Michael Babich MD, Series Editor

Autoimmune Liver Disease Variants

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Autoimmune liver disease variants, which are disease entities that consist of a combination of features of autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis, are relatively uncommon disorders. They can be difficult to diagnose as there are no pathognomonic clinical manifestations, highly specific biochemical/serological markers or radiographic findings. Even after a tentative diagnosis is established, options for treatment remain limited at this time. A wide-ranging effect on mortality may be seen depending on which autoimmune liver disease has its features predominate.

INTRODUCTION

Autoimmune liver disease (AILD) is a category of conditions that include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). As clinicians have learned, diseases oftentimes do not manifest according to their textbook definitions within clearly defined clinical, biochemical, serological and histological parameters and may be said to present atypically. AILD is no exception. Because some patients may present with a mix of features from AIH, PBC and PSC, they were labeled as having an "overlap syndrome", "outlier syndrome" or a variant of AIH.[1,2,3] There is no firm consensus among the international societies on the nomenclature for this subset of disorders, but they cautioned that it would be unwise to ascribe the label of "overlap syndrome" to them all when we still do not fully understand the pathophysiology of AILD well enough to confidently deny that AILD may present as a spectrum of disease instead of entities with distinct boundaries.[4] As such, we will use the preferred terminology of "variants" instead of "overlap" in this review.[5] Variants may be a better descriptive terminology since the International Autoimmune Hepatitis Group (IAIHG) recommends labeling and treating these patients according to their predominant AILD.[4] The AILD variants include AIH and PBC, AIH and PSC, and rarely PBC and PSC (Figure 1). The goal of this review is to describe the natural history of each AILD variant as well as to discuss

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the diagnostic work up and highlight treatment options. It is important to recognize the difference between classic AIH, PBC, PSC and these AILD variants because the management of these disorders differs as well as their overall prognosis.

"Classic" Autoimmune Liver Diseases

Typically, AIH is characterized by inflammation of the liver with predominant elevation of aminotransferases, immunoglobulin G (IgG), and presence of autoantibodies including anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-liver kidney microsomal antibody (anti-LKM), anti-liver cytosol 1 antibody (anti-LC1) and peri-nuclear anti-nuclear cytoplasmic antibodies (PANCA). ANA and ASMA are commonly seen in type 1 AIH while anti-LKM and anti-LC1 are seen in type 2 AIH.[4] In 10% of patients with AIH, none of these autoantibodies may be present.[4] In 1993, the IAIHG devised a scoring system to diagnose AIH based upon the presence or absence of other potential causes, biochemical, serological and histological parameters, and factored in response to treatment.[6] Of note, there is no single definitively diagnostic feature of this disease. The IAIHG scoring system was revised in 1999 to include information from post treatment response, then simplified in 2008.[7,8] In the simplified IAIHG scoring system (Table 1), patients were designated a "definite" diagnosis of AIH if their pretreatment aggregate score was greater than or equal to 7, and "probable" AIH if the pretreatment score was greater than or equal to 6. Patients may be asymptomatic or they may present with nonspecific symptoms of fatigue, pruritus, abdominal pain, nausea, and/or arthralgias.[4,9] On physical exam, they may have jaundice, hepatomegaly, splenomegaly or signs of cirrhosis.[4] Medical treatment includes corticosteroids for induction and an immunomodulator for maintenance.[9] Immunosuppression is absolutely indicated if the patient is symptomatic or for any of the following: aspartate aminotransferase (AST) $\geq$ 10 times the upper limit of normal (ULN), AST $\geq$5 times ULN and gamma globulin $\geq$2 times ULN or if bridging necrosis or multiacinar necrosis is found on liver biopsy.[9] The goal of treatment is to achieve clinical, biochemical and histological remission of disease. Typically it may take between 18-24 months for that to occur.[9] Greater than 75% of patients with AIH will respond to medical therapy though a majority of them will experience relapse upon withdrawal of immunosuppression.[9] Decompensated end stage liver disease and hepatocellular carcinoma are indications for liver transplant.[9] Recurrence of disease after liver transplant can be as high as 30%.[9]

PBC is an autoimmune cholestatic disorder where T cell mediated injury of small-medium intralobular bile duct epithelium occurs, causing degeneration of the bile ductules and focal obliteration.[10,11,12] Patients with PBC most commonly present with fatigue and pruritus that is usually worse at night.[10] The autoantibody that is usually present in these patients is the anti-mitochondrial antibody (AMA).[10] More specifically, the autoantibody is directed against the 2-oxo-acid dehydrogenase complex, including the E2 subunit of pyruvate dehydrogenase (PDC-E2), the branched chain 2-oxo acid dehydrogenase (BCOADC-E2), and the 2-oxoglutaric acid dehydrogenase E2.[1,4] About 5% of patients may present with an AMA-negative phenotype.[1] These patients will usually have a high ANA titer.[1] Historically, ursodeoxycholic acid (UDCA) has been the mainstay of treatment. Between one-quarter to one-third of patients with PBC treated with UDCA will experience improvement of their symptoms or show improvement on biochemical testing and histology.[10] In May 2016, obeticholic acid was approved by the Food and Drug Administration (FDA) for treatment of PBC, either in conjunction with UDCA for those with partial response or as monotherapy for those who are not able to tolerate UDCA.[13] Obeticholic acid works by binding to farnesoid X receptors of liver cells to increase efflux of bile from the liver and decrease bile acid production. It may also have an anti-fibrotic property. In clinical trials it led to a significant decrease in alkaline phosphatase relative to placebo.[13] Liver transplant may be considered for patients with intractable pruritus and end stage liver disease.[10]

PSC is another autoimmune cholestatic disorder, where progressive inflammation and fibrosis affects the medium-large bile ducts of the liver leading to segmental stricture formation.[14,15]

Table 1. Simplified IAIHG Diagnostic Scoring System[8]

Autoantibodies		
ANA or ASMA	≥1:40	+1
ANA or ASMA	≥1:80	+2
Or Anti-LKM-1	≥1:40	
Or Anti-SLA	Positive	
		Maximum 2 points
Immunoglobulin level		
IgG	>ULN	+1
IgG	>1.1 x ULN	+2
		Maximum 2 points
Histological features		
Atypical for AIH		0
Compatible with AIH (presence of interface hepatitis)		+1
Typical of AIH (presence of interface hepatitis, plasma cell infiltration, rosettes)		+2
		Maximum 2 points
Absence of viral hepatitis		
Yes (negative viral serologies)		+2
No		0
		Maximum 2 points
Pretreatment aggregate score		
Definite diagnosis	≥7	
Probable diagnosis	≥6	

ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; LKM-1, liver-kidney-microsomal-1; IgG, immunoglobulin G; ULN, upper limit of normal.

Patients may present, additionally or alternatively, with a small duct phenotype whereby strictures are not visible on magnetic resonance imaging or endoscopic retrograde cholangiopancreaticogram (ERCP) despite gross elevation of alkaline phosphatase and total bilirubin.[16] It should be noted that approximately 75% of the patients who have PSC will also be diagnosed with ulcerative colitis (UC), although the colitis may be diagnosed before, well after or concurrent with the PSC.[4,17] Patients who do not already carry a diagnosis of UC should undergo colonoscopy upon diagnosis of PSC. Once UC is diagnosed, they should undergo surveillance colonoscopy annually thereafter to evaluate for colorectal cancer given high risk for its development.[14,17] PSC patients are also at increased risk for developing cholangiocarcinoma and gallbladder cancer and will need to undergo an annual screening ultrasound evaluation of the gallbadder.[14,17] Cholecystectomy is recommended if a gallbladder lesion is detected, even if it is less than 1 centimeter in size.[14] Unfortunately, at this time there are no known effective treatments for PSC. It does not respond well to either UDCA or immunosuppression.[14] Endoscopic biliary dilation and stenting may be performed for treatment of acute cholangitis due to a dominant stricture.[14] Liver transplant is an option for patients with end stage liver disease or those with intractable

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pruritus, recurrent bacterial cholangitis or, in some cases, cholangiocarcinoma.[14] While post-transplant survival is excellent, recurrence of disease is also high with 20-25% of patients showing signs of recurrence in 5-10 years.[17]

Epidemiology

As a whole AILDs are not very common disorders (Table 2), AILD variants are even rarer. AILD variants were first described in the literature in the late 1970s.[18,19] The exact frequency of each AILD variant is difficult to ascertain as different clinical criteria have been used to diagnose patients over the years and some patients may have received an inaccurate diagnosis. There is no validated diagnostic criterion for each AILD variant.

The IAIHG scoring system has been used inappropriately to look for features of AIH in patients with PBC and PSC in order to diagnose a variant phenotype.[24] The scoring system was applied to cases where patients who were initially diagnosed with AIH were then evaluated for features of PBC and PSC, as well as to patients who were initially diagnosed with PBC or PSC and then evaluated for features of AIH.

AIH-PBC appears to be the most common of all the AILD variants with frequency of disease ranging from 4.8-19% of patients with PBC and 7-13% of patients with AIH. [2,4,25] Though up to 19% of all PBC patients in one study had features of AIH it is important to note that all of those patients had an IAIHG score that placed them in the "probable" AIH diagnosis category and not "definite" AIH.[24] Interestingly, in a separate study of 1476 PBC patients, only 8, or 0.54%, were documented to have features of AIH.[26] Similar to patients with classic PBC, AIH-PBC is also more commonly seen in females. One significant difference in patients with AIH-PBC variant is the younger age at time of diagnosis, with median age of 44 years old versus 59 years old in classic PBC.[27]

8-17% of PSC patients may have features of AIH when the IAIHG scoring system is applied, while 6-11% of AIH patients may have features of PSC.[25] The frequency of this variant ranges more widely, from 2-33%, depending on whether a "definite" or "probable" definition of AIH is used.[25] Notably, up to 16% of AIH patients have coexisting inflammatory bowel disease and 42% of those patients have radiographic evidence of PSC.[28] As in classic PSC, the AIH-PSC variant is seen more commonly in males though the diagnosis is usually made at a younger age. In one study the average age of diagnosis was 21.4 +/- 5 years for those with AIH-PSC variant while the average age of diagnosis for PSC patients was 32.3 +/- 10 years.[27] The combination of AIH with cholestasis is seen more commonly in children.[1,5] That AILD variant has been labeled as AIH with autoimmune sclerosing and is thought to be an early presentation of AIH-PSC.[29]

PBC-PSC is exceedingly rare and has been presented as case reports in the literature.[30,31] In one study the frequency of disease was 0.7%, or 2 out of 261 patients with PBC followed over a 20 year period.[25,32] There was a case report published in 2012 reporting the discovery of the first case of a patient with PBC and small duct PSC.[33]

AILD variants can affect patients of all ethnicities as evidenced by case reports and studies of patients from all around the world including East Asia, South Asia, the Middle East, Western Europe, and North America. One study noted an increased prevalence of AIH-PBC seen in Hispanics.[34]

Pathophysiology

The pathogenesis of AILD and its variants is unclear. Similar to many autoimmune disorders, the causes are likely multifactorial. Patients

Table 2. Incidence and Prevalence of Classic AILD

	Incidence	Prevalence
AIH	1-2/100,000 person-years[9]	11-17/100,000 people[9]
PBC	2.7/100,000 person-years[20]	Females – 65.4/100,000[20] Males – 12.1/100,000[20]
PSC	0.77-1.22/100,000 person years[21,22]	Females – 6.3-8.9/100,000[22,23] Males – 20.4-23.7/100,000[22,23]

with AILD and its variants likely have a genetic predisposition towards developing these disorders, and were exposed to the right environmental trigger leading to an immune activation cascade with subsequent targeted injury of the hepatocytes and/or bile ducts.[35] AILDs have been associated with some human leukocyte antigen (HLA) genes on chromosome 6, though their effect on disease manifestation is unclear.[4] AIH is weakly associated with HLA A3, B8, DR3, DR4 while AMA-positive PBC is associated with DR8 and PSC is associated with B8, DR3 and Drw52.[1,2] Some HLA associations with increased risk for AIH-PBC are B8, DR3, DQ2.[2] HLA-DR7 was found in high frequency in patients with AIH-PBC and it may potentially be used to distinguish AIH from its variants.[2] Of note, it has been suggested that DR4 may have a protective effect against PSC though it predisposes the patient to AIH.[2]

There have been several theories that have been put forth in the literature over the years to explain the process of how these AILD variants may have come about. The theories in IAIHG's 2011 position statement on overlap syndrome include:

1. Sequential occurrence of 2 disorders. An example of this is when AIH features like hepatitis are seen in a patient initially diagnosed with PBC many years ago.
2. Coincident or concomitant presence of 2 disorders. An example of this is the simultaneous presentation of AIH and PSC in children.
3. Continuum of changes between 2 disorders may be revealing a spectrum of disease.
4. Overlap of 2 distinct disorders
5. Atypical presentation of a known primary disorder

AILD variants may be explained by one or more of the theories above. AIH-PSC has been noted to present sequentially usually with AIH features initially followed by PSC and rarely the reverse.[35] With AIH-PBC, PBC is usually the dominant disorder and may present initially prior to onset of AIH or concomitantly with AIH.[29,35]

Clinical Manifestations

Patients with AILD variants may be asymptomatic or they may present with nonspecific symptoms of fatigue, malaise, anorexia, pruritus and/or abdominal pain. Patients with cholestatic variants may also be jaundiced.[4] In one study of AIH-PBC patients, 20% presented with pruritus and 20% presented with jaundice.[27] It is rare for these patients to present with acute hepatitis or with acute liver failure.[27]

Differential Diagnosis

Given the nonspecific nature of many features of these diseases, it is important to rule out viral hepatitis, drug induced liver injury (DILI), take into account alcohol and recreational drug use, and evaluate for other possible causes for abnormal liver enzymes.[24,36] DILI can mimic the presentation of AIH and may trigger an autoimmune response that can lead to AIH or unmask subclinical type 1 AIH.[27] Another potential cause for a mixed pattern of hepatocellular and cholestatic injury that should be excluded is IgG4 cholangiopathy.[37] It can be mistaken for AIH-PSC since it may cause sclerosing cholangitis and hepatitis.[37] One major difference seen on histology is IgG4 positive lymphoplasmacytic infiltration with fibrosis of multiple organs, including lymph nodes in the head and neck, chest and abdomen.[37] These patients will usually respond to steroids and a small case series showed improvement with Rituximab.[37]

Diagnostic Work Up

Unfortunately, due to the small number of patients with AILD variants there are few robust studies and thus there are no validated diagnostic criteria for AIH-PBC or AIH-PSC. The gold standard for making a diagnosis of an AILD variant is still based on clinical judgement.[38] The clinician must take into account the patient's biochemical, serological, histological (if available), and radiographic data before making a diagnosis (Table 3). Experts have warned against making a diagnosis of AILD variant based on the presence of one atypical finding detected on initial evaluation or at a single time point instead of observing how the patient may change clinically over time.[1,39] They also caution against over-diagnosing AILD variants.[28] IAIHG

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recommends diagnosing and treating the AILD variant according to the dominant disorder.[4]

Biochemical Parameters

The expected pattern of abnormal liver enzymes seen in AIH patients is elevated aminotransferases up to 10 times the upper limit of normal, with slightly elevated alkaline phosphatase (AP), total bilirubin and/or gamma glutamyl transpeptidase (GGT).[37] In cholestatic disorders like PBC and PSC the reverse pattern is usually observed though ALT is usually not greater than 500 IU/mL.[37] In PBC, AP will be moderately to markedly raised with only a slight elevation of the aminotransferases.[4] In PSC, AP will be at least 3 times the upper limit of normal, total bilirubin may be normal at time of diagnosis and aminotransferases will be moderately elevated.[4] The total bilirubin may fluctuate over time reflecting development of a dominant stricture and/or acute cholangitis.[37]

For patients with AIH-PBC, aminotransferases may increase to 5-10 times the upper limit of normal.[4] These patients will have more highly elevated aminotransferases than those with just PBC as well as higher elevation of AP and GGT than patients with just AIH.[27] The elevation of AST in patients with AIH-PSC will be between that of patients with solely AIH or PSC.[27]

Serologies

Certain human leukocyte antigens (HLA) have been associated with AIH, PBC and PSC. However, they have a weak association with determining clinical manifestations of the disorder, if present in a patient, and should not be used for diagnosis.[1,25]

Most patients with AIH-PBC will have a positive AMA in addition to positive ASMA and elevated IgG.[4] About 1/3 of these patients may also have a positive ANA.[4] Patients with AIH-PBC with negative AMA will usually have positive antibodies to ANA and ASMA.[4] Other more specific auto-antibodies seen in patients with AIH-PBC include anti-gp210, antiSp100 and anti-double strand DNA (anti-dsDNA), but several of these are not widely available.[4] AntiSp100 is highly specific, with specificity greater than 95%.[4] Anti-dsDNA is seen more commonly in AIH-PBC patients

Table 3. Features of AIH-PBC and AIH-PSC

	AIH-PBC	AIH-PSC
Biochemical	AST & ALT >5-10x ULN AP ≥ 2x ULN GGT ≥ 5x ULN	AST & ALT at least >2x ULN AP >2 x ULN May be normal
Serologies	+AMA, ASMA, ANA, Elevated IgG, IgM Anti-gp210, antiSp100, anti dsDNA	+ANA, ASMA, pANCA Elevated IgM, IgG Absence of AMA
Imaging	Findings of AIH or PBC: reticular fibrosis, periportal halo sign	Biliary tree strictures and segmental dilatation, macrogenerative nodules, peripheral atrophy, ductal beading on MRI
Histology	Lymphocytic interface hepatitis, florid duct lesions, hepatocyte swelling, acidophilic bodies	Fibrous obliteration of bile ducts, concentric periductal fibrosis, portal tract inflammation, piecemeal necrosis, loss of interlobular bile ducts
Diagnostic Scoring System	Paris Criteria	None

AST, aspartate aminotransferase; ALT, alanine aminotransferase, ULN, upper limit of normal, AP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; AMA, anti-mitochondrial antibody; ASMA, anti smooth muscle antibody; ANA, antinuclear antibody; IgG, immunoglobulin G; IgM immunoglobulin M, anti-gp210, anti-glyco protein 210; antidsDNA, anti-double strand deoxyribonucleic acid; pANCA, perinuclear neutrophil antibodies.

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than in AIH or PBC patients alone.[4,40] Antibody to p53 has been identified as a potential marker for favorable treatment response in patients with AIH-PBC receiving immunosuppression.[25]

Patients with AIH-PSC may have positive ANA, ASMA, and/or pANCA though with lower titers than what is usually seen in patients with just AIH.[4] About one half of AIH-PSC patients will have elevated IgG and IgM which correlates with plasma cell infiltration on pathology.[4,25] IgG elevation in patients with AIH-PSC is usually higher than that which is seen in PSC patients.[27] IgM elevation is lower than in patients with AIH alone.[27] If all immunoglobulins are elevated then it will be important to evaluate for cirrhosis as that is a common reason to have nonspecific rise in immunoglobulins.[28]

Imaging

Imaging studies can be specific for the fibrosing duct features of AIH-PSC but they are not very sensitive. A normal cholangiogram does not exclude a diagnosis of AIH-PSC. Early AIH-PSC and AIH-small duct PSC may be missed by ERCP.[1]

Nonspecific findings may be seen on ultrasound including coarsened hepatic echotexture, nodularity, volume redistribution especially in patients with fibrosis or cirrhosis, but these findings do not differentiate those conditions.[41] Ultrasound is still an important tool for hepatocellular carcinoma (HCC) screening in patients with AILD variants who have progressed to cirrhosis. If available, contrast enhancement may be utilized in ultrasound to characterize hepatic nodules that are greater than 1 centimeter (cm).[41] Elastography may be used to identify and stage severity of fibrosis.[41] Triphasic computerized tomography (CT) is not recommended for routine screening for HCC due to exposure to radiation and high cost compared to ultrasound.[41]

Some common findings on magnetic resonance imaging (MRI) in patients with AIH-PSC or PSC-PBC are central macroregeneration, peripheral atrophy, biliary duct beading and/or biliary dilatation.[42] In a retrospective study, 2 radiologists reviewed the MRI of 15 patients with AILD variants whose diagnoses were blinded to them. Specificity for AIH-PSC was 100% if macroregenerative nodules, peripheral atrophy or ductal beading were present on MRI.[42] There was good inter-observer agreement noted with a kappa of 0.76.[42] However, in a prospective study, another group found that minimal abnormalities seen on MRI in 25% of patients were not from AIH-PSC but were likely due to hepatic architecture distortion.[43] They recommended MRI be used in AIH only if patients developed cholestasis or did not respond to steroids.[43]

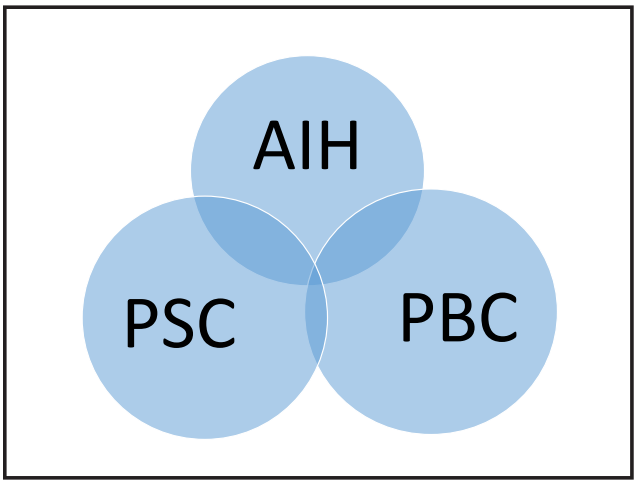

Figure 1. AILD Variants

For AIH-PBC there are no specific imaging findings for the variant.[41] It was noted that in some PBC patients there may be a periportal halo sign which is an hypointensity around the portal venous branches found on T1-weighted and T2-weighted images caused by satellite periportal hepatocellular extinction surrounded by regenerating nodules.[42]

Histology

A liver biopsy is generally required for the diagnosis of AIH.[9] Common findings on histology for AIH include lymphoplasmacytic infiltration of the portal tract and liver lobules and interface hepatitis, which is usually also lymphoplasmacytic; these are nonspecific findings.[1,36] It is rare to see bile duct lesions or granulomatous lesions in AIH and further work up with cholangiogram is warranted if these are found.[1,4] Because the disease may be patchy, the biopsy may appear normal due to sampling error as well.[1]

While a biopsy is not required for the diagnosis of PBC, on histology there may be characteristic features supporting the diagnosis, including

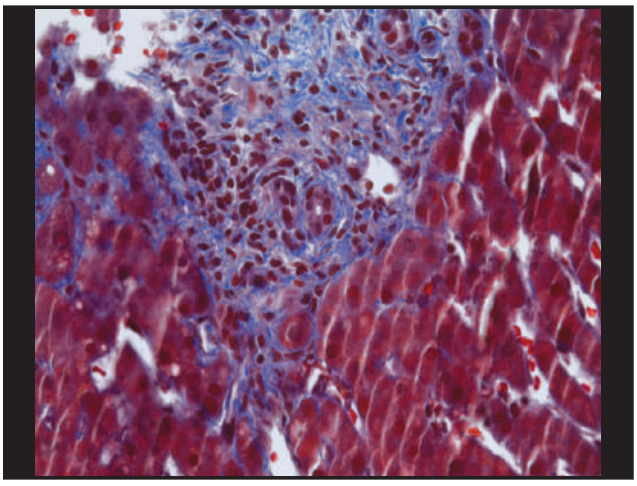

Figure 2. Histology of an AIH-PSC patient showing lymphocytic cholangitis. (trichrome stain, 400x magnification).

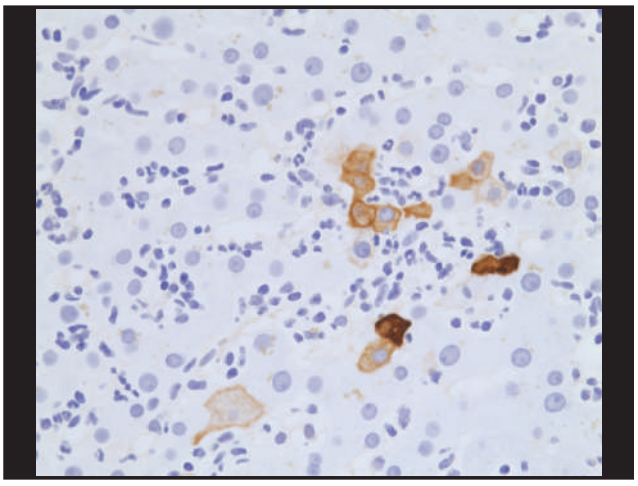

Figure 3. Histology of an AIH-PSC patient with cytokeratin 7 stain highlighting the absence of interlobular bile ducts. (400x magnification)

degenerating bile duct epithelium with focal bile duct obliteration, rare granulomatous bile duct lesions with CD8+T cell interface hepatitis and CD4+T cells in the portal tracts.[1,4,36,37] Interface hepatitis is seen in 30% of PBC patients.[4]

Histological findings in PSC include portal tract inflammation with bile duct lymphocytic infiltration, ductular proliferation, periductal fibrosis and interface hepatitis.[4,36] Classic "onion skinning" is seen only rarely, and again disease activity may be patchy and lead to sampling error. The destruction typically seen in PSC affects the medium to large sized ducts.[37]

In AIH-PBC there will be histological findings of both disorders including lymphoplasmacytic interface hepatitis with florid duct lesions and parenchymal necroinflammation characterized by hepatocyte swelling and acidophilic bodies.[36] Interface hepatitis is more common in AIH-PBC than in PBC alone. In a prospective study of AIH, AIH-PBC and PBC patients, 86% of AIH-PBC had interface hepatitis on biopsy and 93% had lymphocytic cholangitis.[27] The destruction of bile ducts may be patchy so a sampling error may cause a missed diagnosis especially if less than 10 portal tracts are seen on biopsy.[37]

In AIH-PSC fibrous knots or fibrous obliteration of the bile ducts is usually seen (Fig. 2, 3).[36] Bile duct injury may be patchy and rarely there will be concentric periductal fibrosis (also known as onion-skin fibrosis).[36] There may be findings similar to AIH as well, including portal tract inflammation, piecemeal necrosis and loss of interlobular bile ducts.[36]

In PSC-PBC, you may see granulomas on histology.[4]

Scores

Two scoring systems that have been used for diagnosis of AILD variants are the IAIHG scoring system and Paris Criteria. It is important to note that neither scoring system has been validated for use in diagnosis of AILD variants.[4,27] In fact, the IAIHG recommends against using the IAIHG score for this purpose.[4]

When the revised IAIHG score was used to assess patients with PSC for AIH features, it showed an increased specificity of 64.9% to 89.5% when compared to original IAIHG score criteria.[36] However, when the revised and simplified IAIHG score was used to diagnose AIH in PBC patients it had a sensitivity of 40% and specificity of 17% compared to the Paris Criteria.[25]

The Paris Criteria, also known as Chazouilléres Criteria or PBC criteria, is endorsed by the European Association for Study of the Liver (EASL) for diagnosis of AIH-PBC though it has not been validated.[4,44] The score was created using biochemical, serological and histological data while looking at AIH features in PBC patients, and not the other way around, so some patients may

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be missed.[45] When compared to a gold standard of clinical diagnosis, the Paris criteria had 92% sensitivity and 97% specificity.[25] The Paris Criteria requires interface hepatitis to be present and two out of three of the following findings to be present for each AIH and PBC to make the diagnosis.[44]

Associated Autoimmune Diseases

Patients with AILD and AILD variants may have other concomitant autoimmune disorders. For example, CREST, an acronym for a syndrome that includes calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia, can be seen in 15-20% of PBC patients.[37]

Among patients with AIH-PBC, 46.3% have another autoimmune disorder.[27] AIH-PBC is most commonly associated with Sjogren's syndrome but it has been linked to a host of other autoimmune disorders including systemic sclerosis, sicca syndrome, rheumatoid arthritis, idiopathic thrombocytopenic purpura, antiphospholipid syndrome, autoimmune hemolytic anemia, membranous glomerulus nephritis, Raynaud's syndrome, polymyalgia rheumatic, systemic lupus erythematosus, Hashimoto's thyroiditis, Celiac disease, sarcoidosis, fibrosing alveolitis, vitiligo, lichen ruber planus, and bullous pemphigoid.[2,4,40]

The prevalence of inflammatory bowel disease in AIH-PSC is similar to that in PSC alone.[35]

Treatment

Medical Therapy

At this time, there are two schools of thought on treatment of AILD. Some experts recommend a stepwise approach, treating the dominant AILD and assessing response to treatment before considering a diagnosis of AILD variant and changing the therapeutic regimen, while others advocate for a top down method of using combination therapy from the get-go.[28,39] The goals of treatment for AILD variants are the same as in classic AILD; to manage symptoms and prevent progression of disease. At this time there are no evidenced based recommendations for treatment of AIH-PBC or AIH-PSC.[4] It is important to note that patients with AILD variants may respond differently to conventional medical therapies so the experts recommend tailoring treatment to the individual patients.[28,39] The mainstay of treatment for AILD variants includes UDCA and immunosuppressants like corticosteroids and azathioprine.[4] Note, however, that high dose UDCA has been associated with increased risk for death and need for liver transplant in patients with PSC.[25]

In patients with AIH-PBC, initial therapy may include UDCA 15 mg/kg and/or corticosteroids.[4,28] It will be important to counsel premenopausal women that they may be at increased risk for osteoporosis if they require prolonged corticosteroid therapy.[24] Treatment with corticosteroids in patients with AIH-PBC has been shown to decrease AP and lower the rate of progression to cirrhosis when compared to patients with AIH alone.[4,28,46] Treatment with UDCA also slowed progression of fibrosis, depending on the severity of disease when therapy began; better responses were associated with start of treatment at earlier stage disease.[4] Those patients who have histological findings of both PBC and AIH tend to progress faster.[4] A treatment regimen using a combination of UDCA and steroids, compared with either alone, has been associated with greater improvement in lab abnormalities (in 67% vs 27%), greater ability to prevent fibrosis (100% vs 50%), and excellent 5 & 10 year transplant free survival (100 and 92%, respectively).[4,25,40] However, a meta-analysis of 8 small randomized control trials with a total of 214 AIH-PBC patients showed that there was no statistically significant difference in response between UDCA and combination therapy for pruritus and jaundice; those who received

Table 4. Paris Criteria – Need 2 out of 3 criteria from each column to diagnose AIH-PBC[44]

PBC	AIH
AP 2x ULN or GGT 5x ULN	ALT 5x ULN
+AMA	IgG 2x ULN or +ASMA
Florid bile duct lesion on biopsy	Biopsy with moderate-severe periportal or periseptal lymphocytic piecemeal necrosis

combination therapy had greater improvement in their ALT, AP and slower progression of disease on histology but also had higher likelihood of mortality and increased need for liver transplant.[47] There was no difference in occurrence of adverse events. Great response to UDCA and corticosteroids with normalization of lab parameters and decreased frequency of liver failure has been noted in patients with AMA-negative PBC with AIH as well.[25,48] A Japanese study that looked at predictors for nonresponse to steroid treatment found that patients with a high baseline AP, negative ASMA and positive gp210 antibody were less likely to have improvement in liver enzymes or liver histology.[49] EASL recommends using UDCA or combination of both UDCA and corticosteroids as initial therapy.[25] For patients on UDCA only who have a partial response or no response after 3 months, they recommend adding corticosteroids.[4,39] There have been some studies that found no difference on survival or improvement of biochemical parameters for patients who received UDCA or combination therapy.[4]

In patients with AIH who do not respond to immunosuppressive treatment, it is important to evaluate for a concurrent diagnosis of PSC.[28] For patients with AIH-PSC, combination therapy with UDCA and corticosteroid is recommended by EASL while AASLD only recommends immunosuppressive medications.[4,27,35] Their recommendations are not evidence-based since there are no prospective randomized controlled studies on treatment options in this rare disease. Children with AIH-PSC usually respond better to immunosuppressive therapy than adults.[4] Clinicians may consider treating their AIH-PSC patients initially with steroids but these patients tend to have inconsistent response when compared to patients with AIH alone.[1] The data on the effectiveness of combination therapy with UDCA and corticosteroid for patients with AIH-PSC has been conflicting, with response rates ranging from 20% to 100%.[27] AIH-PSC patients treated with both UDCA and immunosuppressive therapy (corticosteroid and/or azathioprine) may have greater improvement of ALT and AP compared with no treatment.[50] Combination therapy in AIH-PSC patients has also been associated with a decreased need for liver transplant, risk for malignancy and death compared with patients with PSC only.[51] However, other studies have shown that AIH-PSC patients who experience a biochemical response after receiving combination therapy with UDCA and an immunosuppressant may not necessarily alter the course of their disease.[28,29,35]

While the corticosteroid medication that is typically used is prednisone, budesonide has also been studied for treatment of patients with AILD variants. In a French study, 41% of AIH-PBC patients who had inadequate response to UDCA and were treated with a combination of Budesonide and mycophenolate mofetil (MMF) experienced normalization of their biochemistries while 47% had ALT decreased to less than 70 IU/L.[37,52] Histological improvement was also noted over time.[37,52] However, budesonide was found to be less effective if liver tissue was fibrotic already.[25,53] In fact, budesonide is contraindicated in cirrhotic patients due to portal systemic shunting and loss of first pass metabolism.[27]

For patients who do not respond to conventional therapy, salvage treatment may be attempted using cyclosporine at 3 mg/kg or MMF 1-3 g/d empirically.[25] A small group of patients with AIH, one potentially with AIH-PSC, who failed corticosteroids and/or Azathioprine were treated with cyclosporine and saw normalization of ALT in 10 weeks along with histological improvement.[54] MMF has been shown to be effective in some AILD variant patients and may be considered as a second line treatment option.[27,35] In one study of patients treated with MMF due to intolerance or nonresponse to azathioprine, 57% of non-responders went into remission while 63% of patients intolerant to azathioprine went into remission.[55]

Endoscopic Therapy

ERCP may be warranted to treat complications associated with dominant strictures in AIH-PSC patients like in classic PSC.[5] Dilation and stenting of the bile duct may be performed during ERCP for treatment of acute cholangitis.[35]

Patients who progress to cirrhosis will require endoscopic screening and surveillance for varices.

Liver Transplant

AILD is the indication for one quarter of all liver transplants performed in the United States

according to a review in 2011.[35,56] The reasons why patients with AILD variants may need to have a liver transplant is the same as for patients with classic AILD, including end stage liver disease (ESLD), intractable pruritus, recurrent bacterial cholangitis and cholangiocarcinoma.[35] It appears that liver transplant is rarely needed in AILD variants. In Japan, living donor liver transplants in AILD were evaluated and 4 out of 375 were performed in AILD variant patients.[57] In one Canadian study only 1% of all liver transplants performed over 20 years were for patients with an AILD variant.[58] These patients tended to be younger, of female gender and had shorter time to liver transplant than those with classic AILD. They were also found to have high likelihood of disease recurrence several years post-transplant, faster time to recurrence and lower graft survival. Patient survival was not significantly different on multivariate analysis.

Investigational Therapies

The potential effectiveness of medical therapies for treatment of AILD variants may eventually be able to be extrapolated from investigations performed in patients with AIH, PBC or PSC. There has not been any randomized controlled trial performed specifically in patients with AILD variants as of yet.

Medical therapies that have been investigated in patients with AIH who failed conventional therapy and salvage therapies include tacrolimus, sirolimus, everolimus, rituximab, and infliximab.[5,27] Tacrolimus, a calcineurin inhibitor, has been shown to be effective in patients with only partial response to or intolerance to conventional treatment, or who were steroid refractory. In several small studies it significantly decreased ALT and induced histological remission even in the setting of cirrhosis, with mild side effects and rare serious adverse reactions.[59,60,61,62] Similar effects on ALT and lower steroid requirement were seen in a small number of patients treated with inhibitors of mammalian target of rapamycin, sirolimus and everolimus, respectively.[27] Rituximab, a monoclonal antibody to CD20 on B cells, was incidentally found to be effective in 2 AIH patients who were being treated for a coincident autoimmune disorder.[63,64] A subsequent single center study with rituximab in AIH patients refractory to conventional therapy showed significant decreases in AST, IgG and inflammation on biopsy.[65] AIH patients who were refractory to conventional treatment were treated at a single center with Infliximab and showed decreased ALT and IgG levels.[66] Basic science research targeting cell signaling pathways for lymphocyte activation, immune cell apoptosis, enzymatic processes that promote fibrosis, and manipulation of T cells in animal models, among other innovations, are ongoing.[38]

Obeticholic acid, a farnesoid X receptor agonist, was approved by the FDA in May 2016 for treatment of PBC based on its significant reduction of AP when compared to placebo.[67] It is indicated for use in combination with UDCA, in those who had a partial response to UDCA or as monotherapy for those patients who are unable to tolerate UDCA. The COBALT Phase 4 study looking at the medication's effect on clinical outcomes such as improvement of disease related symptoms or overall survival is ongoing.[68] At the time this review was drafted, there have not been any published data on effectiveness in patients with AIH-PBC but it could potentially be a new therapy for AIH-PBC. Obeticholic acid is also under current investigation for treatment of PSC.[14]

Vedolizumab, a monoclonal antibody against α4β7 integrin, was investigated in patients with PSC. α4β7integrin is a cell surface glycoprotein expressed on B and T cells and it is involved in leukocyte trafficking in the intestine as well as the liver.[69] This medication has been approved for treatment of moderate to severe Crohn's disease and ulcerative colitis that has not responded to conventional therapies.[69,70,71] From the limited data put forth in 2 abstracts in 2016 it was shown that this medication can lead to improved AP and baseline fatigue but not to AST, total bilirubin or pruritus.[72,73] Unfortunately one abstract was subsequently retracted in January 2017 due to concerns of inconsistencies with their source data and the phase 3 clinical trial was withdrawn prior to enrollment.[74,75] Some other novel treatments for PSC currently under investigation in clinical trials will target pro-fibrotic enzyme, apical sodium-dependent bile acid transporter in the gut, vascular adhesion protein important for T cell signaling in the gut, and altering the gut microbiota.[14]

Prognosis

For the patients with AILD variants who are fortunate enough to experience clinical improvement of their disease through medical treatment, the topic of treatment end points or medication withdrawal will likely come up especially given the serious long term side effects of corticosteroids and immunomodulators. Sustained remission is defined as normal biochemical parameters and histology for more than 12-24 months.[27] Histological improvement may lag behind biochemical normalization by as much as 8 months.[27] However, very few patients are able to achieve sustained remission of disease upon permanent withdrawal of medications. Withdrawal of medical therapy may be attempted but there is a high risk of recurrence of disease that may potentially be more severe. The risk factors for relapse include need for combination therapy, co-existing autoimmune condition, younger age at withdrawal, and cirrhosis.[27]

The prognosis of AIH-PBC patients who respond to treatment is excellent. In the Japanese study, 15 out of 20 patients responded to treatment with steroids while 5 did not.[49] All non-responders experienced progression of their disease, while those who responded had 100% transplant free survival at both 5 years and 10 years, compared to 81% and 54% in non-responders. Compared to patients with PBC, those with AIH-PBC tend to have higher rates of portal hypertension, esophageal varices, gastrointestinal bleeding, ascites, death or need for liver transplant.[24] In essence, those with AIH-PBC have slightly worse outcomes compared to patients with PBC but have similar prognosis to patients with AIH.[76]

Ten year survival for treated AIH is excellent compared to those with AIH-PSC.[1] AIH-PSC patients will likely develop cirrhosis after 10 years.[35] On the other hand, those with AIH-PSC tend to fare better than patients with PSC alone.[29,35] This was shown in a prospective Italian study; AIH-PSC patients were less likely to develop neoplasm or die compared to those with PSC.[76] Part of the reason for their worse prognosis may be that patients with AIH-PSC are less likely to go into remission despite treatment when compared to patients with AIH alone.[77] Those who do not respond to treatment have higher mortality and liver transplant rates.[4] Additionally, patients with AIH-PSC who experience biochemical improvement on treatment may not experience better clinical outcomes. A German case series that followed 16 patients for 12 years noted improvement of ALT within 6 months of immunosuppression but the majority of them also had progression to cirrhosis on biopsy.[51] Though there have not been any reported cases of cholangiocarcinoma, gallbladder carcinoma or colorectal cancer in patients with AIH-PSC, recommendations for surveillance are the same as for patients with PSC.[35,51]

SUMMARY

It has been difficult to learn about the underlying cause, pin down defining features and establish evidence based treatments for AILD variants due to their low prevalence. Much of what has been published about these disorders has been derived from small case series or retrospective reviews using information extrapolated from classic AILDs, like AIH, PBC and PSC. Some of the data may be applicable while other parts may not. What is important to note is that treatment for AILD variants is different from their classic counterparts and administering the appropriate therapy may impact a patient's clinical outcome. Further research into this set of disorders is certainly indicated. ■

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