Chapter 2
Primary Sclerosing Cholangitis

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Introduction

Primary sclerosing cholangitis (PSC) is a chronic, progressive and destructive cholangiopathy that results in fibrotic strictures and dilations of the intra- and extrahepatic biliary tree. The natural history of disease results in clinical cholangitis, secondary biliary cirrhosis, and a risk of hepatobiliary malignancy. In the current era where effective medical therapy remains absent, more than half of the patients ultimately become in need of a liver transplant, although increasingly it is recognised that there is a degree of heterogeneity in the natural history and progression of disease [1].

Unlike the autoimmune lymphocytic cholangitis of primary biliary cirrhosis (PBC), the large bile duct lymphocytic sclerosing cholangiopathy of PSC has a male bias (1.7:1), a pan-age presentation (median age of diagnosis 40) and a notable increased risk of hepatobiliary malignancy. A systematic review investigating the epidemiology of PSC suggested that the incidence rate is 1 per 100,000 person-years [2]. The available data proposes this value to be true for Europe and North America, with little knowledge of the epidemiology in the developing world. Seemingly however, there is a distinction in incidence between Northern and Southern hemispheres, and PSC appears infrequent in Asia.

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Patients are usually non-smokers, which contrasts with PBC [3], and there is an archetypal association with inflammatory bowel disease (IBD), particularly for Northern European Caucasian subjects, wherein one expects a 60–80 % coincidence of PSC and IBD. This compares to a lower rate of PSC-IBD (30–50 %) in southern European and Asian populations. Conversely, the quoted prevalence of PSC in colitis is variably reported, but it seems less than 5–10 % of patients develop clinically significant disease; the rate of so called "occult" cholangiopathy may be higher, and certainly some sensitive MRI studies would support that. Of note gender distinctions are also relevant with women less likely to have IBD.

Ulcerative colitis (UC) is three times more common than Crohn's disease in the setting of PSC, and it is commonly extensive—a large Dutch observational study found that 83 % had pancolitis. The same study noted that 95 % of the Crohn's Disease with PSC patients had (ileo)colitis [4]. An earlier study from Rochester published in 2005 [5] was the first to suggest a distinct "PSC-IBD" phenotype, characterised by a preponderance for colitis with rectal sparing (52 %) and backwash ileitis (51 %), though this was not replicated in the aforementioned Dutch study. Nevertheless, our experience supports the distinctive IBD pattern in PSC, and highlights the increasing frequency with which PSC is diagnosed first, and asymptomatic colitis confirmed through screening colonoscopy and biopsy [6]. A pathologic explanation for this correlation is lacking, and it is worth noting that despite the extent of colitis being associated with a risk of PSC, there is as of yet no evidence to suggest that the activity of the colitis correlates to risk of liver disease. A "Crohn's phenotype" of IBD is however reportedly associated with a milder PSC disease course. What has proved interesting has been the evaluation of genetic risk across UC and PSC-IBD, wherein both shared and distinct risk hallmarks are seen.

Nevertheless, PSC has been shown to be an independent risk factor for colorectal carcinoma (CRC), with a fivefold increased risk compared to the general population, and a tenfold increased risk in the setting of UC with PSC, compared to UC alone [1]. Moreover, CRC is diagnosed considerably earlier compared to UC controls (median age 39 years vs. 59 years) [1].

Pathogenesis

Cholangiography is capable of identifying a sclerosing cholangiopathy, as is histopathology, but the visual appearance of bile duct injury by imaging or histology is insufficient to distinguish primary and secondary etiologies, albeit radiologic or immunohistochemical clues may be present (Table 2.1 and Fig. 2.1). Histologic changes can occur in isolation (so-called small-duct disease) and this raises questions about the course of disease. It is recognised that some small-duct PSC patients, but not the majority, progress to large-duct disease, and cholangiocarcinoma is rarely seen in patients with small-duct disease, unless it has progressed to more classic PSC.

Table 2.1 Differential diagnosis for sclerosing cholangitis

Varying etiologies for sclerosing cholangitis clinically
Cholangitis and chronic biliary infection Acquired immune deficiency syndrome (probably infective from cytomegalovirus or cryptosporidium)
Choledocolithiasis Biliary tract surgery/trauma
Biliary toxin exposure
Biliary strictures (inflammatory/malignant) Cholangiocarcinoma Papillary tumour Choledochal cyst disease
Ischaemic biliopathy Portal biliopathy (portal vein thrombosis)
Graft-versus-host disease
IgG4-associated cholangiopathy

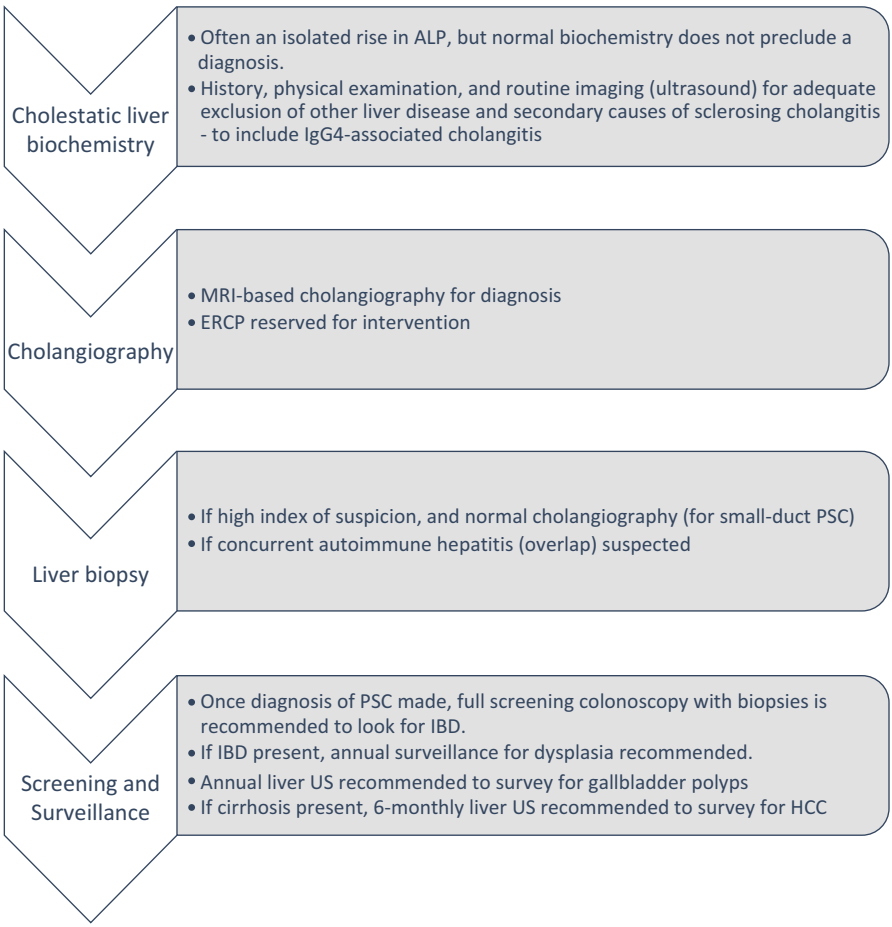

Fig. 2.1 Diagnostic pathway for patients with primary sclerosing cholangitis

Common pathways to biliary injury become apparent when one recognises the myriad of secondary etiologies for sclerosing cholangitis that span vascular, immunologic, septic, toxic and inherited insults. Additionally the co-existence at such a high rate of IBD is important to appreciate and rationalise. The biliary and gut epithelium is a continuum, and the blood supplies are intimately linked, with the healthy liver receiving 70 % of its blood from the gut via the portal vein. This inevitably means the liver is a continued barrier to gut derived toxins and an organ that has evolved to be inherently immunotolerant.

Histology points towards a progressive and chronic injury to predominantly the medium to large bile ducts, that culminates in an obliterative and inflammatory concentric periductal fibrosis, giving the recognisable term "onion-skinning" [7]. On a cholangiogram this manifests as an alternating series of strictures and dilatations—resulting in a beaded appearance. The initial periportal (primarily periductal) infiltrate is predominantly a mixed inflammatory concentrate of lymphocytes, plasma cells and neutrophils. Central to this is the inherently immunologically innocent cholangiocyte, which, in response to injury, becomes a key recruiter and homing destination for the inflammatory mediators. There is an increase in the expression of adhesion molecules and profibrogenic cytokines. The consequence of inflammation is progressive fibrosis, ductopenia, and disorganised ductal proliferation. Immune injury, impaired vascular supply, retention of bile acid, biliary obstruction and altered secretion all seemingly contribute to disease. Clearly biliary homeostasis is undoubtedly interrupted in sclerosing cholangitis, and it is increasingly recognised that the gut-liver bile acid axis/signalling pathways are very active biologic pathways. Normal biliary epithelium is resistant to inherently toxic bile, likely because of a bicarbonate enriched protective "umbrella": human cholangiocytes are continuously exposed to millimolar levels of hydrophobic bile salts; a co-ordinated apical biliary bicarbonate secretion process likely prevents protonation of biliary glycine-conjugated bile salts and uncontrolled, potentially toxic, cell entry of corresponding bile acids. Disease modifies biliary flow and function, and future choleretic therapies are set to focus on ameliorating damage secondary to the consequences of biliary damage. Exposure to bacteria and/or their cellular products, whether it be in the biliary tree, or as a consequence of toxic agents penetrating through a leaky and inflamed colon is likely to also play a role, and may even explain the reactivity patterns of perinuclear antineutrophil cytoplasmic antibodies.

Finally, whilst it is semantic to discuss whether PSC is autoimmune or autoinflammatory, manifestly immunological mechanisms are central to the pathophysiology of disease; the tight genetic HLA association identified strongly points to the importance of immune mediated mechanisms of disease initiation. Genome-wide association studies confirm HLA associations and moreover implicate a battery of susceptibility and modifier genes, with a varied likely biological impact [8]. This is further supported by evaluation of biliary infiltrates that are mainly activated effector or memory T cells, but also include B-cells and players from the innate immune system. Finally there is evidence to suggest that effector lymphocytes in colitis home, via a common adhesion molecule signal, between the colon and liver [9], and

blocking this enterohepatic immune "circuit" is the focus of some proposed targeted monoclonal antibody therapy.

Clinical Presentation and Diagnostic Considerations

Although natural history studies give the impression that the typical PSC presentation is that of a non-smoking 40-year-old man with colitis presenting with abnormal liver biochemistry, it is increasingly recognised to be a stereotype that is challenged by patients presenting with early and milder disease, and in both genders. Thus, the challenge has become not only the natural history of severe disease, but the need to stratify risk and treatment across heterogeneous populations, some of whom are likely to have very benign outcomes, whilst others are either very inflammatory and rapidly progressive, or pre-malignant.

Natural history studies do suggest that the prevalence of asymptomatic PSC may be as high as 40 % of all patients with PSC [10]. Non-specific fatigue and pruritus may similarly provoke a search for a cause of cholestasis. A presentation with decompensated liver disease and portal hypertension can still occur across all ages, and the extremes of age do not infer either overt good or bad prognosis.

Cholangiography: The diagnosis of sclerosing cholangitis requires anatomic evaluation of the biliary tree, and thus, cholangiography (Fig. 2.2). Typical and characteristic findings include multifocal biliary strictures, which may be diffusely

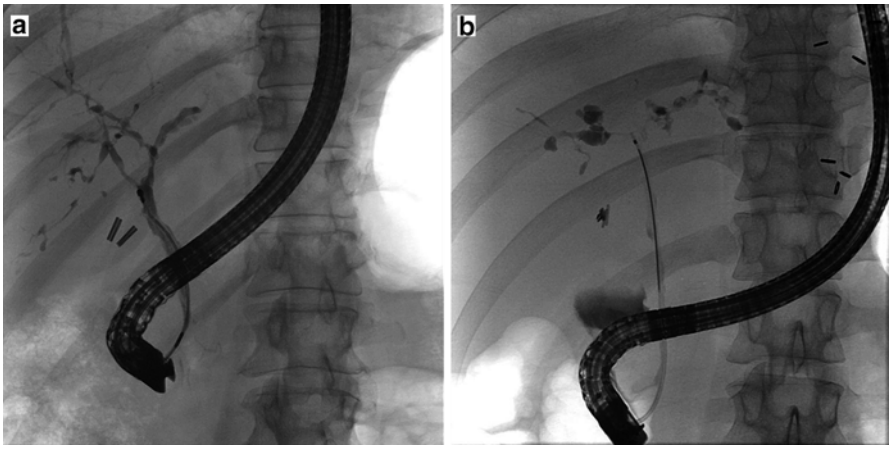

Fig. 2.2 Cholangiographic changes in primary sclerosing cholangitis. Cholangiographic appearances of PSC obtained at time of interventional endoscopy: (**a**) diffuse appearance of marked intrahepatic PSC in a patient with progressive jaundice and pruritus, illustrating the challenge of delivering effective therapy to widespread biliary disease; (**b**) malignant bile duct stricture identified in a patient with PSC, and subsequently evaluated for suitability for liver transplantation according to "Mayo" protocol. Images kindly provided by Dr G May, Head Division of Gastroenterology, St Michaels Hospital, Toronto

distributed to involve both intra- and extrahepatic biliary system. The disease is rarely (5 %) limited to the extrahepatic ducts. Strictures are short, and annular, and alternate with dilated areas to give a "beaded appearance". Biliary diverticula and pruning are also common. Endoscopic retrograde cholangiopancreatography (ERCP) has long been considered the "gold standard" for diagnosis. However, it is an invasive procedure that carries a risk of cholangitis, bleeding, pancreatitis and very rarely death. A recent prospective risk analysis of ERCP in PSC patients by the Dutch PSC Study Group reported a 2 and 14 % complication rate at 1 week in asymptomatic and symptomatic patients, respectively [11]. A retrospective cohort-study highlighted that operator-volume and experience is an independent predictor of uncomplicated ERCP [12], which is reflected in conclusions drawn from data extracted from the Swedish nationwide quality register (comprising 51 ERCP centres), which demonstrated a complication rate of 18 % in those with PSC (compared to 7 % in those without) [13]. Thus, advances in non-invasive imaging such as magnetic resonance cholangiopancreatography (MRCP), have made it the primary diagnostic tool; an added value being the additional insights gained from extra-hepatic imaging of the abdomen. A meta-analysis of the diagnostic performance of MRCP concluded that the overall sensitivity and specificity for PSC detection were 0.86 and 0.94 respectively. The positive and negative likelihood ratios were 15.3 and 0.1, respectively, and even in the worst case scenario (pre-test probability of 50 %) post-test probabilities were 94 % for a positive, and 13 % for a negative MRCP result [14]. Nevertheless, MRCP has its limitations. One case–control study highlighted the risk of false positive results in cirrhotic patients [15]. Furthermore, there is a perceived high interobserver variability in reporting (which is no different from ERCP), which may be particularly relevant in patients with early subtle disease [16]. Moreover, it does not allow for therapy. Nevertheless, two cost-effectiveness studies also support the use of MRCP first, with the selective use of ERCP following [17, 18]. This approach has been estimated to involve 11.7 % lower costs compared with ERCP when sedation and supply costs are included [18].

Histology: In the event of a high pretest probability for PSC, a normal cholangiogram, and no other explanation for persistent cholestasis (in particular negative immunology for PBC), a liver biopsy may be required to allow a diagnosis of small-duct PSC. Histologic evaluation also has value when an "overlap syndrome" with autoimmune hepatitis is suspected, and can be equally relevant if there are other potential confounding diagnoses such as steatohepatitis.

Excluding Known Secondary Etiologies

A diagnosis of PSC requires the exclusion of often clinically apparent potential secondary causes. These include biliary calculi, cholangiocarcinoma, biliary tract surgery, choledochal cyst disease, biliary toxin exposure, chronic biliary infection, portal vein thrombosis/portal biliopathy, ischaemic biliopathy and graft-versus-host disease, to name the more prevalent causes (Table 2.1). For the most part, a good history, physical examination and routine imaging can identify secondary causes.

One specific etiology to proactively exclude is IgG4-associated cholangiopathy (IAC), because of its ability to mimic PSC, yet be highly sensitive to glucocorticoids. IAC is a component of an autoimmune multi-system disease encompassing the spectrum of autoimmune pancreatitis, IgG4 cholangiopathy and extra-hepatobiliary manifestations (e.g. retroperitoneal fibrosis, interstitial nephritis, pulmonary infiltrates, parotitis) [19]. It has an incidence and prevalence of 0.9 and 2.2 per 100,000 population, respectively [20]. It preferentially presents in men (8:1), has a median age of presentation older (60–70) than classic PSC, and is associated with "blue-collar" work, suggesting a potential allied environmental trigger [21]. Diagnosis requires correlation of historical, biochemical, serological, imaging and histopathological markers, and this is reflected in validated diagnostic systems [22, 23].

The laboratory biochemistry results will not be discriminatory, but if IgG4 disease is suspected, then serology can be helpful, and it is recommended that IgG4 levels are measured at least once in all patients at the point of considering PSC as a diagnosis. Cholangiographic changes are not defining, and may resemble cholangiocarcinoma, pancreatic cancer or PSC [24], but associated changes in the pancreas may be more telling. Histopathology is potentially helpful in the diagnosis, with hallmark features of type 1 autoimmune pancreatitis being described as a tumefactive mass with a dense lymphoplasmacytic infiltrate that is organised in a storiform pattern, a moderate eosinophil infiltrate, and a very characteristic obliterative phlebitis; increased immunostaining for IgG4 is also characteristic.

Variant Presentations

The main variant presentations to recognise are small-duct PSC, "overlap" syndrome with autoimmune hepatitis and childhood "autoimmune sclerosing cholangitis".

Small-duct PSC: This is phenotypically a milder version of its medium and large duct counterpart. The diagnosis is made in patients with chronic cholestatic liver disease who have histological changes suggestive of PSC, in the presence of a normal cholangiogram, and in whom other liver and biliary disease has been excluded using standard laboratory and imaging techniques. Natural history studies suggest that small-duct PSC has a better long-term prognosis (13-year median transplant-free survival), and is not associated with cholangiocarcinoma in the absence of large-duct disease. Approximately a quarter will transform to large-duct PSC within 10 years, and progression to end-stage liver disease can occur in the absence of large-duct disease [25]. The two entities are assumed to have a shared etiology. However, a recent study demonstrated that small-duct PSC without IBD had a distinct HLA signature to that with IBD or large duct PSC [26].

Overlap: When coexistent, PSC and autoimmune hepatitis can occur simultaneously, or sequentially. An "overlap syndrome" may be a true representation of two distinct pathologies occurring simultaneously, or a description of a phenotype in which biopsy-proven hepatitis and cholangiographic changes are part of the natural history of a single disease.

Autoimmune sclerosing cholangitis: Overlap presentations seem commoner in younger adults, and a prospective study described 50 % of children with autoimmune hepatitis having cholangiographic changes—this has been termed autoimmune sclerosing cholangitis [27], and it may be more sensitive to immunosuppression.

Prognostic Models

Attempts to mathematically model and predict outcomes in PSC are borne out of datasets from referral programmes, with the Mayo PSC model being well established and of some value in late disease. However, no good model exists for patients at early stages of their disease, reflecting a heterogeneous disease course that can be unpredictable. Dominant strictures, cholangitis and malignancy can portend an accelerated trajectory, but are difficult to risk-stratify for in themselves. Alkaline phosphatase levels do seemingly allow stratification of risk, with those failing to normalise/lower their alkaline phosphatase being at greater risk of adverse events, regardless of intervention with ursodeoxycholic acid (UDCA), or the presence of dominant strictures [28]; this mirrors the experience of using alkaline phosphatase as a stratifier of risk in PBC patients. An unmet need therefore is for better surrogates of disease and its prognosis, and there are efforts to apply markers such as transient elastography readings or the serum of the enhanced liver fibrosis test to patients with PSC over time.

Therapy

UDCA is a hydrophilic bile acid that has a proven beneficial role in cholestatic liver disease. The mechanisms by which UDCA exerts its positive effects are multiple. At doses >10 mg/kg/day it constitutes 50–60 % of the bile acid pool, whereas in normal physiology it accounts for 2–3 %. It exerts a cytoprotective effect by displacing toxic endogenous hydrophilic bile acids, and blocks the dissolution of membrane-bound lipids. A choleretic effect is exerted by the increase in the secretion of bile acids and phospholipids that manifests as an increase in bile flow and decreased acidity of the bile. It solubilises cholesterol in bile, thereby theoretically decreasing the risk of sludge build up behind stenoses. It has also been demonstrated to have an in vitro immunomodulatory effect [29]. Despite its proven efficacy in delaying the need for transplantation in PBC, the evidence in PSC is less convincing, to the point where current guidelines do not support its use. The controversies surrounding the use of UDCA are summarised in Box 2.1.

Modulation of cholestasis and bile flow by the use of bile acid treatment remains an attractive therapeutic avenue to study. 24-Norursodeoxycholic acid is a novel treatment currently being explored in phase 2 clinical trials. It is a derivative of UDCA, which has been shown to stimulate a bicarbonate-rich hypercholeresis (due

Box 2.1 Controversies in the management of patients with PSC

Controversial areas of clinical care

Ursodeoxycholic acid

- Early studies suggested a biochemical and cholangiographic improvement from UDCA, and indicated a possible chemopreventative role against cholangiocarcinoma and CRC at 13–15 mg/kg/day.
- In contrast, contemporary studies suggest no benefit in biochemistry, symptoms, quality of life, cholangiocarcinoma or transplant free survival with doses at 17–23 mg/kg/day; higher doses (28–30 mg/kg/day) carried a greater risk of decompensated liver disease, transplantation, cholangiocarcinoma, CRC and death despite improved liver biochemistry.
- The deleterious effects of high-dose UDCA may be, in part, attributable to a direct toxic effect of UDCA or more likely the colonic accumulation of toxic metabolites of UDCA—namely lithocholic acid, a tertiary and hydrophobic bile salt.
- No substantive recommendation can be given for normal doses, but high-dose regimes should be avoided.

Antibiotics

- Frequently used for cholangitis and occasionally used continuously for recurrent cholangitis, although evidence for efficacy is limited.
- There is no data to support the use of antibiotics as prophylaxis against cholangitis in PSC, but antibiotics peri-ERCP is sensible.
- Thus far, three clinical trials have been completed to investigate the role of antibiotics in disease modification—they all demonstrate an improvement in biochemistry, without an effect on harder end points.

Balloon dilatation versus stentplacementfor dominant strictures

- Dominant strictures are associated with reduced transplant-free survival, and increased risk of carcinoma.
- Endoscopic relief of a dominant stricture has a suggested benefit in extending transplant-free survival—yet no clear guidance exists on the best way to do this.
- Endoscopic balloon dilatation may portend a lower risk of complications despite the need for repeat procedures, compared to sent placement.
- Further studies to compare the two treatment modalities are under way.
- In the absence of data, the benefit of endoscopic intervention in the setting of cirrhosis and jaundice should be weighed up against the high-perceived risk in this cohort.

Colorectal Cancer surveillance

- The risk of CRC is markedly higher in those with PSC-IBD.

(continued)

Box 2.1 (continued)

- Annual surveillance colonoscopies are advocated, although this recommendation would benefit from more supporting data.

Prognostication

- Prognostic scoring models are lacking for early PSC. The Mayo PSC model is of established value in late disease.
- There are no established surrogate markers to predict treatment response, though stratification of future risk by alkaline phosphatase values is effective. Elevated IgG4 values in the absence of overt IgG4 disease are also seemingly stratifying, as are measures of liver elastography.
- The disease is often unpredictable meaning risk stratification and the timing of liver transplantation are challenging.

to its notable chole-hepatic cycling) that protects the liver from cholestatic injury in mouse models of sclerosing cholangitis (Mdr2$^{-/-}$mice) [30].

Nuclear hormone receptors provide another attractive therapeutic avenue. They are critical in co-ordinating and regulating genes involved in bile synthesis and secretion, and small intestinal and hepatic detoxification of bile acids. Farsenoid X receptor agonists (e.g. obeticholic acid) have been explored in PBC, and early-phase PSC trials are planned. However, an important distinction between PSC and PBC is the presence of strictures and relative obstruction to biliary flow in PSC, which raises the concern that a FXR agonist may, through enhanced bile flow, precipitate obstruction; the further concern is the complex interplay that FXR signalling has in oncogenesis. However, only carefully controlled clinical trials can bridge these concerns, which remain theoretical only. Peroxisome proliferator-activated receptor agonists may also have yet unexplored value in PSC [31].

Other Treatment Attempts

Antibiotics offer a mechanistically attractive treatment—to combat the possible contributory effects of the gut microbiota and biliary infection to the pathogenesis and progression of sclerosing cholangitis. A randomised trial comparing UDCA and metronidazole vs. UDCA monotherapy demonstrated improved liver biochemistry in the trial arm, but no effect on disease progression [32]. Vancomycin has been shown to similarly improve liver biochemistry in a paediatric population of PSC [33]. Other published data on the use of other antibiotics are limited to case reports and pilot studies.

Disappointingly steroids, tacrolimus and anti-TNF agents have to date had no meaningful impact on disease. This however, has not reduced the optimism for new strategies. These include anti-fibrosis monoclonal antibody therapies (e.g. against LOXL2—an extracellular matrix protein or anti-VAP1 antibodies) and biologic therapy (Vedolizumab) targeting potential gut-primed lymphocytes, which home to the biliary tree.

Cholangitis and Dominant Strictures

Cholangitis contributes to disease progression [34]. Charcot's triad of fever, jaundice and right upper quadrant pain may not occur, and patients may experience a more insidious onset of non-specific symptoms, or even an asymptomatic worsening of liver biochemical markers. Nevertheless, cholangitis may present as a medical emergency requiring appropriate resuscitative management. The role of endoscopic therapy is not straightforward. ERCP has an overall complication rate of around 10 %, which increases in the presence of newly symptomatic disease and the length of procedure [11, 35]. Biliary sphincterotomy may protect against post-ERCP pancreatitis [11], and whilst the evidence is lacking, it is common practice that all PSC patients have antibiotic prophylaxis peri-ERCP [34, 35].

ERCP has a suggested benefit in potentially extending transplant-free survival in the setting of a dominant stricture; the challenge however is that there is such a wide variability in therapeutic decisions and rates of diagnosing dominant strictures. One definition of a dominant stricture is that of a biliary stenosis of >1.5 mm in the common bile duct, or >1 mm in the main hepatic duct; by this definition they are reported to occur in up to 50 % of patients with PSC, although this does not mirror clinical practice more broadly. True, clinically meaningful, dominant strictures appear associated with a reduced transplant-free survival, and an increased risk of carcinoma, especially in the setting of concomitant IBD, or fungal biliary infection [36, 37]. Relief of dominant strictures may improve transplant free survival, though there remains no clear guidance as to the best way to do this (Box 2.1). The safety of endoscopic biliary stent placement was established early, but retrospective long-term follow-up data suggests that the complication risk is lower in balloon dilatation, even accounting for the increased need for repeat procedures [38]. The longest follow up study described 171 patients who were followed up for 21 years. 500 balloon dilatations were performed which yielded an overall 52 % 10-year transplant-free survival rate; a subset analysis of the jaundiced cohort revealed a 10-year transplant-free survival rate of 44 % [39]. Further study to compare the two modalities is currently underway.

The Risk of Malignancy

PSC is associated with hepatobiliary and colonic malignancy. The lifetime risk of cholangiocarcinoma is 10–15 %, with a third being diagnosed at, or within 1 year of, diagnosis of PSC. Thereafter, the annual incidence is around 1 %. Cholangiocarcinomas are difficult to diagnose and differentiate from benign disease. As things stand, surveillance for cholangiocarcinoma has no firm, evidence-based guidance. They can occur as a biliary stricture, hilar mass or intrahepatic tumour. Unlike hepatocellular carcinoma, it does not have a readily reproducible and specific radiologic signature. Traditional serum markers such as heightened concentrations of carbohydrate antigen 19–9 have a poor sensitivity and specificity, with increased concentrations also resulting from cholangitis, biliary dilatation and endoscopic intervention [40]. Routine cytology from endoscopic aspirates and brushings are close to 100 % specific, but has a poor sensitivity (7–33 %), though endoscopic ultrasound and final-needle aspiration may be more fruitful for distal lesions [41]. Fluorescent in situ hybridisation and digital image analysis allow for the detection and quantification of chromosomal abnormalities and aneuploidy. These techniques have been shown to increase the diagnostic yield of cytology [41, 42]. Early data suggests that transpapillary intraductal ultrasonography may have a significant role in differentiating malignant and benign strictures, and when combined with fluorescent in situ hybridisation and digital-image analysis, the sensitivity and specificity may be >90 % [41, 43]. Other endoscopic techniques such as per-oral cholangioscopy, narrow-band imaging and confocal laser endomicroscopy are still in their infancy, and it is too early to foresee what role they will have.

Cholangiocarcinoma-specific peptide markers can be identified in urine and bile using capillary electrophoresis mass spectrometry. Pilot studies demonstrate they are effective in differentiating PSC from cholangiocarcinoma. This technology is also in its infancy, but if established, may provide a non-invasive tool for surveillance and diagnosis [44].

Hepatocellular carcinoma can arise in those with cirrhosis or advanced fibrosis, and local surveillance strategies should be employed—with 6-monthly ultrasonography. This will also allow for the recognition of gallbladder polyps and screening for gallbladder cancer. In the non-cirrhotic PSC patient this is done by annual ultrasound imaging. In some reports 50 % of gallbladder polyps could be malignant, and the incidence of gallbladder cancer in PSC is approximately 2 % [45].

As already described, the inflammatory bowel phenotype in the setting of PSC is a distinct entity, and the risk of associated CRC is amplified [5]. The risk of CRC in PSC-UC is tenfold higher than that of UC alone [1]. Furthermore, carcinoma generally occurs at an earlier age [1]. For this reason it is recommended to screen for colitis at the onset of disease, and then undertake surveillance annually, if diagnosed. Care should be taken to ensure adequate bowel preparation, and appropriate views of the right-sided colon are obtained, as this is the site of the majority of

dysplastic lesions in this setting. However, it worth bearing in mind, the impact of well-established surveillance and treatments (5-aminosalicylic acid, thiopurines) on this malignant transformation risk remains unclear.

The Management of Symptoms and Complications of Cholestasis

Pruritus of cholestasis is a common affliction in those suffering from PSC. It can be severe enough to be the predominant concern and significantly reduce a patient's quality of life. It is often associated with depression, anxiety, disturbed sleep and can even induce suicidal ideation. In its classic form, the pruritus of cholestasis has a diurnal variation with it being at its most intense in the late evenings, preferentially affecting the soles of the feet and the palms of the hands. Bile salt sequestrants (cholestyramine) and other non-specific agents such as μ-opioid receptor antagonists (naltrexone and nalmefene), serotonin antagonists (sertraline), and pregnane X receptor agonists (rifampicin) have moderate antipruritic action, and have been adopted in treatment algorithms [46]. Intractable pruritus may be amenable to Molecular Adsorbents Recirculating System, and may require consideration towards liver transplantation, irrespective of hepatic function. The discovery of new putative pruritogens (lysophosphatidic acid/autotaxin) and ongoing clinical trials (using apical sodium dependent bile acid transporter inhibitors) may further therapy in this field.

Hepatic osteodystrophy describes the bone disease that occurs as a result of liver disease. In PSC, the osteopathy is multifactorial. Cirrhosis, imbalanced bone turnover, osteomalacia, acquired vitamin D deficiency, reduced physical activity, reduced body mass index and hypogonadism all play a role. PSC patients can have the added burden of cholestasis-induced vitamin K deficiency, which is an essential cofactor for osteocalcin production. Furthermore, the encumbrance of coexistent IBD, its cytokine load, and associated glucocorticoid therapy has a cumulative effect on bone mineral density. A recent 10-year cohort study demonstrated that osteoporosis was found in 15 % of patients and occurred 23.8-fold more frequently in PSC than expected from a matched population [47]. Management algorithms should be individualised to consider both liver and non-liver-related risk (which may be estimated by the World Health Organisation Fracture Risk Assessment Tool), and be guided by objective measures of bone mass. Those with cirrhosis or persistent cholestasis may benefit from calcium and vitamin D replacement, though the benefit of this approach is unproven. Specific therapy may be offered when a secondary treatable contributor is identified (i.e. hormone replacement in secondary hypogonadism). Oral bisphosphonates, when taken appropriately, are safe, and have clinically proven benefit in preventing corticosteroid-induced osteoporosis in liver disease. One must not also forget basic lifestyle measures that have proven benefit in alleviating fracture risk—smoking cessation and regular weight-bearing exercise.

The management of cholestasis- and cirrhosis-associated fatigue (seen in 65–75% of patients) requires the physician to source and treat any contributory factors such as allied thyroid disease, anaemia, depression, adrenal insufficiency and drug side effects (beta-blockers are a common culprit). There is however laboratory data to suggest that the fatigue of cholestasis is biologically driven, and therefore in the future may have specific therapy.

Transplantation

In the absence of reliable and easily applicable disease-specific prognostic models, a suitable patient with PSC is listed for transplantation on similar grounds to those with parenchymal diseases of other aetiologies. In the UK, a UK end-stage liver disease score of 49 or more is deemed to be minimal listing criteria in the presence of a specific indication. The score is calculated by the use of a formula involving the following prognostic variables: bilirubin, sodium, creatinine and international normalised ratio. Other countries apply the similar model for end-stage liver disease score, comprising bilirubin, creatinine and international normalised ratio. Whereas hepatocellular carcinoma is an indication for transplantation, cholangiocarcinoma remains a contraindication in most centres despite optimism from facilities undertaking transplantation for small hilar cholangiocarcinomas after neo-adjuvant chemo- and brachytherapy [48]. Very occasionally, intractable and debilitating symptoms in the absence of significant synthetic failure may warrant assessment of the patient for transplantation.

Sclerosing cholangitis is not uncommon post transplantation, and may be due to secondary causes such as ABO blood group mismatch, ischaemic vascular insults and chronic rejection. Nevertheless PSC can reoccur in as many as 20% of patients within 5 years of transplantation. Male sex and an intact colon at the time of transplantation, acute-cellular rejection and the need for maintenance steroids for UC are independent risk factors [49].

Conclusions

PSC remains a very difficult disease to have and to manage. Fundamentally it is a rare hepatobiliary manifestation of IBD that is frequently progressive can prove pre-malignant, and currently devoid of medical therapy. Better understanding of disease is however driving new hope for novel drug treatments and opportunities are being seized to overcome roadblocks to implementing new therapies, such as the development of better surrogate end points of outcome.

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