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Primary sclerosing cholangitis in India

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Summary: Six patients with PSC have been diagnosed and followed up at a centre in Northern India for periods upto 4 years. They all presented with cholestatic jaundice and cholangitis, but one of them subsequently presented with variceal haemorrhage. Cholangiographic features were the most characteristic and included irregular narrowing and segmental dilatation of the biliary radicles giving them a beaded appearance. Treating them was most frustrating. Two of them died of hepatic encephalopathy, others have also continued to be sick during the follow-up. *Gastroenterol Jpn 1989;24:75–79*

Key Words: *Cholangiography, Cholestatic jaundice, Sclerosing cholangitis, Ulcerative colitis, Ultrasonography*

Introduction

Primary sclerosing cholangitis (PSC) is a well recognised clinical entity with distinct clinical, biochemical, histological and radiological features[1,2]. Most of the case reports and reviews on the subject have however, originated from western countries. Only one case report has been published to date from India[3]. Is it yet another disease that has a predilection for the affluent western societies? This prompted us to report our experience of 6 such cases of PSC diagnosed at the All India Institute of Medical Sciences, New Delhi.

Materials and Methods

During the period, May 1983 - March 1987, six patients were diagnosed as having primary sclerosing cholangitis on the basis of characteristic cholangiographic features (4 cases) and laparotomy findings (2 cases). Each of them was fully assessed clinically as well as with the help of laboratory, endoscopic and radiographic procedures, and then followed closely by us for different time periods. The details of their investigative and clinical data are given below.

Results

The ages of these patients ranged from 19 to 55 years with a mean of 36.1 years; four (66.6%) of them were below 30 years of age. Only one of them was female. The patients presented to our centre after a mean period of 31.1 months (range 8-84 months) following the onset of symptoms, which was insiduous in all cases. Jaundice was the presenting feature in four patients (66.6%) whereas pruritus and pain in the right upper quadrant of the abdomen were the initial symptoms in one patient each. The symptoms and signs of these patients are shown in **Table 1**. Jaundice, generalised weakness and moderate hepatomegaly were seen in all the patients. Episodic fever suggestive of cholangitis, right upper abdominal pain and pruritus were seen in about two-thirds of the patients. Even though splenomegaly was detected in half of the patients, only one patient had an episode of variceal haemorrhage. The mean size of

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Table 1 Clinical features of PSC

Clinical features	No.	%
Jaundice	6	100
Pruritus	4	66.6
Pain in abdomen	4	66.6
Fever	5	83.3
Lethargy & Fatigue	6	100
UGI bleeding	1	16.6
Features of hepatocellular decompensation		
a. Ascites, Oedema	2	33.3
b. Other features	0	0
Hepatomegaly	6	100
Splenomegaly	3	50
Extra hepatic manifestations:		
a. Ulcerative colitis	2	33.3
b. Pyoderma gangrenosum	1	16.6

(N=6)

Table 2 Laboratory parameters in PSC

Laboratory parameters	Mean value	Range
Haemoglobin (G/dl)	10.8	7.4 to 11.8
Total leucocyte count/cu mm	15,766	7,000 to 27,700
S. bilirubin-total (mg/dl)	8.0	3.0 to 26.6
conjugated	6.0	2 to 19.4
Serum alkaline phosphatase (KA units)	57	11 to 102
SGOT (Karmen units)	76	35 to 115
SGPT (Karmen units)	56	40 to 62
Total serum proteins (G/dl)	7.1	5.7 to 8.4
Serum albumin (G/dl)	4.0	3.0 to 4.4
Prothrombin time (seconds)	3.5	0 to 6

(n=6)

hepatomegaly was 4.5 cm below the right costal margin whereas in all the patients with splenomegaly the spleen was palpable less than 2 cm below the left costal margin. None of the patients had features of hepatocellular decompensation on presentation. However, two patients developed ascites and dependent oedema during the follow-up.

Features suggestive of ulcerative colitis were seen in 2 patients in whom a proctosigmoidoscopy and rectal biopsy confirmed the diagnosis. One patient with ulcerative colitis also had pyoderma gangrenosum. In one patient, the features of colitis preceded the onset of PSC by 4 years, whereas in the other the features appeared one year after the development of PSC.

The laboratory parameters are depicted in **Table 2**. All the patients had haematological evidence of 'chronic infection' in the form of low haemoglobin and polymorphonuclear leucocytosis. Serum bilirubin was always less than 10 mg/dl except in one patient in whom it was 26.6 mg/dl. Serum alkaline phosphatase was raised more than three-fold in all the patients except one in whom it was normal. Serum transaminases were moderately raised. Serum proteins were normal in all the patients and the prothrombin time (PT) was slightly prolonged in only two patients. None of the patients showed a positive LE cell phenomenon. Antimitochondrial antibody and HBsAg were absent in all of them.

Ultrasonographic findings were not significant. Only in two patients mild dilatation of the intrahepatic biliary radicles was seen with a slight dilatation of the common bile duct. However, the thickened, irregular hyperechoic wall of the common bile duct in one patient raised a strong suspicion for the diagnosis of PSC before cholangiography was contemplated.

Routine upper gastrointestinal endoscopy revealed the presence of esophageal varices in two patients (33.3%) one of whom bled from the varices at a later stage.

Needle liver biopsy was done in three patients. Extensive intracellular as well as canalicular cholestasis was observed in all the three patients. In one of them, a diagnosis of extrahepatic biliary obstruction was given because of which he was subjected to laparotomy in which the common bile duct was found extensively sclerosed and the liver grossly cirrhotic. In another however, a histologic suspicion of sclerosing cholangitis was made because of the paucity of bile ducts and the presence of inflammatory cell infiltration in the walls of the remaining biliary channels. The third patient simply had intrahepatic cholestasis.

Cholangiography was done in four patients–percutaneous transhepatic cholangiography in one and endoscopic retrograde cholangio-

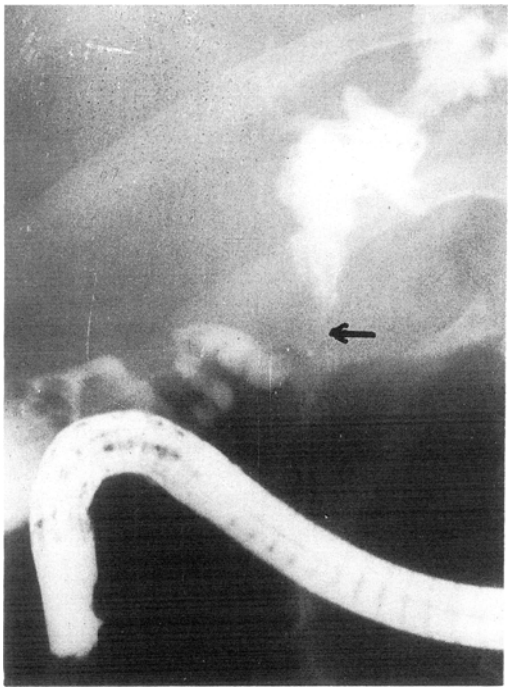

Fig. 1 Endoscopic retrograde cholangiography showing irregular narrowing of the common hepatic duct with proximal dilatation.

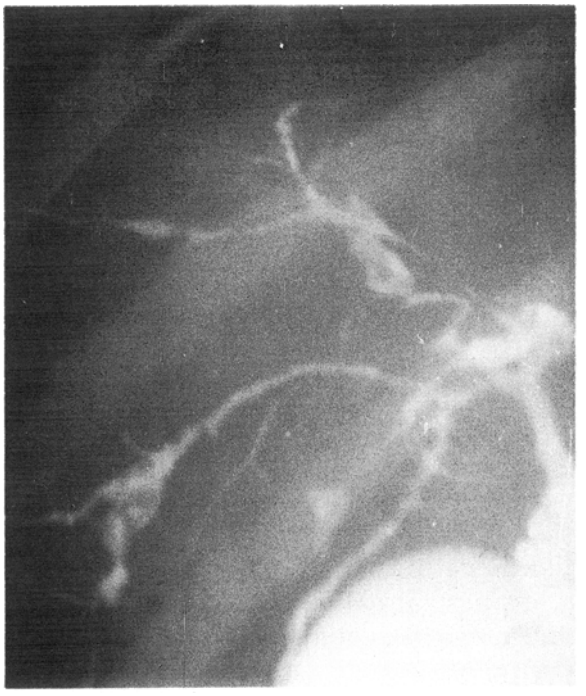

Fig. 2 Endoscopic retrograde cholangiography showing severe sclerosis and beading of intrahepatic biliary ducts.

graphy in three patients. Evidence of involvement of both intra and extrahepatic ducts was seen in three patients. In the fourth patient, only intrahepatic duct involvement was seen. Irregular narrowing with focal dilatation was the most common biliary channel abnormality (**Fig. 1**). Total sclerosis of the CBD and intrahepatic biliary ducts was seen in one case (**Fig. 2**). Gallbladder and pancreatic ducts were normal in all the four patients. The cholangiographic features in all these patients had suggested the diagnosis of primary sclerosing cholangitis. In the other two patients the diagnosis was made on laparotomy, in which the CBD was seen to be sclerosed throughout its length. The status of intrahepatic channels could however, not be assessed in these two patients. One of them also had cirrhotic changes in the liver. None of the patients had any evidence of choledocholithiasis on ultrasonography, cholangiography or laparotomy. Both these patients had left hepaticodocho-jejunostomy with jejuno-jejunostomy.

The two patients who had undergone laparotomy were unfortunately lost to follow-up. The remaining four patients were followed up from 6 months to 4 years (6 months, 6 months, 3 years, 4 years). Two of them died due to hepatocellular decompensation and hepatic encephalopathy–one after 6 months and the other after 4 years of follow up. All these four patients were treated with prednisolone 40-60 mg/day with azathioprine 50 to 100 mg/day and antibiotics as and when necessary, but none showed any improvement in liver function.

Discussion

PSC is known to be the disease of the young, 60% of the patients being below 40 years of age[1-4]. Most of our patients were below the age of 30 years. Males out-number the females in all the series[1], as in the present one. The patients of PSC invariably are symptomatic for about 2 years before the diagnosis is made[4]. In our patients however, more time (mean, 31 months)

had elapsed after the onset of symptoms before a diagnosis of PSC could be made. Such a delay in diagnosis in India is obviously because of lack of wide awareness of the disease and the limited availability of the cholangiographic techniques.

The clinical presentation of our patients comprised of cholestatic jaundice with fluctuations, episodes of cholangitis, right upper abdominal pain, a moderate tender hepatomegaly, frequently encountered minimal splenomegaly with infrequent association of hepatocellular decompensation and variceal haemorrhage. PSC is well known to present in three forms[1,2,5] (a) cholestatic jaundice with fluctuations and cholangitis (b) cryptogenic cirrhosis or chronic active hepatitis with portal hypertension and (c) asymptomatic. The first form of presentation is the most frequent. Indeed, all our patients initially presented with cholestatic jaundice and attacks of cholangitis. Only one patient had variceal haemorrhage although two patients had esophageal varices on endoscopy.

Ulcerative colitis is the disease most commonly associated with PSC (54-74% cases)[1,2]. Two (33%) of our patients had ulcerative colitis confirmed by proctosigmiodoscopy and rectal biopsy. Usually the bowel disease preceeds the cholangitis[5] but in one of our patients the features of ulcerative colitis succeeded the manifestations of PSC. Pyoderma gangrenosum was also seen in one of our patients with ulcerative colitis.

Laboratory tests are not diagnostic. They only indicate the presence of cholestatic jaundice and infection as seen in our patients in the form of raised bilirubin and serum alkaline phosphatase (markedly in 5 patients) and moderately raised serum transaminases, and in that of low haemoglobin and marked leucocytosis. The clinical suspicion of obstructive jaundice was logically followed by ultrasonography in our patients. That did not show the classical dilated intrahepatic biliary radicles. However, in two patients a minimal dilatation of the biliary radicles was seen and in one patient the CBD was irregular, thick walled and dilated, which again was not a specific feature for PSC on ultrasonography. Ultrasonography is therefore not helpful unless the clinical suspicion is high or the latter set of findings are obtained, in either of which case ERCP should be done. In the absence of these however, a negative ultrasonography would be followed by a liver biopsy which is known to provide a variable histological picture in PSC, ranging from intrahepatic cholestasis to cirrhosis of the liver[1-5]. In fact, of three patients in whom liver biopsy was done, only in one was a diagnosis of PSC suspected. Thus, the rational approach in such cases of long-standing cholestasis with cholangitis in whom ultrasonography has not shown the classical features of obstructive jaundice, should be to do a cholangiographic study. Four of our patients had cholangiography and in three of them both extra and intrahepatic biliary radicles were involved with characteristic irregular narrowing and segmental dilatation giving a beaded appearance. In the fourth patient only intrahepatic radicles were involved. In the remaining two patients laparotomy revealed a sclerosed thickened common bile duct, and cirrhosis of the liver. Even though the status of intrahepatic biliary radicles could not be known, the presence of cirrhotic changes in the liver of these patients made us believe that very likely intrahepatic ducts must be involved. Involvement of both intra and extrahepatic biliary ducts at the time of presentation is encountered in 90-95% of the patients with PSC[1,2,6,7]. Isolated involvement of the biliary radicles is a rare feature. The maximum brunt of the disease is at the hilar biliary radicles[1-4,6,7]. In all the three patients with intra and extrahepatic biliary channel involvement in the present series, the hilar radicles were grossly irregular and narrow, with focal dilatation, confirming the characteristic changes described in the literature. None of the patients in our series had pancreatic and gallbladder involvement which is encountered in 7-10% of the cases[1,2]. It is presumed that the disease process in PSC starts in the intrahepatic biliary radicles[2]. However, only serial cholan-

giographic follow-up in patients with isolated intrahepatic biliary channel involvement can answer this question. Unfortunately, the only patient who had an isolated involvement of intrahepatic biliary channels died of hepatic encephalopathy after 6 months of follow up.

Therapy in these patients has remained unsatisfactory[1,2]. The use of corticosteroids[8], immunosuppressive agents[9], cholestyramine[10] and long term antibiotics[6] has been of no avail. One prevailing and promising therapeutic approach is a combination of surgery and interventional radiology[2]. Another one is percutaneous transhepatic biliary dilation or irrigation of biliary three[11-14] and more recently, endoscopic sphincterotomy followed by balloon dilation or stent placement[15]. The prognosis is gloomy although variable[1-4]; the survival after clinical detection is between 2 and 10 years[16]. Although long asymptomatic periods are known to occur in PSC, in none of our patients we encountered a complete symptom-free interval. On the other hand, 2 out of 4 patients in our follow-up expired, hepatocellular failure being the cause of death in both. Both of them had gone to the stage of cirrhosis. To expect any possible improvement in the outcome of patients with PSC, early diagnosis and intervention are necessary and for that an awareness of its clinical as well as cholangiographic features.

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