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MAGNETIC RESONANCE

Intrahepatic cystic biliary dilatation constitutes a significant prognostic factor in patients with primary sclerosing cholangitis

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Abstract

Aims To evaluate the prognostic value of cystic dilatation (CD) of the intrahepatic biliary ducts in patients with primary sclerosing cholangitis (PSC).

Methods A single-center cohort of 205 patients with PSC from 2003 to 2016 was analysed. CD was defined by quantitative and qualitative criteria. Radiological and clinical courses were assessed. A Kaplan-Meier analysis was used to estimate cumulative survival without liver transplantation (LT) from the date of PSC diagnosis. A log-rank test was performed to compare survival time of PSC patients with and without CD.

Results A total of 15 (7.3%) PSC patients (12 males) with a median age of 23 years at diagnosis had CD. Five patients had one CD; seven patients had two or three CDs; and three patients had diffuse CD. CDs ranged in small diameter size from 12 to 32 mm. Radiological evolution of CD was markedly variable. However, a radiological worsening of PSC over time was observed in all patients. The clinical course was characterized by the occurrence of complications in most patients. Half of the patients with CD underwent LT at a median time of 40 months from diagnosis of CD and the median survival time from PSC diagnosis was significantly lower than in PSC without CD (10.7 vs. 23.4 years; HR 3.8, 95% confidence interval: 1.7–8.3, $p = 0.001$).

Conclusions CD in PSC is an unusual condition that mostly affects young patients. It is characterized by a rapid, unfavorable course and constitutes a significant prognostic factor.

Key Points

- *Cystic dilatation of the intrahepatic biliary ducts affects young patients with primary sclerosing cholangitis and is characterized by a markedly variable radiological evolution.*
- *Biliary wall inflammation, found in explanted livers, could be a key feature in the pathogenesis of cystic dilatation.*
- *Cystic dilatation of the intrahepatic biliary ducts is characterized by an unfavorable course and constitutes a significant prognostic factor of primary sclerosing cholangitis.*

Keywords Cholangitis · sclerosing · Cholangiography · Magnetic resonance imaging

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Abbreviations

AIH	Autoimmune hepatitis
CD	Cystic dilatation
ERCP	Endoscopic retrograde cholangiopancreatography
ESLD	End-stage liver disease
IBD	Inflammatory bowel disease
LT	Liver transplantation
MRC	Magnetic resonance cholangiography
MRI	Magnetic resonance imaging
MRS	Mayo risk score
PSC	Primary sclerosing cholangitis
SLE	Systemic lupus erythematous
UC	Ulcerative colitis
UCDA	Ursodeoxycholic acid

Introduction

Primary sclerosing cholangitis (PSC) is a rare, heterogeneous, chronic cholestatic liver disease characterized by inflammation and fibrosis of the biliary tree [1, 2]. Magnetic resonance cholangiography (MRC) is recommended as the first-line non-invasive imaging method for patients with suspected PSC [3–6]. The primary MR cholangiography features of PSC include multifocal intra- and extrahepatic bile duct stenoses alternating with slightly dilated ducts, but these findings are markedly variable and probably related to the stage of the disease process and its pattern [7]. In contrast with other causes of biliary obstruction such as tumors, biliary dilatations in PSC are usually mild to moderate and when a marked dilatation is present a cholangiocarcinoma complicating PSC should be excluded [6, 8].

In our Institution, the policy of the management of PSC includes a routine yearly MRI/three-dimensional (3D)-MRC. In this annual follow-up, we regularly observed an uncommon form of PSC characterized by cystic dilatation (CD) of intrahepatic biliary ducts not related to a downstream biliary stenosis. Only sporadic cases of CD of biliary ducts in PSC have been reported in the literature [9–14]. Moreover, the clinical significance and prognostic value of this particular disease's presentation have not yet been assessed. The goal of the present study was thus to determine the prognostic value of CD in PSC.

Patients and methods

Study population

Radiological files from a series of 310 consecutive patients with PSC were retrospectively reviewed. MRCs were performed between 2003 (implementation of 3D-MRC in our center) and April 2016 (date of inclusion termination). Diagnosis of PSC in these patients was based on the aforementioned criteria [3–5]. Patients who underwent at least two 3D-MRCs with at least a 1-year interval were included in the study. Exclusion criteria were normal MRC, secondary sclerosing cholangitis, cystic fibrosis, patients with only one MRC and small-duct PSC as shown in the flow chart (Fig. 1).

Cystic dilatation of the intrahepatic biliary ducts was defined by a marked dilatation of the intrahepatic biliary ducts measuring at least 10 mm of small diameter with biconvex contours (loss of parallelism of biliary duct edges), not related to a downstream biliary stricture. Connection of CDs with intrahepatic ducts was confirmed by analysis of thin source images. This value of 10 mm corresponds to the double of a previously described major dilatation of the intrahepatic bile ducts (≥ 5 mm) [15] and was the threshold used by Harrison and Hubscher in a previous study [16].

Our faculty hospital's Institutional Review Board approved the review of radiological and clinical data for this study. Informed consent was waived for this retrospective study.

MRC technique

MRI was performed according to the protocol for 3D-MRC previously described by our group and in line with the indications given by the international PSC study group in the recently published position statement [17, 18]. T1-, T2-weighted MR images and 3D-MRC were performed in all cases. When performed, a 3D fat-suppressed T1-weighted ultra-fast gradient-echo acquisition was done before and after intravenous administration of 20 ml of Gd-DOTA (Dotarem, Guerbet, Aulnay-sous-Bois, France), with hepatic arterial,

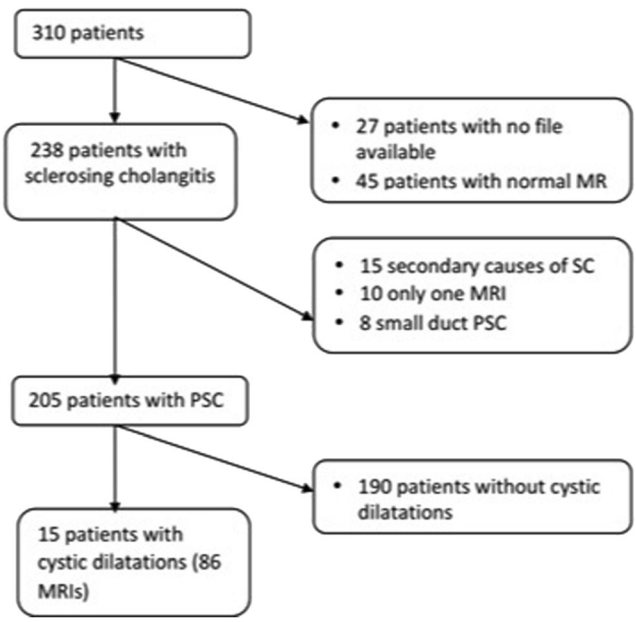

Fig. 1 Patients suspected to have primary sclerosing cholangitis (PSC)

portal venous and equilibrium phase acquisition (30 s, 80 s and 3 min, respectively).

Data analysis

Two radiologists (with 25 and 12 years, respectively, of experience in abdominal imaging) reviewed all MRCs in consensus. The criteria of image analysis included the following:

MRC features of cystic biliary dilatation

a) Number of CDs (only one CD [group 1], two or three CDs [group 2], and more than three CDs [group 3]), location, and maximum size
b) Presence of calculi within CD
c) Contrast enhancement of wall of dilated biliary ducts
d) Evolution of CD over each MRC during patient follow-up. The 'reference MRC' has been defined as the MRC in which the maximum diameter of the CD was present to define a time point that has been used to analyse clinical data.

MRC features of PSC

We analysed the first available MRC and the reference MRC (MRC with maximal diameter of CD) with regard to an interpretation standard model already described [15]. This standard model of interpretation includes analysis of the following:

a) Intrahepatic and extrahepatic biliary ducts with regard to stenosis, dilatation and biliary wall enhancement.
b) Associated liver-related signs including dysmorphy, heterogeneity of liver enhancement after contrast injection and portal hypertension.
c) Two MRI progression risk scores (i.e. 'ANALI' scores) [7] without and with gadolinium were assessed on the first available MRC [MRI progression risk score (without gadolinium) = 1 × dilatation IHBD + 2 × dysmorphy + 1 × portal hypertension and MRI progression risk score (with gadolinium) = 1 × dysmorphy + 1 × parenchymal enhancement heterogeneity.

Clinical characteristics

Information from the medical files was reviewed by an independent hepatologist (with 10 years of experience in hepatology). The following data were collected:

– Clinical presentation of the disease at diagnosis and at reference MRC (symptoms and laboratory values)
– Therapy started before the development of CD (especially type and length of immunosuppressive therapy)
– Clinical evolution of these patients over time: status, development of complications of disease. We considered April 2017, 1 year after the end of inclusion date, to be the end of the follow-up period.

Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation, median (range) or number (%). Continuous variables were compared using the Wilcoxon-Mann-Whitney test. Quantitative variables were compared using the chi-square test or Fisher's exact test when appropriate. The median follow-up of patients was calculated from the diagnosis of PSC to the last follow-up. Kaplan-Meier's survival analysis was performed to estimate cumulative survival from the date of PSC diagnosis. Median survival times of patients with and without CD were calculated for death or liver transplant. The statistical comparison between survival of patients with and without CD and the calculation of the hazard ratio of death or liver transplant were performed using the log-rank test [19]. Statistical analysis was performed using IBM SPSS Statistics 24.

Results

Study population

After reviewing the MRCs of the 310 patients, 205 patients were found to have a typical radiological pattern of PSC. 105 patients were excluded because of a normal MRC, availability of only one MRC or diagnosis of secondary sclerosing cholangitis or small duct PSC as shown in the flow chart (Fig. 1). Finally, 15 of 205 (7.3%) patients were found to have CD-PSC. Clinical features at the time of diagnosis in PSC patients with and without CD are presented in Table 1. The 15 patients with CD were primarily male (n=12), with a young age at diagnosis of PSC (range 14–43 years, median 23 years) and at reference MRC (range 19–63 years, median 29 years). The median follow-up time from PSC diagnosis to the last follow-up date was 8 years (range 3–28 years). A total of 86 MRCs were obtained in these 15 patients (two to ten MRCs for each patient). Eleven (73%) patients developed an inflammatory bowel disease (IBD) before (n=7), at (n=2) or following (n=2) diagnosis of PSC. PSC patients with CD were younger, had higher levels of bilirubin, alkaline phosphatase and aspartate aminotransferase, and more frequently had an intra- and extrahepatic localization than did PSC patients without CD (Table 1).

Table 1 Clinical characteristics of PSC patients with and without CD at the time of PSC diagnosis

	PSC patients with CD (n=15)	PSC patients without CD (n=190)	*p*
Male gender	12 (80%)	122 (64%)	NS
Age at PSC diagnosis (y)	25 ± 10	35 ± 15	0.013
Radiological localization			
- Intrahepatic only	0 (0 %)	85 (50%)	0.001
- Extrahepatic only	0 (0 %)	4(2%)	
- Intra-extrahepatic	15 (100 %)	82 (48%)	
PSC-AIH overlap	2 (13%)	17 (9%)	NS
IBD	11(73%)	130/190 (68%)	NS
Histological stage III-IV (advanced fibrosis cirrhosis) at diagnosis	4/9 (44%)	21/106 (20%)	NS
Total bilirubin (μmol/L)	38.3 ± 27.0	25.7 ± 48.7	0.047
AP (× ULN)	3.2 ± 1.7	1.8 ± 1.4	0.016
AST (× ULN)	3.8 ± 2.3	1.8 ± 1.7	0.004
Albumin (g/L)	39.4 ± 5.7	41.1 ± 5.7	NS
Platelets (*10^9/L)	278 ± 67	297 ± 120	NS

All variables are expressed as mean ± standard deviation

PSC primary sclerosing cholangitis, *CD* cystic dilatation, *AP* alkaline phosphatase, *AST* aspartate aminotransferase, *ULN* upper limit of normal

MRC features of CD

Five patients had a single CD (group 1); seven patients had two or three CDs (group 2); and three patients had diffuse CDs (group 3) (Table 2; Figs. 2, 3 and 4). Connection of CDs with intrahepatic biliary ducts was confirmed by analysis of source images in all cases. All CDs had biconvex contours. CDs were hypointense on T1-weighted MR images and hyperintense on T2-weighted MR images and on MRC images. Maximum CD was located within the left intrahepatic biliary ducts in eight patients, the right intra hepatic biliary ducts in six patients, and within the caudate lobe in one patient. CDs of the intrahepatic biliary ducts ranged between 12 and 32 mm (mean, 19 mm). Calculi were observed within the CD in 12 patients. Calculi were hyperintense on T1- and hypointense on T2- and MRC images in

Table 2 Magnetic resonance cholangiography features of cystic dilatation and primary sclerosing cholangitis (PSC)

Patient	Sex	Age, y	Group	Cystic dilatation size	Calculi	Contrast enhancement	Cystic dilatation on first MRI	Evolution	Anali without injection	Anali with injection
1	M	19	1	12	+	+	+	I	3	1
2	M	42	1	13	+	+	-	S	4	I
3	M	63	1	12	+	-	+	F	5	NA
4	F	23	1	19	+	NA	+	I	4	2
5	F	24	1	29	+	+	-	W	5	2
6	M	24	2	32	+	+	+	I	5	2
7	M	25	2	30	+	+	-	I	4	2
8	M	39	2	21	-	+	-	I	2	NA
9	M	29	2	16	+	+	+	I	5	2
10	M	20	2	20	+	+	+	I	2	1
11	M	21	2	12	+	+	-	I	0	NA
12	M	40	2	14	-	+	-	W	0	NA
13	M	33	3	24	+	+	+	F	4	2
14	M	38	3	16	-	+	-	F	1	NA
15	F	30	3	17	+	+	-	F	2	NA

NA not applicable, *I* improvement, *S* stability, *W* worsening, *F* fluctuation

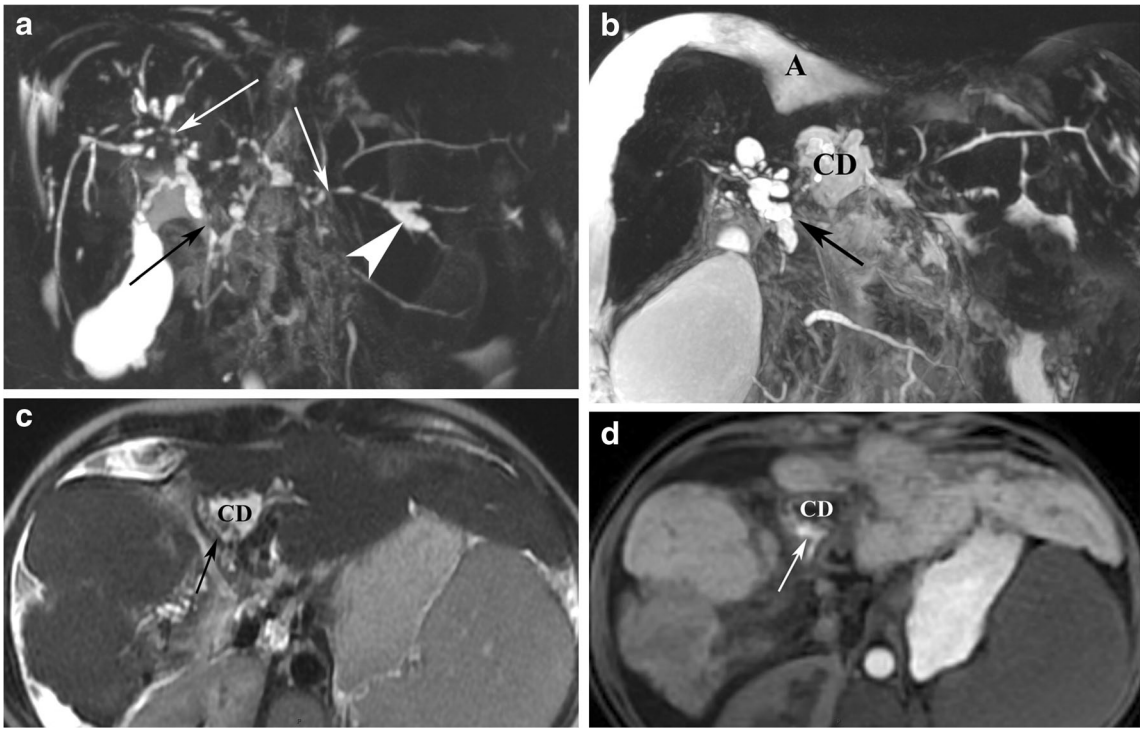

Fig. 2 A 24-year-old woman with a single cystic biliary dilatation. Magnetic resonance cholangiography (MRC) performed 48 months before reference MRC (**a**) demonstrates severe stenosis of main biliary duct (black arrow) and severe and diffuse stenosis of intrahepatic biliary ducts (white arrows). Dilatation of intrahepatic biliary ducts (arrowhead) is also observed. Reference MRC (**b**) demonstrates a long severe stenosis of main biliary duct with dilatation of main biliary duct above (black arrow). Single cystic dilatation of left intrahepatic biliary duct (CD) is demonstrated. Perihepatic ascites (A) is also demonstrated. Corresponding T2- (**c**) and T1-weighted MR images (**d**) demonstrate calculi (arrows) within cystic dilatation (CD)

all cases. On the other hand, calculi were not observed within undilated biliary ducts (Figs. 2 and 4).

In one patient, contrast injection was not performed. In the other 14 patients, contrast enhancement of the CD wall was observed in 13 patients. Contrast enhancement was observed at the arterial phase in ten patients and at portal and equilibrium phases in all 13 patients (Table 2, Fig. 3).

During follow-up, the evolution of CD was markedly variable. CDs were present at the first available MRC in seven patients. In the other eight patients, CD appeared during follow-up. There was an improvement over time for eight patients, including a complete disappearance of CD in four patients. In two patients, CD worsened during follow-up. In four patients, CD was fluctuant with alternation of worsening and improvement (Fig. 4). CD was stable in only one patient (Table 2). With regard to MRC features of CD, we did not observe any significant difference between the three groups.

MRC features of PSC

In the first available MRC, performed at a median time of 2.1 months from the diagnosis of PSC, all patients presented abnormalities of both intra- and extrahepatic biliary ducts. All 15 patients had stenosis of intrahepatic biliary ducts. Fourteen of 15 patients had stenosis of the common bile duct. With regard to liver parenchyma, eight of 15 patients had liver dysmorphy. Six patients had features of portal hypertension. Only nine of 15 patients had an arterial phase contrast-enhanced T1-weighted sequence, and among those, eight had a heterogeneous enhancement of the liver parenchyma. Nine of 15 patients had an ANALI score without gadolinium highly predictive of radiological progression (i.e. ≥ 3). Six of nine patients who had gadolinium injection had an ANALI score with gadolinium of 2 (i.e. highly predictive of radiological progression).

In the reference MRC, all 15 patients had severe stenosis of intrahepatic biliary ducts. Fourteen of 15 patients had stenosis of the common bile duct. With regard to liver parenchyma, 12 of 15 patients had liver dysmorphy. Nine patients had features of portal hypertension. Thirteen of 15 patients had an arterial phase contrast-enhanced T1-weighted sequence, and among those, 11 had a heterogeneous enhancement of the liver parenchyma. Moreover, among these 13 patients, 11 had contrast enhancement of the biliary wall. Despite marked variability over time of CD, all PSC worsened on overall primary course. No cases were stable or improved. With regard to MRC features of PSC, we did not observe any significant differences between the three CD groups.

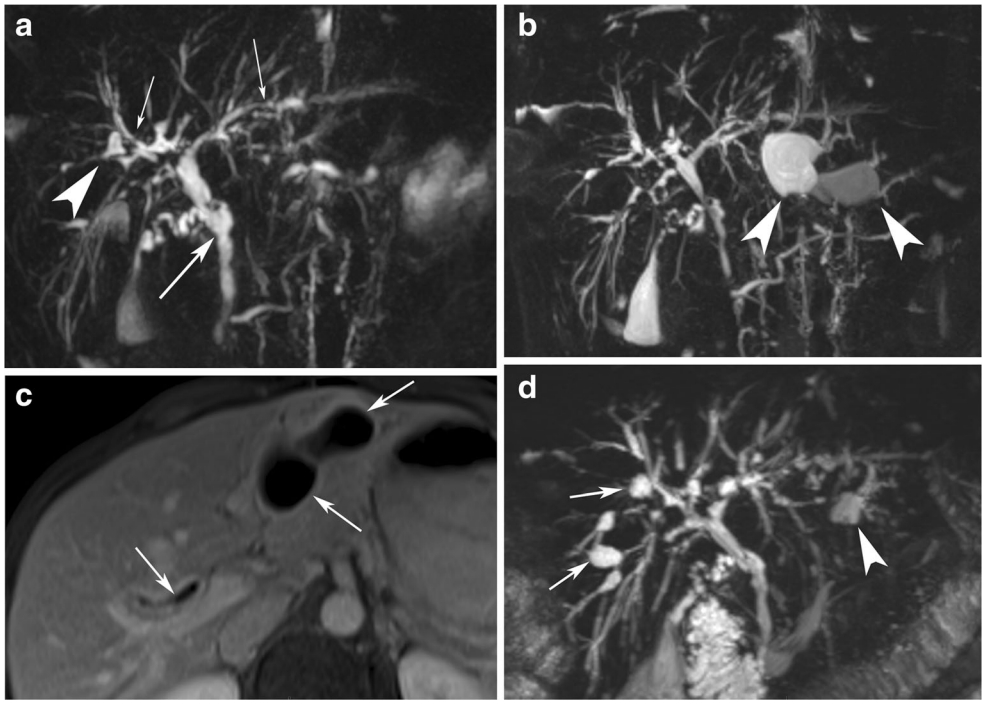

Fig. 3 A 40-year-old man with two cystic biliary dilatations. Magnetic resonance cholangiography (MRC) performed 24 months before reference MRC (**a**) demonstrates mild stenosis of main biliary duct (arrow) and severe stenosis of the intrahepatic biliary ducts (thin arrows). Dilatation of intrahepatic biliary ducts (arrowhead) is also demonstrated. Reference MRC (**b**) demonstrates two cystic biliary dilatations within the left lobe of the liver (arrowheads). Contrast-enhanced T1-weighted MR image (**c**) in the transverse plane demonstrates wall enhancement of cystic dilatation and of right biliary duct (arrows). MRC performed 60 months after reference MRC (**d**) demonstrates diffuse severe stenosis of intrahepatic biliary ducts with dilatation of intrahepatic biliary ducts (arrows). Cystic dilatation of the left intrahepatic biliary duct (arrowhead) has markedly decreased

Clinical characteristics

Regarding medical therapy, all patients were treated with ursodeoxycholic acid (UDCA) since PSC diagnosis at a median dose of 15.5 mg/kg/day for 5 months (range, 0–198 months) before the development of CD. Due to the concomitant presence of overlap syndrome with autoimmune hepatitis (AIH), IBD or other inflammatory disease, 13 (87%) patients underwent immunosuppressive therapy. During the follow-up after the reference MRC, two patients with IBD developed colorectal cancer diagnosed during endoscopic surveillance, seven (44%) patients developed two or more episodes of acute bacterial cholangitis, and two of them underwent multiple therapeutic ERCP. One patient developed a diffuse cholangiocarcinoma at the age of 32 years, three patients developed ascites, and two developed hepatic encephalopathy. Because of severe course of the disease, nine (60%) patients have been listed to LT, and eight of them underwent LT in an average of 40 months (range, 6–42 months) after the diagnosis of CD. The median age at the time of LT was 28 years (range, 20–63 years).

No correlation was observed between the clinical progression observed in all patients and the variable radiological course of the CD.

In the 190 PSC patients without CD, 22 patients underwent LT and 11 patients died during a median follow-up of 9 years (1–35 years). During follow-up patients with CD more frequently developed acute bacterial cholangitis (47% vs. 5%, $p = 0.02$) and more frequently reached the primary end point (liver transplantation or death) (42% vs. 7%, $p = 0.003$).

Histological examination of the eight explanted livers demonstrated the presence of cirrhosis in half of the cases and advanced fibrosis in the other half. All cases showed dilatations of medium and large biliary ducts associated with mural inflammation. Seven cases showed the presence of severe inflammation and presence of ulceration and necrosis of biliary epithelium. The lumen of dilated ducts contained many greenish and brown calculi (Fig. 5) and, in two cases, also polymorphonuclear leukocytes, and an agglomerate of germs and yellowish material.

Five cases showed ductopenia, and two cases showed ductular reaction. Six cases showed periductal concentric fibrosis of medium-size bile ducts, extended to large ducts in five cases and to small biliary ducts in three cases. Fibro-obliterative lesions were present in five cases. Mild-to-moderate inflammation of the parenchyma (A1 to A2 according to the METAVIR score, used to described activity (necrosis and inflammation) and fibrosis of liver parenchyma [20]) was observed in six cases.

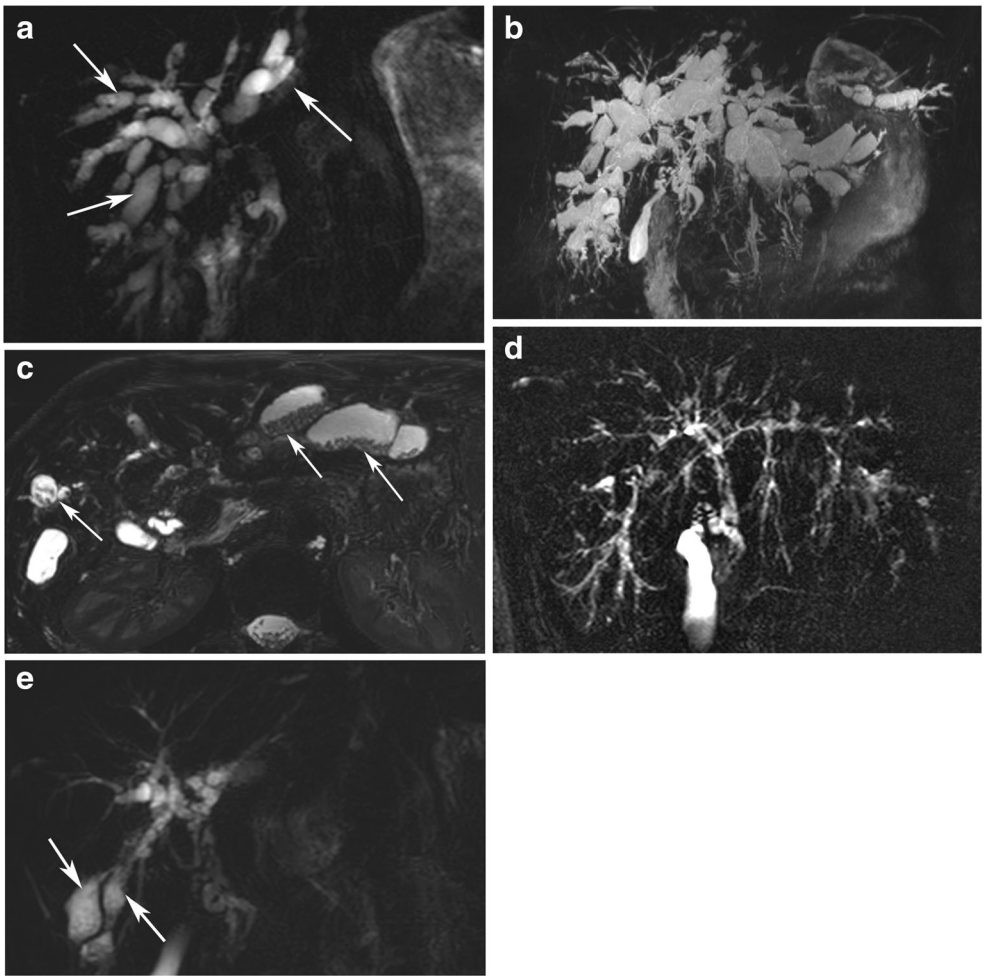

Fig. 4 A 33 year-old-man with diffuse cystic biliary dilatation. Magnetic resonance cholangiography (MRC) performed 3 months before reference MRC (**a**) demonstrates diffuse and severe stenosis of intrahepatic biliary ducts with dilatation of intrahepatic biliary ducts (arrows). Reference MRC (**b**) demonstrates diffuse cystic biliary dilatation. Twenty-millimeter maximum intensity projection reconstructed image in the transverse plan (**c**) demonstrates multiple calculi (arrows) within dilated biliary ducts. MRC performed 12 months after reference MRC (**d**) demonstrates severe diffuse stenosis of the biliary duct without cystic biliary dilatation. MRC performed 40 months after reference MRC (**e**) demonstrates cystic biliary dilatation within the right lobe of the liver (arrows)

Survival analysis

In the 15 patients with intrahepatic CD of biliary ducts, that half-life without LT was 10.7 years (95% CI 6.6–14.8 years) from the diagnosis of PSC, 4.8 years (95% CI 1.8–7.7 years) from the diagnosis of CD, and 4.2 years (95% CI 0–8.4 years) from the reference MRC.

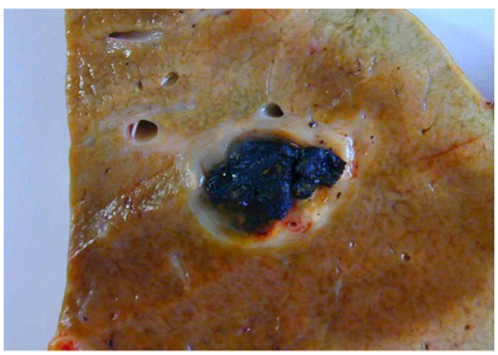

Fig. 5 Transversal section of the VIIth segment of an explanted liver demonstrating a CD of 25 mm of large diameter with whitish bile duct wall and plenty of brown calculi

The 15 patients with CD had a significantly lower survival without LT compared to the control group composed by the other 190 PSC without CD (10.7 vs. 23.4 years, $p < 0.001$). The 5- and 10-year rates of survival were 79% and 45% in PSC patients with CD versus 96% and 84% in the control group (PSC patients without CD) ($p < 0.001$; HR 3.8 [95% CI 1.7–8.3]) (Fig. 6).

Discussion

Of the 205 PSC patients with large duct PSC who were followed in our tertiary center, we found that 15 (7.3%) presented with CD. The main characteristic of CD was its marked variability over time with frequent spontaneous improvement or an alternating of improvement and worsening. Because of variability over time of CD we cannot exclude that CD was missed in some patients at their annual MR follow-up, thereby decreasing the true frequency of CD. On the other hand, as the present study was conducted in a tertiary referral center, it is feasible that the occurrence of CD in patients with PSC represents an overestimation with regard to general population

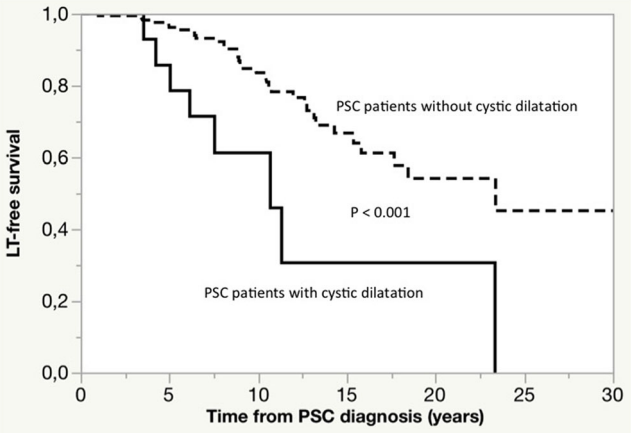

Fig. 6 Survival of primary sclerosing cholangitis (PSC) patients with intrahepatic cystic biliary dilatation (CD) (continuous line) and control PSC patients without CD (dotted line). Survival of PSC patient with CD is significantly lower than patients without CD ($p < 0.001$)

with PSC. The patients with CD-PSC were characterized by a young age, a previous history of immunosuppressive therapy in half of them (mostly for the treatment of associated disease), severity of PSC cholangiographic features, and the overall rapid worsening of the disease in all cases with the necessity of LT in half of them. Furthermore, we observed that patients with CD-PSC had an overall survival rate significantly lower than patients without CD. Indeed, the transplant-free survival from the diagnosis of PSC in patients with CD was 45% at 10 years compared to 84% in PSC patients without CD. Specifically, acute bacterial cholangitis was statistically more frequent in patients with CD, probably because of severe alterations of biliary duct observed in the CD group.

Interestingly, we did not find any difference with regard to CD characteristics, PSC features and clinical or radiological evolution between subgroups of patients with a different number of CDs. This suggests that a single CD may have the same prognostic significance as a diffuse pattern and by itself constitutes a cholangiographic marker of more aggressive disease and of poor outcome. Interestingly, biliary wall enhancement at the arterial phase was commonly observed in CD. Such arterial biliary wall enhancement could be the result of biliary wall inflammation, and this marked inflammation could be a key feature in the pathogenesis of CD. This hypothesis is sustained by the observation that 40% of patients had a history of recurrent cholangitis before the development of the maximum size of CD, and the histological examination of explanted livers showing severe mural inflammation, ulcerations and necrosis of the biliary epithelium. Destructive inflammation was observed in all but one explanted CD-PSC livers, differing from the results previously reported by Harrison and Hubscher, in which it was present in one-third of cases [16]. Ischemia could be an additional mechanism, as severe ischemic cholangitis observed after LT may also exhibit cystic biliary dilatations that may improve during evolution with a pattern similar to our series [21]. On the other hand, we do not assume that cystic dilatation was related to an obstructive pattern because of the specific pattern of cystic dilatation.

To our knowledge, this is the first series focusing on this cystic dilated form of PSC. Only six cases with CD of the intrahepatic bile duct were described as sporadic case reports in the literature [9–14]. As reported in the previously published case reports, we think that it is important to differentiate PSC with CD from other causes of CD such as Caroli's disease [22]. CD in PSC is easily recognized because of the presence of other biliary signs of PSC such as diffuse intra- and extrahepatic biliary strictures and parenchymal abnormalities, which are not present in Caroli's disease. Moreover, the fluctuant course over time appears to be a characteristic feature of PSC-associated CD, which is never observed in Caroli's disease.

The mechanisms involved in the development of CD in PSC patients are still unknown, but we might suggest a possible role for an acquired defect of tight junctions linked to inflammation that could be responsible for deformation of biliary ducts. Moreover, alterations in cholangiocyte primary cilia, as recently reported in polycystic liver disease, that could lead to an increased cholangiocyte proliferation through TGR5 signalling alterations [23] could be involved. Finally, a role for infection in the CD could be a possibility, since recurrent infections of the biliary tree were observed in these patients of whom half had been treated with immunosuppressive therapy before CD development due to concomitant AIH or IBD. Our group already reported different evolution patterns of usual PSC. In a series of 64 patients, we observed a worsening of radiological features in 37 (58%) patients, whereas the disease remained stable in the other 27 (42%) patients [15].

Observational studies have inherent limitations. The number of patients was relatively low and, because of the retrospective nature of the study, contrast-enhanced sequences were not available for all patients and complete clinical data were missing for some. Therefore, external validation of this single-center experience is required.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Lionel Arrivé M.D.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and Biometry One of the authors, Christophe Corpechot, has significant statistical expertise.

Informed Consent Written informed consent was waived by the Institutional Review Board.

Ethical Approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Observational
- Performed at one institution

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