Sclerosing cholangitis and biliary tract calculi —primary or secondary?

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Abstract

The clinical features of 61 patients with sclerosing cholangitis were reviewed. This group included 23 patients with biliary tract calculi, commonly considered as excluding the diagnosis of primary sclerosing cholangitis. The aim of this study was to compare these 23 patients (group A) with 38 patients with sclerosing cholangitis free of calculi (group B). Both groups had the following features in common: (i) age at presentation, (ii) incidence of inflammatory bowel disease, (iii) extent of radiological disease, (iv) prevalence of HLA-B8 and DR3 haplotype, (v) incidence of cholangiocarcinoma, and (vi) progression to hepatic transplantation (mean follow up 49.9 months). All patients in group A were symptomatic at diagnosis compared with 23 of the 38 patients (61%) in group B. Recurrent ascending cholangitis occurred in 12 patients in group A (52%) and two patients (5%) in group B. The similarity between the two groups was maintained when the nine patients in group A who developed calculi after sclerosing cholangitis was diagnosed were excluded. It is concluded that choledocholithiasis is part of the spectrum of primary sclerosing cholangitis and that it is not necessary to invoke choledocholithiasis as the initial lesion of the bile ducts in such patients.

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Primary sclerosing cholangitis is a chronic inflammatory disorder which results in fibrosis and obliteration of the intrahepatic and/or extrahepatic bile ducts leading to the typical radiological appearance of stricturing and beading of the biliary tree. The aetiology is unknown, although immunological factors have been implicated.¹ Between 50% and 75% of cases are associated with inflammatory bowel disease, mostly ulcerative colitis. Ultimately biliary cirrhosis results and the median survival has been estimated to be 12 years.² The diagnosis of primary sclerosing cholangitis is based on typical clinical, histological, and radiological features. By conventional criteria, it is excluded by (a) the presence of biliary tract calculi, (b) a history of previous biliary tract surgery, and (c) the presence of a cholangiocarcinoma.³⁻⁶ Despite these criteria, patients with biliary tract calculi have been included in several studies of primary sclerosing cholangitis.⁷⁻⁹ We have also encountered a number of patients with the radiological features of sclerosing cholangitis but in whom there were also biliary tract calculi. The aim of the present study was to review a group of patients in whom sclerosing cholangitis was present. Twenty three of these patients had, or

subsequently developed, intrahepatic and/or extrahepatic bile duct calculi. The features of these patients were compared with those of patients without calculi. The results indicate that both groups of patients can be considered to have primary sclerosing cholangitis.

Methods

PATIENTS

Sixty one patients diagnosed as having sclerosing cholangitis were seen between 1984 and 1991 at the Gastroenterology and Liver Centre of the Royal Prince Alfred Hospital, Sydney. The diagnosis was made in 57 patients by endoscopic retrograde cholangiopancreatography and in three by percutaneous transhepatic cholangiography. In one patient, the diagnosis of sclerosing cholangitis became apparent only after examination of the native liver after hepatic transplantation. All radiological examinations were reviewed by at least two gastroenterologists and two radiologists. The date of diagnosis was defined as the point when radiological evidence of intrahepatic and/or extrahepatic duct strictures were first demonstrated.

The patients were divided into two groups based on whether or not biliary tract calculi were present, either at diagnosis or at any stage during the course of their illness. Their clinical features were compared, as was the extent of disease, the clinical course, and prognosis. The mean period of follow up was 49.9 months (range 1-192 months).

HLA class I and class II alleles were serologically typed at the Tissue Typing Laboratory, NSW Division, Australian Red Cross Society Blood Transfusion Service using the standard National Institutes of Health test for class I and a modified National Institutes of Health test using immunomagnetic beads for class II.¹⁰ Anti-neutrophil cytoplasmic antibody was measured in 31 patients by indirect immunofluorescence. The substrate used was an alcohol fixed neutrophil rich preparation with patient sera screened at a dilution of 1:20.¹¹

Comparisons between the two groups were made using Fisher's exact test.

Results

In 23 patients (group A) biliary tract calculi were present either at the time of diagnosis (14 patients) (Fig 1) or subsequently developed some time after the diagnosis of sclerosing cholangitis had been made (nine patients). The calculi in these latter nine patients were found at intervals varying from 18 to 156 months (mean 58.7 months) after sclerosing cholangitis had been

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Figure 1: Endoscopic retrograde cholangiopancreatography performed on a patient with ulcerative colitis who presented with right upper quadrant pain, fever, and jaundice. Beading and stricturing of the intrahepatic and extrahepatic bile ducts are evident with numerous calculi being present in the intrahepatic ducts (arrowed).

diagnosed (Fig 2). In each case, the calculi were found on repeat endoscopic retrograde cholangiopancreatography, performed because of recurrent ascending cholangitis (six patients) or progressive liver failure (three patients). Five of these nine patients had undergone cholecystectomy from three months to 30 years previously, making passage of a stone from the gall bladder an unlikely cause of the biliary tract calculi. Thirty eight patients (group B) did not have biliary calculi either on diagnosis or during the course of their illness. Biochemical analysis of calculi was not performed.

The clinical features of the two groups as well as the subgroups in group A – that is, those who had calculi at the time sclerosing cholangitis was diagnosed and those who developed calculi after sclerosing cholangitis was diagnosed, are shown in Table I. Because of the similarities between the two subgroups in group A, they are hereafter referred to as one group. There were proportionally more women in the group with calculi than in the group without (16 of 23 in group A, 17 of 38 in group B; $p=0.04$). The mean age at diagnosis was similar in both groups. No difference was found in the frequency of associated inflammatory bowel disease: in group A, 12 patients of the 23 (52%) had ulcerative colitis, while in group B, 21 patients (55%) had ulcerative colitis and two (5%) had Crohn's disease. HLA typing was performed in 13 patients in group A and 14 in group B. HLA-B8 was present in six of 13 patients in group A (46%) and six of 14 (43%) in group B, while HLA-DR3 was found in six patients tested in group A (46%) and five in group B (36%). Antineutrophil cytoplasmic antibody was measured in 31 patients (12 in group A

and 19 in group B). Of patients in group A, six (50%) had detectable antibody with a perinuclear pattern on immunofluorescent staining compared with three of 19 (16%) in group B. All patients in group A were symptomatic at initial presentation (11 patients had right upper quadrant pain, eight had cholangitis, two had pruritus, and two had symptoms related to hepatic decompensation). This was the case whether or not calculi were present at the time. In contrast, only 23 of the 38 patients in group B (61%) had clinical manifestations of their disease (cholangitis in eight patients, right upper quadrant pain in six patients, pruritus in three patients, and evidence of hepatic decompensation in six patients; $p=0.0002$). The remainder were asymptomatic and were being investigated for abnormal liver function tests.

The radiological extent of bile duct disease was similar in the two groups (Table II). Of the patients in group A, the biliary calculi were present in the intrahepatic ducts in six patients, in both intrahepatic and extrahepatic ducts in a further six and in the extrahepatic ducts alone in 11 patients. In only three patients were single stones found. The remaining 20 had multiple biliary calculi of varying size. Thirteen patients in group A (57%) and seven in group B (18%) had associated cholecystolithiasis, diagnosed either before or at the time of diagnosis of sclerosing cholangitis ($p=0.002$). This excess was largely accounted for by women (10/13 in group A *v* two of seven in group B).

Twelve patients (52%) in group A had recurrent episodes of ascending cholangitis during follow up compared with two patients in group B (5%). This difference was highly significant ($p=0.00005$).

Nineteen patients in group A underwent various therapeutic manoeuvres in an attempt to clear the biliary tree of calculi. Endoscopic sphincterotomy was performed in 16 patients with successful removal of all calculi in seven. In a further five, percutaneous removal of residual intrahepatic stones was possible. Five of these 12 patients had endoscopic insertion of a biliary stent. A further five underwent percutaneous stent insertion in order to achieve biliary decompression. Despite these measures, biliary tract calculi recurred in all 12 patients after removal.

Nine patients in group A (39%) and eight patients in group B (21%) underwent hepatic transplantation because of progressive disease ($p=0.07$; NS). Uncontrollable intrahepatic sepsis, the result of recurrent calculi, complicated the course of three patients in group A, and was the indication for hepatic transplantation. Cholangiocarcinoma occurred in three patients in group A (13%) and five patients in group B (13%).

Six deaths occurred in group A (26%) and 10 in group B (26%) during the follow up period. Three patients in group A died after liver transplantation (one week to 19 months post transplant), two died from postoperative complications after cholecystectomy and one from massive hepatic necrosis of unknown cause. In group B, four patients died as a result of complications after hepatic transplantation (one week to 18 months post transplantation), four others

Figure 2 (A): Endoscopic retrograde cholangiopancreatography showing beading and stricturing of the extrahepatic and intrahepatic bile ducts. (B): repeat endoscopic retrograde cholangiopancreatography performed three years later in the same patient after recurrent episodes of cholangitis. Multiple calculi are present in the common bile duct and gall bladder with a long stricture at the lower end of the common bile duct.

died of progressive hepatic failure while awaiting transplantation and two died from hepatic tumours. On histological review, it was felt that these two tumours were more consistent with hepatocellular carcinoma than cholangiocarcinoma. These two patients have not been included in the analysis of cholangiocarcinomas in the two groups.

Discussion

The findings of this study show that a number of patients with sclerosing cholangitis also have biliary tract calculi. The similarity of the clinical features, the frequency of associated inflammatory bowel disease, age at diagnosis, and radiological extent of disease all indicate that these patients can be considered to have primary sclerosing cholangitis rather than sclerosing cholangitis secondary to calculi damaging the biliary tree and resulting in stricture formation. The clinical and radiological features are similar to those reported in other studies of primary sclerosing cholangitis.^{3 5 12 13} In addition, the prevalence of HLA-B8 and DR3 was similar in the two groups although not as high as reported in previous studies of primary sclerosing cholangitis.^{14 15} The prevalence of HLA-B8, however, was similar to that found in an earlier study of primary sclerosing cholangitis in an Australian population.¹⁶ Antineutrophil cytoplasmic antibody, with a perinuclear pattern on immunofluorescent staining has been reported to have a sensitivity of 65% and specificity of 100% in primary sclerosing cholangitis.¹⁷ In the present study, such antibody was detectable in six of 12 patients (50%) examined in group A and three of 19 in group B (16%). Finally, nine patients with typical primary sclerosing cholangitis subsequently developed biliary tract stones after a mean interval of 58.7 months from diagnosis.

The pathogenesis of the calculi found in patients with primary sclerosing cholangitis may depend on several factors. Increased bile lithogenicity is suggested by the significantly higher frequency of cholecystolithiasis in the patients with bile duct stones (57%), which contrasts with the reported prevalence of 10–20% in developed countries.^{18–20} This would also account for the significantly greater proportion of women in group A, as the incidence of gall stones is higher in women than men and in this study the excess of patients with gall bladder calculi was made up by women. Biliary stasis would further predispose to the development of stones in the presence of lithogenic bile. The same is true of recurrent ascending cholangitis.²¹ It could be argued that in the patients with cholecystolithiasis the calculi had passed from the gall bladder into the bile ducts. Cholecystectomy had been performed for suspected biliary colic three months to 30 years previously, however, in five of nine patients who went on to develop biliary tract calculi, discounting this theory. Further evidence against this is the finding that the occurrence of choledocholithiasis was much higher in patients in group A who underwent cholecystectomy (16/23: 70%) than is generally seen in association with cholecystolithiasis.²² Finally, the presence of multiple intrahepatic calculi is not typical of the pattern of

TABLE I Clinical features of 61 patients with sclerosing cholangitis

	Group A			Group B (n=38)
	Subgroup 1 (n=14)	Subgroup 2 (n=9)	Total (n=23)	
Sex:				
Male	6 (43%)	1 (11%)	7 (30%)	21 (55%)
Female	8 (57%)	8 (89%)	16 (70%)*	17 (45%)
Mean age at diagnosis (yr)	48.3	46.4	47.4	43.3
(range)	(36–78)	(33–60)	(33–78)	(18–74)
Assoc inflammatory bowel disease:				
Ulcerative colitis	8 (57%)	4 (44%)	12 (52%)	21 (55%)
Crohn's	0	0	0	2 (5%)
Clinical presentation:				
Asymptomatic	0	0	0†	15
Cholangitis	6	2	8	8
Pain	6	5	11	6
Pruritus	1	1	2	3
Hepatic decompensation	1	1	2	6

*p=0.04
†p=0.0002

Group A: Patients with sclerosing cholangitis and biliary tract calculi. Subgroup 1: Patients who had biliary tract calculi at the time of diagnosis of sclerosing cholangitis. Subgroup 2: Patients who developed calculi after the diagnosis of sclerosing cholangitis was made.
Group B: Patients with sclerosing cholangitis who did not have biliary tract calculi either at diagnosis or during the course of their illness.

biliary calculi seen after cholecystectomy for cholelithiasis in patients without primary sclerosing cholangitis.^{23 24}

Patients with primary sclerosing cholangitis complicated by biliary tract calculi were more likely to be symptomatic at presentation than those without calculi. They were also more prone to recurrent ascending cholangitis, although the radiological extent of their disease is similar. It would seem reasonable to assume that measures aimed at treating calculi in these patients may reduce the frequency of infection. Attempts at removing the stones and improving biliary drainage, however, led to a reduction in the number of episodes of cholangitis in only four of 16 patients. Moreover, calculi returned in all 12 patients in whom they were removed. This presumably reflects the fact that biliary stasis remains with a nidus of infection already present even after stones are removed. The recurrence of calculi after removal and the lack of substantial reduction in frequency of cholangitis indicates that there may be little to be gained in many of these patients by multiple manipulations of the biliary tree to achieve clearance. These procedures carry the risk of introducing further infection into the biliary tree. Although mean follow up was only 49.9 months, there was no evidence to suggest that removal of stones resulted in any improvement in prognosis. In fact, there was a trend towards a greater likeli-

hood of requiring hepatic transplantation, although this did not reach statistical significance. Mortality was not different between the two groups.

In the long term, the use of ursodeoxycholic acid has been reported to be of benefit in primary sclerosing cholangitis,^{25 26} but the mechanism by which ursodeoxycholic acid exerts a beneficial effect is unknown. The effect of this agent may be a result of its ability to reduce the lithogenicity of bile and it may therefore be of particular benefit in patients with complicating biliary calculi.

In conclusion, the results of this study indicate that biliary tract calculi may complicate the course of otherwise typical primary sclerosing cholangitis and therefore their presence should not necessarily exclude the diagnosis of primary sclerosing cholangitis. Recurrent ascending cholangitis is significantly more common in this group of patients and calculi should be suspected when this complication or hepatic decompensation develops in a patient with known primary sclerosing cholangitis. Measures to remove biliary tract calculi can be considered, although from the present study benefit from such procedures only occurred in four of 16 patients and stones recurred in 12 of 12.

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TABLE II Radiological involvement and biliary tract calculi

	Group A (n=23)			Group B (n=38)
	Subgroup 1 (n=14)	Subgroup 2 (n=9)	Total (n=23)	
Radiological involvement				
IHD only	6 (43%)	3 (33%)	9 (39%)	15 (40%)
EHD only	0	0	0	2 (5%)
IHD and EHD	8 (57%)	6 (67%)	14 (61%)	21 (55%)
Biliary tract calculi				
Cholelithiasis	9 (64%)	4 (44%)	13 (57%)	7 (18%)
IHD only	3 (21%)	3 (33%)	6	–
EHD only	6 (43%)	5 (56%)	11	–
IHD and EHD	4 (29%)	2 (22%)	6	–
Calculi (n)				
Single	2 (14%)	1 (11%)	3	–
Multiple	12 (86%)	8 (89%)	20	–

IHD: intrahepatic ducts; EHD: extrahepatic ducts.

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