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Overlap Syndromes of Autoimmune Liver Disease

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Abstract

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are chronic liver diseases of presumed autoimmune origin. Conditions exhibiting features of two different autoimmune liver diseases are commonly designated overlap syndromes, although there is no current agreement on what constitutes an overlap syndrome or specific diagnostic criteria. Identification of patients with features of overlap syndrome is relevant for management as outcomes may differ from outcomes of patients with diagnosis of classic autoimmune liver diseases and treatment may need to be adjusted. Due to their rarity, no large therapeutic trials are available and treatment of overlap conditions is empirical and based upon extrapolation of data from the primary autoimmune liver diseases. AIH-PBC overlap is the most frequently described overlap syndrome and may be associated with a poor prognosis. This may represent an important and unrecognized cause of resistance to ursodeoxycholic acid (UDCA) in patients with PBC. AIH-PSC overlap is less commonly reported. Prognosis may be better than in patients with PSC alone, however worse than in patients with AIH alone. Further studies are needed for determining diagnosis, natural history and optimal therapeutic strategies of overlap syndromes of autoimmune liver diseases.

Keywords: Overlap syndromes; Autoimmune liver disease; Autoimmune hepatitis; Primary biliary cirrhosis; Primary sclerosing cholangitis

Introduction

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are presumed autoimmune liver diseases. However, there is no single diagnostic test for any of these conditions,

They are generally easily differentiated based on clinical, biochemical, immunological and histological features, and are classically viewed as distinct entities. However, shared patterns exist across the spectrum of these autoimmune liver diseases. Several variants or atypical forms of these diseases are recognized [1-6]. Furthermore, it has been increasingly recognized that some patients present with clinical, biochemical, serological and/or histological features reminiscent of two of these diseases, occurring either simultaneously or during the course of the illness and classification of these patients can be challenging [7]. Much debate has ensured whether these represent presentations within a spectrum of autoimmune liver disease, variants of the classical autoimmune liver diseases, or distinct clinical entities.

These conditions exhibiting features of two different autoimmune liver diseases have commonly been designated overlap syndromes. The so called overlap syndromes include descriptions of simultaneous or consecutive AIH and PBC, simultaneous or consecutive AIH and PSC, and very rarely cases of PBC and PSC[8,9]. Nonetheless, there is no current agreement on what constitutes an overlap syndrome and the nomenclature used to describe these presentations is highly variable.

For purposes of this review, overlap syndromes are defined as distinct clinical entities with concurrent main characteristics of two autoimmune conditions that occur at the same time or during the course of the illness. Regardless of its precise definition, this seems to be an important clinical problem and, despite its rare occurrence, a significant body of literature has emerged concerning this controversial topic.

Overlap syndromes should be suspected in patients with autoimmune liver diseases whose clinical course deviates from the classical course of disease in the absence of a known trigger such as viral infections and drug effects. In patients with chronic cholestatic diseases who present with unusually high transaminases and hypergammaglobulinemia, overlap syndromes should be suspected. In patients with a diagnosis of autoimmune hepatitis, the presence of cholestatic features should also raise the possibility of an overlap syndrome. Sudden deterioration of liver function or suboptimal response to treatment of a previously well controlled autoimmune liver disease should also raise the suspicion of an overlap syndrome.

The recognition of these potentially clinically distinct entities might have important implications not only from a classification standpoint, but also for management [7,10] and for a better approach to understanding the pathophysiology of autoimmune liver diseases [7].

Overview of autoimmune liver diseases

PBC is a chronic cholestatic liver disease of presumed autoimmune etiology that affects predominantly middle-aged women [11]. Antimitochondrial antibody (AMA) is an important serologic marker of the disease, which are present in at least 95% of the patients [12]. Histologically, it is characterized by chronic portal inflammation with infiltration, destruction and loss of the epithelial cells in the small- and medium-sized bile ducts [13], ultimately resulting in cholestasis, advanced fibrosis, cirrhosis, and liver failure. Treatment with ursodeoxycholic acid (UDCA) may delay disease progression and prolong survival free of liver transplantation[14-16], particularly in patients with biochemical response to therapy [17].

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PSC is a chronic cholestatic liver disease of presumed autoimmune etiology that affects predominantly middle-aged men with inflammatory bowel disease. Cholangiography is the gold standard for diagnosis, and often reveals segmental fibrosis of intrahepatic and/or extrahepatic bile ducts with saccular dilatation of normal intervening areas resulting in the characteristic beads on a string appearance [18]. Histologically, it is characterized by injury to medium- and large-sized bile ducts, with resultant smaller duct ductopenia [19]. Fibro-obliterative cholangitis is the histologic hallmark of the disease, but is neither a sensitive nor specific finding for the diagnosis [20]. The fibrosing inflammatory destruction of the intrahepatic and/or extrahepatic bile ducts results in bile stasis, hepatic fibrosis, and ultimately to cirrhosis, end-stage liver disease, and need for liver transplantation. No effective medical therapy for halting disease progression has been identified thus far [21].

AIH is an unresolving inflammation of the liver of unknown cause [1]. The diagnosis of AIH requires a constellation of clinical, laboratory, and histological features that exclude other conditions and support the syndrome[22]. Interface hepatitis is a characteristic histologic finding of the disease, and it may be associated with panacinar hepatitis with or without bridging necrosis or multiacinar necrosis [23].

Autoantibodies are common in autoimmune liver disease, but typically lack disease specificity, and per se do not establish a diagnosis [24]. Therefore, their role in the diagnosis of overlap syndromes is also limited. Antinuclear antibodies (ANA) are the most commonly assessed but least specific, serologic markers of autoimmunity in chronic liver disease [25]. Other autoantibodies in the conventional repertoire for the diagnosis of autoimmune liver disease are smooth muscle antibodies (SMA), antibodies to liver kidney microsome type 1 (anti-LKM1), antimitochondrial antibodies (AMA) and atypical perinuclear antineutrophil cytoplasmic antibodies (atypical pANCA) [24]. ANA can be found in approximately 70% of patients with type 1 AIH, typically coexistent with SMA; ANA is the sole autoimmune marker in 14% of patients with AIH [26]. The specificity of this finding is low. The antigen-specificity of anti-nuclear antibodies is wide, and some of the antigens are specific for PBC, including Sp100, promyelocytic leukemia proteins, gp120, and p62 [27]. ANA are found in approximately 50% of patients with PBC, and often in patients who do have AMA [12]. ANA and SMA are reported in 20 to 60% of patients with PSC, usually in lower titers than those observed in AIH [28]. Approximately 32% of healthy individuals were found to have ANA at low titers in one study [29]. AMA are the diagnostic hallmarks of PBC, and are present in 95% of patients who satisfy clinical, laboratory and histological criteria for PBC[24]. Approximately 10% of patients with AIH are found to have positive AMA [30]. pANCA are present in approximately 80% of patients with PSC but lack diagnostic specificity [31-33].

The histologic findings observed in autoimmune liver diseases are not pathognomonic in PBC, PSC or AIH. In each disorder, certain histopathological changes are considered typical and yet are not necessarily incompatible with the diagnosis of an alternative autoimmune liver disease. Interface hepatitis and other forms of hepatocellular damage are a common component of PBC, and their presence should not automatically lead to a diagnosis of overlap syndrome [13]. Conversely, bile duct injuries can also be observed in patients with a diagnosis of AIH who lack other features of cholestatic liver disease that could alter the diagnosis and/or treatment of AIH [34] (such as destructive cholangitis or ductopenia [23]).

Overlap of AIH and PBC

The overlap syndrome of AIH-PBC is the most frequently reported overlap syndrome. There has been much debate whether AIH-PBC overlap syndrome constitutes a distinct entity or a variant of AIH or PBC. Czaja [1] has considered these patients as variant forms of AIH, and Lohse et al. [35] and Muratori et al. [36] have interpreted the AIH-PBC overlap syndrome as a "hepatic form" of PBC in genetically susceptible individuals. Chazouilleres et al. [10] have suggested that PBC patients with features of AIH suffer from two different diseases, whereas Woodward and Neuberger [20] have suggested that there is no true overlap syndrome, and the term reflects the current imprecision in definition of the individual autoimmune liver diseases.

Despite all the controversy regarding definition of overlap syndrome and optimal diagnostic criteria, it cannot be denied that some patients have features of both diseases that cannot be easily diagnosed based on criteria for either AIH or PBC alone [37]. The consecutive occurrence of the two diseases supports the notion that the patients have two coincident autoimmune diseases and is also consistent with the fact that autoimmune diseases are associated with one another in up to 10% of cases [38]. Response to classical treatment for either one of those diseases alone has not been adequate in many of the patients presenting with overlapping features of autoimmune liver diseases. Identification of a subset of patients with distinct clinical presentations could result in modification of treatment strategies and positively impact their clinical outcome.

Diagnostic criteria: In the absence of consensus on what constitutes an overlap syndrome, diagnosis can be challenging. Extensively validated, stringent criteria are lacking. Several diagnostic criteria have been applied to determine overlap syndromes. The most commonly applied criteria are those defined by Chazouilleres et al. [10], also referred to as "Paris criteria", based upon simplified criteria of PBC alone and AIH alone. These criteria require the presence of at least two of the three accepted criteria for both AIH and PBC, as shown in Table 1, and PBC-AIH overlap syndrome is defined by the association of PBC and AIH either simultaneously or consecutively. Multiple authors subsequently have used these criteria to describe overlap patients [35,38-40]. These criteria have been endorsed by the European Association for the Study of the Liver [41], with the caveat that the presence of histological evidence of interface hepatitis is mandatory to establish the diagnosis of overlap.

The original [22] and revised [42] scoring systems proposed by the International Autoimmune Hepatitis Group (IAIHG) for the diagnosis of AIH have also been frequently used in the diagnosis of AIH-PBC overlap syndrome of patients with a known diagnosis of PBC [36,42-44] (the revised scoring system is shown in Table 2). The presence of several features is scored in these systems, which can be cumbersome

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PBC criteria:
1) serum ALP levels at least two times the upper limit of normal values or serum GGT levels as least five times the upper limit of normal values
2) a positive test for AMA
3) a liver biopsy specimen showing florid bile duct lesions

AIH criteria:
1) serum ALT levels at least five times the upper limit of normal values
2) serum IgG levels at least two times the upper limit of normal values or a positive test for SMA
3) a liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis

PBC-AIH overlap syndrome: both 2 out of 3 PBC criteria are met and 2 out of 3 AIH criteria are met either simultaneously or consecutively

ALP: Alkaline Phosphatase; GGT: Gamma-glutamyl Transpeptidase; AMA: Antimitochondrial Antibodies; ALT: Alanine Transaminase; IgG: Immunoglobulin G; SMA: Smooth Muscle Antibodies

Table 1: Paris criteria [10].

Clinical Feature	Score
Female gender	+2
ALP:AST ratio	
<1.5	+2
1.5-3.0	0
>3.0	-2
Serum globulin or IgG above normal	
>2.0	+3
1.5-2.0	+2
1.0-1.5	+1
<1.0	0
ANA, SMA, or LKM-1	
>1:80	+3
1:80	+2
1:40	+1
<1:40	0
AMA	
positive	-4
Hepatitis viral markers	
Positive	-3
Negative	+3
Drug history	
Positive	-4
Negative	+1
Average alcohol intake	
<25 g/day	+2
>60 g/day	-2
Liver histology	
Interface hepatitis	+3
Predominante lymphoplasmacytic infiltrate	+1
Rosetting of liver cells	+1
None of the above	-5
Biliary changes	-3
Other changes	-3
Other autoimmune disease	+2
Optional additional parameters	
Seropositivity for other defined autoantibodies	+2
HLA DR3 or DR4	+3
Response to therapy	
Complete	+2
Relapse	+3
Interpretation of aggregate scores:	
Pre-treatment	
Definite AIH	>15
Probable AIH	10-15
Post-treatment	
Definite AIH	>17
Probable AIH	12-17

ALP: Alkaline Phosphatase; AST: Aspartate Transaminase; IgG: Immunoglobulin G; ANA: Anti-nuclear Antibodies; SMA: Smooth Muscle Antibodies; LKM-1: Type 1 Liver-kidney Microsomal antibodies; AMA: Anti-Mitochondrial Antibodies; HLA: Human Leucocyte Antigen

Table 2: Revised IAHG Scoring System for the diagnosis of AIH.

to apply. Furthermore, some data are not available for the retrospective diagnosis in many patients, limiting the use of these criteria. Most recently, a simplified scoring system based on only four features has been proposed for clinical diagnosis of autoimmune hepatitis [45] (Table 3), and has been subsequently applied to patients with PBC for the diagnosis of overlap syndromes [45-47].

It is worth emphasizing that the scoring systems proposed for the

diagnosis of AIH were not designed for the diagnosis of AIH in patients with PBC. There are a number of clinical and biochemical features common to AIH and PBC that are assigned with positive scores despite their lack of discriminative ability, such as female gender, presence of other autoimmune disorders and the lymphoplasmacytic infiltrate [48]. Indeed, the IAIHG scoring systems for the diagnosis of AIH have been developed to separate autoimmune liver disease entities rather than look for common features or the possible development of one disease into another [42,49,50]. The frequent use of the scoring systems in the diagnosis of overlap syndromes prompted the publication of a position paper by the IAIHG, in which they suggested that patients with atypical manifestations be classified by their predominant diagnosis and not by their overlapping features [51]. They also state the scoring systems "should not be used to establish subgroups of patients" [51].

Other criteria have been applied less frequently, typically slightly modified versions of the previously described criteria. Those include the response to corticosteroids as an additional feature of the Paris criteria [52] or the elimination of allocations of a negative score for the presence of AMA in revised scoring system [53]. Other authors have used yet different criteria for diagnosis such as Lohse et al. [35], Suzuki et al. [44] and Yamamoto et al. [54], and Gunsar et al. [55].

The determination of the most adequate set of criteria to use for diagnosis of overlap is challenging. The utilization of simplified criteria for the diagnosis of complex autoimmune liver diseases may result in overestimation of the occurrence of overlap syndromes. Limited data are available on the comparative performance of different criteria. Kuiper et al. [56] compared the diagnostic performance of the revised and simplified IAIHG scoring systems by using the Paris criteria as the gold standard. For both definitive and probable AIH together, the sensitivity of the revised system was 60% and that of the simplified system was 73%; the specificity was 83% and 78%, respectively [56]. However, as is frequently the case, the comparison of different systems is challenging in the absence of a gold standard for diagnosis.

Clinical Feature	Score
ANA or SMA	
≥ 1:40	+1
≥ 1:80	+2
LKM-1 ≥ 1:40	+2
SLA positive	+2
Antibodies absent	0
Serum globulin or IgG	
Above upper normal limit	+1
>1.1 upper normal limit	+2
Normal	0
Hepatitis viral markers	
Positive	0
Negative	+2
Liver histology (evidence of hepatitis is a necessary condition)	
Compatible with AIH	+1
Typical AIH	+2
Incompatible with AIH	0
Interpretation of aggregate scores*:	
Probable AIH	≥ 6
Definite AIH	≥ 7

*Addition of all antibodies, maximum +2 points.
IgG: Immunoglobulin G; ANA: Anti-nuclear Antibodies; SMA: Smooth Muscle Antibodies; LKM-1: Type 1 Liver-kidney Microsomal Antibodies; SLA: Soluble Liver Antigen antibodies

Table 3: Simplified Scoring System for the diagnosis of AIH.

Author	Year	Total patients	Overlap patients	Prevalence	Diagnostic criteria
Chazouilleres et al. [10]	1998	130	12	9%	Paris criteria
Czaja [2]	1998	162 with AIH	8	5%	Revised scoring system
		37 with PBC	7	19%	
Joshi et al. [39]	2002	331	16	5%	Paris criteria
Muratori et al. [36]	2002	142	3	2%	Revised scoring system
Talwalkar et al. [43]	2002	137	26	19%	Revised scoring system
Yamamoto et al. [54]	2003	48 with AIH	4	8%	PBC scoring system
Gheorghe et al. [48]	2004	82 with AIH	11	13%	Paris criteria
Chazouilleres et al. [37]	2006	190	17	9%	Paris criteria
Poupon et al. [38]	2006	282	39	14%	Paris criteria/Revised scoring system
Heurgue et al. [40]	2007	115	15	13%	Paris criteria
Neuhauser et al. [47]	2009	368 with PBC	43	12%	Revised scoring system
			23	6%	Simplified scoring system
Bonder et al. [52]	2011	209	6	1%	Paris criteria
			17	3%	"Expanded" Paris criteria
Tanaka et al. [53]	2011	597 with PBC	33	6%	"Modified" Revised scoring system
		1081 with AIH	33	3%	

Notes: Paris criteria–see Table 1; Revised scoring system–see Table 2; Simplified scoring system–see Table 3; PBC scoring criteria, "Expanded" Paris criteria, "Modified Revised scoring system–see references.

Table 4: Large studies reporting prevalence of AIH-PBC overlap syndrome.

Further knowledge of the clinical outcomes of patients diagnosed with different set of criteria might be very helpful for that purpose [57]. Criteria that could help distinguish patients that have poorer outcomes would be preferable, in order to identify a subset of patients at higher risk most likely to benefit from modified treatment regimens. Those criteria would ideally be based on non-invasive, easy to obtain and low cost tests, and would be easy to apply in clinical practice.

Epidemiology: As to be expected, the prevalence of overlap syndromes depends on the diagnostic criteria applied and the population being studied [7]. Table 4 summarizes several large studies published since 1998 including different patient populations and different diagnostic criteria, in which the prevalence of AIH-PBC overlap syndromes vary from 1% to 19% in populations of patients initially diagnosed with PBC and from 3% to 13% in patients initially diagnosed with AIH. The lowest prevalence was 1%, observed by Bonder et al. [52], using the Paris criteria [10] in patients initially diagnosed with PBC. In patients with PBC enrolled in randomized clinical trials, Joshi et al. [39] reported a prevalence of 4.8% when utilizing descriptive criteria [10]. In contrast, Talwalkar et al. [43] estimated "probable" AIH-PBC overlap among PBC subjects to be up to 62% when using the original AIH scoring system [22], whereas it was 19% with a revised AIH scoring system [42]. Czaja [42] estimates that 19% of patients with the original diagnosis of PBC can be redesignated as having an overlap syndrome. Chazouilleres et al. [37] estimate the overall prevalence is about 10% of all the PBC patients; their data showed that 9% of the population of PBC patients exhibited the key features of both AIH and PBC either simultaneously or consecutively. The frequency of overlap syndrome seems to be lower among patients originally diagnosed with AIH. The lowest prevalence was 3%, observed by Tanaka et al. [53] in a study including over one thousand patients with AIH. Czaja [2] determined 5% of 162 patients with type 1 AIH could be redesignated as having AIH-PBC overlap using the revised IAIHG scoring criteria. The highest prevalence was 13%, reported by Gheorghe et al. [48], who applied the Paris criteria to 82 patients with AIH. Obviously, the extent to which a second diagnosis is sought in a patient with an autoimmune liver disease is also an important factor in the estimation of prevalence in this condition. The inclusion of patients who develop features of both AIH and PBC consecutively (in either order) can also influence the estimated prevalence.

Clinical outcomes: A few studies have addressed clinical outcomes of patients with PBC-AIH overlap syndrome, with conflicting results. On the one hand, Joshi et al. [39] found the prognosis of patients initially diagnosed with PBC who were treated with UDCA monotherapy did not differ significantly regardless of whether overlapping features of AIH were present. Similarly, other studies report comparable outcomes over a modest follow-up period, regardless of the presence of overlapping features [2,52,53,56]. Of note, variable treatments, often including combination therapy with UDCA and corticosteroids [52,53,56], were used during follow-up period in these studies, which could account for the comparable outcomes rather than the natural history of the overlap syndrome per se. On the other hand, others have shown that patients with overlap syndrome have poorer prognosis compared to those with either AIH or PBC alone. We have described that patients with PBC diagnosed with overlap syndrome based on the revised IAIHG scoring system had higher prevalence of features of portal hypertension and cirrhosis, and had a survival disadvantage compared to those with PBC alone [58]. In a larger study including 368 patients with PBC, Neuhauser et al. [47] found that patients meeting criteria for AIH-PBC overlap after applying both the simplified and revised IAIHG scoring systems had a poorer outcome compared to those with PBC alone. Furthermore, patients who only fulfilled the criteria for overlap based on the simplified scoring system had a significantly worse prognosis in terms of liver-related death and need for liver transplantation [47]. In a small study including 24 patients with PBC, Jung et al. [59] found that the presence of overlap features of AIH based on the revised scoring system, was an independent predictor of poor outcome in PBC. Outcomes reported vary according to the criteria utilized to determine the presence of overlap syndrome compared to those without overlap.

Limited data are available regarding long-term outcomes in patients who underwent liver transplantation for autoimmune liver diseases. Bhanji et al. [60] examined 231 patients who underwent liver transplantation for autoimmune liver diseases, 12 of whom had an overlap syndrome. In this study, patients who underwent liver transplantation for an overlap syndrome (including patients with AIH-PSC overlap) had a higher probability of recurrence than patients who underwent transplant for a classic autoimmune liver disease (53% vs. 17% in 5 years, 69% vs. 29% in 10 years) and time to recurrence was shorter in patients with overlap syndrome [60]. In a smaller

study including 4 patients with overlap syndrome of AIH-PBC who underwent living-donor liver transplantation, there was no evidence of clinical recurrence during the follow-up period of 6 years [61]. However, protocol biopsies were not obtained in this study.

Less is known about the outcomes of patients initially diagnosed with AIH who are found to have additional features of PBC. Czaja has reported that patients with the overlap syndrome of autoimmune hepatitis and PBC treated with steroids with or without azathioprine entered remission as commonly as patients with definite AIH during comparable periods of follow-up [2,62] and had a lower frequency of progression to cirrhosis [2]. Al-Chalabi et al. [63] reported patients with AIH-PBC overlap were significantly less likely to have a complete response to conventional therapy and significantly more likely to demonstrate no response to therapy than patients with definite AIH. However, they were unable to demonstrate significant differences in the proportions of death or liver-related death/liver transplantation compared to patients with AIH alone and AIH-PSC overlap [63].

Treatment: No large randomized clinical trials examining treatment in overlap syndromes are available. In small uncontrolled studies, results have been variable. Corticosteroids have frequently been used in an empiric fashion to treat the overlap syndromes, and results have been variable, in part because of the arbitrary criteria for diagnosis, inconsistent treatment schedules, and diverse criteria for success [42].

A few studies suggest select patients may still respond adequately to monotherapy. Corticosteroid therapy can be effective in patients with features of AIH and PBC. Czaja et al. [62] have described individuals with AIH and PBC that entered remission during corticosteroid therapy as commonly as individuals with definite autoimmune hepatitis. Corticosteroid-responsive individuals were more likely to have a serum alkaline phosphatase level of less than twofold the reference value [62]. Joshi et al.[39] found that patients included in UDCA trials for PBC had similar improvement in biochemistries under UDCA monotherapy in patients with or without features of PBC-AIH overlap syndrome. Similarly, Gunsar et al. [55] described that response to UDCA in patients with overlap syndrome was comparable with that obtained in PBC, and suggests that UDCA should be first-line therapy, while the combination of UDCA and immunosuppressants should be reserved to non-responders to UDCA. Once again, the heterogeneity in the criteria used to diagnose overlap syndromes in these studies might partially account for the variety of results obtained.

Other studies suggest the overlap syndrome of PBC-AIH may represent an important and unrecognized cause of resistance to UDCA in patients with PBC [10] and/or cause of refractoriness to corticosteroid therapy in patients with AIH [42]. Thus, the combination of UDCA with immunosuppressive therapy could potentially provide benefits among patients with PBC and AIH overlap [37,64]. Several small uncontrolled studies suggest the combination of steroids and UDCA may benefit these patients. Chazouilleres et al. [37] concluded that biochemical response is associated with absence of fibrosis progression and that liver fibrosis rapidly increases in most patients under UDCA monotherapy in contrast to patients receiving combination of UDCA and immunosuppressive therapy. Lohse et al. [35] have also strongly supported treatment of patients with overlap syndromes with a combination of UDCA and corticosteroids, at least for a short period of time. Several recent studies have demonstrated that patients with overlap syndromes who received combination therapy with UDCA and corticosteroids achieved biochemical and occasional histological response, in the absence of liver-related death and liver

transplantation, over modest periods of follow-up, [38,40,52,53,56,65], providing further support to the use of combination therapy in overlap syndromes. The use of steroid-sparing agents such as azathioprine has also been popular in patients with PBC-AIH overlap. A few small case series describe complete biochemical response of most or all patients to the combination of UDCA and corticosteroids, with or without azathioprine [10,35,37,40,55], either as first line therapy in PBC-AIH overlap or after failure to respond to treatment for PBC or AIH alone. This is probably the most common treatment strategy currently in practice. Interestingly, Tanaka et al. [53] found that while applying a stepwise treatment approach, the simplified scoring system was superior to the Paris criteria at identifying overlap patients who required corticosteroids in addition to UDCA. Cyclosporine has also been reported as an alternative treatment for the rare patient not responsive to the UDCA-corticosteroid (with or without azathioprine) combination [40,66].

Based on the risks and benefits of the various treatment strategies and variable results, most agree that treatment should focus initially on the disease that appears to be the predominant entity, and be modified based on initial results of therapy. A large and prospective trial the efficacy of the combination of UDCA and corticosteroids is needed [10], but will likely only be feasible with a global multicenter effort. Several questions still remain unanswered with regard to optimal treatment of overlap syndromes such as ideal pharmacological agents, dosages and administration, and duration of therapy.

Overlap of AIH and PSC

The overlap between AIH and PSC is mainly described in the pediatric population [67-69], but also observed in the adult population [70-72]. One study revealed that half of pediatric patients diagnosis with AIH had overlapping features of PSC when this was sought with cholangiography and liver biopsy [73]. The term "autoimmune sclerosing cholangitis" has been proposed to describe this pediatric population with overlap features of AIH and PSC.

Many of the challenges described for the overlap syndrome of AIH-PBC apply to the overlap syndrome of AIH-PSC. In general, the diagnostic criteria used in this overlap syndrome are more uniform compared to AIH-PBC. The IAIHG scoring systems [22,42,45] and modified versions have been most commonly applied. Some diagnostic challenges are unique to the PSC-AIH overlap syndrome, including the need for cholangiography in the diagnosis of PSC, which is not routinely used in patients with AIH. As a result, the occurrence of AIH in the PSC population has been observed more often and consequently studied in more detail than the occurrence of PSC in populations of AIH patients. An additional challenge is that liver biopsies are not required at the time of diagnosis of PSC, unlikely AIH, though are frequently obtained for staging purposes in several centers.

Diagnostic criteria: The diagnostic criteria used for the overlap syndrome of PSC with AIH are more uniform in comparison to the overlap syndrome of PBC with AIH. Much debate with regard to the use of the international autoimmune hepatitis group scoring system has arisen [74], but mostly the consensus is that it is useful in clinical practice for diagnosis both in children [75] and adults. Most of the recent literature describes the overlap syndrome of PSC with AIH based on applying the IAIHG scoring systems to a group of patients with PSC. In a smaller proportion of studies, diagnosis is based on conventional descriptive criteria [76].

Once again, several of the limitations common to the diagnosis of

AIH-PBC overlap apply to the diagnosis of AIH-PSC overlap, including the extent to which a second diagnosis is sought in a patient with a diagnosis of autoimmune liver disease. Two particular challenges are unique to the diagnosis of AIH-PSC overlap. One is the need for cholangiography in the diagnosis of PSC, not required in the diagnosis of AIH. Failure to evaluate the biliary tree in patients with a diagnosis of AIH may result in underdiagnosis of AIH-PSC overlap syndrome. Nonetheless, there are a few well-described reports both in the pediatric [73] and adult [77] population of patients whose original presentation was of definite AIH, without cholangiographic or histologic features suggestive of PSC, who subsequently developed features of PSC confirmed by ERCP. The increasing use of magnetic resonance cholangiography (MRC), which is not associated with the potential complications of endoscopic retrograde cholangiopancreatography (ERCP), for diagnostic purposes might lead to a higher detection of overlap of PSC in patients originally diagnosed with AIH and significantly affect the prevalence and incidence of overlap of AIH-PSC. Among 79 patients with AIH were evaluated with MRC in a Canadian study [78], approximately 10% had findings consistent with PSC. The authors suggest that routine radiological evaluation of the biliary tree should be performed in adults diagnosed with AIH. A subsequent French study [79], however, including 59 patients with AIH who underwent evaluation with both MRC and liver biopsy, only one patient had findings consistent with AIH-PSC overlap syndrome. Fourteen patients (24%) had mild MRC abnormalities of intrahepatic ducts, thought to be a result of hepatic fibrosis rather than PSC [79]. These data argue against the use of MRC screening in adult patients with AIH in the absence of cholestatic presentation. Further studies are needed to establish the role of screening MRC in patients with AIH.

The second challenge is liver biopsies are rarely required at the time of diagnosis of PSC [18], so little is known about the histologic findings of PSC and possible overlap features of AIH.

Epidemiology: Distinct versions of the AIH scoring system, such as the original [22] and revised [42] versions developed by the IAIHG,

and "adapted" scoring systems [80] with slight variations have been used and may account at least partially for some of the variability among prevalence described in various studies [74]. Table 5 illustrates described prevalence in several large studies including different patient populations and diagnostic criteria.

Evaluation of subjects for overlap syndromes in populations of PSC patients reported in case series published since 1996 reveals the prevalence of definite AIH-PSC overlap within the range of 2 to 7% and probable overlap 6 to 54%. The lowest prevalence was observed by Kaya et al. [81], who describe 1.4% of PSC patients satisfy criteria for definite overlap and 6% for probable overlap syndrome. Boberg et al. [82] describe 2% of the patients could be classified as definite AIH, whereas 33% of the cases fulfilled the criteria of probable overlap. Czaja [2] describes 54% of 26 patients with PSC being redesignated as having PSC-AIH overlap.

In most of the reported cases of PSC-AIH overlap syndrome, PSC and AIH are believed to occur simultaneously [70,72,73]. In a few of these PSC-AIH patients, the diagnosis of AIH preceded that of PSC, often by several years [71,76,77,83]. In other cases, patients with PSC sequentially developed AIH [76,84,85].

As in AIH-PBC overlap, one should be aware of possibility of AIH-PSC overlap, and pursue appropriate evaluation particularly in cases of change in the patient's pattern of liver enzymes, sudden deterioration of liver function or failure of response to a previously adequate treatment regimen in the absence of other known abnormalities.

Treatment: Though no randomized trials are available, the benefits of steroids in this population seem to be more clear-cut than in patients with PBC-AIH. Especially because medical therapy is not yet available for PSC, the identification of subset of patients with features that might be useful for assessing prognosis and planning treatment strategies cannot be underscored [74]. Most studies available describe PSC-AIH overlap syndrome patients treated with corticosteroids

Author	Year	Total patients	Overlap patients	Prevalence	Diagnostic criteria†
Boberg et al. [82]	1996	114 with PSC	2 definite	2%	Original scoring system
			38 probable	33%	
Czaja [2]	1998	162 with AIH	0	0%	Modified IAIHG scoring system
		26 with PSC	14	54%	
Van Buuren et al. [76]	2000	113 with PSC	9	8%	Descriptive
			9 definite 0 probable	8%	Original scoring system
			8 definite 1 probable	7% 1%	Revised scoring system
Kaya et al. [81]	2000	211 with PSC	4 definite 40 probable	2% 19%	Original scoring system
			3 definite 13 probable	1% 6%	Revised scoring system
Gheorghe et al. [48]	2004	82 with AIH	6	7%	Revised scoring system/descriptive PSC
Floreani et al. [90]	2005	41 with PSC	7	17%	Revised scoring system/Descriptive PSC and ERCP
Czaja [46]	2008	24 with PSC	2 definite 7 probable	8% 29%	Revised scoring system
			2 definite 3 probable	8% 13%	Simplified scoring system
Chandok et al. [91]	2010	147 with PSC	0 definite 0 probable	0%	Revised scoring system
			0 definite 2 probable	0% 1%	Simplified scoring system
Hunter et al. [92]	2011	118 with AIH	12*	10%	Descriptive AIH/PSC cholestasis and MRC

Notes:* identified from 24 patients with cholestasis; †please see references for details on diagnostic criteria.

Table 5: Large studies reporting prevalence of AIH-PSC overlap syndrome.

or combination of corticosteroids and azathioprine [5,70,71,86-88]. There are reports of patients that have received cyclosporine [89] and others were given immunosuppression and UDCA successfully [72]. In adults, the therapeutic response to immunosuppressants, in particular the AIH- or hepatocellular component of the overlap syndrome, can be excellent, and can lead to complete remission of disease activity [76]. The response to therapy might be dependent on the predominance of AIH or PSC features [76]. Literature available on this topic is scarce. Interestingly, Gheorghe et al. have reported that their patients with diagnosis of definite AIH had significantly higher response rate to immunosuppressive therapy than those with probable AIH [48].

Clinical outcomes: Limited information is available with regards to long-term outcomes of patients with AIH-PSC overlap syndrome. Studies suggest that patients with AIH-PSC overlap have a better prognosis compared to PSC alone [90] and a worse prognosis compared to AIH alone [2,63,73,88], with more patients experiencing treatment failure or unfavorable outcomes, such as liver transplantation or the development of cirrhosis. Floreani et al. [90] have shown that patients benefit from immunosuppression and UDCA therapy, with lack of progression of Mayo score prognostic index during follow-up and survival that was apparently better than in PSC alone after a median of 207 months; no comparisons were made with survival in patients with AIH alone in this study.

Conclusion

Patients presenting with clinical, biochemical, serological and/or histological features reminiscent of more than one autoimmune liver disease, occurring either simultaneously or during the course of the illness, are commonly diagnosed with overlap syndromes. Though there is no consensus about what constitutes an overlap syndrome or optimal criteria to be used for their diagnosis, it has been increasingly recognized as an important clinical problem. Response to classical treatment for the classical autoimmune liver diseases alone is not adequate in many of these patients and, if untreated, their outcomes seem to be generally worse than outcomes of patients without overlap. Currently, no large therapeutic trials are available and treatment of overlap conditions is empirical and based upon extrapolation of data from the classic autoimmune liver diseases. Recognition of overlap syndromes could have a significant impact in treatment of patients who have suboptimal response with therapy tailored for one of the primary autoimmune liver diseases, perhaps leading to overall improvement of survival and decrease in the need for liver transplantation in patients with autoimmune liver diseases.

References

1. Czaja AJ (1996) The variant forms of autoimmune hepatitis. Ann Intern Med 125: 588-598.

2. Czaja AJ (1998) Frequency and nature of the variant syndromes of autoimmune liver disease. Hepatology 28: 360-365.

3. Ben-Ari Z, Dhillon AP, Sherlock S (1993) Autoimmune cholangiopathy: part of the spectrum of autoimmune chronic active hepatitis. Hepatology 18: 10-15.

4. Sánchez-Pobre P, Castellano G, Colina F, Dominguez P, Rodriguez S, et al. (1996) Antimitochondrial antibody-negative chronic nonsuppurative destructive cholangitis. Atypical primary biliary cirrhosis or autoimmune cholangitis?. J Clin Gastroenterol 23: 191-198.

5. Luketic VA, Gomez DA, Sanyal AJ, Shiffman ML (1997) An atypical presentation for primary sclerosing cholangitis. Dig Dis Sci 42: 2009-2016.

6. Heathcote J (2002) Variant syndromes of autoimmune hepatitis. Clin Liver Dis 6: 669-684.

7. Poupon R (2003) Autoimmune overlapping syndromes. Clin Liver Dis 7: 865-878.

8. Ludwig J, Czaja AJ, Dickson ER, LaRusso NF, Wiesner RH (1984) Manifestations of nonsuppurative cholangitis in chronic hepatobiliary diseases: morphologic spectrum, clinical correlations and terminology. Liver 4: 105-116.

9. Burak KW, Urbanski SJ, Swain MG (2001) A case of coexisting primary biliary cirrhosis and primary sclerosing cholangitis: a new overlap of autoimmune liver diseases. Dig Dis Sci 46: 2043-2047.

10. Chazouillères O, Wendum D, Serfaty L, Montembault S, Rosmorduc O, et al. (1998) Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology 28: 296-301.

11. Talwalkar JA, Lindor KD (2003) Primary biliary cirrhosis. Lancet 362: 53-61.

12. Kaplan MM, Gershwin ME (2005) Primary biliary cirrhosis. N Engl J Med 353: 1261-1273.

13. Scheuer PJ (1998) Ludwig Symposium on biliary disorders--part II. Pathologic features and evolution of primary biliary cirrhosis and primary sclerosing cholangitis. Mayo Clin Proc 73: 179-183.

14. Lindor KD, Dickson ER, Baldus WP, Jorgensen RA, Ludwig J, et al. (1994) Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. Gastroenterology 106: 1284-1290.

15. Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, Dickson ER (1996) Effects of ursodeoxycholic acid on survival in patients with primary biliary cirrhosis. Gastroenterology 110: 1515-1518.

16. Poupon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Poupon R, et al. (1997) Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology 113: 884-890.

17. Angulo P, Lindor KD, Therneau TM, Jorgensen RA, Malinchoc M, et al. (1999) Utilization of the Mayo risk score in patients with primary biliary cirrhosis receiving ursodeoxycholic acid. Liver 19: 115-121.

18. Silveira MG, Lindor KD (2008) Clinical features and management of primary sclerosing cholangitis. World J Gastroenterol 14: 3338-3349.

19. LaRusso NF, Shneider BL, Black D, Gores GJ, James SP, et al. (2006) Primary sclerosing cholangitis: summary of a workshop. Hepatology 44: 746-764.

20. Woodward J, Neuberger J (2001) Autoimmune overlap syndromes. Hepatology 33: 994-1002.

21. Eaton JE, Talwalkar JA, Lazaridis KN, Gores GJ, Lindor KD (2013) Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. Gastroenterology 145: 521-536.

22. Johnson PJ, McFarlane IG (1993) Meeting report: International Autoimmune Hepatitis Group. Hepatology 18: 998-1005.

23. Carpenter HA, Czaja AJ (2002) The role of histologic evaluation in the diagnosis and management of autoimmune hepatitis and its variants. Clin Liver Dis 6: 685-705.

24. Czaja AJ, Norman GL (2003) Autoantibodies in the diagnosis and management of liver disease. J Clin Gastroenterol 37: 315-329.

25. Czaja AJ, Homburger HA (2001) Autoantibodies in liver disease. Gastroenterology 120: 239-249.

26. Czaja AJ (1999) Behavior and significance of autoantibodies in type 1 autoimmune hepatitis. J Hepatol 30: 394-401.

27. Invernizzi P, Selmi C, Ranftler C, Podda M, Wesierska-Gadek J (2005) Antinuclear antibodies in primary biliary cirrhosis. Semin Liver Dis 25: 298-310.

28. Wiesner RH (1994) Current concepts in primary sclerosing cholangitis. Mayo Clin Proc 69: 969-982.

29. Tan EM, Feltkamp TE, Smolen JS, Butcher B, Dawkins R, et al. (1997) Range of antinuclear antibodies in "healthy" individuals. Arthritis Rheum 40: 1601-1611.

30. Czaja AJ, Carpenter HA, Manns MP (1993) Antibodies to soluble liver antigen, P450IID6, and mitochondrial complexes in chronic hepatitis. Gastroenterology 105: 1522-1528.

31. Mulder AH, Horst G, Haagsma EB, Limburg PC, Kleibeuker JH, et al. (1993) Prevalence and characterization of neutrophil cytoplasmic antibodies in autoimmune liver diseases. Hepatology 17: 411-417.

32. Bansi D, Chapman R, Fleming K (1996) Antineutrophil cytoplasmic antibodies

in chronic liver diseases: prevalence, titre, specificity and IgG subclass. J Hepatol 24: 581-586.

33. Chapman RW (1995) The enigma of anti-neutrophil antibodies in ulcerative colitis primary sclerosing cholangitis: important genetic marker or epiphenomenon? Hepatology 21: 1473-1474.

34. Czaja AJ, Muratori P, Muratori L, Carpenter HA, Bianchi FB (2004) Diagnostic and therapeutic implications of bile duct injury in autoimmune hepatitis. Liver Int 24: 322-329.

35. Lohse AW, zum Büschenfelde KH, Franz B, Kanzler S, Gerken G, et al. (1999) 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 29: 1078-1084.

36. Muratori L, Cassani F, Pappas G, Guidi M, Mele L, et al. (2002) The hepatitic/cholestatic "overlap" syndrome: an Italian experience. Autoimmunity 35: 565-568.

37. Chazouillères O, Wendum D, Serfaty L, Rosmorduc O, Poupon R (2006) Long term outcome and response to therapy of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. J Hepatol 44: 400-406.

38. Poupon R, Chazouilleres O, Corpechot C, Chrétien Y (2006) Development of autoimmune hepatitis in patients with typical primary biliary cirrhosis. Hepatology 44: 85-90.

39. Joshi S, Cauch-Dudek K, Wanless IR, Lindor KD, Jorgensen R, et al. (2002) Primary biliary cirrhosis with additional features of autoimmune hepatitis: response to therapy with ursodeoxycholic acid. Hepatology 35: 409-413.

40. Heurgué A, Vitry F, Diebold MD, Yaziji N, Bernard-Chabert B, et al. (2007) Overlap syndrome of primary biliary cirrhosis and autoimmune hepatitis: a retrospective study of 115 cases of autoimmune liver disease. Gastroenterol Clin Biol 31: 17-25.

41. European Association for the Study of the Liver (2009) EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 51: 237-267.

42. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, et al. (1999) International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 31: 929-938.

43. Talwalkar JA, Keach JC, Angulo P, Lindor KD (2002) Overlap of autoimmune hepatitis and primary biliary cirrhosis: an evaluation of a modified scoring system. Am J Gastroenterol, 97: 1191-1197.

44. Suzuki Y, Arase Y, Ikeda K, Saitoh S, Tsubota A, et al. (2004) Clinical and pathological characteristics of the autoimmune hepatitis and primary biliary cirrhosis overlap syndrome. J Gastroenterol Hepatol 19: 699-706.

45. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, et al. (2008) Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 48: 169-176.

46. Czaja AJ (2008) Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. Hepatology 48: 1540-1548.

47. Neuhauser M, Bjornsson E, Treeprasertsuk S, Enders F, Silveira M, et al. (2010) Autoimmune hepatitis-PBC overlap syndrome: a simplified scoring system may assist in the diagnosis. Am J Gastroenterol 105: 345-353.

48. Gheorghe L, Iacob S, Gheorghe C, Iacob R, Simionov I, et al. (2004) Frequency and predictive factors for overlap syndrome between autoimmune hepatitis and primary cholestatic liver disease. Eur J Gastroenterol Hepatol 16: 585-592.

49. Schramm C, Lohse AW (2005) Overlap syndromes of cholestatic liver diseases and auto-immune hepatitis. Clin Rev Allergy Immunol 28: 105-114.

50. Chazouillères O, Poupon R (2002) Ursodeoxycholic acid and primary biliary cirrhosis with features of autoimmune hepatitis. Hepatology 36: 1026-1027.

51. Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, et al. (2011) Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol 54: 374-385.

52. Bonder A, Retana A, Winston DM, Leung J, Kaplan MM (2011) Prevalence of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. Clin Gastroenterol Hepatol 9: 609-612.

53. Tanaka A, Harada K, Ebinuma H, Komori A, Yokokawa J, et al. (2011) Primary biliary cirrhosis-Autoimmune hepatitis overlap syndrome: A rationale for crticosteroids use based on a nation-wide retrospective study in Japan. Hepatol Res 41: 877-886.

54. Yamamoto K, Terada R, Okamoto R, Hiasa Y, Abe M, et al. (2003) A scoring system for primary biliary cirrhosis and its application for variant forms of autoimmune liver disease. J Gastroenterol 38: 52-59.

55. Günsar F, Akarca US, Ersöz G, Karasu Z, Yüce G, et al. (2002) Clinical and biochemical features and therapy responses in primary biliary cirrhosis and primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. Hepatogastroenterology 49: 1195-1200.

56. Kuiper EM, Zondervan PE, van Buuren HR (2010) Paris criteria are effective in diagnosis of primary biliary cirrhosis and autoimmune hepatitis overlap syndrome. Clin Gastroenterol Hepatol 8: 530-534.

57. Heathcote, E.J (2002) Overlap of autoimmune hepatitis and primary biliary cirrhosis: an evaluation of a modified scoring system. Am J Gastroenterol, 97: 1090-1092.

58. Silveira MG, Lindor KD (2007) Overlap syndromes with autoimmune hepatitis in chronic cholestatic liver diseases. Expert Rev Gastroenterol Hepatol 1: 329-340.

59. Jung HE, Jang JY, Jeong SW, Kim JN, Jang HY, et al. (2012) Prognostic indicators in primary biliary cirrhosis: significance of revised IAHG (International Autoimmune Hepatitis Group) score. Clin Mol Hepatol 18: 375-382.

60. Bhanji RA, Mason AL, Girgis S, Montano-Loza AJ (2013) Liver transplantation for overlap syndromes of autoimmune liver diseases. Liver Int 33: 210-219.

61. Yamashiki N, Sugawara Y, Tamura S, Kaneko J, Takazawa Y, et al. (2012) Living-donor liver transplantation for autoimmune hepatitis and autoimmune hepatitis-primary biliary cirrhosis overlap syndrome. Hepatol Res 42: 1016-1023.

62. Czaja AJ, Shums Z, Norman GL (2002) Frequency and significance of antibodies to soluble liver antigen/liver pancreas in variant autoimmune hepatitis. Autoimmunity 35: 475-483.

63. Al-Chalabi T, Portmann BC, Bernal W, McFarlane IG, Heneghan MA (2008) Autoimmune hepatitis overlap syndromes: an evaluation of treatment response, long-term outcome and survival. Aliment Pharmacol Ther 28: 209-220.

64. Czaja AJ (2006) Overlap syndrome of primary biliary cirrhosis and autoimmune hepatitis: a foray across diagnostic boundaries. J Hepatol 44: 251-252.

65. Wu CH, Wang QH, Tian GS, Xu XY, Yu YY, et al. (2006) Clinical features of the overlap syndrome of autoimmune hepatitis and primary biliary cirrhosis: retrospective study. Chin Med J (Engl) 119: 238-241.

66. Duclos-Vallée JC, Hadengue A, Ganne-Carrié N, Robin E, Degott C, et al. (1995) Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. Corticoresistance and effective treatment by cyclosporine A. Dig Dis Sci 40: 1069-1073.

67. el-Shabrawi M, Wilkinson ML, Portmann B, Mieli-Vergani G, Chong SK, et al. (1987) Primary sclerosing cholangitis in childhood. Gastroenterology 92: 1226-1235.

68. Mieli-Vergani G, Lobo-Yeo A, McFarlane BM, McFarlane IG, Mowat AP, et al. (1989) Different immune mechanisms leading to autoimmunity in primary sclerosing cholangitis and autoimmune chronic active hepatitis of childhood. Hepatology 9: 198-203.

69. Wilschanski M, Chait P, Wade JA, Davis L, Corey M, et al. (1995) Primary sclerosing cholangitis in 32 children: clinical, laboratory, and radiographic features, with survival analysis. Hepatology 22: 1415-1422.

70. Rabinovitz M, Demetris AJ, Bou-Abboud CF, Van Thiel DH (1992) Simultaneous occurrence of primary sclerosing cholangitis and autoimmune chronic active hepatitis in a patient with ulcerative colitis. Dig Dis Sci 37: 1606-1611.

71. McNair AN, Moloney M, Portmann BC, Williams R, McFarlane IG (1998) Autoimmune hepatitis overlapping with primary sclerosing cholangitis in five cases. Am J Gastroenterol 93: 777-784.

72. Gohlke F, Lohse AW, Dienes HP, Löhr H, Märker-Hermann E, et al. (1996) Evidence for an overlap syndrome of autoimmune hepatitis and primary sclerosing cholangitis. J Hepatol 24: 699-705.

73. Gregorio GV, Portmann B, Karani J, Harrison P, Donaldson PT, et al. (2001) Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology 33: 544-553.

74. Chazouillères O (2000) Diagnosis of primary sclerosing cholangitis--

autoimmune hepatitis overlap syndrome: to score or not to score? J Hepatol 33: 661-663.

75. Ebbeson RL, Schreiber RA (2004) Diagnosing autoimmune hepatitis in children: is the International Autoimmune Hepatitis Group scoring system useful? Clin Gastroenterol Hepatol 2: 935-940.

76. van Buuren HR, van Hoogstraten HJE, Terkivatan T, Schalm SW, Vleggaar FP (2000) High prevalence of autoimmune hepatitis among patients with primary sclerosing cholangitis. J Hepatol 33: 543-548.

77. Abdo AA, Bain VG, Kichian K, Lee SS (2002) Evolution of autoimmune hepatitis to primary sclerosing cholangitis: A sequential syndrome. Hepatology 36: 1393-1399.

78. Abdalian R, Dhar P, Jhaveri K, Haider M, Guindi M, et al. (2008) Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: evaluating the role of routine magnetic resonance imaging. Hepatology 47: 949-957.

79. Lewin M, Vilgrain V, Ozenne V, Lemoine M, Wendum D, et al. (2009) Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: a prospective magnetic resonance imaging and histological study. Hepatology 50: 528-537.

80. Czaja A, Carpenter HA (1996) Validation of scoring system for diagnosis of autoimmune hepatitis. Dig Dis Sci 41: 305-314.

81. Kaya M, Angulo P, Lindor KD (2000) Overlap of autoimmune hepatitis and primary sclerosing cholangitis: an evaluation of a modified scoring system. J Hepatol 33: 537-542.

82. Boberg KM, Fausa O, Haaland T, Holter E, Mellbye OJ, et al. (1996) Features of autoimmune hepatitis in primary sclerosing cholangitis: an evaluation of 114 primary sclerosing cholangitis patients according to a scoring system for the diagnosis of autoimmune hepatitis. Hepatology 23: 1369-1376.

83. Hatzis GS, Vassiliou VA, Delladetsima JK (2001) Overlap syndrome of primary sclerosing cholangitis and autoimmune hepatitis. Eur J Gastroenterol Hepatol 13: 203-206.

84. Domschke W, Klein R, Terracciano LM, Jung P, Kirchner T, et al. (2000) Sequential occurrence of primary sclerosing cholangitis and autoimmune hepatitis type III in a patient with ulcerative colitis: a follow up study over 14 years. Liver 20: 340-345.

85. Hong-Curtis J, Yeh MM, Jain D, Lee JH (2004) Rapid progression of autoimmune hepatitis in the background of primary sclerosing cholangitis. J Clin Gastroenterol 38: 906-909.

86. Perdigoto R, Carpenter HA, Czaja AJ (1992) Frequency and significance of chronic ulcerative colitis in severe corticosteroid-treated autoimmune hepatitis. J Hepatol 14: 325-331.

87. Wurbs D, Klein R, Terracciano LM, Berg PA, Bianchi L (1995) A 28-year-old woman with a combined hepatitic/cholestatic syndrome. Hepatology 22: 1598-1605.

88. Lüth S, Kanzler S, Frenzel C, Kasper HU, Dienes HP, et al. (2009) Characteristics and long-term prognosis of the autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome. J Clin Gastroenterol 43: 75-80.

89. Lawrence SP, Sherman KE, Lawson JM, Goodman ZD (1994) A 39 year old man with chronic hepatitis. Semin Liver Dis 14: 97-105.

90. Floreani A, Rizzotto ER, Ferrara F, Carderi I, Caroli D, et al. (2005) Clinical course and outcome of autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome. Am J Gastroenterol 100: 1516-1522.

91. Chandok N, Silveira MG, Lindor KD (2010) Comparing the simplified and international autoimmune hepatitis group criteria in primary sclerosing cholangitis. Gastroenterol Hepatol (N Y) 6: 108-112.

92. Hunter M, Loughrey MB, Gray M, Ellis P, McDougall N, et al. (2011) Evaluating distinctive features for early diagnosis of primary sclerosing cholangitis overlap syndrome in adults with autoimmune hepatitis. Ulster Med J 80: 15-18.