Digestive Diseases and Sciences, Vol. 50, No. 10 (October 2005), pp. 1839–1843 (© 2005)
DOI: 10.1007/s10620-005-2948-3

ORIGINAL REPORT

Steroid-Responsive (Autoimmune?) Sclerosing Cholangitis

JASJEET S. SEKHON, PhD,* RAYMOND T. CHUNG, MD,† MARK EPSTEIN, MD,‡ and MARSHALL M. KAPLAN, MD‡

KEY WORDS: sclerosing cholangitis; glucocorticoids; prednisone; bile ducts.

Primary sclerosing cholangitis (PSC) is a chronic, progressive cholestatic liver disease characterized by inflammation, fibrosis and destruction of the intrahepatic and extrahepatic bile ducts (1). Although the natural history of PSC is variable, it is almost always progressive and leads to cirrhosis and liver failure (2–5). The etiology of PSC is unknown, and there is no effective medical treatment. We report on all patients who first presented to us between January 1999 and December 2001 with confirmed sclerosing cholangitis of a highly inflammatory nature. Six such patients presented in this time-period out of 80 patients with PSC. All six of these patients improved dramatically in response to glucocorticoid treatment. Biochemical tests of liver function normalized in five patients and improved greatly in the sixth, cholangiograms improved in those who had cholangiograms before and after treatment and symptoms resolved in all six. The response of these patients to immunosuppressive therapy suggests that their sclerosing cholangitis may be of autoimmune etiology. Based on this experience, we suggest that PSC may be a syndrome with different etiologies, rather than one discrete disease, and that our patients have an autoimmune variant. That sclerosing cholangitis may be a family of diseases with different etiologies would explain the disparate results found in the PSC literature concerning the efficacy of medical treatments.

Manuscript received December 18, 2004; accepted January 25, 2005.

From the *Harvard University, Cambridge, †Gastrointestinal Unit, Massachusetts General Hospital and Harvard Medical School, and ‡Gastroenterology Division, New England Medical Center, Boston, Massachusetts, USA.

Address for reprint requests: Raymond T. Chung, MD, Director of Hepatology, GRJ 825, GI Unit, Massachusetts General Hospital, Boston, Massachusetts 02114, USA; rtchung@partners.org.

CASE REPORTS

Case 1

A 24-year-old East-Indian Caucasian male presented at another medical center in January 1996 with universal ulcerative colitis. His serum alkaline phosphatase was markedly elevated (911 IU), with lesser elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Baseline clinical and biochemical data for all patients are presented in Tables 1 and 2. Endoscopic retrograde cholangiopancreatography (ERCP) was consistent with PSC. The colitis failed to respond to prednisone (60 mg q.d.), sulfasalazine and a short course of 6-mercaptopurine. A subtotal colectomy was performed 6 months later. Despite the failure of the colitis to respond to immunosuppressive therapy, the elevated liver enzymes improved rapidly. The prednisone was gradually tapered and discontinued in January 1997.

The patient was well until February 2000 when he presented to us with elevated liver enzymes. Fatigue, anorexia, and weight loss subsequently developed. Repeat ERCP in May 2000 was again consistent with PSC (Figure 1A). Direct examination of the bile duct showed diffuse erythema and ulceration. Biopsies demonstrated intense mononuclear inflammation. A liver biopsy demonstrated "onion skin" fibrosis of small bile ducts and was consistent with stage 2 PSC. The patient was placed on ursodiol (600 mg t.i.d.) in May 2000. Methotrexate (0.25 mg/kg body weight per week) was added in August because of worsening symptoms and increasing serum bilirubin (2.0 mg/dL) and alkaline phosphatase (1156 IU). Liver function tests and symptoms continued to worsen and prednisolone (36 mg q.d.) was added in February 2001, with rapid improvement in symptoms, serum bilirubin and liver enzymes (Table 2). A third ERCP performed in May 2001 demonstrated improvement in the common bile duct (Figure 1B) with reduced inflammation by biopsy. In 2001, his serum IgG4 level was tested and found to be normal (0.6 g/L, normal <1.3 g/L). Ursodiol was stopped in early 2002 because of diarrhea. Prednisone was tapered and discontinued in July 2002 because he was diagnosed with bilateral osteonecrosis which required bilateral total hip replacements. Methotrexate was stopped in December 2002. He currently has no symptoms related to PSC, and his serum bilirubin and liver enzymes remain normal without further treatment for PSC.

TABLE 1. BASELINE CLINICAL DATA

Patient	*Age*	*Sex*	*Wt (kg)*	*Ulcerative colitis*	*Pancreatitis*	*Bile duct involvement*	*Histologic stage*
1	24	M	70	Y	N	IH, EH	2
2	20	M	71	N	Y	IH, EH	N.D.
3	52	M	83	N	Y	IH, EH	N.D.
4	68	M	80	N	Y	IH, EH	N.D.
5	29	M	79	Y	N	IH	2
6	16	M	64	Y	N	IH	1

Note. IH: intrahepatic bile ducts, EH: extrahepatic bile ducts, N.D.: not done.

Case 2

A 20-year-old African American male presented in June 1998 with pruritus, painless jaundice, acholic stool, and 25 pound weight loss. Serum bilirubin was 8 mg/dL and alkaline phosphatase 446 IU. Ultrasound of the abdomen demonstrated a distended gallbladder, a dilated common bile duct and two cystic masses in the upper abdomen. An abdominal CT scan suggested two pancreatic pseudocysts and perisplenic varices. ERCP demonstrated a tight common bile duct stricture along with diffuse intrahepatic ductal stricturing and dilatation and diffuse irregularity and narrowing of the pancreatic duct. Endoscopic ultrasound-guided biopsies of the pancreas were consistent with chronic pancreatitis. The bile duct stricture was stented and the patient begun on ursodiol (300 mg b.i.d.). There were recurrent episodes of right-upper-quadrant abdominal pain, jaundice, and fever during the next year despite replacement of the bile duct stents and surgical exploration with a choledochoduodenostomy and cholecystectomy. The resected specimen demonstrated lymphoplasmacytic infiltration of the bile duct and gallbladder consistent with sclerosing cholangitis/cholecystitis. In March 1999 the serum bilirubin was 8 mg/dL and serum albumin 3.0 g/dL. He was listed for liver transplantation. In March 2000 prednisone (40 mg q.d.) was started. The jaundice and fatigue disappeared and serum bilirubin, liver enzymes and serum albumin returned to normal (Table 2). The patient was tapered off prednisone in mid-2001 and methotrexate (0.25 mg/kg body weight per week) was added. He continues to do well on methotrexate.

Case 3

A 52-year-old Caucasian male presented in March 1999 with jaundice and acholic stools. The serum bilirubin was 23.1 mg/dL and alkaline phosphatase 310 IU. A CT-scan of the abdomen demonstrated dilatation of the intra- and extrahepatic bile ducts and prominence of the head of the pancreas. ERCP demonstrated marked dilatation of the bile ducts above a strictured lower end of the common bile duct and a stricture of the distal pancreatic duct, a "double duct sign" suggestive of cancer of the head of the pancreas. A biliary stent was placed and the serum bilirubin and alkaline phosphatase improved. A pancreaticoduodenectomy and choledochojejunostomy were performed on April 1999. Pathology showed changes of chronic pancreatitis. Postoperatively the serum bilirubin and alkaline phosphatase returned to normal but the patient developed daily fevers to 102 F and night sweats. Cultures of blood and bile were repeatedly negative and there was no response to broad-spectrum antibiotics. The serum bilirubin and alkaline phosphatase began to increase and were at preoperative levels in May, one month postoperatively. ERCP showed diffuse stricturing and dilatation of the extra- and intrahepatic bile ducts and was diagnostic of PSC (Figure 2A). There was no response to ursodiol (600 mg b.i.d.). Repeat ERCP demonstrated further stricturing of bile ducts and the patient was listed for liver transplantation. Prednisone (60 mg q.d.) was begun in early July. There was a rapid improvement in symptoms and normalization of serum bilirubin, albumin and liver enzymes (Table 2). Repeat ERCP at that time was nearly normal (Figure 2B). Prednisone was tapered and discontinued in December 1999. Pruritus recurred and liver enzymes and bilirubin (3.2 mg/dL) were elevated in March 2000. Prednisone (30 mg q.d.) was restarted with prompt improvement in pruritus and liver function tests. Methotrexate (0.25 mg/kg body weight per week) was added and the prednisone tapered and discontinued. In 2003, his serum IgG4 level was tested and found to be elevated (1.39 g/L, normal 0.2–1.1 g/L). The

TABLE 2. LABORATORY VALUES BEFORE AND AFTER PREDNISONE

	Alkaline phosphatase		*Bilirubin*		*Albumin*		*ALT*	
Patient	*Before Rx*	*After Rx*	*Before Rx*	*After Rx*	*Before Rx*	*After Rx*	*Before Rx*	*After Rx*
1	911	139	4.2	0.4	3.4	3.8	135	36
2	350	95	8.4	1.6	3.1	3.6	78	53
3	310	77	23.1	0.4	2.5	3.6	27	17
4	550	285	7.6	1.4	3.3	3.7	74	69
5	831	47	0.8	0.5	3.4	4.5	N.D.	22
6	715	58	0.6	0.3	3.6	3.7	53	10
Mean ± SD	611 ± 250	140 ± 96.8	7.45 ± 8.34	0.767 ± 0.575	3.22 ± 0.387	3.82 ± 0.343	73.4 ± 40	46.7 ± 44.1
Wilcoxon *P*-value*	0.0313		0.0313		0.0355†		0.438	
Paired *t*-test *P*-value	0.011		0.106		0.0158		0.418	

Note. N.D.: not done. Before Rx is defined as the labs right before glucocorticoid treatment. This may differ from labs at presentation.
*Exact paired Wilcoxon signed rank test.
†Cannot compute exact *p*-value because of ties. Continuity correction used.

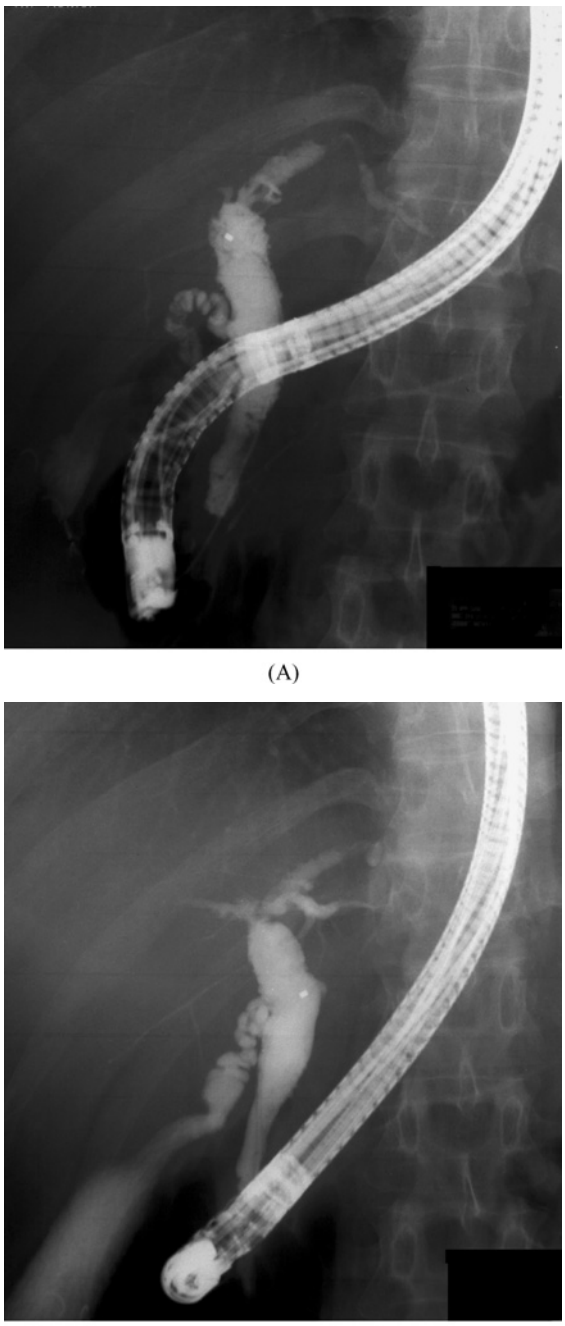

Fig 1. (A) Endoscopic retrograde cholangiopancreatography (ERCP) obtained prior to the start of therapy for case 1. There is mild dilation of the common bile duct, but no strictures are observed. A diffuse, irregular appearance of the biliary epithelium is present in the entire common duct. The biliary tree shows diffuse erythema and ulceration. Courtesy of Dr. David Carr-Locke, Endoscopy Center, Brigham and Women's Hospital. (B) ERCP obtained after 3 months of corticosteroid therapy for case 1. The mucosa in the lower common bile duct is relatively normal and there is evidence of healed and healing ulceration in the upper common bile duct. Courtesy of Dr. David Carr-Locke, Endoscopy Center, Brigham and Women's Hospital.

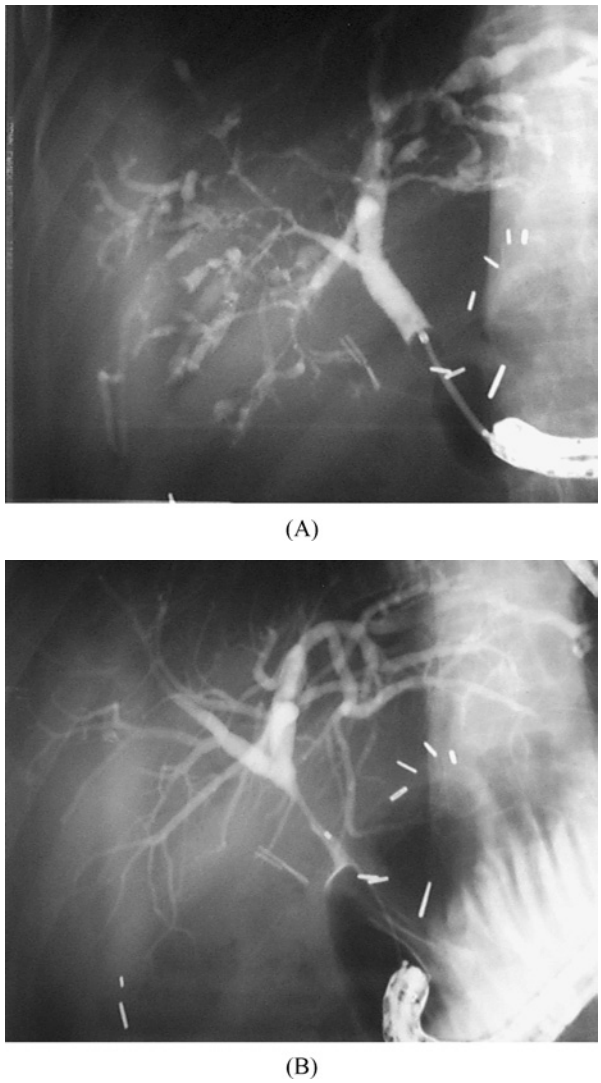

Fig 2. (A) ERCP obtained prior to initiation of therapy for case 3. Diffuse stricturing and dilation of the bile ducts is observed. (B) ERCP obtained after 2 months of corticosteroid therapy for case 3. The diffuse stricturing and dilation of the bile ducts previously observed is greatly reduced. The appearance is very close to normal.

patient remains well, and his liver function tests are all normal on methotrexate.

Case 4

A 68-year-old Caucasian male presented in April 1999 with jaundice and a palpable gallbladder. Serum bilirubin was 7.6 mg/dL and alkaline phosphatase 550 IU. Abdominal ultrasound and abdominal CT scan demonstrated dilated bile ducts and a mass in the head of the pancreas. ERCP demonstrated double duct sign. A stent was placed across the bile duct stricture. CT-scan-guided biopsies of the pancreas yielded only necrotic material and inflammation. The patient declined to have surgery and was treated with ursodiol, pancreatic enzymes, broad-spectrum antibiotics, and replacement of stents when they

became occluded. Bilirubin and alkaline phosphatase levels remained elevated and repeat ERCPs demonstrated progressive stricturing of the intrahepatic bile ducts in a pattern diagnostic of PSC. The bile duct stent was removed in October 1999. Bilirubin and alkaline phosphatase levels remained elevated and the patient had lost 40 pounds since disease onset. Prednisone (30 mg q.d.) was begun in June 2001, with prompt improvement in liver function tests and appetite (Table 2). Serum bilirubin fell to 1.2 mg/dL and alkaline phosphatase to 250 IU. The patient regained his lost weight and remains well on prednisone (5–10 mg q.d.). Repeat ERCP was declined.

Case 5

A previously healthy 29-year-old Caucasian male presented in March 2000 with bloody diarrhea that was found to be caused by universal ulcerative colitis. His serum alkaline phosphatase was markedly elevated (831 IU) and there were lesser elevations of AST and ALT. An ERCP demonstrated marked pruning of the intrahepatic biliary tree without significant dilation and was consistent with PSC. Prednisone (40 mg q.d.), mesalamine (800 mg q.i.d.) and ursodiol (250 mg q.i.d.) were started. His symptoms improved rapidly and his liver enzymes returned to normal within two months. A liver biopsy demonstrated portal inflammation and scarring, bile duct injury and concentric periductal fibrosis, changes consistent with PSC.

The prednisone dose was decreased to 10 mg q.d. in July 2000, and he began to experience symptoms of colitis. His liver enzyme tests remained normal (Table 2). Azathioprine (2.5 mg/kg/d) was added, and the prednisone was successfully tapered. Repeat liver biopsy in July 2001 was markedly improved and showed no inflammation. The patient remains well on azathioprine and his liver enzymes remain normal.

Case 6

A previously healthy 16-year-old Caucasian male presented in October 2001 with ulcerative colitis. His serum alkaline phosphatase was greatly elevated (983 IU) and there were lesser elevations of: AST 138 UL, ALT 180 UL and serum bilirubin 1.4 mg/dL. An ERCP demonstrated intrahepatic stricturing and was consistent with PSC. A liver biopsy was consistent with stage 1 PSC. Prednisone (40 mg q.d.) and mesalamine were begun in December. The patient's symptoms promptly resolved and his liver function tests returned to normal (Table 2). He successfully tapered off prednisone, 6-mercaptopurine (1 mg/kg/d) was added, and he remains well on this regimen.

DISCUSSION

These patients differ from most patients with PSC in that all were symptomatic at the time of their initial presentation and all clearly responded to prednisone. Symptoms remitted and mean serum bilirubin decreased from 7.5 mg/dL ($SD = 8.3$) to 0.8 mg/dL ($SD = 0.6$), $p = 0.031$; alkaline phosphatase from 611 IU ($SD = 250$) to 140 IU ($SD = 97$), $p = 0.031$; and albumin increased from 3.2 ($SD = 0.4$) to 3.8 ($SD = 0.3$), $p = 0.036$ (Table 2). Those who had liver biopsies had early stage disease (stages 1 or 2). There was unequivocal improvement in cholangiograms in the two patients who had these studies done before and after treatment and improvement in liver histology in the patient who had liver biopsies done before and after treatment. Three of these patients had concomitant pancreatitis and three had ulcerative colitis. Notwithstanding their response to corticosteroids, none of these patients have "definite" or "probable" autoimmune hepatitis as judged by the scoring system of the international autoimmune hepatitis group (6). We believe that these patients differ from most with PSC and have an autoimmune variant of sclerosing cholangitis. In addition, they were diagnosed and treated early in the course of their disease, at a time when their bile duct strictures were caused mainly by inflammation rather than by scarring.

One of us has also noted different clinical presentations in patients with primary sclerosing cholangitis; an acute one that occurs in approximately 10 percent of patients and a chronic indolent one that occurs in 90 percent (1, 7). Patients with the acute type were more likely to respond to methotrexate (7). These patients are similar to those with acute pericholangitis described earlier by Mistilis (8, 9) and most likely have an autoimmune type of sclerosing cholangitis.

That sclerosing cholangitis is a syndrome, one of whose etiologies is autoimmune, rather than one disease, would explain some of the disparities in the literature about the efficacy of immunosuppressive treatment. Case reports describing successful treatment of sclerosing cholangitis with azathioprine, prednisone and methotrexate most likely included a selected subgroup of patients who had autoimmune sclerosing cholangitis (10–16).

At least three of the patients (2, 3, and 4) had evidence of pancreatitis. While it is possible that these cases overlap with autoimmune or sclerosing pancreatitis (case 3 had elevated IgG4 levels) (17), they differ in that pancreatic biopsies did not disclose the characteristic lymphoplasmacytic infiltrate of that entity. Further, the jaundice in these cases failed to resolve with surgical or endoscopic decompression, indicative of the predominance of intrahepatic biliary involvement in these cases. It is quite conceivable that this variant of PSC falls on a continuum with autoimmune sclerosing pancreatitis.

We have described six cases of clinically and radiographically confirmed sclerosing cholangitis that fully responded to corticosteroids with or without other immunomodulatory therapy. Only Case 1 experienced significant side effects due to corticosteroids. This clinical entity, which we propose to call autoimmune sclerosing cholangitis, a subgroup of PSC, should be entertained in patients who present with abrupt and marked changes in liver tests, usually great elevations of alkaline phosphatase relative to ALT and AST. While cholangiography may

not be distinctive, liver biopsy will disclose a predominance of inflammatory changes with a paucity of fibrosis. A trial of full-dose corticosteroids should be considered for such patients. A successful response to corticosteroids would support the hypothesis that a patient has this autoimmune variant of PSC. Further prospective study and characterization of this subgroup is warranted, as there are potentially profound implications for the natural history of disease progression.

REFERENCES

1. Lee YM, Kaplan MM: Primary sclerosing cholangitis. N Engl J Med 332:924–933, 1995
2. Kim W, Therneau TM, Wiesner RH, Poterucha JJ, Benson JA, Jr, Malinchoc M, LaRusso N, Lindor K, Dickson ER: A revised natural history model for primary sclerosing cholangitis. Mayo Clin Proc 75:688–694, 2000
3. Dickson ER, Murtaugh PA, Wiesner RH, Grambsch PM, Fleming TR, Ludwig J, LaRusso NF, Malinchoc M, Chapman RW, Kaplan MM, *et al.*: Primary sclerosing cholangitis: refinement and validation of survival models. Gastroenterology 103:1893–1901, 1992
4. Wiesner RH, Grambsch PM, LaRusso N, Dickson ER: Is primary sclerosing cholangitis a progressive disease or not? Hepatology 8:970–972, 1988
5. Wiesner RH, Grambsch PM, Dickson ER, Ludwig J, MacCarty RL, Hunter EB, Fleming TR, Fisher LD, Beaver SJ, LaRusso NF: Primary sclerosing cholangitis: Natural history, prognostic factors and survival analysis. Hepatology 10:430–436, 1989
6. Alvarez FBP, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, Chapman RW, Cooksley WG, Czaja AJ, Desmet VJ, Donaldson PT, Eddleston AL, Fainboim L, Heathcote J, Homberg JC, Hoofnagle JH, Kakumu S, Krawitt EL, Mackay IR, MacSween RN, Maddrey WC, Manns MP, McFarlane IG, Meyer zum Buschenfelde KH, Mieli-Vergani G, Nakanuma Y, Nishioka M, Penner E, Porta G, Portmann BC, Reed WD, Rodes J, Schalm SW, Scheuer PJ, Schrumpf E, Seki T, Toda G, Tsuji T, Tygstrup N, Vergani D, Zeniya M: International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 31:929–938, 1999
7. Kaplan MM: Medical approaches to primary sclerosing cholangitis. Semin Liver Dis 11:56–63, 1991
8. Mistilis SP: Pericholangitis and ulcerative colitis. I. Pathology, etiology, and pathogenesis. Ann Int Med 63:1–16, 1965
9. Mistilis SP, Skyring AP, Goulston SJM: Pericholangitis and ulcerative colitis; II. Clinical aspects. Ann Int Med 63:17–26, 1965
10. Javett S: Azathioprine in primary sclerosing cholangitis. Lancet 1:810, 1971
11. Wagner A: Azathioprine treatment in primary sclerosing cholangitis. Lancet 2:663–664, 1971
12. Myers RN, Cooper JH, Padis N: Primary sclerosing cholangitis: complete gross and histologic reversal after long-term steroid therapy. Am J Gastroenterol 53:527–538, 1970
13. Burgert SL, Brown BP, Kirkpatrick RB, LeBrecqque DR: Positive corticosteroid response in early primary sclerosing cholangitis (abstract). Gastroenterology 86:1037, 1984
14. Kaplan MM, Arora S, Pincus SH: Primary sclerosing cholangitis and low dose oral pulse methotrexate. Ann Intern Med 106:231–235, 1987
15. Knox TA, Kaplan MM: -Treatment of primary sclerosing cholangitis with oral methotrexate. Am J Gastroenterol 86:546–552, 1991
16. Schramm C, Schirmacher P, Helmreich-Becker I, Gerken G, Meyer zum Büschenfelde K, Lohse A: Combined therapy with azathioprine, prednisolone, and ursodiol in patients with primary sclerosing cholangitis. Ann Intern Med 131:943–946, 1999
17. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K: High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 345:147–148, 2001