Chronic pancreatitis: a cause of cholestasis¹

J. SCOTT, J. A. SUMMERFIELD, E. ELIAS, R. DICK, AND
SHEILA SHERLOCK

From the Departments of Medicine and Radiology, Royal Free Hospital, London

SUMMARY The bile ducts were visualised using endoscopic retrograde cholangiopancreatography (ERCP), percutaneous or intravenous cholangiography in 38 patients with non-gallstone chronic pancreatitis. Stenosis of the intrapancreatic portion of the distal common bile duct was demonstrated in 11 patients. Ten of the 11 developed transient cholestasis during exacerbations of their chronic pancreatitis. In six cholestasis eventually persisted requiring surgical relief. Secondary biliary cirrhosis was present in one patient. No evidence of pancreatic carcinoma was found in the patients explored surgically. Ten of the patients are alive more than one year after diagnosis. Chronic pancreatitis was of alcoholic aetiology in 10 of the patients with biliary stenosis. Cholestasis and biliary stricture are common but poorly recognised complications of non-gallstone chronic pancreatitis, especially when pancreatitis is severe and due to alcohol.

Although extrahepatic biliary obstruction is a well known presenting feature of pancreatic carcinoma (Sherlock, 1975), it is not recognised as a common complication of chronic pancreatitis in the absence of gallstones. Hitherto it has not been possible, without surgery or necropsy, to delineate the anatomy of the distal common bile duct and pancreatic duct in patients with non-gallstone pancreatitis, who are jaundiced (DuVal, 1957; Weinstein *et al.*, 1963; Marks *et al.*, 1968; Owor, 1972; McCollum and Jordan, 1975; Snape *et al.*, 1976). The advent of endoscopic retrograde cholangiopancreatography (ERCP) (Kasugai *et al.*, 1972a, b) and Chiba needle percutaneous cholangiography (Okuda *et al.*, 1974) have allowed this to be done.

The morphology of the bile ducts was assessed in 38 patients with non-gallstone chronic pancreatitis. In 11 of them stenosis of the intrapancreatic portion of the distal common bile duct was demonstrated.

Methods

Thirty-eight patients with non-gallstone chronic pancreatitis were studied by means of ERCP (30 patients), Chiba needle percutaneous cholangiography (two patients), and infusion cholangiography (six patients).

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In conformity with the Marseilles symposium on pancreatitis (Perrier, 1964) chronic relapsing pancreatitis was defined as an exacerbation of abdominal symptoms in a patient known to have pancreatic insufficiency; and chronic pancreatitis as pancreatic insufficiency without acute exacerbations.

Cholestasis was defined by a serum bilirubin level greater than $50 \mu\text{mol l}^{-1}$ (normal range 5-17) with serum alkaline phosphate greater than 30 KA units dl^{-1} (normal range 3-13) (Sherlock, 1975) and liver histology consistent with obstruction of the large bile duct (Scheuer, 1973). Persistent cholestasis was defined as cholestasis lasting more than four weeks.

The diagnosis of chronic pancreatitis was established by pancreatic histology from surgical biopsy or necropsy (Nakamura *et al.*, 1972; Baggenstoss 1973), or by the presence of two or more of the following abnormalities: (1) pancreatic calcification (Sarles, 1974) shown on anteroposterior and lateral plain radiographs of the abdomen; (2) abnormalities of the pancreatic ducts characteristic of chronic pancreatitis (Kasugai *et al.*, 1972b; 1973; Rohrmann *et al.*, 1974); (3) abnormal ⁷⁵Se-selenomethionine pancreatic scanning (Bouchier *et al.*, 1972) and diminished duodenal tryptic activity after a standard Lundh test meal (James, 1973) assessed by measurement of radioselenium in duodenal aspirate (Youngs *et al.*, 1971).

The radiology of the pancreas and of the biliary tract was assessed blind by three experienced

observers. Chronic pancreatitis was classified by the criteria of Kasugai (Kasugai *et al.*, 1973) as minimal, moderate, and advanced, and defined as dilatation and irregularity of the main pancreatic duct and branch ducts.

Results

PATIENTS WITH BILIARY STENOSIS

Eleven patients with chronic pancreatitis were found to have distal common bile duct stenosis with or without cholestasis. The aetiology of chronic pancreatitis was alcoholic in 10 of these patients.

Clinical course (Table 1)

Repeated attacks of cholestasis occurred in nine patients in association with painful relapses of their pancreatitis. Cholestatic jaundice persisting for more than four weeks developed in five of these patients and was the presenting feature in a sixth. The eleventh patient had distal common bile duct stenosis but had never had cholestatic jaundice.

Five of the six patients who came to surgery are well more than one year afterwards. One patient died three weeks after surgery from a pancreatic abscess. Choledochojunostomy was the surgical procedure of choice. The remaining five patients, who had presented with transient cholestasis during the relapses of chronic pancreatitis, have remained well for more than one year. Four of these patients were alcoholic and have now stopped drinking.

Evidence of chronic pancreatitis

The data on which the diagnosis of chronic pancreatitis was established are presented in Tables 2 and 3. Attacks of upper abdominal pain occurred in 10 patients and were associated with a raised serum amylase in five of them. Oral glucose tolerance was impaired in seven patients and faecal fat excretion

exceeded 6 g/24 h in eight patients. Pancreatic scanning was abnormal in all patients. Tryptic activity was reduced in the four patients in whom it was measured. Three patients had pancreatic calcification on plain radiographs of the abdomen. In nine patients endoscopic retrograde pancreatography showed irregularity and tortuosity of the main pancreatic duct and its secondary radicles consistent with the presence of moderate to advanced chronic pancreatitis (Figs. 1 and 2b). Two patients had pancreatic cysts (Fig. 3) in addition to the duct changes of chronic pancreatitis. Another patient had a pseudocyst communicating with the main pancreatic duct. The pancreatic duct was normal in one patient. The diagnosis of chronic pancreatitis was confirmed histologically in four patients, in whom there was no evidence of pancreatic carcinoma.

Evidence for extrahepatic biliary obstruction (Tables 2 and 3)

Ten patients had extrahepatic cholestasis. Nine of them had had one or more episodes of transient cholestasis. Liver biopsy showed histological features consistent with large duct obstruction in six patients. Secondary biliary cirrhosis was present in one patient and alcoholic cirrhosis in another. Liver biopsy was not performed in three patients. Stenosis of the intra-pancreatic portion of the distal common bile duct (Figs. 1, 2a, and 3) was demonstrated by endoscopic retrograde cholangiography (seven patients), Chiba needle percutaneous cholangiography (two patients), and infusion cholangiography (two patients).

PATIENTS WITHOUT BILIARY STENOSIS

Twenty-seven patients had non-gallstone chronic pancreatitis without cholestasis. The aetiology was alcoholic (13 patients), cystic fibrosis (one patient), type IV hyperlipoproteinaemia (one patient), and nutritional (one patient of East African origin). No

Table 1 Clinical data: 11 patients

Patient	Age (yr)	Abdominal pain	Pruritis	Cholestasis	
				Transient attacks	Persistent
1	38	+	++	5	+
2	62	+	++	2	+
3	55	+	++	0	+
4	62	+++	○	0	○
5	29	++	++	2	+
6*	53	+	○	2	+
7	43	++	++	3	+
8	45	+	○	2	○
9	47	+	○	3	○
10	51	○	+	4	○
11	52	+	○	1	○

*Non-alcoholic chronic pancreatitis.

Table 2 *Biochemical data: 11 patients*

Patient	Serum				Oral glucose intolerance	Faecal fat excretion (g/24 h)	Tryptic† activity
	Bilirubin $\mu\text{mol l}^{-1}$ *(n.r. 5-17)	Alkaline phosphatase KAU dl^{-1} (n.r. 3-13)	Aspartate transaminase IU l^{-1} (n.r. 4-15)	Amylase IU l^{-1} (n.r. 150-350)			
1	310	37	49	273	+	18	
2	155	30	27	160	+	15	↓
3	10	34	18	270	+	40	
4	10	11	15	600	+	8	
5	95	32	23	340	○	8	↓ ↓
6	85	28	31	350	○	—	
7	100	31	110	555	○	6	
8	30	27	50	220	+	7	↓ ↓
9	60	36	33	400	+	10	
10	52	35	23	750	+	—	
11	60	32	20	390	○	7	↓

*n.r.: normal range values.

†Assessed in patients indicated.

Table 3 *Scanning, radiology, histology: 11 patients*

Patient	Abnormal pancreatic scan	Radiology		Histology	
		Common bile duct	Pancreas	Liver	Pancreas
1*	+++	DS	CP	EHBO*	CP
2*	+++	DS	Calcification CP	EHBO	Calcific pancreatitis
3*	+++	DS	Calcification CP cyst CP	Secondary biliary cirrhosis Cirrhosis	Calcific pancreatitis
4	++	DS	CP	—	—
5*	+	Stenosis cyst lower common duct	Calcification CP	—	—
6*	+	DS	Pseudocyst	EHBO	CP
7	+	DS	CP	—	—
8*	+	DS	CP	EHBO	—
9	++	DS	CP cyst	EHBO	—
10	+	DS	CP	EHBO	—
11	+	DS	Normal duct	—	—

*Laparotomy performed.

EHBO: histology associated with extrahepatic biliary obstruction. DS: distal stenosis. CP: chronic pancreatitis.

Fig. 1 (Patient 1) There is stenosis of the distal third of the common bile duct (arrowed). The main pancreatic duct is dilated and irregular.

Fig. 2 (Patient 2) (a) There is a smooth narrowing of the lower third of the common bile duct (black arrow). Calcification (white arrow) is present in the head of the pancreas. (b) The main pancreatic duct is tortuous, irregular and dilated.

Fig. 3 (Patient 3) There is marked narrowing (black arrow) of the distal common bile duct. A short length of irregular, main pancreatic duct ends in a small cyst. Calcification is present in the head of the pancreas (white arrow).

cause was found in the other 11 patients. Twenty-five of the patients without cholestasis had minimal to moderate chronic pancreatitis. In only two patients were changes advanced.

None of these 27 patients had serum bilirubin levels greater than $25 \mu\text{mol l}^{-1}$. Two of the patients had raised alkaline phosphatase levels of 18 and 21

KA units dl^{-1} . Cholangiography was normal in all 27 patients: and none of those in whom liver biopsy was performed had evidence of mechanical cholestasis.

Discussion

Cholestasis is said to complicate non-gallstone chronic pancreatitis in 3 to 25% of patients (Comfort *et al.*, 1946; Coffey, 1954; Bockus *et al.*, 1955; DuVal, 1957; Owor, 1972). In our series 11 of the 38 patients (27%) with non-gallstone chronic pancreatitis had evidence of extrahepatic biliary obstruction. All except one of our patients with cholestasis had alcoholic chronic pancreatitis. The high frequency of biliary complications in our series probably reflects the special role of the Royal Free Hospital as a referral centre for the assessment of hepatobiliary disease, but is also likely to result from an increased facility in demonstrating the pathological anatomy of this complication by use of ERCP and Chiba needle percutaneous cholangiography.

Distal common bile duct stenosis was shown by ERCP, Chiba needle percutaneous or infusion cholangiography to be the anatomical basis for both recurrent and persistent cholestasis. The anatomical basis for the transient jaundice occurring during exacerbations of non-gallstone chronic pancreatitis has not previously been adequately demonstrated (Weinstein *et al.*, 1963; Snape *et al.*, 1976; Warshaw *et al.*, 1976). It has been variously attributed to such causes as bile duct compression (Weinstein *et al.*, 1963; Snape *et al.*, 1976; Warshaw *et al.*, 1976), parenchymal liver disease (Beckett, *et al.*, 1961; Goldberg and Thompson, 1961), or gallstones which have been passed (Acosta and Ledesma, 1974).

Transient jaundice is probably the result of oedema

and swelling of the pancreas with compression of the bile duct in its intrapancreatic course. Persistent cholestasis complicates severe destructive chronic pancreatitis and has been shown, by dissection of surgical and necropsy specimens, to be due to cicatrization of the lower common bile duct within the head of the pancreas (DuVal, 1957; Weinstein *et al.*, 1963; Marks *et al.*, 1968; Owor, 1972; McCollum and Jordan, 1975). Prolonged persistent cholestasis was the cause of a secondary biliary cirrhosis in one of our patients.

The pronounced pancreatic duct changes which are demonstrated by ERCP have been shown to correlate most closely with severe deforming pancreatic pathology (Howard and Nedwich, 1971; Nakamura *et al.*, 1972). Such advanced disease is unusual in non-alcoholic chronic pancreatitis (James *et al.*, 1974; Sarles, 1974). In the western world, excessive consumption of alcohol is the most common cause of non-gallstone chronic pancreatitis (Dreiling *et al.*, 1964; Howat, 1968; James *et al.*, 1974). It is noteworthy that, of the 27 patients without cholestasis in our series, only two had advanced pancreatic duct abnormalities and only 13 admitted alcohol abuse.

In the management of the jaundiced alcoholic patient, needle liver biopsy in conjunction with ERCP or Chiba needle percutaneous cholangiography have proved useful in making the important distinction between alcoholic liver disease, benign biliary stricture, gallstones, and pancreatic carcinoma. Gradual tapering of the bile duct within its intrapancreatic course in association with the pancreatic duct changes of chronic pancreatitis is more characteristic of the benign stricture which may complicate chronic pancreatitis than of pancreatic carcinoma.

We conclude that cholestasis is a common but poorly recognised complication of severe alcoholic chronic pancreatitis and that ERCP and Chiba needle percutaneous cholangiography are useful techniques in demonstrating this association.

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