Unusual variant of primary sclerosing cholangitis

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SUMMARY Two cases of primary sclerosing cholangitis are described, in which the characteristic bile duct lesions were unusual because there was an exuberant and exaggerated fibrous replacement of the ducts which produced dense fibrotic scars in portal tracts.

Primary sclerosing cholangitis, first reported by Delbet in 1924,1 is a disorder of unknown aetiology characterised by non-specific inflammatory obliteratorive fibrosis of the biliary tree, which leads to irregular stenosis, usually of both the intrahepatic and extrahepatic bile ducts.2 4 Intrahepatic disease, however, can occur in the absence of extrahaepatic disease. Furthermore, within the liver small duct and large duct disease may occur independently, suggesting that there is a disease spectrum,5 although with progression of the disease all segments of the biliary tree may be affected.

The features of the bile duct lesions in primary sclerosing cholangitis were highlighted by Bhathal and Powell.3 They comprise a fibro-obliteratorive process producing an “onion-skin” pattern of periductal fibrosis that is accompanied by degeneration and atrophy of the duct epithelium and eventual replacement of the bile duct by fibrous cords.3 4 These lesions are highly specific for primary sclerosing cholangitis but may be present in less than 40% of biopsy specimens; indeed, in one series in which only one liver biopsy specimen was available for study this diagnostic lesion was found in less than 12% of cases.6 In this paper we report two cases of primary sclerosing cholangitis in which the histological appearances were characterised by an exuberant and exaggerated fibro-obliteratorive process, producing thick dense collagenous cords in portal tracts and fibrous septa.

Case reports

CASE 1

This patient, aged 21, presented in December 1965 with jaundice during pregnancy. She had splenomegaly but no hepatomegaly and no stigmata of chronic liver disease. She went into spontaneous labour at 30 weeks' gestation but the baby died after six hours. Liver function tests showed a bilirubin of 55 μmol/l, alkaline phosphatase activity four times the normal limit, and normal transaminase activities. A needle biopsy of liver showed intrahepatic cholestasis but no portal tract was present. Trans-splenic portal venography showed numerous varices at the gastric fundus and “spontaneous” portocaval shunting via the lienorenal ligament and the left renal vein. Transhepatic cholangiography showed dilatation of the intrahepatic ducts but a normal extrahepatic biliary tree. She remained jaundiced over the next 18 months with serum bilirubin concentrations varying from 90–130 μmol/l, alkaline phosphatase activity two to six times above normal, and serum enzymes which rose to a serum aspartate aminotransferase (SGOT) of 790 IU/l and serum alanine transaminase (SGPT) of 400 IU/l in March 1966; both remained high at twice to three times above normal.

Over the next three years her condition remained stable, with mild jaundice, bilirubin concentration of 20–30 μmol/l, alkaline phosphatase activity three to four times above normal and SGOT and SGPT two to four times above normal. Serological tests for anti-mitochondrial antibody, smooth muscle antibody, antinuclear antibody and hepatitis B surface antigen were negative. Her jaundice became more severe in 1970; she had persistent itch requiring treatment with Questran (cholestyramine).

In 1973 she had a spontaneous abortion at 19 weeks’ gestation complicated by prolonged post-abortal vaginal bleeding: this was attributed to hypersplenism with thrombocytopenia (platelet count 75 x 10⁹/l). In early 1976 she developed diabetes requiring small doses of soluble insulin for control. Later in the year she developed features of hepatic failure responding initially to conventional regimens but progressing to death in hepatorenal failure in March 1977.

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**Case 2**

A 49 year old woman had had multiple sclerosis for 12 years. Her clinical course was punctuated by recurrent episodes of urinary tract infections with occasional septicaemia. She had persistently raised serum alkaline phosphatase activity ranging from one and a half to eight times the normal value; serum SGOT activities were persistently raised, the highest being 155 IU/l. She did not have a full investigation of her liver disease, and in particular her serum was not screened for antimitochondrial antibody. She died after a septicaemic episode complicated by meningitis.

**Pathological findings**

**Macroscopic**

The liver in case 1 weighed 1200 g, was intensely stained with bile, and showed a predominantly micronodular biliary cirrhosis (fig 1); the extrahepatic biliary tree appeared normal; one small pigment stone was found in the gallbladder; the spleen weighed 650 g; the portal venous system was dilated; there was some recent gastrointestinal haemorrhage with superficial gastric erosions but no demonstrable gastro-oesophageal varices. The liver in case 2 weighed 1400 g and showed some fine nodularity and fatty change but was not cirrhotic; the extrahepatic biliary tree appeared normal and there were no gallstones; the spleen was not enlarged; there was severe acute or chronic pyelonephritis.

**Microscopic**

There was an established cirrhosis in case 1 showing a micronodular and monolobular (biliary) pattern; there was severe hepatocellular and canalicular cholestasis, predominantly peripheral, in nodules and with numbers of bile infarcts. The striking feature in both cases was the presence of extensive thick hypocellular fibrous tissue scars replacing the intrahepatic biliary radicles (fig 2). In case 1 these were hyalinised and contained scanty elastic fibres, but in case 2 they contained abundant elastic fibres (fig 3). The size of the scars indicated that they comprised both the component which had replaced the bile ducts and also a surrounding periductal fibrous element. Some preserved bile ducts were identified, more readily in case 1 than in case 2; some appeared normal; surrounding others there was periductal fibrosis, with some lymphocytic infiltrate (fig 4), and the duct epithelium...
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Fig 2 These illustrations show large dense fibrotic lesions seen in portal area and fibrous septa. (a) Case 1: dense hyalinised fibrous scars are hypocellular; note mild degree of inflammation and regular margin between fibrous septum and nodular parenchyma, in which peripheral canalicular cholestasis is evident. (Masson's trichrome.) (b) Case 2: fibrous scar is again hypocellular but is less compact than in case 1 and is not hyalinised. There is surrounding light chronic inflammatory cell infiltrate. (Haematoxylin and eosin.)

Fig 3 Case 2: orcein stained section showing prominent degree of elastic fibre deposition within fibrous scars; copper-protein accumulation is seen in periportal hepatocytes (inset, b).
Fig 4  Case 1: surviving bile ducts showing some periductal fibrous and chronic inflammation but with irregular degenerate and atrophic epithelium. (Haematoxylin and eosin.)

showed a degenerate atrophic appearance. In both cases copper associated protein deposits were seen in periportal and periseptal hepatocytes (fig 3).

Discussion

A diagnosis of primary sclerosing cholangitis was accepted in these two cases because there were no clinical or pathological features to suggest a secondary form of the disease that could have been attributable to congenital abnormalities of the bile ducts, operative trauma, choledocholithiasis, or a bile duct tumour. While endoscopic retrograde cholangiopancreatography was not carried out, the presence of obliterative fibrotic lesions substantiate a diagnosis of primary sclerosing cholangitis.3 5

In neither patient was there evidence of recognised disease associations—namely, chronic inflammatory bowel disease found in 50–70% of patients with primary sclerosing cholangitis,7 8 or less commonly, retroperitoneal and mediastinal fibrosis, Riedel’s thyroiditis, orbital pseudotumour, and others.3 The absence of antimitochondrial antibodies helps to exclude primary biliary cirrhosis in case 1. Fibroobliterative lesions may be found in only a minority of patients with primary sclerosing cholangitis, and the definitive diagnosis is established on the basis of clinical cholestatic syndrome and the demonstration of characteristic findings on endoscopic retrograde cholangiopancreatography, such as diffuse narrowing, tortuous irregularity, and multiple strictures with beading of ducts between the narrowed segments.9

In most cases the histological findings comprise paucity or loss of intrahepatic bile ducts; periductal fibrosis or inflammation; a non-specific chronic inflammatory cell infiltrate of the portal tracts; and periportal cholestasis with ballooning of hepatocytes, copper associated protein accumulation and Mallory bodies. The distinction from primary biliary cirrhosis may be difficult on the basis of histological features alone.

The fibro-obliterative lesions in primary sclerosing cholangitis were described in the single case reports of Klemperer11 and Bhalal and Powell.3 An additional seven cases were previously reported in the studies of Moschowitz12 and Rubin et al.,13 in which the lesions had been regarded as variants of primary biliary cirrhosis. It should be noted, however, that the serological and radiological techniques which aid the clinical distinction between primary sclerosing cholangitis and primary biliary cirrhosis were not available to these early workers. Obliterative fibrotic lesions in our experience are not seen in primary biliary cirrhosis and can be regarded as the bile duct lesions on which a diagnosis of primary sclerosing cholangitis can be made.3

Our two cases are unusual because of the extent and degree of the fibro-obliterative process. This produced a striking histological pattern of fibrous scarring at the sites of the intrahepatic biliary radicles. We believe this represents a variant of primary sclerosing cholangitis. We suggest that in addition to the lesion spectrum of small duct primary sclerosing cholangitis and large duct primary sclerosing cholangitis emphasised by Wee and Ludwig,4 there is also a lesion spectrum extending from the simple disappearance of biliary radicles through a mild to moderate degree of fibro-obliterrative cholangitis to the exuberant and exaggerated fibrous replacement which characterises the histological findings in the two cases reported here.

References


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