Chapter 14
Autoimmune Liver Diseases: Primary Sclerosing Cholangitis

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Abbreviations

AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CT	Computerized tomography
DEXA	Dual energy X-ray absorptiometry
ERC	Endoscopic retrograde cholangiography
FISH	Fluorescent in situ hybridization
IBD	Inflammatory bowel disease
IgG4	Immunoglobulin G4
MELD	Model for end-stage liver disease
MRC	Magnetic resonance cholangiography
MRI	Magnetic resonance imaging
P-ANCA	Perinuclear antineutrophil cytoplasmic antibodies
PSC	Primary sclerosing cholangitis
PTC	Percutaneous transhepatic cholangiography
SAM-E	S-adenosylmethionine

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TIPS	Transjugular intrahepatic portosystemic shunt
UDCA	Ursodeoxycholic acid
UNOS	United Network for Organ Sharing

Patient Questions and Answers

What Is Primary Sclerosing Cholangitis and How Did I Get It?

Primary sclerosing cholangitis, or PSC for short, is a chronic liver disease that leads to strictures or narrowing of the large and small bile ducts in the liver. The bile ducts are the plumbing of the liver and serve to move products produced in the liver to the small intestine, where they perform functions necessary for survival. While the exact cause of PSC remains unclear, it is frequently classified as an autoimmune disease. This means that it may be the result of an overactive or abnormal immune system. Patients with PSC frequently have other autoimmune disorders with the most common being inflammation of the colon, or colitis. Unfortunately, there is no effective therapy that prevents the progression of PSC and many patients will develop advanced liver disease and possibly cirrhosis which is severe, irreversible scarring of the liver. It is important to recognize that PSC is not associated with alcohol use, specific diets or behaviors. Primary sclerosing cholangitis is not the result of an infection or exposure to other individuals. You cannot transmit PSC to other individuals.

What Can I Do to Treat Primary Sclerosing Cholangitis?

It is important to remember that your PSC is not the result of anything you have done wrong. While not related to alcohol, it is important to avoid alcohol as regular alcohol use can by

itself lead to liver damage. As with all chronic liver diseases, you should be checked for immunity or protection to hepatitis A and B. If tests show that you are not protected, you should undergo vaccination. Both of these vaccines are safe and effective. It is important to maintain a healthy diet as patients who are able to accomplish this are better able to tolerate chronic illnesses, including PSC. Because of the strong association with colitis (inflammation of the colon), you should undergo a colonoscopy (a test to examine your colon) unless you have already had one. Primary sclerosing cholangitis can also lead to difficulty absorbing certain vitamins such as vitamin D. When patients have low vitamin D levels it can lead to thinning of the bones, osteoporosis and possible bone fractures. Because of this, you should undergo a test known as a bone densitometry to determine whether you are at risk for developing bone disease.

There is no specific medicine that has been shown to be effective in slowing the progression of PSC. While it is classified as an autoimmune disorder, it does not respond to medications that are effective against other autoimmune conditions. While you may want to explore alternative or natural therapies such as herbal therapies, I would discourage you from using these substances as they are frequently not regulated by the Food and Drug Administration and in some cases have also been shown to be harmful to the liver. You should always let all of your doctors know of any medicine you are taking, as some medicines may not be as well tolerated by patients with liver disease such as PSC.

Will I Need a Liver Transplant?

The natural history of PSC is highly variable. Some patients present at a young age and have an aggressive course leading to the need for liver transplantation, while others will carry a diagnosis of PSC for many years and not require liver transplantation or die from this condition. Since PSC is a progressive disease and there is no known effective medical therapy,

it will be important that you follow-up with a hepatologist or liver doctor on a regular basis even if you do not have any symptoms. During these visits you will be asked about symptoms as well as undergo a physical exam and blood tests that will allow your hepatologist to determine the overall status of the PSC and when a liver transplant evaluation should be considered. Your hepatologist may determine that a repeat examination of your bile ducts is necessary, particularly if there is suspicion that a cancer has developed in the bile ducts. Cancer of the bile ducts is known as cholangiocarcinoma. You should have an ultrasound of the liver and gallbladder every year as there in an increased risk of developing both liver and gallbladder cancer. You should contact your physicians immediately if you experience symptoms including jaundice or yellowing of the eyes and skin, worsening itching throughout your body which is most noticeable at night, fever, weight loss, and abdominal pain which most commonly occurs in the area over your liver.

Autoimmune Liver Diseases: Primary Sclerosing Cholangitis

Summary

Primary sclerosing cholangitis (PSC) is a chronic condition characterized by inflammation, fibrosis and obliteration involving the intra as well as extrahepatic bile ducts. Initially described in 1924 and once considered a rare condition, the condition can no longer be considered rare as advancements in cholangiography have led to more frequent diagnosis. While the etiology remains elusive, it is commonly classified as an autoimmune liver disease and other immune-mediated conditions, most notably inflammatory bowel disease, are frequently concurrently encountered. Genetic predisposition also appears to play a contributory role based on the finding of associated as well as protective haplotypes. Complications of PSC are both nonspecific and associated with chronic cho-

lestatic liver disease as well as those specific to PSC. The natural history is highly variable with the potential for progression to cirrhosis, end-stage liver disease and the need for liver transplantation. Patients with PSC are also at an increased risk for the development of cholangiocarcinoma as well as colorectal, gallbladder and hepatocellular carcinoma. Despite the evaluations of multiple pharmacologic agents, there is currently no medical therapy that has been shown to alter the timeline to death or the need for liver transplantation. Liver transplantation is the only effective therapy for long-term survival in those who develop complications of end-stage liver disease and is associated with excellent long-term results. Variants of PSC include small-duct PSC, overlap PSC and autoimmune hepatitis and immunoglobulin G cholangiopathy.

Epidemiology

Various epidemiological studies have placed the incidence of PSC from 0.9 to 1.31 cases per 100,000 person-years and the prevalence at 8.5 to 13.6 cases per 100,000 persons [1, 2]. There is however, significant regional variability which supports the theory of genetic predisposition playing a role. Sixty to 70 % of affected patients have underlying inflammatory bowel disease (IBD), more frequently chronic Ulcerative Colitis than Crohn Disease with colonic involvement [3, 4]. The IBD is typically diagnosed several years prior to PSC [5]. In addition, while associated with IBD, the two disorders' activity level and progression do not necessarily correlate. Approximately two-thirds of those affected with PSC are male with the median age at diagnosis of approximately 37 [2].

Etiology

While the exact etiology of PSC remains unknown, it appears that both genetic and immunologic factors play prominent roles.

Genetics

Evidence supporting a genetic cause includes strong familial patterns as well as a strong association with specific haplotypes, most notably B8DR3, B8DR13, and B8DR15. Conversely, haplotypes DRB1*040, DRB1*070, and MICA*002 are associated with a decreased risk of developing PSC [6–9].

Immune-Mediated

An immune mechanism is supported by the findings of serum autoantibodies in a large number of those with PSC, the most common being perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) which are found in up to two-thirds of patients. Other autoantibodies occasionally encountered include antinuclear and anti-smooth muscle antibodies [10]. Additionally, hypergammaglobulinemia is common as is the association with other autoimmune disorders, most notably inflammatory bowel disease.

Other potential etiologies that may play minor roles in PSC include infectious causes, toxin exposure and vascular complications.

Infectious

The association of PSC with IBD has led to the theory that damaged colonic mucosa leads to translocation of bacteria that enter the blood stream and bile ducts. The failure to identify specific organisms, the absence of portal phlebitis, failure of antibiotics or colectomy to alter the natural history and the fact that not all patients with PSC have IBD argues against an infectious etiology.

Toxin-mediated

Toxin exposure as a cause of PSC is based on the theory that imbalances between hydrophilic and hydrophobic bile acids, such as lithocolic acid, can lead to biliary epithelial damage and strictures. Other toxic agents that have been evaluated include iron and copper, both of which are shown to be elevated in many patients with PSC. Elevated iron and copper levels however, are nonspecific findings and can be associated with both hepatocellular and cholestatic disorders.

Vascular Injury

Vascular injury to the hepatic artery has long been associated with biliary strictures in liver transplant recipients; however, examination of the hepatic vasculature in PSC has failed to demonstrate damage to the hepatic artery, portal vein, or hepatic vein.

Clinical Presentation

The clinical presentation of patients affected by PSC is highly variable. At one end of the spectrum is the asymptomatic patient who is diagnosed based on cholestatic hepatic biochemistries obtained in the setting of IBD. The majority of patients with PSC will be diagnosed when presenting with symptoms that lead to further investigation. The most common presenting symptoms are pruritus, jaundice, right upper quadrant abdominal pain and acute cholangitis. Unfortunately, some patients will present with advanced liver disease manifested by weight loss, ascites, hepatic encephalopathy, portal hypertensive bleeding, or cholangiocarcinoma.

Diagnosis

Laboratories

The majority of patients with PSC will demonstrate cholestasis on hepatic biochemistries. Alkaline phosphatase values greater than 2.5-fold normal values are seen in the majority of patients. As a result, elevated alkaline phosphatase values which are confirmed to be of biliary origin should result in a thorough evaluation and consideration for PSC. Total bilirubin values are elevated in over 50 % of affected patients and 90 % demonstrate a two- to threefold elevation in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Serum iron and copper values are frequently elevated, but as previously mentioned, are nonspecific and therefore not helpful for diagnostic purposes. Despite the finding of p-ANCA autoantibodies in the majority of PSC patients, their presence is nonspecific and should not be utilized to make a diagnosis of PSC. This is in contrast to other autoimmune hepatic disorders such as autoimmune hepatitis and primary biliary cirrhosis where serum autoantibodies play a pivotal role in diagnosis.

Cholangiography

The diagnosis of PSC is made based on the classic cholangiographic findings of diffuse strictures with intervening areas of normal appearing bile ducts leading to the so-called "beading." Seventy-five percent of strictures involve both the intra and extrahepatic bile ducts, with 15 % having strictures limited to the extrahepatic system. The cystic duct and gallbladder are involved in approximately 15 % of patients and a smaller number have pancreatic duct involvement [11–13]. Dominant strictures, defined as a diameter less than 1.5 mm in the common bile duct and less than 1.0 mm in the hepatic duct, are present in approximately half of PSC

patients. Pseudodiverticula, particularly in the common bile duct, are occasionally seen. While initially used as exclusionary criteria in PSC patients, the presence of biliary stones are now well-recognized as a common finding and frequent cause of cholangitis. There are three current modalities that can be used to image the biliary system. Endoscopic retrograde cholangiography (ERC) allows direct biliary visualization as well as also providing the opportunity to perform cytologic analysis, stricture dilation, removal of stones and biliary stenting. Potential complications of ERC include bleeding, cholangitis and pancreatitis [14]. Percutaneous hepatic cholangiography (PTC) also allows direct access to the biliary system but has similar complications to ERC and requires experienced radiologists as intrahepatic bile ducts are generally not dilated in PSC. The test of choice when attempting to make a diagnosis of PSC is the magnetic resonance cholangiography (MRC). The noninvasive nature of MRC limits complications and is more cost-effective than ERC or PTC. These advantages must be weighed against the fact that MRC unlike ERC and PTC does not offer the opportunity to perform biliary brushings for cytology nor intervene therapeutically. Magnetic resonance cholangiography also lacks sensitivity compared to ERC when assessing for peripheral bile duct changes. Once a diagnosis of PSC is established, there is no indication for further instrumentation of the biliary system unless there is a change in the patient's clinical status.

Histology

Liver biopsy at the present is not felt to be necessary to establish a diagnosis of PSC, nor to determine disease severity. Liver biopsy should be considered in all patients suspected of having small-duct PSC or overlap syndrome with autoimmune hepatitis. The classic finding when a liver biopsy is performed in PSC patients is the concentric fibrosis (onion-skinning) involving the periductal region. This lesion however is observed in only a minority of patients [12].

Additionally, biopsy sampling variation may fail to detect these lesions in patients who otherwise have classic cholangiographic findings.

Natural History

The natural history of PSC is highly variable and while it is a progressive disease, the rate of progression per year varies significantly in individual patients. Multiple studies have attempted to determine the time period from diagnosis to the need for liver transplantation or death and estimates range from 7 to 18 years from presentation [4, 15, 16]. Much of this variability is associated with the fact that some patients present early in their disease course without symptoms but have abnormal liver biochemistries, while others' initial presentation may be a complication of advanced disease with portal hypertension or cholangiocarcinoma.

Various prognostic models have been utilized in an attempt to predict future outcomes but their value is questionable in this clinical setting due the highly variable nature of PSC. The most common employed of these prognostic models is one proposed by the Mayo Clinic and utilizes the following variables: total bilirubin, age, presence or absence of variceal bleeding, serum albumin and aspartate aminotransferase values [17].

Primary Sclerosing Cholangitis Variants

Small-Duct Primary Sclerosing Cholangitis

Small-duct PSC is characterized by cholestatic biochemistries with a normal cholangiogram. Liver biopsy is essential in this group for diagnostic purposes and may demonstrate the periductal damage and onion-skinning previously described. Small-duct PSC represents approximately 10 % of all PSC cases. Small-duct PSC patients may have symptoms but a

greater percentage are asymptomatic when compared to large-duct PSC. Approximately 10–15 % of those with small-duct PSC will progress to large-duct PSC, typically over 5–10 years. Patients with small-duct PSC have a better long-term prognosis with fewer complications when compared to their large-duct counterparts [18, 19].

Overlap Syndrome with Autoimmune Hepatitis

Between 1 and 17 % of patients with PSC will also have an overlap syndrome with autoimmune hepatitis [20–22]. These patients will present with a hepatocellular injury as well as cholestasis and have detectable antinuclear antibodies and anti-smooth muscle antibodies. Immunoglobulin G elevations, as in classical autoimmune hepatitis, are typically seen. Liver biopsy should therefore be performed in all patients with PSC who have aminotransferase values greater than five times the upper limit of normal or IgG values greater than two times the upper limit of normal. Liver biopsy demonstrates histologic findings of both conditions; the periductal "onion-skinning" damage seen in PSC and the interface hepatitis and prominent plasma cell infiltration which is classically described in autoimmune hepatitis. The autoimmune hepatitis component unlike the PSC component is responsive to immunosuppression, with the most common agents utilized being corticosteroids and azathioprine. Patients with overlap PSC and autoimmune hepatitis may progress more rapidly than those affected by PSC alone due to the combination of the hepatocellular and cholestatic components.

Primary Sclerosing Cholangitis in Association with Autoimmune Pancreatitis

Autoimmune pancreatitis is a manifestation of a systemic disorder affecting multiple organs and is associated with an elevated serum immunoglobulin G4 (IgG4). Histology of the

pancreas shows a predominantly lymphocyte and plasma cell infiltrate. Pancreatic abnormalities include lesions that are frequently difficult to differentiate from malignancy as well as pancreatic duct strictures. A subset of these patients will have biliary strictures similar to those seen in PSC occasionally in the absence of pancreatic abnormalities, a condition occasionally referred to as IgG4 cholangiopathy. Those with IgG4 cholangiopathy tend to have a more aggressive disease course compared to those with PSC and normal IgG4 values [23, 24]. Primary sclerosing cholangitis associated with elevated IgG4 levels are frequently responsive to corticosteroid therapy and it is recommended to measure IgG4 levels in all newly diagnosed PSC patients [25].

Secondary Sclerosing Cholangitis

There are various conditions that can affect the biliary system and produce findings that mimic the strictures seen in PSC. Prior to making a diagnosis of PSC these secondary causes must be carefully looked for and eliminated as potential etiologies. Secondary causes include congenital biliary tract disorders such as biliary atresia and Caroli's Disease, AIDS cholangiopathy, ischemic strictures, biliary malignancies such as cholangiocarcinoma not associated with PSC, previous biliary injuries as a result of surgery and chemical exposure to toxins such as floxuridine, a pyrimidine analogue infused via the hepatic artery in patients with metastatic colon cancer to the liver [26].

Complications of Primary Sclerosing Cholangitis

Complications of PSC can be classified as those that are related to the cholestatic nature of the disorder and those that are unique to PSC.

Complications of Cholestatic Liver Disease

Cholestasis-related complications include pruritus, bone disease, fat soluble vitamin deficiency and portal hypertension.

Pruritus

Pruritus can be one of the most disabling complications of cholestatic liver diseases with failure to respond to therapy frequently leading to frustration in both patients and clinicians. While much attention has been focused on the accumulation of biliary compounds in various tissues, the exact mechanism remains unknown [27]. There does not appear to be a strong correlation with the severity of liver disease and patients with mild to moderate biliary strictures may have the most severe symptoms. The subjective nature of pruritus makes accurate measurement difficult and while multiple tools including visual aids are available, they are not generally utilized in clinical practice. The treatment of pruritus generally involves a stepwise approach. First line therapy typically involves anion exchange resins such as cholestyramine initially at four grams twice daily (before and after breakfast if the gallbladder is present) and increasing to four times daily as necessary [28]. Patients must communicate with their pharmacist in order to ensure that cholestyramine does not interfere with the absorption of other medications or fat-soluble vitamins. Side effects include mild constipation, diarrhea, abdominal pain, flatulence, nausea, and vomiting. If the pruritus remains refractory, rifampin at doses of 150 mg to 300 mg twice daily can be added with careful monitoring of serum liver and renal biochemistries [29]. Additional first line agents include Sertraline, a selective serotonin uptake inhibitor, at 100 mg daily and nighttime antihistamines due to their sedative side-effect profile. Second line therapies include naltrexone, an opioid antagonist, at 50 mg daily and phenobarbital at doses of 60 mg to 100 mgs nightly [30]. Third line therapies

include plasmapheresis which is effective but cumbersome. Therapies that have been proposed but lack supporting data include dronabinol, ondansetron, ultraviolet light, and S-adenosylmethionine (SAM-E). Liver transplant has been proposed for patients with severe, refractory pruritus despite low Model for End Stage Liver Disease (MELD) scores. Exception points for patients with low MELD scores can be requested due to refractory pruritus but the subjective nature of this complication has led to few exceptions being granted.

Bone Disease

Bone disease in the setting of chronic liver diseases is frequently referred to as hepatic osteodystrophy and includes osteopenia and osteoporosis. Both are now recognized as a frequent finding in all patients with chronic liver diseases but are most pronounced in those with cholestasis [31]. The mechanism for bone disease in PSC is likely multifactorial and includes decreased formation and increased resorption. Vitamin D deficiency may play a minor role. Longer duration of IBD, older age, female gender and low body weight are other contributing factors. All patients with newly diagnosed PSC should undergo bone mineral density assessment (DEXA) and at intervals of 2–3 years based on initial results [32, 33]. Treatment includes calcium 1200 mg daily and vitamin D 1000 IU supplementation. This supplementation should be in conjunction with a regular exercise regimen. Hormone replacement while effective is not generally employed due to the side-effect profile. Bisphosphonate therapy is beneficial in patients with osteoporosis and primary biliary cirrhosis and is also indicated for those with osteoporosis and PSC [34]. Bisphosphonates should be avoided in those patients with esophageal varices as they have been shown to increase the risk of bleeding due to esophageal ulcerations. Intravenous bisphosphonates are effective options in those with osteoporosis who have contraindications to oral therapy due to esophageal varices.

Fat-Soluble Vitamin Deficiency

Patients with cholestatic hepatic disorders including PSC are at risk for developing malabsorption and deficiency of vitamins A, D, E and K due to decrease in the availability of bile salts [35]. While bile salt production from cholesterol and bile acids is normal, the impaired flow of bile salts due to biliary strictures results in a relative deficiency in bile salt function in the small intestine. Vitamin A deficiency is rarely of clinical consequence. Levels can be measured and effective supplementation is available. Care must be taken to avoid vitamin A toxicity from over-supplementation. Vitamin D deficiency is the most clinically significant of all the fat-soluble vitamin deficiencies. As previously mentioned, by itself it is not responsible for bone disease, but likely plays a contributing role. Vitamin D levels are also easily measured and supplemented. Vitamin E deficiency is rare and can be supplemented if serum levels are decreased. Vitamin K deficiency can lead to elevated prothrombin times and typically responds well to supplementation.

Portal Hypertension

Patients with PSC frequently progress to cirrhosis and develop portal hypertension complicated by esophageal and gastric varices, ascites and hepatic encephalopathy. These patients should be treated similar to non-PSC cirrhotic patients. While current recommendations are for all patients with cirrhosis to undergo an upper endoscopy to evaluate for varices, those affected by PSC are also at risk for the development of pre-cirrhotic, pre-sinusoidal portal hypertension and should therefore undergo endoscopic evaluation. Non-selective beta blockade for primary prophylaxis of documented varices is effective with band ligation utilized in those intolerant of beta blockers. Sodium restricted diets in combination with diuretics, most commonly spironolactone and furosemide, are the standard of care in patients with

ascites. Beta blockers should be avoided in PSC patients with refractory ascites due to concerns for the development of acute kidney injury. Avoidance of factors that precipitate hepatic encephalopathy including intravascular volume depletion, infections, gastrointestinal bleeding and electrolyte disturbances are paramount. Minimal hepatic encephalopathy, as well as overt encephalopathy, should be treated with lactulose and if necessary the addition of rifaximin as a second agent.

Complications Specific to Primary Sclerosing Cholangitis

Disease specific complications associated with PSC include IBD and colorectal cancer, peristomal varices, dominant strictures, biliary stones, gallbladder carcinoma, and cholangiocarcinoma.

Inflammatory Bowel Disease and Colorectal Carcinoma

The majority of patients with PSC will have concurrent IBD, more frequently ulcerative colitis than Crohn Disease with colonic involvement. Up to 7.5 % of IBD patients will be affected by PSC [3, 4]. The IBD is typically diagnosed prior to PSC in the majority of patients, but can vary with some patients' first symptoms of IBD being years after the diagnosis of PSC or even following liver transplantation. Inflammatory Bowel Disease in the setting of PSC differs from those not affected by PSC with more rectal sparing, greater right-sided disease, more backwash ileitis and more quiescent disease in those with PSC [36, 37]. While all patients with chronic colitis are at increased risk for the development of colorectal cancer, those IBD patients with PSC are at a much greater risk [38]. Current recommendations include colonoscopy every 1–2 years in those IBD patients who also

carry a diagnosis of PSC. Colon biopsies should always be obtained to evaluate for dysplastic changes. The use of ursodeoxycholic acid (UDCA) has been advocated by some as decreasing the risk of colonic dysplasia and colorectal carcinoma based on two small studies [39, 40], but subsequent studies have not supported its effectiveness. Patients with PSC and IBD who undergo liver transplant have been shown as a group to have more difficult to manage IBD despite the fact that their post-transplant medical regimen includes one or more immunosuppressive agents.

Peristomal Varices

Patients with concurrent IBD and PSC have frequently undergone proctocolectomy with ileostomy formation due to refractory colitis or colorectal cancer. These patients will occasionally develop peristomal varices. While not associated with the mortality seen in patients with esophageal or gastric variceal bleeding, the morbidity and impact on quality of life can be significant. Local temporizing measures have been of limited efficacy with transjugular intrahepatic portosystemic shunt (TIPS) proving to be beneficial in refractory cases if no contraindications exist.

Dominant Biliary Strictures

Dominant strictures, defined as a diameter less than 1.5 mm in the common bile duct and less than 1 mm in the hepatic duct, are seen in up to half of all PSC patients [41, 42]. The length of these strictures varies but are typically short. Dominant strictures can result in deterioration of previously stable disease and lead to worsening jaundice, pruritus and cholangitis. Strictures should be promptly addressed with endoscopic therapy being the preferred method. Following sphincterotomy, balloon dilation of the stricture with stent placement is frequently necessary. The need for

stents, their associated exchanges and instrumentation increases the risk of cholangitis and mandates the need for pre and post-procedure antibiotics. Unfortunately, strictures in the intrahepatic region are not always accessible endoscopically and may require a percutaneous approach. Finally, it is imperative to perform brush cytology of dominant strictures whether by endoscopic or percutaneous approaches to differentiate dominant non-malignant strictures from cholangiocarcinoma.

Biliary Stones

As previously mentioned, biliary stones, once considered exclusionary for PSC, are now recognized as a common finding. Strictures, in particular dominant strictures, and impaired bile flow play key roles in stone formation. Complications include pain, cholangitis, and clinical deterioration. Aggressive antibiotic use particularly for biliary pathogens and prompt endoscopic stone retrieval are indicated. While there may be a role for UDCA to prevent stone formation and improve bile flow, little data currently exists.

Gallbladder Disease Including Adenocarcinoma

Primary sclerosing cholangitis involves the gallbladder as well as the cystic duct in 15 % of patients. Gallstones, which are common in the general population, are seen in up to 26 % of PSC patients [13]. Patients with PSC are also at risk for the development of mass lesions. Gallbladder polyps in particular are common and can lead to dysplasia and adenocarcinoma [43]. Current recommendations include performing annual gallbladder ultrasounds to evaluate for mass lesions and if present for the patients to undergo cholecystectomy regardless of the size of the lesion unless contraindications exists [32].

Cholangiocarcinoma

One of the most feared complications of PSC is the development of cholangiocarcinoma. Approximately 50 % of patients diagnosed with cholangiocarcinoma will be diagnosed within one year of their PSC diagnosis. Afterwards the annual risk is 0.5–1.0 % with a 10-year risk of 7–10 % [44–47]. Unfortunately, a large number have advanced disease including locoregional as well as distant disease at the time of diagnosis. It remains unclear as to what specific factors in PSC patients predispose them to develop cholangiocarcinoma. The differentiation between benign strictures and cholangiocarcinoma, particularly in dominant strictures, remains a challenge. Biochemical testing with CA19-9 is limited by the fact that it is nonspecific and can be elevated from benign strictures and cholangitis. Patients who lack the Lewis antigen will not demonstrate detectable CA19-9 even in the presence of cholangiocarcinoma. Imaging studies with computerized tomography, ultrasound, MRC, and ERC fail to consistently differentiate benign from malignant strictures. Biliary brushing done at the time of ERC have long been recognized to have good specificity but sensitivities under 50 %. Newer approaches to aid in the diagnosis of cholangiocarcinoma include fluorescent in situ hybridization (FISH). This technique evaluates cells obtained from suspicious lesions by brush cytology and evaluates for polysomy (the duplication of two or more chromosomes) in greater than five cells [48]. At the present time, there are no formal recommendations from any society regarding cholangiocarcinoma screening and surveillance with CA19-9, MRC, cholangioscopy during ERC or other imaging modalities.

Treatment of cholangiocarcinoma has traditionally been limited. The diffuse biliary nature of PSC has made surgical resection an option for a limited few and chemotherapy has not been shown to be of significant benefit. More recently, liver transplant in a highly selected group of patients with hilar lesions less than three cm in diameter and without evidence of spread has been evaluated. These patients undergo external beam as well as brachytherapy in conjunction with

chemotherapy. Percutaneous transhepatic cholangiography should be avoided in these patients for fear of seeding the peritoneum with malignant cells. Some centers are reporting 5-year survival comparable to non-cholangiocarcinoma patients [49]. Transplant centers with an active protocol in place can petition regional review boards for MELD exception points for these patients.

Hepatocellular Carcinoma

While not unique to cholestatic liver diseases or PSC, patients with established cirrhosis are at risk for developing hepatocellular carcinoma (HCC). Screening and surveillance for HCC is indicated in all cirrhotic patients regardless of age and involves ultrasound examination every 6 months with suspicious lesions warranting further evaluation with a dynamic study such as CT or MRI [50]. The role of alpha fetoprotein for screening of HCC remains controversial and no recommendations can be made at this time.

Medical Therapy in Primary Sclerosing Cholangitis

Numerous agents have been evaluated in the treatment of PSC and there is no evidence to suggest that there is effective medical therapy. Agents that have been evaluated in small trials include corticosteroids, cyclosporine, tacrolimus, azathioprine, methotrexate, penicillamine, and colchicine. Antibiotics while indicated for invasive procedures and for episodes of cholangitis, do not alter the natural history of PSC. The most studied of all agents is ursodeoxycholic acid (UDCA) which has been shown to slow disease progression and alter the natural history in patients with primary biliary cirrhosis (PBC) at doses ranging from 13 to 15 mg/kg/day [51]. Similar doses in PSC patients resulted in biochemical improvement but failed to alter the natural history [52]. Due

to the large bile duct involvement in PSC relative to PBC, it was theorized that greater doses would be necessary for a benefit to be seen. Despite increasing doses, this benefit did not materialize and a multicenter trial evaluating doses of 28 to 30 mg/kg/day was terminated due to an increased frequency of decompensation, need for transplant and death in the treatment group [53]. As previously mentioned, corticosteroid therapy is indicated in patients with IgG4-associated cholangitis and in combination with azathioprine in those with PSC-AIH overlap.

Liver Transplantation for Primary Sclerosing Cholangitis

Liver transplantation has been shown to be the only effective therapy that alters the natural history of PSC with approximately 250 transplants performed annually in the USA for PSC. Listing for liver transplantation is overseen and regulated by the United Network for Organ Sharing (UNOS) and utilizes the MELD score to determine listing priority. Refractory pruritus, recurrent bacterial cholangitis, and cholangiocarcinoma are PSC-specific complications that will be considered by regional review boards for MELD exception points [54]. Due to the diffuse biliary strictures associated with PSC as well as the risk of future cholangiocarcinoma in the recipient remnant bile duct, the biliary anastomosis performed at the time of transplantation is a Roux-Y-choledochojejunostomy. Overall results following liver transplant for PSC are excellent with 5-year survival of approximately 85 %. Recurrent PSC in the transplant liver occurs in approximately 20 % of patients and will occasionally result in the need for retransplantation [55, 56]. Biliary strictures which can be due to other factors including ischemia and hepatic artery injury are frequently difficult to differentiate from recurrent PSC strictures. Biliary access for interventional purposes following liver transplant typically involves a percutaneous approach due to the Roux-Y-choledochojejunostomy biliary anastomosis.

Future Trends

There are three major areas in PSC that will require greater attention if we are to make significant impact on morbidity and mortality.

First, there is no effective medical therapy and this requires immediate attention. Large, multicenter, randomized controlled trials are urgently needed. Without medical therapy, physicians are forced to address complications while taking a wait and see approach regarding liver transplantation.

Second, consensus recommendations regarding cholangiocarcinoma screening and surveillance need to be developed. Imaging studies and/or biomarkers that are both cost-effective and have acceptable sensitivity and specificity are currently lacking. This has resulted in multiple imaging modalities usually in combination with CA 19-9 being employed despite lack of supporting data.

Finally, once a lesion that is suspicious for cholangiocarcinoma develops, current diagnostic testing including brush cytology and FISH are suboptimal. While the negative predictive value for the combination of brush cytology and FISH is 90 %, the positive predictive value is only 50 % [48]. Liver transplantation is now an effective therapy in selected patients with cholangiocarcinoma. It is essential that patients with cholangiocarcinoma be identified as early as possible in order to undergo transplant evaluation at centers with established protocols.

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