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Primary Sclerosing Cholangitis and Ulcerative Colitis

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1. Introduction

Primary Sclerosing Cholangitis (PSC) is a chronic hepatobiliary disease characterized by progressive inflammation and fibrosis of the intra and extra biliary tree. This phenomenon leads to diffuse stricturing of the biliary tree and, if left untreated, can result in cirrhosis, portal hypertension and end stage liver disease. There are treatments aimed at delaying the progression of disease and reducing symptoms. However, the definitive treatment at the end stage of this disease is liver transplant.

The etiology and pathogenesis of the disease is largely unknown although some researchers have speculated that immunologic and genetic factors may be involved. Ulcerative colitis (UC) is also a chronic inflammatory disorder of the colon of unknown etiology with possible genetic and environmental triggers. The correlation between both these diseases would suggest that the etiology could be immune mediated.

2. Immune system involvement

Current theories postulate that an autoimmune process leading to lymphocytic infiltrate causes biliary destruction (Aron 2009). Some studies have found an increased number of serum autoantibodies being expressed in patients with PSC. For example, antineutrophil cytoplasmic, antinuclear, and anticardiolipin antibodies are seen with increased frequency in PSC (Angulo 2000). A study of 73 patients with definite PSC found that 81% were positive for the above listed antibodies (Angulo 2000). Also, a study of 25 PSC patients showed that 75% tested positive for pANCA (Gur 1995). These serum markers lack specificity for PSC. Nonetheless, the involvement of the immune system remains apparent.

In addition, some other autoimmune disorders are associated with the occurrence of PSC. A few case reports found males under the age of 25 that were diagnosed with PSC, to have UC and Type 1 Diabetes Mellitus (Gluch 1999 and Kay 1993). Chronic liver diseases, such as Primary Biliary Cirrhosis and Autoimmune Hepatitis have also been noted to have some overlapping features. More importantly, there is evidence that PSC has significant overlap features with autoimmune hepatitis. Three patients with elevated liver function tests, positive Antinuclear Antibody and/or Anti-smooth muscle antibodies were found to have histological and cholangiographic evidence of PSC (Gohike 1996). This supports the overall theory that the immune system is significantly involved with the development of PSC.

Undoubtedly an association between UC and PSC exists, however the mechanism by which they are related remains largely unknown. Some have suggested that a shared autoantibody between biliary and colon epithelium exists. An epitope that was common to the colon and biliary epithelial cells was discovered. Using this finding, a study was conducted to determine if a cross-reactive antibody exists that is common to PSC and UC (Mandal 1994). This study found that sera from patients with PSC contained autoantibodies against a cross-reactive peptide shared by colon and biliary epithelial cells. Therefore, this antibody could suggest a molecular association between PSC and UC.

Based on the premise that PSC and UC are strongly related, some theorist have postulated that infectious agents may be involved in the development of PSC. That is, when the colonic mucosa is significantly inflamed, toxic agents can invade the blood circulation and thereby cause PSC. 26 patients with AIDS-related cholangiopathy were found to have CMV and Cryptosporidium infection (Benhamou 1993). The most common infectious agents isolated from patients with AIDS-related cholangiopathy include microsporidium and cryptosporidium. Non-infectious agents have been linked to the development of PSC. For example, patients receiving hepatic artery infusion of chemotherapeutic agents were reported to have cholangiographic evidence of PSC (Barnett 2001). However, UC disease activity does not correlate with the appearance of PSC.

3. Genetics

The understanding of certain genetic associations between US and PSC has gained increased importance. For example, one study illustrated that several members of three families had PSC and UC (Quigley 1983). It has been suggested that specific human leukocyte antigen (HLA) haplotypes may be more likely to occur in the setting of well-defined PSC. Several specific HLA haplotypes have been found to strongly correlate with the development of PSC. In one study, HLA-DRw52a was present in 100% of 29 patients studied with PSC (Prochazka 1990). Also, of these patients 15 shared a common haplotype 12 of who had previously diagnosed UC (Prochazka 1990). The most common haplotypes associated with PSC include the following: HLA-B8, DR3, Dr2 and DR6 (Prochazka 1990). Also, in patients with both PSC and UC an increased presence of MICA and MICB alleles were demonstrated (Wiencke 2001). These alleles are primarily expressed in the gastrointestinal epithelium (Wiencke 2001). Some authors have suggested that this may represent a link between colonic and biliary disease. However, whether one specific gene is involved with the occurrence of PSC remains controversial.

The use of certain HLA haplotypes to determine disease progression is also under investigation. One study found that the HLA-DR3, DQ2 heterozygote genotype was associated with rapid progression of PSC and that the DR4, DQ8 haplotype was related to the development of cholangiocarcinoma (Boberg 2001). This finding could have an impact on determining disease progression. However, this genetic association requires further investigation before it can take center stage in determining prognosis and therapy.

4. Epidemiology

PSC is most often seen in Northern European populations. In some Nordic countries it is considered the primary indication for liver transplant (16). According to the NIH, PSC affects less than 200,000 people in the United States Population. This disease is most commonly seen between the ages of 20-30 years and is most common in men. PSC occurs in

5 % of patients with UC, and, conversely, UC occurs in 60-75 % of patients with PSC. The mean survival is 10- 12 years after diagnosis, with an increased risk for cholangiocarcinoma. Despite the known association with UC, there is a small subset of patients with retroperitoneal fibrosis who have been diagnosed with PSC (Bartholomew 1963). There are varying reports of the actual incidence and prevalence of PSC, which is likely due to the inconsistency in its presentation and lack of sufficient data. A population-based study in the United States demonstrated that the incidence of PSC was approximately 0.54 to 1.3 per 100,000, and the prevalence is 6.3 to 20.9 per 100,000 (Bambha 2009). Most of the patients described in this study had underlying UC.

5. Clinical presentation and diagnosis

Most patients are initially asymptomatic and therefore present with abnormal liver function tests or hepatomegaly on physical exam. The most common lab abnormalities include, an elevated serum alkaline phosphatase level, usually twice the upper limit of normal, and an
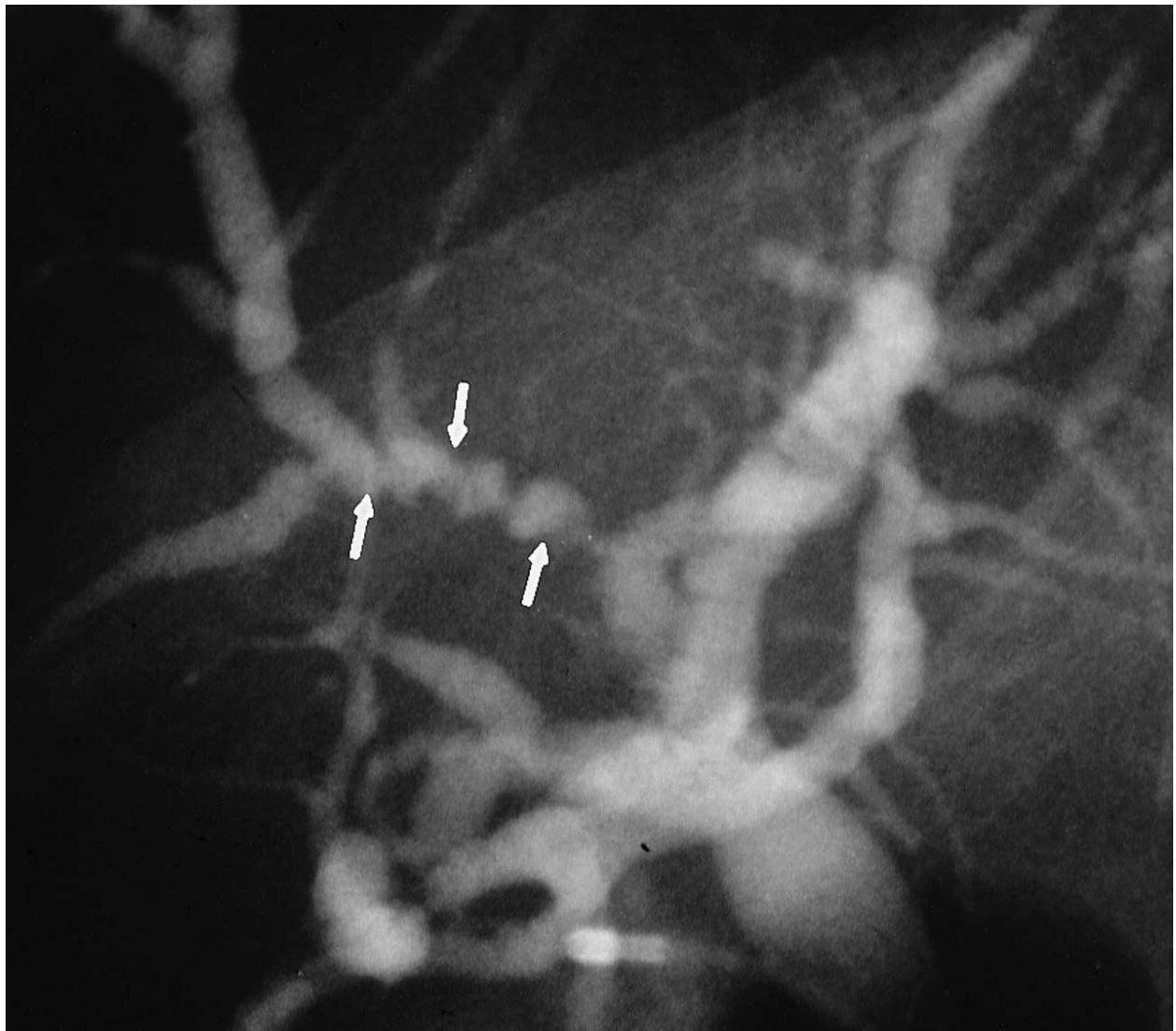

Fig. 1. Arrows indicate the characteristic beaded appearance (Vitellas K M et al. Radiographics 2000;20:959-975)

elevated Gamma glutamyltransferase. Also, the serum bilirubin and transaminases will demonstrate a cholestatic pattern. PSC develops insidiously and symptoms are often non-specific in their initial presentation. However, as the disease progresses, the most notable symptoms include, jaundice, right upper quadrant pain, pruritis, fever, weight loss and fatigue. Waxing and waning symptoms are typical of PSC.

The diagnosis of PSC can be confirmed by liver biopsy or characteristic changes on cholangiogram. Endoscopic Retrograde Cholangio Pancreatography (ERCP) has been considered the gold standard in diagnosing PSC. However, ERCP is more invasive in
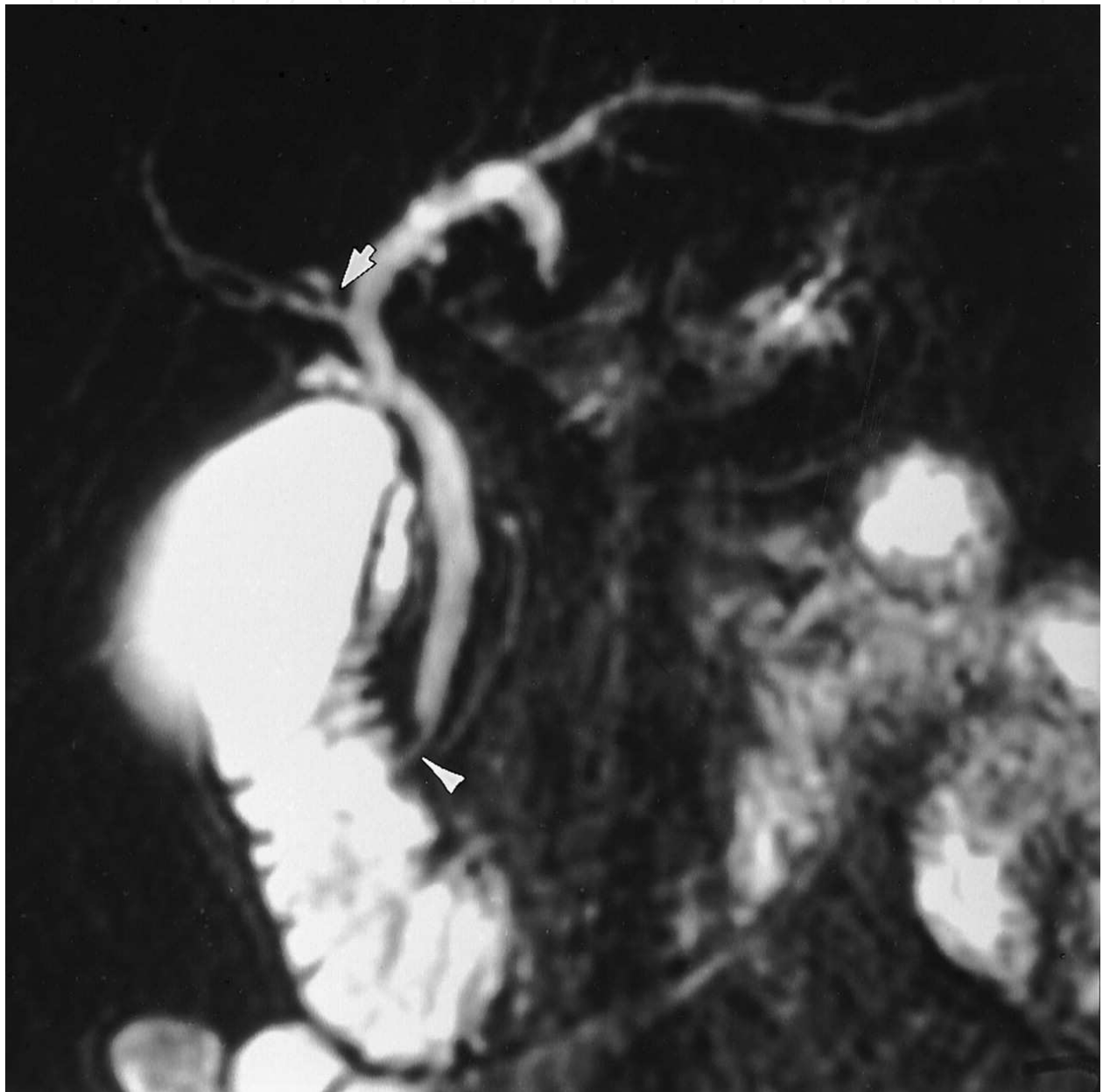

Fig. 2. Early PSC in a 45-year-old man with ulcerative colitis and elevated results of liver function tests. Coronal MRCP image shows a stricture at the distal common bile duct (arrowhead), extrahepatic and left intrahepatic ductal dilatation and irregularity, and a subtle stricture at the bifurcation of the posterior right hepatic duct (arrow). (Vitellas K M et al. Radiographics 2000;20:959-975)
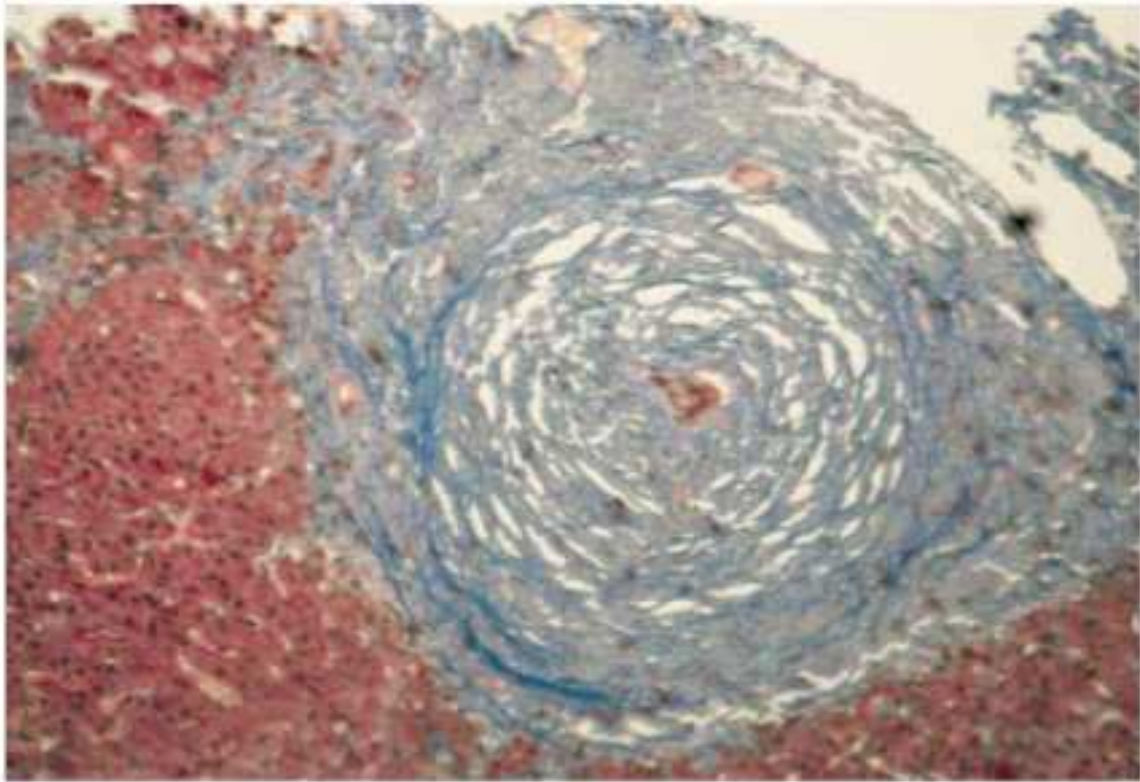
Fig. 3. Stage 2 lesion (Lee, Young-Mee, Kaplan M. Primary sclerosing cholangitis. NEJM 1995)
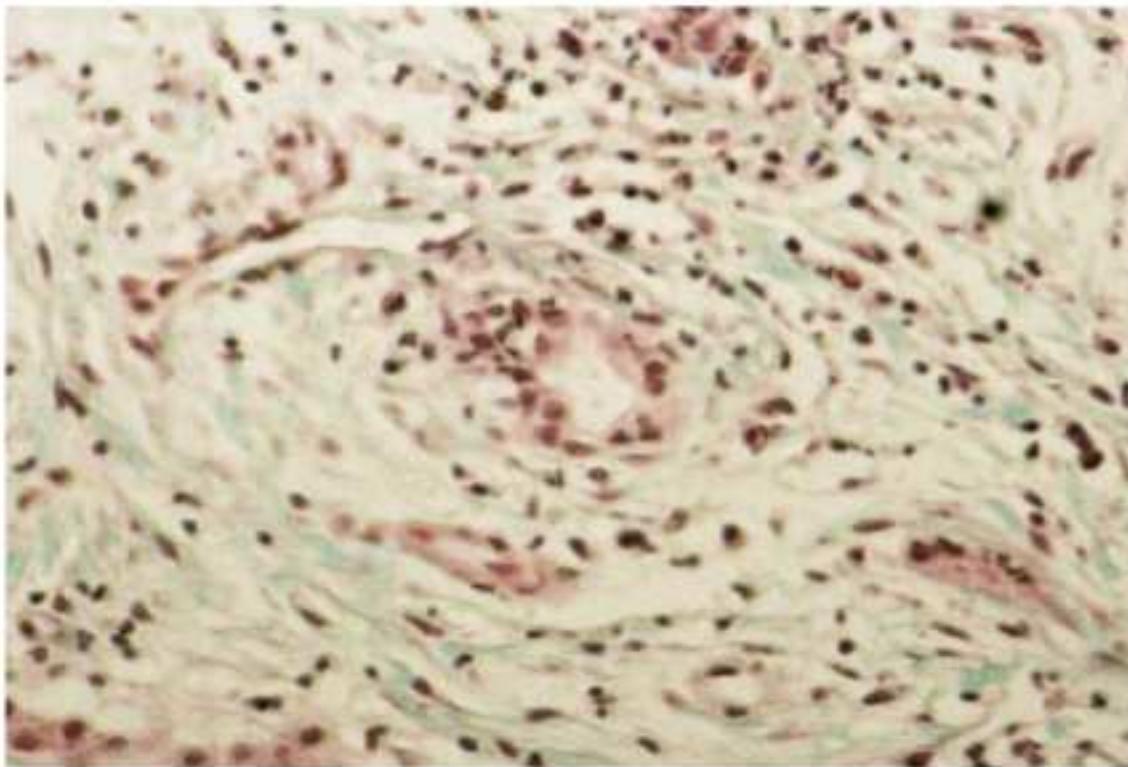

Fig. 4. Early stage 1 disease (Lee, Young-Mee, Kaplan M. Primary sclerosing cholangitis. NEJM 1995)

comparison to Magnetic Resonance CholangioPancreatography (MRCP), which has comparable accuracy. In cases with a high pretest probability of PSC with a negative MRCP, an ERCP would be indicated to visualize small ductal disease. The characteristic findings on imaging include, multiple segmental strictures with intervening segments that appear normal, otherwise known as a "beaded appearance"(figure 1). Figure 2 is an image of a patient with UC and abnormal LFTS that was found to have a stricture in the common bile duct and the bifurcation of the hepatic duct, with luminal irregularities.

Liver biopsy is not indicated for diagnosis in cases with a positive finding on cholangiogram. However, liver histology can be useful in staging the disease. The characteristic histological feature of PSC is the "onion skin appearance", which occurs due to periductal fibrosis (figure 3). However, this finding is rarely found on biopsy specimens. Stage 1 is defined as the portal triad of edema, scarring and mono/polynuclear cell infiltrate (figure 4). Stage 1 remains confined to the portal triad. Stage 2 refers to expansion of the portal triads with fibrosis into parenchyma (fig 3). Stage 3 and 4 are defined by bridging fibrosis and eventual cirrhosis.

6. PSC & UC association

There is a high prevalence of UC in patients with PSC while a minority of patients with UC have PSC as an extra intestinal manifestation. The current data approximates that 50-75% of all patients with PSC have IBD, and in contrast the incidence of patients with UC developing PSC is 2.5-7.5 % (Raj 1999). This association is an important one for many reasons. A study of 1500 cases of UC established that 3.7 % had PSC and within this subset the prevalence of substantial colitis was 5.5%, in contrast to 0.5 % with distal colitis (Olsson1991). This suggests that cases with more severe and extensive UC are more likely to develop PSC. However, a few case reports have demonstrated a milder course of colonic disease in patients that developed PSC (Schrumpf 2001 ad Moayyeri 2005). Therefore, regardless of the strong association between these two diseases, for the most part they seem to progress autonomously.

The definitive treatment for UC when patients remain refractory to medical management is surgery. Proctocolectomy with ileal reservoir is the most widely accepted surgical procedure. A common issue with this ileal reservoir, referred to as the pouch, includes the development of pouchitis. This diagnosis is characterized by diarrhea that is occasionally bloody and abdominal discomfort. In the subset of UC patients that develop PSC, pouchitis after ileal pouch-anal anastomosis (IPAA) is being diagnosed with increasing frequency.

A study was performed to determine the frequency of pouchitis in patients with and without PSC who had an IPAA for UC (Penna 1995). Patients with indeterminate colitis or other constructions of reservoirs were excluded in this study. The results showed that one or more episodes of pouchitis occurred in 63% of patients with PSC (Penna 1995). In addition, of these patients the overall risk for pouchitis increased at 1, 2, 5, and 10 years after IPAA.

Interestingly Aitola et al also demonstrated that patients with PSC had more chronic, but not acute inflammation in the pouch mucosa than patients without cholangitis (Aitola 1998). In comparison to patients receiving IPAA for other diseases such as Familial Adenomatous Polyposis, the frequency of pouchitis was higher in the PSC-UC patient. Therefore, based on this data it is unlikely that the cause of pouchitis is surgery and more likely a consequence of PSC-UC. A matched case control study was performed to describe the clinical features and outcomes in patients with PSC and IBD. This study found that a significant number of

patients in the PSC-IBD group developed back wash ileitis and had an increased incidence of colorectal neoplasia (Loftus 2005).

Some speculate that the significant bowel inflammation is due to a possible change in bile acid fecal output. This phenomenon is thought to lead to the development of pouchitis, but, this is purely speculation. Nonetheless, an underlying immunologic association exists between UC-PSC patients and the later development of pouchitis.

7. Malignancy

In comparison to the general population, patients with PSC are at higher risk for developing Cholangicarcinoma. This malignancy is defined as an adenocarcinoma of the biliary ducts that is rapidly progressive, with an average life expectancy of 5 months at the time of diagnosis. It is considered a rare disease within the general population, with a lifetime risk of less than 1 %. In contrast, PSC patients have an estimated lifetime risk of 10-15% for developing cholangiocarcinoma (Berqquist 2002). This disease is the second leading cause of death in PSC patient. Cholangiocarcinomas are most commonly found in the common hepatic duct or common bile duct, but can also be detected at the cystic duct. The sites at which this disease originates allows rapid dissemination to the liver, gallbladder, pancreas and duodenum. Also, intra-peritoneal seeding is not an uncommon consequence of this disease. Therefore, cholangiocarcinoma is most frequently diagnosed when it's metastatic.

The pathogenesis of PSC is believed to be due to chronic inflammation and obstruction of the bile ducts. This ongoing insult to the biliary epithelium is believed to result in malignant conversion of the biliary epithelium. In support of this theory, south Asian patients with Clonorchis sinesis were at increased risk for developing cholangiocarcinoma (Schwartz 1986). The precise molecular mechanism by which chronic inflammation leads to cholangiocarcinoma still remains unclear.

Early diagnosis of cholangiocarcinoma is important, especially in PSC patients because it is considered a contraindication to liver transplantation. The diagnosis of Cholangiocarcinoma in PSC patients is significantly difficult. The use of tumor markers to detect early disease has been studied. The CA 19-9 and carcinoembryonic antigen (CEA) has been noted to be significantly elevated in patients with cholangiocarcinoma. However, whether they are useful as markers of early cholangiocarcinoma is debatable. A study was conducted to investigate the utility of measuring CA 19-9 and CEA in patients with PSC for early diagnosis of cholangiocarcinoma (Bjournsson 1999). This study found that the levels of CA 19-9 could rise along with elevations in alkaline phosphatase, which indicates a relapse of PSC. However, the sensitivity of the combination of CA 19-9 and CEA was low, but the specificity was high (88%). Bile levels of these tumor markers were evaluated in this study and didn't reveal any clinically useful differences. Therefore, the use of these tumor markers for detection of cholangiocarcinoma remains controversial.

The use of conventional radiologic imaging such as Magnetic resonance or CT scans are of low sensitivity in diagnosing cholangiocarcinoma. Patients with PSC often have cholangiographic evidence of biliary strictures, which make malignant strictures indistinguishable. Hence, obtaining tissue is essential for diagnosis. The use of advanced endoscopic techniques, such as, Endoscopic Ultrasound (EUS) with fine needle aspiration (FNA) is increasingly important for obtaining cytology.

The combination of brush cytology and FNA increases sensitivity for diagnosis of Cholangiocarcinoma (Eloubeidi 2004). The reported sensitivity of EUS with FNA is 89 %

(Eloubeidi 2004). Figure 5 is an image of EUS diagnosing cholangiocarcinoma. Other endoscopic techniques, such as Intraductal Ultrasound (IDUS) and Choledoscopy have increased sensitivity in cases of negative brush cytology or tissue biopsy using EUS. IDUS uses a smaller caliber probe that can be passed through an endoscope into the biliary and pancreatic duct. This procedure increases the sensitivity of the ultrasound to detect lesions in the pancreatic or biliary ducts. In PSC patients, this technique can assist in distinguishing between benign and malignant strictures (Tischendorf 2007). Cholangioscopy is also useful because it allows for direct visualization of the biliary stricture (Figure 6). The use of these endoscopic procedures increases the overall sensitivity for detection of cholangiocarcinoma especially in patients with PSC.
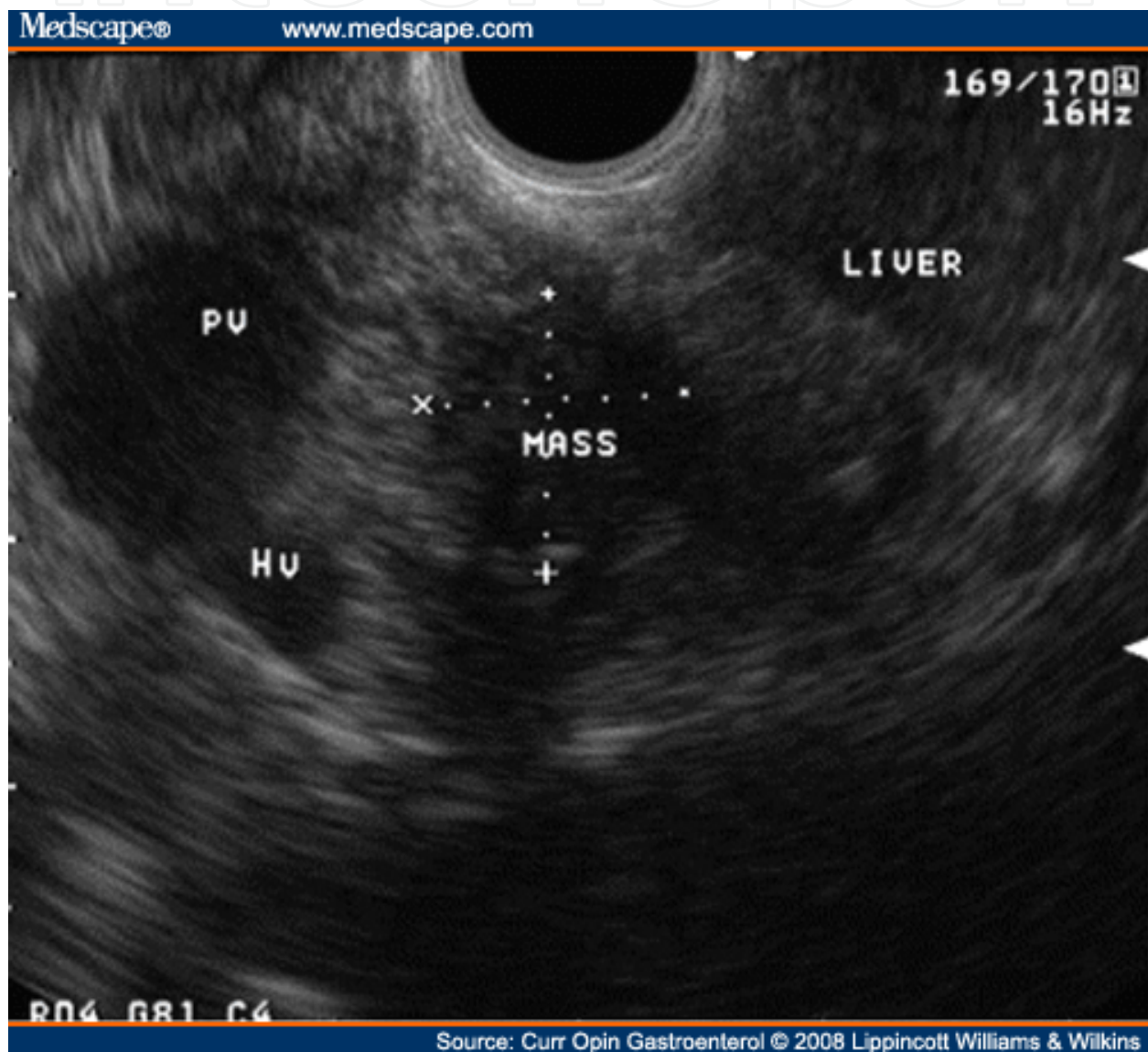

Fig. 5.

UC has a well-known association with the development of colorectal neoplasia. The risk in these patients increases with the duration and extent of disease. A study published in the New England Journal of Medicine found that the relative risk of colorectal cancer (CRC) was 14.8 for patients with pan colitis, 2.8 for those with left-sided colitis, and 1.7 for those with

Proctitis (Ekbom 1990). It has been suggested that patients with both PSC and UC are at even higher risk for CRC. A cohort study was performed comparing patients with UC and PSC, and random samples of UC controls without PSC (Shetty 1999). These patients were analyzed from diagnosis of the disease until an outcome. They found that thirty-three (25%) of 132 UC patients with PSC developed CRC or dysplasia compared with 11 (5.6%) of 196 controls (adjusted relative risk 3.15, 95% confidence interval 1.37-7.27) (Shetty 1999). They also found that patients with PSC and CRC were more likely to have more proximal and advanced CRC. This finding has a significant impact on disease surveillance and management.

Fig. 6. Bile duct tumor on direct video cholongioscopy (www.cpmc.org/liver)

There are several theories regarding the pathogenesis of CRC in patients with PSC and UC. Some suggest that the increased bile acids in the colon may contribute to the development of dysplasia. Based on this notion, a study was conducted to evaluate the effect of ursodeoxycholic acid in preventing the occurrence of colonic dysplasia. This was a cross-sectional study that evaluated patients with UC and PSC that were undergoing routine endoscopic colonic surveillance. This study found that ursodiol use was associated with a statistically significant decrease in prevalence of colonic dysplasia (Tung 2001). However, this medication has not been evaluated in prospective study, therefore its utility remains controversial.

The risk of CRC has been noted to increase with the length of UC exposure. PSC patient are a t even higher risk for CRC and therefore require yearly surveillance colonoscopies (Eaden 2002). It has been suggested that the cumulative risk of CRC in PSC patients is estimated to be 9 % after 10 yrs, 31% after 20 yrs and 50 % after 25 yrs of disease (Broome 1995). A study of PSC patients undergoing Liver transplants with hx of UC and pancolitis were found to be at increased risk of CRC (Silva 2004). Therefore, in post-transplant patients yearly colonoscopies are still recommended.

8. Medical treatment for PSC

Various medications have been studied to evaluate whether they would have a curative role in PSC. Immunosuppressive medications have been extensively studied because of their role in suppressing inflammatory cytokines. These medications include, glucocorticoids, azathioprine, methotrexate, and pentoxifylline. It has been postulated that the upregulation of inflammatory cells leads to biliary ductal destruction. Bharucha et al gave 20 patients with PSC sustained release pentoxifylline for approximately one year. The serum bilirubin, transaminases and alkaline phosphatase were followed every three months. The overall study showed no significant improvements in the liver biochemistry and the disease (Bharucha 2000). Also, a prospective study using pulse dosing of methotrexate was conducted on patients with clinical and histologic evidence of PSC (Knox 1994). This study also showed no significant benefit in preventing the progression of PSC. Therefore, the data overwhelmingly shows that these immunosuppressive agents are unable to halt the progression of the disease.

The use of ursodeoxycholic acid (UDCA) may have a role in reducing the levels of the liver biochemistries. UDCA assists in the regulation of cholesterol by reducing the rate at which the intestine absorbs cholesterol. Some studies have suggested that it acts as an immunosuppressant. In PSC patients, UDCA is thought to be protective to the cholangiocytes by reducing bile exposure. Some studies have shown a mild improvement in serum liver chemistry, however the evidence on liver histology remains unchanged. A study was done to evaluate the use of high dose UDCA to determine whether the change in the bile acid pool would affect the outcome of PSC patients (Cullen 2008). Thirty-one patients were randomized to 10 mg/kg, 20 mg/kg or 30 mg/kg of UDCA daily for 2 years. They found that the higher doses of UDCA were well tolerated and the mayo survival risk score improved over 1-4 year period. However, some other studies have found contradicting results. A study also aimed at evaluating high dose UDCA and its effects on survival, symptoms, and quality of life was conducted. This study was a randomized placebo-controlled trial that included 219 patients followed for a 5-year period (Olsson 2005). The endpoints included quality of life assessments, changes in liver biochemistry, death and liver transplantation. They found that the serum alkaline phosphatase and alanine aminotransferase decreased within the first 6 months. However, there were no significant differences in overall symptoms, survival and quality of life. Despite the findings of an initial decrease in liver biochemistry, the use of UDCA as an aid in symptomatic management still remains controversial.

Managing the complications associated with PSC with use of medications and supplements is still useful. These complications include the development of bacterial cholangitis, deficiency in fat-soluble vitamins and pruritis. In PSC, recurrent episodes of bacterial cholangitis is not uncommon and if not managed appropriately can become life threatening. Antibiotic prophylaxis can be used and is helpful in these recurrent cases. Any procedure that involves manipulation of the biliary always requires antibiotic prophylaxis. The antibiotics commonly used are cephalosporins, fluroquinolones and beta lactamase inhibitors. Ultimately, these patients will require liver transplantation given the severity of the disease.

9. Prognostic models

In an effort to appropriately counsel patients regarding prognosis, models have been created to predict survival and indication for liver transplant. The most popular models include, Mayo clinic, Kings College, Multicenter, and Revised Mayo (Table 1).

MAYO CLINIC MODEL	REVISED MAYO MODEL	MULTICENTER MODEL	KINGS COLLEGE MODEL
Age	Age	Age	Age
Bilirubin	Bilirubin	Bilirubin	Hepatomegaly
Histologic Stage	Albumin	Splenomegaly	Splenomegaly
Hemoglobin	AST	Histologic Stage	Histologic Stage
IBD	Variceal Bleed		Alkaline Phosphatase

Table 1. Predictors of Survival

The Mayo clinic model was able to predict blood usage, length of stay in ICU and occurrence of significant complications in patients undergoing liver transplant (Dickson 1992 and Kim 1999).

The revised Mayo Model predicts survival based upon age, liver biochemistry and history of variceal bleed (Kim 2000). The estimated probability of survival is based on a scale over 1-4 yr period. The Multicenter Model was based upon a survival analysis that identified significant variables, which predicted survival in approximately four hundred patients with PSC (Dickson 1992). The Kings College Model was based upon a multivariate analysis that found hepatomegaly, splenomegaly, serum alkaline phosphatase and histologic stage to be independent prognostic factors (Farrant 1991). All of these models utilize mathematic formulas to determine the management of PSC. The models can be used to assess the appropriate time to consider liver transplant. Also, it helps to determine survival post liver transplant. The Child-Pugh classification can also be used to determine overall survival. These models however, are unable to predict the development of associated malignancies or harmful effects of PSC.

Determining the rate of recurrence of PSC post-transplant has also been evaluated. A large cohort study was conducted, which followed patients for 55 months after liver transplant (Graziadei 1999). This study found that 20 % of PSC patients developed histologic features of PSC and biliary strictures. Also, the average time to diagnosis of PSC was 360 and 1350 days respectively. However, this study was unable to delineate the factors that lead to the recurrence of PSC. In the current literature, there is limited information on what clinical variables may influence recurrence. A retrospective analysis was performed, which focused on the risk factors leading to allograft failure in PSC patients (Alexander 2008). The three most important factors that lead to failure included; acute cellular rejection, steroid-resistant acute cellular rejection and HLA-DRB1 association. These findings suggest that a strong immunologic association exist. What implications this may have on future liver transplant decision-making remains controversial.

10. Conclusion

Primary Sclerosing Cholangitis is a well known but uncommon extraintestinal manifestation of Ulcerative Colitis. This disease association can have a significant impact on the overall management and prognosis of both diseases. The focus of this literature review and chapter was to present the most current understanding of the pathophysiology, diagnosis and management of PSC as an extra intestinal manifestation of UC and to enumerate the special

circumstances pertaining to patients having both diseases. Overall, the reader should have gained an understanding of the many ways in which PSC can manifest and how the association with UC can alter their overall management and prognosis.

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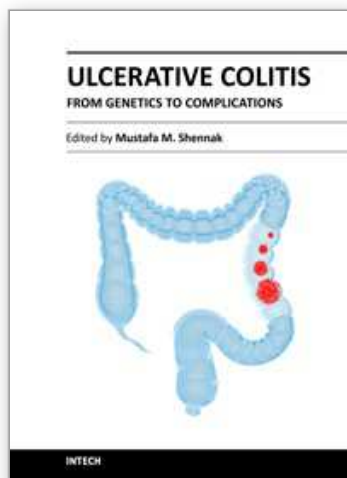
Ulcerative Colitis from Genetics to Complications

Edited by Prof. Mustafa Shennak

Ulcerative Colitis (UC) is a rapidly evolving medical field, and will continue to be very exiting in the next few decades. Although the underlying cause of this disease is still unknown, results in research dealing with various issues related to this disease are published every day. Chapters included in this book review the most recent literature on related advancements in regard to this chronic disease, which is controllable but not curable. Aspects like epidemiology, pathophysiology, genetics, incriminated etiologies, clinical aspects, complications, and disease management, including advancements in the diagnostic and therapeutic options, were documented by well known clinicians, researchers, and world wide authorities in their fields. This book on UC will be a valuable addition to each doctor's library interested in this subject, or for physicians dealing with patients suffering from this disease. Authors have also included figures and diagrams to depict their point, and to easily reach the minds of the readers in the simplest way.

How to reference

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