REVIEW ARTICLES

MEDICAL PROGRESS

PRIMARY SCLEROSING CHOLANGITIS

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PRIMARY sclerosing cholangitis, a chronic cholestatic liver disease of unknown cause, is characterized by ongoing inflammation, destruction, and fibrosis of intrahepatic and extrahepatic bile ducts.[1-4] Over time, bile ducts become irregularly narrowed and obliterated, and small intrahepatic ducts disappear. Focal bile-duct dilatation proximal to areas of stricture produces a characteristic beaded appearance on cholangiography.[5,6] Primary sclerosing cholangitis, although only about 1 percent as common as alcoholic liver disease,[7,8] is the fourth leading indication for liver transplantation in adults in the United States.[9] The disease progresses silently, but relentlessly, in most patients and leads to cirrhosis, portal hypertension, and liver failure.[10,11]

Seventy percent of patients with primary sclerosing cholangitis are men, and the mean age at diagnosis is 39 years.[12] The disease typically occurs in patients with inflammatory bowel disease, but it may also occur alone or in association with retroperitoneal or mediastinal fibrosis.[13] Of the approximately 75 percent of patients with primary sclerosing cholangitis who have inflammatory bowel disease, about 87 percent have ulcerative colitis and 13 percent Crohn's disease.[14-21] Seen another way, 2.5 to 7.5 percent of patients who present with ulcerative colitis have, or will have, primary sclerosing cholangitis.[22-24] The true frequency of primary sclerosing cholangitis in patients with ulcerative colitis may actually be higher. Some patients who, in fact, have primary sclerosing cholangitis may not undergo cholangiography because they are asymptomatic and the results of their biochemical tests of liver function are only minimally abnormal. The prevalence of ulcerative colitis in the United States is estimated to range from 40 to 225 per 100,000.[25,26] On the basis of this figure, the prevalence of primary sclerosing cholangitis would be approximately 1 to 6 cases per 100,000.

At the present time, there is no effective treatment for the disease.[4] Preliminary data on drugs such as ursodiol[27-29] and methotrexate[30,31] show improved results in biochemical tests of liver function, particularly decreases in serum alkaline phosphatase levels, as well as occasional improvement in symptoms. However, there are no data to show that these drugs can favorably alter the course of primary sclerosing cholangitis. Nevertheless, in addition to medical therapy, a variety of endoscopic, radiologic, and surgical procedures have been used to relieve the mechanical obstruction of the bile ducts that the disease produces. The availability of liver transplantation has also greatly improved patients' prospects for long-term survival.

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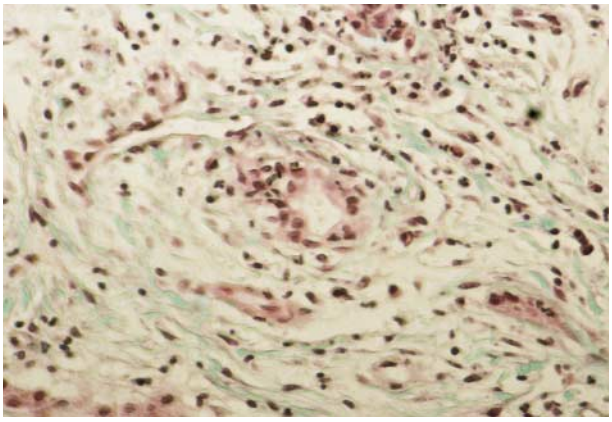
PATHOLOGICAL FEATURES

Thickening and induration of the common bile duct, seen at laparotomy, are characteristic of primary sclerosing cholangitis.[32] In early stages of the disease, the liver may appear grossly normal. However, as the condition progresses, the liver becomes coarsely nodular and stained with bile.

Four histologic stages of primary sclerosing cholangitis have been identified.[32] Stage 1 represents the initial lesion; the other stages presumably develop with time and the progression of the disease. Stage 1 is characterized by the degeneration of epithelial cells in the bile duct and by infiltration of the bile duct by lymphocytes and, occasionally, neutrophils. There is inflammation, scarring, and enlargement of the portal triads and, at times, portal edema. At stage 1, however, these findings are not present outside the portal triads (Fig. 1A and 1B). In some cases, there may be proliferation of bile ducts in the portal triads, vacuolation of ductular epithelial cells, and the formation of onionskin lesions, concentric layers of connective tissue surrounding bile ducts (Fig. 1C and 1D).[33] Primary sclerosing cholangitis typically involves less inflammation in the portal triads than other chronic cholestatic liver diseases, such as primary biliary cirrhosis. In stage 2, the lesion is more widespread. The fibrosis and inflammation infiltrate the periportal parenchyma, where they eventually destroy periportal hepatocytes in piecemeal necrosis. Portal triads are often enlarged. Bile ductopenia is a prominent feature; concentric periductal fibrosis is less obvious. As the disease progresses to stage 3, portal-to-portal fibrous septa form. Bile ducts disappear or undergo severe degenerative changes. Cholestasis may be prominent, primarily in periportal and paraseptal hepatocytes. Stage 4, the end stage, is characterized by frank cirrhosis; the histologic features differ little from those seen in other forms of that disease. In primary sclerosing cholangitis, however, there may also be changes associated with large-duct obstruction: the proliferation and dilatation of interlobular bile ducts and increased numbers of periportal neutrophils (Fig. 1D).

It is noteworthy that the pathognomonic sign of primary sclerosing cholangitis — the onionskin lesions — is rarely seen on percutaneous biopsy of the liver. It is more common to find only a paucity of normal bile ducts and nonspecific fibrosis and inflammation in the portal triads. The diagnosis is therefore usually made by cholangiography. Histologic examination of the liver is used for confirmation and to determine the stage of disease. Since the progress and extent of the disease seen in biopsy tissue may vary,



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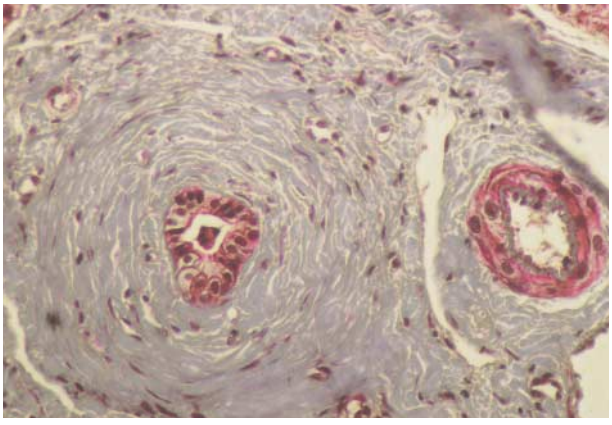

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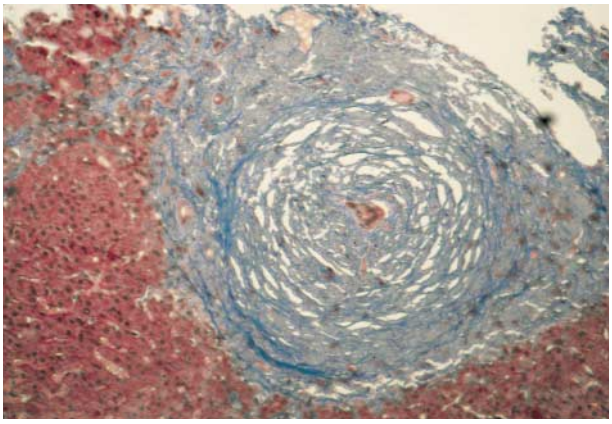

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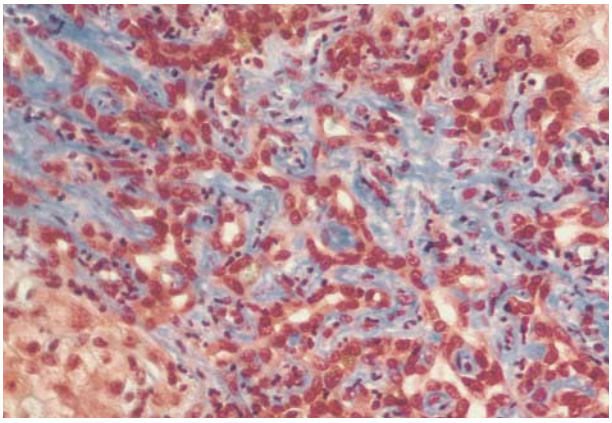

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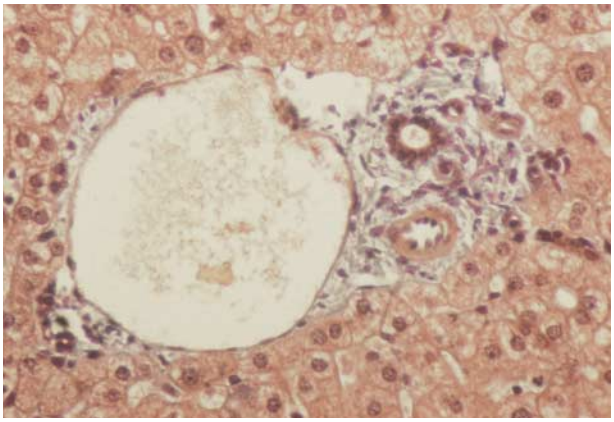

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Figure 1. Lesions in Primary Sclerosing Cholangitis.

Panel A shows acute bile-duct injury in a patient with early stage 1 disease. The bile duct at the center is infiltrated with neutrophils and lymphocytes. Epithelial cells are damaged. There are loosely arrayed concentric rings of connective tissue, separated by clear zones of edema and inflammatory cells that surround the damaged bile duct. Panel B shows a stage 1 lesion. A bile duct contains vacuolated, degenerating epithelial cells and is infiltrated by lymphocytes. The duct is surrounded by concentric rings of connective tissue with scant lymphocytic infiltrate. An arteriole is visible on the right. Panel C shows a stage 2 lesion. A necrotic bile duct is at the center of an enlarged, scarred portal triad. Note the onionskin appearance of the concentric rings of connective tissue. The inflammation and scar tissue extend into the periportal parenchyma. Panel D shows another type of stage 2 lesion, an enlarged portal triad with proliferating bile-duct tissue and neutrophils. These lesions are not specific to primary sclerosing cholangitis and may be seen in many types of chronic cholestasis. Panel E shows a normal portal tract, which contains a branch of the portal vein, an interlobular bile duct, and small arterioles. (Masson trichrome, ×190.)

accurate histologic staging requires the examination of a sufficiently large specimen.

Pathogenesis

The cause of primary sclerosing cholangitis is unknown. However, a number of factors have been proposed that might cause recurring damage to the bile ducts and lead to development of the disease. These include chronic portal bacteremia, toxic bile acid metabolites produced by enteric flora, toxins produced directly by enteric bacteria, chronic viral infections, ischemic vascular damage, and genetic abnormalities of immunoregulation.

The close association between primary sclerosing cholangitis and ulcerative colitis led researchers to the hypothesis that chronic portal bacteremia might cause chronic biliary tract infection, inflammation, portal fibrosis, and ultimately, primary sclerosing cholangitis.[34-36] One study reported portal bacteremia in some patients with ulcerative colitis who had had colonic surgery.[35] However, further research did not confirm the observation. In these later studies, patients with primary sclerosing cholangitis did not have evidence of portal-vein phlebitis, a typical feature of portal bacteremia.[37-39]

Other researchers have suggested that primary sclerosing cholangitis is the result of toxic bile acid me-

tabolites generated by the gut flora.[40] Lithocholic acid, formed from chenodeoxycholic acid by bacterial 7-α-dehydroxylation in the colon, is hepatotoxic in animals.[41] However, no major abnormalities in the composition and concentration of bile acids have been found in the bile and portal blood of patients with either primary sclerosing cholangitis or chronic inflammatory bowel disease.[42] Moreover, lithocholic acid is rapidly sulfated and rendered nontoxic in human tissue. This metabolic process has not been found to occur in animals, in which lithocholic acid can induce liver disease.[43-45]

Research on animals suggests a third possible cause of primary sclerosing cholangitis: bacterial products acting as toxic proinflammatory agents. *N*-formyl L-methionine L-leucine L-tyrosine is a peptide produced by enteric flora. When this peptide, labeled with iodine-125, was introduced into the colons of rats with experimentally induced colitis, it was absorbed, underwent enterohepatic circulation, and appeared undegraded in bile.[46] Histologic changes in the livers of the rats resembled those in primary sclerosing cholangitis, including periportal inflammation with neutrophils and eosinophils clustered around bile ducts. The injection of killed, nonpathogenic *Escherichia coli* into the portal veins of rabbits produced portal-vein fibrosis.[47] Similar hepatic lesions developed in rats with experimentally created blind loops in the jejunum after polymers prepared from the cell walls of intestinal bacteria were injected into the animals' portal veins.[48]

The natural history of primary sclerosing cholangitis, however, argues against a major pathogenetic role for portal bacteremia or bacterial metabolites. Antibiotic treatment, for example, is not effective against the disease.[49] There is also no correlation between the severity of ulcerative colitis and that of primary sclerosing cholangitis.[21] Primary sclerosing cholangitis may develop years before the onset of colitis or years after patients have had total colectomies.[50]

Chronic viral infections and ischemic damage to bile ducts have also been implicated as causative factors in primary sclerosing cholangitis.[51,52] Cholangitis caused by cytomegalovirus in patients with acquired immunodeficiency has a cholangiographic similarity to primary sclerosing cholangitis.[53] However, there are no data that suggest any relation in immunocompetent patients.[54,55] Likewise, no pathological data suggest that ischemic damage to bile ducts is a cause of primary sclerosing cholangitis. Ischemia had been proposed because intraarterial injections of the chemotherapeutic agent floxuridine resulted in a clinical syndrome similar to that seen in primary sclerosing cholangitis.[52] Intraarterial floxuridine has been shown to cause narrowing and obliteration of the arteries supplying the bile duct.

Genetic and immunologic factors appear to play a part in primary sclerosing cholangitis, although the disorder is not inherited in any distinct pattern. There are familial occurrences of this uncommon disease,[56,57] as well as an association between primary sclerosing cholangitis and HLA-B8, DR3, DR2, and DR4.[58-61] HLA-B8 and DR3 are associated with autoimmune diseases such as Graves' disease, systemic lupus erythematosus, and myasthenia gravis.[62] HLA-DRw52a is found in a high proportion of patients with primary sclerosing cholangitis, but not in all, as was initially reported.[63,64] In patients with HLA-DR4, the course of primary sclerosing cholangitis tends to be accelerated.[61]

Patients with primary sclerosing cholangitis have signs of abnormal immunoregulation, including infiltration and destruction of bile ducts by lymphocytes,[38] hypergammaglobulinemia with a disproportionate increase in serum IgM,[65] perinuclear antineutrophil cytoplasmic antibodies,[66] anticolon epithelial autoantibodies,[67] circulating immune complexes,[68] increased metabolism of complement component C3,[69] and activation of the complement system by the classic pathway.[70] Primary sclerosing cholangitis is associated with other disorders of immunoregulation, including inflammatory bowel disease,[21] thyroiditis, and type I diabetes.[62]

The cellular immune system appears to play a part in primary sclerosing cholangitis. The total number of circulating T cells is decreased, whereas T cells are increased in the portal tracts.[71-73] The ratio of CD4 to CD8 lymphocytes in the circulation is increased, as are the number and percentage of B cells.[71] There is inhibition of leukocyte migration in the presence of biliary antigens[74] and enhanced autoreactivity of portal T lymphocytes.[75] Finally, the aberrant expression of class II antigens on bile-duct epithelial cells suggests that bile-duct epithelial cells act as autoantigens to host lymphocytes.[76,77] It is unknown whether these immunologic abnormalities are primary events or are due to the underlying disease, although the ligation of bile ducts in rats causes an aberrant expression of class II antigens on bile-duct cells.[78]

Diagnosis

The current criteria used to diagnose primary sclerosing cholangitis are based on characteristic changes in the intrahepatic and extrahepatic biliary tree seen with endoscopic retrograde cholangiopancreatography or transhepatic cholangiography. Before the diagnosis of primary sclerosing cholangitis is established, disorders that cause secondary sclerosing cholangitis must be ruled out. These include chronic bacterial cholangitis in patients with bile-duct stricture or choledocholithiasis, ischemic bile-duct damage due to treatment with floxuridine,[52] infectious cholangiopathy associated with the acquired immunodeficiency syndrome,[53] previous biliary surgery, congenital biliary-tree abnormalities, and bile-duct neoplasms. The presence of these disorders is typically ruled out by the use of patient histories, blood-test results, characteristic cholangiographic or ultrasound findings, or pathological findings from bile-duct scraping and biopsies.

Laboratory tests in patients with primary sclerosing cholangitis usually show a cholestatic pattern, but biochemical abnormalities alone are never diagnostic. The serum alkaline phosphatase level is usually elevated, although there are reports of patients in whom the disease has been diagnosed by cholangiography who have normal levels.[79] Most patients have slight increases in serum aminotransferase levels, but the

level of serum albumin is normal early in the disease. Patients with active inflammatory bowel disease, however, have decreased serum levels of albumin, reflecting the severity of that illness. In early stages of primary sclerosing cholangitis, serum bilirubin values are usually normal, but they gradually increase as the disease progresses. Occasionally, striking fluctuations in bilirubin levels may occur even at early stages. The cause is unknown, but the changes may reflect transient blockage of strictured bile ducts by inflammation, infection, sludge, or small gallstones. Hypergammaglobulinemia is found in about 30 percent of patients, and increased IgM levels in 40 to 50 percent.[26] Autoantibodies are less frequent than in autoimmune chronic active hepatitis and primary biliary cirrhosis. About 65 percent of patients with primary sclerosing cholangitis have perinuclear antineutrophil cytoplasmic antibodies[80] and HLA-DRw52a.[64] Anti–smooth-muscle antibodies are present in 11 percent of patients and antinuclear antibodies in 6 to 35 percent, but antimitochondrial antibodies are almost never observed.[26] As in other chronic cholestatic liver diseases, levels of hepatic and urinary copper are increased, as is the serum ceruloplasmin level. Because copper is excreted primarily in bile, the amount of copper in the body increases as cholestasis worsens.

Visualization of the biliary tract is essential for making the diagnosis of primary sclerosing cholangitis. Endoscopic retrograde cholangiopancreatography is the method of choice. Percutaneous cholangiography is technically more difficult in patients with the disease because intrahepatic bile ducts are often attenuated or reduced in number. Transhepatic cholangiography is performed only if endoscopic retrograde cholangiopancreatography is unsuccessful. The characteristic radiologic findings of primary sclerosing cholangitis include multifocal strictures and dilatations, usually involving both the intrahepatic and extrahepatic biliary tree (Fig. 2). Diffuse strictures with short intervening segments of normal or dilated bile duct produce the classic beaded appearance. In early stages, the only cholangiographic abnormality may be fine ulcerations of the common bile duct similar to those seen in the colon in early ulcerative colitis (Fig. 3). In other patients, there may be deep ulcerations in the common duct (Fig. 4). In our experience with more than 100 patients with primary sclerosing cholangitis, 87 percent had involvement of both intrahepatic and extrahepatic bile ducts, 11 percent had involvement of the intrahepatic bile ducts alone, and 2 percent had involvement of only the extrahepatic bile ducts (unpublished data). The gallbladder and cystic duct are involved in as many as 15 percent of patients.[81,82]

There is one putative variant, called small-duct primary sclerosing cholangitis, in which the affected bile ducts are too small to be seen by cholangiography. Hence, cholangiograms appear normal. The prevalence of small-duct primary sclerosing cholangitis is unknown. It is diagnosed in patients with inflammatory bowel disease who have biochemical tests of liver function that show cholestasis and characteristic liver biopsies, but whose endoscopic retrograde cholangiopancreatograms are normal.[83] This disease is probably the same as the condition called pericholangitis in ulcerative colitis.[84,85]

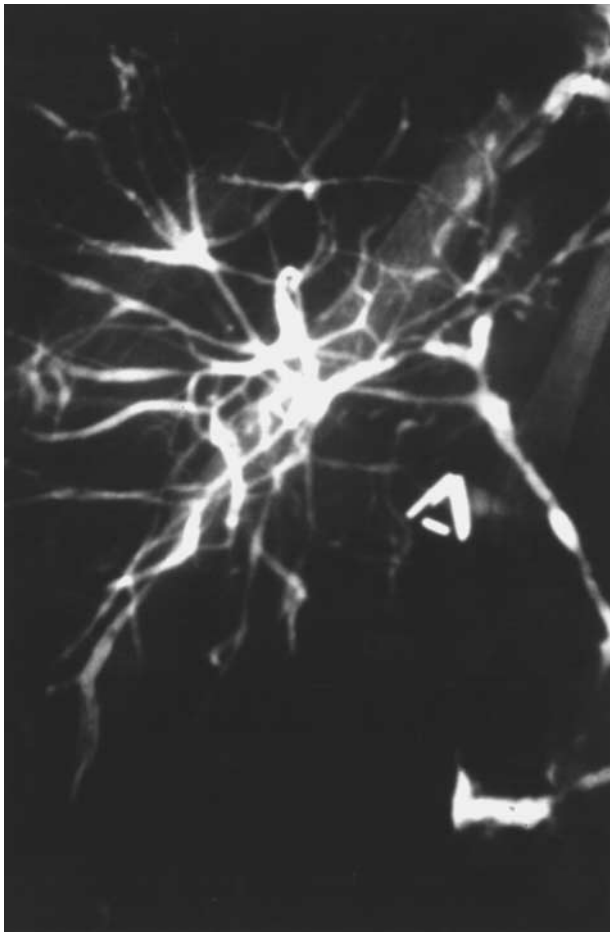

Figure 2. Endoscopic Retrograde Cholangiogram of a 62-Year-Old Woman with Primary Sclerosing Cholangitis.
There are multiple narrowings and dilatations of intra- and extrahepatic bile ducts.

Although percutaneous liver biopsy may support the diagnosis of primary sclerosing cholangitis, it is rarely definitive. Rather, it is useful in staging and in determining the prognosis. Neither histologic examination nor cholangiography alone will reliably reflect the severity of the disease. Both must be used with blood tests and with imaging or endoscopic tests that show the presence and severity of portal hypertension.

Clinical Features

The majority of patients are initially asymptomatic, but can typically be identified on the basis of abnormal results on biochemical tests of liver function, particularly elevated levels of serum alkaline phosphatase or γ-glutamyltransferase. These abnormalities persist, and eventually cholangiography, liver biopsy, or both, are performed. Liver-biopsy findings are usually either nonspecific or suggestive of primary sclerosing cholangitis; the cholangiogram shows the characteristic changes. Although asymptomatic, some patients may have surprisingly advanced disease, as measured both histolog-

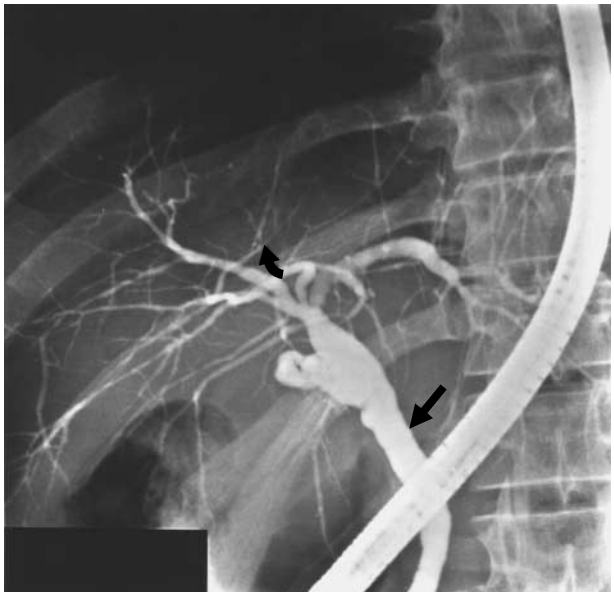

Figure 3. Endoscopic Retrograde Cholangiogram of a 28-Year-Old Man with Ulcerative Colitis and Early Primary Sclerosing Cholangitis.

The patient presented with intense pruritus and a fivefold increase in the serum alkaline phosphatase level. There are fine ulcerations (straight arrow) of the common bile duct and subtle narrowings (curved arrow) and dilatations of the intrahepatic bile ducts.

ically and radiologically. Some patients may remain asymptomatic for many years. Eventually, the serum bilirubin level begins to increase or the serum albumin level decreases (or both). When symptoms of itching, fatigue, jaundice, and weight loss develop, the patients usually have advanced disease.

In 10 to 15 percent of patients, fever, night sweats, chills, pain in the right upper quadrant, itching, or jaundice is present at the time of diagnosis.[86] Despite these symptoms, blood-test results, histologic features of the liver, and cholangiographic findings are similar to those in asymptomatic patients. The episodes of fever and chills are often accompanied by transient worsening of the results of biochemical tests of liver function; these episodes are indistinguishable from those produced by acute bacterial cholangitis. They may last from hours to days, but usually end without specific treatment. Antibiotics are rarely helpful, and blood cultures rarely positive. It is not known whether these episodes are caused by bacterial infections in areas near strictured and transiently occluded bile ducts or whether they are simply part of the underlying inflammatory process.

Natural History

Although the majority of patients with primary sclerosing cholangitis are asymptomatic at the time of diagnosis, most eventually have symptoms of fatigue, itching, and jaundice. Cirrhosis, portal hypertension, and liver failure follow. In one study, the mean age of patients at diagnosis was 39.9 years; the median length of survival was 11.9 years from diagnosis.[12] Patients who were symptomatic at diagnosis lived less long than those who were asymptomatic, and the survival of asymptomatic patients was significantly shorter than that of a matched control population. Other studies have reported similar findings, with median survival of 9 to 12 years from diagnosis.[87-90] There is no relation between the course of primary sclerosing cholangitis and that of accompanying inflammatory bowel disease. Primary sclerosing cholangitis often occurs and worsens in patients whose inflammatory bowel disease has become quiescent after colectomy.

Multivariate analysis has been used to identify prognostic variables and to develop models that predict the progression of primary sclerosing cholangitis. In a recent study of patients at five referral centers, the variables that adversely affected survival were age, serum bilirubin and hemoglobin levels, hepatic histologic stage, and the presence of splenomegaly.[91] According to the study's model, the probability of surviving five years from the time of diagnosis was 78 percent. In another study, prognostic variables included hepatomegaly, splenomegaly, serum alkaline phosphatase level, histologic stage, and age.[90] Although these models are useful in classifying participants in therapeutic trials, they may have limited application to the timing of liver transplantation in individual patients because of the great variability of the disease.

Treatment

It is important to recognize a major difference between cholestatic liver diseases, such as primary sclerosing cholangitis, in which bile ducts are the targets of the inflammatory and destructive processes, and chron-

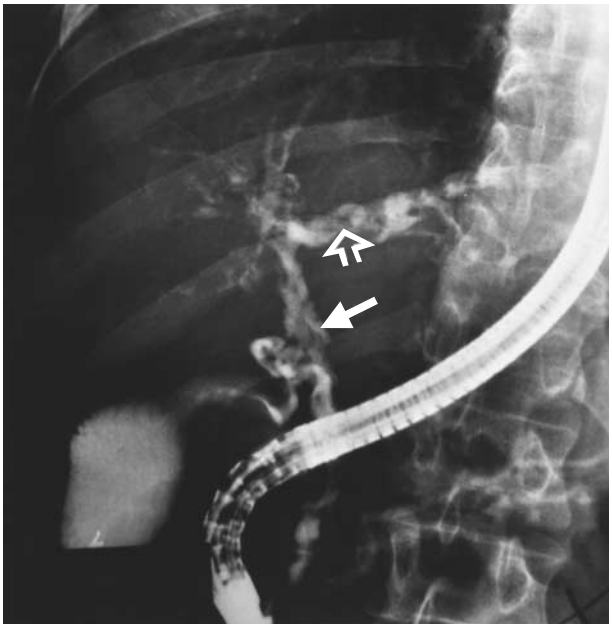

Figure 4. Endoscopic Retrograde Cholangiogram of a 44-Year-Old Man with Primary Sclerosing Cholangitis and Crohn's Ileocolitis.

There are deep ulcerations (solid arrow) in the common hepatic duct and left intrahepatic bile duct, similar to those seen in the colon in patients with colitis. There are filling defects (open arrow) consistent with intraductal stones. The partially filled gallbladder is visible on the left, and the endoscope is in place.

ic hepatocellular diseases, such as hepatitis, in which hepatocytes are the targets. When bile ducts are destroyed, they do not regenerate or they do so ineffectively.[86] An example of this is the vanishing-bile-duct syndrome associated with rejection in orthotopic liver transplantation.[92] In contrast, hepatocytes have an enormous capacity to regenerate. If patients with fulminant hepatitis survive, they recover fully and regain normal liver function. Likewise, patients with autoimmune hepatitis who are deeply jaundiced and have striking hypoalbuminemia may respond dramatically to glucocorticoids and regain normal liver function. However, there appears to be only a finite number of bile ducts, which do not regenerate adequately when destroyed. Primary sclerosing cholangitis should therefore be treated early in its course, before the serum level of bilirubin becomes permanently elevated. A serum bilirubin level persistently greater than 1.5 mg per deciliter (26 μmol per liter) is a sign of a poor prognosis and may indicate irreversible, medically untreatable disease.[3]

The treatment of primary sclerosing cholangitis has been limited by uncertainty about its cause. As yet, no medical therapy has been proved effective. The medical response to the illness may be divided into the management of symptoms and complications, and the treatment of the underlying disease process. But for patients with end-stage disease who have symptomatic portal hypertension, liver failure, and recurrent or intractable bacterial cholangitis, liver transplantation is the only effective treatment.

Management of Chronic Cholestasis and Its Complications

Many of the symptoms of primary sclerosing cholangitis are similar to those of other cholestatic diseases, such as primary biliary cirrhosis. However, unique problems result from the mechanical bile-duct obstruction characteristic of the disease, including bacterial cholangitis, sepsis, and the formation of pigment stones within the obstructed bile ducts. In addition, patients with primary sclerosing cholangitis are at risk for bile-duct cancers. These cancers may be very difficult to distinguish from the tight bile-duct strictures typically seen in primary sclerosing cholangitis.

Symptoms of primary sclerosing cholangitis include fatigue, pruritus, and steatorrhea. One of the more bothersome symptoms is pruritus. Itching is worse at bedtime and in warm weather and may be exacerbated by eating rich, fatty meals. It can be severely debilitating, interfere with sleep, and provoke extensive excoriations. The cause of the pruritus is unknown. The retention of bile acids and their sequestration in skin are not the cause. Nevertheless, bile acid–binding resins are an effective treatment, presumably because they bind to the true pruritogenic agent excreted in bile.[93] More recently, the accumulation of endogenous opiates has been proposed as a cause of the pruritus. Opiate antagonists may decrease pruritus, and there are increased serum concentrations of endorphin-like substances in patients with other chronic cholestastic liver diseases, such as primary biliary cirrhosis.[94]

The pruritus can be effectively treated in most patients. Cholestyramine is effective for patients who have adequate bile flow.[93] The dose is 4 to 8 g taken two or three times daily. It usually takes two to four days for cholestyramine to relieve itching. The drug is not helpful if bile flow has already been greatly decreased. Colestipol hydrochloride, another ammonium resin, may be an alternative for those who cannot tolerate cholestyramine. Other therapies that have been used in patients unresponsive to cholestyramine include naloxone,[95] methyltestosterone,[96] phenobarbital,[97] rifampin,[98] plasmapheresis,[99] ondansetron,[100] antihistamines, ursodiol,[101] *S*-adenosylmethionine,[102] and ultraviolet light.[103]

Steatorrhea and malabsorption of fat-soluble vitamins may occur late in the course of primary sclerosing cholangitis. Fat malabsorption in patients with jaundice is usually related to decreased secretion of conjugated bile acids into the small intestine. Other causes are pancreatic insufficiency[104,105] and celiac disease,[106] both of which may be associated with primary sclerosing cholangitis. Asymptomatic vitamin A deficiency was found in almost 50 percent of patients with primary sclerosing cholangitis in one study.[107] A clinically important vitamin K deficiency rarely occurs unless the patient has chronic jaundice and takes cholestyramine regularly. Similarly, deficiencies of vitamins D and E are uncommon and infrequently associated with clinical symptoms.[108] However, there have been reports of metabolic bone disease and compression fractures of the spine.[109] As in primary biliary cirrhosis, the bone disease is due to osteoporosis rather than osteomalacia. Fat-soluble vitamin levels should be monitored and deficiencies treated with supplements.

Antibiotics have no role in slowing the progression of primary sclerosing cholangitis but have been used to treat recurrent episodes of cholangitis. Bacterial cholangitis is typically associated with biliary surgery, bile-duct stones, or obstructing strictures. Tetracycline was determined to be ineffective in one small study of patients with primary sclerosing cholangitis,[49] but prophylactic antibiotics, usually amoxicillin, ciprofloxacin, or trimethoprim–sulfamethoxazole, are often used for recurrent episodes of cholangitis. Anecdotal reports suggest that such drugs reduce the frequency and severity of bacterial cholangitis. Additional controlled trials are needed to test this hypothesis.

Dominant strictures of the extrahepatic bile ducts, which cause or exacerbate symptoms, occur in 15 to 20 percent of patients with primary sclerosing cholangitis.[110] Endoscopic balloon dilation of strictures, with or without the placement of stents, has relieved symptoms of jaundice, pruritus, and fever, and has reduced serum levels of alkaline phosphatase and aminotransferases in selected patients.[110] In several retrospective studies, patients appeared to have fewer episodes of cholangitis if they were treated endoscopically with papillotomy of Oddi's sphincter, nasobiliary catheter irrigation of the common bile duct with glucocorticoids, or dilation of strictures with either balloons or stents.[111-113] Results of biochemical tests and cholangiographic findings improved in some patients so treat-

ed. There are no controlled trials evaluating endoscopic therapy, but there appears to be little risk and some potential benefit from this approach.

Another method of managing dominant strictures, surgical dilation, or choledochojejunostomy, is now rarely used. Surgery carries the risk of postoperative infection and increases scarring in the porta hepatis, potentially complicating future liver transplantation.[114] The development of stomal varices is a complication unique to patients with advanced primary sclerosing cholangitis who have undergone colectomy and ileostomy.[115] Treatment of bleeding from the stomal varices is difficult and usually requires either a central portosystemic shunt or liver transplantation.

There is an increased incidence of cholangiocarcinoma in patients with primary sclerosing cholangitis, about 9 to 15 percent.[116,117] Patients with long-standing ulcerative colitis and cirrhosis are at highest risk.[118,119] The early diagnosis of bile-duct carcinoma is hampered by the lack of sensitive, specific serologic markers as well as the insensitivity of biliary cytology. Often an unsuspected cholangiocarcinoma is found after liver transplantation, when the resected liver is examined in the pathology laboratory.[120] Unfortunately, there is no reliable way to distinguish a dominant stricture from a cholangiocarcinoma, even after repeated imaging, endoscopic biopsies, and cytologic examination. Most experts suggest that patients with a high likelihood of cholangiocarcinoma should be referred for liver transplantation and should undergo pretransplantation laparotomy in order to rule out the extrahepatic spread of cancer.[116,120,121] Unfortunately, treatment of cholangiocarcinoma by resection, chemotherapy, and radiation has had discouraging results, as has liver transplantation for clinically apparent tumors.[120]

Medical Therapy for Primary Sclerosing Cholangitis

A variety of immunosuppressive, antiinflammatory, and antifibrotic agents have been used to treat primary sclerosing cholangitis. However, no drug has been shown to improve the natural history of the disease. The evaluation of treatment has been limited by the indolent course of primary sclerosing cholangitis in most patients and the spontaneous exacerbations and remissions in others. Hence, it takes years before any treatment can be shown to alter the natural history. Of the various drugs used to treat primary sclerosing cholangitis, only a few have been evaluated in randomized, controlled trials.

Corticosteroids

Despite anecdotal reports of improvement in patients with primary sclerosing cholangitis who took corticosteroids,[122,123] there is little enthusiasm for their use for several reasons. Approximately 75 percent of patients with primary sclerosing cholangitis have chronic inflammatory bowel disease and are already being treated with corticosteroids while primary sclerosing cholangitis develops and progresses. Furthermore, combined treatment with both corticosteroids and colchicine neither improved biochemical test results nor slowed the progression of disease.[124] Finally, corticosteroids may hasten the onset and progression of osteoporosis and increase spontaneous bone fractures. There is, however, one favorable report. In an uncontrolled trial of corticosteroid use, 10 patients with prefibrotic primary sclerosing cholangitis had improvements in the results of both blood tests and histologic examination of the liver. Four of these patients remain well after 11 years and are still receiving low-dose prednisone (LaBrecque DR: personal communication).

Penicillamine

Penicillamine has been evaluated in a double-blind prospective trial of patients followed for 36 months.[125] The drug produced the expected urinary excretion of copper, but had no beneficial effect on symptoms, biochemical test results, liver histology, disease progression, or survival. In addition, 21 percent of the patients had major side effects from penicillamine. The toxicity and the lack of efficacy have discouraged further use of penicillamine.

Ursodiol

Ursodiol has been associated with a clear improvement in the results of biochemical tests of liver function in primary sclerosing cholangitis. Therapy with the drug leads to a two-to-threefold increase in the serum bile acid concentration. There is an increase in the biliary and urinary excretion of bile acids and an increase in bile flow. In vitro, ursodiol stabilizes liver-cell membranes exposed to toxic concentrations of the naturally occurring bile acid chenodeoxycholic acid.[126] Several open-label trials of ursodiol have reported improvements in symptoms and in the results of liver-function tests.[27,28,127,128] There is no information on the cholangiographic appearance of the biliary tree. In a prospective, randomized, double-blind, placebo-controlled trial, there was improvement in the results of biochemical tests of liver function and liver histology in those patients receiving ursodiol.[29] However, there was no difference in patient survival or in referral for liver transplantation. There are no data on the long-term efficacy of ursodiol.

Methotrexate

On the basis of clinical and histologic improvements in 2 patients with primary sclerosing cholangitis, we conducted an open-label trial of oral methotrexate in 21 patients with the disease, 7 of whom had cirrhosis as well[30,129,130] (and unpublished data). No patients with cirrhosis had improvement in their condition. In patients without advanced disease, there was improvement in symptoms and in the results of biochemical tests of liver function. Follow-up liver biopsies revealed histologic improvement, primarily decreased inflammation. Most patients in this group had less stricturing on cholangiography after one to eight years of methotrexate. However, in a recently concluded prospective, double-blind study, methotrexate produced no therapeutic benefit.[31] Although methotrexate, as compared with placebo, significantly reduced the serum levels of alkaline phos-

phatase, it had no effect on serum levels of bilirubin, aminotransferases, or albumin, or on the rate of referral for liver transplantation. Half the patients in this study already had cirrhosis and may have had medically irreversible disease. A larger randomized, controlled trial including only patients without cirrhosis is needed to evaluate methotrexate further.

Other Medical Agents

There have been anecdotal reports of the treatment of primary sclerosing cholangitis with azathioprine, colchicine, cholestyramine, antibiotics, and cyclosporine, but no convincing evidence that any of these agents is effective.[131-135]

Proctocolectomy

The close association between primary sclerosing cholangitis and ulcerative colitis, along with the hypothetical role of enteric bacteria in the disease's pathogenesis, has led some to consider proctocolectomy as a treatment. But in one retrospective study of patients with both primary sclerosing cholangitis and chronic ulcerative colitis, patients who underwent proctocolectomy had no improvement in biochemical test results, cholangiography, hepatic histology, or survival.[50] Proctocolectomy should be performed only because of the severity of proctocolitis.

Liver Transplantation

Liver transplantation is now the treatment of choice for patients with advanced liver disease. Indications for liver transplantation include hemorrhage due to esophageal varices or portal gastropathy, intractable ascites (with or without spontaneous bacterial peritonitis), recurrent episodes of bacterial cholangitis, progressive muscle wasting, and hepatic encephalopathy. Most of the patients with these conditions are jaundiced. However, jaundice alone, in the absence of other signs of liver failure, is not an absolute indication for transplantation. Three-year survival after liver transplantation is 85 percent at most centers.[136,137] A post-transplantation problem, more common in patients with primary sclerosing cholangitis than in other groups, is the development of strictures in the transplanted bile ducts. The pattern is similar to that seen in the natural course of the disease.[138,139] Possible causes of the strictures include the recurrence of primary sclerosing cholangitis, ischemia, chronic rejection, and infectious cholangitis related to the Roux-en-Y biliary anastomosis and immunosuppression. Current data point to infection as the cause. Creation of longer jejunal loops in the Roux-en-Y anastomosis and treatment with appropriate antibiotics are usually effective in preventing or treating this complication. In patients with primary sclerosing cholangitis and inflammatory bowel disease who undergo liver transplantation, the symptoms of their bowel disease generally improve after transplantation.[140] On the other hand, there are reports of colon cancer developing after liver transplantation in two patients who had both primary sclerosing cholangitis and chronic ulcerative colitis.[141] Thus, even after transplantation, it is important to continue monitoring for colon cancer in patients with primary sclerosing cholangitis who also have chronic ulcerative colitis.

Conclusions

Primary sclerosing cholangitis remains an enigmatic, difficult-to-treat disease. Progress in treating or preventing this disease will be slow until its cause is better understood. The indolent beginnings of the illness for most patients and its slow rate of progression belie its true severity. Often, physicians delay treatment, or the referral of patients to centers conducting controlled trials, until the disease has become symptomatic and hence untreatable. Most symptomatic patients have advanced and medically irreversible disease. In the future, asymptomatic patients with only early cholangiographic and histologic changes should be included in prospective trials of new therapies. New strategies that employ combinations of drugs such as ursodiol, methotrexate, antibiotics, and other immunomodulatory compounds appear to be the most promising approach to treatment at this time.

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