Portal cholangiopathy: radiological classification and natural history

Elba Llop,[1] Carmen de Juan,[2] Susana Seijo,[1] Ángeles García-Criado,[2] Juan G Abraldes,[1,3] Jaume Bosch,[1,3] Juan Carlos García-Pagán[1,3]

[1]Hepatic Hemodynamic Laboratory, Liver Unit, Institut de Malalties Digestives i Metaboliques, Hospital Clínic-Institut de Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain
[2]Centre de Diagnostic per l'Imatge, Hospital Clinic, Barcelona, Spain
[3]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain

Correspondence to
Juan Carlos García-Pagán, Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clínic, Villarroel 170, Barcelona 08036, Spain; jcgarcia@clinic.ub.es

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ABSTRACT

Background/aim Portal cholangiopathy (PC) is identified in over 80% of patients with portal vein thrombosis (PVT), but the true impact of this condition is not well known. This study investigated the relationship between cholangiographic abnormalities and clinical symptoms and their evolution over time.

Patients/methods 67 consecutive patients with non-tumoral non-cirrhotic PVT following a standardised diagnostic protocol were studied. Findings at magnetic resonance angiography and cholangiography (MRA/MRC) were classified as no PC, grade I PC (minimal irregularities), grade II PC (stenosis without dilation) and grade III PC (stenosis with dilation). These changes were related to the presence of symptoms.

Results 22 patients were diagnosed with acute PVT and 45 presented with chronic PVT. Overall, 52 patients had PC (6 grade I, 12 grade II and 34 grade III). 14 patients developed symptoms, all of whom had grade III PC. 30% of patients with acute PVT developed grade III PC within 1 year. In those without grade III PC, follow-up MRC showed no progression of the biliary lesions to grade III. The 5-year probability of developing symptoms of PC after acute PVT was 19%. In 45 patients with chronic PVT, MRA/MRC showed grade III PC in 26. In those without grade III PC, no progression of PC was observed at further follow-up MRC. The prevalence of symptoms of PC in these patients was 22%.

Conclusions PC is a frequent complication that develops and stabilises early after PVT and becomes symptomatic in its more severe form (grade III). These data suggest that follow-up MRA/MRC is not mandatory and strategies to prevent the development of symptoms of PC should be tested in patients with grade III PC.

Significance of this study

What is already known about this subject?

- Portal cholangiopathy (PC) is an entity that consists of abnormalities of the intrahepatic and extrahepatic biliary system and gallbladder that occur in patients with portal cavernoma.
- PC is identified in over 80% of patients by means of cholangiographic imaging techniques. However, clinical effects (cholecystitis, cholangitis, jaundice) are uncommon with a reported frequency up to 38%.
- To date, all reported series of PC have been cross-sectional.

What are the new findings?

- PC is a frequent complication in patients with non-tumoral non-cirrhotic portal vein thrombosis (NC-PVT). This study develops a novel radiological classification for PC that, for the first time, shows a correlation with the probability of developing biliary symptoms.
- Not all abnormalities of the biliary tree found at cholangiography are associated with the same risk of developing symptoms; PC symptoms seem to occur only in patients with grade III PC.
- Grade III PC is present in about 50% of patients with NC-PVT.
- PC develops early after acute PVT if non-recanalisation is achieved. Once it occurs, the capacity of biliary abnormalities to progress after 1 year of evolution is extremely low.

How might it impact on clinical practice in the foreseeable future?

- The finding of grade III PC at cholangiography may be useful for identifying patients with a higher risk of developing symptoms of PC and therefore potential candidates to test strategies to prevent the development of symptoms of PC.
- Future studies are needed to evaluate possible risk factors for developing PC and to determine the best treatment for patients who develop symptoms of PC.

INTRODUCTION

Portal cholangiopathy (PC) is an entity that consists of abnormalities of the intrahepatic and extrahepatic biliary system and gallbladder that occurs in patients with portal cavernoma.[1–5] These abnormalities are identified by means of cholangiographic imaging techniques in over 80% of patients with portal vein obstruction.[1 6] Despite the high rate of biliary tract abnormalities, clinical consequences such as cholecystitis, cholangitis and jaundice are uncommon with a reported frequency ranging from 5% to 38% in different series.[1 6 7] To date, all reported series of PC have been cross-sectional.[1 2 6 8–11] There are limited data on the relationship between radiological abnormalities and clinical manifestations and on the evolution of these radiological changes over time. In addition, the natural history of PC after the acute episode of portal vein thrombosis (PVT) has not been studied. The aim of this study was to evaluate these issues in a cohort of patients with portal cavernoma and, in particular, in a subgroup of patients in which the episode of acute PVT was recognised.

METHODS

Patients

From January 1996 to September 2008, 93 consecutive patients with non-cirrhotic non-tumoral portal vein thrombosis (NC-PVT) seen at our unit were considered eligible for the study. In all patients liver cirrhosis, Budd–Chiari syndrome, idiopathic portal hypertension and malignancy were excluded according to clinical history and follow-up, biochemical data (including markers of viral infection and autoimmunity), liver imaging tests and/or liver biopsy when necessary. Patients with NC-PVT were managed and followed according to the protocol established at the Liver Unit, including complete screening for known inherited or acquired prothrombotic disorders.[12–15] The diagnosis of thrombosis and evaluation of its extension is initially performed with Doppler ultrasound, CT scanning, MR angiography (MRA) and/or arteriography. Patients are followed up 3 months after the initial diagnosis and every 6 months thereafter or whenever a clinical manifestation appears. Since 2003, MR cholangiography (MRC) coupled with MRA (MRA/MRC) was included in the routine evaluation of incidental patients and of those previously diagnosed and in active follow-up. MRA/MRC permits simultaneous evaluation of extension of the vascular thrombosis, the distribution of collateral veins and the biliary tree to assess the presence and degree of PC in a single non-invasive investigation. In addition, MRA/MRC is scheduled during follow-up to assess the development or progression of PC and is repeated whenever the patient develops symptoms related to PC.

MRA/MRC images were reviewed by the same radiologist (CdJ) who was blind to the clinical history. MR was performed in a 1.5 T MR imaging unit using a phased-array coil. The MRC protocol consisted of heavily T2-weighted images using breath-hold single-shot-fast-spin-echo sequences and included multiple thin slabs (4 mm) orientated in the axial and coronal plane and multiple oblique thick slabs (30–60 mm) orientated radially around the common bile duct. MRA was performed in the axial or coronal plane using fast-spoilt gradient-echo sequence during the administration of intravenous gadolinium (gadopentate dimeglumine) and arterial, portal and delayed phases were obtained. Post-processing of images was performed to obtain three-dimensional reconstructions of the vascular map. Liver MR included also axial T2-weighted and in and out of phase T1-weighted sequences. MRC images were evaluated for the presence of biliary stenoses (number and location), upstream dilation, angulations, indentations and irregularities of the parietal duct. An abnormal increase in the calibre of the ducts located proximal to a relatively narrow segment was considered significant for ductal dilation. Abnormalities of the biliary tree were classified into different degrees of severity: no abnormalities; grade I (irregularities or angulations of the biliary tree); grade II (indentations or strictures without dilation); and grade III (strictures with dilation; biliary dilation was considered when the intrahepatic duct was ≥4 mm or when the extrahepatic duct was ≥7 mm) (figure 1). Biliary abnormalities were also classified according to a previous classification suggested by Chandra and Sarin[16] as type I (involvement of extrahepatic bile duct), type II (involvement of intrahepatic bile ducts only), type IIIa (involvement of extrahepatic bile duct and unilateral intrahepatic bile duct left or right) and type IIIb (involvement of extrahepatic bile duct and bilateral intrahepatic ducts). The presence of gallstones or common bile duct stones was also reported. Extension of the thrombosis to the different segments of the portal venous axis, the presence of portal–systemic collaterals and of extrahepatic or intrahepatic cavernoma was also evaluated.

In a subgroup of patients an episode of acute PVT was identified. Acute PVT was defined as an episode of recent abdominal pain in which imaging studies showed a normal liver with absence of flow in part or all of the lumen of the portal venous vessels and solid material in the vessel lumen or in its left and right branch without evidence of porto–portal or portal–systemic collateral circulation.[13]

Patient charts were retrospectively reviewed and epidemiological, clinical and MRA/MRC data were recorded on a previously designed case report form. Data were collected up to September 2008, death, loss to follow-up or liver transplantation.

Statistical analysis

SPSS Version 15.0 was used to perform the analysis. Data are reported as frequencies, means with SE of the mean or range. Categorical variables were compared by the χ^2 test. Quantitative data were compared with the Student t test or ANOVA when necessary. The cumulative risk of developing symptoms associated with PC was evaluated by Kaplan–Meier curves. Significance was established at $p<0.05$.

RESULTS

Ninety-three patients with portal cavernoma were considered eligible for the study. In 26 patients there was no MRA/MRC available (4 patients had claustrophobia and 22 were lost to follow-up, 15 because they were sent to their original centre

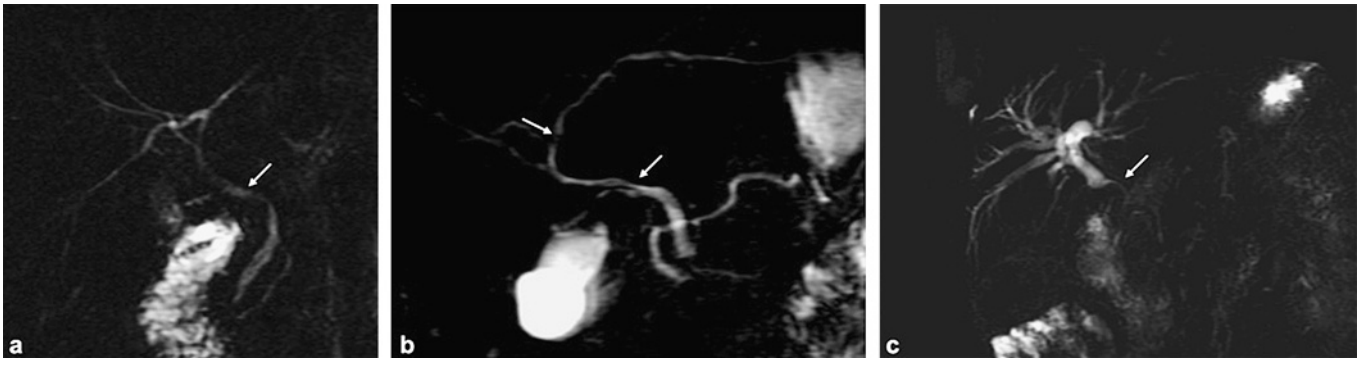

Figure 1 Thick-slab magnetic resonance cholangiography images. (A) Parietal irregularities affecting the intrahepatic and extrahepatic ducts (arrow) consistent with grade I portal cholangiopathy (PC). (B) Grade II PC: strictures of the biliary ducts (arrows) without dilation. (C) Grade III PC: presence of strictures (arrow) with dilation affecting the intrahepatic and extrahepatic ducts.

after diagnosis). Thus, 67 patients were included in the final analysis. The median age of the patients at the time of the first MRA/MRC was 47 years (range 19–77) and 61% of them were men. All patients had a complete aetiological investigation except the *JAK2*V617F mutation which was assessed in 79% of patients. Twenty-two patients were diagnosed during acute PVT but, despite the use of early anticoagulation, progressed to chronic cavernoma during follow-up. The remaining 45 patients were diagnosed in the chronic phase (chronic PVT) and anticoagulation was initiated in 10 after the underlying thrombophilic disorder was identified. The aetiology and clinical characteristics of the patients are summarised in table 1.

Radiological findings

Table 2 shows the radiological findings obtained at MRA/MRC of the more severe grade of PC developed for each individual patient. As shown in table 3, no significant differences in clinical or radiological data were observed between patients with normal MRA/MRC or with different grades of PC. Also, no significant differences were observed between patients with grade III PC and those without PC or with less than grade III PC (data not shown). No progression of vascular thrombosis of the portal venous axis was observed after inclusion in the study.

Development of PC after acute PVT

Twenty-two of the 67 patients were followed up after a recognised episode of acute PVT. The median time between diagnosis of acute PVT and index MRA/MRC was 33 months (range 1–102), without significant differences in those without PC (37 months (range 6–77)) or those with grade I PC (8 months (range 4–102)), grade II PC (41 months (range 21–94)) or grade III PC (37 months (range 1–67)), (p=0.8).

Table 1 Clinical features of the 67 patients included in the study

	Portal cavernoma (n=45)	APVT (n=22)
Median (range) age, years	45 (19–77)	50 (29–73)
Sex (M/F), n	32/13	9/13
Aetiology, n (%)		
Myeloproliferative disease	10 (22)	12 (56)
Protein C deficiency	2 (4)*	1 (4)
Protein S deficiency	0 (0)	1 (4)
Prothrombin gene mutation	2 (4)	1 (4)
Antiphospholipid syndrome	3 (7)	0 (0)
Isolated local factors	7 (15)	6 (28)
Idiopathic	21 (48)	1 (4)
Median (range) time between diagnosis (months)	136 (3–784)	49 (7–146)
Clinical manifestations before first MRC		
Previous variceal bleeding, n (%)	18 (40)	6 (12.2)
Previous ascites, n (%)	3 (6.7)	3 (14.3)
Portosplenomesentericography findings		
PVT ± intrahepatic branches, n (%)		
without extension to mesenteric or splenic vein	19 (42.2)	4 (14.3)
with extension	26 (57.8)	18 (81.8)
Purely intrahepatic cavernoma, n (%)	0 (0)	0 (0)
Purely extrahepatic cavernoma, n (%)	8 (17.8)	6 (27.3)
Intrahepatic and extrahepatic cavernoma, n (%)	37 (82.2)	16 (72.7)
Portosystemic collaterals, n (%)	42 (93.3)	19 (86.4)

*One associated to a local factor.
APVT, acute portal vein thrombosis; MRC, magnetic resonance cholangiography; PVT, portal vein thrombosis.

Table 2 Cholangiography findings at magnetic resonance cholangiography (MRC) in the complete series of patients with the more severe grade of portal cholangiopathy (PC) developed for each individual patient

	MRC (n=67)
Biliary stenosis	37 (55%)
Proximal EHBD	13
without dilation	2
with dilation	11
Mid EHBD	11
without dilation	1
with dilation	10
Distal EHBD	4
without dilation	0
with dilation	4
Left IHBD	
with dilation	6
Right IHBD	
with dilation	3
Indentations	19 (28%)
Irregularities	6 (9%)
Pseudocholangiocarcinoma	6 (9%)
Angulations	2 (3%)
Cholelithiasis	5 (7%)
PC grades:	
Grade 0	15 (22%)
Grade I	6 (9%)
Grade II	12 (18%)
Grade III	34 (51%)
PC types (Sarin):	
Type 0	15 (22%)
Type I	15 (22%)
Type II	10 (15%)
Type IIIa	5 (8%)
Type IIIb	22 (33%)

EHBD, extrahepatic bile duct; HBD, intrahepatic bile duct.

In 10 of these patients MRA/MRC was performed during the first year of follow-up. Six patients already had PC (3 grade III, 3 grade I). Remarkably, two of these patients had had a previous MRA/MRC performed within 1 month of acute PVT showing no PC or grade I PC, which progressed to grade I and grade III PC, respectively, when MRA/MRC was performed 6 and 4 months later.

Of the four patients without PC in the first year, three continued to be without PC when MRA/MRC was performed a median of 36 months (range 14–53) after acute PVT and one patient developed PC grade II at MRA/MRC performed 49 months later (figure 2). Of the three patients with PC grade I, no further progression was observed in two at MRA/MRC performed after 1 and 3 years, respectively, while no further assessment of PC was performed in the remaining patient.

In 12 patients the first MRA/MRC was performed >1 year after acute PVT. Three patients had no PC at a median of 54 months (range 39–77) after acute PVT while nine patients had PC (1 grade I, 3 grade II, 5 grade III) at MRA/MRC performed a median of 49 months (range 21–102) after acute PVT. Interestingly, two of the four patients with less than grade III PC in whom an additional MRA/MRC was performed 17 and 26 months later, respectively, showed no progression. Overall, in 16 of the 22 patients (73%), PC was identified at MRA/MRC performed a median of 33 months (range 1–102) after acute PVT (4 grade I, 4 grade II and 8 grade III; 5 Sarin's type I, 4 type II, 5 type IIIa and 2 type IIIb) and six patients remained without

Table 3 Clinical and radiological characteristics of patients without or with portal cholangiopathy (PC)

	No PC (n=15)	PC grade I (n=6)	PC grade II (n=12)	PC grade III (n=34)	p Value
Mean (SD) age, years	42 (15)	41 (18)	50 (18)	48 (15)	0.4
Sex (M/F)	8/7	5/1	9/3	19/15	0.4
Symptoms associated with PC	0 (0%)	0 (0%)	0 (0%)	14 (41%)	0.001
Anticoagulation before MRC*	7 (47%)	4 (67)	3 (25%)	8 (23%)	0.1
Treatment with β-blockers before MRC	7 (38.9%)	1 (16.7%)	5 (41.6%)	19 (55.9%)	0.2
Bleeding before MRC	4 (27%)	3 (50%)	4 (33%)	13 (38%)	0.5
Ascites before MRC	0 (0%)	0 (0%)	2 (17%)	3 (9%)	0.1
Oesophageal varices before MRC	11 (61.1%)	5 (83.3%)	6 (50%)	25(73.5%)	0.3
Previous surgical shunt	3 (20%)	0 (0%)	0 (0%)	1 (2.9%)	0.07
Liver tests, n (SD)					
ALT (IU/l): normal up to 40	30 (14)	27 (7)	53 (74)	39 (32)	0.4
AST(IU/l): normal up to 40	35 (19)	26 (6)	40 (43)	35 (15)	0.7
GGT (IU/l): normal up to 40	73 (68)	51 (20)	66 (72)	77 (73)	0.9
ALP (IU/l): normal up to 290	235 (137)	160 (13)	245 (111)	227 (123)	0.6
Bilirubin (mg/dl)	1.5 (0.8)	1.2 (1.2)	0.9 (0.5)	1.4 (1.7)	0.5
Cholestasis†	5 (33%)	3 (50%)	5 (42%)	17 (50%)	0.8
Purely extrahepatic cavernoma	5(33%)	1 (17%)	4 (33%)	4 (12%)	0.2
Intrahepatic and extrahepatic cavernoma	10 (67%)	5 (83%)	8 (67%)	30 (88%)	
Portosystemic collaterals	13 (86.6%)	6 (100%)	10 (83.3%)	33 (97.0%)	0.5
Portal vein thrombosis ± branches:					
without extension to mesenteric and/or splenic vein	6 (40%)	1 (17%)	6 (50%)	10 (29%)	0.4
with extension to mesenteric and/or splenic vein	9 (60%)	5 (83%)	6 (50%)	24 (71%)	

Because in some patients the PC grade progressed, the grade of PC shown in the table refers to the more severe grade of PC developed for each individual patient.
*Anticoagulation at MRC was considered when patients were under chronic anticoagulation when it was performed.
†Cholestasis was defined by an increase in GGT and ALP.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; MRC, magnetic resonance cholangiography; PVT, portal vein thrombosis.

PC a median of 46 months (range 12–77) after the acute PVT episode. Eleven of the 14 patients without grade III PC at first MRA/MRC in whom further MRA/MRCs were performed showed no progression to grade III after a median follow-up of 43 months (figure 2).

PC in patients with chronic PVT at diagnosis

Forty-five patients were diagnosed with chronic PVT. The time between diagnosis of chronic PVT and first MRA/MRC was 67 months (range 0–749). Nine patients had no PC. Of the 36 patients with PC, 3 had grade I, 7 had grade II and 26 had grade III. Additional MRA/MRCs were performed in 14 of the 19 patients without grade III PC (7 without PC, 3 with grade I and 4 with grade II; figure 2). Only in one patient did PC progress from grade I to grade II 22 months later.

Symptoms

Overall, 14 of the 67 patients (21%) experienced episodes of symptomatic PC. Six patients presented with abdominal pain with raised levels of hepatic enzymes (three with choledochal

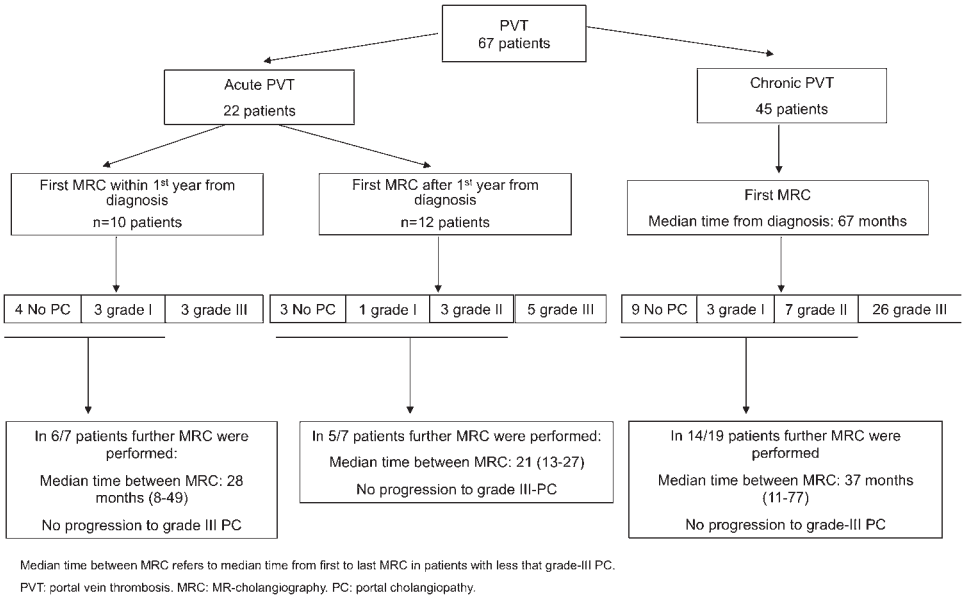

Figure 2 Flowchart describing time and findings of magnetic resonance cholangiography (MRC) in patients followed after a diagnosis of acute or chronic portal vein thrombosis (PVT). PC, portal cholangiopathy.

stones), three patients presented with acute cholangitis (two with choledochal stones), four patients had obstructive jaundice (one with choledochal stones) and one patient had acute lithiasic cholecystitis. As expected, liver enzymes were raised during symptomatic PC: aspartate aminotransferase (AST): 90±96 IU/l; alanine aminotransferase (ALT): 85±56 IU/l; gamma-glutamyl transferase (GGT): 311±374 IU/l (normal up to 40 IU/l); alkaline phosphatase: 977±803 IU/l (normal up to 250 IU/l); bilirubin: 5.6±7.8 mg/dl.

When the clinical characteristics of patients with and without symptoms were compared, there were no significant differences in the presentation of PVT (acute vs chronic), sex, length of follow-up or the presence of previous complications of PVT such as variceal bleeding or ascites (table 4).

Sixty-one patients had at least one MRA/MRC without having previous biliary symptoms; eight of them developed symptoms of PC during follow-up. As shown in table 5, these eight patients had significantly higher levels of alkaline phosphatase, GGT and bilirubin while asymptomatic than the 53 patients who did not develop symptoms of PC. This was also observed when we excluded from the analysis patients with less than grade III PC who were without symptoms (table 5). However, no differences between these two populations were observed in relation to the extension of PVT, cavernoma or the presence of systemic collaterals (not shown).

Incidence and prevalence of symptomatic PC

Acute PVT

Four of the 22 patients (18.2%) followed up after acute PVT developed symptoms of PC a median of 42 months (range 11–120) after the diagnosis. The 5-year actuarial probability of developing symptoms of PC after acute PVT was 19%. Interestingly, all patients had PC grade III at the last MRA/MRC before developing symptoms. According to Chandra and Sarin's classification, two of these patients had type I PC and two had type IIIa PC.

Chronic PVT

In two (4.4%) of the 45 patients with chronic PVT, PC symptoms were the initial manifestation of the disease and in four additional patients symptoms appeared in patients with known chronic PVT but without previous evaluation of the biliary tract. These six patients had MRC for the diagnosis of biliary symptoms and in all cases grade III PC was observed. In four of them further MRA/MRCs were performed after symptom resolution and all remained with grade III PC. All six patients had type IIIb PC according to Chandra and Sarin's classification.[16]

Four additional patients developed symptoms a median of 118 months (range 5–193) after the diagnosis of chronic PVT and 9 months (range 2–20) after the previous scheduled MRA/MRC which, in all cases, showed PC grade III (or type IIIb PC according to Chandra and Sarin's classification).[16]

The prevalence of symptomatic PC was 10/45 (22.2%). The 5-year and 10-year actuarial probability of symptomatic PC after diagnosis of chronic PVT was 9% and 13%, respectively.

Table 4 Clinical characteristics of patients with and without symptoms of portal cholangiopathy

	Symptoms* (n=14)	No symptoms (n= 53)	p Value
Mean (SD) age (years)	47 (19)	45 (16)	0.7
Median (range) time between diagnosis of PVT and symptoms or end of follow-up (months)	75 (0–601)	70 (3–742)	0.5
Form of presentation of PVT:			0.7
Acute PVT, n	4	18	
Chronic PVT, n	10	35	
Sex (M/F)	8/6	33/20	0.7
Previous anticoagulation, n (%)	7 (50%)	22 (41.5%)	0.6
β-blocker treatment, n (%)	6 (42.9%)	21 (39.6%)	0.9
Variceal bleeding, n (%)	7 (50%)	22 (41.5%)	0.6
Ascites, n (%)	1 (7.1%)	5 (9.4%)	0.6
Previous surgical shunt, n (%)	0 (0%)	6 (11.3%)	0.2
Oesophageal varices,† n (%)	12 (85.7%)	32 (60.3%)	0.07
Small	4	10	
Large	8	22	

*In patients with symptoms, their characteristics at the development of symptoms and, in patient without symptoms, their characteristics at the end of follow-up are shown.
†No differences were observed when the six patients with surgical shunts were not considered 32/39 (82%).
PVT, portal vein thrombosis.

Prognostic value of Sarin's classification of PC and the current classification

Overall, 52 patients had PC, 34 of them grade III. As already mentioned, all patients with symptoms had grade III PC. The presence of grade III PC has a positive predictive value (PPV) of developing symptoms of 41% and a negative predictive value (NPV) of 100% with a sensitivity of 100%. Thus, the absence of grade III PC at MRA/MRC removes the possibility of developing symptoms of PC.

By contrast, according to Chandra and Sarin's classification,[16] of the 14 patients with symptoms, 10 had type IIIb, two had type IIIa and two had type I. The PPV of having symptoms with PC type IIIb was 45% and the NPV was 91%, with a sensitivity of 71%.

Treatment

The six patients with choledochal stones were treated with sphincterotomy and stone extraction; in addition, three of them received ursodeoxycholic acid. One of these patients had a residual cholelithiasis and a cholecystectomy was attempted but was abandoned because of a severe haemoperitoneum during the surgical procedure; this patient is alive and symptom-free. In another patient, despite initial improvement, the symptoms recurred but were successfully controlled with a repeat sphincterotomy. One further patient persisted with obstructive jaundice and was successfully treated with derivative biliary surgery.

Two other patients (one with cholangitis and one with obstructive jaundice, both without biliary stones) were successfully treated with sphincterotomy plus ursodeoxycholic acid. Five additional patients with abdominal pain and cholestasis were treated with ursodeoxycholic acid which resulted in disappearance of the symptoms and improvement in liver tests. Finally, one patient with acute lithiasic cholecystitis underwent a successful cholecystectomy.

DISCUSSION

In patients with chronic PVT, several transversal studies have described a high prevalence of PC.[1–11 14 16–18] However, to date there are no data on the natural history of PC in patients with PVT. In addition, the relationship between radiological abnormalities of the biliary tree and the presence of clinical symptoms or the factors that may predict their appearance are not well known.

The results of the present study, in a large cohort of patients with PVT, show a high prevalence of PC (77%) that is in the range of that previously reported.[1–9 17 18] Thus, our

Table 5 Clinical characteristics at the time of index MRC in patients developing and not developing symptoms during follow-up

	Symptomatic PC* (n=8)	Asymptomatic PC (n=53)	Asymptomatic grade III PC (n=20)	p1 Value	p2 Value
Liver tests, mean (SD)					
ALT (IU/l)	58 (60)	35 (38)	30 (8)	0.1	0.05
AST (IU/l)	43 (23)	34 (24)	32 (10)	0.3	0.09
GGT (IU/l)	124 (101)	63 (63)	58 (63)	0.04	0.07
ALP (IU/l)	302 (96)	210 (106)	184 (81)	0.05	<0.01
Bilirubin (mg/dl)	2.4 (3.2)	1.0 (0.6)	1 (0.5)	<0.01	0.09
Cholestasis†	7 (87.5%)	19 (35.8%)	6 (30%)	<0.01	<0.01
Median (range) time between diagnosis and symptoms or end of follow-up (months)	75 (5–193)	70 (3–742)	100 (35–742)	0.4	0.2

p1, significance between symptomatic and asymptomatic patients with all grades PC.
p2, significance between symptomatic and asymptomatic patients considering only those with PC grade III.
*Patients in whom symptomatic PC was the initial diagnostic clinical manifestation of chronic portal vein thrombosis (n=2) or did not have magnetic resonance cholangiography prior to symptoms (n=4) were excluded, leaving 61 patients included in this analysis.
†Cholestasis defined as raised GGT and ALP.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; PC, portal cholangiopathy.

classification does not increase the number of patients diagnosed with PC but allows, for the first time, the classification of PC into different morphological patterns with different clinical outcomes. Similar to previous studies, there were no clinical or laboratory data predicting the presence of PC at MRA/MRC. Indeed, 33% of those patients without PC had an increase in cholestatic enzymes. By contrast, normal liver tests were found in 50% of patients with PC, even in those with grade III. Imaging studies of the biliary tree are therefore essential to dismiss or confirm the presence of PC.

An important finding of our study is the observation that not all abnormalities of the biliary tree found at MRA/MRC are associated with the same risk of developing symptoms: symptomatic PC only occurred in patients with grade III PC. The overall prevalence of symptomatic PC in our cohort was 21%. However, this figure increases to 41% when only patients with grade III PC are considered. These data suggest that the finding of grade III PC at MRA/MRC may be useful to identify patients with a higher risk of developing symptomatic PC, and these patients are potential candidates in whom to test prophylactic strategies to prevent the development of symptomatic PC. This concept is even more relevant when considering the other two important findings of the study: (1) the appearance of PC is an early event in the natural history of PVT and (2) once it appears, the abnormalities of the biliary tree remain stable. According to our data, after a non-recanalised episode of acute PVT, the development of PC occurs mainly during the first year of follow-up. The early evolution of the biliary abnormalities was suggested by the two patients in whom a very early MRA/MRC performed just 1 month after the diagnosis of acute PVT showed no or only minimal changes in the biliary tree but had clearly progressed in a second MRA/MRC performed only a few months later (5 and 7 months, respectively). In contrast, the capacity of biliary abnormalities to progress after 1 year of

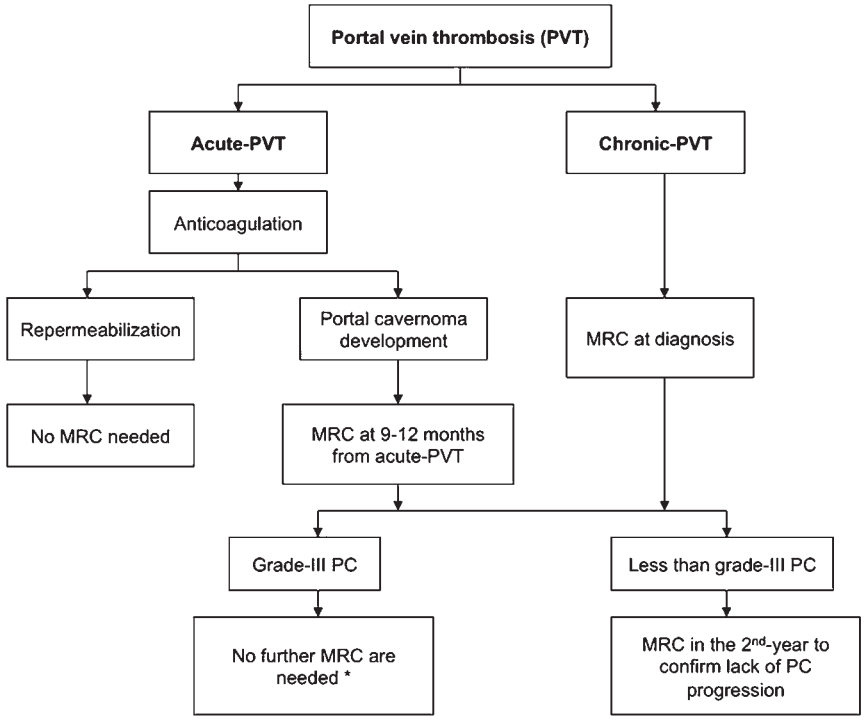

Figure 3 Proposed algorithm for the diagnosis of portal cholangiopathy (PC) in patients with portal vein thrombosis (PVT). MRC, magnetic resonance cholangiography.

MRC: MR-cholangiography.
* In case of symptomatic PC a MRC is recommended to evaluate the presence of biliary complications as cholecystitis or choledocolitiasis.

evolution is extremely low. In fact, only one patient showed progression of PC 1 year after the diagnosis of acute PVT, and only one patient of the current cohort with chronic PVT had PC grade I that progressed to grade II. Remarkably, none of these cases reached grade III PC which, according to our data, is the threshold biliary lesion at risk for developing symptoms. Our data are not contradictory with previous findings showing that the prevalence of symptomatic PC increases over time. Indeed, patients who develop grade III PC seem to have a high risk of developing symptoms. Therefore, the longer the period of time that patients are in this high-risk situation, the higher the probability of developing symptoms.

Together these data suggest that MRA/MRC should be performed 6–12 months after acute non-recanalised PVT and at diagnosis of chronic PVT. Patients in whom MRA/MRC shows grade III PC, especially those with high GGT and alkaline phosphatase levels, are at risk of developing symptoms of PC. This is not surprising because dilation of the biliary tract is a major risk factor for developing biliary stones, which were the trigger of symptoms in 50% of our patients with symptoms. In contrast, if grade III PC is not found and because of the small risk of these lesions progressing or causing symptoms, no further follow-up MRA/MRCs are needed. Figure 3 shows a proposed algorithm for the diagnosis of PC in PVT that should be prospectively validated.

Previous studies suggested that patients with symptoms are older, have a longer duration of disease, more frequent oesophageal varices and previous variceal bleeding and the presence of solid tumour-like cavernoma.[6 7] However, we could not confirm this in our patients. The only differences found between patients with and without symptoms were the grade of PC and the previous elevation of liver tests. The cause of cholestasis in patients with PVT may be multifactorial. However, the presence of cholestasis in patients with grade III PC seems to provide an additive risk for developing symptoms of PC. Symptomatic PC has been reported in previous studies ranging from 5% to 38%.[1 2 5 6 8 9 19] In our cohort, symptoms of PC developed in 18.2% of patients after a diagnosis of acute PVT and in 22.2% of those with chronic PVT. However, the 5-year actuarial probability of developing symptoms was 19% after the acute PVT episode and only 9% after the diagnosis of chronic PVT. We do not have a clear explanation for this finding, but it may be related to the previously-mentioned fact that severe (grade III) PC establishes and stabilises early during the first year after acute PVT. Thus, those patients with chronic PVT and grade III PC who have not yet developed symptoms may be a selected population of patients with a lower risk of developing symptomatic PC.

Our series confirms that, once symptomatic PC appears, it is generally severe, life-threatening and usually requires to be treated with invasive procedures, especially when biliary stones are present.[20] However, it is important to mention that less severe forms presenting with abdominal pain and cholestasis but without choledochal stones may respond to ursodeoxycholic acid. In three of our patients a surgical intervention was performed (a cholecystectomy in two, in one this was not possible because he developed a severe haemoperitoneum). In the remaining patient a biliary derivative procedure was performed after failure of previous medical and endoscopic treatment. Despite the successful intervention, due to the presence of large collateral veins in the hepatic hilium, biliary derivations should only be considered after medical and endoscopic therapy have failed and a surgical derivative shunt fails or is not possible.[6 19 21 22]

In the present study the radiological changes in the biliary tree were classified by one of us without knowledge of the clinical data of the patients. The classification of radiological abnormalities was made according to their effect on the biliary tree (from irregularities to strictures with dilation) instead of being classified exclusively according to their location, as is the case in previous classifications.[16] Our hypothesis in developing the classification was that the presence of symptoms is probably related more to the presence or absence of biliary dilation, independent of the location and number of abnormalities based on their location in the biliary tree. However, using our classification, all patients with symptoms among those with grade III PC fit into the three groups in the classification of Chandra and Sarin.[16] As a consequence, our classification is associated with a better NPV and sensitivity for predicting symptomatic PC than that of Chandra and Sarin,[16] suggesting that it is more clinically meaningful.

In conclusion, radiological PC is a frequent complication which usually develops and stabilises early after PVT and becomes symptomatic in its more severe form (grade III). These data suggest that follow-up MRA/MRCs are not mandatory and strategies to prevent the development of symptoms of PC should be tested in patients with grade III PC.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the ethical committee of the Hospital Clinic, Barcelona.

Contributors Study concept and design: JCGP, EL, CdJ; acquisition of data: EL, SS, CdJ, AGC; analysis and interpretation of data: EL, SS, CdJ, JGA, JB, JCGP; drafting of the manuscript: EL; critical revision of the manuscript for important intellectual content, statistical analysis: EL, JGA, JCGP; obtained funding: JB, JCGP; technical or material support: CdJ, AGC; study supervision: JB, JCGP.

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Editor's quiz: GI snapshot

ANSWER

From the question on page 852

A contrast enhanced CT examination demonstrated a large right-sided pleural effusion with compressive atelectasis of the underlying right lower lobe. Large volume ascites was confirmed with evidence of extensive omental infiltration or 'caking'. Abnormal omental tissue anterior to the ascending colon had a maximal thickness of 5 cm (see figure 1 in the question). An ill-defined 1.9-cm aorto-caval lymph node was also noted (see figure 2 in the question). The CT features were reported as typical of disseminated intraperitoneal malignancy, most likely an adenocarcinoma. Cytology demonstrates homogeneous, medium-sized lymphoblasts with basophilic cytoplasm and vacuolation (figure 3 in the question). Cell surface marker analysis from the ascitic fluid confirmed clonal B cells, negative for CD2, CD5 and TdT, but positive for CD19, CD20, CD22, CD38 with λ light chain restriction. The patient received intravenous fluids and methylprednisolone;however, he died 3 days later. Ki-67 staining of ascitic lymphoblasts was unsuccessful. Fluorescence in-situ hybridisation (FISH) studies using a dual fusion probe looking for the characteristic IGH/MYC gene rearrangement associated with Burkitt lymphoma, posthumously confirmed rearrangement in 50/55 interphase nuclei examined (Figure 1, below).

Burkitt lymphoma is a highly aggressive lymphoma, often presenting at extranodal sites, but very rarely as omental 'caking'.[1–3] Frequently, patients present with a high tumour burden due to its short doubling time (as little as 24 h). This can be associated with a markedly elevated LDH, hypercalcaemia and severe constitutional symptoms including night sweats and rapid weight loss.

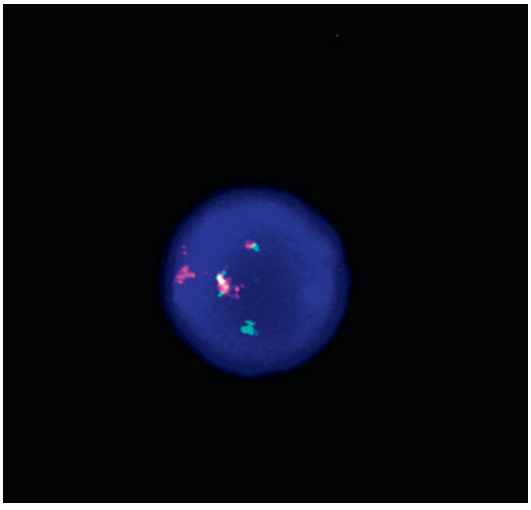

Figure 1 Fluorescence in situ hybridisation (FISH) studies showing evidence of an IGH/MYC rearrangement associated with Burkitt lymphoma.

Burkitt lymphoma has three forms: sporadic (as in this case), endemic (mostly seen in Africa, especially children) or associated with immunodeficiency, particularly HIV infection. It is a B-cell neoplasm, with the cytological features of diffuse proliferation of monotonous medium-sized cells with basophilic cytoplasm and lipid vacuoles. The presence of apoptotic cells within scattered macrophages is a feature responsible for the 'starry sky' appearance often seen in this disorder under low-power microscopy. Ki-67 staining as a marker of dividing cells and by definition, is >99% positive in Burkitt lymphoma.[4 5] Immunophenotyping classically reveals a clonal B cell phenotype with surface IgM, Bcl-6, CD19, CD20, CD22, CD10, and CD79a, and are negative for CD5, CD23, and TdT.[5] Burkitt lymphoma is caused by characteristic chromosomal translocations occurring between chromosome 8 (band q24, the c-myc gene, responsible for cell cycle regulation—seen as the red signal in figure 1) and one of the immunoglobulin (Ig) gene-containing chromosomes, most frequently chromosome 14 (band q32, IgH gene—seen as the green signal in figure 1, below) as in our case or alternatively chromosomes 2 (band p12, Ig κ) or 22 (band q11, Ig λ).[4 5] Such translocations disrupt normal cell cycle regulation, leading to rapid tumour growth. FISH may be used to detect these translocations, and in this case, is confirmed by the presence the two yellow signals (figure 1).

Burkitt lymphoma can be cured with aggressive chemotherapy ± radiotherapy.[5] Diagnosis is best established with a lymph node or tumour mass biopsy. However, cytology and flow cytometry on ascitic or pleural fluid can aid the diagnosis. These tests are relatively easy to perform with a rapid turn around time (usually <8 h). Confirmatory FISH studies can be performed within 48 h. Prompt diagnosis can lead to early aggressive treatment with long-term survival of up to 50%.[4]

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Portal cholangiopathy: radiological classification and natural history

Elba Llop, Carmen de Juan, Susana Seijo, Ángeles García-Criado, Juan G Abraldes, Jaume Bosch and Juan Carlos García-Pagán

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Notes