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Portal Hypertension as a Complication of Cystic Echinococcosis: A 20-Year Cohort Analysis

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Abstract. Cystic echinococcosis (CE) is a parasitic disease caused by the larval forms of species of the tapeworm *Echinococcus*. The most common location is the liver. To assess the frequency and clinical characteristics of portal hypertension (PH) and the risk factors for PH development, we performed a retrospective observational study of inpatients diagnosed with hepatic CE and PH from January 1998 to December 2018, at Complejo Asistencial Universitario de Salamanca, Spain. Of 362 patients analyzed with hepatic CE, 15 inpatients (4.1%) had a portal vein diameter ≥ 14 mm, and the mean diameter of the portal vein was 16.9 (standard deviation [SD] ±2.1) mm. Twelve patients were men. The mean age was 59.5 years (SD ± 17.8 years). Four patients had ascites (26.6%), four had collateral circulation (26.6%), 14 had hepatosplenomegaly (93.3%), five had esophageal varices (33.3%), four had hematemesis, and three had jaundice. Other causes of PH included hepatitis B virus (1 patient) and hepatitis C virus (1 patient) infections and alcohol abuse (1 patient). The host variables associated with PH development were male sex (odds ratio, 4.6; 95% confidence interval, 1.1–20.9; $P = 0.030$) and larger cyst size (10.8 ± 6.3 versus 7.6 ± 4.1; $P = 0.004$). Hepatic CE is an infrequent cause of PH that usually occurs without indications of liver failure. Larger cyst size and male sex were the main risk factors associated with this complication. Mortality was higher for patients with hepatic CE with PH than for patients with hepatic CE without PH.

INTRODUCTION

Cystic echinococcosis (CE) is a parasitic disease with worldwide distribution caused by the larval forms of species of the tapeworm *Echinococcus granulosus* sensu lato; dogs are a definitive host and humans are an accidental host.[1] Human echinococcosis is prevalent in northern and eastern Africa, central Asia, South America, Australia, and Mediterranean Basin countries, such as Greece, Italy, Portugal, and Spain.[2]

Human infection causes cysts in any organ, although the most common locations are the liver (> 65%) and lung (25%).[3] CE can be acquired at any time, with the risk increasing with increased time exposed to or living in endemic areas. Infected patients are frequently asymptomatic for years or decades.[4] Accidental findings of CE are sometimes found during clinical autopsies.[5]

Complications of CE or CE recurrence can occur secondary to surgical procedures[6,7] because of the need to handle the cyst, spontaneous rupture of the cyst wall with the development of a fistula (biliary, bronchial, pleural, and other types), and superinfection by bacterial or fungal species.[8] Additionally, immunological reactions such as urticaria and anaphylaxis have been observed with complications caused by cysts.

During a recent retrospective study, we evaluated spontaneous complications of CE. Unexpectedly, we found that some patients with hepatic CE presented clinical characteristics of portal hypertension (PH), such as ascites and variceal hemorrhage.[9] Therefore, in the present study, we aimed to examine the frequency and clinical characteristics of PH and the risk factors for PH development in patients with hepatic CE.

PATIENTS AND METHODS

Study design and participant selection. A retrospective, longitudinal, descriptive study was designed to review all patients diagnosed with CE at Complejo Asistencial Universitario de Salamanca (CAUSA) between January 1998 and December 2018. CAUSA is a tertiary care hospital that covers an area of 12 350 km^2. In, 2018, there were 333,603 inhabitants (National Institute of Statistics [INE}; http://www.ine.es/) located in midwestern Spain.

All patients included in the study fulfilled the following four criteria: diagnosed with CE according to code 122 of the *International Classification of Disease*, 9th edition, Clinical Modification (ICD-9-CM) during 1998 to 2015, or with code B67 of the *International Classification of Disease*, 10th edition (ICD-10) during 2016 to 2018; liver disease caused by *Echinococcus granulosus*; highly suggestive clinical setting of PH, such as encephalopathy, splenomegaly, esophageal varices, variceal hemorrhage, portal hypertensive gastropathy, and

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ascites; and radiological signs consistent with PH using ultrasonography/tomography or higher than F3 using FibroScan (Echosens, Waltham, MA). The exclusion criteria were missing data, extrahepatic CE, and no adequate portal image. The clinical and epidemiological data were collected after a review of the medical records. All data analyzed were anonymized.

We defined PH syndrome if the patient had symptoms or signs usually associated with PH (including variceal hemorrhage, portal hypertensive gastropathy, ascites, and spontaneous bacterial peritonitis) and radiological signs on ultrasonography or tomography (such as ascites, splenomegaly, portal flow mean velocity <12 cm/second, inversion of flow in the portal vein, portosystemic collaterals of a patent paraumbilical vein or spleen-renal collaterals, dilated left and short gastric veins, portal vein diameter >13 mm, decreased or no respiratory variation in the diameter of the splenic and superior mesenteric veins, and portal, splenic, or superior mesenteric vein thrombosis). We also considered PH if liver stiffness was >13.6 kPa as measured by FibroScan (FibroScan Touch 502; Echosens).

Data analysis. To perform statistical analyses, descriptive analysis was conducted for each individual variable. For categorical variables, the results are expressed as absolute values (n), proportions (n/N), or percentages (%). For quantitative variables, the results are expressed as the mean and standard deviation (SD), median and interquartile range (IQR; quartile 1–quartile 3), and range (minimum value–maximum value). The strength of the association between categorical variables was measured using Pearson's χ^2 contrast statistic and odds ratio (OR) estimates. An analysis of variance (F-test) was used to statistically assess the equality of means between groups. $P \leq 0.05$ was considered statistically significant (significance level of 0.05). The SPSS 26.0 (SPSS, IBM, Armonk, NY) statistical package was used.

Ethics statement. The study protocol was approved by the Clinical Research Ethics Committee of the Complejo Asistencial Universitario de Salamanca (Salamanca, Spain). The procedures described here were performed in accordance with the ethical standards described in the 2013 revised Declaration of Helsinki.

RESULTS

Between January 1998 and December 2018, a total of 594 patients received a diagnosis of CE; 88 patients with no data were excluded and 506 inpatients with a diagnosis of CE were included in the initial study. After checking all cases, 144 patients were excluded because of extrahepatic CE without hepatic involvement (65), the absence of an adequate portal image, or nonvalid imaging test results (79). Therefore, 362 (71.5%) patients underwent portal studies via radiological examinations (ultrasonography, computed tomography, or magnetic resonance imaging) or elastography, including complementary tests, and they were included as study subjects. Fifteen (4.1%) included patients fulfilled the criteria for PH syndrome. Figure 1 shows the flowchart of participant inclusion in this study.

Clinical and epidemiological data of the 15 patients with CE and PH are shown in Table 1. Twelve patients (80%) were male and three (20%) were female. The mean age ($\pm$SD) of the sample was 59.5 years ($\pm$17.8 years) (median, 61 years; IQR, 50–70 years; range, 22 to 93 years). These patients presented with one hepatic cyst (10 patients; 66.6%), two cysts (4 patients; 26.6%), and three or more (1 patient; 6.6%). Cysts were most frequently located in liver segments VII and VIII (5 patients; 33.3%) (Figure 2) The World Health Organization (WHO) classifications most frequently presented were stage II (7 patients; 46.7%), stage V (4 patients; 26.7%), stage IV (2 patients; 13.3%), and stage III (1 patient; 6.7%). For one patient, there were no detailed radiological data. The mean size ($\pm$SD) of the cysts was 10.7 cm (SD $\pm$ 6.3) cm (median, 10 cm; IQR 5–16; range, 3–23 cm). For 9 (60%) patients, the mean cyst size was larger than 7 cm.

We studied the risk factors for PH in patients with hepatic CE. Among the variables of the host associated with PH, only male sex was associated an increased risk of PH (OR,

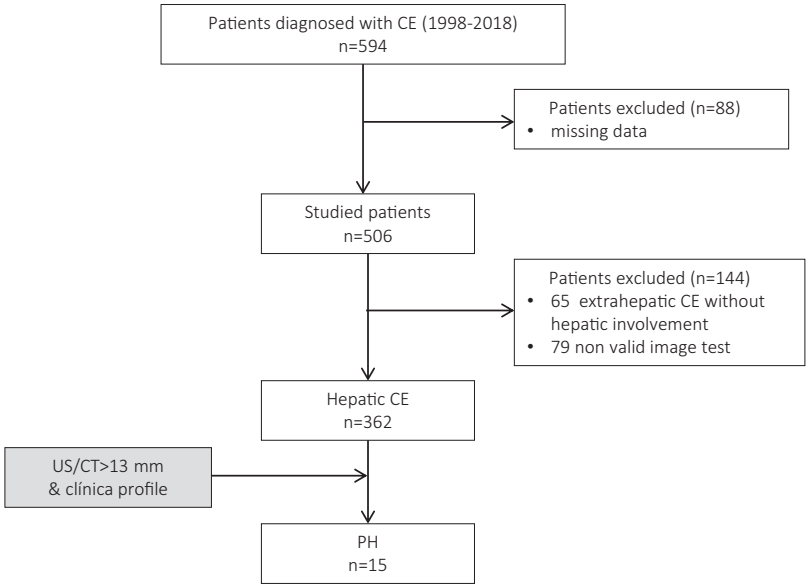

FIGURE 1. Participant profile.

TABLE 1
Main clinical and radiology characteristic of patients included in the study

Sex	Age	Time to diagnosis, months	Cyst, no.	Cyst size, cm	Location	Liver segments	WHO stage	Clinical criteria for PH*	Portal size, ECO/CT	Radiological complications	Elastography results, kPa	Others causes					Treatment	Outcome
												Alcohol	NASH	Viral hepatitis	Autoimmune	Posthepatic		
M	62	1	1	8	Liver	3	V	A, HE, EV, J, T	17	No	NR	Yes	No	ND	ND	No	Watch and wait	Exitus
M	53	180	1	3	Liver	ND	ND	HE, J	20	No	NR	No	No	No	No	No	Watch and wait	Well
M	49	8	1	16	Liver	4–8	II	HE	18	No	NR	No	No	ND	ND	No	Surgery	No follow-up
M	82	1	1	4	Liver	8	V	A, E, HE, EV, VH	15	No	NR	No	No	RNA− HCV+	No	No	Watch and wait	Exitus
M	54	180	1	5	Liver	8	II	HE	17	No	NR	No	No	No	No	No	Surgery and drugs	Well
M	50	1	1	23	Liver	4, 6, 7	II	C, HE	15	No	NR	No	No	No	No	No	Surgery and drugs	Well
M	93	11	1	18	Liver	7	II	HE	14	No	NR	No	No	ND	ND	No	Drugs	Exitus
F	22	1	1	5	Liver	8	V	HE	15	No	NR	No	No	No	No	No	Watch and wait	Well
M	62	101	2	10	Liver	2, 3	II	A, C, HE, EV, VH	15	No	NR	No	No	ND	No	No	Watch and wait	No follow-up
M	37	1	2	11	Liver	6, 7	II	C, HE, EV, VH	20	Portal thrombosis and cavernomatosis	NR	No	No	No	No	No	Surgery & drugs	Well
M	63	4	2	16	Liver	7	II	A, HE, J	16	No	10.4	No	No	No	No	No	Surgery	Well
F	54	1	5	11	Liver & renal	3–8	III	T	16	No	NR	No	No	No	No	No	Surgery and drugs	Well
M	61	1	2	19	Liver & lung	6	IV	HE	20	Portal thrombosis and cavernomatosis	NR	No	No	No	No	No	Watch and wait	Well
M	70	26	1	5	Liver	3	V	C, HE, VH	20	Portal thrombosis	NR	No	No	HBcAc + DNA HBV− HBsAg−	No	No	Watch and wait	Well
F	81	1	1	6	Liver	5, 6	IV	HE, EV	16	No	9.3	No	No	No	No	No	Watch and wait	Well

E = encephalopathy; HE = hepatosplenomegaly; J = jaundice; EV = esophageal varices; VH = variceal hemorrhage; PHG = portal hypertensive gastropathy; A = ascites; T = telangiectasias; C = collateral circulation; F = female; M = male; NASH = nonalcoholic steatosis hepatitis caused by metabolic syndrome; NR = not realized; ND = no data. Viral hepatitis: active or past infection caused by hepatitis B virus (HBV) or hepatitis C virus (HCV). Anti-liver-kidney microsomal antibodies type 1 (LKM-1), autoantibodies against the soluble liver antigen (SLA), antimitochondrial autoantibodies (AMA), antinuclear autoantibodies (ANA), anti-smooth muscle antibodies (ASMAs).

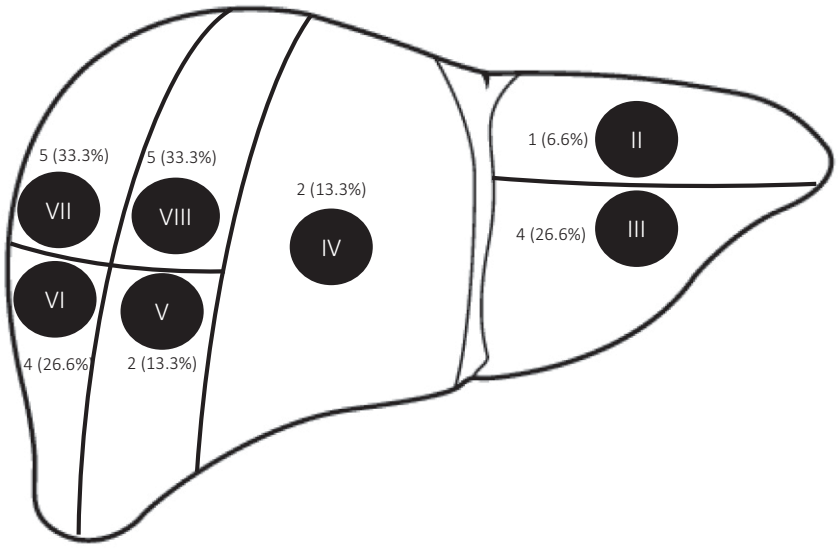

FIGURE 2. Main cyst location for patients with cystic echinococcosis included in the study.

4.6; 95% CI, 1.1–20.9; $P = 0.030$). Patients with hepatic CE with PH had larger cysts than patients with hepatic CE without PH (10.8 ± 6.3 compared with 7.6 ± 4.1; $P = 0.004$).

The mean diameter of the portal vein was 16.9 mm (SD ± 2.1 mm) (median, 16 mm; IQR, 15–20; range, 14–20 mm). The signs most frequently found during radiological examination were portal vein diameter > 14 mm (15 patients; 100%), ascites (4 patients; 12%), splenomegaly (7 patients; 21%), portosystemic collaterals (5 patients; 15%), portal thrombosis (2 patients; 13.3%), and cavernomatosis (1 patient; 6.6%). Two patients had elastography results of 9.85 (SD ± 0.55) kPa.

The most frequently observed symptoms or signs associated with PH were hepatosplenomegaly (2 patients; 14.3%), ascites (4 patients; 26.6%), esophageal varices (5 patients; 33.3%), hematemesis (4 patients; 26.6%), and jaundice (3 patients; 20%). There were asymptomatic patients with cytopenia (thrombocytopenia, leukopenia, and anemia) and hypoalbuminemia. Among the studied patients, other causes of PH were detected in 3 (20%) patients: alcohol abuse for 1 (6.6%) patient, hepatitis B virus infection for 1 patient, and hepatitis C virus infection for 1 patient. The patients analyzed did not have liver failure, and their mean Child-Pugh score was 5.86 (SD ± 1.08). Other posthepatic causes of PH such as suprahepatic vein or cava vein thrombosis were ruled out with ultrasonography and tomography studies. No patient had right heart failure.

During a mean follow-up of 70.9 (SD ± 64.5 months), 10 (66.6%) patients had positive evolution, 2 (13.3%) patients had no follow-up data available, and 1 male patient died because of PH complications. Mortality was higher for patients with hepatic CE with PH than for patients with hepatic CE without PH, although the difference was not significant.

DISCUSSION

PH syndrome has often been described as a complication of different parasitic diseases. The most frequent parasitic infection associated with PH is schistosomiasis, which is caused by chronic infection of a trematode species of *Schistosoma* such as *S. mansoni* or *S. japonicum*.[10] The authors found that more than 5% of all patients with intestinal schistosomiasis had a severe form of hepatosplenic schistosomiasis and, consequently, PH.[11] However, another species of *Echinococcus*, *Echinococcus multilocularis*, has also been established as a cause of PH because of its characteristic invasion of liver tissue.[12]

Unlike previous parasites, CE has never been included (to our knowledge) on the list of causes of PH. However, this syndrome has been referred to in case records in the literature.[13,14] Therefore, we aimed to assess the frequency, risk factors, clinical characteristics, and prognosis of PH in our cohort of patients with hepatic CE.

An academic definition of PH is portal vein pressure higher than 5 mmHg.[15] Nevertheless, to measure this pressure, it is necessary to introduce a venous catheter into the suprahepatic veins. However, this technique for the diagnosis of PH syndrome is not usually performed outside of specialized hemodynamic and transplantation liver units. In clinical practice, we usually diagnose PH syndrome if patients have liver or systemic vein portal disease in addition to clinical characteristics of secondary complications of PH, such as ascites, splenomegaly, and variceal hemorrhage, or suggestive radiological signs.

Therefore, during this retrospective study, we included only patients who presented unequivocal symptoms or signs associated with PH and complementary signs on radiological (ultrasonography, computed tomography, or magnetic resonance imaging) or elastography examinations. Computed tomography and magnetic resonance imaging do not offer functional imaging to establish a diagnosis of PH; however, they detect secondary changes in PH, such as portosystemic collateral formation, splenomegaly, portal hypertensive gastropathy, and ascites.[16]

During our study, we found 15 patients with clinical and complementary data suggestive of PH; 4% of those patients had hepatic CE. This low frequency of PH syndrome supports the scarcity of data presented in the literature. Therefore, it is

possible that those patients with long-term parasitic infection have a higher possibility of PH development. However, during our study, we did not find an association between older age and PH or between comorbidities and PH. Our data showed no association of PH with the stage or location of the cyst inside the liver; however, it did show an association with the cyst size. Moreover, there is no clear relationship between PH and endovascular invasion of the parasite because only three patients had portal thrombosis.

The patterns of symptoms and signs detected in patients with PH and CE suggested differences between schistosomiasis and *E. multilocularis* infection. Schistosomiasis usually causes presinusoidal PH, and patients have ascites, hepatosplenomegaly, and variceal hemorrhage.[17] Alveolar echinococcosis spreads to suprahepatic veins, and the pattern is usually postsinusoidal PH with clinical characteristics compatible with Bud-Chiari syndrome and indications of liver failure. In a series from Poland, *Echinococcus multilocularis* was a cause of transplantation for 13% of patients.[18]

Patients with PH associated with CE usually present with abdominal pain, ascites, splenomegaly, variceal hemorrhage, and encephalopathy, but no indications of liver failure. However, it was an accidental finding for approximately one-third patients.[19]

We know that PH is a cause of mortality for patients with schistosomiasis or *E. multilocularis* infection. In our cohort, we found a mortality rate of 20% for patients with hepatic CE who had PH, which was higher than the rate we found for our overall cohort. We previously reported that, for patients with CE, PH was the main cause of death. Superinfections and biliary fistula were the main causes of mortality in that cohort. During this study, we found that PH complications could also be causes of mortality.

The pathogenic mechanisms involved in the development of PH in patients with CE are not clear. It is possible that the presence of a cyst could increase the resistance of portal blood flow into the liver. This possibility is consistent with the larger cyst size observed in patients with CE with PH than that in patients with CE without PH. These data support the idea that liver tissue compression caused by cysts could explain PH. However, we did not find an association between the cyst location and PH; therefore, direct compression of the portal vein is unlikely to be the mechanism of PH development involved in this cohort.

There could be factors related to endothelial dysfunction in patients with CE, however. Nitric oxide (NO) is a molecule associated with vasodilator effects in the portal vein. Therefore, NO donor drugs, such as nitrates, are frequently used in the treatment of PH syndrome. Some parasitic infections, such as *Schistosoma mansoni*, have been found to alter endothelial cell function, thus decreasing the expression of endothelial NO synthase and, consequently, NO production.[20] Patients with CE have NO concentrations lower than those of the healthy population and present a slight increase after surgery.[21]

Finally, liver fibrosis induced by CE has been observed in an experimental mouse model of infection.[22] In our cohort, it was interesting that liver fibrosis was demonstrated in two of the only two patients who underwent liver elastography (F3 stage of fibrosis) using FibroScan (FibroScan Touch 502; Echosens).

Various mediators are involved in liver fibrosis. It has been proposed that vascular endothelial growth factor acts in the PH development pathway, and that its inhibition improves PH, hyperdynamic splanchnic circulation, portosystemic collateralization, and liver fibrosis.[23] Egg antigens of *Schistosoma* and other parasitic infections cause VEGF upregulation in endothelial cells.[24] *E. granulosus* has also been shown to increase VEGF in infected patients.[21] VEGF is associated with fibrogenesis periportal fibrosis and angiogenesis, and it could be involved in the PH development pathway.[25]

Another mediator involved in fibrosis in patients with CE is transforming growth factor-β. *E. granulosus* increases the level of transforming growth factor-β1 in advanced stages or infection, thus contributing to the development of the fibrocyst wall and inhibiting the expression of miR-19, consequently promoting liver fibrosis and secondary PH.[26]

Finally, in our cohort of patients with hepatic CE and PH, we found other possible causes of PH, such as alcohol abuse and hepatitis C and B virus infections, in only three patients. Although it is difficult, especially during retrospective studies, to assess how different factors can contribute to PH, we think that CE could have had an important role in the development of PH in these patients. This fact has been highlighted for other parasitic infections as well; therefore, hepatosplenic schistosomiasis patients coinfected with HCV and HBV could be at higher risk for PH.[27]

Based on all these findings, it is difficult to know the definitive cause of PH. It is possible that it could be caused by multiple factors, such as portal compression, invasion of the portal system, and induction into fibrosis.

Our work was retrospective; therefore, it had some limitations, such as a scarce number of patients and limited selection criteria. Nevertheless, it is difficult to perform other types of studies of CE because of the chronic characteristics of this infection and its long follow-up. Therefore, the results should be interpreted with caution. Multicenter works should be performed in the future to verify our results.

CONCLUSIONS

Liver CE is a rare cause of PH, which usually occurs without indications of liver failure. Larger cyst size and male sex were the main risk factors associated with this complication of CE. Mortality was higher for patients with hepatic CE with PH than for patients with hepatic CE without PH.

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