Autoimmune hepatitis variants: Definitions and treatment

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INTRODUCTION

Patients with variant forms of autoimmune hepatitis have clinical and serologic findings of autoimmune hepatitis plus features of other forms of chronic liver disease. As will be discussed below, the taxonomy of these variants (often referred to as overlap syndromes) is controversial. The overlap syndromes of autoimmune hepatitis with primary biliary cholangitis and primary sclerosing cholangitis will be reviewed here. The discussion is generally consistent with an international consensus statement published in 2011 [1].

DEFINITIONS

Autoimmune hepatitis is a chronic hepatitis of unknown etiology characterized by hyperglobulinemia, the presence of circulating autoantibodies, and inflammatory changes on liver histology [2]. Most cases respond to therapy with immunomodulating drugs such as prednisone and azathioprine or 6-mercaptopurine. (See "Management of autoimmune hepatitis".)

Patients with certain cholestatic liver diseases (such as primary biliary cholangitis [PBC] and primary sclerosing cholangitis [PSC]) have clinical and serologic features suggesting the presence of autoimmune hepatitis and also may respond to immunosuppressive therapy. Conversely, some patients with features predominantly suggesting autoimmune hepatitis have

findings compatible with other forms of chronic liver disease. In a report from the Mayo Clinic, for example, 225 patients with either type I autoimmune hepatitis, PBC, or PSC (162, 37, and 26 patients, respectively) defined by standard criteria, were analyzed for serologic and clinical features suggesting variant forms of autoimmune hepatitis [3]. Among these patients, 18 percent had diseases with overlapping features, including:

- 7 percent with autoimmune hepatitis/PBC
- 6 percent with autoimmune hepatitis/PSC
- 11 percent with autoimmune hepatitis/autoimmune cholangitis

The nomenclature and diagnostic criteria for these variant forms of autoimmune hepatitis have not been standardized, making interpretation and comparison among studies difficult. Despite these difficulties and the lack of a well-established gold standard, overlaps of autoimmune hepatitis with PBC and PSC have been widely recognized (table 1) [4-6]. Some authorities also recognize additional overlap syndromes, including "autoimmune hepatitis-cryptogenic hepatitis," "autoimmune hepatitis-sarcoidosis," and "autoimmune hepatitis-chronic hepatitis C" [7]. However, the existence of these disorders as distinct overlap syndromes is less clear. A 2011 international consensus statement proposed that autoimmune liver disease be categorized as autoimmune hepatitis PBC, PSC/small duct primary sclerosing cholangitis, noting that patients with PSC or PBC who have features of autoimmune hepatitis be considered for immunosuppressive treatment [1].

SCORING SYSTEMS

A scoring system proposed by the International Autoimmune Hepatitis Group has had excellent test characteristics for diagnosing autoimmune hepatitis. Its accuracy in diagnosis of autoimmune hepatitis variants requires further study. At present, an international consensus statement recommends that it not be used to subclassify autoimmune hepatitis into variants [1] (see "Overview of autoimmune hepatitis"). Another classification system, the Paris diagnostic criteria [8], performed better than the International Autoimmune Hepatitis Group system in one validation study, but more data are needed [9].

AUTOIMMUNE HEPATITIS-PBC OVERLAPS

Immunologic and clinical characteristics suggest a variant form of autoimmune hepatitis in 1 to 14 percent of patients with primary biliary cholangitis (PBC) [3,10,11]. Features of autoimmune hepatitis may be present at diagnosis or develop during follow-up; clinical recognition is

somewhat easier in the latter case. PBC may also develop in patients who present with autoimmune hepatitis [10]. (See "Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis".)

Patients with autoimmune hepatitis-PBC overlap generally fall into two categories:

- Patients who have histologic features of autoimmune hepatitis, but have the serologic findings of PBC (ie, antimitochondrial antibodies [AMA] directed toward enzymes in the 2-oxoacid dehydrogenase family) [12]. The clinical course and response to therapy in this variant, which is sometimes referred to as AMA-positive autoimmune hepatitis, appear to be almost identical to that seen in type 1 autoimmune hepatitis [13].

- Patients who have histologic features suggesting PBC, but are often seronegative for AMA and generally have circulating antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA). This category has been referred to by a variety of terms, including immune cholangiopathy, autoimmune cholangiopathy, immune cholangitis, and autoimmune cholangitis [8,14-18]. However, some authorities do not accept the concept of overlap in this situation and consider this syndrome to be AMA-negative PBC [8,17]. Furthermore, some of these patients have detectable AMA when using the most sensitive assays [19].

These distinctions have not been apparent in all reports. In one study, for example, the serologic and histologic features of 20 patients with autoimmune hepatitis-PBC overlap (based upon histologic or serologic criteria) were compared with 20 patients with typical PBC and 20 patients with typical autoimmune hepatitis [20]. On careful evaluation, the majority of overlap patients had disease more closely resembling PBC. The authors hypothesized that patients with autoimmune hepatitis-PBC overlap have underlying PBC but have a genetic predisposition to develop a more hepatitic pattern of liver histology; they propose the term "PBC, hepatitic form" to describe these patients.

Similar conclusions were reached in another report that focused on a subset of 16 of 331 patients (4.8 percent) who had participated in a multicenter placebo-controlled trial of UDCA for PBC [21]. The patients (all of whom were AMA-positive) also had features suggestive of autoimmune hepatitis, including two or more of the following:

- Serum alanine aminotransferase >5x the upper limit of normal
- Immunoglobulin G (IgG) >2x the upper limit of normal or positive anti-smooth muscle antibodies
- Moderate to severe lobular inflammation on pretreatment liver biopsy

At the end of two years, the median change in serum biochemical and IgM values were similar to the PBC patients without these autoimmune features. Improvement in biochemical values and serum IgG levels were also observed in the "overlap" patients who received placebo. Furthermore, little change in histologic features of autoimmune hepatitis was observed. The authors concluded that the above features of autoimmune hepatitis may be transient in patients with PBC and that such patients may have a similar response to ursodeoxycholic acid (UDCA) as PBC patients without these features. These results suggest that the value of adding corticosteroids to the treatment regimen of such patients is questionable.

One group found that patients with autoimmune hepatitis-PBC overlap were more likely to have concomitant AMA/anti-dsDNA seropositivity than patients with pure AMA-positive PBC (47 versus 2 percent). AMA/ANA positivity was present in 60 percent of these overlap patients [22]. Such patients responded to combination therapy with UDCA and glucocorticoids.

In an attempt to clarify the serologic profile of patients who were considered to have autoimmune hepatitis-PBC overlap, one group evaluated 174 patients (79 AMA-negative and 95 AMA-positive) with extensive serologic testing for a variety of autoantibodies. The serologic profile was compared with histologic and biochemical findings. The authors concluded that there were three distinct subgroups of patients [23]:

- AMA-positive or AMA-negative patients with ANA-PBC-related antibodies
- AMA-negative patients with non-PBC-related ANAs
- Patients with autoimmune hepatitis-related antibodies together with serum PBC markers

Whether these categories are important clinically is uncertain. One group suggested that autoimmune hepatitis superimposed upon PBC can result in rapid progression to cirrhosis and liver failure [10]. Another group found that patients with overlap were more likely to develop esophageal varices, gastrointestinal bleeding, ascites, and liver failure compared with patients with more classical PBC [24]. Further studies will be needed to see whether these groups have a different natural history or response to treatment.

AUTOIMMUNE HEPATITIS-PSC OVERLAPS

Patients with autoimmune hepatitis-primary sclerosing cholangitis (PSC) overlap have serologic features of autoimmune hepatitis but have cholangiographic abnormalities characteristic of primary sclerosing cholangitis [25-30]. The proportion of patients with autoimmune hepatitis who have PSC overlap is not well established. A study that included 79 adults with autoimmune hepatitis found that 10 percent had features consistent with PSC on magnetic resonance

cholangiography and liver biopsy [30]. By contrast, only 1.7 percent of 59 adults with autoimmune hepatitis had cholangiographic abnormalities suggestive of PSC in a later report [31]. Studies in children with PSC or autoimmune hepatitis have described overlap in an even higher proportion of patients with overlapping features (30 to 50 percent) and are frequently labeled autoimmune sclerosing cholangitis [29,32].

Overlap should be suspected in patients who have clinical and serologic features of autoimmune hepatitis and also have [7]:

- Pruritus
- Chronic ulcerative colitis (present in up to 16 percent of patients with autoimmune hepatitis [33])
- Bile duct abnormalities on histology (such as portal edema, cholestasis, and fibrous or obliterative cholangitis)
- Cholestatic laboratory changes (an alkaline phosphatase greater than twice the upper limit of normal)
- No response to corticosteroid therapy
- An abnormal cholangiogram (present in up to 42 percent of patients with autoimmune hepatitis and ulcerative colitis [33])

Overlap should also be suspected in patients diagnosed with PSC who have high levels of immunoglobulin G, circulating antinuclear antibodies or smooth muscle antibodies (titer >1:40), and moderate to severe interface hepatitis on liver biopsy [28]. Evolution from autoimmune hepatitis to primary sclerosing cholangitis has also been described [34].

One study compared the clinical features of 7 patients with autoimmune hepatitis-PSC with 34 patients with classical PSC [35]. Patients with autoimmune hepatitis-PSC were significantly younger at presentation (mean age 21 versus 32), had significantly higher aminotransferases, prevalence of autoantibodies, and serum immunoglobulin levels. The authors stressed the difficulty in establishing the diagnosis. All patients had clinical features of autoimmune hepatitis at presentation, while PSC was diagnosed subsequently when immunosuppression failed to achieve clinical remission.

TREATMENT

Patients who have antimitochondrial antibodies (AMA)-positive autoimmune hepatitis-primary biliary cholangitis (PBC) overlap should be treated like patients with classic type 1 autoimmune hepatitis; such patients usually respond to corticosteroids [13] (see "Management of

autoimmune hepatitis"). In contrast, patients with autoimmune hepatitis AMA-negative PBC generally respond poorly to corticosteroids. The approach below is generally consistent with the approach suggested by the International Autoimmune Hepatitis Group (algorithm 1) [1].

AMA-positive without histologic evidence of PBC — Treatment is usually initiated with 20 to 30 mg of prednisone (or its equivalent) per day [13] (see "Management of autoimmune hepatitis"). Younger patients with severe disease may sometimes require higher doses, which are associated with an increased risk of major side effects. In older patients who may tolerate steroid side effects poorly, initial therapy using a combination of a glucocorticoids and azathioprine may be preferable. (See "Major side effects of systemic glucocorticoids".)

The goal of therapy should be to obtain normal serum aminotransferase levels and histologic improvement. Normalization of serum aminotransferases usually occurs rapidly (often within one month) and within six months in almost all patients who are destined to respond. Once normal serum aminotransferases are established, patients are maintained on the lowest dose of corticosteroids possible to maintain normal values. We usually perform a follow-up liver biopsy one to two years after initiating treatment to be sure that the biochemical response is accompanied by histologic improvement.

In addition to attention to the usual adverse effects of steroid therapy, patients should be monitored for bone loss. (See "Prevention and treatment of glucocorticoid-induced osteoporosis".)

In some cases (usually after one to two years) therapy may be withdrawn without subsequent relapse. Azathioprine may be effective as maintenance monotherapy although, in our experience, higher doses may be required compared with those used in type 1 autoimmune hepatitis.

ANA and/or SMA-positive with histologic changes suggesting PBC — Glucocorticoids and ursodeoxycholic acid (UDCA) have been recommended for treatment of patients with autoimmune hepatitis-PBC overlap whose liver histology is consistent with PBC. In a series of four patients, three responded rapidly to corticosteroids [14]. However, subsequent reports and our own experience suggest that the majority of patients do not respond to corticosteroids [8].

UDCA alone may improve serum biochemical values. However, it is unclear if UDCA mitigates the necroinflammatory process and retards progression of the disease. It has been suggested that combining UDCA and corticosteroids has a synergistic effect. The combination of the two drugs was associated with further biochemical improvement and resolution of symptoms in a series of 11 patients with incomplete histologic and biochemical response to UDCA or prednisone alone [8]. In a later series from the same group, combination therapy with UDCA

plus immunosuppression appeared to be more effective than UDCA alone in improving or stabilizing liver histology, with up to seven years of follow-up in those patients conforming to a strictly defined autoimmune hepatitis-PBC syndrome [36].

A reasonable approach to treatment of patients with autoimmune hepatitis-PBC overlap is a trial of corticosteroids. Even though only a minority of patients will respond, biochemical and histologic improvement may be achieved. If values of serum aminotransferases and alkaline phosphatase do not improve, corticosteroids should be discontinued, and treatment initiated with UDCA (13 mg/kg per day). In addition, UDCA and/or azathioprine may be added as steroid-sparing agents in patients who respond to corticosteroids. We often perform a follow-up liver biopsy after one to two years of treatment to document histologic amelioration in responding patients.

The role of other drugs is even less well defined [16,37]. In a case report, the addition of cyclosporine appeared to be beneficial in a patient with autoimmune hepatitis-PBC overlap syndrome who did not respond to corticosteroids and UDCA [16].

Autoimmune hepatitis-PSC overlap — The experience with corticosteroids and other immunomodulators for patients with autoimmune hepatitis (AIH)-primary sclerosing cholangitis (PSC) have been limited to small case series. Most have indicated that such patients respond poorly to treatment.

Corticosteroids alone are unlikely to result in clinical, biochemical, and histologic remission. In a report from the Mayo Clinic that included nine such patients, clinical remission was observed in only two patients following corticosteroid treatment [3]. Response was more likely if patients had lower levels of alkaline phosphatase and higher serum concentrations of gamma globulin and immunoglobulin G.

Regimens that include corticosteroids with azathioprine may be more effective than corticosteroids alone. A series of five patients showed marked responses to combinations of prednisolone and azathioprine, with relapses occurring during reduction or withdrawal of treatment [28]. In contrast to the study from the Mayo Clinic, all five patients fulfilled criteria for "definite" autoimmune hepatitis. Another report of three patients found a beneficial response to a regimen consisting of corticosteroids, azathioprine, and UDCA [27].

A third report compared the clinical course of 7 patients with AIH-PSC with 34 patients with classical PSC [35]. Patients with AIH-PSC were treated with a combination of UDCA, corticosteroids, and azathioprine while patients with classical PSC received UDCA alone. The Mayo score increased progressively in the classical group but remained stable in the overlap group during five years of follow-up. Serum AST decreased significantly in the AIH-PSC group

but other liver biochemical tests were not significantly improved. No significant change in liver biochemical tests was observed in the classical PSC group. There were no deaths in the AIH-PSC group compared with nine in the classical group, suggesting better cumulative survival for AIH-PSC but the sample size was small.

A separate study evaluated the long-term outcomes of patients with AIH-PSC overlap seen at King's College Hospital over a 35-year period [38]. A reduction in survival was identified between patients with AIH-PSC and those without, including patients with AIH-PBC (hazard ratio: AIH-PSC versus AIH = 2.08, AIH-PSC versus AIH-PBC = 2.14; p = 0.039).

In children with refractory autoimmune liver disease, rescue therapy with mycophenolate mofetil appears to be less effective in those with autoimmune sclerosing cholangitis than in autoimmune hepatitis [39].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Autoimmune hepatitis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Autoimmune hepatitis (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- The nomenclature and diagnostic criteria for variant forms of autoimmune hepatitis have not been standardized, making interpretation and comparison among studies difficult. Despite these difficulties and the lack of a well-established gold standard, overlaps of autoimmune hepatitis with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) have been widely recognized. (See 'Definitions' above.)

- Patients with these variant forms of hepatitis can have a confusing serologic and histologic profile. Diagnosis is generally easier when overlapping disorders occur sequentially over time compared with when they present concurrently. Furthermore, treatment is based upon somewhat subjective interpretation of serologic and biopsy findings and assessment of response to empiric pharmacologic trials. As a result, such patients are probably best managed in referral centers.

- Our approach is generally consistent with a consensus statement from the International Autoimmune Hepatitis Group (algorithm 1). In patients who are antimitochondrial antibodies positive but histologically appear to have autoimmune hepatitis rather than PBC, we suggest treatment for autoimmune hepatitis (**Grade 2C**). (See "Management of autoimmune hepatitis".)

- In patients who are antinuclear antibodies and/or smooth muscle antibodies positive who have histologic changes suggesting PBC with concomitant features of autoimmune hepatitis, we suggest a trial of corticosteroids (**Grade 2C**). In patients who do not respond biochemically, we suggest discontinuing steroids with a taper and adding ursodeoxycholic acid.

- In patients with autoimmune hepatitis-PSC overlap, optimal treatment is uncertain. Our treatment decision is highly influenced by the findings on liver biopsy. In patients who have features of autoimmune hepatitis, namely significant interface hepatitis, we suggest a trial of corticosteroids (**Grade 2C**).

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Topic 3636 Version 26.0

GRAPHICS

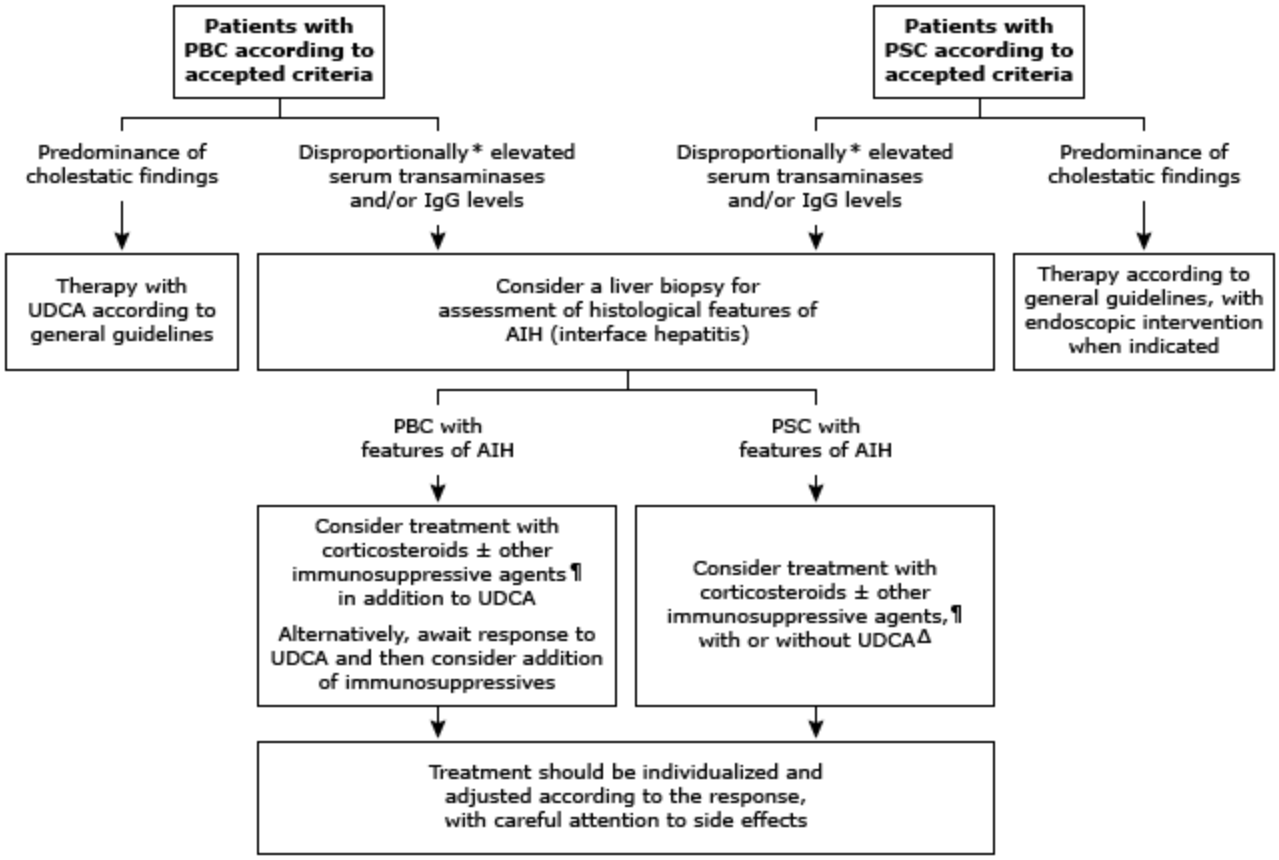
Autoimmune hepatitis overlap syndromes

Autoimmune hepatitis-primary biliary cholangitis overlap
a. AMA-positive with histological evidence suggesting autoimmune hepatitis but not primary biliary cholangitis
b. ANA and/or SMA-positive with histologic changes suggestive of primary biliary cholangitis (autoimmune cholangitis)
Autoimmune hepatitis-primary sclerosing cholangitis overlap

AMA: antimitochondrial antibodies; ANA: antinuclear antibodies; SMA: smooth muscle antibodies.

Graphic 80676 Version 2.0

Approach to patients with PBC or PSC and features of AIH



Refer to UpToDate content on the management of patients with autoimmune hepatitis variants and overlap syndromes.

PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; UDCA: ursodeoxycholic acid; AIH: autoimmune hepatitis; EASL: European Association for the Study of the Liver; ULN: upper limit of normal.

* There are no established definitions of the required degree of elevation of serum transaminases or IgG levels. ALT at least 5×, ULN and IgG at least 2× ULN, as previously suggested as criteria for AIH, may serve as guidelines.

¶ Immunosuppressive treatment is not evidence-based. It can be suggested that initial treatment is given according to guidelines for AIH.

Δ The American Association for the Study of Liver Diseases guidelines recommend against UDCA in patients with PSC, whereas the EASL guidelines acknowledge that UDCA is widely used in PSC, although the long-term efficacy remains unproven.

Graphic 73139 Version 5.0

Contributor Disclosures

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