The Natural History of Small-Duct Primary Sclerosing Cholangitis

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Background & Aims: **The long-term prognosis of patients with small-duct primary sclerosing cholangitis (PSC) remains incompletely characterized. We aimed at determining the natural history and long-term outcomes of a large number of patients with small-duct PSC.** ***Methods:*** **Data from 83 patients with well-characterized small-duct PSC from several medical institutions in Europe and the United States were combined. Each patient with small-duct PSC was randomly matched to 2 patients with large-duct PSC by age, gender, calendar year of diagnosis, and institution.** ***Results:*** **The median age at diagnosis in both groups was 38 years (61% males). Nineteen (22.9%) of the 83 patients with small-duct PSC progressed to large-duct PSC in a median of 7.4 (interquartile range [IQR], 5.1–14) years. One patient with small-duct PSC who progressed to large-duct PSC was diagnosed with cholangiocarcinoma but after progression to large-duct PSC; 20 patients with large-duct PSC developed cholangiocarcinoma. Patients with small-duct PSC had a significantly longer transplantation-free survival compared with large-duct PSC patients (13 years [IQR, 10–17] vs 10 years [IQR, 6–14], respectively; hazard ratio, 3.04; 95% confidence interval: 1.82–5.06; $P < .0001$). Two patients with small-duct PSC who underwent liver transplantation had recurrence of small-duct PSC in the graft 9 and 13 years, respectively, after transplantation.** ***Conclusions:*** **Small-duct PSC is a disease of progressive potential but associated with a better long-term prognosis as compared with large-duct PSC. Small-duct PSC may recur after liver transplantation. Cholangiocarcinoma does not seem to occur in patients with small-duct PSC, unless the disease has progressed to large-duct PSC.**

The natural history of classic (ie, cholangiography confirmed) large-duct primary sclerosing cholangitis (PSC) has been well characterized in many long-term follow-up studies.[1–7] In cohorts of patients with PSC diagnosed mostly in the 1970s and 1980s, a median transplantation-free survival of approximately 12 years was observed.[2,3,5] However, a Dutch cohort that also included patients from 1990 to 1999 reported a median transplantation-free survival of 18 years.[7] Cholangiocarcinoma, the most feared complication of PSC, develops in up to one third of patients with PSC.[8] A minority of patients with sclerosing cholangitis of unknown etiology with similar cholestatic and histologic features as those with classic PSC have normal cholangiograms, and they have been referred to as *small-duct PSC*.[9] This subgroup of PSC has been less well characterized than the classic large-duct PSC. Three studies analyzing the long-term prognosis of patients with small-duct PSC were published in 2002.[10–12] The results from these 3 different studies suggested a better prognosis in patients with small-duct than in large-duct PSC.[10–12] Subsequently, only 1 other series of 6 patients with small-duct PSC with a limited follow-up has been published.[13] All these previous studies,[10–13] however, have included limited numbers of patients with a relatively short follow-up. Thus, those studies[10–13] had minimal or no power for an appropriate analysis of long-term survival. In addition, because small-duct PSC is a condition affecting only microscopic bile ducts (ie, bile ducts seen only on liver biopsy), it remains uncertain whether cholangiocarcinoma develops in small-duct PSC and whether liver-related morbidity and liver-related mortality in patients with small-duct PSC differ from that seen in patients with large-duct PSC. Hence, we aimed at determining the natural history and long-term prognosis of a large number of patients with well-characterized small-duct PSC. In the current investigation, we extended the follow-up of patients with small-duct PSC reported in those 3 series.[10–12] We sought to determine the outcomes and long-term survival of this series of patients with small-duct PSC and compare their outcomes and survival to that seen in a group of appropriately matched patients with classic, large-duct PSC.

Materials and Methods

The results presented in the current study originate from cohorts of small-duct PSC patients from Nor-

Abbreviations used in this paper: IQR, interquartile range; MRC, magnetic resonance cholangiography; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

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way, Sweden, the United Kingdom, and the United States.[10–12] The criteria for identification of these patients; the diagnostic criteria; and the clinical, biochemical, and histologic variables assessed have previously been reported in detail.[10–12] Briefly, the diagnostic criteria for small-duct PSC included (1) chronic cholestatic liver disease of unknown etiology; (2) percutaneous liver biopsy sample with features suggestive of PSC; (3) normal cholangiogram (ie, endoscopic retrograde cholangiography, percutaneous cholangiography, magnetic resonance cholangiography [MRC]); and (4) appropriate exclusion of other liver or biliary disease using standard clinical, laboratory, imaging, and histologic criteria. None of the patients with small-duct PSC fulfilled the criteria for autoimmune hepatitis according to the International Autoimmune Hepatitis Study Group.[14] Also, none of the patients with small- or large-duct PSC had known risk factors for viral hepatitis, and, in most cases, viral serology was investigated either at baseline or at some point during the follow-up. In the Mayo Clinic cohort,[12] all patients with small-duct PSC were required to have inflammatory bowel disease (IBD), whereas IBD was not a mandatory criteria in the European patients.[10,11] The diagnosis criteria of large-duct PSC were the same as for small-duct PSC, except that a positive cholangiogram showing the typical features of PSC was mandatory.

In the summer of 2006, the different centers reexamined their respective cohort of patients with small-duct PSC who were reported in the original publications. A detailed and comprehensive review of the medical files of these patients was performed by the principal investigator in each center, and data on clinical outcomes and survival were recorded. The starting point (ie, time zero) for follow-up was the date of the diagnostic cholangiogram (ie, normal in small-duct PSC and abnormal in large-duct PSC) as previously described[10–12]; the follow-up was extended until mid-2006. The end points recorded were death, date of liver transplantation, and last date of follow-up. The following information was obtained in all patients: date of diagnosis, date of last follow-up, and total duration of follow-up. Laboratory tests at last follow-up and information about symptoms and signs developing during follow-up were obtained. Liver-related signs recorded included gastroesophageal varices, variceal bleeding, ascites, encephalopathy, and itching. Data on the histologic stage (extent of fibrosis) at diagnosis were recorded and divided into early (stage I–II) and advanced (stage III–IV) disease. Serum bilirubin values at diagnosis were also recorded and compared between the 2 groups. Presence and type of IBD were recorded in each case. Data on immunosuppressive therapy for IBD were collected and the proportion with long-term immunosuppression (at least 1 year of treatment with azathioprine or methotrexate or treatment with corticosteroids for more than 6 months) was compared between the 2 groups. The proportion of patients treated with ursodeoxycholic acid (UDCA) was analyzed, and the total duration of UDCA treatment in months was recorded. The number of patients undergoing repeated cholangiography (endoscopic retrograde cholangiography, percutaneous cholangiography, MRC) during the follow-up was recorded. The cholangiography images were interpreted by radiologists with experience in biliary tract disease in each participating center. In patients with small-duct PSC, repeated cholangiographies were performed solely for the purpose of this study in the vast majority of patients from Sweden as described.[11] Cholangiographies were only repeated when considered clinically indicated in patients from the Mayo Clinic[12] and in the Norwegian and United Kingdom cohorts.[10] The indication for a repeated cholangiography was based on worsening of liver tests such as increase in alkaline phosphatase and/or serum bilirubin and new symptoms such as cholangitis, itch, or pain considered clinically significant by the treating physician. The development of cholangiocarcinoma was noted, and the number and causes of death were analyzed and divided into liver-related and non-liver–related deaths. The study was approved by appropriate regulatory bodies in all participating medical institutions, and all patients had given informed consent for participation in medical research.

Matching Process

Each patient with small-duct PSC was randomly matched to 2 patients with well-characterized large-duct PSC (1:2 matching design) by gender, age (±3 years), calendar year of diagnosis (±3 years), and medical institution. In the 3 original cohorts, a total of 83 patients with small-duct PSC were reported including 32 from Sweden, 22 from Oxford, 18 from the Mayo Clinic, and 11 from Oslo.[10–12] This matching process was accomplished in all except some patients from the Oslo center. Specifically, for the 11 patients with small-duct PSC from Oslo, only 13 controls with large-duct PSC were identified who could be appropriately matched because of large difference in either age or calendar year of diagnosis. Thus, a total of 157 patients with large-duct PSC were compared with the 83 patients with small-duct PSC.

Statistical Analysis

Continuous variables are presented as medians and interquartile range (IQR). The comparison of continuous variables between the 2 groups was performed by the nonparametric Wilcoxon rank sum test; dichotomous variables were compared using the χ^2 or the Fischer exact test where appropriate. The Kaplan–Meier product limit was used for estimating survival free of liver transplantation. The comparison of survival distribution between the small- and the large-duct PSC patients was performed using the log-rank test.[15]