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The Relationship between the Rate of Biliary Fistula Development and Hydatid Cyst Diameter: Experience of a Single Center in Istanbul

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Abstract **Original Research Article**

The clinical presentation of the hydatid cyst disease is varied by its localization, growth rate, cyst size, and involved organ. Intrabiliary rupture (IBR) involving the connection of a high-pressure cyst cavity with the biliary system is the most troublesome complication. In the past, surgery has been the preferred method for the diagnosis and management of IBR complications, but today, non-invasive and minimally invasive methods are used for both the diagnosis and management of these complications. This study was conducted at a single center in Istanbul, Turkey between January 2011 and December 2015. Study data were obtained from the patients' medical records in a retrospective fashion. Those with a radiologic cyst size greater than 10 cm were named as the major cysts group, as and smaller than 10 cm were grouped as minor cyst group. Both groups were compared with respect to the rate of postoperative biliary fistula (PBF) development. The type of surgical procedure, PBF development status, and PBF management approach were recorded. Liver function tests and cholestasis enzymes were measured in all patients. An indirect hemagglutination test was performed for serological confirmation of the diagnosis. The correlation between laboratory findings and the rate of PBF development was also analyzed.
Keywords: Biliary fistula; cyst diameter; hydatid disease; liver.

INTRODUCTION

Hydatid disease is an infection caused by Echinococcus granulosus, an infectious agent endemic to Mediterranean, South American, North African, Middle Eastern, and Eastern European countries [1, 2]. Liver is commonly involved by the infection. The infection is particularly endemic and an important public health problem in Mediterranean countries where shepherding is widely practiced. In Turkey, approximately 4000 persons are diagnosed with hydatid disease annually [3]. Although this zoonotic disease is rare in the USA and Europe, its prevalence in these areas has been increasing as a consequence of touristic travels to and mass emigrations from endemic areas [4].

The clinical presentation of the hydatid cyst disease is varied by its localization, growth rate, cyst size, and involved organ. Intrabiliary rupture (IBR) involving the connection of a high-pressure cyst cavity with the biliary system is the most troublesome complication [5] and occurs in 2-42% of the affected persons [6, 7]. Other complications include rupture into abdominal cavity, invasion of other organs, compression of biliary tree and adjacent structures, and infection [8]. Depending of the size of the cystobiliary connection, the clinical presentation of IBR includes jaundice, cholecystitis, cholangitis, liver abscess, pancreatitis, and septicemia. Unrecognized ruptures may result in complications such as biliary leaks, biloma, cavity infection, and obstructive jaundice after hepatic hydatid cyst (HHC) surgery [9, 10].

In the past, surgery has been the preferred method for the diagnosis and management of IBR complications, and it has been associated with a mortality and morbidity risk of 4.5% and 50%, respectively. Today, non-invasive and minimally invasive methods are used for both the diagnosis and management of these complications at both preoperative and postoperative periods. In clinical practice, the widely recognized indications for endoscopic retrograde cholangiopancreatography (ERCP) include postoperative complications such as persistent biliary fistula and jaundice, or preoperative conditions that are clinically (jaundice), radiologically (dilated main biliary ductal system or hydatid elements in bile ducts), or biochemically (overt cholestasis) suspected for IBR. However, most IBRs are occult, and many cases may remain clinically silent. The presence

of postoperative biliary fistula (PBF) determines the prognosis of these patients [11].

There is limited information about the natural history and outcomes of patients who are poorly treated for intrabiliary rupture (IBR) and subsequently develop PBF. In this study we aimed to the determine the clinical significance of PBF and factors associated with its development in a group of surgically treated patients with hepatic hydatid disease (HHD).

Materials and Methods

This study was conducted at Istanbul, Turkey between January 2011 and December 2015 after obtaining approval of the Local Ethics Commitee. Study data were obtained from the patients' medical records in a retrospective fashion. Those with a radiologic cyst size greater than 10 cm were named as the major cysts group, and those with a cyst size smaller than 10 cm were grouped as minor cyst group. Both groups were compared with respect to the rate of PBF development. The type of surgical procedure, PBF development status, and PBF management approach were recorded. Liver function tests and cholestasis enzymes were measured in all patients. An indirect hemagglutination test was performed for serological confirmation of the diagnosis. The correlation between laboratory findings and the rate of PBF development was also analyzed.

Statistical analysis

All statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software package. Descriptive data were reported as mean, standard deviation, median, frequency, percentage, minimum, and maximum. Independent groups were compared using the Student t Test for normally distributed quantitative data and the Mann Whitney-U test for non-normally distributed quantitative data. Qualitative data was compared using the Fisher-Freeman-Halton test and the Yates' Continuity Correction test (Yates corrected Chi-square). Statistical significance was set at $p<0.01$ and $p<0.05$.

Results

The study included a total of 112 patients, of whom 43 (38.4%) were male and 69 (61.6%) were female. The study population had an age range of 18-84 years and a mean age is 41.85 years. Standard deviation (SD) for age is ±16.49. Seventy-two (64.3%) patients had a cyst size smaller than 10 cm (minor cyst group), and 40 (35.7%) had a cyst size greater than 10 cm (major cyst group) (Table 1).

Table-1: Demographic properties

		Min-Max	Mean±SD
Age*(years)*		18-84	41.85±16.49
		n	%
Sex; *n (%)*	Male	43	38.4
	Female	69	61.6
Cyst diameter; *(cm)*	<10 (minor)	72	64.3
	≥10 (major)	40	35.7

There was significant difference between both groups in terms ofthe rate of PBF development ($p=0.010$; $p<0.01$). The rate of PBF was significantly greater in cases with major cysts compared to those with minor cysts (Figure 1).

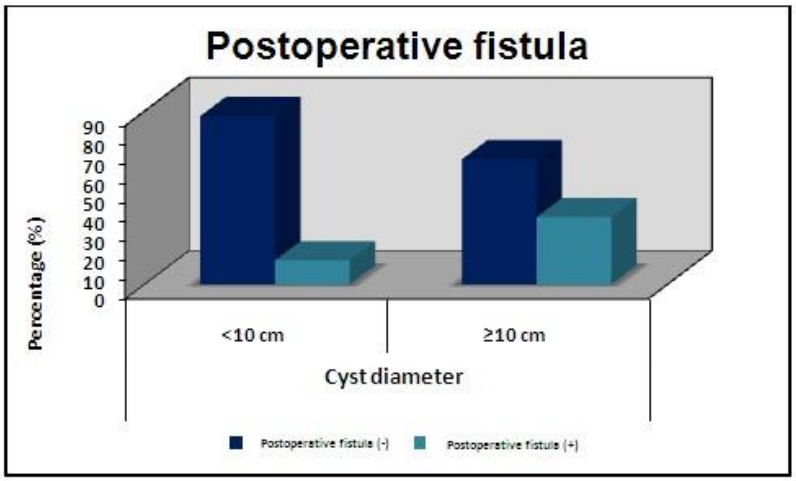

Fig-1: Distribution of rates of PBF by cyst diameter

There were no significant differences between the major and minor cyst groups with regard to IHA, AFP, ALT, GGT, and LDH levels (p>0.05). Mean IHA level is 1,93 and SD is 1,13 in minor cyst group while mean IHA level is 2,33 and SD is 1,67 in major cyst group. Mean AFP level is 30,97 and SD is 50,63 in minor cyst group while mean AFP level is 48,05 and SD is 91,85 in major cyst group. Mean ALT level is 55,79 and SD is 88,23 in minor cyst group while mean ALT level is 101 and SD is 179,65 in major cyst group. Mean GGT level is 223,47 and SD is 96,66 in minor cyst group while mean GGT level is 222,80 and SD is 99,35 in major cyst group. Mean LDH level is 92,14 and SD is 55,25 in minor cyst group while mean LDH level is 118,35 and SD is 73,88 in major cyst group (Table 2).

Major cyst group had a significantly greater AST (p=0.019; p<0.05) and total bilirubin (p=0.035; p<0.05) levels than the minor cyst group. Mean AST level is 41,07 and SD is 54,17 in minor cyst group while mean AST level is 52 and SD is 96,11 in major cyst group. Mean total bilirubin level is 0,34 and SD is 0,49 in minor cyst group while mean total bilirubin level is 0,41 and SD is 0,51 in major cyst group (Table 2).

While there was no significant difference between the ALP levels of the major and minor cyst groups, (p=0.069; p>0.05), the major cyst group had notably higher ALP levels. Mean ALP level is 0,70 and SD is 0,67 in minor cyst group while mean ALP level is 0,81 and SD is 0,66 in major cyst group (Table 2).

Table-2: Descriptive properties by cyst diameter ([a]Yates' Continuity Correction [b]Mann Whitney-U Test **p<0.01 *p<0.05)

			Cyst Diameter		p
		Total (n=112)	<10 cm (n=72) (Minor)	≥10 cm (n=40) (Major)	
Sex; *n (%)*	*Male*	43 (38.4)	26 (36.1)	17 (42.5)	[a]0.643
	Female	69 (61.6)	46 (63.9)	23 (57.5)	
	Min-Max (Median)	16-84 (39.5)	14-84 (41.5)	16-77 (34)	
IHA Level	*Negative*	22 (19.6)	17 (23.6)	5 (12,5)	[a]0.242
	Positive	90 (80.4)	55 (76.4)	35 (87,5)	
AFP	*Mean±SD*	2.07±1.35	1.93±1.13	2.33±1.67	[b]0.140
	Min-Max (Median)	0.40-10.50 (1.7)	0.40-6.45 (1.6)	0.93-10.50 (1.8)	
AST	*Mean±SD*	37.07±68.35	30.97±50.63	48.05±91.85	[b]0.019*
	Min-Max (Median)	11-588 (20)	11-424 (19)	14-588 (22)	
ALT	*Mean±SD*	44.97±71.76	41.07±54.17	52.0±96.11	[b]0.437
	Min-Max (Median)	5-480 (22)	5-374 (21)	6-480 (26)	
GGT	*Mean±SD*	72.58±129.51	55.79±88.23	101.0±179.65	[b]0.380
	Min-Max (Median)	7-968 (31.5)	7-604 (31)	9-968 (32.5)	
LDH	*Mean±SD*	223.23±97.18	223.47±96.66	222.80±99.35	[b]0.865
	Min-Max (Median)	115-650 (195)	115-581 (195)	129-650 (197)	
ALP	*Mean±SD*	101.50±63.47	92.14±55.25	118.35±73.88	[b]0.069
	Min-Max (Median)	41-399 (82)	41-399 (79.5)	50-346 (87.5)	
Total Bilirubin	*Mean±SD*	0.74±0.67	0.70±0.67	0.81±0.66	[b]0.035*
	Min-Max (Median)	0.16-4.10 (0.5)	0.16-3.69 (0.4)	0.22-4.10 (0,5)	
Direct Bilirubin	*Mean±SD*	0.37±0.499	0.34±0.49	0.41±0.51	[b]0.002**
	Min-Max (Median)	0.07-3.30 (0.23)	0,07-2.80 (0.2)	0.12-3.30 (0.3)	
Postoperative Biliary Fistula (PBF)	*No*	89 (79.5)	63 (87.5)	26 (65.0)	[a]0.010**
	Yes	23 (20.5)	9 (12.5)	14 (35.0)	

Although partial cystectomy was sufficient for the surgical management of minor cysts, primary biliary leak (suture ligation) was often needed along with partial cystectomy and omentopexy (Figure 2).

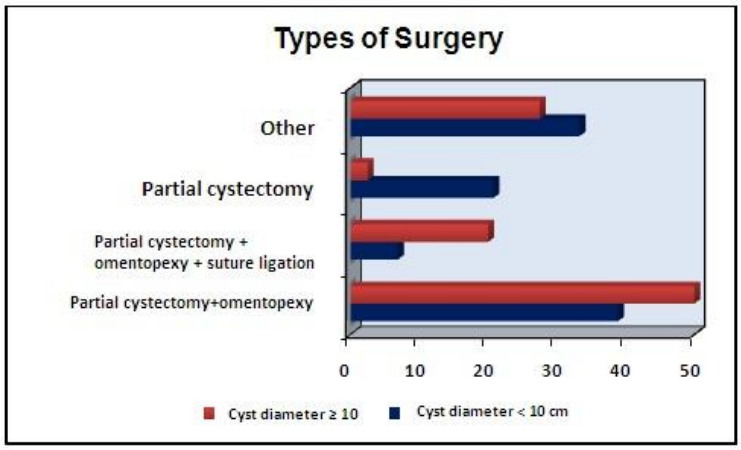

Fig-2: Distribution of types of surgery by cyst diameter

Eighty-nine (79.5%) patients did not develop PBF whereas 23 (20.5%) patients developed PBF. The management of complications was achieved by ERCP in 10 (43.5%) patients who developed PBF.

Conservative approach was selected in 10 (43.5%) cases while percutaneous drainage was performed in 3 (13%) cases (Table 3). Re-operation was not needed in any of the cases.

Table-3: Management of postoperative biliary fistula (PBF)

		n	%
Postoperative biliary fistula (PBF); *n (%)*	*No*	89	79.5
	Yes	23	20.5
Sphincterotomy by ERCP		1	4.35
Sphincterotomy + sweeping of the common bile duct by ERCP		4	17.4
Sphincterotomy + sweeping of the common bile duct + stent implantation into the common bile duct		2	8.7
Sphincterotomy + bile mud and hydatid cyst material extraction from the common bile duct by ERCP		1	4.35
Sphincterotomy + daughter vesicle extraction from the common bile duct by ERCP		1	4.35
Sphincterotomy + stone extraction from the common bile duct + stent implantation into the common bile duct by ERCP		1	4.35
Conservative		10	43.5
Percutaneous drainage		3	13.0

DISCUSSION

Although 80-90% of patients with hepatic hydatid disease (HHD) have a connection between cysts and the biliary system, this condition is clinically significant in only 13% to 37% of cases [12-15]. Intrabiliary rupture of hepatic hydatid cyst can be in two forms, namely overt rupture and occult rupture. The incidence of overt rupture is 5-17% [16-18]. Despite having a high morbidity and mortality, the management of cystobiliary connection poses no significant challenge. The occult cystobiliary connection which is seen in 10-37% of patients, on the other hand, is difficult to diagnose because it may be associated with subtle symptoms and unclear preoperative radiological signs [19]. An occult rupture existed in all of 112 patients involved in this study, of which 23 developed postoperative biliary fistulas (PBF). The criteria for cystobiliary connection include the detection of cystobiliary connection during operation or alternatively by ERCP in patients developing postoperative jaundice or biliary leak [13]. ERCP may reveal a cystobiliary connection in strongly suspected cases such as patients with jaundice prior to surgery. In this study we correlated cyst diameter and laboratory parameters with hydatid disease with occult preoperative cystobiliary connection manifested as PBF. In the literature, cyst diameter [16], ALP [20-23], GGT [20,22,23] and bilirubin levels [21-23] have been reported to be risk factors for cystobiliary connection. We found cyst diameter, AST, ALP, and bilirubin levels as risk factors but failed to identify IHA, AFP, ALT, GGT, and LDH levels as risk factors. The majority of cases of occult cystobiliary connection manifest with postoperative biliary leak. Cystobiliary connection is the most common complication of hepatic hydatid cystdisease and manifests itself with PBF in 14% to 25% of cases [13]. In our study the incidence of biliary leak was 20.5%. Adjunctive surgical intervention and percutaneous or endoscopic interventions may be needed for the management of this complication, or it may be managed conservatively [21]. In our study, this complication was managed using ERCP in 10 (43.5%) of 23 patients with PBF while percutaneous drainage was performed in 3 (13%)

patients and conservative management in 10 (43.5%). Re-operation was not needed in any of the cases.

Under the light of our results, it may be suggested that surgeon should suspect of an occult cystobiliary connection in cysts with a diameter greater than 10 cm and elevated AST, ALT, and bilirubin levels. In such cases, percutaneous drainage should be avoided to prevent septic complications. Instead, wide spectrum antibiotics should be added to the treatment regimen and surgical intervention should be scheduled as soon as possible. Since the rate of biliary leak remains high in cases with risk factors, an aspiration drainage catheter should be placed into cyst cavity even if no active bile leak is observed after evacuation of all cyst content. Despite a high spontaneous closure rate, PBFs persist in 4-27.5% of cases. A PBF should be primarily managed by conservative methods [24]. In biliary fistulae that persist despite all preventive measures (that persist for more than 3 weeks or have an output of more than 300 ml/day) an endoscopic sphincterotomy is indicated [21, 25].

Postoperative biliary leak is associated with increased morbidity. In the present study we concluded that an occult cystobiliary connection presenting with biliary leak after hepatic hydatid cyst surgery can be predicted by cyst diameter, ALP and bilirubin levels. In cases of PBF development despite all preventive measures conservative management methods should be tried first, followed by endoscopic procedures when PBF persists.

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