

PRIMARY SCLEROSING CHOLANGITIS

by

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PRIMARY sclerosing cholangitis is a rare disease of unknown aetiology in which progressive obliteration of the extrahepatic and often also the intrahepatic bile ducts occurs. Delbet¹ is generally credited with the first case report in 1924 and there are still only 100 cases in the literature.² The association with ulcerative colitis is well known.³ We report twelve cases of primary sclerosing cholangitis seen and followed up at the Royal Victoria Hospital during an eighteen-year period (1964-1982).

DEFINITIONS

The term 'primary sclerosing cholangitis' is used to describe non-traumatic benign fibrosis of the bile ducts causing thickening of the wall with consequent narrowing of the lumen. In recent years considerable controversy has arisen over the criteria to be used in diagnosis. The most stringent are those of Myers and his colleagues⁴ who list the following essential features: (1) progressive obstructive jaundice, (2) absence of biliary calculi, (3) no prior biliary surgery, (4) generalised thickening of the walls of the bile ducts, (5) the exclusion of cholangiocarcinoma by a long follow-up period, (6) no evidence of primary biliary cirrhosis on liver biopsy, (7) the absence of associated diseases such as ulcerative colitis, Crohn's disease and retroperitoneal fibrosis. However, others consider that these criteria are too rigid⁵ and may result in some true cases of sclerosing cholangitis being missed.^{5, 6} Dilatation of intrahepatic ducts, which usually occurs above traumatic strictures, is seldom seen in sclerosing cholangitis.⁷ Exclusion because of the presence of gallstones may prevent consideration of cases in which stones have formed secondary to sclerosing cholangitis.⁶ Cholangiocarcinoma may also pose a problem. Duct biopsy has been recommended^{6, 8} but well differentiated cholangiocarcinoma may have a low degree of malignancy and it may be difficult to distinguish the histological features from those of benign cicatrization. Prolonged survival can also occur in patients with cholangiocarcinoma while conversely some patients with primary sclerosing cholangitis die within a few years of the onset of the disease.^{5, 6}

It is generally agreed that patients with ulcerative colitis, retroperitoneal fibrosis and Riedel's thyroiditis should not be excluded from consideration as these conditions may be part of the same disease process.⁵

The criteria used in the twelve patients in this series have been the presence of diffuse or segmental sclerosis of the bile duct that could not be attributed to gallstones or previous biliary surgery, the exclusion of primary biliary cirrhosis by serological tests and where possible liver biopsy, and of cholangiocarcinoma by a reasonably long period of follow-up.

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DIAGNOSIS

Clinical Features

Ten of our twelve patients were male. The average age at the onset of symptoms was 42.5 years with a range of 19-69 years. The initial symptom in eight patients was abdominal pain which in four was typical of biliary colic. Two of the remaining four patients experienced a dull ache in the epigastrium and in the other two it was felt in the right upper quadrant. In three patients the initial symptom was obstructive jaundice with dark urine and pale stools while one patient experienced only pruritus. When the diagnosis of primary sclerosing cholangitis was confirmed, eleven patients had obstructive jaundice and in four of these the liver was slightly enlarged. Eight patients had pruritus, three had diarrhoea and in two weight loss was a major symptom.

In five patients a diagnosis of ulcerative colitis had been made on the sigmoidoscopic, radiological and histological findings four to ten years before the symptoms of sclerosing cholangitis commenced. One patient suffered from Raynaud's phenomenon and another was diabetic. One patient had several attacks of acute pancreatitis during the ten years prior to the diagnosis of sclerosing cholangitis and required drainage of a pseudocyst. One patient had a cholecystectomy four years before the diagnosis of primary sclerosing cholangitis was made. No gall stones were found but the operative cholangiogram showed slightly irregular extrahepatic ducts. One patient had a cholecystostomy when definite evidence of primary sclerosing cholangitis was demonstrated by the operative cholangiogram. One patient had required a laparotomy and cholecystostomy for a biliary leak following a diagnostic percutaneous needle liver biopsy.

One patient had a sister with ulcerative colitis, the father of another had pernicious anaemia and the mother of a third had diabetes mellitus.

Laboratory Investigations

All patients had a normal haemoglobin (mean 13.3 g), the W.B.C. was elevated in only three patients and in none was there eosinophilia. Erythrocyte sedimentation rate was raised in eight patients (mean 45 mm/hour Westergren). Serum bilirubin was elevated in eleven of the twelve patients (range 8-188 micromols/l; mean 63.3 micromols/l). There were minor increases in AST and ALT in all patients (AST range 44-173 U/l; mean 97 U/l). However, the predominant biochemical abnormality was a high serum alkaline phosphatase, present in all but one patient when first seen, the range being 125-1545 with a mean of 460 units/l (normal range 35-105 units/l).

Initial serum IgG and IgM levels were normal in all seven patients in whom they were estimated but six patients had elevated IgA levels (range 4.4-5.9 g/l, mean 4.80 g/l). Serum protein electrophoresis showed slightly reduced albumin in two patients, normal alpha₁ and gamma globulin levels, minor increases in alpha₂ globulin and an elevated beta globulin level in half the patients. Tests for antinuclear factor, smooth muscle antibody, antimitochondrial antibody, LE cells and Australia antigen were negative in all patients. Blood culture was repeatedly positive in one patient with recurrent cholangitis in whom Klebsiella were grown on culture.

Liver biopsy was carried out in five patients and features were suggestive of large duct obstruction with chronic inflammatory cell infiltrates. Some bile ductule reduplication was noted in two of the biopsies.

Radiology

The diagnosis of primary sclerosing cholangitis was made by percutaneous transhepatic cholangiography in nine patients, the typical narrowing and beading with segmental strictures being found. In one patient the diagnosis was made by ERCP which was unfortunately followed by ascending cholangitis. In the remaining two patients the lesions were demonstrated by operative cholangiography. Intravenous cholangiography was attempted in seven patients but only in one was the biliary tree satisfactorily visualised.

TREATMENT

Surgical Management

In two patients T tube drainage of the common bile duct was carried out prior to referral for definitive surgery. One patient underwent Longmire's procedure of left hepaticoduodenostomy. Four years later a distal splenorenal shunt was performed for portal hypertension and two years thereafter she required excision of a cystadenocarcinoma of the ovary which caused her death one year later. The other patient had a hepaticoduodenostomy (en-Y) and the anastomosis had to be refashioned four years later. Apart from four bouts of mild ascending cholangitis he has remained well on 10 mg of prednisolone daily. A further patient with a localised stricture of the common bile duct underwent a choledochoduodenostomy. This also required to be refashioned ten years later and apart from one attack of ascending cholangitis, he has remained well on 10 mg of prednisolone daily. Portal hypertension developed in four patients, one of whom required a distal splenorenal shunt for bleeding varices four years after the diagnosis of primary sclerosing cholangitis.

Medical Treatment

Eleven patients were treated with prednisolone, usually beginning with 15-25 mg per day, the dose then being gradually reduced to a maintenance level of 5-10 mg per day. Response to steroids was usually good with rapid clinical and biochemical improvement. One patient was also given azathioprine for a short period. Three patients received short courses of cholestyramine for pruritus with some improvement.

Side Effects

Three patients developed back pain due to osteoporosis and one suffered compression-collapse of a lumbar vertebra. Muscle wasting also occurred in these three patients. Two patients became hypertensive and one developed diabetes mellitus. Ascending cholangitis occurred in half of the patients and several had multiple episodes. In those patients who had bile culture, *E coli* or *Klebsiella* were the offending organisms. Response to treatment with tetracycline, ampicillin or a cephalosporin was usually rapid.

Response to Treatment

There have been four deaths. One patient died of renal failure and severe hepatic dysfunction four years after the initial diagnosis, one patient died of cirrhosis and ovarian carcinoma after ten years and another died of liver failure and portal hypertension after four years. The fourth patient, who had ulcerative colitis, developed a carcinoma of the colon which was successfully resected but died of an oat cell carcinoma of the lung four years after the diagnosis of sclerosing cholangitis.

The remaining eight patients are alive. Four are symptom-free, three have troublesome pruritus and one has a persistent biliary fistula. The period of follow-up ranges from 1-18 years, the average being 6.2 years.

DISCUSSION

Primary sclerosing cholangitis is a disease, the aetiology of which is at present unknown. Various causes have been suggested, including bacterial or viral infection, damage by gallstones and chemical injury by deconjugated bile salts. However the relative sparing of the mucosa casts doubt on these aetiologies and the most accepted theory at present is a disorder of immunity.⁵

In common with other series the majority of our patients were male with a wide age range when first seen.⁹ The usual presentation in the literature is obstructive jaundice,^{6, 8, 10} but in our patients abdominal pain was a frequent initial symptom. The association between sclerosing cholangitis and ulcerative colitis has been widely recognised^{3, 6, 8, 11} and sclerosing cholangitis is one of several forms of hepatic disorder that can occur with inflammatory bowel disease.¹² Recent data suggest that the prognosis of patients with ulcerative colitis and sclerosing cholangitis may not be as favourable as was originally thought.¹³ An association has also been noted with Crohn's disease,¹⁴ retroperitoneal fibrosis and Riedel's thyroiditis,¹⁵ but none of our patients had any of these conditions. The ESR was usually increased but few other haematological disturbances were found in our patients though others have reported lymphocytosis and eosinophilia.^{7, 10, 15} Biochemical analysis confirmed the obstructive nature of the jaundice with grossly elevated alkaline phosphatase levels being also a constant finding in other series.^{8, 9, 16} In common with others we found immunological screening to be negative in our patients although occasionally weakly positive SMA, AMA and ANF have been reported.^{9, 11} Immunological levels in sclerosing cholangitis are usually normal¹⁷ though raised IgM has been reported.⁹ Six of our patients had increased IgA; this finding has not previously been noted.

Routine liver biopsy provided only non-specific information and this has also been the experience of others. Attempts have been made to improve diagnostic accuracy by staining for copper deposits⁹ but these also occur in the late stage of primary biliary cirrhosis.

Several reports have suggested that laparotomy is essential for accurate diagnosis^{11, 16} but percutaneous transhepatic cholangiography using the Chiba needle is the investigation of choice^{5, 9} and displays the beaded appearance of the bile ducts, decreased arborisation and bile duct strictures of varying length.¹⁸ In sclerosing cholangitis proximal bile duct dilatation rarely occurs unlike traumatic strictures.⁷ ERCP is also a useful adjunct to diagnosis but, in already obstructed ducts, there is some risk of precipitating acute cholangitis. Intravenous cholangiography was unhelpful.

Treatment of this rare condition is difficult to evaluate as there have been no controlled trials. Antibiotics have a definite role in treating bouts of ascending cholangitis and cholestyramine usually relieves pruritus. Most controversy surrounds the use of steroids. Schwartz and Dale considered steroids to be of benefit¹⁰ and in 1973 Schwartz reported a satisfactory response in nine out of eleven cases.¹⁹ Myers and his colleagues⁴ noted reversal of abnormal radiological findings but others have observed only temporary remission.^{1, 6, 11, 16} Very few encouraging results of treatment with azathioprine have been reported²⁰ and occasionally natural remission of the disease was thought to have occurred.¹⁴ Our experience closely corresponds to that of Schwartz and a dose of 5-10 mg of prednisolone daily appears to keep the disease in remission for prolonged periods though careful monitoring is required to avoid steroid-induced side effects such as osteoporosis.

A variety of surgical procedures designed to decompress the biliary tree have been advocated and some reports have suggested that this is the only effective form of treatment.^{6, 11} Prolonged T tube drainage until there is radiographic evidence of remission of the disease has been proposed.^{6, 7} For patients with diffuse bile duct involvement either prolonged decompression using an external T tube or internal drainage with a T tube following hepaticojejunostomy¹ have been advised. Temporary transhepatic biliary drainage has also been used. For patients with localised strictures considerable benefit has been obtained from choledochoduodenostomy or choledochojejunostomy for distal strictures and hepaticojejunostomy with Roux-en-Y for proximal strictures. Our patients who required surgical by-pass have had encouraging results though the numbers are small. Recently Pitt and his colleagues have reported an aggressive surgical policy in which they carried out choledochenteric anastomoses in patients with a major area of extrahepatic blockage or primary involvement of the extrahepatic ducts. At a mean follow-up of 52 months after surgery thirteen out of seventeen patients were considered to have had a good result.²¹

Widely differing prognoses for this condition are given in the literature. Although Schwartz and Dale reported only one death in their six patients,¹⁰ most authors conclude that the prognosis is poor.^{1, 5, 6} Recently Thompson and his colleagues²² have suggested that primary sclerosing cholangitis is a heterogenous disease with four subgroups each with differing prognoses, namely: (1) sclerosing cholangitis affecting primarily the distal common bile duct, (2) sclerosing cholangitis occurring soon after an attack of acute necrotising cholangitis, (3) chronic diffuse sclerosing cholangitis and (4) chronic diffuse sclerosing cholangitis associated with inflammatory bowel disease. Group 1 seemed to benefit from choledochenteric anastomosis and to do well. If the patients in Group 2 survived the initial acute attack, they also seemed to have a good outlook. Eight deaths occurred at a mean of 4.3 years among the 29 patients in Groups 3 and 4. However, there were eleven long-term survivors. In those patients with ulcerative colitis, colectomy appeared to confer no benefit on the biliary disease.

In this series eight of the twelve patients are still alive at mean follow-up of 6.2 years and there are six long-term survivors of more than five years. There were two deaths from liver failure and the other two patients died from ovarian carcinoma and oat cell carcinoma of the lung respectively. We consider that long-term

maintenance treatment with prednisolone combined with internal choledochenteric anastomosis for tight strictures, especially of the distal ducts, has proved satisfactory.

Ascending cholangitis requires prompt treatment with an appropriate antibiotic and close monitoring of the dose of steroids is needed in order to minimise side-effects. There may be a future role for dilatation of localised strictures under radiological screening and the place of endoscopic transnasal biliary drainage awaits evaluation.

SUMMARY

The clinical features, investigation, treatment and prognosis of twelve patients with primary sclerosing cholangitis are presented. Ten patients were male. The initial symptom in eight was abdominal pain, sometimes recurrent, and jaundice developed in all but one of the twelve patients. A raised serum alkaline phosphatase level was the most consistent biochemical abnormality and percutaneous transhepatic cholangiography showed good evidence of the extent of the changes in the biliary tree. Eleven patients were treated with prednisolone and three underwent definitive surgery. Four deaths have occurred in the series; two from liver failure, one from an ovarian carcinoma and the other from a malignant lung tumour. Of the remaining eight patients, six have been alive for more than five years. All are receiving a small maintenance dose of prednisolone.

We are grateful to Dr E. M. McIlrath for radiological assistance and our thanks are also due to Miss S. Campbell and Miss M. Hazlett for secretarial help.

REFERENCES

- 1 Shearman DJC, Finlayson NDC. *Diseases of the gastrointestinal tract and liver*. London: Churchill Livingstone, 1982: 764-765.
- 2 Delbet MP. Retrecissement du cholédoque—Cholecystoduodenostomie. *Bull Mém Soc Natn Chir* 1924; **50**: 1144-1146.
- 3 Warren GH, Kern F. Inflammatory bowel disease — primary sclerosing cholangitis. *Clinics in Gastroenterology*. London: Saunders, 1983: 259-265.
- 4 Myers RN, Cooper JH, Padis N. Primary sclerosing cholangitis. Complete gross and histological reversal after long-term steroid therapy. *Am J Gastroent* 1970; **53**: 527-538.
- 5 Smith R, Sherlock S. *Surgery of the gall bladder and bile ducts*. 2nd ed. London: Butterworths 1981: 456-478.
- 6 Warren KW, Athanassiades S, Monge JI. Primary sclerosing cholangitis—a study of forty-two cases. *Am J Surg* 1966; **111**: 23-38.
- 7 Smith MP, Loe RH. Sclerosing cholangitis. *Am J Surg* 1965; **110**: 239-246.
- 8 Holubitsky IB, McKenzie AD. Primary sclerosing cholangitis of the extrahepatic bile ducts. *Can J Surg* 1964; **7**: 277-283.
- 9 Chapman RWG, Marborgh BA, Rhodes JM, Summerfield JA, Dick R, Scheuer PJ, Sherlock S. Primary sclerosing cholangitis: a review of its clinical features, cholangiography and hepatic histology. *Gut* 1980; **21**: 870-877.
- 10 Schwartz SI, Dale WA. Primary sclerosing cholangitis. *Arch Surg* 1958; **77**: 439-451.
- 11 Thorpe MEC, Scheuer PJ, Sherlock S. Primary sclerosing cholangitis, the biliary tree, and ulcerative colitis. *Gut* 1967; **8**: 435-448.

- 12 Dew MJ, Thompson H, Allan RN. The spectrum of hepatic dysfunction in inflammatory bowel disease. *Quart J Med* 1979; **48**: 113-135.
- 13 Schrupf E, Fausa O, Kolmannskog F, Elgjo K, Ritland S, Gjone E. Sclerosing cholangitis in ulcerative colitis. *Scand J Gastroent* 1982; **17**: 33-39.
- 14 Atkinson AJ, Carroll WW. Sclerosing cholangitis—Association with regional enteritis. *JAMA* 1964; **188**: 183-184.
- 15 Bartholomew LG, Cain JC, Woolner LB, Utz DC, Ferris DO. Sclerosing cholangitis — its possible association with Riedel's struma and fibrous retroperitonitis. report of two cases. *N Engl J Med* 1963; **269**: 8-12.
- 16 Thompson BW, Read R, White HJ. Sclerosing cholangitis. *Arch Surg* 1972; **104**: 460-463.
- 17 Danzi JT, Makipour H, Farmer RG. Primary sclerosing cholangitis. *Am J Gastroenterol* 1976; **65**: 109-116.
- 18 Krieger J, Seaman WB, Porter MR. The roentgenologic appearance of sclerosing cholangitis. *Radiology* 1970; **95**: 369-375.
- 19 Schwartz SI. Primary sclerosing cholangitis—a disease revisited. *Surg Clin North Am* 1973; **53**: 1161-1168.
- 20 Javett SL. Azathioprine in primary sclerosing cholangitis. *Lancet* 1971; **1**: 810.
- 21 Pitt HA, Thompson HH, Tompkins RK, Longmire WP. Primary sclerosing cholangitis—results of an aggressive surgical approach. *Ann Surg* 1982; **196**: 259-268.
- 22 Thompson HH, Pitt HA, Tompkins RK, Longmire WP. Primary sclerosing cholangitis — a heterogenous disease. *Ann Surg* 1982; **196**: 127-136.