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BILIARY CYSTADENOMA AND CYSTADENOCARCINOMA IN PATIENTS OPERATED FOR LIVER HYDATID CYSTS: A RETROSPECTIVE CLINICAL STUDY AND LITERATURE REVIEW

Feyzi KURT[1], Kalbim ARSLAN[2]✉, Hasan BESIM[2]

[1] Seyhan State Hospital, General Surgery Clinic, Adana, Turkey
[2] Near East University, Medical School, General Surgery Department, Nicosia, Cyprus

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Abstract

Introduction. Biliary cystadenoma (BCA) and biliary cystadenocarcinoma (BCAC) are rare, unusual lesions, that most commonly appear in the right lobe of the liver. Clinical and radiological findings are very similar with liver hydatid cysts. Therefore, the differential diagnosis with liver hydatid cyst (LHC) is usually made by pathological examination, postoperatively.
The objective of the study was to detect the prevalence of BCA and BCAC in patients who were treated for hydatid cysts.
Material and methods. Data of 720 cases with operated liver hydatid cysts (LHC) at the General Surgery Clinics of Seyhan State Hospital Adana, Turkey, and Near East University Nicosia, Cyprus, were retrospectively reviewed. The study included 10 patients with BCA and two patients with BCAC, who were operated with a preliminary diagnosis of liver hydatid cyst.
Results. Of the 12 patients included in the study, 5 were male and 7 were female. The mean age of the patients was 43.58 years. All patients were pre-diagnosed with liver hydatid cyst after preoperative laboratory and radiological evaluations and all underwent partial cystectomy. The results of histopathological

Résumé

Le cystadénome biliaire et le cystadénocarcinome chez des patients opérés pour des kystes hydatiques du foie: étude clinique rétrospective et revue de la littérature

Introduction. Le cystadénome biliaire (BCA) et le cystadénocarcinome biliaire (BCAC) sont des lésions rares et inhabituelles, qui apparaissent le plus souvent dans le lobe droit du foie. Les résultats cliniques et radiologiques sont très similaires avec les kystes hydatiques du foie. Par conséquent, le diagnostic différentiel avec kyste hydatique du foie (LHC) est généralement posé par examen pathologique, postopératoire.
L'objectif de l'étude était de détecter la prévalence du BCA et du BCAC chez les patients traités pour des kystes hydatiques.
Matériel et méthodes. Les données de 720 cas avec kystes hydatiques du foie opérés (LHC) dans les cliniques de chirurgie générale de l'hôpital d'État de Seyhan Adana, en Turquie, et de la Near East University de Nicosie, à Chypre, ont été examinées rétrospectivement. L'étude a inclus 10 patients avec BCA et deux patients avec BCAC, qui ont été opérés avec un diagnostic préliminaire de kyste hydatique du foie.

✉ Address for correspondence: Kalbim ARSLAN
Near East University, Medical School, Nicosia, Cyprus
E-mail: kalbimarslan@hotmail.com; Phone: 90 533 8742950

examination showed that 10 of these patients had BCA and two had BCAC. The mean follow–up was 28.4 months. During this period, recurrence was seen in 3 out of 10 patients with BCA and total cystectomy was performed in these 3 patients. Two patients with BCAC underwent right hepatectomy.

Conclusions. The follow-up and evaluation of the histopathological results are very important in patients operated with the diagnosis of liver hydatid cyst. Cases with biliary cystadenoma and cystadenocarcinoma, which are difficult to detect, especially in the preoperative period, should be re-evaluated and complementary operations should be performed.

Keywords: hydatid cyst, biliary cystadenoma, biliary cystadenocarcinoma.

Résultats. Sur les 12 patients inclus dans l'étude, 5 étaient des hommes et 7 des femmes. L'âge moyen des patients était de 43,58 ans. Tous les patients ont reçu un diagnostic préalable de kyste hydatique du foie après des évaluations préopératoires de laboratoire et radiologiques et tous ont subi une cystectomie partielle. Les résultats de l'examen histopathologique ont montré que 10 de ces patients avaient un BCA et deux un BCAC. Le suivi moyen était de 28,4 mois. Au cours de cette période, une récidive a été observée chez 3 patients sur 10 avec BCA et une cystectomie totale a été réalisée chez ces 3 patients. Deux patients atteints de BCAC ont subi une hépatectomie droite.

Conclusions. Le suivi et l'évaluation des résultats histopathologiques sont très importants chez les patients opérés pour un diagnostic de kyste hydatique hépatique. Les cas de cystadénome biliaire et de cystadénocarcinome, difficiles à détecter, notamment dans la période préopératoire, doivent être réévalués et des opérations complémentaires doivent être réalisées.

Mots-clés: kyste hydatique, cystadénome biliaire, cystadénocarcinome biliaire.

Introduction

Biliary cystadenoma (BCA) and biliary cystadenocarcinoma (BCAC) originating from bile ducts are extremely rare diseases. Although the histopathogenesis is controversial, it is accepted that they originate from the foregut during the embryonic development. BCAs are usually lined by mucus-secreting columnar epithelium and polypoid and papillary structures developing towards the lumen and focal intestinal metaplasia in the epithelium may be seen[1]. BCA constitutes 5-10% of cystic lesions developing from intrahepatic biliary ducts[2]. They are usually intrahepatic and consist of a large number of lobules[3]. These lesions are common in young and middle-aged women and may often achieve large diameters without any symptoms[4]. Patients generally present with abdominal mass sensation, pain and sometimes jaundice due to the blockage of the bile ducts[5]. Abdominal mass can be palpated at the physical examination and icterus can be seen on the skin and eyes. There is no specific diagnostic test for BCA. These cysts have similar features with liver hydatid cyst (LHC) at the X-ray. Ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) show multiloculated cystic structures with internal septation. Although they are seen in both lobes of the liver, they are frequently located in the right lobe[6]. Because of recurrences and their malignancy potential, the treatment of BCA cases is different from the treatment of LHC cases. The definitive treatment of these lesions is surgical, with total excision of the cyst.

The objective of the study was to detect the prevalence of BCA and BCAC in patients who were treated for hydatid cysts.

Material and methods

Data of 720 cases with LHC operated at Seyhan State Hospital General Surgery Clinic Adana (Turkey) and Near East Unıversity General Surgery Clinic Nicosia (Cyprus), between January 2005 and April 2019, were retrospectively reviewed. Laboratory parameters, serology results, radiology imaging and pathology results of the patients were evaluated. Twelve patients whose histopathological results revealed BCA and BCAC were included in the study. Gender, age, pre-operative diagnoses, surgical and pathological results of these patients were examined.

Statiscical analysis

Statistical analysis was performed using the SPSS/PC version 13 computer software (Prentice-Hall; Chicago, IL). The student's t test was used to compare the mean values between the two groups. The Chi square test (X2) with Yate's correction was used for comparison between categorical qualitative values. Fisher's exact test was used for comparing

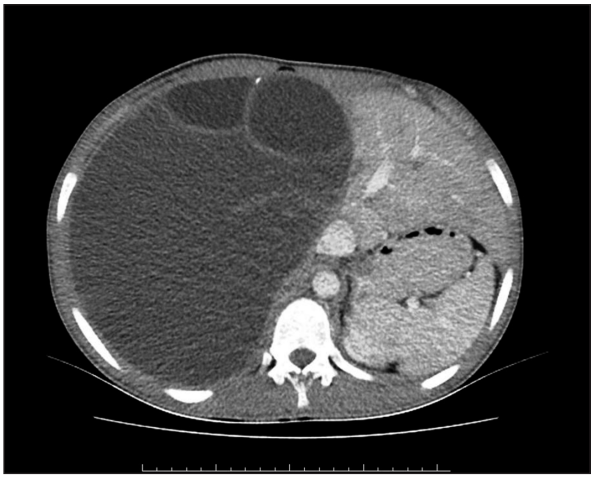

Fig. 1. CT scan, the mass in liver with hydatid cyst.

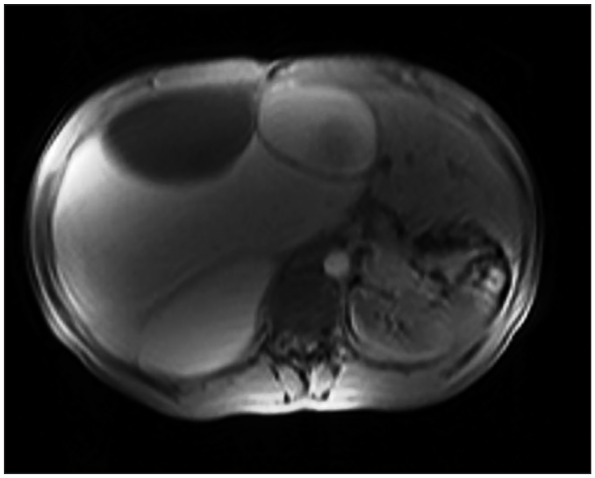

Fig. 2. MRI scan, mass in the liver with hydatid cyst.

recurrence between the two study groups. A p level of <0.05 was accepted as statistically significant.

Results

Of the 720 LHC cases operated in the General Surgery Clinic, ten (1.38±88%) and two (0.27±77%) patients were found to have BCA and BCAC, respectively. Of the patients with BCA and BCAC, five (41.6±66) were male and seven (58.33±33) were female. The mean age of the patients was 43.58 years, 44.4 in male and 43 in female patients, respectively. The youngest patient was a 20-year-old male patient and the oldest patient was a 64-year-old female patient. One of our malignant patients was a 52-year-old male patient and the other patient was a 32-year-old female patient. Recurrence was observed in three patients (25%). Although the preliminary diagnosis of all patients was LHC, it was found to be accompanied by a mass in the liver in two patients (Fig. 1, 2). In 622 (86.38±88%) patients with hydatid cyst at serology, indirect hemagglutination (IHA) was found to be positive, whereas two of the BCA and BCAC cases were found to be positive for IHA (16±66%). Seven patients (58.33±33%) with BCA and BCAC had lesions in the right lobe, two (16.66±66%) had lesions in the left lobe and four (33.33±32%) had lesions in both lobes. The masses of both malignant

Table 1. Demographic characteristics of patients and their diagnosis, treatment and pathology

N	Gender	Age	Preliminary diagnosis	Localization (Liver)	Recurrence	Surgery	Pathology
1	F	38	Hydatid cyst	Right lobe	+	Total cystectomy	Biliary cystadenoma
2	M	20	Hydatid cyst	Right + left lobe	–	Partial cystectomy	Biliary cystadenoma
3	F	28	Hydatid cyst	Right lobe anterior segments	+	Total cystectomy	Biliary cystadenoma
4	F	47	Hydatid cyst	Right lobe posterior segments	+	Total cystectomy	Biliary cystadenoma
5	F	46	Hydatid cyst	Right + left lobe	–	Partial cystectomy	Biliary cystadenoma
6	M	52	Hydatid cyst	Left lobe	–	Partial cystectomy	Biliary cystadenoma
7	F	64	Hydatid cyst	Right + left lobe	–	Partial cystectomy	Biliary cystadenoma
8	M	62	Hydatid cyst	Left lobe	–	Partial cystectomy	Biliary cystadenoma
9	M	52	Hydatid cyst + mass	Right lobe	–	Right hepatectomy	Biliary cystadenocarcinoma
10	F	46	Hydatid cyst + mass	Right lobe anterior segments	–	Partial cystectomy	Biliary cystadenoma
11	M	36	Hydatid cyst	Right lobe	–	Partial cystectomy	Biliary cystadenoma
12	F	32	Hydatid cyst	Right lobe anterior segments	–	Right hepatectomy	Biliary cystadenocarcinoma

Table 2. Tumour sizes of the cases and treatments applied.

N	Gender	Age	Tumour size (cm)	IHA test	Preliminary Diagnosis	Surgery	Pathology
1	F	38	4.5	Negative	Recurrence	Total excision	Benign
2	M	20	25	Positive	Hydatid cyst	Partial excision	Benign
3	F	28	3.5	Negative	Recurrence	Total excision	Benign
4	F	47	10	Positive	Recurrence	Total excision	Benign
5	F	46	4	Negative	Hydatid cyst	Partial excision	Benign
6	M	52	6	Negative	Hydatid cyst	Partial excision	Benign
7	F	64	3.5	Negative	Hydatid cyst	Partial excision	Benign
8	M	62	4.5	Negative	Hydatid cyst	Partial excision	Benign
9	M	52	6	Negative	Hydatid cyst	Right hepatectomy	Malign
10	F	46	30	Negative	Hydatid cyst	Partial excision	Benign
11	M	36	15	Negative	Hydatid cyst	Partial excision	Benign
12	F	32	10	Negative	Hydatid cyst	Right hepatectomy	Malign

patients were in the right lobe (Table 1). All hydatid cyst patients underwent partial cystectomy. Partial cystectomy was performed in patients with BCA who underwent surgery for LHC. Treatment of three cases with BCA who had recurrences was completed with total cystectomy (Table 2). Two patients with malignancy underwent right hepatectomy in the hepatobiliary surgery clinic at an external center. The mean follow-up duration of the patients was 28.4 months. In the follow-up of all patients, USG was used, as well as CT and MRI, when needed.

Discussion

BCAs originate from the biliary tract and account for about 5% of these tumours[7,8]. These tumours grow slowly, but may eventually achieve great dimensions[7]. The first surgical resection of BCA was performed by Keen in 1892[9]. The pathology was first described by Edmondson as a multilocular cystic lesion lined by columnar epithelium accompanying a densely cellular „ovarian-like" stroma[10]. Approximately 90% of BCAs are seen in the fifth decade[11]. However, BCAC, which accounts for approximately 40% of malignant hepatic epithelial tumours, are seen in older ages[12,13]. BCAs are more common in women compared to men[13]. The mean age in the present study was 43.58 years, with the youngest patient having 20 year-old and the oldest patient 64 years-old. The reason for obtaining results different from the literature could be attributed to the fact that our cases were selected from LHC patients. Of the patients with BCAC, one patient was 32 year-old and the other was 64 year-old. Seven of our patients were female (58.33%), similar with data from the literature.

Of the BCA and BCAC, 80-90% were reported to be intrahepatic and 10-20% were extrahepatic[14]. All of the lesions in our cases were intrahepatic. In the literature, it has been reported that about 50% of liver BCAs are located in the right lobe, 30% in the left lobe, and 15-20% in both lobes[15]. The lesion was in the right lobe in seven of our cases (58.33%), in the left lobe in four cases (33.33%), and in both lobes in two cases (46.66%). Our results were similar with the literature.

The diameters of BCA usually range from 1.5 cm to 40 cm[16]. The mean tumour diameter in the present study was 9.54 cm (min. 3.5 cm, max. 30 cm). The tumour diameter of two patients with BCAC was measured as 6 cm and 10 cm (mean 8 cm).

Laboratory tests of patients with BCA reveal normal results. Alpha-fetoprotein and carcinoembryonic antigen tumour markers are usually detected as normal. However, in some patients, cancer antigen 19-9 (CA 19-9) may be several times higher than the normal limit[17].

Laboratory tests of our patients did not show any characteristics related to the disease. Only two of our cases were positive for IHA.

The pathogenesis of BCA and BCAC has not been clearly identified yet. Although they are claimed to occur congenitally from the aberrant biliary ducts, there are studies stating that the reaction caused by a local injury could be involved in their pathogenesis[18]. Although subepithelial tissue has been involved due to its histological similarity with ovarian stroma and ectopic ovarian tissue is located in the liver, histochemical studies do not sustain this theory[19].

The following diseases should be considered in the differential diagnosis of BCA: LHC, simple liver cysts, cystic hamartoma, primary and secondary

malignant tumours, hepatic abscess, Caroli's disease, and polycystic liver disease. Although radiological imaging methods are helpful in the diagnosis of BCA, they are not sufficient for the differential diagnosis of BCA and BCACs. Anechoic cystic lesions presenting with echoic internal septations might be seen at USG, and CT shows a smooth and thick-walled cyst, with internal septation[20]. The fluid inside the cyst and septations might be revealed through MRI[21]. None of the above mentioned imaging results performed in the present study were interpreted as the preliminary diagnosis of BCA and BCAC. All our cases were reported as LHC. In only two cases, CT revealed a liver mass accompanying the LHC. One of these cases had BCA and the other had BCAC. A study has reported that the intraoperative cholangiography may be useful in differentiating these tumours from other liver cysts, because it may show the communication between the tumour and biliary tract[22]. Biopsy from these masses is not recommended, because of the multifocal feature of these tumours and the risk of peritoneal implantation developing secondarily to a biopsy obtained from BCAC[23].

Although BCACs can grow very slowly, they might achieve great dimensions. However, local invasion and metastasis are rare[24]. The prognosis of BCAC with local invasion and distant metastasis is poor. Furthermore, the prognosis of patients with BCAC lacking ovarian-like stroma is even worse[25]. Compared to other malignant tumours of the liver, such as hepatocellular carcinoma and cholangiocarcinoma, the prognosis of BCAC is better[26].

BCAs are more common in women than in men, suggesting that progesterone and estrogen may be effective in the development of these tumours[27]. Some studies suggest that oral contraceptive use may be involved in the development of these tumours, however, most of the patients included in the studies do not have a history of oral contraceptive use[27,28]. In the present study, although the number of women was higher than of men, there was no history of oral contraceptive use.

The most significant characteristics of BCA are higher recurrence rates and malignant transformation. In the literature, 25% of BCAs cases have been reported to turn into malignancy[29]. Two patients included in this study had malignant disease (16.66%) and recurrence was observed in three patients (25%).

Treatments for BCA include sclerotherapy, percutaneous aspiration, internal drainage, marsupialization, and partial and total excision. However, there are many studies in the literature reporting that there are recurrences and malignant transformation in BCA cases[24,31]. The definitive treatment of BCA is, therefore, the total excision of the cyst.

Although these patients were diagnosed as hydatic cysts at the initial steps, later findings and pathological results ended up as a neoplastic diagnosis at the final stage. Turkey, Cyprus and other endemic countries have numerous hydatic cysts to handle but this neoplastic cysts should be taken into account during the initial diagnostic steps. Preoperative diagnosis may prevent future surgical interventions and incomplete surgeries. We did not do parasitological studies during surgical interventions. Serological tests may be used but they do not reflect active disease in all times. Percutaneous biopsy may be the next step in suspected cases although we did not perform it.

Conclusions

Although BCAs are common in women, they can be also seen in men. Since they might have malignant transformation and there is the possibility of recurrence, their treatment is different from other cysts of the liver and LHC. Frozen biopsy should be taken and the treatment plan should be reviewed in case of LHC or if there is suspicion of BCA or BCAC during surgery. Such cases can be treated with surgery, involving total excision of the cyst.

In the diagnosis and treatment of LHC, which is a serious public health problem for some countries, BCA and BCAC should be taken into consideration.

Author Contributions:

Conceptualization: FK and KA, Methodology: FK, KA, Software: KA, FK, HB, Validation: FK, KA, Formal analysis: FK, KA, Investigation: FK, KA and HB, Resources: FK, KA, Data curation: KA, FK, Writing – original draft preparation: FK, KA and HB, Writing – review and editing: FK, KA and HB, Visualization: FK, KA Supervision:HB, Project administration: HB.

All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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