THE FIFTH CARLOS E. RUBIO MEMORIAL LECTURE

Sclerosing Cholangitis: Pathogenesis, Pathology, and Practice

NICHOLAS F. LARUSSO, MD*

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic syndrome of unknown etiology characterized by diffuse inflammation and fibrosis of the biliary system. The pathologic process leads to obliteration of intrahepatic and extrahepatic bile ducts and to cirrhosis. The course is variable but often is one of slow progression, perhaps over decades, to portal hypertension and death from liver failure. PSC may occur alone, but is commonly (>70%) associated with inflammatory bowel disease, usually chronic ulcerative colitis (CUC).

PSC is among the four most common indications for liver transplantation in adults in the United States. Approximately 70% of patients with PSC are male and the mean age of, most commonly, under 40 years of age at the time of diagnosis. The disease most commonly occurs in patients with previously diagnosed inflammatory bowel disease; nearly 90% of patients with PSC, who have associated inflammatory bowel disease, have CUC with approximately 10% having Crohn's disease. Indeed, approximately 5% of patients with CUC have, or will, develop PSC.

Symptoms and Signs

PSC usually begins insidiously; this makes it difficult to determine the onset of the disease accurately. Nevertheless, most patients have had symptoms for an average of 24 months before diagnosis. The gradual onset of progressive fatigue and pruritus followed by jaundice is the most frequent symptom complex that leads to the diagnosis of PSC. Clinical evidence of cholangitis (recurrent right upper quadrant pain, fever, and jaundice) is uncommon unless previous bile duct reconstructive surgery has been done. More recently, totally asymptomatic patients with PSC are being diagnosed because of abnormalities on routine blood tests which prompt further workup, including cholangiography. Although some patients with PSC may have a normal physical examination, most patients have some abnormality, most commonly hepatomegaly, jaundice, and splenomegaly.

Biochemical Tests

Virtually all patients with PSC have a cholestatic biochemical profile. The serum alkaline phosphatase is almost always abnormal, although it may fluctuate; indeed, in rare instances, it may even normalize. The vast majority of patients have an increase in serum aspartate transaminase level, usually to a mild degree. Approximately one-half the patients will have a modest increase in their total serum bilirubin; however, these values may be normal or sometimes very high. Serologic tests of antibodies to mitochondria (i.e., AMA) and nuclei (i.e., ANA) are usually (>90%) negative. Recently, we described the presence of antibodies to as yet unidentified antigens present in the cytoplasm of neutrophils in approximately 70% of patients with PSC (i.e. antineutrophil cytoplasmic antibodies, or ANCA); others have described anticolon and neutrophil cytoplasmic antibodies in patients with PSC alone, CUC alone, and PSC with CUC.

Tests related to copper metabolism are virtually always abnormal in patients with PSC. For example, hepatic copper levels are elevated in approximately 90% of patients while urine copper levels are increased in up to two-thirds; in both cases, the levels are increased to the degree seen in primary biliary cirrhosis, Wilson's disease, and Indian childhood cirrhosis. Similarly, serum copper and ceruloplasmin levels are usually increased in patients with PSC as they commonly are in patients with primary biliary cirrhosis.

Radiologic Features

Early articles, based largely on findings at surgery, emphasized the extrahepatic location of the ductal changes in PSC. Recently, however, use of improved

*Professor of Medicine, Biochemistry and Molecular Biology, Mayo Medical School. Chairman Division of Gastroenterology, Mayo Clinic. Distinguished Investigator of the Mayo Foundation, Rochester, MN. Visiting Professor, University of Puerto Rico School of Medicine, San Juan, PR December 1998.

Address for correspondence: Nicholas F. LaRusso, MD, Director Division of Gastroenterology, Mayo Clinic Rochester, 200 1st St. Southwest, Rochester, MN 55905.

This conference was made possible thanks to an Educational Grant from GlaxoWellcome Inc.

cholangiographic techniques indicates that the intrahepatic ducts are usually involved radiographically in this syndrome, often to a greater degree than the extrahepatic ducts. Endoscopic or transhepatic cholangiography show diffusely distributed strictures of the intrahepatic and extrahepatic bile ducts in virtually all patients. Most commonly, the strictures are short (1-2 cm long) and annular with intervening segments of apparently normal or slightly dilated ducts which produce the characteristic "beaded" appearance. Focal dilatation of bile ducts between strictures is also a common finding, but diffuse nonsegmental dilatation is unusual. In a minority of patients, the cholangiogram may be normal because disease is limited to the small intrahepatic ducts (i.e., small duct PSC).

Liver Histology

In virtually all patients with PSC, histologic abnormalities are present on liver biopsy specimens. The characteristic features on liver biopsy specimens are bile duct proliferation, periductal fibrosis, periductal inflammation, ductal obliteration, and loss of bile ducts. Most commonly, the disease begins with enlargement of portal tracts (stage I), characterized by some edema, connective tissue and proliferation of interlobular bile ducts; inflammatory infiltrates are not prominent. With progression, tongues of connective tissue grow into the periportal parenchyma (stage II), again with only mild cellular inflammation. This process leads to the formation of fibrous septa (stage III) and biliary cirrhosis (stage IV). The pathognomonic histologic changes on liver biopsy specimens occur in the early stages; these changes are characterized by fibrous obliterative cholangitis leading to replacement of duct segments by solid cords of connective tissue and to complete loss of interlobular and adjacent septal bile ducts with time.

Pathogenesis

The cause of PSC is unknown; genetic factors, acquired factors, or both, could be involved. Several recent observations are consistent with an important role for genetic factors in PSC. For example, the frequency of HLA-B8 is significantly higher in patients with PSC (60%) than in control subjects (25%). Also, recent reports have described the familial occurrence of both PSC and chronic ulcerative colitis, further evidence suggesting a genetic component to the disease.

Important acquired factors could theoretically include toxins, infectious agents, or altered immunity. Although elevated hepatic copper was initially thought to be an important potential toxin in the initiation and/or perpetuation of the disease, recent negative results from a controlled trial with D-penicillamine (see below) make it unlikely that elevated hepatic copper levels are pathogenetically important. Recently, extrahepatic biliary tract disease closely mimicking PSC has been described following infusions with the chemotherapeutic agent, 5-fluorodeoxyuridine. This drug apparently causes small vessel arteriopathy which likely leads to bile duct fibrosis and destruction. This syndrome, however, represents a type of secondary rather than primary sclerosing cholangitis. Only a few data are available concerning the possible role of infectious agents in the etiopathogenesis of PSC. Results of several studies have excluded the hepatitis B and C viruses as causative agents. Cytomegalovirus may affect intrahepatic bile ducts, but the histologic picture differs from that seen in PSC. Reovirus type 3 has been associated with neonatal biliary atresia which, like PSC, is characterized by obliterative cholangitis. However, reovirus infections have not so far been directly linked to the development of PSC and a preliminary report indicates that elevated titers of antibody to reovirus type 3 are not more prevalent in patients with PSC than in the general population.

Currently, the pathogenesis of PSC is most closely linked with alterations in the immune mechanisms. Although serologic markers (e.g. mitochondrial or smooth muscle antibodies) are generally absent, other data strongly support disturbed alterations in immunity. For example, PSC is associated with HLA-B8, DR3, DR2, and DR4. HLA-B8 and DR3 are associated with autoimmune diseases including systemic lupus and myasthenia gravis. Recent data have raised the possibility that patients with PSC or HLA-DR4 positive have an accelerated disease course. Other more direct lines of evidence supporting an immunological basis include the inhibition of leukocyte migration by biliary antigens, elevated IgM levels, the presence of circulating immune complexes, decreased clearance of immune complexes, and increased complement metabolism. Also, cells involved in the destruction of bile ducts in PSC have recently been shown to be T lymphocytes and abnormalities in lymphocyte subsets in peripheral blood have also been demonstrated. In addition, patients with PSC consistently show hyper-gamma globulinemia with an increase in serum IgM, anticolon epithelial autoantibodies, perinuclear antineutrophil cytoplasmic antibodies, and associations with, in addition to inflammatory bowel disease, thyroiditis, and type I diabetes. Finally, enhanced autoreactivity of suppressor/cytotoxic T lymphocytes from peripheral blood of patients with PSC has been reported. All these studies support alterations in the immune system as being patho-

genetically related to the development and/or perpetuation of PSC, although the exact mechanisms are still not understood. One of the reasons for our inadequate understanding of the pathogenesis of PSC relates to inadequate animal models for this disease. Recently, we have described an animal model of immunologic cholangitis with some features resembling both PSC and PBC; others have described a model of PSC associated with intestinal bacterial overgrowth. It seems likely that as these models are further developed and evaluated, additional insight into the pathogenesis of PSC will be forthcoming.

Natural History

Based on prospective follow up of large numbers of PSC patients, there appears to be growing evidence that PSC is frequently a progressive syndrome leading to significant complications related to chronic cholestasis. Investigators at several institutions have published studies on the natural history of PSC suggesting disease progression and a poor prognosis in most patients. Our own experience indicates that: (i) PSC has a median survival of approximately 12 years; (ii) both symptomatic and asymptomatic patients have reduced survival relative to controls; and (iii) one-third of patients with the disease will die from it or from a complication like cholangiocarcinoma.

One of the main purposes of analyzing the natural history of PSC is to more accurately determine the rate of disease progression and to be able to estimate survival for the individual patient at any particular point in the course of the disease. Predicting survival based on clinical, biochemical, and histologic features of PSC at any point in time is also very important for liver transplantation. Attempts to evaluate prognosis and estimate survival have employed both univariate and multivariate approaches. We first reported an association between increased hepatic and urinary copper levels and diminished survivals, an example of the univariate approach. The multivariate approach, while requiring more sophisticated statistics, most notably the Cox Multivariate Regression Analysis, is more appropriate in a disease with a fluctuating course like PSC. The first report using the Cox Regression Analysis was by Helsburg et al who found that the presence of hepatomegaly and serum bilirubin of >1.5 mg/dl were independent predictors of poor prognosis in patients with PSC. More recently, we developed a prognostic model based on five independent variables in which risk score could be calculated and translated into a survival curve to estimate survival for the individual patient at any time in the course of the disease. The variables identified included age, serum bilirubin, hepatic histologic stage, and splenomegaly. While these and other models do provide some objective evidence with regard to disease severity and estimation of survival, none have been cross-validated, and their general application to all PSC patients remains unknown.

Management

The management of PSC provides a real challenge to the clinician, given the array of symptoms and complications that can develop and the absence of any effective specific therapy. The first decision regarding management relates to whether or not any therapeutic intervention is necessary in a patient with newly diagnosed PSC. In the asymptomatic patient with mild liver test abnormalities and early histologic disease by liver biopsy, since no specific therapy is available, observation would be reasonable. Alternatively, therapy might be considered in the context of a randomized trial. If a decision is made to intervene therapeutically, one needs to identify the goal of treatment. Specifically, therapy should be directed towards either symptoms, complications, or the underlying hepatobiliary disease. For example, pruritus and fat soluble vitamin deficiencies are common problems in patients with PSC; conventional approaches to management of these problems, which will not be reviewed here, are reasonable. Also, when complications such as variceal bleeding develop, appropriate intervention (such as variceal sclerosis) should be considered.

Treatment of complications. There are, however, complications which are relatively specific for PSC, including recurrent cholangitis and bacteremia, dominant strictures, and cholangiocarcinoma. Patients with recurrent episodes of cholangitis without dominant stricture formation should be treated with broad spectrum antibiotics as needed. Prophylactic antibiotics are favored by some in patients with frequent episodes of cholangitis, but the efficacy of this approach has not been established. Also, patients may develop dominant strictures in the biliary tract that can lead to rapid increases in serum bilirubin levels, recurrent episodes of cholangitis, or pruritus. Consideration of dilatation of these strictures in the symptomatic patient is reasonable; depending upon their location, a transhepatic or endoscopic approach with or without stent placement may be useful. Indeed, our experience with the transhepatic approach in symptomatic patients with PSC and dominant strictures suggests that balloon dilatation is very effective in alleviating pruritus and in diminishing the frequency of cholangitic episodes secondary to dominant strictures. Our experience also suggests that cholangiocarcinoma develops in probably 10-15% of patients with PSC. Indeed, PSC should be

considered a pre-malignant disease of the biliary tract. Because PSC patients often have longstanding CUC, they are also at increased risk for developing carcinoma of the colon. It also appears that PSC may itself be an independent risk factor for the development of colorectal cancer in CUC. The management of a suspected or established cholangiocarcinoma superimposed on PSC is complicated and is currently in evolution. Unfortunately, it has been difficult to diagnose bile duct cancer early in patients with PSC, since fine needle aspiration, brush cytology, and exfoliative cytology have been rather insensitive. Recently, we reported that a specific, circulating tumor marker (i.e., CA 19-9) may be both sensitive and specific for detecting bile duct cancer in patients with PSC. If the cholangiocarcinoma is surgically resectable and the patient is not currently a candidate for liver transplantation, an attempt at surgical resection would seem reasonable; unfortunately, based on our experience, this approach is usually unsuccessful. Altematively, if the cholangiocarcinoma is not surgically resectable, or if it is but the patient has advanced parenchymal liver disease, consideration should be given to orthotopic liver transplantation, recognizing that the outcome of liver transplantation for cholangiocarcinoma complicating PSC has been poor.

Surgical treatment of the underlying hepatobiliary disease. Currently, there is no specific treatment for the underlying hepatobiliary disease in PSC. This reflects, in part, our lack of knowledge about the exact pathogenesis of the disease. Nevertheless, therapeutic approaches for the underlying hepatobiliary disease can be categorized as mechanical, medical, and surgical. Advocates have suggested that balloon dilatation of dominant strictures may be beneficial to the natural history of the underlying hepatobiliary disease. There are no studies to support this position and intuitively, given the diffuse nature of the disease and the fact that patients die from parenchymal dysfunction and liver failure, it is not attractive. Thus, we recommend balloon dilatation of dominant strictures only for symptomatic relief of jaundice or pruritus and not for treatment of the underlying hepatobiliary disease.

There are three surgical procedures that have been considered of potential benefit in the treatment of PSC: biliary tract reconstructive procedures, proctocolectomy in a patient with PSC and CUC, and orthotopic liver transplantation. We consider biliary tract reconstructive procedures in the same category as balloon dilatation of dominant strictures; that is, as palliative procedures to alleviate symptoms and ones which are unlikely to affect the natural history of the disease. However, no good published data are currently available to allow one to confidently evaluate the role of biliary tract reconstructive procedures in treatment of the underlying liver disease. Our own data, which is currently being evaluated, suggests no beneficial effect of these types of procedures on the natural history of the disease.

Some have suggested that proctocolectomy in a patient with PSC and CUC may favorably affect the hepatobiliary disease. This is an important issue, not only because beneficial treatment for PSC is needed, but because proctocolectomy in patients with PSC and CUC may be associated with considerable morbidity. We have prospectively studied the effects of proctocolectomy on the progression of clinical, biochemical, cholangiographic, and hepatic histologic features in 53 patients with PSC and CUC. Patients with both diseases who had undergone proctocolectomy (n=23) were compared to those who had not (n=30) over four years. New onset of complications, serial changes in biochemical tests, histologic progression on liver biopsy, and survival did not differ in the two groups. We concluded that proctocolectomy for chronic ulcerative colitis is not beneficial for primary sclerosing cholangitis in patients with both diseases.

Finally, liver transplantation is a serious consideration for patients with any form of advanced liver disease, including PSC. Indeed, at many major transplant centers, including our own, PSC is one of the most frequent indications for liver transplantation in adults. Although data are still evolving, recent preliminary results suggest that the outcome of liver transplantation in patients with PSC is no different from that in patients with other forms of noninfectious, nonmalignant, chronic liver disease, with 5-year survivals of approximately 75-85%. Our own preliminary experience supports this conclusion; indeed, our 5-year estimated survival in patients undergoing liver transplantation for PSC is over 80%. In a very small number of patients (i.e., <5%), the disease has been reported to recur in the transplanted liver.

Medical treatment of the underlying hepatobiliary disease. Medical approaches for the treatment of the underlying hepatobiliary disease in PSC have centered primarily on the use of cupruretic, antifibrogenic, immunosuppressive, and choleretic agents. The finding of elevated hepatic copper levels in PSC prompted us to initiate a therapeutic trial of D-penicillamine in PSC in 1980. In a randomized prospective double-blind trial, 30 patients received penicillamine (250 mg three times a day) and 31 received a placebo. The two groups were highly comparable at entry with regard to clinical, biochemical, radiologic, and hepatic histologic features. Although a predictable cupruresis and a decrease in levels of hepatic copper were achieved in patients taking penicillamine there was no beneficial effect on disease progression

within 36 months or on overall survival. Progressive symptoms, deterioration in serial hepatic laboratory values, and histologic progression on sequential liver biopsy specimens were similar in both groups. The development of major side effects led to the permanent discontinuation of penicillamine in 21% of the patients taking the drug. We concluded from this study that the use of penicillamine in PSC is not associated with a beneficial effect on disease progression or survival and has considerable toxicity.

Corticosteroids have been used both topically and systemically in several small studies in PSC. A small controlled trial of nasobiliary lavage with corticosteroids versus placebo has recently been reported; the results were negative. Uncontrolled observations in a small number of patients with a marked inflammatory component to their PSC have shown impressive responses to orally administered corticosteroids. Previous smaller uncontrolled studies have not shown any beneficial effect of corticosteroids. Azathioprine has been used in at least two instances without apparent benefit. Also, low-dose methotrexate has also been used in PSC. In controlled studies, methotrexate caused improvement in biochemical studies, apparently stabilized bile duct scarring, and led to improvement in liver histology. The potential hepatotoxicity of methotrexate and the very small number of patients in this report necessitate that this drug not be used until results from controlled trials are available. Cyclosporine, a new immunosuppressive drug that inhibits the production of interleukin 2 by T lymphocytes resulting in decreased T lymphocyte activation and proliferation, was recently studied by us in a double-blind, controlled trial. Preliminary results are not encouraging. We recently reported our preliminary experience with combined prednisone and colchicine in 12 patients with PSC compared to 12 untreated patients matched for age, sex, initial biochemical levels, and liver histology. We observed impressive improvement in bilirubin, alkaline phosphatase, and aspartate aminotransferase levels when patients were re-evaluated at 6 and 12 months after entry. Unfortunately, no differences were seen at two years; thus, we do not consider this drug combination a viable option in PSC. Considerable interest has recently been focused on the use of ursodeoxycholic acid in the treatment of PSC. A variety of preliminary reports in small numbers of patients suggest its potential efficacy. Currently, we and others are conducting randomized controlled trials of ursodeoxycholic acid in PSC. At the present time, there is no effective medical treatment for PSC. Preliminary results suggest improvement in the results of biochemical tests of liver function in patients with PSC on ursodeoxycholic acid. Whether or not these changes will result in evidence of slowing of histologic progression, improvement in patient survival, or decreased referral for liver transplantation, remains to be determined.

Summary and Conclusions

Primary sclerosing cholangitis is a generally progressive, sometimes fatal, chronic hepatobiliary disorder for which no effective medical or surgical therapy now exists. The syndrome occurs most frequently in young men and is characterized by chronic cholestasis, frequent association with CUC, a paucity of serologic markers, hepatic copper overload, and characteristic abnormalities in some liver biopsy specimens and in virtually all cholangiograms. The natural history of the syndrome is still somewhat unclear; the disease likely progresses slowly and relentlessly over a decade or longer from an asymptomatic stage to a condition characterized by symptoms of cholestasis and complicated by cirrhosis and portal hypertension and carcinoma of the bile ducts. Management should first involve a thoughtful decision to observe, which is reasonable in the asymptomatic patient with early disease, or to intervene, particularly in patients with symptoms. Therapeutic goals should be defined and should concentrate on either alleviating symptoms, dealing with complications, or attempting to affect the underlying hepatobiliary disease. Symptomatic treatment and therapy for complications is similar to that employed in other chronic liver diseases, but also involves balloon dilatation of dominant strictures in appropriately selected symptomatic patients. Biliary tract reconstructive surgery may alleviate symptoms in selected patients with PSC, but its effect on the natural history of the syndrome has not been determined. Proctocolectomy for CUC in a patient with CUC and PSC does not beneficially affect the progression of the underlying hepatobiliary disease. In contrast, orthotopic liver transplantation may be life-saving for patients with advanced disease. Medical therapy directed at arresting the progression of the underlying hepatobiliary disease is currently experimental and includes cupruretic, immunosuppressive, antifibrogenic, and choleretic agents. Although a single recently completed controlled trial makes it unlikely that cupruretic agents will be helpful in this syndrome, immunosuppressive (i.e. cyclosporin A and methotrexate) and choleretic (i.e. ursodeoxycholic acid) agents alone or in combination are currently undergoing evaluation in randomized trials.

Bibliography

Reviews

1. Wiesner RH, LaRusso NF. Clinicopathologic features of the

syndrome of primary sclerosing cholangitis. Gastroenterology 1980;79:200-206.
2. LaRusso NF, Wiesner RH, Ludwig J, MacCarty RL. Primary sclerosing cholangitis. N Engl J Med 1984;310: 899-903.
3. Chapman RWG, Orborgh BAM, Rhodes JM, et al. Primary sclerosing cholangitis: a review of its clinical features, cholangiography and hepatic histology. Gut 1980;21:870-877.
4. LaRusso NF. Inflammatory and degenerative disorders of the biliary system. In: Principles and practice of gastroenterology and hepatology. Gitnick G, editor. New York: Elsevier Inc; 1995. p. 967-997.
5. Lindor KD, Wiesner RH, LaRusso NF. Recent advances in the management of primary sclerosing cholangitis. In: Seminars in liver disease. Berk PD, editor.New York: Thieme Medical Publishers; 1987. p. 322-327.
6. Ludwig J, LaRusso NF, Wiesner RH. The syndrome of primary sclerosing cholangitis. In: Progress in liver diseases. Popper H, Schaffner F, editors. Philadelphia: WB Saunders Co; 1990. p. 555-566.
7. LaRusso NF, Wiesner RH. Sclerosing cholangitis. In: Liver and biliary diseases. Kaplowitz N, editor. Baltimore: Williams and Wilkins; 1992. p. 686-697.
8. Wiesner RH, Porayko MK, LaRusso NF, Ludwig J. Primary sclerosing cholangitis. In: Diseases of the liver, Schiff L, Schiff E, editors, Philadelphia: JB Lippincott Company; 1993. p. 411-426.
9. Lee YM, Kaplan MM. Primary sclerosing cholangitis. N Engl J Med 1995;332:924-933.
10. Lefkowitch JH. Primary sclerosing cholangitis. Arch Intern Med 1982;142:1157-60.

Complications of PSC

11. Wee A, Ludwig J, Coffey RJ, LaRusso NF, Wiesner RH. Hepatobiliary carcinoma associated with primary sclerosing cholangitis and chronic ulcerative colitis. Human Pathology 1985;16: 719-726.
12. MacCarty RL, LaRusso NF, May GR, Bender CE, Wiesner RH, King JE, Coffey RJ. Cholangiocarcinoma complicating primary sclerosing cholangitis: cholangiographic features. Radiology 1985;156:43-46.
13. Gluckin LE, Payne JA. Cystic dilation as a radiographic sign of cholangiocarcinoma complicating sclerosing cholangitis. Am J Gastroenterol 1983;78:661-664.
14. Wiesner RH, LaRusso NF, Dozois RR, Beaver SJ. Peristomal varices after proctocolectomy in patients with primary sclerosing cholangitis. Gastroenterology 1986;90:316-322.
15. LaRusso NF. Sclerosing cholangitis and gallstones. In: Cohen S, Soloway RD, editors. Contemporary issues in gastroenterology. Gallstones. New York: Churchill Livingstone; 1985. p. 231-236.
16. Rosen CB, Nagorney DM, Wiesner RH, Coffey RJ Jr, LaRusso NF. Cholangiocarcinoma complicating primary sclerosing cholangitis. Ann Surg 1991;231:21-25.
17. Hay JE, Lindor KD, Wiesner RH, Dickson ER, Krom RAF, LaRusso NF. The metabolic bone disease of primary sclerosing cholangitis. Hepatology 1991;14:257-261.
18. Kartheuser AH, Dozois RR, Wiesner RH, LaRusso NF, Ilstrup DM, Schleck CD. Complications and risk factors after ileal pouch-anal anastomosis for ulcerative colitis associated with primary sclerosing cholangitis. Ann Surg 1993;217:314-320.
19. Nichols JC, Gores GJ, LaRusso NF, Wiesner RH, Nagorney DM, Ritts RE. Diagnostic role of serum CA 19-9 for cholangiocarcinoma in primary sclerosing cholangitis. Mayo Clinic Proceedings 1993;68:874-879.
20. Brentnall TA, Haggitt RC, Rabinovitch PS, Kimmey MB, Bronner MP, Levine DS, et al. Risk and natural history of colonic neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis. Gastroenterology 1996;110:331-338.
21. Loftus EV Jr, Sandborn WJ, Tremaine WJ, Mahoney DW, Zinsmeister AR, Offord KP, et al. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis. Gastroenterology 1996;110:432-440.
22. Ahnen DJ. Controlled clinical trials: the controls are the key. Gastroenterology 1996;110:628-630.

PSC and Radiology

23. MacCarty RL, LaRusso NF, Wiesner RH, Ludwig J. Primary sclerosing cholangitis: findings on cholangiography and pancreatography. Radiology 1983;149:39-44.
24. Li-Yeng C. Goldberg HI. Sclerosing cholangitis: broad spectrum of radiographic features. Gastrointest Radiol 1984;9:39-47.
25. Brandt DJ, MacCarty RL, Charboneau JW, LaRusso NF, Wiesner RH, Ludwig J. Gallbladder disease in patients with primary sclerosing cholangitis. Am J Rad 1988;150:571-574.
26. Craig DA, MacCarty RL, Wiesner RH, LaRusso NF, Grambsch PM. Primary sclerosing cholangitis: value of cholangiography to determine the prognosis. Am J Roent 1991;157:959-964.

PSC and Hepatobiliary Histology

27. Ludwig J, Barham SS, LaRusso NF, Elveback LR, Wiesner RH, McCall JT. Morphologic features of chronic hepatitis associated with primary sclerosing cholangitis or chronic ulcerative colitis. Hepatology 1981;1:632-640.
28. Ludwig J, MacCarty RL, LaRusso NF, Krom RAF, and Wiesner RH. Intrahepatic cholangiectases and large-duct obliteration in primary sclerosing cholangitis. Hepatology 1986;6:560-568.
29 Ludwig J, LaRusso NF, Wiesner RH. Primary sclerosing cholangitis. In: Peters RL, Craig JR, editors. Liver pathology. Contemporary Issues in Surgical Pathology. New York: Churchill Livingstone; 1986. p.193-214.

Etiopathogenesis of PSC

30. MacFarlane IG, Wojeica BM, Tsantoulas DC, et al. Leukocyte migration inhibition in response to biliary antigens in primary biliary cirrhosis, sclerosing cholangitis, and other chronic liver diseases. Gastroenterology 1979;76:1333-1340.
31. Bodenheimer HC Jr, LaRusso NF, Thayer WR Jr, Charland C, Staples P, Ludwig J. Elevated circulating immune complexes in primary sclerosing cholangitis. Hepatology 1983;3:150-154.
32. Chapman RW. Role of immune factors in the pathogenesis of primary sclerosing cholangitis. Semin Liver Dis 1991;11:1-4.
33. Quigley EMM, LaRusso NF, Ludwig J, MacSween RNM, Birnie GG, Watkinson G. Familial occurrence of primary sclerosing cholangitis and chronic ulcerative colitis. Gastroenterology 1983;85:1160-1165.
34. Lindor KD, Wiesner RH, Katzmann JA, LaRusso NF, Beaver SJ. Lymphocyte subsets in primary sclerosing cholangitis. Dig Dis Sci 1987;32:720-725.
35. Lindor KD, Wiesner RH, LaRusso NF, Homburger HA. Enhanced autoreactivity of T-lymphocytes in primary sclerosing cholangitis. Hepatology 1987;7:884-888.
36. Gross JB, Ludwig J, Wiesner RH, McCall JT, LaRusso NF. Abnormalities in tests of copper metabolism in primary sclerosing cholangitis. Gastroenterology 1985;89:272-278.
37. Duerr RH, Targan SR, Landers CJ, LaRusso NF, Lindsay KL, Wiesner RH, et al. Neutrophil cytoplasmic antibodies: a link between primary sclerosing cholangitis and ulcerative colitis. Gastroenterology 1991;100:1385-1391.
38. Mehal WZ, Hattersley AT, Chapman RW, Fleming KA. A survey of cytomegalovirus DNA in primary sclerosing cholangitis liver

tissues using a sensitive polymerase chain reaction based assay. J Hepatol 1992;15:396-399.
39. Hay JE, Rosser BG, Espy MJ, et al. Cytomegalovirus and primary sclerosing cholangitis (PSC): no evidence for pathogenic association. Gastroenterology 1993;104:A913.

Natural History of PSC

40. Helzberg JH, Peterson JM, Boyer JL. Improved survival with primary sclerosing cholangitis. A review of clinicopathologic features and comparison of symptomatic and asymptomatic patients. Gastroenterology 1987;92:1869-1875.
41. LaRusso NF, Wiesner RH, Ludwig J. Is primary sclerosing cholangitis a bad disease? Gastroenterology 1987;92:2031-2033.
42. Wiesner RH, Grambsch P, Dickson ER, Ludwig J, McCarty R, Hunter EB, et al. Primary sclerosing cholangitis: natural history, prognostic factors, and survival analysis. Hepatology 1989;10:430-436.
43. Wiesner RH, Grambsch P, LaRusso NF, Dickson ER. Is primary sclerosing cholangitis a progressive disease or not? Hepatology 1988;8:970-972.
44. Porayko MK, Wiesner RH, LaRusso NF, Ludwig J, MacCarty RL, Steiner BL, et al. Patients with asymptomatic primary sclerosing cholangitis frequently have a progressive disease. Gastroenterology 1990;98:1594-1602.
45. Dickson, ER, Murtaugh PA, Wiesner RH, Grambsch PM, Fleming TR, Ludwig J, et al.Primary sclerosing cholangitis: refinement and validation of survival models. Gastroenterology 1992;103:1893-1901.
46. Wiesner RH, Porayko MK, Dickson ER, Gores GJ, LaRusso NF, et al. Selection and timing of liver transplantation in primary biliary cirrhosis and primary sclerosing cholangitis. Hepatology 1992;16:1290-1299.
47. Mehal WZ, Lo YM, Wordsworth BP, et al. HLA DR4 is a marker for rapid disease progression in primary sclerosing cholangitis. 1994; Gastroenterology 106:160-167.

Management of PSC

48. May GR, Bender CE, LaRusso NF, Wiesner RH. Nonoperative dilatation of dominant strictures in primary sclerosing cholangitis. Am J Rad 1985;145:1061-1064.
49. LaRusso NF, Wiesner RH, Ludwig J. Recent advances in the diagnosis and management of primary sclerosing cholangitis. Current Concepts in Gastroenterology 1983;8:6-9.
50. Wiesner RH, Ludwig J, LaRusso NF, MacCarty RL. Diagnosis and treatment of primary sclerosing cholangitis. In: Schaffner F, editor. Seminars in Liver Disease, New York: Thieme Inc. 1985; p. 241-253.
51. Pitt HA, Thompson HH, Tompkins RL, Longmire WP: Primary sclerosing cholangitis. Results of an aggressive surgical approach. Ann Surg 1984;199:637-647.
52. LaRusso NF, Wiesner RH, Ludwig J, MacCarty RL, Beaver SJ, Zinsmeister AR: A prospective trial of penicillamine in primary sclerosing cholangitis. Gastroenterology 1988;95:1036-1042.
53. Cangemi JR, Wiesner RH, Beaver SJ, Ludwig J, MacCarty RL, Dozois RR, et al.The effect of proctocolectomy for chronic ulcerative colitis on the natural history of primary sclerosing cholangitis. Gastroenterology 1989;96:790-794.
54. LaRusso NF Wiesner RH. Sclerosing cholangitis: Treatment or transplant? In: Difficult Decisions in Digestive Diseases. Barkin JS , Rogers AI, editors. Chicago: Year Book Medical Publishers Inc; 1989. p. 298-304.
55. Cotton PB, Nickl N. Endoscopic and radiologic approaches to therapy in primary sclerosing cholangitis. Semin Liver Dis 1991;11:40-48.
56. Kaplan M. Medical approaches to primary sclerosing cholangitis. Semin Liver Dis 1991;11:56-63.
57. Marsh JW Jr., Iwatsuji S, Makawka L, Esquivel CO, Gordon RD, Todo S, et al. Orthotopic liver transplantation for primary sclerosing cholangitis. Ann Surg 1988;207:21-25.
58. Hayashi H, Higuchi T, Ichimiya H, Hishida N, et al. Asymptomatic primary sclerosing cholangitis treated with ursodeoxycholic acid. Gastroenterology 1990;99:533-535.
59. Kaplan MM, Arora S, Pincus SH. Primary sclerosing cholangitis and low-dose oral pulse methotrexate therapy. Ann Intern Med 1987; 106:231-235.
60. McEntee G, Wiesner RH, Rosen C, Cooper J, Wahlstrom E. A comparative study of patients undergoing liver transplantation for primary sclerosing cholangitis and primary biliary cirrhosis. Transplant Proc 1991;23:1563-1564.

Miscellaneous

61. Balasubramanian K, Wiesner RH, LaRusso NF. Primary sclerosing cholangitis with normal serum levels of alkaline phosphatase. Gastroenterology 1988;95:1395-1398.
62. Hay JE, Wiesner RH, Shorter RG, LaRusso NF, Baldus WP. Primary sclerosing cholangitis and celiac disease: a novel association. Ann Intern Med 1988;109:713-717.
63. Lindor KD, Wiesner RH, LaRusso NF, and Dickson ER. Chronic active hepatitis: Overlap with primary biliary cirrhosis and primary sclerosing cholangitis. In: Czaja AJ, Dickson ER, editors. Chronic active hepatitis: the Mayo Clinic experience. New York: Marcell Dekker Inc; 1986. p. 171-187.
64. Ueno Y, Phillips JO, Ludwig J, LaRusso NF. Nonsuppurative cholangitis induced in rodents by cholangiocyte immunization: An experimental model for immune cholangiopathies. Hepatology 1993;18: Part 2.A170.