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Primary sclerosing cholangitis, autoimmune hepatitis and overlap syndromes in inflammatory bowel disease

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Abstract

Primary sclerosing cholangitis (PSC) is a chronic progressive disorder of unknown aetiology characterised by chronic inflammation and stricture formation of the biliary tree. Symptoms include itch and lethargy and in advanced cases cholangitis and end-stage liver disease, however increasing numbers of asymptomatic individuals are being identified. The disease is rare in the general population but is strongly associated with inflammatory bowel disease (IBD) affecting up to 5% of patients with Ulcerative Colitis, with a slightly lower prevalence (up to 3.6%) in Crohn's disease. The strength of this association means that the vast majority (> 90%) of patients with PSC also have IBD, although many may have only mild gastro-intestinal symptoms. Usually IBD presents before PSC, although vice-versa can occur and the onset of both conditions can be separated in some cases by many years. Mean age of diagnosis of PSC is in the fifth decade of life with a strong male predominance. Risk is increased in those with a family history of PSC, suggesting a genetic predisposition and the disease is almost exclusive to non-smokers. The ulcerative colitis associated with PSC is characteristically mild, runs a quiescent course, is associated with rectal sparing, more severe right sided disease, backwash ileitis and has a high risk of pouchitis post-colectomy. Most worrisome is the high risk of colorectal malignancy which necessitates routine colonoscopic surveillance. Cholangiocarcinoma is also a frequent complication of PSC with a 10%-15% lifetime risk of developing this condition. Treatment with high dose ursodeoxycholic acid offers some chemoprotective effects against colorectal malignancy and may decrease symptoms, biochemical and histological progression of liver disease. Small duct PSC patients characteristically have normal cholangiography, and liver biopsy is required for diagnosis, it appears to have a more favourable prognosis. Autoimmune Hepatitis (AIH) is also more prevalent in patients with IBD, with up to 16% of patients with AIH also having ulcerative colitis. A small subgroup of patients have a AIH-PSC overlap syndrome and the management of these patients depends on liver histology, serum IgM levels, autoantibodies, degree of biochemical cholestasis and cholangiography as some of these patients may respond to immunosupression.

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INTRODUCTION

The first association between colonic ulceration and liver disease was made in 1874 by Thomas CH, who described a young man who died of a 'much enlarged, fatty liver in the presence of ulceration of the colon'[1]. The association was confirmed by James Lister in 1899, who reported a patient with ulcerative colitis and secondary diffuse hepatitis[2]. Over the next 100 years it has become well established that there is a close relationship between inflammatory bowel disease and various hepatobiliary disorders. These disorders are listed in Table 1.

PRIMARY SCLEROSING CHOLANGITIS

First described by Smith and Loe in 1965[3] Primary sclerosing cholangitis (PSC) is a chronic progressive disorder of unknown aetiology characterised by inflammation, fibrosis and stricture formation in medium and large sized ducts in the biliary tree[4,5]. Common symptoms include itch and lethargy although many patients (up to 45%) are asymptomatic, even with advanced disease[5]. The disease is strongly associated with Inflammatory Bowel Disease and may be detected as an incidental finding of a raised serum alkaline phosphatase. Magnetic resonance

Table 1 Hepatobiliary disorders associated with inflammatory bowel disease

Hepatobiliary disorders	Associated with	
	Ulcerative colitis	Crohn's disease
Primary sclerosing cholangitis (PSC)		
Large duct PSC	+	+
Small duct PSC ('pericholangitis')	+	+
Cirrhosis	+	+
Hepatoma	+	+
Cholangiocarcinoma	+	+
Miscellaneous disorders		
Fatty liver	+	+
Granulomas		+
Amyloidosis		+
Hepatic abscess		+
Gallstones		+
Autoimmune hepatitis	+	
Primary biliary cirrhosis	(+)	
Budd-Chiari syndrome	(+)	(+)

+: Definite association; (+): Possible association.

Table 2 Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis

Country of origin	Number of patients with ulcerative colitis	Percentage with primary sclerosing cholangitis
Oxford, UK[9]	681	2.9
Oslo, Norway[12]	336	4
Stockholm, Sweden[11]	1500	3.7 (5.5 in total colitis)

Figure 1 Endoscopic Retrograde Cholangiogram showing the classic 'beaded' appearance of bile ducts in Primary Sclerosing Cholangitis.

patients with ulcerative colitis had significant histological abnormalities on hepatic histology compared with 10% of 100 unselected patients with Crohn's disease; none of these patients underwent cholangiography[9,10]. Studies (Table 2) using selected patients include a large Swedish study of 1500 patients with UC where it was found that 5% of patients had increased serum Alkaline Phosphatase and, of those who underwent ERCP, 85% had evidence of PSC, being more common in men and those with pancolitis[11]. Other reports have found similar results. In a study from Oslo, 14% of patients had evidence of hepatobiliary pathology with 4% of patients with UC having PSC[12]. Thus it is generally accepted that approximately 5% of patients with UC will have associated PSC.

The percentage of Crohn's disease patients affected by PSC is much smaller[13]. In one study of 262 patients, 38 (15%) had abnormal liver function tests and underwent ERCP and liver biopsy, 9 of these (3.4% of the total) had PSC[14]. Crohn's disease associated with PSC is generally seen in patients who have extensive colonic or ileocolonic disease, or in paediatric populations.

IBD in PSC

Vice versa the great majority of patients with PSC have underlying IBD. The frequency with which it is recognised again varies widely depending on the intensity with which it is sought, varying from a minimum 25% of all PSC patients having IBD if identified by clinical history alone to 90% of patients if biopsies of rectum and sigmoid are taken at the time of flexible Sigmoidoscopy[15]. There are also large geographical variations in the prevalence of IBD in PSC (Table 3). Since the recognition of inflammatory bowel disease has important implications in terms of risk of colorectal cancer (PSC patients without IBD are not at increased risk of colorectal cancer and do not require colonoscopic surveillance[16]) it is the authors practice to perform colonoscopy and serial biopsies in all patients with newly diagnosed PSC.

Aetiology

The aetiology of PSC itself is unknown. The 2:1 male to female gender ratio of patients and the relatively poor response of the disease to immunosuppression suggest that PSC is not a classic autoimmune disease. However the association of PSC with IBD, autoimmune diseases, and a host of other humoral and cellular immune abnormalities

cholangography (MRCP) and endoscopic cholangiography (ERCP) are diagnostic, demonstrating the diffuse multifocal strictures and dilatation giving rise to a characteristic 'beaded' appearance (Figure 1).

Prevalence

PSC is rare in the general population. Data from Olmsted County (USA) in the year 2000 identified 20.9 cases of PSC per 100 000 of the population in men and 6.3 per 100 000 in women[6], which is similar to that seen in the UK[7]. There has been a suggestion that the incidence may be rising. In Spain the prevalence in 1988 was 2.24 per million having been 0.78 cases per million in 1984[8]. It is however unclear if this represents a true increase in the disease or improved case recognition due to improved diagnostics particularly in asymptomatic individuals.

PSC in IBD

Because of its strong association with inflammatory bowel disease (IBD) PSC is far more common in patients with ulcerative colitis (UC). The prevalence quoted in different case series varies widely, largely due to differences in the number of patients included with severe, active, or extensive inflammatory bowel disease studied and also in the method used to investigate liver dysfunction. Studies on unselected patients provide the most accurate data but are ethically difficult as both liver biopsy and ERCP are associated with significant morbidity. In an early study of unselected adult patients from Oxford, 5%-6% of the 300
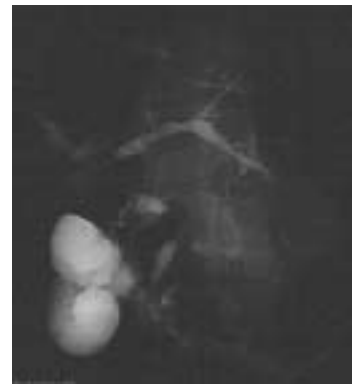
Table 3   Prevalence of inflammatory bowel disease in patients with primary sclerosing cholangitis (PSC)

Institution (country of origin)	Number of patients with PSC	Percentage with IBD
Royal Free Hospital (UK)[17]	29	72
Mayo Clinic (USA)[18]	50	70
Huddinge (Sweden)	305	72
King's College London (UK-children)	13	77
Okolicsanyi (Italy)[19]	82	54
Escorsell (Spain)	43	47
Okada (Japan)[20]	155	23

(Table 4) make an immunopathogenic mechanism likely. Particularly common serological abnormalities are raised IgM levels in up to 50% and positive anti-smooth muscle antibodies and antinuclear antibodies in up to 75%[21]. Anti Neutrophil Cytoplasmic Antibodies with a pericellular pattern (pANCA) are also a common finding, being present in 80% of patients being and unrelated to the presence or absence of UC. Cellular immunity anomalies include portal tract infiltration of functional T cells, restricted T cell receptor repertoire, and aberrant expression of HLA and costimulatory molecules on biliary epithelial cells.

Immunogenetic studies have identified a number of key HLA haplotypes (Table 5) associated with PSC, HLA-B8/DR3 haplotype being particularly common in patients with PSC and UC and infrequent in patients with PSC alone[22]. This haplotype is also associated with other organ-specific autoimmune disease including coeliac disease, thyrotoxicosis, lupoid autoimmune hepatitis, myasthenia gravis, and type 1 diabetes mellitus. However PSC, independent of HLA type, is also associated with a range of autoimmune diseases, diabetes mellitus and Graves disease being the most common. Saarinen *et al* found that 25% of patients with PSC had one or more autoimmune disease, compared to 9% of patients with inflammatory bowel disease alone[23].

Possible explanations for the PSC association with IBD include the development of autoantibodies to an unknown antigen in an immunogenetically susceptible host which cross reacts with biliary and colonic epithelium and is capable of inducing complement activation[24]. Alternatively, the initiation of the immune response may be the ingress of bacteria or other toxic metabolites through the diseased bowel wall.

CLINICAL COURSE

Onset

PSC is a disease of middle age with a mean age of diagnosis is 40 years in men and 45 years in women. Bowel symptoms have usually developed before those of PSC and UC is therefore usually diagnosed several years before PSC. However occassionally symptoms of PSC may precede IBD by up to 4 years[25]. The age of onset of the symptoms also has important implications as there is evidence to suggest patients with Colitis in childhood have a high prevalence

Table 4   Evidence for the influence of immune mechanisms on the aetiology of PSC

Humoral immunity	Increased circulating immune complexes
	Elevated immunoglobulin levels (IgG and IgM)
	Low titres of non-organ specific autoantibodies (ANA and SMA)
	High titres of antineutrophil antibodies
	Autoantibodies to BEC surface antigens
Cell mediated immunity	Decreased levels of circulating peripheral CD8+ve Tcells
	Portal T cell and NK cell infiltrate
	Increased activated and memory T cells
	Restricted T cell receptor repertoire (Vβ3)
	Aberrant expression of HLA-DR on BEC
	Coexpression of costimulatory molecules and HLA-DR on BECs
	Increased circulating and tissue bound adhesion molecules
Immune effector mechanisms	Enhanced cytokine expression in the liver
Immunogenetic mechanisms	HLA associations

Table 5   Key HLA haplotypes associated with primary sclerosing cholangitis

Haplotype	Significance in PSC
B8-TNF*2-DRB3*0101-DRB1*0301-DQA1*0501-DQB1*0201	Strong association with disease susceptibility
DRB3*0101-DRB1*1301-DQA1*0103-DQB1*0603	Strong association with disease susceptibility
DRB5*0101-DRB1*1501-DQA1*0102-DQB1*0602	Weak association with disease susceptibility
DRB4*0103-DRB1*0401-DQA1*03-DQB1*0302	Strong association with protection against disease
MICA*008	Strong association with disease susceptibility

of liver abnormalities than adults, with up to 60% children having abnormal liver function tests[26].

Risk factors

Unlike other immune mediated diseases PSC is far more common in men with 70% of all PSC patients being male. This male preponderance is absent in PSC patients without associated IBD, being equally common in both males and females[27]. In addition to IBD and male sex, another recognised risk factor is a family history of the disease, There is a 0.7% risk in first degree relatives of patients with PSC rising to 1.5% in siblings of affected individuals[28].

Smoking is a well recognized protective factor against the development of ulcerative colitis, and three studies have suggested that cigarette smoking may also additionally protect against the development of PSC. Moreover, this protective effect was more marked in patients with primary sclerosing cholangitis than ulcerative colitis and was seen in patients with and without inflammatory bowel disease[29-31]. The mechanism of protection in both disorders remains unknown.

Clinical characteristics of IBD associated with PSC

There are a number of unique features of Ulcerative

Colitis associated with PSC (Table 6). The colitis is often mild, asymptomatic and runs a quiescent course[32]. It is associated with rectal sparing[33]; and therefore not seen on rigid sigmoidoscopy; is often more severe proximally and associated with backwash ileitis. It may be visible microscopically with a relatively normal macroscopic appearance and pouchitis is far more common after colectomy and ileo-anal pouch formation, occurring in up to 60% of PSC patients compared to 15% in patients with UC alone[34].

Most importantly PSC is a significant risk factor for the development of carcinoma of the colon in patients with inflammatory bowel disease[35-37]. A meta-analysis demonstrated a four fold increase in colon cancer in UC patients with PSC when compared to UC alone (RR 4.26 95% CI 2.8-6.48)[38]. The risk of proximal cancer is particularly increased[37,39]. Additional risk factors are duration and extent of disease and a family history of colorectal cancer[40]. Current U.K. guidelines therefore recommend annual screening colonoscopy in IBD patients with PSC[41].

Treatment of PSC with ursodeoxycholic acid appears to have a chemopreventative effect decreasing the incidence of carcinoma of the colon and is therefore recommended[42]. Treatment with 5-aminosalicylic acid (5-ASA) compounds have also been shown to reduce the risk of colorectal cancer in general patients with UC[43]. There are no studies specific for PSC/IBD patients in this context but it is reasonable to infer that it will be protective and is also therefore recommended.

Prognosis

Despite treatment however PSC is generally progressive and prognosis poor. Median survival without liver transplantation after diagnosis is approximately 12 years[44] with survival worse for those who are symptomatic at presentation[45].

The major cause of mortality is the occurrence of cholangiocarcinoma, which is significantly increased in patients with PSC who display a 10%-15% lifetime risk of developing the disease. This risk is higher in patients with associated inflammatory bowel disease than those with PSC alone, with an estimated annual incidence of 0.5%-1%[46-48]. Unfortunately there remains no validated screening tool for cholangiocarcinoma and therefore tumours often present at an advanced stage and have a poor prognosis. Other complications of PSC include osteoporosis, this is a frequent finding the mechanism of which remains unclear[49]. Bone density measurement should therefore be considered in these patients.

PSC treatment

Treatments which have been tried in an attempt to prevent progression of the liver disease to cirrhosis and to decrease the risk of complications especially malignancy include tacrolimus[50], methotrexate[51], corticoteroids[52], D-penillamine[53], etanercept[54], cyclosporin[55], azathioprine, 6-mercaptopurine[56] and pentoxifylline[57]. None of these agents have demonstrated any consistent benefit.

Ursodeoxycholic acid (UDCA) is the only drug which

Table 6 Clinical, Endoscopic, and Histological findings that characterize IBD-PSC
Male predominance
Quiescent colitis
Pancolitis
Rectal sparing
Backwash ileitis
Pouchitis
Colorectal dysplasia/carcinoma
Different extracolonic manifestations

has been demonstrated to have a positive effect. It is also the most extensively studied[58] with some, but not all, studies showing improvements in biochemistry, symptoms and histology[59-64]. The most promising data is for long term UDCA used at high dose, 20-30 mg/kg per day (in divided doses), as this may increase clinical benefit and decrease histological progression of disease[65,66]. In view of its chemopreventative effect against colon cancer and its low incidence of side effects, high-dose UDCA is currently the best available treatment for PSC.

The concurrence of both conditions also requires that the impact of treatment of either disease on the other must be considered. Proctocolectomy appears to have no effect on liver biochemistry, histology or survival of patients with PSC and chronic UC[67]. However the natural history of UC following liver transplantation is variable[68-72]. One study showed approximately a third had improvement in colitis, a third remained unchanged and a third suffered increased activity of colonic disease[73]. Several series report increased rates of colon cancer and colectomy after liver transplantation[74-76]. It remains unclear if this is due to longstanding immunosuppressant use or confounding variables such as long duration of disease.

SMALL DUCT PSC

A variant of the disease called 'small duct PSC' is applied to the small percentage of patients with characteristic clinical findings but who have a normal cholangiogram. The absence of macroscopic abnormalities necessitates liver biopsy for the diagnosis of small-duct PSC. Characteristic features of PSC on liver biopsy are concentric rings of connective tissue around bile ducts, the so-called 'onion ring' appearance[77]. Other features which are less specific include enlargement of the portal triads, periportal inflammation with mononuclear and polymorphonuclear cells, oedema and bile duct proliferation. Extension into the hepatic parenchyma with bridging fibrosis and ultimately cirrhosis represents advanced disease.

Small duct PSC appears to have a more favourable prognosis with a median survival 29.5 years compared to 17 years for classical PSC[78-81], although occasionally patients with small duct PSC progress to large duct disease.

AUTOIMMUNE HEPATITIS AND OVERLAP SYNDROMES IN IBD

Patients with IBD are also at increased risk of other of

immune mediated liver disease including autoimmune hepatitis (AIH). In one study, UC was present in 16% of patients with AIH[82]. AIH and PSC may also occur within the same individual and it remains unclear if this represents the independent occurrence of both diseases, either sequentially or concurrently, the presence of a distinct overlap syndrome or different stages in the evolution of a single disease entity.

Difficulties with definitions and thus classification of these patients has led to widely varying estimates as to the frequency of the coexistence of the two conditions with studies ranging from 7.6% to 53.8%. of patients with PSC have features of AIH[83-89]. and conversely an abnormal cholangiogram being present in 42% of patients with AIH and UC. The association between AIH and PSC appears more common in the paediatric population.

Patients with PSC should be suspected of having associated AIH or AIH-PSC overlap if they have interface hepatitis on biopsy, high serum IgG levels, lower ALP and the presence of autoantibodies (ANA or SMA titre > 1:40). It is important to identify these patients as they maybe responsive to treatment with steroids[85].

Patients with AIH should be suspected of having associated PSC or AIH-PSC overlap[90] if they have pruritis, UC, bile duct abnormalities on histology, cholestatic liver biochemistry (ALP × 2 ULN) and abnormal cholangiography. These patients tend to be unresponsive to steroids[87,91-93].

CONCLUSION

From the original descriptions of liver disease associated with disease of the bowel over a century ago much progress has been made. The association of inflammatory bowel disease with PSC, AIH and overlap syndromes is now well established and much is known on the epidemiology and course of the conditions. Although there remain many more questions than answers, an increasingly developed concept of hepatobiliary disorder in inflammatory bowel disease has emerged. It is suggested that the major hepatobiliary diseases seen in association with both UC and Crohn's disease, namely PSC, cirrhosis, cholangiocarcinoma, and most cases of autoimmune hepatitis, represent different aspects of the same spectrum of hepatobiliary disease. However what is cause, what is consequence and what is coincidence remains to be seen.

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