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Gallbladder disease in patients with primary sclerosing cholangitis☆

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***Background/Aims*: Gallbladder abnormalities may be part of the spectrum in primary sclerosing cholangitis (PSC). The aim of the present study was to evaluate the occurrence and prognostic importance of gallbladder abnormalities in patients with PSC.**

***Methods*: Presence of gallbladder abnormalities was assessed in 286 patients with PSC treated at the Liver Unit, Karolinska University Hospital, Huddinge, between 1970 and 2005.**

***Results*: One or more gallbladder abnormalities were found in 41% of the patients. Gallstones were found in 25% and cholecystitis in 25%. Cholecystitis among patients with extrahepatic involvement of PSC (30% (65/214)) was significantly higher than among those with intrahepatic involvement (9% (6/70)) ($P < 0.0001$). A gallbladder mass lesion with a mean size of 21 (±9) mm (S.D.) was found in 18 (6%) patients, in 56% (10/18) of whom it constituted gallbladder carcinoma. In 9 patients without a gallbladder mass lesion, histological re-evaluation disclosed epithelial dysplasia of the gallbladder.**

***Conclusions*: Gallbladder disease is common in patients with PSC. Dysplasia and carcinoma are commonly found in gallbladder epithelium, suggesting that regular examination of the gallbladder in PSC patients could be of value for early detection of a gallbladder mass lesion. Cholecystectomy is recommended when such a lesion is detected, regardless of its size.**

***Keywords*: Gallbladder polyps; Gallbladder stone; Cholecystectomy; Gallbladder carcinoma; Sclerosing cholangitis**

1. Introduction

Primary sclerosing cholangitis (PSC) is an idiopathic chronic cholestatic inflammatory liver disease with a close association to inflammatory bowel disease (IBD) [1]. PSC is characterized by diffuse fibrosing inflammation of the intrahepatic and/or extrahepatic bile ducts, resulting in bile-duct obliteration, biliary cirrhosis, and eventually hepatic failure [2,3]. The prevalence of gallbladder abnormalities, including gallstones, thickening of the gallbladder wall and malignancy, has previously been reported to be 41% [4]. Complicated gallstone disease can lead to secondary sclerosing cholangitis, with radiological changes similar to PSC [5]. Differentiating between primary and secondary sclerosing cholangitis can be difficult when gallstones are present, especially in cases without concomitant inflammatory bowel disease. However, gallstones seem to be part of the spectrum of PSC and have also been shown to be associated with symptoms such as abdominal pain, pruritus and bacterial cholangitis [6].

Patients with PSC run an increased risk of developing cholangiocarcinoma. The reported prevalence of this

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Abbreviations: PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; CT, computerized tomography; ERC, endoscopic retrograde cholangiography; MRC, magnetic resonance cholangiography; UC, ulcerative colitis; UDCA, ursodeoxycholic acid.

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complication ranges from 8% to 20% [7–9], while the risk of gallbladder carcinoma is not known. Buckles et al. recently showed that in PSC patients, gallbladder polyps are malignant in as many as 57% of cases [10], whereas the reported prevalence in patients without PSC is no more than 0.2–20% [11–14]. Cholecystectomy has therefore been recommended to be considered in all PSC patients in whom a polyp is identified, whereas in patients without PSC it is safe to keep polyps smaller than 10 mm under observation. However, surveillance of the gallbladder for identification of polyps in PSC is still controversial.

The aim of the present study was to assess the occurrence of gallbladder abnormalities, including gallstones, cholecystitis and gallbladder mass, in a large cohort of PSC patients. We also wanted to study the impact of gallbladder abnormalities on the prognosis of PSC.

2. Patients and methods

2.1. Definitions

The diagnosis of PSC was based on typical cholangiographic findings in combination with clinical, biochemical, and histological data [15–17]. Secondary causes of sclerosing cholangitis were excluded before establishing the diagnosis of PSC. The cholangiographic methods used were either endoscopic retrograde cholangiography (ERC; $n = 185$), magnetic resonance cholangiography (MRC; $n = 96$), percutaneous transhepatic cholangiography ($n = 4$) or peroperative cholangiography ($n = 1$). The diagnosis of small bile duct PSC was based on chronic cholestasis, characteristic histological features of PSC but normal cholangiographic findings and exclusion of other cholestatic liver diseases [18–20]. The onset of PSC was defined as the time of first presentation of typical cholangiographic findings consistent with PSC. Histological diagnosis of cirrhosis and staging of fibrosis were based on internationally established criteria [16]. The diagnosis of hepatobiliary carcinoma was based on radiological findings with histological or cytological confirmation. Cholecystitis was defined to include cases with acute cholecystitis, based on established criteria including clinical, biochemical, radiological and histological findings [21], as well as chronic cholecystitis, based on radiological and histological findings. Bacterial cholangitis was defined as an episode of liver test abnormalities combined with fever, elevated CRP, right upper quadrant abdominal pain and absence of radiological signs of acute cholecystitis. The endpoint of the study was either the time of liver transplantation, death or the date of the latest clinical visit. The diagnosis of IBD was based on a typical clinical history and characteristic endoscopic and histological findings [22,23].

2.2. Patients

All patients with a well-defined PSC treated at the Liver Unit, Karolinska University Hospital, Huddinge, between January 1970 and June 2005 were included in the study. We identified and evaluated 286 PSC patients. All variables were obtained by reviewing the patients' records. The following data were collected and recorded in a protocol: demographic characteristics, substance use, onset, extension, stage, duration and treatment of PSC, symptoms and signs attributable to PSC including abdominal pain, jaundice, pruritus, fever, weight loss, ascites, and bleeding from esophageal varices, hepatobiliary malignancy, information about IBD (type, onset, extension, duration, treatment, surgery, presence of colon dysplasia/colon cancer), gallbladder abnormalities including cholecystitis, stones, polyps and malignancy, and cholecystectomy. Gallstones were confirmed by one or more radiological methods, including abdominal ultrasonography, computerized tomography, and/or MRC.

2.3. Histology

Available gallbladder specimens taken at cholecystectomies or liver transplantation ($n = 53$) were re-reviewed histologically regarding presence of inflammation, dysplasia and cancer. Paraffin sections were stained with hematoxylin–eosin, periodic acid–Schiff diastase, and iron stain. Extent of inflammation was divided into two subgroups; absence-to-mild and moderate-to-severe. Cellular dysplasia was diagnosed when loss of polarity, cellular enlargement, increased nuclear/cytoplasm ratio and mitotic figures and/or nuclear pleomorphism were present.

2.4. Statistics

All data were analyzed using Statistica software (v 7.0, StatSoft Inc.). Values are expressed as means and standard deviation (S.D.). For comparison of categorical data the Chi-square analysis was used or Fisher's exact test when appropriate. P-values < 0.05 were considered significant. Survival analysis was done with Kaplan–Meier estimates, using the log rank test.

The study was approved by the Ethics Committee at Karolinska University Hospital, Huddinge.

3. Results

3.1. General features

The clinical characteristics of the 286 patients included in the study are shown in detail in Table 1. Of the patients with IBD, 10% had Crohn's colitis. None of these patients had substantial ileal involvement. Liver biopsies were available in 215 (75%) patients. Among these patients, 16 (6%) had stage I, 63 (22%) stage II and 62 (22%) stage III fibrosis, while 73 (26%) had stage IV (cirrhosis). Twenty-six patients had either colon carcinoma ($n = 9$) or high-grade colonic dysplasia ($n = 17$). Nine (3%) patients had diabetes mellitus and five (2%) had celiac disease. Mean body mass index (BMI) in 45 female patients was 23 (± 3) and 24 (± 4) in 110 male patients; information on height and weight was missing in 121 patients. Thirteen (4.5%) of the patients presented with acute variceal bleeding and 14 (5%) with ascites. The frequency of hepatobiliary malignancy was 16% (46/286); 33 (11.5%) had cholangiocarcinoma, 10 (3.5%) had gallbladder carcinoma and 3 (1%) had hepatocellular carcinoma.

3.2. Gallbladder abnormalities

Gallbladder abnormalities, including cholecystitis, gallstones, gallbladder mass and gallbladder malignancy, are presented in Table 2. Gallbladder abnormalities in patients with PSC were not associated with gender or occurrence of IBD, whereas a significant association was found between gallbladder abnormalities and extrahepatic involvement of PSC ($P < 0.001$).