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A Case Report of Secretin Therapy for Primary Sclerosing Cholangitis

Yohei Fukumoto, Muneko Okazaki, Nobuhiro Kajii, Ryosuke Omura*, Keisuke Hino, Mitsuru Yasunaga and Kiwamu Okita*

First Department of Internal Medicine, Yamaguchi University School of Medicine, Ube, Yamaguchi 755, Japan, *Shimonoseki National Hospital, Shimonoseki 751, Japan
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Abstract Primary sclerosing cholangitis (PSC) is a rare liver disease which is characterized by fibrous stenosis of both intra- and extra-hepatic bile ducts. No definite therapy has been established yet and the prognosis is very poor. The patient had persistent jaundice for about five years and levels of the serum total bilirubin fluctuated from 14.2 to 33.4 mg/dl (mean value 20.1 mg/dl). In order to improve jaundice, secretin, one of gut hormones, was administered intravenously in a dose of 150 to 200 units. As a result, the serum bilirubin was significantly decreased for about 8 months as compared to levels one year before secretin administration. It seemed that secretin was effective to improve the prognosis. Secretin therapy for PSC is entirely new strategy and appears to be useful as a medical treatment before induction of curative therapy such as liver transplantation.

Key Words : Primary sclerosing cholangitis; Secretin; Cholestasis; Bile flow

Introduction

Primary sclerosing cholangitis (PSC) is a disease of unknown etiology which is hallmarked by chronic inflammation and fibrosis of intra- and extra-hepatic bile ducts. The natural history of PSC is progressive and carries a poor prognosis.[1-3] As an effective therapy has not been established yet, the patient with a terminal stage of PSC resorts to only symptomatic treatment.

Recently, we have reported that secretin, one of gastrointestinal hormones, has choleretic effects in man and was beneficial in the resolution of jaundice to patients with acute intraheatic cholestasis.[4] As PSC is a liver disease categorized in the chronic intrahepatic cholestasis, we tried secretin to a terminal PSC patient accompanied with persistent jaundice for several years. In this patient, stenosis of intrahepatic bile ducts was so advanced that the third or more further branches of bile ducts had not been demonstrared by examinations of endoscopic retrograde cholangio-pancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC).

Diagnostic procedures of this patient have already been reported with two other cases of PSC.[5] The present report discussed about the treatrment for terminal PSC, especially whether secretin therapy was an accurate treatment from view point of improvement of the prognosis.

Case: a 47-year-old female

Table 1. Data of serum chemistry on the first admission.

S. Prot	8.5 g/dl	RBC	381×10^4/mm^3
(Alb 50.9%, α_1 3.8%, α_2 8.1%,		Ht	33.9%
β 9.3%, γ 26.1%)		Hb	11.3g/dl
B. Sug	108mg/dl	WBC	6800/mm^3
T. Bil	2.0mg/dl	(N. Band 1.0%, N. Seg 33.9%, Eosi 2.5%	
(D. Bil 80.0%)		Lym 34.0%, Mono 5.5%, Baso 0.5%)	
Alb	3.3g/dl		
Glob	5.2g/dl	Ig G	2200mg/dl
Cho E	0.75Δph	Ig A	310mg/dl
ALP (n: 16~48)	303 u	Ig M	230mg/dl
Cholest	295mg/dl		
GOT (n: 4~17)	46 u	ANA	(−)
GPT (n: 4~17)	46 u	AMA	(−)
γ-GTP	258 u	Thyroid test	(−)
		Microsome test	(−)
PPT	12.2sec	RA test	(+)
(c 11.4sec)			
PTT	33.6sec	HBs Ag	(−)
(c 27.8sec)		HBs Ab	(−)

Past history: The patient underwent left sided pneumonectomy for pulmonary tuberculosis at 31-year-old and uterectomy for myoma at age of 41 year. She received blood transfusion on the first occasion, but did not develop to chronic hepatitis thereafter.

Present illness and clinical course: On April 1975, the patient visited a medical office at her town with some signs of general fatigue, pruritis and pain of her elbow and wrist joints. Then, a mild hepatic dysfunction and rheumatoid arthritis were pointed out. She received medical treatments, but could not have satisfactory responses on her subjective and objective symptomes. For further examination and therapy, she was referred to the Yamaguchi University Hospital.

As shown in Table 1, studies of blood chemistry on admission revealed anemia, mild jaundice, elevated serum biliary enzymes and γ-globulin, and positive reaction for RA test. Endoscopic retrograde cholangio-pancreatography (ERCP) was performed to examine biliary trees, but infused contrast medium mostly flowed into gallbladder so that intrahepatic bile ducts were not fully demonstrated. Liver biopsy showed moderate fibrosis in portal area with infiltrations of lymphocytes and few eosinocytes. Bile duct epithelial cells were degenerated and disappeared in some parts. In the second trial of ERCP, the stenosis of the common bile duct was disclosed and deformities of intrahepatic bile ducts were visualized. By means of these findings, her liver disease was strongly suspected to be PSC. After three and half months admission, the level of serum total bilirubin (T. Bil) was reduced from 2.0 to 1.4 mg/dl and she was discharged.

On May 1977, when the patient attended an outpatient clinic of other general hospital, she suddenly had an abdominal pain and melena. Under X-ray examination of barium enema for large intestine, she was diagnosed as ulcerative colitis and admitted again to the Yamaguchi University Hospital.

Studies of blood chemistry on the second admission showed hyperbilirubinemia (T. Bil 6.1 mg/dl) and anemia due to melena, on June 1977 (Table 2). We started to administer corticosteroid (Predonine 40 mg/day) to treat jaundice and ulcerative colitis. After steroid therapy, the serum level of T. Bil was decreased to 1.7 mg/dl. But, during steroid reduction in dosage, the T. Bil level began to vary from 4.0 to 10.0 mg/dl. In the third examination of ERCP on September 1977, the common bile duct was found to be markedly stenosed and the intrahepatic bile ducts became more irregular (Fig. 1).

The patient was kept on steroid therapy, but the effect on jaundice was not well. Since

Table 2. Changes of serum chemistry in the clinical course.

	'75/11/25	'77/ 6/17	'79/ 6/ 5	'79/ 9/18	'80/12/23	'81/ 5/12
RBC	381×10^4	263×10^4	352×10^4	392×10^4	333×10^4	$361\times10^4/mm^3$
WBC	6800	9200	16600	15800	10100	$9300/mm^3$
S. Prot	8.5	7.3	7.2	6.1	7.1	6.7g/dl
T. Bil	2.0	6.1	15.1	33.4	19.1	12.2mg/dl
Alb	3.3	2.4	2.9	2.4	2.3	2.5g/dl
Glob	5.2	4.9	4.3	3.7	4.8	4.2g/dl
ChE	0.75	0.39	0.60	0.48	0.41	0.59Δph
ALP (n: 16~48)	303	416	195	248	235	169u
Cholest	295	283	455	476	374	305mg/dl
GOT (n: 4~17)	46	67	44	112	63	69u
GPT (n: 4~17)	46	48	45	58	38	69u
γ-GTP	258	269	215	398	161	188u

Fig. 1 Schemas of ERCP on September 1977 (left), in which the common bile duct was stenosed and peripheral bile ducts became more dilated and irregular, and PTC on June 1979 (right), in which intra-hepatic bile ducts markedly stenosed and hardly demonstrated.

the stenosis of the common bile ducts was below the cystic duct of gall bladder, cholecyst-jejunostomy was considered to improve jaundice. On March 1978, she was transferred to the department of surgery. In this operation, the lesion of common bile duct was confirmed to be a fibrous stenosis, because open liver biopsy revealed proliferation of connective tissue around bile ducts but a little change in parenchyma of the liver. At about 3 months after cholecyst-jejunostomy, the serum T. Bil level was decreased to 2.4 mg/dl.

In December 1978, however, the serum T. Bil rose to 16.6 mg/dl suddenly with symptoms of cholangitis such as abdominal pain and fever. After administration of antibiotics jaundice subsided temporarily, but serum levels of T. Bil were kept over 14.0 mg/dl. On June 1979, a PTC study showed a marked stenosis of intrahepatic bile ducts so that appearances of biliary tree were by far more irregular and tortuous, and peripheral bile ducts were hardly demonstrated (Fig. 1). Blood chemistry showed elevated serum T. Bil (15.1 mg/dl), biliary enzymes and cholesterol. Although the patient was given steroid preparation and antibiotics, the serum T. Bil was gradually increased to 33.4 mg/dl on September 1979 (Table 2). Since then, T. Bil levels fluctuated from 20.0 to 30.0 mg/dl.

As the hyperbilirubinemia continued for about one year, the patient was initiated a high-dose administration of cholegogue agent (Cospanon 640 mg/day) from August 1980. Soon after the treatment, the T. Bil level decreased from 21.0 to 11.2 mg/dl. However, the serum T. Bil rose again to 19.1 mg/dl on December 1980 (Table 2), when the dose of Cospanon was withdrawn to a regular dosage (320 mg/dl). Since the serum T. Bil level showed no tendency to decline in spite of medical and surgical therapies, we resorted to secretin for the improverment of jaundice which has been demonstrated to have a potent effect on choleresis. Secrepan® (Eisai Co., Ltd., Tokyo, Japan), which is a secretin

preparation extracted from porcine intestine, was administered intravenously in a dose of 150 units (3 ampoules) a day mixed with 500 ml of 5% glucose solution. As shown in Fig. 2, when the dose of Secrepan was increased to 200 units (4 ampoules), the T. Bil level decreased to 13.6 mg/dl and became stable at about 14.0 mg/dl in May 1981.

When the administration of Secrepan was discontinued following a gradual reduction in dosage, the serum T. Bil elevated steeply again to 25.6 mg/dl. Then, the treatment of Secrepan was resumed in a dose of 200 to 250 units daily (4 to 5 ampoules), and the T. Bil level decreased to 12.1 mg/dl. When daily dosage of Secrepan was increased to 5 ampoules, the serum GOT level elevated to 220 unit and also T. Bil level rose to some extent (Fig. 2). This liver dysfunction means that 5 ampules was overdose and 4 ampoules was appropriate. Increased bile secretion due to Secrepan caused the injury to hepatocyte, judging from PTC findings of biliary stenosis.

Although jaundice of the patient was stabilized by the secretin therapy, a treatment by the plasma exchange was considered for a further reduction of the serum T. Bil level. On October 1981, five sessions of plasma exchange were performed. After that, the serum level of T. Bil temporarily declined to 6.5 mg/dl, however, it was increased to 26.0 mg/dl again. Soon after the readministration of Secrepan, the T. Bil level was decreased to 17.0 mg/dl.

As the general condition of the patient did not change and no side effect was detected over a long period of secretin therapy, she hoped to return to her house and discharged from our hospital on March 1982. At about three months later she had a severe hematemesis and died suddenly. Her clinical course of PSC with apparent jaundice counted 6 years and 8 months.

In Table 3, statistical analysis of difference (Student' s t-test) for serum levels of T. Bil (mean value) between the period of secretin therapy (December 1980 through June 1981) and the preceding period of steroid therapy (September 1979 through August 1980) was shown. Mean value of the serum T. Bil was significantly lower during the period of secretin as compared with that of the period of one year before. It appears that secretin therapy was effective for jaundice even to the patient with terminal PSC.

Discussion

Primary sclerosing cholangitis is a liver disease of unknown etiology which is char-

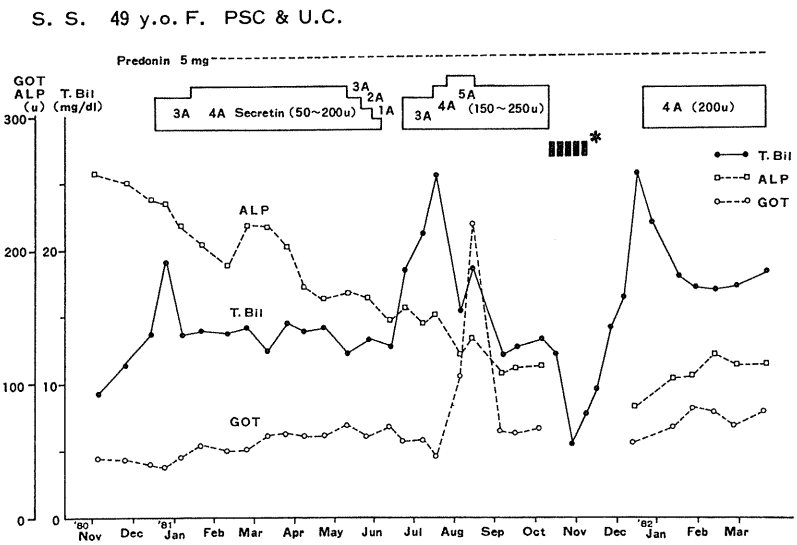

Fig. 2 Clinical course of secretin therapy in November 1980 to March 1982. (* plasma exchanges)

Table 3. Effects of secretin in the serum bilirubin level.

Serum total bilirubin (mean ± S.E.)		
Steroid treatment (Sep. 1979 to Aug. 1980)	20.1±6.8 mg/dl	* P<0.05
Secretin treatment (Dec. 1980 to Jun. 1981)	14.4±2.6 mg/dl	

* statistical significance determined by Student's t-test comparing Steroid with Secretin treatment.

acterized by a chronic biliary inflammation and fibrosis. It was described by a French surgeon Delbet as an obliterated cholangitis in 1924 for the first time.[6] PSC is a rare disease, but in recent years the number of case reports was increasing with a progress of the diagnostic method, such as ERCP. According to the summarized report about Japanese PSC patients by Ichida,[7] there were 37 originally published cases and 64 presented in medical meetings in the period of 20 years from 1965 through 1984.

In 1958, Schwartz et al.[8] designated this syndrome as PSC and proposed the following diagnostic criteria. They were ① absence of biliary stones; ② no prior biliary surgery; ③ chronic inflammatory thickening of the extrahepatic bile ducts; and ④ exclusion of biliary tumors. And, in 1967, Thore et al.[9] reported 4 cases of PSC complicated by ulcerative colitis and pointed out that the biliary stenosis was seen in both extrahepatic and intrahepatic bile ducts.

Moreover, in 1970, Meyers et al.[10] showed more strict diagnostic criteria: ① progressive jaundice of the obstructive type, ② absence of biliary calculi, ③ no prior biliary surgery, ④ generalized thickening and stenosis of the biliary ductal system, ⑤ absence of malignancy determined by a reasonable long follow-up, ⑥ no evidence of primary biliary cirrhosis as determined by liver biopsy, ⑦ absence of associated disease (ulcerative colitis, regional enteritis or retroperitoneal fibrosis, etc.). On the other hand, in 1984, LaRusso et al.[11] called the syndrome as Primary Sclerosing Cholangitis with regardless of a complication of ulcerative colitis, and designated the same syndrome due to obvious biliary calculi or stenosis after biliary surgery as Secondary Sclerosing Cholangitis. This criterion which was intended to broaden the diagnostic range for PSC has widely been supported now.

Our patient, which was accompanied by ulcerative colitis, fulfilled both diagnostic criteria by Schwarzt and LaRusso. The complication rate of ulcerative colitis in PSC has been reported to be 46% or 70% in Western countries.[2,3] In Japan, Ito et al. reported two PSC patients with ulcerative colitis out of 54 cases.[12] The rate of complication with the colitis in Japan seems to be lower than that in Western countries.

PSC patients were classified into asymptomatic and symptormatic types by Weisner et al..[13] But, asymptomatic cases eventually become symptomatic in which cholestatic jaundice and itching develop. According to Lebovics et al.,[14] 41% of 29 cases with symptomatic PSC died within 6.3 years or developed hepatic insufficiency. Taub et al.[15] also reported that 51% of symptomatic patients died within 9 years.

On the other hand, there are some reports that the clinical course of PSC is not necessarily poor. Helzberg et al.[16] observed 11 patients with asymptomatic PSC for 37 months and found that they had no subjective symptomes throughout the course of observation. Twenty-seven patients diagnosed as nearly asymptomatic were followed for 4.4 years by Aadland et al. and were detected a little change in their hepatic function.[17] PSC patients without jaundice may have an uneventful course, but the prognosis of the patient aggravates rapidly when jaundice once manifested itself.

Therapy for PSC remains unsatisfactory despite many medical and surgical approaches. In Japan, PSC patients are often operated for the purpose of the differential diagnosis from biliary malignancy.[12] Surgical treatment of PSC is usually undertaken in the

following three ways. The first is a biliary tract reconstruction including the procedure which was performed in our patients. The next is a proctocolectomy for cases of PSC complicated with ulcerative colitis. The third is an orthotopic liver transplantation which may produce a curable effect, but the problem still remains such as the recurrence.[18,19] Although the liver transplantation may develop to save patients with PSC in the future, a necessity of the medical treatment by drugs is obvious.

Some therapeutic trials using drugs have been applied for PSC, but none of them could lead to remission. D-penicillamine decreased a copper content in the hepatocyte, but failed to inhibit the progression of this disease.[20] Immuno-suppressive agents, azathioprine, cyclosporine A, have been studied for effects on PSC. In a small control study for predonisone, there was no significant difference between treated group and placebo group.[21] But, in another report predonisone inhibited the histological progression over long periods of administration.[22] But, azathioprine was found to have no beneficial effects, and cyclosporine A also had same results.

In our case, corticosteroid could not produce any remarkable results, but secretin showed effects in the improvement of jaundice. Serum level of T. Bil was clearly reduced over period of 10 months during secretin administration in comparison to the level in a preceding period of the steroid therapy. We have already shown that secretin increased the bile flow in man, and found that the bile volume was elevated at about 3-times as compared to the basal flow.[4] In animal experiments, it was presumed that the choleretic effect of secretin resided in the production of bile flow from the bile duct epithelial cells accompanied with an increase of biliary bicarbonate concentration.[23,24] This reaction is considered to be an active secretion which mediated by the cyclic AMP system, when secretin acts on the receptor of the bile duct epithelium.[25] Concerning the effect of secretin to biliary bile acid excretion in man, the total bile acid excretion was increased after secretin administration, but the concentration of bile acid in bile was decreased. This may indicate that secretin has no direct effect on the bile acid excretion in bile.

Effects of biliary washout by secretin could be expected to improve a jaundice to some extent in patients with the terminal PSC such as marked biliary stenosis, judging from results in our patient. An optimal dose of Secrepan to PSC patients is not determined yet for a lack of experience. As serum levels of GOT, GPT and T. Bil were elevated in this case after an excessive dose of Secrepan, the dose should be established in an individual case according to data of blood chemistry.

Ursodeoxycholic acid (UDCA) is also a cholegogue agent which increases biliary bicarbonate concentration like secretin. Recently, Beuers et al.[27] used UDCA to patients with PSC and reported that serum level of T. Bil was reduced by 50% after one year administration of UDCA. But, sujects were mild PSC, where the level of serum total bilirubin was 0.8 to 1.9 mg/dl. Above all, it suggests that cholegogue agents are beneficial for PSC patients rather than immunosuppressive and/or metabolic ameliorate drugs.

This case was perhaps the first report to use secretin in PSC patient with persistent jaundice. Although secretin does not provide a curative therapy for PSC, it seems to be useful to suppress a progression of the liver disease before introduction of a curative therapy such as liver transplantation. Further studies must be undertaken to confirm secretin effects in large numbers of patients with PSC.

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