestation more lobular hepatitis
	Presence of AIH-specific autoantibodies (e.g. anti-SLA/LP) or high titres of anti-SMA	Increased grade of inflammatory activity (mHAI $\geq$ 4)
When to suspect a PBC–AIH variant syndrome in a AIH patient?		
Disproportionate elevation of cholestatic liver enzymes (GGT, ALP)	Elevation of IgM	Florid bile duct lesion, nonsuppurative destructive granulomatous cholangitis
	Presence of PBC-specific autoantibodies (AMA, sp100, gp210)	Characteristics of chronic cholestasis, such as such copper deposition or cytokeratin 7 (CK7) positive metaplasia of hepatocytes

AIH, autoimmune hepatitis; IgG, immunoglobulin G; PBC, primary biliary cholangitis; SLA/LP, soluble liver antigen/liver–pancreas.

general, a hepatocellular or cholestatic pattern of liver enzymes is defined by the "R ratio", which is calculated by the formula R=(alanine aminotransferase, ALT value/ALT ULN) / (ALP value/ALP ULN) with an R ratio of >5 defined as hepatocellular injury and an R ratio <2 defined as cholestatic injury [12]. According to the "Paris Criteria", if transaminases exceed a value 5 × ULN in a PBC patient, this constellation supports the diagnosis of a PBC–AIH variant [1▪]. Some experts consider this cut-off to be too high since it potentially misses patients who might benefit from immunosuppressive treatment. However, a relatively high threshold protects PBC patients from being treated unnecessarily with immunosuppressants.

A PBC–AIH variant should also be suspected in a PBC patient with the detection of autoantibodies indicating an AIH. Most of the antibodies that are associated with AIH are not disease-specific [6,8,13]. However, in the "Paris Criteria" the presence of anti-SMA, irrespective of the height of the titer, is one of the main criteria to support a PBC–AIH variant [1▪]. Anti-SLA/LP are highly specific for AIH and should be tested if a variant syndrome is suspected [14]. Additionally, antibodies directed against double-stranded deoxyribonucleic acid (antidsDNA) have been associated with variant syndromes of PBC–AIH and were detected in 60% of patients with variant syndromes, but only in 4% of classical PBC and in 26% of AIH patients [15].

SUSPICION OF PBC–AIH IN PATIENTS WITH AIH

Since the first description of AIH, it has been recognized that some patients develop signs of cholestasis, compatible with PBC–AIH variant syndrome [16]. AMA-positivity can occur in AIH patients without histological signs of PBC. In two studies, none of the AMA-positive AIH patients developed further signs of PBC during follow-up [10,17]. The rate of AMA-positivity in AIH patients in one of these studies was about 12% [10]. The follow-up period was 8 and 4 years, respectively. It is unclear whether this period of time is long enough to exclude the development of the full manifestation of PBC. Still, it is unclear, whether AMA-positivity in AIH represents an early form of PBC–AIH variant and histological changes will occur over time.

DIAGNOSIS

A key consideration in diagnosing PBC–AIH variant syndromes is the potential for phenotypic evolution, which necessitates ongoing clinical reassessment. Two early pivotal studies first described the temporal relationship between PBC and AIH. Poupon *et al.* reported that about 4% of patients with PBC subsequently developed AIH features, with intervals ranging from 6 months to 13 years [18]. Lohse *et al.* proposed that PBC may initiate the autoimmune process, with genetic predispositions (notably HLA-B8, DR3, or DR4) facilitating progression toward an inflammatory hepatitis phenotype with AIH characteristics [19]. More recently, in a multicenter analysis of several thousand AIH and PBC patients, about 3% of fulfilled the "Paris Criteria" for a variant syndrome [20]. Of those patients with an initial diagnosis of AIH, 1.4% developed a variant features after a median of two years, and among those with PBC, 1.0% met variant criteria after a median of three years. Simultaneous manifestation of both variant characteristics were observed in 1.6% of cases.

There is broad consensus supporting a multidimensional and integrative diagnostic strategy, recognizing

that the disease phenotype may evolve. The diagnosis of PBC–AIH should be based on a combination of biochemical, serological, and histological findings, rather than reliance on a single parameter or overly strict criteria.

LIVER BIOPSY INDICATIONS

Liver biopsy is mandatory for making the diagnosis of AIH, but it is rarely needed for the diagnosis of PBC. Therefore, two different approaches exist with regard to liver biopsy, if PBC–AIH variant syndrome is suspected. In an AIH patient, the combination of PBC-specific autoantibodies and elevated ALP is sufficient to make the diagnosis of PBC–AIH variant syndrome. In addition, re-evaluation or a second opinion on the existing liver biopsy which was performed for the diagnosis of AIH should be considered to support the correct diagnosis. Only in unclear cases a new liver biopsy should be performed. If PBC–AIH variant syndrome is suspected in a PBC patient, a liver biopsy is now needed, since it was probably not previously required for diagnosing PBC.

It is important to recognize that lesions indicative of autoimmune or immune-mediated liver diseases can show heterogeneous distribution across the liver. If histological evaluation does not bring the expected results, the limitations of liver biopsy in light of sampling errors should be considered. In doubt, increased cholestatic liver enzymes or transaminases represent the global situation of the liver better than the small sample of a liver biopsy. Another warning sign that intrahepatic developments are missed by biochemistry or serology is increasing liver damage over time which could be detected noninvasive tests for liver fibrosis, such as transient elastography [21]. A liver biopsy should be considered if progressive liver damage is detected, in order to confirm a variant syndrome, exclude a concomitant liver disease such as steatotic liver disease [22] and/or quantify liver fibrosis, inflammation and degree of bile duct loss histologically.

DIAGNOSTIC HISTOLOGICAL FEATURES

In the original diagnostic criteria for AIH, histological bile duct involvement was considered a feature that reduced the likelihood of an AIH diagnosis [23]. This view has been changed over time. It has recently been agreed upon by several international liver pathologists, that bile duct affection does not exclude the diagnosis of AIH [24▪]. The key, but open question is the degree to which bile duct lesions are compatible with classical AIH. On the other side of the spectrum, the bile duct involvement that is clearly associated with classical PBC is the florid bile duct lesion, which is defined as a nonsuppurative destructive granulomatous cholangitis (Fig. 1). In detail, this implies lymphoplasmacellular infiltrates surrounding the bile duct with evident basement membrane disruption, the dissolution of the bile duct epithelium, and frequently the presence of bile duct-associated epithelioid granulomas.

The histological hallmark of chronic AIH is interface hepatitis [24▪,25]. The lymphocyte and plasma

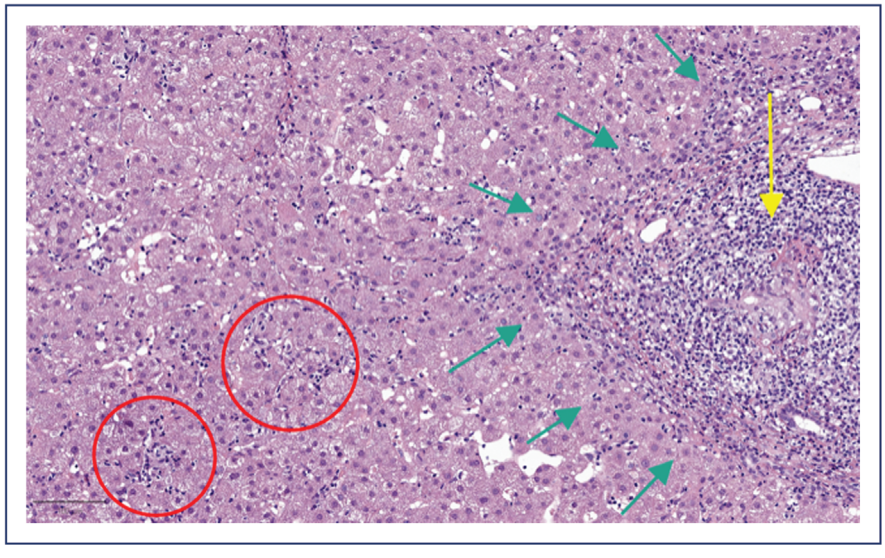

FIGURE 1. Histological hallmarks of PBC–AIH variant syndromes. A florid bile duct lesion (yellow arrow) as the characteristic histological sign of PBC presents simultaneously to interface hepatitis as the typical sign for chronic AIH (green arrows). In this case, inflammatory activity of AIH even expands to the liver lobule (red circles). AIH, autoimmune hepatitis; PBC, primary biliary cholangitis.

cell infiltrates exceed the periportal limiting plate with a finger-formed pattern into the liver lobule. Additional bile duct involvement seem to be relatively frequent in classical AIH (Fig. 1). In a study of 84 AIH patients, nearly 25% of patients had biliary changes such as destructive cholangitis or ductopenia [26]. In another study, bile duct injury and ductular reaction was frequently detected in liver biopsies of newly diagnosed, untreated AIH patients, without other signs of a PBC–AIH variant syndrome [9▪]. In contrast, histological signs of chronic cholestasis, such as copper deposition or cytokeratin 7 (CK7) positive metaplasia of hepatocytes, support the component of PBC and favor the presence of a PBC–AIH variant syndrome.

In addition to single histological features, the grading of inflammatory activity supports the diagnosis of a PBC–AIH variant syndromes, with a higher inflammatory activity being present in variants than in classical PBC. Currently, the mHAI seems to be the best histological score to grade inflammatory activity in this scenario. It is the recommended score to grade histological activity in chronic AIH [27,24▪]. In a study comparing histopathological lesions in classical PBC and patients with PBC–AIH variant syndromes, the mean mHAI score was significantly lower in the PBC group (4.1 points) than in the PBC–AIH variant group (5.3 points) [28].

Recently, a deep learning-based model was applied on digitalized liver biopsies in order to differentiate AIH from PBC [29]. The model demonstrated high accuracy in differentiating AIH from PBC and histological areas with increased inflammation were predominantly associated with AIH. Such AI models will be helpful for standardizing liver tissue analysis and better defining the histology characteristics of PBC–AIH variant syndromes [30].

TREATMENT

The most important immediate consequence of diagnosing a variant syndrome is a change in treatment, which adds ursodeoxycholic acid (UDCA) treatment to an AIH patient and immunosuppressive treatment to a PBC patient. Immunosuppressive treatment prolongs survival in classical AIH [31], but is not recommended for PBC. First-line treatment for PBC is UDCA which has choleretic effects and is cytoprotective on cholangiocytes.

It has been reported that UDCA alone is able to control mild interface hepatitis activity. However, marked inflammatory activity cannot be managed by UDCA alone and classical immunosuppression is required [32–34]. In a study by Chazouillères *et al.*, biochemical response and nonworsening of fibrosis on a histological level were achieved in 3 out of 11 variant patients who were treated with UDCA alone. 8 patients were nonresponders and 4 of them showed increasing grade of fibrosis at follow-up liver biopsy [33]. In contrast biochemical response was achieved in 4 out of 6 patients treated with UDCA in combination with immunosuppression and none of them showed fibrosis progression over time [33].

In a randomized placebo-controlled trial the immunosuppressive effect of budesonide in addition to UDCA was analyzed in classical PBC patients with marked inflammatory activity [35]. The median mHAI score at baseline was 7 in the budesonide group and 6 in the placebo group, which could be interpreted that these cases were actually patients with PBC–AIH variant syndromes. After 6 months of treatment, liver histology showed no significant change with regard to inflammatory activity under budesonide in comparison to placebo, but cholestatic liver enzymes declined significantly under budesonide. Still, the role for budesonide in classical PBC or PBC-variant syndrome remains controversial.

PROGNOSIS

Conflicting results on the prognosis of PBC–AIH variant syndromes have been published. The reason for these heterogenous data lies in differing diagnostic criteria and follow-up periods. In a retrospective study with a median follow-up of 7 years the survival rate between patients with PBC–AIH variant syndromes and those with classical PBC was comparable [36]. In contrast, others have reported worse clinical outcomes for variants, with higher rates of progression to cirrhosis, liver-related death and need for liver transplantation [20,37,38]. Overall, the majority of studies underlines that the prognosis of PBC–AIH variants deviates from classical AIH or PBC. This data supports the clinical need to better define these variants since they obviously require different clinical management.

It is not clear which surrogate markers for prognosis are suitable for PBC–AIH variant syndromes. Is it a combination of cholestatic markers and transaminases? Or is one of these biomarkers dominating over the other? It also needs to be considered that transaminases are also part of prognostic scores assessing the treatment response in classical PBC, such as the Paris II criteria or the UK PBC Score [5].

A recent study showed that PBC patients with IgG >ULN and aminotransferases of >2.5× ULN at diagnosis not receiving immunosuppression seem to show worse liver transplantation-free survival than those recognized as PBC–AIH variants and treated with immunosuppression accordingly [39▪]. However, further data is needed to clearly define the subgroup of patients who benefits from immunosuppressive treatment in terms of improved prognosis.

CONCLUSION

Although a consensus process has been completed for PBC–AIH variant syndromes, this does not imply that all questions on this topic have been answered. It is more like an agreement on a very controversial topic serving as a starting point in order to perform clinical studies to either confirm or challenge the current statements and recommendations. The most important task is to clearly identify those cases, that deviate with their prognosis from classical AIH or PBC and therefore require different clinical management and treatment.

Acknowledgements

The authors thank Giorgio Cazzaniga, Pathology Department, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy for providing the histological pictures. A. G. declares that this study was supported by Italian MUR PRIN 2022 PNRR P2022H7JYZ "Noninvasive biological and molecular characterization of autoimmune liver diseases and variant syndromes" and Bando Giovani "Early Career Award" FRRB – CUP H53C24000630002 "AIVAR – Artificial Intelligence-Enhanced Diagnosis of PBC–AIH Variant Syndrome.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Chazouillères O, Wendum D, Serfaty L, *et al.* Primary biliary cirrhosis-auto-
■ immune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology 1998; 28:296–301.

The "Paris Criteria" have been widely applied in the past for the definition of so-called overlap syndromes of PBC and AIH. The exact criteria are presented in this publication.

2. Zhang W, De D, Mohammed KA, *et al.* New scoring classification for primary biliary cholangitis-autoimmune hepatitis overlap syndrome. Hepatol Commun 2018; 2:245–253.
3. Boberg KM, Chapman RW, Hirschfield GM, *et al.* Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol 2011; 54:374–385.
4. Doniach D, Walker JG. A unified concept of autoimmune hepatitis. Lancet 1969; 1:813–815.
5. European Association for the Study of the Liver. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatol 2017; 67:145–172.
6. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of autoimmune hepatitis. J Hepatol 2025; 83:453–501.
7. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2021 practice guidance update from the American Association for the Study of Liver Diseases. Hepatology 2022; 75:1012–1013.
8. 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.
9. Verdonk RC, Lozano MF, van den Berg AP, Gouw AS. Bile ductal injury and
■ ductular reaction are frequent phenomena with different significance in autoimmune hepatitis. Liver Int 2016; 36:1362–1369.

Bile duct injury and ductular reaction are frequently observed in newly diagnosed autoimmune hepatitis (AIH) and cannot be predicted based on biochemical findings. While bile duct injury often resolves in most treated AIH cases, ductular reaction typically persists during follow-up, suggesting a possible regenerative role.

10. O'Brien C, Joshi S, Feld JJ, *et al.* Long-term follow-up of antimitochondrial antibody-positive autoimmune hepatitis. Hepatology 2008; 48:550– 556.
11. 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.
12. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol 2017; 112:18–35.
13. Adams LA, Lindor KD, Angulo P. The prevalence of autoantibodies and autoimmune hepatitis in patients with nonalcoholic fatty liver disease. Am J Gastroenterol 2004; 99:1316–1320.
14. Vergani D, Alvarez F, Bianchi FB, *et al.* Liver autoimmune serology: a consensus statement from the committee for autoimmune serology of the International Autoimmune Hepatitis Group. J Hepatol 2004; 41: 677–683.
15. Muratori P, Granito A, Pappas G, *et al.* The serological profile of the autoimmune hepatitis/primary biliary cirrhosis overlap syndrome. Am J Gastroenterol 2009; 104:1420–1425.
16. Cooksley WG, Powell LW, Kerr JF, Bhathal PS. Cholestasis in active chronic hepatitis. Am J Dig Dis 1972; 17:495–504.
17. Muratori P, Efe C, Muratori L, *et al.* Clinical implications of antimitochondrial antibody seropositivity in autoimmune hepatitis: a multicentre study. Eur J Gastroenterol Hepatol 2017; 29:777–780.
18. Poupon R, Chazouilleres O, Corpechot C, Chrétien Y. Development of autoimmune hepatitis in patients with typical primary biliary cirrhosis. Hepatology 2006; 44:85–90.
19. Lohse AW, zum Büschenfelde KH, Franz B, *et al.* Characterization of the overlap syndrome of primary biliary cirrhosis (PBC) and autoimmune hepatitis: evidence for it being a hepatitic form of PBC in genetically susceptible individuals. Hepatology 1999; 29:1078–1084.
20. Graf M, Lange CM, Langer MM, *et al.* Primary biliary cholangitis (PBC)-autoimmune hepatitis (AIH) variant syndrome: clinical features, response to therapy and long-term outcome. J Clin Med 2023; 12: 7047.
21. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on noninvasive tests for evaluation of liver disease severity and prognosis – 2021 update. J Hepatol 2021; 75:659–689.
22. Zachou K, Azariadis K, Lytvyak E, *et al.* Treatment responses and outcomes in patients with autoimmune hepatitis and concomitant features of nonalcoholic fatty liver disease. JHEP Rep 2023; 5:100778.
23. 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.
24. Lohse AW, Sebode M, Bhathal PS, *et al.* Consensus recommendations for
■ histological criteria of autoimmune hepatitis from the International AIH Pathology Group: Results of a workshop on AIH histology hosted by the European Reference Network on Hepatological Diseases and the European Society of Pathology: Results of a workshop on AIH histology hosted by the European Reference Network on Hepatological Diseases and the European Society of Pathology. Liver Int 2022; 42:1058–1069.

In this consensus report seventeen expert liver pathologists established consensus criteria for the histopathological diagnosis of chronic and for the first time acute manifestation of autoimmune hepatitis (AIH). Bile duct involvement was explicitly no exclusion criterion to diagnose AIH.

25. Cazzaniga G, Bolis F, Caime C, *et al.* Diagnosing autoimmune hepatitis: histological correlations and emerging technologies. Liver Int 2025; 45: e70377.
26. Czaja AJ, Carpenter HA. Autoimmune hepatitis with incidental histologic features of bile duct injury. Hepatology 2001; 34:659–665.
27. Ishak K, Baptista A, Bianchi L, *et al.* Histological grading and staging of chronic hepatitis. J Hepatol 1995; 22:696–699.
28. Drebber U, Mueller JJ, Klein E, *et al.* Liver biopsy in primary biliary cirrhosis: clinicopathological data and stage. Pathol Int 2009; 59:546–554.
29. Gerussi A, Saldanha OL, Cazzaniga G, *et al.* Deep learning helps discriminate between autoimmune hepatitis and primary biliary cholangitis. JHEP Rep 2024; 7:101198.
30. Cazzaniga G, L'Imperio V, Bonoldi E, *et al.* Automating liver biopsy segmentation with a robust, open-source tool for pathology research: the HOTSPoT model. NPJ Digit Med 2025; 8:455.
31. Cook GC, Mulligan R, Sherlock S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. Q J Med 1971; 40:159–185.
32. Nakamura K, Yoneda M, Yokohama S, *et al.* Efficacy of ursodeoxycholic acid in Japanese patients with type 1 autoimmune hepatitis. J Gastroenterol Hepatol 1998; 13:490–495.

33. Chazouillères O, Wendum D, Serfaty L, *et al.* Long term outcome and response to therapy of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. J Hepatol 2006; 44:400–406.
34. Ozaslan E, Efe C, Heurgué-Berlot A, *et al.* Factors associated with response to therapy and outcome of patients with primary biliary cirrhosis with features of autoimmune hepatitis. Clin Gastroenterol Hepatol 2014; 12: 863–869.
35. Hirschfield GM, Beuers U, Kupcinskas L, *et al.* A placebo-controlled randomised trial of budesonide for PBC following an insufficient response to UDCA. J Hepatol 2021; 74:321–329.
36. Joshi S, Cauch-Dudek K, Wanless IR, *et al.* Primary biliary cirrhosis with additional features of autoimmune hepatitis: response to therapy with ursodeoxycholic acid. Hepatology 2002; 35:409–413.
37. Neuhauser M, Bjornsson E, Treeprasertsuk S, *et al.* Autoimmune hepatitis-PBC overlap syndrome: a simplified scoring system may assist in the diagnosis. Am J Gastroenterol 2010; 105:345–353.
38. Yang F, Wang Q, Wang Z, *et al.* The natural history and prognosis of primary biliary cirrhosis with clinical features of autoimmune hepatitis. Clin Rev Allergy Immunol 2016; 50:114–123.
39. Stoelinga AEC, Biewenga M, Drenth JPH, *et al.* Diagnostic criteria and long-
■ term outcomes in AIH-PBC variant syndrome under combination therapy. JHEP Rep 2024; 6:101088.
In this retrospective study, patients outside the Paris Criteria were frequently labeled as having PBC-AIH variant syndrome and were successfully treated with combination therapy. Prognosis was worse in patients with PBC and hepatic inflammation than in those treated as having PBC-AIH variant syndrome.