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The Identification of Risk Factors that Predict Occult Cystobiliary Communication in Liver Hydatid Cysts

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Abstract

Background Post-operative biliary leakage in patients with liver hydatid diseases is still a major problem especially after conservative surgery. Radiologic and intraoperative findings may not be helpful to detect occult biliary communications in asymptomatic patients.

Objective To identify the risk factors to predict occult cystobiliary communications (CBC) preoperatively to avoid development of biliary leakage after surgery.

Methods This prospective study conducted at the Gastroenterlogy and Hepatology Teaching Hospital in Medical City, Baghdad from the 1st of December 2013 to the 29th of March 2016. Clinical assessment, laboratory tests and imaging studies were under taken for 85 patients with uncomplicated liver hydatid cysts. Endocystectomy and or partial pericystectomy were undertaken. Post-operative follow up and management of biliary leakage for those with cysto-biliary communication not detected intra operatively. Data were analyzed to predict risk factors for occult CBC.

Results Of the 85 patients, 64 patients had no evidence of CBC neither intra nor postoperative, while the remaining 24 patients had an occult CBC, that have been discovered during operation or evident in the following days. Significant clinical predictors of communication were cyst size ≥ 10 cm, elevated total serum bilirubin (TSB) and gamma glutamyl transferase (GGT) ($P < 0.001$). Other findings were associated more with patients having CBC than those without, including high white blood cell count (WBC), alkaline phospatase (ALP), aspartate transaminase (AST) and alanine transaminase (ALT) levels. Nine of 13 patients who developed post-operative bile leak stopped spontaneously, the other 4 patients mandate endoscopic retrograde cholangiopancreatgraphy (ERCP) to close their fistulas.

Conclusion Awareness about the risk factors for CBC can predict preoperative diagnosis of occult CBC. Endoscopic biliary interventions should be considered as a part of complementary treatment of those cases with refractory CBC and to be discussed in patients's consent preoperatively.

Keywords Liver hydatid cyst, cystobiliary communication, biliary leakage.

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List of abbreviation: ALT = Alanine Aminotransferase, ALP = Alkaline Phosphatase, AST = Aspartate Aminotransferase, ERCP = Endoscopic retrograde cholangiopancreatography, GGT = Gama Glutamyl Transferase, TSB = Total Serum Bilirubin, WBC = White blood cells count

Introduction

Hippocrates describes hydatid disease as 'liver full of water' [1]. It is endemic in Mediterranean region and in Iraq it is a well-known health problem [2,3]. Although hydatid disease was uncommon in united State and Europe, now it is considered as

recognizable cause of morbidity and mortality in these regions due to travel and migration [4].

In general, hydatid disease affect liver in 50-70% of cases [1,5]. Of the most interesting complication encountered in 13-37% of patients with liver hydatid is the communication between cyst cavity and biliary radicles (CBC) secondary to rupture of the cyst into the biliary system [6-8].

Intrabiliary rupture could be an overt frank or silent occult [9]. In overt situations, a major cyst contents, like debris, daughter cysts and fragments of the laminated membrane may go down into the common bile duct [10]. Patients usually present with features of obstructive jaundice during the course of the disease [11]. Diagnosis in these patients is easy, and managed either surgically or by endoscopic retrograde cholangiopancreatography (ERCP) [12]. However, most CBCs are occult in nature without specific clinical, radiological or laboratory findings due to relatively small communication and discovered only during or after surgery as a postoperative biliary fistula (PBF) [13,14].

In this instance, undesired complications could be happened such as prolonged biliary leakage, biliary peritonitis and abscess, an increased morbidity, cost and hospital stay will ensure [15].

Bile usually not seen in the cyst cavity in cases of occult CBC due to high intracystic biliary pressure gradient (80 vs. 20 cm H_2O subsequently). After cyst evacuation, bile flow back into the cyst due to reversed pressure gradient [16,17].

Radical surgeries i.e. formal hepatectomy and pericystectomy have a rare incidence of postoperative biliary leakage and recurrence, at the same time they carry a more perioperative risk of bleeding and need expert hepatobiliary surgeon in a specialized center, on the contrary, conservative surgery; endocystectomy or partial pericystectomy, usual performed type of surgery in endemic regions, they have a high incidence of postoperative biliary leakage and local recurrence although less perioperative risk of bleeding [17].

ERCP has a beneficial role in showing the dilatation in the biliary duct and the relationship between the cyst and the bile ducts before operation. However, it is not usually possible to demonstrate minute CBC [14]. Moreover, it is not feasible to perform prophylactic ERCP in all patients. Accordingly, it is important to predict the CBC in asymptomatic patients. The sizes of cyst, levels of alkaline phosphatase (ALP), Gama Glutamyl Transferase (GGT) and Total Serum Bilirubin (TSB) have been reported as risk factors for CBC, it has been reported that ALP concentrations greater than 250 U L^{-1}, a total bilirubin level above 17.1 µmol L^{-1}, GGT higher than 34.5 U L^{-1}, and cyst size greater than 8.5 cm in the preoperative period were independent predictors of occult CBC [15,18].

GGT is present in hepatocytes and biliary epithelia lcells; its elevation is the most sensitive marker of hepatobiliary disease. However, its routine clinical use is not recommended, as it cannot by itself indicate a specific cause of liver disease, although measuring the GGT level can help determine a hepatic origin for an isolated elevation of alkaline phosphatase [19].

The presence of these risk factors should rise the suspicion of asymptomatic CBC and a clear hydatid fluid content without bile in the cyst does not mean an intact cyst wall, in such, the use of scolicidal agents should be avoided because septic complications and risk of sclerosing cholangitis [20].

Management should be planned in these patients, antibiotic chosen for prophylaxis, ERCP if possible and surgical intervention whenever possible. If the CBC is revealed during operation, an effort should be paid to suture with absorbable material, with or without cystic duct drainage (or T-tube insertion), otherwise if biliary opening cannot be identified, an adequate external drainage, preferably with suction drainage. Methylene blue injection into the common bile duct or

intraoperative cholangiogram can help in localization of communication [21].

Most of biliary fistulas close without intervention, failure of closure may occur in 4-27.5% of cases [22]. Endoscopic sphincterotomy is indicated if no evidence of healing within three weeks or persistent high output exceeding 300 mL/d [23].

This study aimed to identify and manage patients with occult CBC preoperatively, therefore, the clinical and laboratory parameters associated with such type of communication were studied in patients who developed biliary leakage after hydatid liver surgery.

Methods

A prospective study conducted at the Gastroenterology and Hepatology Diseases Teaching Hospital in Medical City, Baghdad, from the 1st of December 2013 to 29th of March 2016; (98) patients with liver hydatid cysts had been admitted to the hospital, (85) patients with uncomplicated hepatic cyst whether primary or recurrent, had been enrolled in the study, those with frank CBC (10) patients, and those underwent radical surgery (3) patients had been excluded from the study. Clinical assessment, laboratory and imaging studies had been done for all patients. Liver function tests with their reference normal value including TSB (0.2-1.2 mg/dL), AST (≤41 U/L), ALT (≤ 44 U/L), ALP (53-128 U/L) and GGT (5-35 U/L) were recorded in addition to WBC (4-10 * 10^9/L). The diameter, location, number and types of the cysts also reported utilizing the ultrasound and computerized tomography (CT) findings. The above data were analyzed as potential predictors of occult cystobiliary communication. Patients were prepared for surgery, preoperative Albendazol for two weeks, antibiotics at time of induction of anesthesia and deep venous thrombosis (DVT) prophylaxis. Access to the liver was through a midline, subcostal or right anterolateral 7th intercostals space thoracotomy incisions depending on the cyst location. Identification of the cyst, aqueous povidon socked packs or hypertonic soaked packs used to isolate cysts, injection of scolicidal agent was not done. Endocystectomy and or partial pericystectomy were undertaken with the control of suction. CBC had been looked for intra operatively for 5 minutes and sutured whenever found, drain was left inside cavity.

Postoperatively drains were removed on the 3rd to 5th postoperative day if they provided no biliary drainage. Patients who continued to have biliary drainage in the first 10 days postoperatively were considered to have biliary leakage. Longer biliary drainage was classified as biliary fistula. The fistulas were categorized into low and high-output types based on the fistula output, less or more than 300 mL/day, respectively.

Drains were kept in patients who developed biliary fistulas and amount was recorded daily. Sinogram then Endoscopic sphincterotomy was performed in patients in whom no reduction in biliary flow rate or a spontaneous termination of biliary leakage was unlikely within one month.

Included patients were divided into two groups, those who had no CBC; labeled as group A and those who had occult CBC as group B. Statistically the two groups were compared according to the clinical findings, laboratory tests, imaging and operative results.

The results are presented as the mean (and standard deviation SD), number (and %), significance was set at ($P<0.05$), sensitivity, specificity, positive predicative value, negative predicative values and accuracy.

Results

Eighty-five patients had been divided into group A 61 (72%) (Patients without CBC) and B 24 (28%) (Patients with occult CBC) based on intraoperative findings of bile spillage into the cyst cavity after endocystectomy or postoperative bile drainage through abdominal drain.

The overall CBC in this series was 34 (34.6 %) patients; those with frank communication had

been excluded as mentioned above 10 (10.2 %) patients and 24 (24.4%) patients had occult CBC.

The mean age was higher for those with CBC than those without communication, (41.4) versus (36.04) years. Female predominance was in both groups, A and B, (57.4%), (54.2%) subsequently although no significant relation to the development of CBC.

Patients from rural areas were predominating in both groups (A; 62.3%) and (B; 71%), still no statistical relation to the development of CBC. Abdominal discomfort was the presenting symptom in more than two third of patients, group A (83.6%) and group B (79.1%).

In relation to the size of the cysts, CBC were significantly associated with increased hydatid cyst size, most of those with CBC (79.9%) have cyst size more than 10 cm (P<0.001).

The cysts were located in the right lobe in 38(62.3%), in the left lobe in 17 (27.8%), and in both lobes 6 (9.8%) patients in Group A. The cyst locations were right, left and bilateral in 16 (66.6%), 5 (20.8%), 3 (12.5%) patients respectively in group B.

Majority of patients had single liver cyst, group A; 42 (68.8%) and group B; 18 (75%), usually they were unilocular. No significant statistical differences in relation to the other features of cysts in both groups as shown in (Table 1)

Table 1. Demographic and clinical data

Clinical features			Patients group A: 61 (72%)	Patients group B 24 (28%)	Significance *P* value
Age (Mean ± SD) year			36.04±12.9	41.4±15.5	0.5
Sex	Male		26 (42.6%)	11 (45.8%)	0.812
	Females		35 (57.4%)	13 (54.2%)	
Region	Urban		23 (37.7%)	7 (29%)	0.615
	Rural		38 (62.3%)	17 (71%)	
Presentation	Discomfort		51 (83.6%)	19 (79.1%)	0.744
	Fullness or swelling		29 (47.5%)	8 (33.3%)	
	Incidental		12 (19.6%)	3 (12.5%)	
Features of cyst	Size	< 10 cm	39 (63.9%)	5 (20.1%)	< 0.001
		≥ 10cm	22 (36.1%)	19 (79.9%)	
	Site	Rt. lobe	38 (62.3%)	16 (66.6%)	0.780
		Lt. lobe	17 (27.8%)	5 (20.8%)	
		Bilateral	6 (9.8%)	3 (12.5%)	
	No. of cyst	Single	42 (68.8%)	18 (75.0%)	0.792
		Multiple	19 (31.1%)	6 (25.0%)	
	Morph-ology	Unilocular	31 (50.8%)	14 (58.3%)	0.807
		Multilocular	22 (36.0%)	7 (29.1%)	
		Degenerative	8 (13.1%)	3 (12.5%)	
	Recurr-ence	No	48 (78.7%)	20 (83.3%)	0.768
		Yes	13 (21.3%)	4 (16.7%)	

Although the laboratory findings were not statistically different between two groups, the mean value for WBC, ALP, ALT, AST were lower in group A (7.3±2.39, 0.98±0.7, 85.4±41.5, 26.6±10.9, 26.6±10.9) than in group B (8.77±2.43, 1.7±0.82, 90.2±51.7, 39.7±20.2, 37.5±19.4) subsequently, except GGT and TSB levels were significantly different between the two groups (P< 0.001) as shown in (Table 2).

Table (3) shows the results of multivariate analyses for the risk factors of occult CBC presenting as biliary leakage after surgery. Cyst size ≥ 10, TSB >1.2 mg/dL and GGT >35 U/L levels were significant clinical factors that predict the risk of occult CBC with sensitivity of 79.1%, 70.1%, 83.3% subsequently, although positive predicted value was high only for the GGT 71.4%. Combination of these risk factors if present in patients with hydatid cyst; an accuracy of 95.2% can be yield in prediction of CBC.

Table 2. Laboratory tests

Test	Group A (mean ± SD)	Group B (mean ±SD)	P value
WBC (4-10 * 10^9/L)	7.3±2.385	8.77±2.43	0.072
TSB (mg/dL)	0.98±0.7	1.7±0.82	**<0.001**
ALP (U/L)	85.4±41.5	90.2±51.7	0.41
ALT (U/L)	26.6±10.9	39.7±20.2	0.53
AST (U/L)	23.9±11.3	37.5±19.4	0.31
GGT (U/L)	24.8±13.45	82.7±42.9	**<0.001**

Table 3. Risk factors associated with occult CBC on multivariate analysis

Variables	TP	TN	FP	FN	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%
Cyst size >10 cm	19	39	22	5	79.1	64	46.3	88.6	68.2
WBC >10000*10^9/L	8	52	9	16	33.3	85.2	47.1	76.4	70.5
TSB >1.2 mg/dL	17	42	19	7	70.1	68.8	47.2	85.7	69.4
ALP >45 U/L	8	47	14	16	33.3	77.04	36.3	74.6	64.4
GGT >35 U/L	20	53	8	4	83.3	86.8	71.4	92.9	85.8
If above risks are positive	6	75	2	2	75	97.4	75	97.4	95.2

TP = true positive, TN = true negative, FP = false positive, FN = false negative, PPV = positive predicted value, NPV = negative predictive value

Endocystectomy and or partial pericystectomy were done for the patients, 61 patients without CBC run a smooth postoperative period regarding absence of bile leak through their abdominal drains. Twenty four patients with occult CBC managed accordingly; 11 of them had an obvious bile coming from a visible biliray tributary adherent to the residual cyst cavity, intra operative suturing were under taken by long absorbable suture, there after they follow free postoperative period from any bile discharge, the remaining 13patients (15.3% of total number), no obvious intra operative biliray communication were detected, in 9 of them low output fistula developed that managed expectantly and almost closed spontaneously within 10 days, a high output fistula were developed in the remaining 4 patients to whom sinogram through draining tube to delineate anatomical relationship followed by ERCP successfully within one month from the surgery (Figures 1 and 2), the fistulas closed within two to three days later, (Table 4) showed the fate of those patients suffer CBC. The overall hospital stays were 4.3 days in group A, while10.2 days in group B ($P < 0.05$).

Discussion

Liver hydatid cysts may grow average 1-30 mm per year and cause compressive atrophy of surrounding hepatocytes and fibrosis. CBC due to spontaneous rupture may occur at the point of contact with a biliary duct [18].

The incidence of frank and occult CBC ranges 5-17% and 10-37% of cases, respectively [7,8, 24]. In this series, the frank and occult CBC were 10.2% and 24.4% subsequently.

Figure 1. Sinogram shows cysto-biliary communication

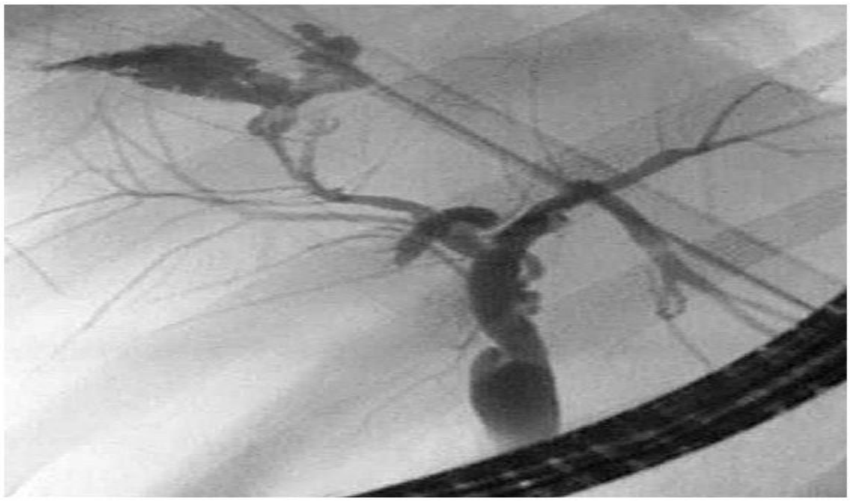

Figure 2. Endoscopic cholangiogram shows cystobiliary communication

Table 4. Fate of group B

Patients		No. (%)	Management
Intra operative leak		11 (46%)	Primary repair
Postoperative bile leak	<300 ml/d	9 (37.5%)	Expectant
	>300 ml/d	4 (16.5%)	ERCP

The mean age for group A was 36.4 years while 41.4 years for group B, Demircan et al. [29] found that a mean age for patients without CBC was younger than those with CBC 42.2, 44.4 years respectively. This explained by the longer the history and so the larger size of hydadit cyst is associated with increasing risk of complications.

Female preponderance was observed in both groups (Table 1), Sawady showed a female to male ratio of 1.5:1 in their study at Al Basrah city [3]. Khader Faheem et al. found in their study carried at Andhra Pradesh (India) a male to female ratio of 2.5:1, the differences in the reports were due to difference in socioeconomic, livelihood activities of farming, routine labor, animal breeding and agriculture variations in different regions in the world [25].

More than two third of patients in both groups were from rural area, which is expected as the disease is common where dogs and cattle are kept [26].

Although liver hydatid cysts are usually asymptomatic, in our series the most common symptoms were abdominal pain and swelling or fullness. A study done by Rukmangadha et al. showed that overall commonest presentation was incidental asymptomatic finding, while abdominal pain comes next, fever and jaundice may accompany complicated cysts [27].

The size of the cyst was one of the significant preoperative predictors of CBC with a cut-off value of ≥ 10 cm, (P <0.001). Zeybek et al. analysis also showed that a high preoperative cyst diameter (>10 cm) were significantly more common in patients who develop postoperative biliray fistula [28]. Demircan et al. found that cyst diameter greater than 8.5 cm were independent clinical predictors of occult CBC in multivariate logistic regression analysis [29].

Although majority of patient with CBC had their cyst location in the right lobe, no significant statistical relation was found with CBC. This applied for the other clinical findings of the cysts such as number, unilocular or multilocular, degenerative or recurrent. At Al-Basrah city, Sawady found that the frequency of biliary leakage was not affected by cysts being single or multiple, primary or recurrent or in which hepatic lobe they found (P >0.05) [3].

In the present study, whether or not the pre-operative laboratory findings are indicators for occult CBC was determined. None of the laboratory findings except GGT and TSB were useful as indicators of occult CBC (P <0.001).

Although most of patients with occult CBC were clinically not jaundiced, their TSB levels were mildly elevated biochemically. Sawady found that TSB level was upper normal in those patients with occult CBC [3]. GGT is a biliary enzyme that is especially useful in the diagnosis of obstructive jaundice, intrahepatic cholestasis, and pancreatitis. GGT is more responsive to biliary obstruction than are (AST) and (ALT). GGT is helpful to work up elevated ALP values and more specific for hepatic disease than is ALP [29]. Sing et al. found that the outcome of GGT was significantly higher in occult CBC group (P <0.05), they consider GGT level as useful for predicting of occult CBC in hepatic hydatid diseases preoperatively [30].

Cyst size, WBC, bilirubin, ALP and GGT have been reported as risk factors for CBC in literature [15]. We found that positive and negative predictive values were 46.3%, 88.6% for cyst size, 47.1%, 76.4% for WBC, 47.2%,

85.7% for total bilirubin, 36.3%, 74.6% for ALP and, 71.4%, 92.9% for GGT respectively.

Whenever a combination of these risk factors is present, positive, negative predictive value and accuracy of 75%, 97.4% and 95.2% will be obtained respectively. Unalp et al. [31] found in their series that the above parameters (except WBC) were independent risk factors for occult CBC in multivariate analysis, they found that, positive and negative predictive values were 41%, 95%for cyst size; 57%, 76%for total bilirubin; 43%, 96% for ALP and 50%, 97% for GGT respectively. Leukocytosis was a poor predictor, with positive predictive value of 17% and negative predictive value of 84%. However, if a combination of these 5 factors is present, the positive and negative predictive values increased to 100% and 90%, respectively.

The rate of external biliray fistula was 15.3%, 9 patients had a low output and closed spontaneously without intervention, the other 4 patients necissate ERCP (about one month from the surgery date) to close their high output fistula. Accordingly, the hospital stay was significantly higher for those with postoperative biliray fistula (10.2 days versus 4.3 days for those without fistula, P<0.05). Kemal et al found that the rate of external biliary fistulas was 22%, most of them closed spontaneously; they may persist in few cases. In their study, low-flow fistulas (< 300 mL/day) were present in 11 of 15 patients with fistulas; these fistulas closed spontaneously. The remaining 4 patients had high-flow fistulas and three of them closed after ERCP, whereas one patient underwent a fistula-enterostomy. Endoscopic sphincterectomy is performed after a 3-week waiting period, the overall hospital staying days were 5.3 days in patients without external biliray fistula and 21.2 days in patients with fistulas (p<0.05) [17].

This study concluded that a surgeon should suspect an occult CBC if asymptomatic patient has the above risk factors, endoscopic biliary interventions should be considered as a part of complementary treatment of those cases with refractory CBC and to be discussed in patients' consent preoperatively.

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Conflict of interest

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