Case reports

Sclerosing cholangitis and histiocytosis X

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SUMMARY Three patients with biopsy proven histiocytosis X who developed a clinical and pathological picture compatible with sclerosing cholangitis are reported. In one patient, operative biopsy of the common bile duct revealed histiocytosis X in the granulomatous/xanthomatous phase. At necropsy, however, only fibrosis of the biliary tree was seen, a picture consistent with sclerosing cholangitis. Fibrotic obstruction of the biliary tree led to death from liver failure in all three patients. The aetiology of primary sclerosing cholangitis is unknown and may be multifactorial. Perhaps involvement of the biliary tree by histiocytosis X is one cause.

Sclerosing cholangitis may be primary or related to congenital malformations of the biliary tract, duct calculi, operative trauma, or cancer of the bile ducts.¹ Primary sclerosing cholangitis is rare,² and its aetiology unknown. Viral, bacterial and auto-immune theories have been proposed,³ but evidence for them is lacking. The association between sclerosing cholangitis and other diseases, including ulcerative colitis, Crohn's disease, Riedel's thyroiditis, retroperitoneal fibrosis and pancreatitis, has been reported,^{4,5} but the significance of these associations has yet to be determined. Perhaps primary sclerosing cholangitis has more than one cause, as suggested by the very variable course of the disease.⁶

Biliary obstruction in an adult resulting from involvement of the intra- and extrahepatic biliary tree by histiocytosis X has been reported recently from this institution.⁷ The patient has subsequently died and further review of her clinical course, radiology, and pathology reveals many features identical to those of primary sclerosing cholangitis. Review of our patients^{8,9} with a clinical picture compatible with sclerosing cholangitis has revealed two additional patients with histiocytosis X. We report here the case histories of these three patients and discuss the possible nature of the association between these two rare conditions.

Case reports

CASE 1

A 44 year old woman was admitted with a history of fatigue, epigastric pain, and jaundice. Five years previously she had developed diabetes insipidus after a road traffic accident. This resolved over the next two years. A vulval ulcer biopsied nine months before admission was diagnosed as eosinophilic granuloma. Examination showed jaundice and several bluish nodules in the left axilla, biopsy of which also showed eosinophilic granuloma. Relevant investigation results were: serum bilirubin 42 $\mu\text{mol/l}$, serum aspartate aminotransferase (AST) 167 u/l (normal <40), serum alkaline phosphatase 966 u/l (normal 30-105). Radiological skeletal survey showed no lucent areas.

A laparotomy was performed. The gall bladder, which contained no stones, was excised. The common bile duct was noted to have a very thick, firm wall. Biopsy of it showed the characteristic features of eosinophilic granuloma, namely, a dense infiltrate of foamy 'histiocytes' with lobulated grooved nuclei and numerous eosinophils (Fig. 1). A T tube was inserted in the common duct. A cholangiogram showed the intrahepatic ducts to be irregular and without the normal tapering as they coursed peripherally ('pruned tree appearance'). The distal common duct appeared 'ragged'.

Postoperatively, she had episodes of cholangitis. Steroids (prednisone 60 mg/day), radiotherapy (3000 rads) to the region of the biliary tree and a

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Fig. 1 Section of common bile duct from case 1 showing a dense inflammatory infiltrate in wall. The infiltrate is composed primarily of 'histiocytes' and eosinophils (H and E $\times 40$ original magnification)

trial of vinblastine were given but with no symptomatic or objective improvement. A cholangiogram, carried out 15 months after her laparotomy, showed a stricture of the right hepatic duct. A further laparotomy was performed, the stricture dilated and the T tube replaced. A postoperative cholangiogram revealed sparse and tenuous intrahepatic ducts (Fig. 2). Despite this procedure, her liver function deteriorated and she died of hepatic failure four months later. Necropsy showed advanced biliary cirrhosis and dense fibrosis at the porta hepatis. The diagnosis of histiocytosis X would have been difficult to make from histopathological examination of the necropsy material.

CASE 2

A 65 year old man was admitted with a recent history of pruritus and jaundice. At laparotomy the liver appeared cirrhotic and the extrahepatic bile ducts were embedded in a mass of fibrous tissue. A cholecystectomy was performed. The common duct contained 'sludge' and its distal portion appeared occluded. The common duct was drained externally. Liver biopsy showed biliary cirrhosis. The gall bladder, which contained no stones, showed the microscopic features of chronic cholecystitis. Biopsies from around the extrahepatic bile ducts were reported as showing fibrosis and chronic inflammation. Postoperatively, he complained of polydipsia and polyuria.

He was transferred to UCLA Medical Center. On admission his serum bilirubin was 100 $\mu\text{mol/l}$. A second laparotomy confirmed the previous findings. In addition, an operative cholangiogram showed

small, irregular right biliary radicles with non-visualisation of the left intrahepatic biliary tree and distal common bile duct. A choledochojejunostomy was performed. After this operation, his urine output greatly exceeded his fluid intake (in one day,

Fig. 2 T tube cholangiogram performed soon after second laparotomy in case 1.

intake 1.4 l, urine output 6.25 l). A diagnosis of diabetes insipidus was made, but the cause not ascertained. He died in liver failure six months after his first laparotomy. Necropsy showed a liver weighing 0.7 kg with the microscopic features of biliary cirrhosis. Microscopic examination of the neurohypophysis showed histiocytosis X (Fig. 3).

CASE 3

A 17 year old girl with an 11 year history of histiocytosis X involving lymph nodes, lung and skull, presented with episodes of abdominal pain and jaundice. A laparotomy was performed. The gall bladder was found to be fibrotic and the common duct strictured. Both the gall bladder and the bile ducts contained soft, black stones. A cholecystectomy, choledocholithotomy, and choledochojunostomy were performed. Post-operatively, she suffered from episodes of cholangitis. Steroid therapy was instituted. At the age of 19 years, her choledochojunostomy was found to be strictured and was revised.

At the age of 21 years, she was admitted to UCLA Medical Center. Liver function tests at that time were: serum bilirubin 400 $\mu\text{mol/l}$, serum AST 193 u/l, serum alkaline phosphatase 809 u/l. A further laparotomy revealed a dense mass of fibrous tissue at the porta hepatis, in which no bile duct could be identified. An attempt to perform a cholangiojunostomy failed as no suitable duct for anastomosis could be identified after amputating the left lateral segment of the liver. Histology of the resected liver showed secondary biliary cirrhosis with no features of histiocytosis X. She was

discharged from hospital but died soon after from hepatic failure. A necropsy was not performed.

Discussion

The three patients reported had both a clinical picture consistent with sclerosing cholangitis and histopathological evidence of histiocytosis X. Two cases presented in adult life with no evidence of bone involvement. This is atypical of histiocytosis X.¹⁰ The generic term, histiocytosis X, was proposed by Lichtenstein¹¹ to stress the histopathological similarities between the Hand-Schüller-Christian syndrome, Letterer-Siwe disease and eosinophilic granuloma of bone. Other authors^{12, 13} consider it unwarranted to group them together and have proposed other classifications, but none have gained widespread acceptance. Histiocytosis X may be a misnomer as the predominant cell in the lesions is the Langerhans cell rather than the histiocyte. Langerhans cell granulomatosis has been suggested as an alternative term.¹⁴

The liver is frequently involved in infants with the acute disseminated form of histiocytosis X (Letterer-Siwe disease).¹⁵ Pathological changes initially consist of infiltration of the portal tracts by histiocytes, with fibrosis and cirrhosis occurring subsequently.¹⁶ Single case reports of children with involvement of the extrahepatic bile ducts by histiocytosis X have been made.^{15, 17, 18} In addition, LeBlanc *et al*¹⁹ described three childhood cases, in one the common duct was affected and in two there was partial stenosis at the confluence of the left and

Fig. 3 Section of neurohypophysis from case 2 showing an inflammatory infiltrate containing characteristic 'histiocytes' with folded grooved nuclei (H and E $\times 160$ original magnification)

right hepatic ducts. This latter appearance is frequently seen in primary sclerosing cholangitis.⁸ Also cholangiography in those patients with histiocytosis X and cholestasis shows an appearance of the intrahepatic ducts similar to that seen in primary sclerosing cholangitis.¹⁹

In addition to the reports in children, Parker and Lichtenstein²⁰ described an adult with involvement of the extrahepatic ducts by histiocytosis X, but without biliary obstruction. Histiocytosis X and biliary obstruction has been reported⁷ in an adult whose case history and necropsy findings are included in this paper (case 1). In this patient, the initial biopsies of the tissue encasing the extrahepatic bile ducts showed histiocytosis X. Microscopic examination of tissue taken from this site at necropsy, however, revealed only chronic inflammation and fibrosis. In case 2, the thickened gastrohepatic ligament was biopsied at two laparotomies. On both occasions, the tissue was reported as showing chronic inflammation and fibrosis. No features of histiocytosis X were present. This diagnosis was only made after postmortem examination of the neurohypophysis. In case 3, histological confirmation of histiocytosis X was made from cervical lymph node and mandibular biopsies at age 6 and 10 respectively. At age 17, a biliary stricture was found at her first laparotomy. Subsequently, she sclerosed the whole of her biliary system. No biopsies were taken from the bile ducts or from the tissue surrounding them.

Engelbreth-Holm *et al*²¹ described four histopathological stages through which a lesion of histiocytosis X may progress: (i) a hyperplastic or proliferative phase, (ii) a granulomatous phase, (iii) a xanthomatous phase and (iv) a fibrous phase. Once a lesion has entered the last phase, it loses the histological features which permit the diagnosis histiocytosis X to be made. In case 1, the biopsy taken at the first laparotomy showed the lesion encasing the bile ducts to be in the granulomatous/xanthomatous phase, whereas examination of the same tissue obtained at necropsy showed it to be in the fibrous phase. Perhaps the fibrosis surrounding the bile ducts in case 2 represents the fibrous phase of a histiocytosis X lesion.

Different authors^{1, 8, 22} have used different criteria for inclusion of patients under the diagnosis of primary sclerosing cholangitis. Case 1 had clinical and radiological features of primary sclerosing cholangitis, but would be excluded from having this diagnosis by some authors because the biliary obstruction was due to involvement of the biliary system by histiocytosis X. This diagnosis was made because the biopsy was taken while the lesion was in the granulomatous/xanthomatous phase. It is

conceivable that this diagnosis would have been substituted by that of primary sclerosing cholangitis if the biopsy had been taken later, when the lesion had entered the fibrous phase. Case 2 could be considered a classic example of primary sclerosing cholangitis, fulfilling the most rigid criteria²² necessary for making the diagnosis. Case 3, at age 17, had stones in both the gall bladder and the bile ducts. These stones were soft and black and may have resulted from stasis in a strictured biliary system rather than have been the cause of the sclerosing cholangitis.

One may speculate as to whether some cases of primary sclerosing cholangitis are caused by involvement of the biliary tree by histiocytosis X. The characteristic histopathological features of histiocytosis X may not be appreciated because the lesion has entered the fibrous phase at the time of biopsy. It is likely that more than one causal agent may result in a clinical picture consistent with primary sclerosing cholangitis.⁸ Perhaps involvement of the bile ducts by histiocytosis X represents one pathogenic mechanism for the development of primary sclerosing cholangitis. Until more is known about the aetiology of these two diseases, however, the nature of their association must remain speculative.

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