World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i3.361

World J Gastroenterol 2011 January 21; 17(3): 361-365
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Intrahepatic biliary cystic neoplasms: Surgical results of 9 patients and literature review

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Received: August 12, 2010 Revised: September 18, 2010
Accepted: September 26, 2010
Published online: January 21, 2011

Abstract

AIM: To investigate the eligible management of the cystic neplasms of the liver.

METHODS: The charts of 9 patients who underwent surgery for intrahepatic biliary cystic liver neoplasms between 2003 and 2008 were reviewed retrospectively. Informed consent was obtained from the patients and approval was obtained from the designated review board of the institution.

RESULTS: All patients were female with a median (range) age of 49 (27-60 years). The most frequent symptom was abdominal pain in 6 of the patients. Four patients had undergone previous laparotomy (with other diagnoses) which resulted in incomplete surgery or recurrences. Liver resection (n = 6) or enucleation (n = 3) was performed. The final diagnosis was intrahepatic biliary cystadenoma in 8 patients and cystadenocarcinoma in 1 patient. All symptoms resolved after surgery. There has been no recurrence during a median (range) 31 (7-72) mo of follow up.

CONCLUSION: In spite of the improvement in imaging modalities and increasing recognition of biliary cystadenoma and cystadenocarcinoma, accurate preoperative diagnosis may be difficult. Complete surgical removal (liver resection or enucleation) of these lesions yields satisfying long-term results.

Key words: Biliary cystadenoma; Cystadenocarcinoma; Enucleation; Hepatic resection

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Emre A, Serin KR, Özden İ, Tekant Y, Bilge O, Alper A, Güllüoğlu M, Güven K. Intrahepatic biliary cystic neoplasms: Surgical results of 9 patients and literature review. *World J Gastroenterol* 2011; 17(3): 361-365 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i3/361.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i3.361

INTRODUCTION

The first account of an intrahepatic biliary cystadenoma (IHBCA) was published in 1887 and the first resection was performed in 1892[1]. The tumor was redefined by Edmondson in 1958 as a multilocular lesion with an ovarian-like stroma[2]. However, in subsequent years, unilocular cystadenomas as well as cystadenomas without an ovarian-like stroma have been reported. Only 38 cases could be included in an extensive review in 1977[3]. With

the widespread availability of modern imaging techniques and developments in safe liver surgery, the number of reported cases increased to approximately 150 by 1994 (approximately 100 patients in the 1994 review by Devaney *et al*[2], and other earlier papers[4-6] not included in the review).

Biliary cystadenocarcinoma was first described in 1943[7]; a review published in 1998 included 113 patients[8]. Devaney *et al*[2] proposed three subsets of cystadenocarcinoma based on the pathology material submitted to their institutional laboratories for primary diagnosis or consultation: (1) cystadenocarcinoma originating from a benign cystadenoma with ovarian-like stroma (occurs exclusively in women); (2) *de novo* cystadenocarcinoma occurring almost only in men; and (3) cystadenocarcinoma that occurs in women but does not contain an ovarian-like stroma.

The long list of possibilities in the differential diagnosis includes simple cysts, parasitic cysts, degenerated metastatic tumors, mucin-producing metastatic tumors, congenital cystic dilation, cystic hemangioma, lymphangioma, hepatic foregut cyst, mesenchymal hamartoma and teratoma[2,9-11]. Imaging techniques are the primary diagnostic tools. However, the relative scarcity of the cystadenomas and cystadenocarcinomas diagnosed by different techniques and reported over a longer period than a century renders making definite statements on pathognomonic findings difficult. Also, the high frequency of simple cysts in patients older than 40 years of age (14%-24% depending on age) greatly complicates the problem in patients with unilocular cystadenomas[12]. It is possible that some IHBCAs are misdiagnosed as simple liver cysts.

IHBCA is a premalignant lesion; intrahepatic biliary cystadenocarcinoma (IHBCAC) cannot be reliably differentiated from IHBCA by imaging or preoperative aspiration cytology. Therefore both types of lesion should be excised[4,10,11,13-17].

In this article, we communicate our institutional experience on IHBCA and IHBCAC and review the related surgical literature.

MATERIALS AND METHODS

The charts of patients examined for cystic liver lesions between 2003 and 2008 were studied retrospectively.

The diagnosis of IHBCA was made by radiologic criteria (ultrasonography with computed tomography or magnetic resonance imaging). Important radiologic features were[18-23]: (1) Presence of a multilocular or unilocular mass with a well-defined capsule; and (2) Presence of one or more of the following structures exhibiting contrast enhancement: papillary projections, internal septations with nodular areas, wall thickness irregularities and mural nodules.

Because the necessity and utility of performing cyst fluid aspiration for tumor marker [carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9)] measurements and cytologic examination have been controversial issues until recently, the decisions in individual patients were left to the discretion of the attending surgeon.

Surgical intervention was performed if radiologic findings suggested an IHBCA or IHBCAC. All specimens were sent for histopathological examination. Frozen section was performed after enucleation procedures without any diagnosis of malignancy.

All patients were followed by computed tomography for possible recurrences every 6 mo in the first two postoperative years and then annually.

RESULTS

In the study period, 210 patients with cystic liver lesions were examined at our unit; 168 patients had parasitic cysts; 33 of the 42 nonparasitic cystic lesions were simple hepatic cysts. The final diagnoses in the remaining patients were IHBCA (n = 8) and IHBCAC (n = 1). These nine patients were all female with a median (range) age of 49 (27-60) years.

The most common symptom was abdominal pain observed in 6 patients. Three patients were asymptomatic; cystic liver masses had been discovered incidentally during radiological examinations for other purposes.

Four patients had undergone previous laparotomy (with other diagnoses) which resulted in incomplete surgery or recurrences. Two of these patients were operated on with the preoperative diagnosis of cystic echinococcal disease (one at our hospital). At surgery, the cystic lesions were misdiagnosed as simple liver cysts and unroofing was performed. However, histopathologic examination showed IHBCA in one and IHBCAC in the other. The remnant tumors in both patients were resected with appropriate surgical margins. Another patient was operated on with the diagnosis of echinococcal cyst at another hospital in the third month of her pregnancy. Operative findings did not confirm the preoperative diagnosis; a partial resection was performed and the histopathological diagnosis was IHBCA. In the course of the pregnancy, the size of the remnant cystic lesion increased from 12 to 27 cm in diameter. After a successful delivery, she was referred to our institution for hepatic surgery. A 58 year-old woman was operated on for cholecystolithiasis at another hospital; however, there was a suspicion of a malignant cystic lesion in segment V of the liver, the operation was stopped and she was referred to our hospital.

None of the patients had clinical or biochemical findings of cholestasis. Serum CEA levels were within normal range in all patients; serum CA 19-9 levels were within the normal range in 7 patients (including the single patient with IHBCAC) and were increased in 2 other patients (99 and 77 U/mL respectively; range 0-34 U/mL).

Preoperative percutaneous cyst fluid aspiration was performed in 4 patients. CA 19-9 levels were markedly increased in all samples (above 10000 U/mL; normal range for serum: 0-34 U/mL) and CEA levels were increased in 2 (15 and 18 ng/mL, respectively; normal range for serum: 0-4 ng/mL). Cyst fluid samples for postoperative examination were obtained intraoperatively in 4 other patients; both CA 19-9 (10000 U/mL and 379 U/mL) and CEA (27 U/mL and 651 U/mL respectively) were increased in 2 patients and within normal range in the other 2.

CEA and CA 19-9 measurement was not performed in the patient with cystadenocarcinoma.

Cytologic examination results were nondiagnostic, including the single patient with cystadenocarcinoma.

Preoperative evaluation of the period is the same as hepatobiliary operation's. The operative technique was determined according to the location of tumor in the liver and proximity to major vascular structures. Six patients were treated by hepatic resection: 4 by major hepatectomies (1 by right hepatic lobectomy, 1 by left hepatectomy, 1 by left lateral sectionectomy, and 1 by central bisegmentectomy) and 2 by nonanatomic resections. In 3 patients, the tumor was removed by enucleation. Enucleation was performed as in hemangiomas as described by Alper *et al*[24]. Frozen section was performed routinely after enucleation procedure and no invasive malignancy was diagnosed in these 3 patients. Therefore, no additional hepatic resection was performed.

Perioperative findings, length of the operation time and blood loss were uneventful in 9 patients.

There was no major complication and mortality.

Histopathologic examination revealed IHBCA in 8 patients and IHBCAC in 1. An ovarian-like mesenchymal stroma was observed in 8 patients including the patient with IHBCAC.

All patients were followed up for median (range) 31 (7-72) mo without recurrence.

DISCUSSION

Although the incidence of IHBCA and IHBCAC has been reported to be less than 5% of all hepatic cystic lesions[25], this figure, which is quoted in other papers[11,26] should be interpreted with caution since the frequency of simple cysts in patients older than 40 years of age varies between 14% and 24%[12]. The true incidences of both lesions are probably much lower since the largest surgical series reported includes 34 IHBCAs[13] and 6 IHBCACs[6]. The controversy in the literature stems from the lack of established criteria for preoperative diagnosis especially in the case of unilocular IHBCAs[4,10,27].

In spite of the improvements in imaging techniques, the differential diagnosis of simple hepatic cysts and IHBCAs is still problematic. In a Cleveland Clinic series, 10 of 18 patients underwent incorrect and unnecessary procedures such as percutaneous aspiration, ethanol injection, unroofing and omentoplasty[16]. In 1 of the patients in the present series, a patient with right upper abdominal quadrant pain was diagnosed as having cholecystolithiasis and a simple hepatic cyst in segment V of the liver. However, during surgery, the surgeon suspected the possibility of a cystic tumor and terminated the operation. Although radiologic features such as papillary projections, internal septations with nodular areas, wall thickness irregularities and mural nodules suggest the possibility of a IHBCA[28,29], all of these except papillary projections may be observed in simple cysts as well albeit at a lower frequency[29].

Liver echinococcal cysts pose another diagnostic problem in endemic countries[30]. In our series, 3 cases underwent inappropriate initial procedures with the misdiagnosis of hydatid disease. Although that absence of a germinative membrane and daughter cysts may have alerted the surgeons intraoperatively, their lack of experience precluded further interventions in the first operation. In 1 of these patients, the incidental observation of the natural history of an IHBCA under the hormonal milieu of pregnancy is interesting. The patient underwent unroofing of a 12 cm cyst at the 3rd month of pregnancy; the lesion size increased to 27 cm in a matter of 6 mo. This is in accordance with the female hormone-dependency of these lesions, previous observations in pregnant patients[11,25,31-34] and possible association with oral contraceptive use[34].

Although serum levels of CA19-9 and CEA may be increased in some patients[26,27,35-37], this is not a universal finding[10]. In the present series serum CA 19-9 levels were high in 2 patients (the single patient with IHBCAC not among them); all serum CEA levels were within the normal range.

Levels of cystic fluid CA 19-9 have been proposed "as a diagnostic help in liver cysts of unknown nature"[38] and some centers incorporated cyst fluid tumor marker (CA19-9 and CEA) measurements into their management algorithm[13]. However, definite diagnostic criteria for CA19-9 and CEA levels have not been established because the published data were largely limited to the reports on increased levels in small numbers of IHBCA patients without statistically robust comparison with levels in simple cysts. Consequently, the same problem occurred in the differentiation of IHBCAs and IHBCACs[26,35,36,38-40].

In the widely cited important contribution by Koffron *et al*[13], the cyst fluid CEA and CA 19-9 levels of 22 IHBCA patients were compared with the levels in 4 patients with simple cysts and 4 patients with polycystic liver disease. All 8 control cases had normal levels; in contrast CA19-9 was markedly increased in all IHBCA patients; there were mild to marked increases in CEA levels as well[13]. This paper was given serious consideration by some of our attending physicians who experienced dilemmas in some patients. For example, a 75-year-old woman underwent complete aspiration of two hepatic cysts in the right lobe; the CA 19-9 levels were above 10 000 U/mL whereas CEA levels were within the normal range. The presumptive diagnosis at that time was an IHBCA; surgery was not offered due to the comorbid illnesses. That she has not had a recurrence for 2.5 years suggests that the lesions might be simple cysts rather than cystadenomas and an operation would have been unnecessary.

Two important papers published in 2009 shed more light to this issue. Waanders *et al*[41] conducted cyst fluid CA 19-9 measurements in 109 polycystic liver disease patients and 24 simple cyst patients and detected "extremely high" levels in both groups. Although the absence of pathologic confirmation is a potential weakness in interpretation (i.e. some of the patients may have had unilocular cystadenomas), the universally increased levels in all 24 patients are strong evidence for increased levels in simple cysts. Although the number of patients in the other paper[29] is smaller (14 patients with hepatic simple cysts), a major

strength is that all patients had pathologically confirmed diagnoses. Both normal and dramatically increased CA 19-9 and CEA levels were detected in simple cyst patients; there were no significant differences between the simple cyst patients (n = 14) and IHBCA patients (n = 17). These recent data suggest that cyst fluid tumor marker levels do not provide additional information in patients with suspected IHBCA.

Cyst fluid cytology has not been found to be useful in the differentiation of IHBCA and IHBCAC[33,42] because demonstration of malignant cells is rare, i.e. a negative cytology result will give a false sense of security. Needle biopsy of papillary projections or mural nodules may be more useful for this purpose[13]; however this is generally unnecessary since there is a surgical indication for IHBCA and definite preoperative diagnosis of IHBCAC is not strictly required[8]. Since there is a risk of tumor cell implantation due to the aspiration procedure[42], routine aspiration of hepatic cystic lesions should be avoided.

There is a general consensus that an IHBCA should be removed completely either by enucleation or liver resection because lesser procedures are associated with recurrence rates as high as 90%[4,40,43,44]. Satisfactory results with enucleation using the dissection plane between tumor and liver tissue have been reported[4,13,45]. Enucleation, which allows maximum preservation of hepatic parenchyma, is an appropriate procedure for benign lesions. One concern is that the IHBCA may harbor a malignancy which may be missed by preoperative imaging. In such instances, enucleation would be inappropriate even in patients with noninvasive carcinoma[2]; therefore hepatectomy with negative surgical margins is preferred. Although frozen section examination may sometimes yield a false-negative result for cancer[42], it is still wise to perform it on samples from solid parts of enucleated tumors[13] because resection of the adjacent parenchyma may be conducted in patients with carcinoma. Some groups advocate routine resection for these lesions[27]. Left hepatectomy was performed in this series for the only patient with IHBCAC in whom the tumor was located at median and lateral sections. Two patients with lesions in lateral and 1 patient in posterior sections were treated by enucleation. Frozen section was performed after enucleations and no invasive malignancy was detected. Major hepatectomies had to be performed in 3 IHBCA patients with lesions very close to vascular structures. Nonanatomic resections were carried out in 2 cases.

In conclusion, with the improvement and widespread availability of radiologic modalities, cystic biliary liver neoplasms are being detected more frequently. However, the differential diagnosis from simple cysts and in endemic countries, from ecchinococcal cysts, is still challenging. Although there are no pathognomonic findings except for papillary projections (not present in many cases), radiological imaging finding such solid parts, papillary projections and septation or mural nodules in cystic lesion are the basis of preoperative diagnosis. Cyst fluid examination with cytology and CEA and CA 19-9 level measurement do not provide additional information. Partial resections are inappropriate. The treatment of choice is total excision either enucleation of IHBCAs and formal resection for IHBCACs and suspicious lesions.

COMMENTS

Background

Biliary cystadenomas and cystadenocarcinomas are both rare neoplasms of the biliary system. They may be easily misdiagnosed and operated on as simple cysts or hydatid cysts. Inappropriate drainage and unroofing operations result in recurrences. Reliable preoperative differentiation of the premalignant form-cystadenoma- and the malignant form cystadenocarcinoma is difficult except in obviously invasive lesions.

Research frontiers

Contrary to the previous popular opinion, recent data suggest that cyst fluid tumor marker levels do not provide additional information in patients with suspected intrahepatic biliary cystadenoma. Also, cyst fluid cytology has not been found to be useful in the differentiation of intrahepatic biliary cystadenoma and intrahepatic biliary cystadenocarcinoma, because demonstration of malignant cells is rare, i.e. a negative cytology result will give a false sense of security. Reliable techniques should be developed for reliable preoperative differential diagnosis of simple hepatic cysts, biliary cystadenomas and cystadenocarcinomas.

Innovations and breakthroughs

Surgical removal of the whole cyst with negative resection margins is recommended by many authors in order to avoid recurrences. In some cases, this is impossible because of the proximity to the vascular structures and importantly, aggressive surgery is unnecessary for a benign lesion. In three patients, the authors performed enucleation due to proximity to the vascular structures; frozen section revealed no malignancy. These patients have experienced no recurrence.

Applications

The treatment of choice is total excision; either enucleation of intrahepatic biliary cystadenomas and formal resection for intrahepatic biliary cystadenocarcinomas and suspicious lesions. Frozen section should be routine after enucleation.

Peer review

It's an interesting review of a very rare neoplasm of the biliary system.

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