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Original Article

Diagnostic uncertainty of hepatobiliary cystadenoma: Report of 11 cases and review of the literature

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الملخص

أهداف البحث: أجري هذا البحث لتسليط الضوء على عدم دقة التشخيص قبل الجراحي للأورام الكيسية الغدية الكبدية الصفراوية، واقتراح استراتيجيات لتحسين إمكانية التشخيص.

طرق البحث: تم ضم جميع المرضى المنومين على التوالي الذين لديهم الورم الكيسي الغدي الكبدي الصفراوي في الفترة من يوليو ٢٠٠٧ حتى يوليو ٢٠١٤ في هذه الدراسة. تم مراجعة السجلات الطبية للمرضى المؤهلين من أجل: التركيبة السكانية، والمظاهر السريرية، والفحوصات المخبرية، ونتائج الأشعة، والإجراءات الجراحية، والخزعة المجمدة، والمضاعفات، والتشريح المرضي، والمتابعة في العيادات الخارجية ، والأمراض والوفيات.

النتائج: تم علاج ١١ مريضا تم تشخيصهم بالأورام الكيسية الغدية الكبدية الصفراوية في وحدتنا. أجري لجميع المرضى أشعة صوتية وأشعة مقطعية مسحية للبطن، بينما تم عمل تصوير بالرنين المغناطيسي لثلاثة مرضى مشتبه بإصابتهم بالأورام الكيسية الغدية الكبدية الصفراوية. خضع ستة مرضى لجراحة نهائية، بينما تم تشخيص خمسة مرضى بالخطأ حيث اعتقد أنه ليس لديهم ورم كيسي غدي كبدي صفراوي (٢ كيس عداري و٣ كيس بسيط)، وذلك وفقا للأشعة الصوتية والأشعة المقطعية المسحية قبل الجراحة. وقد أجري للخمسة مرضى إزالة جراحية لسطح الكيس. كانت الخزعة المجمدة إيجابية لدى اثنين من المرضى وسلبية كاذبة عند واحد منهم وتم تشخيصه بكيس بسيط. بينما أظهر التشريح المرضي النهائي أورام كيسية غدية كبدية صفراوية لدى جميع المرضى.

الاستنتاجات: الأورام الكيسية الغدية الكبدية الصفراوية نادرة، وغالبا يتم تشخيصها بالخطأ كأضرار كبدية كيسية ينتج عن ذلك عدم كفاية العلاج الجراحي. إن تشخيص الأورام الغدية الكيسية الكبدية الصفراوية يجب أن يؤخذ في الاعتبار لدى جميع المرضى الذين لديهم أضرارا كبدية كيسية غير معتادة. المزيد من التقييم قبل الجراحة بالتصوير بالرنين المغناطيسي، وإجراء الخزعة المجمدة أثناء العملية يمكن أن يحسن إمكانية التشخيص وبالتالي يوفر فرصة الاستئصال الجذري النهائي.

الكلمات المفتاحية: الورم الكيسي الغدي الكبدي الصفراوي؛ كيس كبدي؛ نسيج شبيه المبيض؛ الخزعة المجمدة؛ التصوير بالرنين المغناطيسي

Abstract

Objectives: This research was conducted to highlight the pre-operative diagnostic uncertainty of hepatobiliary cystadenomas and to suggest strategies to improve its diagnostic yield.

Methods: All consecutive patients admitted with hepatobiliary cystadenomas from July 2007 to July 2014 were recruited in this study. The following information was retrieved from the medical records of eligible patients: demographics, clinical features, laboratory tests, imaging results, operative procedures, frozen sections, complications, histopathology, outpatient follow-up, and morbidity and mortality.

Results: Eleven total patients with a diagnosis of hepatobiliary cystadenomas were treated in our unit. Abdominal ultrasounds and computed tomography (CT) scans were performed in all patients; magnetic resonant imaging (MRI) was performed in three patients with suspicion of hepatobiliary cystadenomas. Six patients underwent a definitive surgery; five patients were incorrectly diagnosed with non-hepatobiliary cystadenoma liver cysts (2 hydatid cysts and 3 simple cysts) by the pre-operative ultrasound and CT scan. These five patients underwent surgical deroofing. The frozen section was positive in two patients and was falsely negative in one patient who was diagnosed with simple cysts. The final

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histopathology results identified hepatobiliary cystadenomas in all patients.

Conclusions: Hepatobiliary cystadenomas are rare and are frequently misdiagnosed as hepatic cystic lesions with resultant inadequate surgical treatments. A diagnosis of hepatobiliary cystadenomas should be considered in all patients with atypical liver cystic lesions. Further preoperative assessment with MRIs and intra-operative frozen sections may improve the diagnostic yield and provide an opportunity for a definitive radical resection.

Keywords: Frozen section; Hepatobiliary cystadenoma; Liver cyst; MRI; Ovarian-like stroma

Introduction

Hepatobiliary cystadenomas (HBCAs) are extremely rare benign tumours that constitute less than 5% of all cystic lesions of the liver.[1] Although they are considered to be benign cystic tumours, HBCAs are highly recurrent after an incomplete excision (up to 90%) and malignant degeneration (30%).[2–5] Due to the rarity of HBCAs, many clinicians are unfamiliar with the natural history, diagnostic features and therapeutic management of these liver neoplasms. A correct preoperative diagnosis and complete tumour excision with negative margin are the mainstays of adequate treatment. However, it is hard to distinguish between HBCAs and other cystic lesions of the liver due to the lack of specific presenting clinical features along with normal laboratory blood results and non-specific imaging features. There are similarities with other cystic lesions, such as simple cysts, hydatid cysts, liver abscesses, Caroli's disease, post-traumatic cysts, polycystic liver disease and malignant cystic lesions, making it extremely difficult to accurately diagnose them preoperatively.[1,5–8] This study presents a consecutive series of HBCAs treated over 7 years from a hepatobiliary surgery unit in a tertiary-care centre, highlighting the preoperative diagnostic uncertainty and suggesting ways to improve the diagnostic yield.

Materials and Methods

This retrospective study was conducted in the hepatobiliary unit of King Saud Medical City in the KSA between July 2007 and July 2014 among patients with a final diagnosis of HBCAs. Only those patients with liver cysts that were confirmed to be HBCAs by histopathological examination were included in the study. Patients with liver cysts that were not HBCAs after a histopathological examination were not included.

All patients were referred to this unit from other institutions for further management after they were diagnosed with liver cysts by imaging studies. All patients were re-evaluated. A complete blood count (CBC) and liver function tests (LFTs) were performed on all patients; a serum carbohydrates antigen 19-9 (CA 19-9) test was performed in patients with a preoperative suspicion of HBCAs. Patients were further imaged by an abdominal ultrasound and a dedicated computed tomography (CT) scan. MRIs were only obtained to further characterize the wall thickness, septations and mural nodularity when the CT scan was inconclusive. Patients with a preoperative diagnosis of HBCA or suspicion of HBCA underwent a definitive surgery in the form of a liver resection or a complete enucleation. Patients who were presumed to have a simple cyst or hydatid liver cysts had a de-roofing surgery. Those who were subsequently discovered to have an HBCA in the histopathology examination were re-submitted to a definitive surgery during the index admission. A frozen section was used selectively whenever there was an intraoperative suspicion of HBCA. After discharge from the hospital, all patients were evaluated in the outpatient clinic every 3 to 6 months by clinical, laboratory and imaging studies. The charts of eligible patients were used to retrieve the following data: demographics, comorbidities, symptoms and signs, laboratory tests, imaging results, operative procedures, frozen sections, operative time, blood transfusion, length of stay, complications, and outpatient follow-up. All follow-up images were reviewed by a consultant radiologist. The pathological slides of all included patients were reviewed by a consultant pathologist upon beginning the study. Ethical approval was obtained from the hospital research and ethical committee before beginning this study. A Medline search was used to retrieve relevant literature in English.

Results

Eleven total patients with a confirmed diagnosis of HBCAs were treated in our unit over a 7-year period (Figure 1). All of the patients were women, with a mean age of 45.91 $\pm$ 3.7 years. Two patients were asymptomatic, while nine patients presented with variable symptoms (Table 1). Laboratory values (CBC, LFTs) were normal in all patients except for one with an HBCA in segment IV where LFTs (mainly alkaline phosphatase, total bilirubin and direct bilirubin) were elevated. A serum carbohydrates antigen 19-9 (CA19-9) test was performed in 6 patients suspected to have an HBCA and was normal in all patients. A fine needle aspiration cytology (FNAC) and analysis of the cystic fluid for CA19-9 and CEA were not performed in any patients. An abdominal ultrasound and CT scan were performed in all patients; an MRI was performed in three patients to better characterize the suspicious cysts, which confirmed the diagnosis of HBCAs in all of them (Figure 2). An ultrasound and CT scan correctly diagnosed HBCA preoperatively in 3 patients, while the studies indicated high suspicion of HBCA due to the presence of

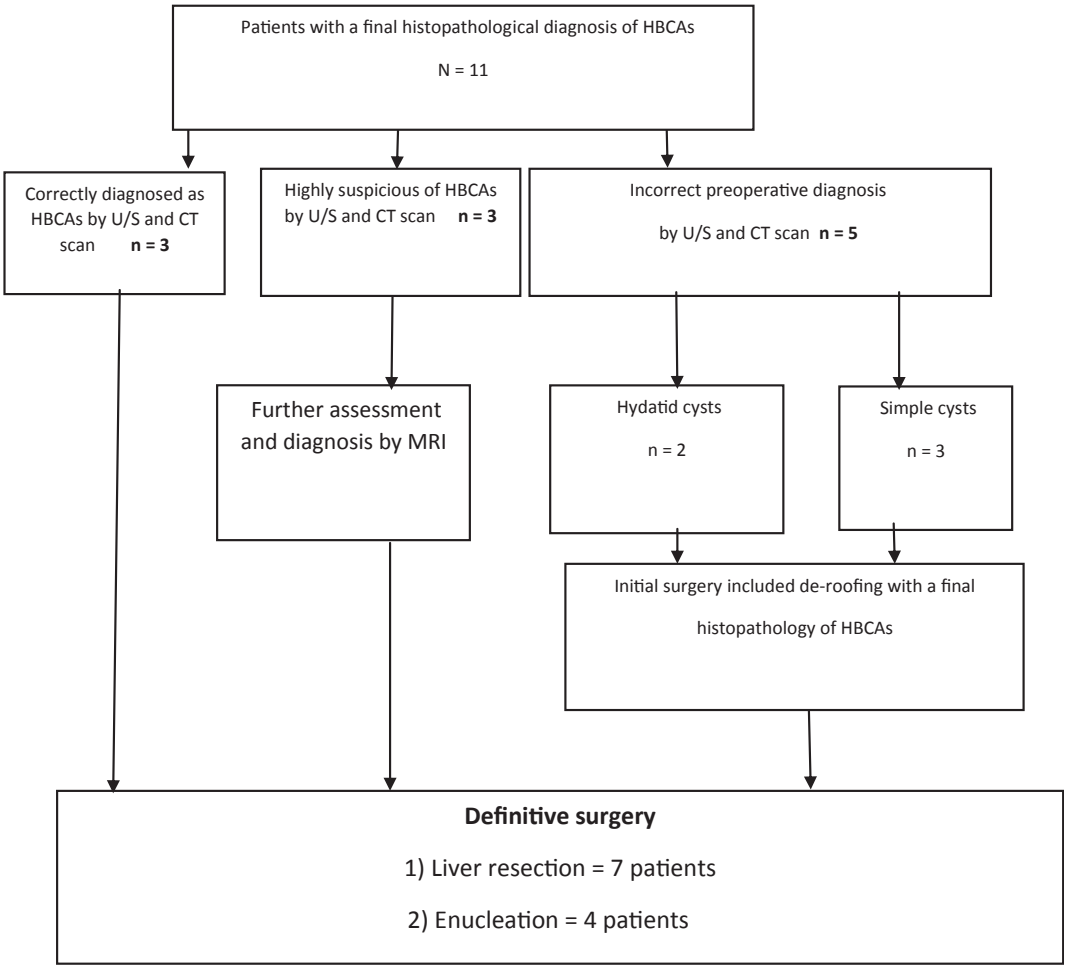

Figure 1: Flowchart of patients who were diagnosed with hepatobiliary cystadenoma.

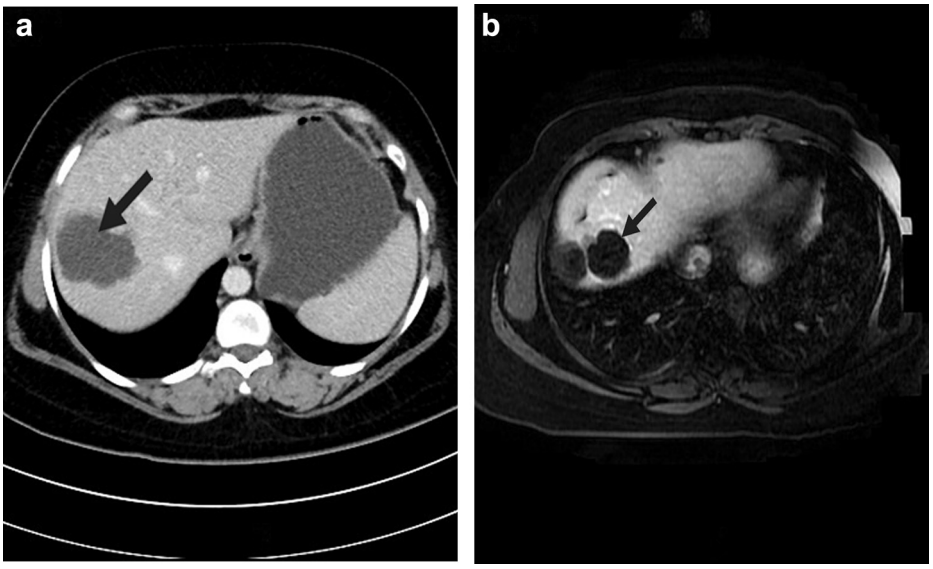

Figure 2: (a) Computed tomography showing a suspicious diagnosis of hepatobiliary cystadenoma confirmed by (b) MRI with internal septations.

Table 1: Details of clinical and radiological features of patients (n = 11) diagnosed with hepatobiliary cystadenomas.

Case no	Age (years)	Clinical features (Symptoms and Signs)	Involved segment	Preoperative diagnosis	Operative procedure	Follow-up period
1	47	Epigastric pain	Left lobe (IV)	Hepatobiliary cystadenoma	Left hepatectomy	76 months
2	42	Right upper quadrant pain, early satiety, vomiting	Right lobe (VI,VII)	Simple cyst	De-roofing followed by Enucleation	71 months
3	48	Asymptomatic	Right lobe (V)	Hydatid cyst	De-roofing followed by Enucleation	64 months
4	45	Epigastric pain, early satiety	Left lobe (II,III)	Hepatobiliary cystadenoma	Left lobectomy	59 months
5	38	Asymptomatic	Left lobe (II,III)	Hepatobiliary cystadenoma	Enucleation	55 months
6	44	Right upper quadrant pain	Right lobe (VII)	Hepatobiliary cystadenoma	Right hepatectomy	52 months
7	46	Right upper quadrant pain, postprandial vomiting, weight loss	Right lobe (VI, VII)	Simple cyst	De-roofing followed by Right hepatectomy	48 months
8	52	Epigastric pain, early satiety	Left lobe (II,III)	Hydatid cyst	De-roofing followed by Left lobectomy	45 months
9	47	Epigastric pain	Left lobe (II, III)	Hepatobiliary cystadenoma	Left lobectomy	36 moths
10	47	Epigastric pain, early satiety, vomiting, jaundice	Left lobe (IV)	Simple cyst	De-roofing followed by Left hepatectomy	18 months
11	49	Right upper quadrant pain	Right lobe (VI, VII)	Hepatobiliary cystadenoma	Enucleation	5 months

septations, thick wall and mural nodules in 3 patients. All six patients were submitted to a definitive surgery.

Five patients were incorrectly presumed to have non-HBCA liver cysts (simple cysts n = 3 and hydatid cysts n = 2) in the preoperative US and CT scan studies. Three of them were misdiagnosed as simple cysts because there was no evidence of internal septations, thick wall or mural nodularity in the imaging studies (Figure 3). However, they were submitted to frozen sections because of intraoperative suspicion due to the absence of endocysts, presence of mural cysts, clear fluid and septations. Frozen sections

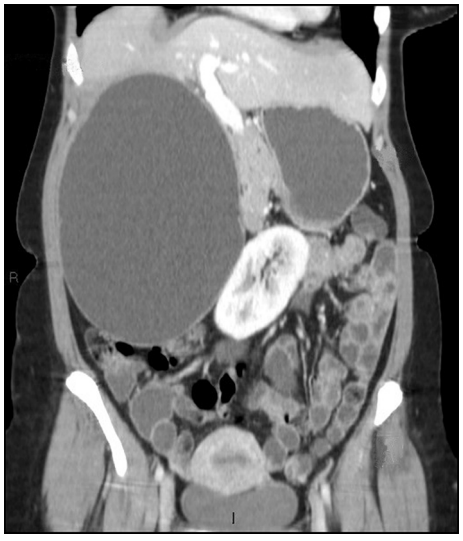

Figure 3: Computed tomography of hepatobiliary cystadenoma that was incorrectly diagnosed as simple cysts, with no evidence of internal septations or papillary projections.

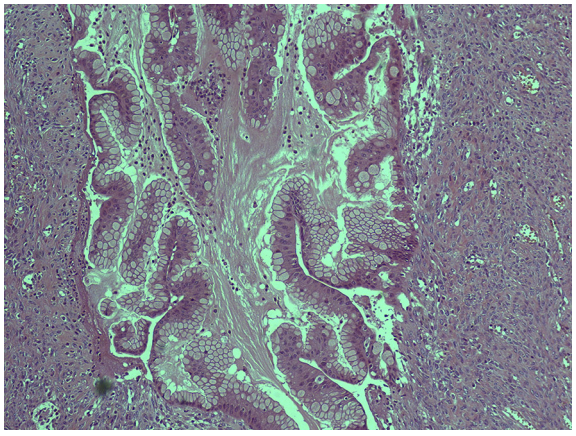

Figure 4: Selected histopathology of a frozen section with hepatobiliary cystadenomas, showing the ovarian-like stroma layer.

established the diagnosis of HBCA in two patients (Figure 4) but were falsely negative in one patient. Two patients were misdiagnosed as hydatid cysts and were intraoperatively suspected to have HBCA due to the presence of multiple mural cysts with mucinous fluid contents. However, a frozen section could not be performed due to logistical reasons. All 5 patients underwent a de-roofing procedure during the initial surgery, followed by definitive surgery after the final histopathological confirmation of HBCA during the index admission.

Intraoperatively, all cysts had a smooth surface (Figure 5). However, some showed internal septations, multiple mural cysts and internal papillary projections, while some were internally featureless. There was no biliary

communication to any of these cysts. The final histopathological analysis revealed mucinous cystic neoplasms (MCN) with "ovarian-like stroma" in all patients with no evidence of dysplasia or invasive cancer in any of them. However, one patient had a huge HBCA in the right lobe of the liver that showed large wall nodularity and septations, and the CT scan was highly suggestive of a malignant lesion. Extensive histopathological analysis of the cyst in this patient did not show any evidence of dysplasia or malignancy. One patient developed bile leaks after a right hepatectomy that was controlled by a temporary endoscopic biliary stent. There was no mortality in the series. All patients after follow-up for a variable

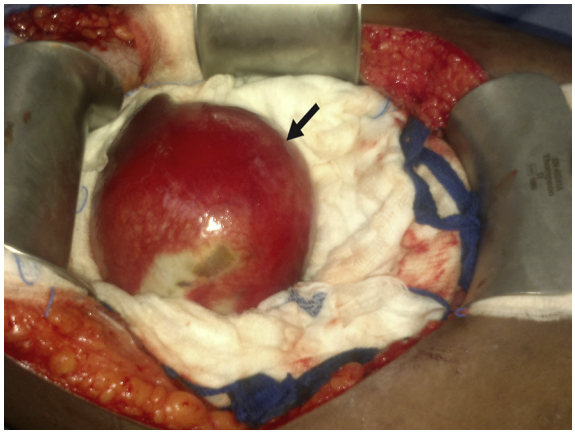

Figure 5: Selected intraoperative photograph showing large hepatobiliary cystadenomas with smooth surfaces.

period were doing well. None showed any evidence of recurrence until the commencement of this study.

Discussion

Hepatobiliary cystadenomas are uncommon, slow-growing, unilocular or multilocular cystic lesions of biliary tract origin. Although the cystadenomas can arise from any portion of the biliary tract, they predominantly originate from intrahepatic components.[9,10] Intrahepatic lesions involve the right lobe (55%) more frequently than the left lobe (29%), with bilobar lesions in 16%.[7] Although occasionally reported among children, HBCA occurs most frequently among middle-aged women, with a mean age of 50 years at presentation.[2,11–13] Hence, there is a possibility of hormonal pathogenesis of these cystic lesions.[2,5,13] In the current study, all of the patients were women with a mean age of 45.91 ± 3.7 years. The neoplasms originated from the right lobe in five patients (45%) and the left lobe in six patients (55%).

Intrahepatic HBCAs may arise from primitive hepatobiliary stem cells or from congenitally misshapen bile ducts.[14] These cystic neoplasms do not usually communicate with the bile ducts and are associated with ovarian-like subepithelial stroma.[3] The presence of biliary communication indicates intraductal papillary mucinous neoplasm (IPMN) rather than HBCAs.[15] Communication with the biliary tract was not observed in any patient in this study, and the final histopathology revealed "ovarian-like stroma" in all patients.

Hepatobiliary cystadenomas are generally symptomatic but have been accidentally discovered on rare occasions during radiological imaging for other reasons.[5,16] When symptomatic, the clinical presentation is nonspecific. Patients may present with symptoms of mass effects, including abdominal pain, fullness in the upper abdomen, abdominal distension, nausea, vomiting, indigestion, and a palpable abdominal mass.[4,5,7,12] The tumour may occasionally cause biliary compression, resulting in jaundice and possibly cholangitis.[16,17] Rarely, the tumours may rupture, bleed, become infected, or cause vena caval compression and obstruction.[18–20] In the present study, nine patients (82%) presented with symptoms, while only two patients were asymptomatic. Abdominal pain was the most common presenting symptom. One patient presented with features of a gastric outlet obstruction and a huge palpable abdominal mass due to HBCA in the right hepatic lobe. Another patient presented with epigastric pain and jaundice due to a large HBCA in segment IV.

The laboratory blood results are generally normal in most patients with HBCA. However, mild elevations in the liver enzymes and hyperbilirubinaemia may be seen in some patients with biliary compression. Serum levels of tumour markers, including AFP, CA19-9, CA125, and CEA, are usually within normal limits.[20] Some recent studies have examined the role of CA19-9 and CEA levels in the cystic fluid of the HBCA in preoperatively diagnosing HBCA with mixed results.[9,21] The FNAC of the HBCA also did not provide adequate diagnostic information.[12,22] Laboratory results, including CBC and CA19-9 (done in 6 patients), were normal in all study patients. Total bilirubin, direct bilirubin and alkaline phosphatase levels were elevated in one patient with a large HBCA in segment IV; however, this information did not help with the diagnosis. The FNAC and analysis of cystic fluids for CA19-9 were not performed in these patients because these investigations were not available during the study period.

The most commonly used imaging studies in these patients are ultrasound and CT scan to characterize the cystic lesion and detect any hepatic vascular or biliary duct involvement. Further assessment with MRI is used when the diagnosis is still uncertain.[4,5,7] Ultrasounds usually reveal anechoic cystic lesions with sharp demarcations and fine septations.[23] The presence of a large, solitary, multiloculated cystic lesion with internal septations and well circumscribed smooth margins is the typical feature of HBCAs in CT and MRI imaging.[7,24] The wall of the cystic lesion is often thick and irregular with internal papillary protrusions that are rarely enhanced and calcified.[4,7] In spite of these characteristic radiological features, several recent reports have shown a high rate of preoperative misdiagnosis of HBCAs in imaging methods.[14,25] HBCA is often misdiagnosed as a simple cyst, hydatid cyst or a liver abscess, if unilocular.[26] Five patients in this study did not have the characteristic radiological features and were misdiagnosed. Furthermore, distinguishing between benign and malignant lesions can be difficult using radiological imaging; however, the presence of solid components in the cystic lesion increases the possibility of malignancy (cystadenocarcinoma).[25,27]

An accurate preoperative diagnosis is critical for definitive treatment because incomplete excision of these cystic lesions is associated with a high recurrence rate and risk of malignant transformation into cystadenocarcinoma[2–5] and sarcoma.[28] Complete surgical excision remains the treatment of choice to prevent malignant degeneration and recurrence via formal liver resection[5,7,9,29,30] or more conservative resection with free resection margins.[7,9] Due to the benign nature of the lesions, the prognosis is excellent after a complete excision.[4,5,31] Misdiagnosis results in inadequate surgical treatment in the form of a simple de-roofing reoperation and radical resection with clear margin.[16]

Preoperatively, there should be high suspicion for HBCA, particularly in middle-aged women who have no risk factors for hydatid disease, liberal use of MRIs, intraoperative suspicion of the diagnosis in the presence of clear fluids, multiple mural cysts adherent to the wall of the main cysts, and absence of endocysts, which can help minimize misdiagnoses. The role of intraoperative frozen section analysis has been reported to be ineffective at ruling out HBCA.[2] However, in this series, the frozen section was performed in three patients presumed to have simple cysts; these sections confirmed the HBCA diagnosis in two patients and were falsely negative in one patient. Although helpful in some patients, frozen sections could not be performed in all patients with suspicious lesions due to logistical reasons.

Macroscopically, these lesions are characterized by a smooth external surface with internal multiloculated cavities that contain mucinous fluid.[10,32] Microscopically, they are lined with biliary-type columnar or cuboidal, non-ciliated cells and are generally surrounded by dense "ovarian-like" stroma.[10,31] The lesions are similar to the mucinous cystic neoplasms in the ovaries and pancreas.[26] Recently, the presence of ovarian-like stroma has been accepted as a prerequisite for diagnosing cystadenomas; hence, this feature differentiates it from IPMN.[25] Cystic lesions in this study were described as mucinous cystic neoplasms according to the most recent classifications of the World Health Organization.[3] A microscopic analysis of these lesions in all patients demonstrated a well-defined capsule, a single layer of simple cuboidal, columnar or flat epithelium, a basement membrane underneath a layer of mesenchymal tissue that resembles normal ovarian stroma, mucin-containing vacuoles and no evidence of invasion.

Conclusion

HBCAs are rare and frequently misdiagnosed hepatic cystic lesions with subsequent inadequate surgical treatments. Diagnosing HBCAs should be considered in all patients with atypical liver cystic lesions, particularly if patients are middle-aged women and have no risk factor for hydatid disease. Liberal use of MRIs and intraoperative frozen sections may improve the diagnostic yield, leading to a definitive radical resection and minimizing reoperation.

Author's contribution

HHA conceived and designed the study, conducted research, provided research materials, and organized data. He also analysed, interpreted data and prepared the final draft. He is responsible for the content and similarity index of the manuscript.

Conflict of interest

The author has no conflict of interest to declare.

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