Review Article

Overlap Syndromes: An Emerging Diagnostic and Therapeutic Challenge

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ABSTRACT

Overlap syndrome in hepatology is emerging as a diagnostic and therapeutic challenge, which is further complicated by the present gaps in the information regarding the immunopathogenesis of these diseases. The present review represents a concise review of literature on overlap syndromes with emphasis on prevalence, etiopathogenesis, clinical presentation, diagnosis, and management of true overlap syndromes.

Keywords: Autoantibodies, autoimmune, biliary, overlap

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Autoimmune liver diseases are a group of disorders characterized by aberrant, self-directed immune response on hepatocytes or cholangiocytes, subsequently leading to fibrosis and cirrhosis. The three main categories of autoimmune liver diseases are autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC), each regarded as a distinct entity with constellation of specific clinical, biochemical, immunological, and histological profiles. The characteristic histological patterns are a chronic hepatitis pattern of injury with prominent plasma cells in AIH, destruction of small intrahepatic bile ducts and canals of Hering in PBC, and periductal fibrosis and inflammation involving large bile ducts with variable small duct damage in PSC. Serological findings include the presence of antimitochondrial antibody (AMA) in PBC, antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA) and anti-liver kidney microsome (LKM)-1 antibody in AIH, and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) in PSC.[1] Overlap syndrome describes variant forms of AIH and autoimmune cholangiopathies with composite hepatic and cholestatic profiles of AIH and PBC or PSC that do not fit readily into the usual diagnostic categories.[2,3]

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In addition to AIH-PBC and AIH–PSC overlap syndromes, autoimmune cholangitis (AIC; AMA negative PBC) as outlier syndrome[4] and transition from one autoimmune hepatopathy to another (e.g. PBC to AIH,[2,5] AIH to PBC, and AIH to PSC)[6,7] as sequential syndrome have been described.[8,-11] The term overlap syndrome should not be used when comorbidity, for example, chronic hepatitis C in a patient with PBC or sarcoidosis in a patient with PSC or hepatitis C with nonalcoholic steatohepatitis, exists.[12] The problems faced while diagnosing overlap syndromes include presence of features of AIH in many patients of PBC [mild interface hepatitis, raised immunoglobulin G (IgG)] and presence of raised immunoglobulin M (IgM) and AMAs in patients of AIH.[13-16] These overlap syndromes represent a diagnostic and therapeutic challenge as no established serological, biochemical, or histological markers have been accepted equivocally. Nevertheless, it is important to recognize these clinical entities as it has important therapeutic and prognostic implications.[17] The present review represents a concise review of literature on overlap syndromes with emphasis on prevalence, etiopathogenesis, clinical presentation, diagnosis, and management of true overlap syndromes. AIC (outlier syndrome) and AIH–AIC are not described here as they represent a heterogeneous category that encompasses patients with atypical, early, or transitional features of classical disease.[18]

EPIDEMIOLOGY OF OVERLAP SYNDROMES

Overlap syndromes, previously thought to be a rare entity, have been the subject of various studies in the last decade. Some formal studies suggest that nearly 20% of patients with

an autoimmune liver disease have, at presentation, features suggestive or characteristic of a second autoimmune liver disease, that is, they present with overlap syndrome.[19] The existence of PBC–AIH overlap was reported around 35 years back.[20] Since then, a number of PBC–AIH overlap patients have been described in genetically and environmentally different geographic areas, such as Europe,[2,3,21-23] Turkey,[24] United States,[25,26] Canada,[27] Japan,[28] India,[11,29] and China.[30] Chazouilleres *et al.* provided evidence for AIH–PBC overlap in 8% of 199 patients with AIH ($n = 162$) or PBC ($n = 37$) and in 9% of 130 patients with PBC.[2] A recent analysis of a smaller cohort of 82 consecutive patients with definite or probable AIH based on the revised AIH score of International Autoimmune Hepatitis Group (IAIHG)[31] found overlap with PBC in 13% of patients.[22] Another comparative study by Heurge *et al.* demonstrated a prevalence of 13.9% of overlap syndrome in patients of PBC and AIH ($n = 115$).[23]

In short, occurrence rate of overlap syndrome ranges from 5% of patients initially diagnosed as having AIH to 19% of patients initially diagnosed as having PBC.[32] Contrary to AIH–PBC overlap, AIH–PSC overlap syndromes are more common in young patients with autoimmune liver disease and may comprise 6% of patients with AIH and 8% of patients with PSC.[33-36]

In a landmark 16-year prospective study conducted in Kings College, London, authors followed-up a group of 55 children with AIH. Among these children, 23 presented cholangiographic findings typical of PSC. This overlap of AIH and PSC was termed autoimmune sclerosing cholangitis (ASC).[6] In adult patients of AIH, histological changes of lymphocytic, pleomorphic, or fibrous cholangitis, concurrent inflammatory bowel disease (IBD), or failure to respond to glucocorticoids constitute indications for cholangiography. Around 41% of these patients demonstrate changes of PSC. Furthermore, 54% of patients who have PSC have histological features that support a probable or definite diagnosis of AIH.[9,19,32,37] In a recent study, magnetic resonance cholangiography has demonstrated unsuspected PSC of large bile ducts in 8% of adults with AIH.[38] PBC–PSC and AIH–AIC overlap syndrome/coexistence have been described in certain case reports.[39-42]

AIH–PBC OVERLAP SYNDROME

AIH–PBC overlap syndromes are the most common ones among autoimmune hepatopathies, with a reported prevalence of 4.8–19% in PBC patients and 5–8.3% in AIH patients.[2,25,27,32,43]

Etiology

Both PBC and AIH share an autoimmune pathogenesis. Lohse *et al.* identified human leukocyte antigen (HLA), B8;DR3;DQ2 haplotype as a risk factor for the development of AIH–PBC overlap.[3]

Preliminary studies have been done to define genetic susceptibility and immunopathogenesis in AIH–PBC overlap syndrome, though no conclusive evidence has been presented so far.[44,45] A recent report suggests that HLA DR7 could help in differentiating the overlap syndromes from pure AIH.[46]

Clinical presentation

Simultaneous presence of features of both AIH and PBC at initial presentation is the most frequent and easily recognizable form of overlap syndrome.[17] There are reports of AIH and PBC occurring sequentially or consecutively,[10,47-52] or appearing after liver transplantation done for a different autoimmune hepatopathy.[53-57] Patient of AIH–PBC overlap presenting with fulminant hepatic failure as the initial form of presentation has also been reported.[58] Patients with features of PBC–AIH overlap have been reported to be at greater risk of developing symptomatic portal hypertension [with esophageal varices, gastrointestinal (GI) bleeding, and ascites] and having an adverse outcome (death and/or orthotopic liver transplantation).[26]

Interestingly, the reports describing AIH–PBC overlap do not discuss any specific clinical features that distinguish overlapping PBC–AIH overlap versus PBC or AIH alone, but the focus has entirely been on laboratory and histological features.[3]

Laboratory features

The biochemical features of patients with the AIH–PBC overlap syndrome include high serum levels of transaminases plus markers of cholestasis and increased levels of IgM and IgG.[52] Histologically, features of both diseases are evident, i.e. interface hepatitis and bile duct destruction.[52] The usefulness of IgG and IgM immunostaining for the distinction of AIH and PBC and their staining pattern in cases of AIH–PBC overlap syndrome have been investigated in certain studies, but no conclusive evidence has been found.[59]

Serologically, there is positivity for ANA, ASMA, and AMA. Although ANA positivity is seen in 40% of pure PBC patients also, the pattern is specific for the disease (multiple nuclear dots).[60,61] Although a systemic and complete analysis of the serological profile of cases of AIH–PBC overlap syndrome is lacking, in a recent study, Muratori *et al.* compared the serological profiles of PBC ($n = 120$), AIH ($n = 120$), and AIH–PBC overlap syndrome patients ($n = 15$), and found a high frequency of anti-dsDNA antibodies in overlap syndrome patients (60%) compared to that in patients suffering from pure form of the disease (4% in PBC and 26% in AIH).[62]

In another report, in a small subgroup (3.9%) of 233 patients with PBC, the presence of soluble liver antigen antibodies (SLA/LP) was a marker of AIH–PBC overlap syndrome with a good response to immunosuppressive therapy,[63] although these findings were not validated by other groups.[64] Furthermore, a study of immunoreactivities of AMA against branched chain acyltransferase in the sera of patients with PBC and AIH–PBC overlap syndrome demonstrated absence of immunoreactivity against C-terminal sequences of the enzyme in overlap patients compared to those with pure forms of disease, which may serve as a marker for differentiating patients with PBC from those with overlap syndrome of PBC with AIH.[65]

Diagnosis

To diagnose AIH–PBC overlap syndrome, there are three different proposals to date:

1. The simple fulfillment of the IAIHG score in PBC patients[21]
2. The inclusion criteria suggested by Lohse *et al.*, which are as follows:[3]
   - Presence of bile duct damage and hepatic lesions in the biopsy specimen of AMA-positive patients
   - Alanine aminotransferase (ALT) levels above twice the normal in an AMA-positive patient or the presence of high-titer ANA or ASMA or any titer SLA/LP autoantibodies in an AMA-positive patient.

   The criteria proposed by Chazouilleres *et al.* (Paris criteria)[2]
3. An AIH–PBC overlap syndrome is accepted when two or three criteria of PBC as well as AIH are fulfilled. For PBC:
   Alkaline phosphatase (ALP) >2 times the upper normal limit or gamma-glutamyl transferase (GGT) >5 times the upper normal limit
   AMA positivity
   Florid bile duct lesions.

   For AIH:
   ALT > 5 times the upper reference range, IgG > 2 times the upper reference range, or ASMA positivity
   Portal or periportal lymphocytic inflammation and moderate to severe periportal lymphocytic piecemeal necrosis

Out of these, the criteria suggested by Lohse *et al.* are very subjective. For the use of IAIHG scoring system, there is a recent report by the IAIHG which suggests that IAIHG scoring system for AIH should not be used to diagnose overlap syndrome.[66]

Although there is no consensus till date on the diagnostic criteria for PBC–AIH overlap syndrome, the Paris criteria proposed by Chazouilleres *et al.* have been validated individually by certain groups.[67,68] In a study done by Kuiper *et al.* on 134 patients of PBC–AIH overlap syndrome, the sensitivity and specificity of Paris criteria for diagnosing overlap syndrome were found to be 92% and 97%, respectively.[68]

Non-hepatic manifestations and associations

There are various reports of PBC–AIH overlap presenting with other autoimmune manifestations like concurrent Idiopathic Thrombocytopenic Purpura ITP and systemic sclerosis,[69] antiphospholipid syndrome,[70] concomitant ITP and Hashimoto's disease,[71] autoimmune hemolytic anemia,[72] and membranous glomerulonephritis,[73] which suggest the presence of shared genetic susceptibility factors in multiple autoimmune conditions.

Treatment and prognosis

In clinical practice, it is essential to differentiate AIH–PBC overlap syndrome from the isolated pure forms of the disease, as the therapeutic approach is rather different: The standard immunosuppressive treatment of AIH (steroids with or without Azathioprine)[74] might have a negative effect on the calcium metabolism of pure PBC patients,[75] whereas isolated ursodeoxycholic acid (UDCA) treatment seems to be inadequate in controlling liver inflammation in AIH–PBC overlap syndrome. In Lohse's series, 16 out of 20 patients diagnosed with an overlap syndrome were given immunosuppressive agents for a minimum of 2 years. During follow-up, the serum aminotransferase levels improved as did the ALP levels in 12 of 16 patients, but these were additionally given UDCA.[3] Currently, a combination of UDCA and immunosuppressants seems to be the best therapeutic option for AIH–PBC overlap syndrome.[2,3,76] For corticosteroid-resistant patients with AIH–PBC overlap syndrome, intermediate treatment with immunosuppressants such as Cyclosporine A has been considered.[77] Liver transplantation should be considered for end-stage liver disease.

Prognosis has been predicted on the basis of AMA autoantibody status, with AMA-negative patients having more severe bile duct damage, ductopenia, ductular hyperplasia, and a higher METAVIR fibrosis score than AMA-positive overlap syndrome, indicating that AMA status affects the clinical presentation and liver disease severity of overlap syndrome.[78]

AIH–PSC OVERLAP SYNDROME

Overlap of AIH and PSC has been described in a number of reports during the last decade in both children and adults.

Etiology

The etiology of AIH–PSC overlap is unknown. PSC shares genetic risk factors with AIH (HLA B8, DR3, and Drw52), and this host-related predisposition may result in similar clinical expressions or transitions between the diseases. Conversely, HLA DR4, which predisposes to AIH, protects against PSC, and its presence does not support a strong PSC component of the variant syndrome.[79-83] As both AIH and PSC can be associated with IBD, there is a study suggesting that the liver disease is driven by the recruitment of effector lymphocytes that were activated in the gut.[84] Twenty percent of the T cells infiltrating the liver in AIH/PSC complicating IBD are a4b7 + CCR9 + and thus of gut origin, whereas these cells are found at very low frequencies in other liver diseases,[85,86] although this hypothesis does not explain the presence of liver disease in the absence of IBD.

Clinical presentation

The presentation of AIH–PSC overlap shows subtle differences between children and adults. Wilschanski and colleagues had described 32 children with radiological evidence of PSC, out of whom 9 were originally described as AIH. Intrahepatic biliary disease had predominated. Also, the age of AIH–PSC patients group was higher.[36] Gregorio *et al*., in their largest 16-year prospective study, evaluated 55 children who underwent endoscopic retrograde cholangiography (ERCP). Twenty-three (41.8%) had abnormal cholangiography, but only two had typical structuring and beading pattern as described in adults. They also observed that IBD was more common in those with overlap (12 patients, 44%) than in those with AIH alone (5 patients, 18%).[6]

The subjects affected present with stenosis and dilatation of biliary ducts during ERCP, with typical histological "chronic hepatitis like" lesions and high ANA titers in the serum.[79]

Co-existence of AIH–PSC appears to be much less frequent in adults than in children. Abdo *et al*. had presented a series of six adults with AIH in whom (mean 4.6 years) PSC was first demonstrated by ERCP only later. In this series, similar to children with AIH-PSC overlap, no evidence of biliary pathology was found initially.[7]

There are no particular differences between AIH–PSC overlap syndrome and PSC with regard to the clinical features or the serological parameters, except for IgG levels, which seem to be higher in overlap syndrome than in PSC alone, and for ANA and ASMA, which also have a higher prevalence in overlap syndrome.[80] AIH and PSC may be sequential in their occurrence and this has been described both in children[81] and adults.[82] Diagnostic difficulties occur mainly in children and adults with normal cholangiograms. ASC is a disorder described in children who have the clinical phenotype of AIH but with abnormal cholangiogram. IBD is typically absent, and response to corticosteroid therapy is similar to that in classical type 1 AIH.[6,87-90]Adults with AIH, cholestatic features, seronegativity for AMA, and normal cholangiograms are another diagnostic problem as they may have small duct PSC.[91,92] High serum ALP activity or a ratio of serum ALP level to aspartate aminotransferase level (ALP: AST) that exceeds 1.5 suggests the existence of an AIH–PSC overlap, especially if biliary changes are evident on liver biopsy examination and IBD is present.[93] Recently, the use of Cytokeratin 7 stain showed that it may facilitate the identification of early intrahepatic biliary obstruction.[94]

Non-hepatic manifestations

Both AIH and PSC can be associated with IBD.[95] Association of AIH–PSC overlap syndrome with ulcerative colitis (UC) is more common than with Crohn's disease.[96]

Diagnosis

The diagnosis of AIH–PSC overlap syndrome is based on clinical and histological criteria, together with typical ERCP findings. A scoring system for the diagnosis of AIH–PSC overlap syndrome was devised,[97-98] but it is possibly biased by patients' age and the range of autoantibodies considered, and a call for more and better validated data was made.[98]

Magnetic resonance cholangiopancreatography MRCP has been proposed in certain studies as a preliminary non-invasive imaging modality in the detection of PSC-induced changes, especially in children.[99]

Therapy

Since transaminitis is not unusual in the initial stages of PSC which could be attributed to stones or cholangitis, it is possibly prudent to start treatment with UDCA to improve cholestasis prior to introduction of any immunosuppressive therapy. This has been shown to improve the biochemical picture of cholestasis, liver histology, and even the cholangiographic features of this disease, particularly in a dose >20 mg/kg/day.[100,101] In individuals presenting with features of AIH, it is probably optimal for immunosuppressive therapy to be the first line of treatment, particularly in patients who have florid symptoms and/or bridging necrosis on liver histology. UDCA in combination with an immunosuppressive regimen (Azathioprine ± corticosteroids) may be adequate medical treatment for most patients with AIH–PSC overlap, although data from controlled trials are lacking. Recently, the clinical benefit of UDCA has been under debate. In many single-center and multicenter trials, UDCA was found to improve disease manifestation in PSC.[102-104] But another

multicenter trial with high doses of UDCA demonstrated that despite the improvement of diagnostic parameters, patients either developed varices or had to undergo liver transplantation.[105] Similarly, inconsistent results have been reported regarding the chemopreventive role of UDCA in cholangiocarcinoma and colon cancer.[106-109] On the other hand, a recent study showed that patients treated with high-dose UDCA had a significantly higher risk of developing colorectal neoplasia, compared with those who received placebo.[108] For the same reasons, the American Association for the Study of Liver Diseases (AASLD) does not recommend the use of UDCA in any patient with PSC, while it is recommended by the European and German guidelines. The pediatric patients usually respond to corticosteroids, unlike patients with classical PSC, although as the biliary features progress, response to immunosuppression may be lost. The reasons for the relative treatment resistance of AIH with biliary features are not known. One possibility is that biliary epithelial cells maintain effector cell survival by providing anti-apoptotic signals through cell-surface integrin ligands such as vascular cell adhesion molecule 1 (VCAM-1) and by secreting cytokines.[110] Endoscopic therapy (ERCP) may be required for dilatation of strictures, stone removal, and other standard indications. Liver transplantation may be required earlier in a younger population than adults.

Prognosis

There are conflicting reports regarding the prognosis of patients with AIH–PSC overlap syndrome. In Wilschanski's study of children with overlap, 5 out of 9 (55.6%) required liver transplantation, while only 5 of 22 (22.7%) with PSC and only minor features of AIH progressed to liver transplantation.[36] Gregorio *et al*. also noticed in their study that four children required liver transplantation, three of whom had ASC and ductopenia on liver biopsy.[6] Hence, overlap of AIH with PSC has a poorer prognosis than AIH alone.

A systematic review of presentation and outcomes of patients with overlap syndromes at a tertiary referral center has also demonstrated that the survival of patients with PSC–AIH overlap syndrome was significantly lower than that of patients with definite AIH or PBC–AIH overlap syndrome.[111]

PBC–PSC: OVERLAP SYNDROME OR COEXISTENCE?

Different from AIH–PBC and AIH–PSC overlap syndromes, evidence for a PBC–PSC overlap syndrome is limited at best and is based only on single case reports.[39-41] In a recently described case, a 64-year-old woman with PBC of 17-year duration revealed typical benign strictures and dilatation of common bile duct with typical beading suggestive of PSC on ERCP done for worsening cholestatic features.[41]

Whether sclerosing bile duct injury can be regarded as a primary event in late stage hepatopathies of other cause remains elusive.

CONCLUSION

Overlap syndrome in hepatology is emerging as a diagnostic and therapeutic challenge. This in turn emphasizes our current ignorance regarding the immunopathogenesis leading to these diseases. The diagnostic strategies currently available are summarized in Table 1. In future, certain steps should be taken to exactly delineate the clinical issue and find probable solutions:

1. Collect a large database of autoimmune liver diseases, keeping in mind the sample size, biases in the methods used and selection of patients by uniform application of a systemic algorithm
2. Immunogenetic studies to illuminate the pathogenesis of disease
3. Develop a comprehensive scoring system and reevaluate the available ones in a more rigorous manner
4. Large randomized studies to evaluate the impact of drug therapy on the natural history of overlap syndrome
5. Define biomarkers for diagnosis, prognosis, as well as for susceptibility testing.

With the ultimate goal of predicting and possibly preventing autoimmune liver diseases, it will be important to thoroughly investigate individual areas of pure as well as overlapping forms of the disorder. This is needed as the chances of progression to liver transplant remains high in cases like AIH–PSC overlap and early recognition may alter the course of the illness.

Table 1: Diagnostic strategies for overlap syndromes

Overlap syndrome	Diagnostic strategies		
	Biochemical features	Immunological features	Histological features
AIH-PBC overlap syndrome	Elevated AST and ALT Markers of cholestasis	Increased IgG and IgM Positive ANA (multiple nuclear dots) ASMA AMA Anti-dsDNA Soluble liver antigen antibodies (SLA/LP)	Interface hepatitis Bile duct lesions
AIH-PSC overlap syndrome	ALP: AST>1.5	Elevated IgG Positive ANA ASMA	Intrahepatic biliary changes Chronic hepatitis like lesions

AIH: Autoimmune hepatitis, PBC: Primary biliary cirrhosis, PSC: Primary sclerosing cholangitis, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ANA: Antinuclear antibody, AMA: Antimitochondrial antibody, ASMA: Anti-smooth muscle antibody, SLA/LA: Soluble liver antigen antibodies

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