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PRIMARY SCLEROSING CHOLANGITIS: COMPLICATIONS AND CONSEQUENCES

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Natural course of primary sclerosing cholangitis (PSC)

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PSC is a progressive disease. However, the rate of progression is very variable. Thus, it is nearly impossible to predict the natural course in the individual patient. It is generally assumed that the median survival is in the range of 10-12 years after diagnosis. Today due to a greater awareness and better diagnostic tools PSC is often detected in an early stage, resulting in a large number (up to nearly 50%) of asymptomatic cases.

Unfortunately, both groups, asymptomatic as well as symptomatic patients, seem to have a decreased survival as compared to a matched control group. Data, however, are conflicting:
In Sweden, the survival rate for asymptomatic patients was estimated as 70% at 16 years, whereas results from the US disclosed a survival of 88% of the asymptomatic patients after only 5 years of observation.

The natural course of PSC is further complicated not only due to the slowly progressive liver insufficiency but also to the predisposition to cholangiocarcinoma (CCC) and colorectal cancer.
The prevalence of CCC varies in various studies (range: 6-36%). It is assumed that 0.5-1% of PSC patients will develop CCC per year.
Unfortunately up till now diagnosis of CCC remains extremely difficult, especially in the early stages. Contrary to early believe, the duration of PSC seems not to be correlated with the development of this severe complication. Some new data suggest that the activity (and stage) of the underlying liver disease could be correlated with the risk for this malignancy.

How to predict survival?
It is still difficult to predict the survival in the individual PSC patient despite the existence of various mathematical models (e.g. Mayo model, King’s model, Swedish model, etc.).
For practical purposes it should be remembered that the readily available Child-Pugh classification could serve as a discriminating tool with 7-year survival rates of 89.8% (Child A), 68% (Child B) and 24.9%, respectively (Child C).

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Histopathology of primary sclerosing cholangitis (PSC)

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PSC - a chronic cholestatic syndrome characterized by fibrosing inflammation in the intrahepatic and extrahepatic bile ducts leading to narrowing and, eventually, obliteration of the bile ducts and development of cirrhosis.

Ethiolog[y and Pathogenesis: PSC is a heterogeneous disease entity. Theoretic pathogens include toxins, infectious agents, and abnormalities in immune regulation. Although excess copper has been implicated, patients have not responded to chelation with penicillamine, suggesting that elevated hepatic copper levels are a secondary phenomenon (as in primary biliary cirrhosis). Both cytomegalovirus and reovirus type 3 may affect the intrahepatic bile ducts, there is little evidence that these viruses are present in all patients with PSC. The association of primary sclerosing cholangitis with other autoimmune disorders indicates a genetic predisposition for this disease. HLA-B8 and HLA-DR3, often found in autoimmune diseases, have also been associated with PSC. Destruction of the bile ducts in PSC involves T lymphocytes, and alterations in many arms of the immune system have been noted: lymphoplasmacytic infiltration, many eosinophils, and obliterative phlebitis. Immunohistochemically, marked lymphoplasmacytic infiltration and many IgG4-positive plasma cells were found in the bile duct lesions of all PSC cases.

Histopathology: The early changes of PSC (stage I) may be inconspicuous. Interlobular bile ducts may show only mild, epithelial irregularity, with focal atrophy. The hyperplastic epithelial changes seen in PBC are not seen in PSC. Instead, partial lumen obliteration and focal branching of bile ducts may be seen. Portal tracts have a mild chronic inflammatory cell infiltrate, mostly lymphocytes, is confined to the portal tract; interface hepatitis usually is not seen in early stage PSC. Lymphoid aggregates may be seen, but germinal centers are not characteristic. Granulomas are only rarely seen. Stage II PSC is characterized by more extensive inflammatory interface hepatitis, sometimes mimicking chronic hepatitis C or autoimmune hepatitis. Bile ductular proliferation is usual but may be minimal and only focal. Mild fibrosis of the portal tracts may be evident. Parenchymal changes are prognostically more important than bile duct alterations. Stage III PSC has the characteristic, but not pathognomonic, pattern of periductal fibrosis. The "onion skinning" type of fibrosis becomes more obvious in later stages of PSC but can be present earlier. Ultimately, there is bile duct loss and complete replacement of the bile duct with a characteristic fibrous scar, described as "smudgy". Unfortunately, this scarring is not uniformly distributed and often is not seen in biopsy samples. At this stage progressive, biliary-type fibrosis is more extensive and porto-portal bridging usual. The inflammatory infiltrate is generally less prominent. With many original interlobular bile ducts lost, portal tracts contain only hepatic arteries and portal vein tributaries. Periportal/periseptal hepatocytes show cholate stasis, similar to that in PBC, with accumulation of copper and copper-binding protein, and occasionally Mallory hyalin. Despite extensive loss of interlobular bile ducts, there is very little bile duct proliferation. Centrolobular cholestasis is seen only when large bile ducts are affected and is an exceptional finding in the small duct variant of PSC. Stage IV PSC has extensive
biliary-type fibrosis imparting the typical picture of biliary-type cirrhosis. The advanced stages of PBC and PSC may be indistinguishable, and the correct diagnosis requires clinical information.

PSC and cholangiocarcinoma (CC): PSC confers a high risk of CC development. The presence of carcinoma in situ in areas of fibrous cholangitis, the multicentric origin of the tumor, the presence of tumor-free large-duct PSC or small-duct PSC (pericholangitis) at a distance from the carcinomatous areas, and the documentation, in some cases, of long-standing inflammatory hepatobiliary disease prior to the discovery of the tumors would seem to confirm the clinical impression that carcinomas may develop in pre-existing PSC. The appearance of hepatobiliary carcinomas in patients with classic PSC and in patients with pericholangitis supports previous evidence indicating that cholangiographically diagnosed large-duct PSC and histologically diagnosed small-duct PSC (pericholangitis) are manifestations of a shared condition that could be named PSC syndrome.
Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by diffuse inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts. The histopathologic evolution of PSC results in irreversible damage to the bile ducts and ultimately leads to cholestasis, cirrhosis, liver failure, and premature death from liver failure unless liver transplantation is performed.

The diagnostic criteria for PSC are focused on the characteristic cholangiographic findings, which continue to be considered the diagnostic standard. They include (1) diffusely distributed multifocal annular strictures with interventing segments of normal or slightly ecstatic ducts; (2) short band-like strictures, and (3) diverticulum-like outpouchings. In addition, compatible clinical features (i.e., history of IBD, cholestatic symptoms) and a characteristic biochemical profile (i.e., three-fold increases in serum alkaline phosphatase for longer than 6 months) may aid in the diagnosis.

Characteristic feature of PSC is the male predominance, with male:female ratio of approximately 2:1. PSC patients are rather young, with a mean age at diagnosis between 30 and 40 years. About 50% of patients have symptoms of hepatobiliary disease at diagnosis.

The diagnostic criteria for PSC include the absence of previous surgical trauma to the biliary tree, absence of stones in the gallbladder and common bile duct, stenosis involving the majority of the hepatobiliary system and exclusion of malignant disease.

In current clinical practice, liver biopsy is not generally required to establish the diagnosis of PSC. Hepatic histology is useful to exclude other causes of liver injury in difficult to diagnose cases of PSC; to define the stage of PSC for prognosis and to diagnose small duct PSC.

The differential diagnosis for PSC includes causes of secondary sclerosing cholangitis such as previous biliary tract surgery, bile duct neoplasm, AIDS cholangiopathy, choledocholithiasis, congenital abnormalities, history of caustic sclerosis of the bile ducts, ischemic strictures post transplantation or caustic/chemical injury to the bile ducts via infusion.

Finally, in the differential diagnosis of PSC, other hepatobiliary diseases must be considered such as primary biliary cirrhosis, idiopathic adulthood ductopenia, drug-induced cholestasis, cholestasis associated with alcoholic liver disease, and overlap syndrome. These conditions can be excluded on the basis of clinical history, serology, and hepatic histology.
Is small duct PSC a separate disease?

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A proportion of 10-20% of all patients with primary sclerosing cholangitis do not demonstrate the typical scarring lesions of the large bile ducts, but nonetheless demonstrate sclerosing cholangitis on biopsy. On ERCP the only pathological finding that can be detected is a difficulty of filling the intrahepatic ducts with contrast material, requiring balloon occlusion of the common bile duct and injection of contrast material with relatively high pressure in order to fill the major segmental ducts and their branches with sufficient contrast material to allow high-quality X-ray pictures. However, even with this technique, typical scarring can often not be demonstrated in these intrahepatic ducts, but a certain rarefication may be observed. On the other hand, while in normal PSC liver biopsy may fail to detect the characteristic sclerosing lesions at initial diagnosis because of the focal nature of sclerosing cholangitis, in patients with small duct PSC the lesions seem to be much more evenly distributed over the whole liver, thus giving liver biopsy a relatively high accuracy rate for detecting this condition.

Two large series, and a number of smaller reports, suggest that patients with small duct PSC in many respects represent a separate entity. In contrast to “normal” PSC, there does not seem to be a major preponderance in small duct PSC. The disease course is clearly much more benign with only a small proportion of patients progressing towards cirrhosis within 10 years. Some of the patients appear to have some overlap with autoimmune hepatitis and may benefit from immunosuppression. Liver enzymes clearly improve in these patients with UDCA-treatment, but in view of the small number of cases and the relatively benign spontaneous course, it is not clear, if this treatment changes the natural course of the disease. Only very few of the patients with small duct PSC seem to progress towards large duct PSC. However, this appears to be so uncommon, that the question arises, if these patients indeed did initially already have large duct lesions, which were overlooked on the primary diagnostic radiological testing of the bile ducts. So far, there are no reports of cholangiocarcinoma in patients with long-standing small duct PSC underlining the relatively benign prognosis of this condition.

It is likely, that small duct PSC in some ways represents a separate disease entity from large duct PSC. The clinical picture is slightly different, the disease course is more benign and at present there is no association with malignancy. Only a few patients seem to progress from small duct PSC to large duct PSC. As long as we do not know the etiology of either large duct PSC or small duct PSC, the exact disease definition remains speculative, but the clinical differences that we know are meaningful to the patients. Patients with small duct PSC have a much better prognosis. Nonetheless, it is strongly recommended, that they receive long-term treatment, which depending on the activity of the disease may consist of UDCA monotherapy or, in more aggressive forms, also of additional immunosuppression.
Autoimmune hepatitis/PSC-overlap syndrome

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The hepatitic autoimmune liver diseases include autoimmune hepatitis type I and II (AIH), the autoimmune hepatitis of the autoimmune polyendocrine syndrome and probably a high percentage of patients with a so-called cryptogenetic chronic hepatitis. The group of cholestatic autoimmune liver diseases comprises primary biliary cirrhosis (PBC), autoimmune cholangitis or AMA-negative primary biliary cirrhosis (AIC), primary sclerosing cholangitis (PSC), pericholangitis, which probably represents a subclinical course of PSC and the rare sclerosing pancreatocholangitis.

Overlap syndromes are clinical features in which two different autoimmune or chronic liver diseases are present in one patient. There is no clear definition of overlap syndromes. According to the prevalence of serological and morphological criteria, the overlap syndrome AIH/PBC is seen in about 8% of all patients with autoimmune liver diseases. The overlap syndrome AIH/PSC in about 6%. This means that overlap syndromes are rare. The autoimmune hepatitis/PSC-overlap syndrome is best described in children, but also seen in adults. 60-70% of the patients are male, the mean age is 20-30 years. The question as to whether there is an overlap syndrome between autoimmune hepatitis and primary sclerosing cholangitis is not disputed.

Laboratory tests reveal typical findings as seen in autoimmune hepatitis: SMA, ANA, p-ANCA and hyperggammaglobulinemia and as seen in PSC: an increase of alkaline phosphatase and gamma-glutamyltranspetidase.

The AIH/PSC-overlap syndrome is characterized by the typical morphological picture of PSC seen in ERC, MRC and liver histology: Irregular alterations of the intra- and extrahepatic bile duct system, histologically onion skin like layers of connective tissue surrounding bile ducts and an inflammation of the portal tract. But also features of autoimmune hepatitis can be detected, as e.g. lobular infiltrates. Like AIH and PSC the overlap syndrome may proceede to liver cirrhosis.

Clinically the AIH/PSC-overlap syndrome is associated with chronic inflammatory bowl disease, ulcerative colitis or Crohn’s disease. The association of the overlap syndrome with ulcerative colitis is less frequent as in PSC not overlapping with autoimmune hepatitis, Crohn’s disease is rare or even missing.

There is no confirmed treatment concept for these patients. In most studies unconvincing or even negative results with glucocorticoids were reported. Some positive results were published in smaller studies. Negative results with glucocorticoids have been found, e.g. in about 80% of patients with the AIH/PSC overlap syndrome, whereas with “pure” autoimmune hepatitis this has been the case in 20% only. More than 40% of patients with autoimmune hepatitis/PSC-overlap syndrome died or had to be transplanted during the initial treatment period, whereas for autoimmune hepatitis this figure was 8% only. Ursodeoxycholic acid (UDCA) at a dosage of 15-20 mg per kg body weight per day or even higher is, therefore, to be preferred to steroid treatment.
The etiology of the autoimmune hepatitis/PSC-overlap syndrome is unclear. There are clear cut cases of autoimmune hepatitis reported to lose their hepatitis characteristics and to develop classical features of PSC. In none of these few case reports has an exogenous precipitating factor been observed to play a role. Since components of the immune system such as HLA will not change during the course of the disease it is believed that an inapparent exogenous agent, which has been proposed for the initiation of loss of tolerance to PDC-E2 in PBC may also play a role in the development of the AIH/PSC-overlap syndrome.

Reference:

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Mechanisms of action of ursodeoxycholic acid for treatment of primary sclerosing cholangitis

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Ursodeoxycholic acid (UDCA) has been shown to improve serum liver tests and histological features as well as surrogate markers of long-term survival in primary sclerosing cholangitis (PSC) when administered at adequate doses and accompanied by endoscopic procedures if needed. Recent data also suggest that UDCA lowers the risk to develop hepatic and extrahepatic malignancies in PSC, i.e. cholangiocellular and colon carcinoma. The exact mechanisms and sites of the anticholestatic action of UDCA in PSC are still a matter of debate, but three major mechanisms of action of UDCA which have been unraveled by clinical observations and experimental work may contribute to its beneficial effect in PSC:

(i) **Protection of cholangiocytes** by UDCA conjugates against cytotoxicity of hydrophobic bile acids may be caused by rendering bile less toxic and modulating the composition of mixed phospholipid-rich micelles in bile. UDCA-induced impairment of apical uptake of hydrophobic bile acids by cholangiocytes has also been observed in vitro.

(ii) **Stimulation of impaired biliary secretion by UDCA** has been demonstrated in patients with cholestatic liver disease as well as in various experimental models of cholestasis. UDCA is a potent stimulus of hepatocellular secretion acting mainly by posttranscriptional mechanisms. Synthesis of key canalicular carrier molecules like the bile salt export pump (BSEP, ABCB11) or the phospholipid translocator (MDR3, ABCB4) is upregulated in human liver. UDCA conjugates stimulate targeting and insertion of carrier molecules like Bsep and the conjugate export pump (Mrp2, ABCC2) into the canalicular membranes of rat hepatocytes by modulation of intracellular signalling cascades (e.g., protein kinase C\(\alpha\), [Ca\(^{++}\)], p38MAPKs, extracellular signal regulated kinases [Erk]) and improve biliary secretion of bile acids and many other cholephiles. Secretion of chloride and bicarbonate by cholangiocytes is also stimulated by UDCA in cholestatic patients as well as in experimental models.

(iii) **Protection of hepatocytes (and cholangiocytes?) against bile acid-induced apoptosis** by UDCA is associated with a reduction of mitochondrial membrane permeability transition (MMPT) which is enhanced in hepatocytes by a number of apoptotic stimuli including hydrophobic bile acids. In addition, activation of the epidermal growth factor receptor as well as transcriptional effects of UDCA are considered as potential factors contributing to its antiapoptotic effect.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic hepatobiliary disease characterised by progressive obliterating fibrosis of the biliary system leading to biliary cirrhosis, portal hypertension and liver failure. The hydrophilic bile acid Ursodeoxycholic acid (UDCA) is used for the treatment of a number of cholestatic conditions. A number of groups have studied the effect of low (< 10 mg/kg body weight) or medium (12-15 mg/kg body weight daily) dose UDCA in PSC. All have showed a significant improvement in liver enzymes but no studies have shown clinical benefit in terms of improvement in clinical symptoms or survival free of liver failure or transplantation. Recent evidence suggests that UDCA in medium doses reduces the incidence of colonic dysplasia, polyps and colorectal cancer in patients with associated inflammatory bowel. The effect of UDCA on the incidence of cholangiocarcinom in PSC remains unclear

Novel approaches to the treatment of PSC have included the use of higher doses UDCA and the combination of UDCA with endoscopic balloon dilatation. Three recent studies have evaluated the role of high dose UDCA (> 25 mg/kg body weight daily) in the treatment of PSC. In the first study from the Mayo Clinic 30 patients with PSC were treated for one year\(^1\). The study showed a significantly improved expected survival at four years using the Mayo Risk Score when compared with historical placebo controls. In a second pilot study from our unit 26 patients with PSC were randomised to receive either high dose UDCA or placebo for two years\(^2\). High dose UDCA did not influence symptoms but the study showed a significant reduction in progression of cholangiographic appearances and liver fibrosis as assessed by disease staging. In both the above studies high dose UDCA produced no significant side effects, in particular no exacerbation of inflammatory bowel disease.

These promising results suggest that high dose UDCA may have a clinical benefit in PSC, and a recent large double blind placebo controlled trial from Scandinavia has shown a positive trend in favour of UDCA, although due to small numbers this did not achieve statistical significance\(^3\).

Other novel approaches include the combination of UDCA with long term antibiotic therapy such as metronidazole which has provided promising results after two years of therapy. The addition of immunosuppressive agents to standard doses of UDCA has yielded evidence of efficacy.

Studies from Germany with repeated endoscopic biliary dilatation in combination with UDCA also have provided encouraging results over a six year mean follow up period\(^4\).

It is likely that combination therapy probably including UDCA will provide the basis for future medical management.
References:


Primary sclerosing cholangitis, inflammatory bowel disease and treatment options

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Epidemiology: The frequency of inflammatory bowel disease (IBD) in primary sclerosing cholangitis (PSC) varies between different parts of the world from around 80% in Northern Europe to 20% in Japan. The other way round: PSC is found in around 5% of IBD patients with total colitis – both in ulcerative colitis (UC) and Crohn’s colitis.

PSC-IBD phenotype: IBD in PSC has been characterized by rectal sparing, “backwash ileitis” and an increased rate of colorectal neoplasia suggesting that IBD in PSC represents a distinct IBD phenotype (1). The increased risk of development of pouchitis among PSC-IBD patients supports this theory. In a recent study 17% of “ordinary” UC patients were found to have inflammatory changes in the distal ileum (2). Traditionally ileitis in UC has been explained by reflux of colonic content into the distal ileum due to an incompetent ileocecal valve. This explanation has been questioned as also UC patients with limited pathology in the cecal area had concomitant ileitis (2). In PSC-IBD an even higher rate of “backwash ileitis” (51%) was found, again suggesting that PSC-IBD may be a distinct IBD phenotype (1).

Outcome of PSC-IBD: The IBD in PSC usually runs a quiescent course – with some exceptions. After liver transplantation some patients experience an aggressive course in spite of heavy immunosuppression (3). Patients with UC and PSC are also more prone to chronic pouchitis than UC patients without PSC (see 4). It has been suggested – but not proven - that presence of “backwash ileitis” is a risk factor for development of colorectal malignancy giving further support for increased risk of colorectal malignancy in PSC-IBD. The published data on the risk of developing colorectal malignancy in PSC have been conflicting, although a recent meta-analysis concluded that PSC is an independent risk factor for development of colorectal malignancy in patients with UC (see 4). Interestingly has been demonstrated that treatment with ursodeoxycholic acid (URSO) decreased the risk of developing colorectal malignancy in PSC (5). Whether 5-ASA also protects against development of colorectal malignancy in these patients is less clear.

PSC-IBD/treatment options: Treatment of IBD in PSC is identical to medical treatment of IBD in general – with some modifications. As the effect of URSO on PSC itself is still debated, we recommend this treatment to PSC patients with colonic disease – particularly PSC patients with UC due to the chemopreventive effect in these patients (5). Support for a chemopreventive effect on cholangiocarcinoma development in PSC suggests that not only PSC patients with concomitant UC should receive URSO treatment (6). Proctocolectomy should be based on the same indications as in other IBD patients as the hepatobiliary disease itself does not represent an additional indication: proctocolectomy does not improve the outcome of the hepatobiliary disease. However, one group has shown that patients who had the colon removed before liver transplantation had a reduced risk of recurrent PSC after transplantation (7).
References:


New aspects of UDCA therapy: Primary sclerosing cholangitis and malignancies

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Patients with PSC have an increased risk of bile duct carcinomas. There is evidence that such patients also may have an increased incidence of colonic dysplasias and carcinomas (1). The observation of more frequent pancreatic carcinomas needs confirmation in further studies (1).

In patients treated with ursodeoxycholic acid, the incidence of bile duct carcinomas was very low compared to studies on the natural course of the disease (2). In two controlled study on the effect of UDCA the incidence of bile duct carcinomas was lower in the UDCA group compared to the placebo group but the difference was not significant (3,4). In another study, the incidence of dysplasias and/or carcinomas in livers explanted at the time of transplantation was lower in the ursodeoxycholic acid treated group compared to the control group (5). These data appear encouraging but need confirmation in larger trials.

Patients with PSC and colitis may develop colonic carcinomas. In some but not all studies their incidence in colitis with PSC was higher than in colitis without PSC. Two controlled studies have shown that the incidence of colonic dysplasias and carcinomas may be reduced after UDCA treatment (6,7). In this context the reduced recurrence rate of colonic adenomas after polypectomy in PBC (8) is a remarkable finding and raises the important question whether the effect UDCA on the colon is specific for PSC.

References:


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