A Case of Primary Intrahepatic Sclerosing Cholangitis (PISC) Complicated with Atypical Biliary Epithelial Proliferation

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A 70-yr-old woman was admitted to our hospital with duodenal ulcer and anemia. The result of liver function test was abnormal and showed persistent elevated alkaline phosphatase levels. Thus, after recovery from duodenal ulcer, endoscopic retrograde cholangiopancreatography (ERCP) was performed; the characteristic "beaded" appearance with band-like strictures and saccular outpouchings affecting the intrahepatic biliary system were found. The diagnosis of primary intrahepatic sclerosing cholangitis (PISC) was made on the basis of the generally accepted diagnostic criteria of primary sclerosing cholangitis (PSC). However, the histological finding from a liver biopsy specimen revealed highly atypical epithelial proliferation of bile ducts. This case of PISC complicated with atypical biliary glandular changes is described, and the distinction between PISC and carcinoma of the bile duct is discussed. (Internal Medicine 31: 114–121, 1992)

Key words: intrahepatic, bile duct carcinoma

Introduction

Recently, wider usage of endoscopic retrograde cholangiopancreatography (ERCP) and greater clinical awareness have led to an increased frequency of diagnosis of primary sclerosing cholangitis (PSC). Thus, the number of cases reported annually have increased, although it is an uncommon disease in Japan. With the increased diagnosis of PSC, however, it can be expected that the distinction between sclerosing cholangitis and bile duct carcinoma will be more difficult. Here, we report a case of primary intrahepatic sclerosing cholangitis (PISC) complicated with atypical biliary epithelial proliferation.

Case Report

A 70-yr-old woman with a chief complaint of epigastric pain is reported. Unfortunately, we were not able to obtain details of her family history. Regarding her past history, she had a moderate degree of mental retardation, flexion articulatory contractures of the right elbow and wrist due to trauma at 3 yr of age, and duodenal ulcer at 68 yr of age with no previous surgery

nor history of choledocholithiasis. She had been anemic since February 1990, and treated as an outpatient with intravenous administration of an iron compound. Her anemia did improve, but again became worse with the symptom of epigastric pain. She was therefore admitted to our hospital on May 15, 1990.

On admission, she was of a small build, 132 cm in ht and 47 kg in wt. Her consciousness was clear. Her temperature was 36.4°C, blood pressure 160/80 mmHg, and pulse 78/min and regular. The conjunctive were anemic, but not icteric. The superficial lymph nodes were not palpable. A grade II/VI ejection systolic murmur was heard over the base of the heart. There was no other abnormal sign in the thorax. In the abdomen, there was tenderness in the epigastrium but muscle guarding and rebound tenderness were not present. Neither the liver nor the spleen was palpable. The legs were not edematous. No neurological abnormalities were present.

Laboratory findings on admission (Tables 1, 2).

Urinary findings were normal. Occult blood in feces was positive. The red blood cell count was $342 \times 10^4/\text{mm}^3$, Ht 26.3%, and Hb 8.2 g/dl. Erythrocyte sedimentation rate (ESR) was 34 mm/h, and C-reactive protein (CRP)

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Table 1. Laboratory Data on Admission

Urine		Blood chemistry	
Protein	(-)	TP	6.1 g/dl
Sugar	(-)	Alb	3.4 g/dl
Blood	(-)	T. Bil	0.77 mg/dl
Urobilinogen	normal	D. Bil	0.66 mg/dl
Stool		GOT	18 IU/l
Occult blood	(+)	GPT	16 IU/l
Hematological exam.		LDH	367 IU/l
RBC	$342 \times 10^4/\text{mm}^3$	Al-P	798 IU/l
Hb	8.2 g/dl	γ -GTP	319 IU/l
Ht	26.3%	Amylase	66 IU/l
WBC	$9,400/\text{mm}^3$	BUN	25.7 mg/dl
Ba 0% St 8% Seg 74%		Cr	1.1 mg/dl
Eo 0% Mo 2% Lym 16%		Uric acid	10.2 mg/dl
T cell 87% B cell 2%		Na	140 mEq/l
Plt	$33.8 \times 10^4/\text{mm}^3$	Cl	108 mEq/l
ESR	34 mm/h	K	4.5 mEq/l
CRP	0.7 mg/dl	Fe	41 $\mu\text{g}/\text{dl}$
Bleeding time	1 min 00s	Cu	92 $\mu\text{g}/\text{dl}$
Prothrombin time	12.8s (control 12.9s)	Ferritin	86 ng/ml
		Ceruloplasmin	28.3 mg/dl

Table 2. Laboratory Data during Admission

STS (-), TPHA (-)	HLA	A2, A11
HBsAg (-)		B5, B16
Tuberculin test 21 $\times$ 27 mm		CW7
Thyroid test (-)		DR4
Microsome test (-)	IC (CIQ)	<1.5 $\mu\text{g}/\text{ml}$
LE test (-)	Serum immunoglobulin	
Anti-nuclear antibody $\times 40$	IgG	1,870 mg/dl
Anti-SS-A antibody (-)	IgA	110 mg/dl
Anti-SS-B antibody (-)	IgM	421 mg/dl
Anti-mitochondrial antibody (-)	IgD	3.1 mg/dl
Anti-smooth muscle antibody (-)	IgE (RIST)	200 IU/ml
Anti-parietal cell antibody (-)	CEA	2.1 ng/ml

0.7 mg/dl.

The result of blood biochemical examinations revealed a significant alkaline phosphatase (Al-p) level of 798 IU/l and gamma glutamyl transpeptidase (γ -GTP) of 319 IU/l, each showing more than 3 fold the normal value. However, the serum bilirubin value was normal. The Al-P isozyme of hepatic origin was increased. Serum immunoglobulin G level was 1,870 mg/dl and immunoglobulin M level was elevated to 421 mg/dl. The ceruloplasmin level was within normal range. Anti-nuclear antibody was weakly positive, but anti-mitochondrial antibody was negative. Immune complex was negative by Clq solid-phase assay. Human lymphocyte antigen typing of this patient showed HLA-A2, -A11, -B16, -B5, and -DR4.

Upper gastrointestinal endoscopic findings. Reflux esophagitis was found mainly in the distal esophagus and consisted of longitudinal erosions and shallow ulcers on the edematous mucosa. Findings of esophageal and gastric varices were not present. In the gastric mucosa, there were irregular red patches of chronic gastritis. Active duodenal ulcer with a few coagula on its base was

shown in the proximal anterior wall of the duodenal bulb which was markedly deformed and stenotic.

Ultrasonographic findings (Fig. 1). Wall thickening of the extrahepatic bile duct was not present. Mild dilatation of the intrahepatic ducts was shown with slightly increased echogenicity of the biliary walls around the dilated lumens. Findings of the bile ducts in the left lobe were not obtained due to the presence of bowel gases. The gallbladder wall was slightly thickened with an increased echogenicity, and the boundary was not clear.

Computed tomography (CT) findings (Fig. 2). The

Fig. 1. Sonogram shows mild and irregular dilatation of bifurcating intrahepatic bile ducts, and a slightly thickened gallbladder wall.

Fig. 2. Plain CT demonstrates marked dilations of the bile ducts in the left lobe, while focal areas of minimal or mild dilatation are shown in the bile ducts of the right lobe, producing a "beaded" appearance.

liver was atrophic and Chilaiditi's syndrome was a complication. Focal, discontinuous areas of mild intra-hepatic biliary dilatation were found with no associated mass lesions in the right lobe of the liver, while more prominent biliary dilations were recognized in the left lobe which was in the shape of hemispherical masses with groove-like concavities between them.

Course after admission. The main medical treatment was administration of an H₂-receptor antagonist and coating agents for duodenal ulcers. Barium enema and colonoscopy (CFS) were concurrently performed to exclude ulcerative colitis as the cause of anemia. This was because she had bloody diarrhea in April 1989, and proctoscopic examination had shown diffuse redness of the mucosa. Barium enema showed a smooth, "lead-pipe" appearance of the left side of the colon with a decreased mucosal pattern. However, CFS revealed no inflammatory findings. The histology of the biopsied specimens from the rectum indicated mild inflammation of the mucosa with goblet cell depletion. She was suspected of chronic ulcerative colitis with remission.

Because the liver function tests continued to show abnormal results, ERCP was performed on June 11, 1990 after she recovered from duodenal ulcer. The findings of pancreatic ducts were not abnormal; however, the intrahepatic bile ducts were found to have irregular luminal dilations with a "beaded" appearance in some areas (Fig. 3). From the oblique view, the branch of the lateral segment in the left lobe of the liver showed marked dilatation and an area of stenosis in its distal portion (Fig. 4). Thus, surgical open biopsy was done to exclude cholangiocarcinoma, albeit on suspicion of PISC. From the macroscopic view, the left lobe of the liver was atrophic with hemispherical shaped appearances on its antero-inferior surface of the lateral segment. The liver surface was nearly smooth with small depressions; the color was not greenish, but reddish brown with a

white tint (Fig. 5). The histological examination of the biopsy specimen from the left lobe revealed that there was an enlargement of the portal tracts accompanied by a formation of fibrous septa, though it had not yet developed into cirrhosis. There were a few copper deposits demonstrated by orcein stain in the periportal parenchyma (Fig. 6). No centrilobular bile stasis nor a bile lake was observed. In the portal tracts, there were periductal fibrosis and inflammation without granulomatous lesions, some bile duct obliteration, and mild to moderate inflammatory infiltrates consisting mainly of lymphocytes and neutrophils (Fig. 7). In addition to fibrous-obliterative cholangitis, the epithelial cells of the interlobular and septal bile ducts focally appeared highly atypical with abnormal polarity and stratification, similar

Fig. 4. The oblique view of ERC shows the bile duct of the lateral segment distending to a marked degree (0.8 cm in diameter) in the presence of stenosis downstream.

Fig. 3. ERC reveals irregular luminal dilations and strictures of bile ducts with "beaded" appearances.

Fig. 5. The left lobe of the liver, by surgical open biopsy, is atrophic with spherical shaped appearances and a groove-like concavity on the surface of the lateral segment.

Fig. 6. Minimal copper deposits in the periportal parenchyma are shown with orcein stain ($\times 200$).

Fig. 8. Highly atypical epithelial proliferation of the interlobular bile duct is noted with abnormal polarity and stratification ($\times 400$, hematoxylin and eosin stain).

Fig. 7. Periductal fibrosis with degeneration of epithelial cells is shown in the portal tract with moderate degree of inflammatory infiltrates ($\times 100$, hematoxylin and eosin stain).

Fig. 9. ERCP with a balloon-tipped cannula more clearly reveals the finding of saccular outpouchings (arrow head) and band-like strictures (arrow).

to cholangiocarcinoma *in situ* (Fig. 8).

She was discharged on July 13, 1990 and followed up as an outpatient. Due to the histological findings in the surgical open biopsy results, she was re-admitted on October 2, 1990 for reassessment, and ERCP was performed again the next day. The second ERCP was carried out with a balloon-tipped cannula, so that a sufficient amount of the contrast material could be injected to fill peripheral bile ducts. As a result, the findings of very short, 1 to 2 mm in width, band-like strictures and saccular outpouchings were definitely shown on the cholangiogram (Fig. 9). Compared with the first ERCP, there was no change in the findings which were related to the bile duct of the lateral segment in the left lobe. Plain CT of the abdomen was performed 1 h after ERCP, when contrast was still clear in the bile ducts (Fig. 10). Several bile ducts were dilated focally, and did not continue centrally to the hepatic hilum. The

findings showed no signs of suspected malignancy.

She was discharged on October 8, 1990, due to personal reasons, and was followed up as an outpatient. Since the first consultation, more than 2 yr and 3 months ago, she has remained asymptomatic with no deterioration in the liver tests.

Discussion

Primary sclerosing cholangitis (PSC) was first reported in 1924 by Delbet (1). Particularly in the past decade, frequency of the diagnosis of PSC has been increasing. In Japan, about 100 cases have been reported in the literature following the first reported case of PSC in 1965 by Hayashida et al (2) until 1990 (3).

On the other hand, sclerosing cholangitis localized in

Fig. 10. Plain CT 1 h after ERCP yields an excellent contrast radiology comparable to that of ERCP.

the intrahepatic biliary tree was reported in 1966 by Hellstrom and Perez-Stable (4) in a patient who also had retroperitoneal fibrosis and disseminated vasculitis. Later, in 1969 Bhathal and Powell (5) described a 64-yr-old man with sclerosing cholangitis confined to the intrahepatic biliary tree, and characterized histologically by the replacement of most interlobular bile ducts by fibrous cords. They suggested that their case, together with nine histologically similar cases which had been labelled in the literature as "primary biliary cirrhosis (PBC)," represented not PBC but primary intrahepatic sclerosing cholangitis (PISC) as a distinctive entity.

Regarding the involvement of the bile ducts in PSC, both extra- and intrahepatic ducts are affected radiologically in about 80% and extrahepatic ducts alone in 20% of cases. Intrahepatic ducts alone are involved only in a small number of patients (6). In contrast, Kashiwara et al (3) and Helzberg et al (7) showed the involvement of intrahepatic bile ducts alone in 11 and 21% of patients, respectively. In Japan only 7 cases have been reported in the literature before 1990 (8–14).

Although the concepts of PSC and accordingly, the diagnostic criteria have been changing, it is not clear whether PISC may represent a separate disease caused by a different mechanism. We followed the diagnostic criteria described in 1984 by LaRusso et al (15) for PSC and it includes the following: 1) a twofold or higher elevation in the serum alkaline phosphatase level, 2) diffusely distributed multifocal strictures associated with irregularity and tortuosity of the extra- and intrahepatic bile ducts on cholangiography, 3) compatible findings characterized by fibrous-obliterative cholangitis on liver-biopsy specimens (16–18), and 4) neither previous bile duct surgery excluding simple cholecystectomy, nor previously documented choledocholithiasis. The present case fulfilled this criteria, except the extrahepatic bile duct was normal on the cholangiogram. First, the Al-P

level of 798 IU/l was more than 3 times the normal value. Secondly, the cholangiographic findings of a "beaded" appearance and a "diverticula-like outpouching," which are reported to be highly specific for PSC (15), were observed by ERCP using a balloon-tipped cannula to obtain adequate filling of the biliary tree. In making the final diagnosis of PSC, the pertinent cholangiogram and detailed evaluation of the biliary tree are critical (19, 20). In this connection, all the cholangiograms in the literature of PSC and the 1st ERCP here were not relevant, possibly because the contrast material was injected at a pressure too great to fill the peripheral bile ducts, resulting in leakage through the ampulla Vater due to the sclerotic and stenotic changes of the biliary tree. Thus, we thought that in order to obtain a high quality cholangiogram it is necessary to intubate an ERCP cannula deep enough into the common bile duct, or to use a balloon-tipped cannula after dilating the ampulla with a dilator catheter. Lastly, the histology showed obliteration of some bile ducts, changing into fibrous cords, that was described to be practically diagnostic for the hepatic manifestation of PSC (16). The microscopic findings in this case corresponded to the stage 3 according to the histological staging proposed by Ludwig et al (18).

Due to the increased use of ultrasonography (US) and computed tomography (CT) as one of the primary imaging methods to assess suspected biliary tract diseases, the number of reports concerning the evaluation and differentiation of PSC has also recently increased. The US findings included echogenic bands around the bile ducts representing wall thickening, and increased echogenicity of the gallbladder wall with irregular, luminal dilatation of the extrahepatic and the intrahepatic biliary tree (21–24). Although not striking, the US findings of the present case showed similar findings with the exception of the extrahepatic ducts. However, bile duct wall thickening is a non-specific finding that must be differentiated among neoplastic and inflammatory processes. Thus, it was useful in assessment of the compatibility of PSC rather than to obtain a definitive diagnosis. The CT findings of focal, discontinuous areas of minimal intrahepatic biliary dilatation are usually not seen in the more common forms of biliary obstruction due to tumor, stone, inflammatory mass, or other focal lesion, which are reported to be highly suggestive of PSC (25, 26). In addition to this, Teefey et al (26) reported that CT is a useful modality in the diagnosis of PSC to define its extent and to follow-up patients for potential complications such as portal hypertension or cholangiocarcinoma. We performed plain CT of the abdomen 1 h after ERCP; the bile ducts were still clearly outlined with the injected contrast material. In contrast to plain CT, the CT after ERCP yielded excellent contrast radiology of the biliary system and also illustrated the above-mentioned CT findings; moreover, it was useful to

physiologically diagnose the possible delay of contrast material clearance corresponding to the focal "hot spots" of cholescintigram with Tc-99m-labelled DISIDA (27). Recently, some of the laparoscopic findings suggestive of PSC reported to be hemispherical regenerative masses and a deep trench-like concavity on the surface of the liver (28). In this case, there were similar laparoscopic findings, and the CT findings also possibly corresponded to those findings.

As mentioned above, this patient was diagnosed as PISC. However, the findings of the liver from the surgical open biopsy showed highly atypical epithelial cells in areas of the interlobular and septal bile ducts, similar to carcinoma findings *in situ*. Consequently, it was necessary to differentiate whether the highly atypical glandular changes or the bile duct carcinoma developed secondarily on the basis of PISC or whether the bile duct carcinoma primarily existed and thus spread along the bile duct lumens giving a cholangiographic appearance similar to PSC.

To date, this patient has remained asymptomatic for over 2 yr of follow-up. PSC in earlier reports was characterized by progressive cholestatic jaundice, leading to liver failure and death (29). However, in accordance with the greater awareness of PSC and an increase in the rate of diagnosis, the natural history of PSC is now better understood and thus it has been suggested that PSC might not follow the severe clinical course as previously suspected (30, 31). Chapman et al (31) described 3 patients who, despite extensive involvement of the biliary tree, remained completely well without any treatment for 3, 7, and 15 yr. Helzberg et al (7) demonstrated that 75% of the patients were alive 9 yr after the diagnosis of PSC with 64% being asymptomatic and mildly symptomatic patients. On the other hand, a rare form of primary bile duct carcinoma which must be differentiated from PSC is the diffuse sclerosing form of cholangiocarcinoma. The diffuse sclerosing form may mimic PSC cholangiographically, and it comprises about 10% of cholangiocarcinoma, and its pathologic grade of malignancy is relatively high in all cases (32). The average duration of survival of diffuse sclerosing carcinoma is the shortest of all the forms, at about 3 months; the onset is invariably characterized by progressive jaundice and there is no surgical cure (32, 33). Moreover MacCarty et al (20) state that the band strictures or "diverticula-like outpouching" is not observed in patients with bile duct carcinoma, and that these changes are characteristic of PSC. In the present case, the asymptomatic period of over 2 yr, the cholangiographic observation of a "beaded" appearance, band-like strictures, and the marginal outpouchings without fine intraluminal irregularities, and additionally the focally apparent stenosis with marked dilatation in the proximal bile duct in the left lateral segment, all led to the diagnosis of PISC complicated with bile duct carcinoma rather than primary bile duct

carcinoma.

The increased frequency of bile duct cancer in patients with ulcerative colitis is well established. As for the possibility of complication with cholangiocarcinoma in relation to PSC, Coffey et al (34) supported the hypothesis that PSC predisposes bile duct carcinoma, by evaluating 68 cases with PSC in which 5 cases were complicated with cholangiocarcinoma. Conversely, according to Nichols et al (33), bile duct carcinoma is a relatively rare malignancy with an autopsy incidence of 0.01 to 0.45%, while 4 of 82 patients with biopsy proven bile duct carcinoma had the clinical diagnosis of PSC, of whom two had no clinical evidence of ulcerative colitis. Thus, they concluded that PSC by itself is a premalignant condition.

Recently, cholangiographic findings which suggest the development of cholangiocarcinoma in patients with PSC, were reported by MacCarty et al (35). These included markedly dilated bile ducts, the appearance of a polypoid mass, 1 cm or more in diameter, and progressive stricture formation or progressive ductal dilatation. Further, Teefey et al (26) indicated the significance of CT to provide valuable information about the complication of PSC including the superimposed cholangiocarcinoma. In the cholangiogram of the present case, the bile duct of the lateral segment was distended to a marked degree (0.8 cm in diameter), in the presence of stenosis downstream. Four months later, we performed ERCP again, however, no progression was shown. Therefore, in order to exclude superimposed cholangiocarcinoma in this case, it was necessary to surgically obtain the hepatic tissue rather than to exclude cholangiocarcinoma, as Chapman (36) emphasized, after a prolonged follow-up period. While the clinical and morphological findings of this patient seem consistent with PISC complicated with cholangiocarcinoma, this diagnosis can be accepted as definitive only after a longer follow-up period, owing to the patient's personal reasons.

In 1982 Ito et al (37), after reviewing 51 cases with PSC, indicated some differences between the clinical features reported in Japan and those from abroad. These included an older onset age (the average being 54 yr), less frequent association with ulcerative colitis (6%), and poor prognosis (average survival period being 13 months). Kumazawa et al (38) obtained interesting results after evaluating 59 reported Japanese cases. These were classified as either the intrahepatic dominant type or extrahepatic dominant type according to the degree of involvement of bile ducts in the cholangiographic findings. They indicated that the intrahepatic dominant type showed the following characteristics: 1) a predilection for younger individuals, 2) a clear female predominance, 3) a longer follow-up duration, and 4) less presentation of jaundice. These reports may demonstrate a variation in the natural history and pathology of PSC with different etiologies. A number of possible factors

have been suggested to have a role in the pathogenesis of PSC in which genetic and immunological factors have been reported to be important (39–42). Thus, the disease presentation may be not simple but rather heterogenous, as a result of the reaction of the bile duct to a heterogenous group of agents in the pathogenesis of PSC.

Conclusions

PSC is a rare disease in Japan, and PISC is considered to be an even rarer disease. In this case, PISC was diagnosed on the basis of the generally accepted diagnostic criteria of PSC. To our knowledge, this is the first reported case of PISC which was complicated with atypical proliferation of the bile duct epithelium. It will be necessary to carry out a more detailed investigation of PISC in a larger series in Japan.

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