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Review Article

Extrahepatic autoimmunity in autoimmune liver disease

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ABSTRACT

The most important autoimmune liver disease include: autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis. In general, about one in three patients with an autoimmune liver disease have a concomitant extrahepatic autoimmune disease, which may include rheumatological, endocrinological, gastrointestinal, pulmonary or dermatological conditions. The pathogenesis of these conditions includes the production of both innate and adaptive immune responses targeting cholangiocytes as well as different extrahepatic tissues. In this sense, extrahepatic autoimmunity represent a continuous spectrum of autoimmunity involving liver and extrahepatic tissues. This review aims to focus the clinical and pathophysiological aspects of extrahepatic autoimmunity associated to autoimmune liver diseases.

1. Introduction

Autoimmune liver diseases include: autoimmune hepatitis (AIH) characterized by necro-inflammation, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) both characterized by progressive cholestasis. Furthermore, the spectrum of autoimmune liver disease includes the overlap syndromes: AIH/PBC and AIH/PSC. The three common themes that underlie the induction and perpetuation of autoimmunity are: 1. genetic predisposition; 2. environmental factors; 3. defects in immune regulation. It is rather common that an autoimmune liver disease co-exists with another extrahepatic autoimmune condition. In general, about one in three patients with an autoimmune liver disease have a concomitant extrahepatic autoimmune disease, which may include rheumatological, endocrinological, gastrointestinal, pulmonary or dermatological conditions. The pathogenesis of these conditions includes the production of both innate and adaptive immune responses targeting cholangiocytes as well as different extrahepatic tissues. In this sense, extrahepatic autoimmunity represent a continuous spectrum of autoimmunity involving liver and extrahepatic tissues. This review aims to focus the clinical and pathophysiological aspects of extrahepatic autoimmunity associated to autoimmune liver diseases.

2. Autoimmune hepatitis

AIH is an acute or chronic disease of the hepatic parenchyma characterized by a loss of tolerance to hepatocyte-specific autoantigens [1]. The etiology of AIH remains to be fully understood, but it is well established that it requires both immunogenetic susceptibility and environmental triggers, finally converging to a pathologic attack of the immune system against hepatocytes [2]. Therefore, AIH can be defined as a multifactorial polygenic disease, caused by the interaction between a trigger and different environmental factors that occurs in a genetically susceptible individual. The overlap between AIH and other hepatic autoimmune diseases, such as PBC or PSC is well documented by numerous studies, as well as their epidemiologic details and clinical course [3–6]. However, only few studies [7,8] investigated the frequency of concurrent autoimmune diseases other than PBC or PSC in large numbers of patients. Clinical observations revealed that AIH patients may show signs or symptoms typical of extrahepatic autoimmune or immune-mediated disorders [9]. The presence of an extrahepatic autoimmune disease has been reported in a percentage of AIH patients ranging from 30 to 42%, depending on the cohort of patients with AIH enrolled in the study [6,8,10–12].

Among the different extrahepatic diseases, the most frequent association is with autoimmune thyroid diseases (including Hashimoto thyroiditis, Graves' disease and unspecified autoimmune thyroiditis),

Abbreviation: AIH, autoimmune hepatitis; AITD, autoimmune thyroid diseases; ASC, autoimmune sclerosing cholangitis; CD, Crohn's disease; IBD, inflammatory bowel disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; SSc, Systemic sclerosis; UC, ulcerative colitis

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autoimmune skin disease (alopecia, vitiligo, psoriasis), coeliac sprue, rheumatoid arthritis, Sjogren's syndrome and inflammatory bowel disease (IBD).

2.1. Autoimmune hepatitis and autoimmune thyroid diseases

According to the all the studies investigating the frequency of extrahepatic immune disorders and AIH [7,8,11,12], autoimmune thyroid diseases (AITDs), such as Hashimoto thyroiditis, Graves' disease, and unspecified autoimmune thyroiditis were the most common autoimmune disorders among AIH patients. Further information on the relationship between AIH and thyroid disorders came from the analysis of the serological subtypes, since it has been observed that AITDs were more common in type 2 AIH, together with hyperthyroidism, whereas hypothyroidism was more common in autoantibody-negative AIH. Although this association is the most common, to our knowledge there are no studies devoted to the selective understanding of the molecular and clinical basis of AIH and AITDs. In general, it is well known that autoimmune diseases are the result of a complex series of interactions between susceptibility genes, environmental factors and immune system. However, relatively limited results are available about the pathophysiological pathways of concomitant autoimmune diseases. Recently, new information came thanks to the development of molecular genetics, human genome-wide association studies (GWAS) and risk-associated single nucleotide polymorphism (SNP) [10]. In particular, the use of these approaches revealed that these patterns of coexistence/overlap depend predominantly on genetic determinants, since they are associated with inheritance of multiple gene loci that encode low-risk susceptibility alleles. However, the connections that have been reported by genetic approaches between autoimmune liver and thyroid diseases are usually referred to PBC and PSC, and not to AIH.

2.2. Autoimmune hepatitis and autoimmune skin diseases

Although skin diseases are sometimes underdiagnosed in AIH [13], some recent studies reported the association between AIH and some autoimmune cutaneous disorders, especially psoriasis, alopecia and vitiligo [14]. In particular, a retrospective study from the UK [12] described an association between a family history of autoimmunity and the presence of cutaneous extrahepatic autoimmune diseases in AIH patients. Furthermore, a number of case reports have been published describing this association [14].

As far as psoriasis is concerned, the coexistence with AIH has been documented, and it has been reported that the association AIH/psoriasis is the most common among those with cutaneous autoimmune diseases [15]. This observation is not surprising considering that, as in AIH [16], the involvement of Th17 (a CD4 + T-cell subset characterized by production of IL-17) seems to be crucial in psoriasis [17], although this is a general mechanistic observation regarding many autoimmune diseases, that needs to be studied in depth. Another study [18] reported a higher incidence of AIH in psoriasis patients, attempting a connection with the common pathogenetic role of tissue resident memory T cells in both diseases. However, since the role of this T cell subtype has been demonstrated in the etiopathogenesis of psoriasis and not AIH, this mechanistic conclusion remains to be further demonstrated.

As far as vitiligo is concerned, an Indian [19] and an Italian study [8] reported that AIH patients had an increased vitiligo prevalence, or at least a coexistence of these two autoimmune diseases. Another study analyzed a cohort of Brazilian patients, 82% of which had pediatric onset of AIH [20]. This study demonstrated that the group of AIH patients affected by extrahepatic autoimmune diseases were older than the patients without such conditions. The reported skin autoimmune diseases in this study were vitiligo, discoid lupus, scleroderma, and Weber panniculitis. Taken together, the results of this study indicated that extrahepatic autoimmune diseases were more frequent in the adult cohort, and the authors could thereby conclude that such conditions are probably due to the longer life span in adults and are usually diagnosed after AIH. Other studies involving both children and adults with AIH essentially confirmed this conclusion, and definitely pointed at vitiligo, alopecia areata and psoriasis as the main skin autoimmune comorbidities in AIH patients [14].

2.3. Autoimmune hepatitis and autoimmune rheumatic disorders

Historical descriptions of AIH were in association with systemic lupus erythematosus (SLE) and elderly patients with AIH have higher frequency of concurrent rheumatic conditions than young adults [21]. Among rheumatic diseases, Sjogren's syndrome (SS) and rheumatoid arthritis (RA) are more often associated to AIH, since SS can be diagnosed in up to 7% of patients with AIH, whereas the coexistence of AIH and RA ranges from 2% to 4% [22]. Although liver dysfunction has been reported in up to 60% of patients with SLE, the coexistence with AIH rarely occurs [23]. It is worth noticing that the epidemiologic links between AIH and systemic rheumatic manifestations are a signal of shared pathogenic mechanisms, as well as a common pattern of antinuclear antibody (ANA) positivity [24] and common laboratory abnormalities, e.g. hypergammaglobulinemia [25].

2.4. Autoimmune hepatitis, coeliac disease and inflammatory bowel disease

Coeliac disease is a common (1–2% of population is affected) autoimmune disease of the small intestine, which is also called gluten-sensitive enteropathy [26]. The pathology is driven by a well-recognized T-cell reactivity against dietary gluten [27] and its diagnosis is usually difficult because of the different symptoms and clinical expressions. Although the small bowel is usually the primary target, since the disease is manifesting as diarrhea, flatulence, and weight loss due to malabsorption, a systemic disease presentation is now recognized in approximately half of the patients [28,29]. In particular, elevated transaminases are detected in nearly 60% of untreated patients [30,31] and are sign of a portal hepatitis which is usually reverted by the gluten-free diet [32]. The pathogenesis of liver damage in coeliac disease remains to be defined in detail. However, the impairment of gut mucosa integrity, together with the overgrowth of intestinal bacteria, known to be features of coeliac disease, have been proposed to cause the delivery of bacterial products to the liver via the portal circulation [32]. Coeliac disease can also be associated with autoimmune liver diseases, such as PBC (with 6% of prevalence), followed by AIH (4%), and PSC (2%). It has been demonstrated that most coeliac patients (nearly 95%) are HLA-DQ2 positive, a serotype which is strongly associated to HLA-DR3, a risk factor for AIH [33]. In coeliac patients, the impairment of gut membrane (a phenomenon known as “leaky gut”) favors the entrance of non-well-digested gluten peptides from the lumen to the lamina propria, and this act as a trigger of autoimmune liver response [34].

Another intestinal condition, i.e. inflammatory bowel disease (IBD) has been associated to AIH, although most of the data concerning this association have been obtained in studies focusing on PSC, since the AIH/PSC overlap syndromes is more frequent [35–37]. Only few studies described patients with IBD and AIH alone, and they are mainly conducted in cohorts of pediatric patients [38,39], and on the few studies conducted in adults, AIH is often associated with ulcerative colitis [40].

Coeliac disease and IBD, both being inflammatory disorders of the intestine, share common characteristics, since they often diagnosed in young individuals, the prevalence is higher in women, and T cells are involved in their pathogenesis [41]. Furthermore, T cells are also involved in the relationship between liver and intestinal disorders, since in an impairment of regulatory T-cell function, which is a hallmark of both IBD and coeliac disease has been associated to hepatitis by both pre-clinical and clinical studies, so that there is a general consensus that they are important in maintaining tolerance to liver antigens [42].

Table 1
Extrahepatic autoimmune diseases possibly associated with primary biliary cholangitis.

Site-specific	Diseases
Rheumatologic diseases	Sjogren's syndrome
	Scleroderma
	CREST syndrome
	Rheumatoid arthritis
	Systemic lupus erythematosus
Endocrinologic diseases	Autoimmune thyroid diseases
	Autoimmune diabetes mellitus
Gastrointestinal diseases	Coeliac disease
	Ulcerative colitis
Dermatological diseases	Vitiligo (?)
	Psoriasis (?)
	Amicrobial pustulosis (?)
Pulmonary diseases	Interstitial lung diseases
	Pulmonary sarcoidosis

3. Primary biliary cholangitis

PBC is an autoimmune chronic cholestatic liver disease characterized by cholestasis, serological activity to antimitochondrial antibodies (AMA) or specific antinuclear antibody (ANA) reactivity and histological evidence of chronic non-suppurative, granulomatous, lymphocytic small bile duct cholangitis [25]. PBC can be associated to other extrahepatic autoimmune diseases namely rheumatologic, endocrine, gastrointestinal, dermatological diseases [43]. Moreover, an autoimmune involvement of pulmonary system [44] has been also described. To date no clear evidence exists regarding the impact of concomitant extrahepatic autoimmune diseases in natural history of PBC and its complication. On the other hand, the prompt recognition of these diseases is fundamental to ensure appropriate patient referral and treatment since extrahepatic autoimmune diseases may strongly impact on quality of life of these patients. Table 1 summarizes the most important extrahepatic autoimmune conditions associated to PBC.

3.1. Rheumatologic diseases

The prevalence of Sjogren's syndrome (SS) in PBC patients ranges between 3.5% to 100% in different studies [43,45–51] and the two diseases shared a common immunopathogenesis determining an immune-mediated destruction of epithelia and they are now both considered “autoimmune epithelitis” [52]. Indeed, in both diseases an interaction between genetic predisposition and environmental factors (probably bacteria in PBC and virus in SS) has been recognized to determine the disease onset. Then, once the immune response is initiated, other pathogenetic mechanisms determining the autoimmune epithelitis develop and appear to be similar in PBC and SS [52].

To date, the clinical impact of the association of PBC and SS has not completely elucidated since only one retrospective have compared clinical outcomes in patients with PBC and SS (PBC-SS) to patients with PBC alone [53]. In this study patients a higher percentage of death for all causes with a significant reduction of overall survival was observed in patients with PBC and concomitant SS compared to patients with PBC alone. Moreover, patients with PBC and SS had a higher cumulative incidence of spontaneous bacterial peritonitis and interstitial lymphocytic pneumonia compared to patients with PBC alone, thus suggesting a possible aggravation of immune deficiency in patients with the combination of the two diseases [53].

Systemic sclerosis (SSc) is a chronic autoimmune systemic disease characterized by fibrosis and vascular endothelial damage in multiple organs. Traditionally SSc is distinguished in two types, the diffuse type characterized by generalized dermal sclerosis and the limited type that affects only hands and fingers. The limited type, more frequently associated to PBC, further includes a subtype referred to as CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia) syndrome. Many case reports, but a few epidemiologic studies, have reported the association between PBC and SSc and overall the prevalence of SSc among patients with PBC ranges in different countries and according different diagnostic criteria between 1 and 20% [54–56]. The CREST variant is rather common in Italian PBC patients where is present in 6–15% of cases [8,43]. On the other hand, the prevalence of PBC among patients with SSc appeared to be less variables in different studies. A recent large multicentric disease registry-based study conducted in Spain and including 1572 patients with SSc found that 7.5% of patients with the disease had an associated hepatobiliary disorder and PBC constitutes the primary cause (4.3%) [57]. Similarly, a retrospective study from Japan including 225 patients with SSc found a prevalence of concomitant PBC of 9.8% [58].

Rheumatoid arthritis (RA) is another rheumatic disease possibly associated to PBC. Studies in this field are scarce and most studies use different classification criteria for RA instead of the standardized ACR/EULAR criteria. Epidemiologic data found a prevalence of RA in PBC patients of 1.8–5.6% [59]. Finally, the association between PBC and SLE has been also reported in 34 cases in literature and have been recently reviewed [60].

3.2. Endocrine diseases

Several studies have investigated the presence of overall thyroid dysfunction and/or AITD alone in PBC patients and the prevalence of AITD ranges between 5.6 and 22% [43,54,61–66]. Hypothyroidism is the more prevalent AITD in PBC varying between 63% and 86% of total AITD in different studies [43,64,66]. To date, the pathogenic mechanisms responsible of the association between PBC and AITD have not yet been elucidated. Recently, a significant association between the polymorphism of the protein tyrosine phosphatase non-receptor 22 (PTNP22) and the risk of development of PBC and PBC associated to AITD have been described [67]. Moreover, other AITD-triggering polymorphisms have been associated with a more severe hepatic disease, an increased risk of cirrhosis development and the need of liver transplantation [67]. Comparing PBC patients with and without AITD, no significant differences regarding the concomitant presence of other extrahepatic autoimmune disease [64], the stage and severity of liver disease [64,66], the response to ursodeoxycholic acid therapy and development of major clinical events (hepatocellular carcinoma, cirrhotic decompensation and liver transplantation) during follow-up [66,67] were observed. This suggest that the presence of concomitant AITD do not impair the prognosis of PBC patients.

Autoimmune diabetes or type 1 diabetes mellitus is an autoimmune disease with an early-onset caused by the immune-mediated destruction of insulin-producing beta cells of the pancreas, resulting in early insulin dependence. Regarding the possible association between PBC and type 1 diabetes data are rare and discordant thus not allowing conclusion in this point. Gershwin et al. observed that the prevalence of diabetes mellitus in PBC patients was similar to the control group, as well as the prevalence of diabetes mellitus in PBC relatives was similar to that of the relatives' control group [54]. Similarly, a previous study demonstrated the lack of association of autoimmune diabetes and PBC but a higher frequency of autoantibodies directed to the islet cell antigen glutamic acid decarboxylase (GAD65) in PBC patients compared to the control group was observed [68]. A Swedish study assessing familial association of type 1 diabetes and other autoimmune diseases observed that type 1 diabetes in offspring was associated with 13 autoimmune diseases in parents, including PBC, with a standardized incidence ratio (SIR) for PBC of 3.63 higher than that of other autoimmune disease i.e. Hashimoto's thyroiditis, Graves' disease or RA [69]. Finally, a case report described the association between latent autoimmune diabetes and PBC with portal hypertension phenotype [70]. To date, there is no sufficient evidence to conclude for an increased prevalence of autoimmune diabetes in PBC compared to general population.

3.3. Gastrointestinal diseases

3.3.1. Coeliac disease

Since the publication of the first 4 patients affected by the association between PBC and coeliac disease in 1978 [71] a number of case reports were published and collectively the prevalence of the two disease associated ranges between 0 and 11% [72]. Two large epidemiological studies conducted in Northern Europe at the end of the 90s evaluated the association between PBC and coeliac disease. The first study, based on a disease registry including patients with gastroenterological and liver diseases from South Wales revealed that PBC was present in 3% of 143 coeliac diseases patients and the coeliac disease was present in 6% of 67 PBC patients [73]. The second study based on the Danish National Registry and the Swedish National Inpatient Registry found that patients with coeliac disease were at increased risk of having PBC as assessed by significant standardized incidence ratio [74]. However, an Italian study examining 336 adult patients with coeliac disease and 65 PBC patients followed up for a median of 6 and 7 years respectively, showed that only one patient with coeliac disease received a diagnosis of PBC and in patients with PBC no cases of coeliac disease were found [75]. Moreover, another Italian study evaluating IgA and IgG tissue transglutaminase antibody prevalence in patients with connective tissue disease, inflammatory bowel disease and PBC found that the highest rate of false anti-transglutaminase positivity was present in PBC patients (10.4%) [76]. Taken together these studies did not provide evidence in favour of the necessity to screen PBC patients for coeliac disease, unless a clinical suspicion is present.

3.3.2. Inflammatory bowel diseases

The clinical association between ulcerative colitis (UC) and PBC has been reported in 18 patients in the form of case reports [77–80]. To date, only 3 cases describing the association between Crohn's disease (CD) and PBC have been published [81–83]. Recently, a large population based registry study including 47,325 patients with IBD in Denmark that aimed to evaluate association between IBD and other autoimmune disease found that PBC was more frequent in patients with UC compared to controls [84]. No any increase in prevalence of CD was observed in PBC patients compared to the control group. However, a common genetic disease susceptibility between CD and PBC compared to controls has been reported [85].

3.4. Pulmonary diseases

Patients with PBC might displayed pulmonary involvement secondary to SS, scleroderma and interstitial lung diseases [44].

The reduction of mean diffusion capacity observed in 39% of PBC patients [86] was associated with the severity of liver disease [87], to SS [86] or the presence of complete or incomplete scleroderma and serum anti-centromere antibody positivity [88]. Moreover, the presence of subclinical alveolar inflammation observed in PBC patients [89] was suggested to be associated to SS [90].

Pulmonary fibrosis, lymphoid interstitial pneumonia, non-specific interstitial pneumonia and bronchiolitis obliterans with organizing pneumonia are interstitial lung disease and were found to be significantly associated with PBC. This association is more relevant in patients with concomitant SS [53,91] or other rheumatologic disease such as RA, scleroderma, CREST syndrome and undifferentiated connective tissue diseases [92]. Lymphoid interstitial pneumonia and interstitial fibrosis with vascular hyperplasia histologically was documented in a small number of PBC patients [92]. Pulmonary fibrosis prevalence in PBC patients ranges between 5% and 13% [93,94] and finally bronchiolitis obliterans with organizing pneumonia associated to PBC is typical of patients with associated connective tissue disease [44].

Sarcoidosis is a non-autoimmune granulomatous systemic disease with main lung involvement that is typically associated to one or more autoimmune diseases. Despite many case reports have described the association of pulmonary sarcoidosis and PBC [95–102] raising the question of whether they share an autoimmune pathogenesis with some overlapping symptoms or they are different manifestations of the same clinical entity [96], an epidemiological study failed to identified a significant association between sarcoidosis and PBC [103].

3.5. Dermatological disease

Data regarding dermatological diseases and PBC and rare and discordant and no conclusion regarding an association of skin diseases and PBC could be made [14]. Three skin diseases, namely vitiligo, psoriasis and amicrobial pustulosis of the folds could be possibly associated to PBC.

An interview- based French study found a higher frequency of vitiligo but not psoriasis in PBC patients compared to controls [84,104], however a UK study found a significant association between personal history of psoriasis and risk of PBC [105]. Previously, Gershwin et al. described the association between vitiligo or psoriasis with PBC [54]. In an Italian cohort of 361 PBC the frequency of cutaneous skin diseases, vitiligo and lichen planus considered together was 5% of the total population, but data regarding the single disease were not available [43]. Lichen planus, one the most previously reported skin condition in PBC patients, was not found to be associated with PBC in different epidemiological studies [14].

4. Primary sclerosing cholangitis

PSC is a progressive cholestatic liver disease, mainly affecting the male gender presenting with chronic inflammation features of the bile ducts of any size, with significant morbidity and mortality. The most important characteristics are: 1. The high association with IBD which is nearly 70% [106]; 2. The risk for neoplastic diseases (cholangicarcinoma and colo-rectal cancer).

A number of secondary causes can mimic PSC including: infections, benign and neoplastic obstruction of the biliary tree, IgG4-related sclerosing cholangitis, ischemic forms, and congenital and/or idiopathic forms of sclerosing cholangitis. A variety of autoimmune diseases have been associated with PSC [107] including: membrano-proliferative glomerulonephritis, IBD, hypothyroidism, AIH, autoimmune haemolytic anemia, type 1 diabetes mellitus.

4.1. Primary sclerosing cholangitis associated with inflammatory bowel diseases

Among 47,325 patients with IBD included in the Danish National Patient Registry, twenty different immune-mediated disease were significantly more frequent than in 92,839 sex, age-, and municipality-matched controls [84]. PSC was predominant in men and most frequent in ulcerative colitis [84]. This strong correlation suggests a common pathogenic background between the two conditions. Although the exact pathogenesis of PSC is unknown, PSC develops in genetically susceptible individuals after exposure to some unknown environmental trigger [108]. Twenty-two susceptibility loci for PSC have been established at a genome-wide significance level, with the HLA complex representing the strongest findings by several orders of magnitude [109]. However, about half of the susceptibility genes overlap with the genetic architecture of other autoimmune diseases, i.e. type 1 diabetes mellitus, RA and multiple sclerosis [109]. This strong association between HLA-genes supports the involvement of adaptive immune responses in disease pathogenesis and position PSC as an autoimmune disease [109]. Nevertheless, genetic correlation between UC and PSC is substantially weaker, and between CD and PSC not statistically significant [110]. In a large multicentre, retrospective observational study including 8212 patients between January 1980 and December 2010 with one of the following diagnoses: PSC, small duct PSC, PSC with features of AIH, PSC

Table 2
IBD associated to primary sclerosing cholangitis.

- Most often classified as UC [113]
- Rectal sparing [114] and possibly backwash ileitis [115]
- Mild course [114]
- More severe predilection in right colon [116–120]
- High risk of pauchitis in patients undergoing proctocolectomy [115]
- High risk of cancer [119]
- IBD co-existing with PSC is genetically and clinically distinct from IBD alone [121]
- Colectomy associated to a decreased risk of recurrent PSC after liver transplant [122]

Table 3
Prevalence of primary sclerosing cholangitis/autoimmune hepatitis overlap syndrome by use of the modified AIH score.

Author	Country	N. of PSC patients	% with overlap
Van Buuren, 2000 [125]	Netherlands	113	8%
Kaya M, 2000 [126]	USA	211	1.4%
Floreani A, 2005 [36]	Italy	41	17%
Al-Chalabi T, 2008 [127]	UK	211	6.1%

with features of IgG4-associated cholangitis, IBD was found in 71% of patients [111]. Using MRC analysis of 322 patients with long-term IBD, a prevalence of PSC was found in 8.1% of cases, which is around 3-fold higher than that detected based on symptoms [112]. The most important features of IBD associated to PSC are summarized in Table 2 (refs [113–122]).

It is noteworthy that in a Danish population based cohort study from 1977 to 2011 the cumulative risk of colo-rectal cancer was significantly higher in PSC-IBD patients than in IBD controls [121]. PSC-IBD has been reported to be associated with a more severe inflammation in the right colon, whereas CU alone usually has a worse course distally [116–119]. Finally, the phenotype of PSC-IBD is genetically and clinically distinct from IBD alone [121].

4.2. Primary sclerosing cholangitis/autoimmune hepatitis

In paediatrics, sclerosing cholangitis is often associated with florid autoimmune features, including elevated titres of autoantibodies, in particular ANA and SMA; elevated IgG; and interface hepatitis [123]. This AIH/sclerosing cholangitis overlap syndrome, called autoimmune sclerosing cholangitis (ASC) has the same prevalence as AIH type 1 in childhood, as shown in a prospective study conducted over a period of 16 years [123]. In this study, all children with serological (i.e. positive autoantibodies, high IgG levels) and histological (i.e. interface hepatitis) features of autoimmune liver disease underwent a cholangiogram at the time of presentation. Approximately 50% of the patients enrolled in this prospective study had alterations of the bile ducts characteristic of sclerosing cholangitis and were diagnosed as having ASC. A quarter of the children with ASC, despite abnormal cholangiograms, had no histological features suggesting bile duct involvement, and the diagnosis of sclerosing cholangitis was only possible because of the cholangiographic studies. Virtually all ASC patients were seropositive for ANA and/or SMA. ASC was diagnosed in a similar proportion of boys and girls.

The mode of presentation of ASC was similar to that of AIH-1. Inflammatory bowel disease, mostly asymptomatic or paucisymptomatic, was present in 45% of children with ASC compared to 20% of those with typical AIH, and 90% of children with ASC had greatly increased serum IgG levels. At the time of presentation, standard liver function tests did not help in discriminating between AIH and ASC, although the alkaline phosphatase/aspartate amino transferase ratio was significantly higher in ASC. Atypical perinuclear anti-neutrophil cytoplasmic antibody (atypical pANCA, also termed pANNA) was present in 74% of patients with ASC compared with 45% of patients with AIH-1 and 11% of those with AIH-2.

In adults overlap syndrome between PSC and AIH has been described in both large duct PSC and in the small-duct variant [124]. The diagnosis of PSC/AIH is difficult to establish. Using the modified AIH score, the prevalence of overlap syndrome ranges between 1.4% and 17% among series of PSC patients in different countries (Table 3, refs [36, 125–127]). In our experience, AIH/PSC overlap syndrome is a variant of PSC that mainly affects young people [36]. It should be suspected in the case of little or no response to immunosuppression in a patient with AIH [36].

Conflict of interest

The authors declare no conflict of interest.

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