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Intrahepatic biliary cystadenoma—diagnosis and treatment options

BILIARY

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Original Article

ABSTRACT

Background/Aims: Liver cystadenomas are rare conditions accounting to approximately 5% of all cystic lesions. The aim of our study was to establish a new diagnostic and complex therapeutic approach.

Materials and Methods: In all, 12 female patients primarily diagnosed with cystadenoma of the liver were evaluated. Enucleation of the cystadenoma was performed in six (54.5%) and liver resection in four (33.3%) patients. Due to the localization, complete enucleation or radical liver resection could not be performed in two patients.

Results: In three patients, grade III-a complications were recorded after surgery. The 30-day mortality was 0%. The length of hospitalization was 27 (7–52) days. Malignant transformation occurred in two patients with incomplete removal of the cystadenoma. In both cases, carbohydrate antigen 19-9 serum levels were elevated during the follow-up period. The first patient died 28 months after primary surgery. The second patient failed to attend any further appointments. The remaining patients are in the good conditions, with no signs of recurrence.

Conclusion: The only possible treatment of cystadenomas is their radical surgical removal. Any other incomplete surgical treatment is insufficient and associated with a high risk of malignant transformation. For patients in whom R0 resection or complete enucleation cannot be performed for technical reasons, liver transplantation should be considered.

Keywords: Liver cystadenoma, diagnosis, treatment

INTRODUCTION

Cystadenomas of the liver are rather rare cystic lesions of the liver. They are often asymptomatic and are found accidentally when the abdominal cavity is examined for a different indication. Their preoperative diagnosis is difficult and opinions regarding surgical treatment of cystadenomas differ considerably. The aim of our study is to establish an optimal diagnostic and therapeutic approach toward liver cystadenomas (1,2).

MATERIALS AND METHODS

This retrospective study was approved by the Local Ethics Committee of the University Hospital and School of Medicine in Pilsen, Czech Republic. Between January 2000 and August 2015, we operated a total of 12 patients with cystic tumors of the liver. Due to the small sample size, we used a descriptive statistic method. All patients were women with an average age of 57.7 (36–75) years. Of the 1452 patients operated for benign lesions or malignant tumors of the liver during the same period, cystadenomas were identified in 12. Six patients were symptomatic (with symptoms such as obstructive jaundice, abdominal mass, and abdominal discomfort). In six patients, the cystadenoma was discovered accidentally during abdominal examination for different reasons. Preoperative diagnosis routinely involved ultrasonography (USG) and computed tomography (CT; Figure 1). In unclear cases, these methods were complemented by magnetic resonance imaging (MRI; Figure 2). Carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) serum levels were preoperatively determined in six (50%) patients. Enucleation of benign

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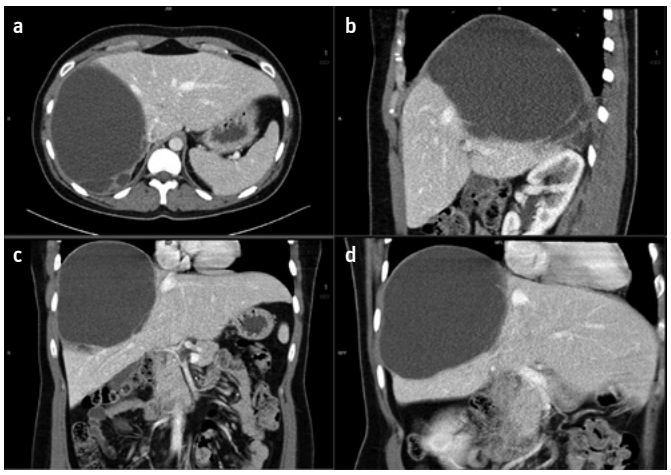

Figure 1. a-d. Large biliary cystadenoma of the right liver lobe-multiple detector computed tomography (MDCT); (a) axial, (b), sagittal, (c) coronal, (d) oblique reconstructions

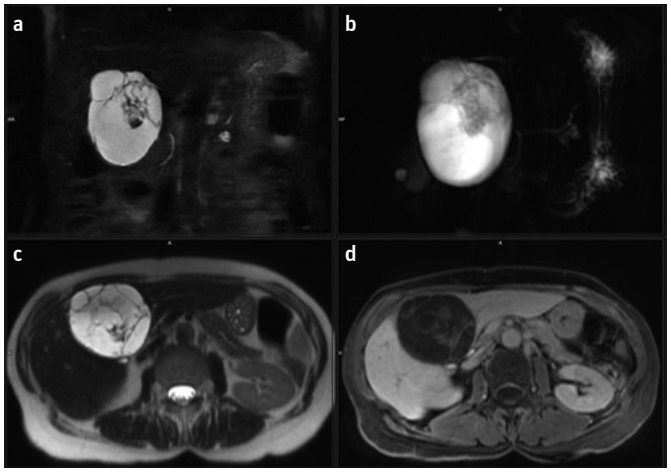

Figure 2. a-d. MRI of a biliary cystadenoma with T2-weighted sequences using high definition imaging (a) coronal plane, (c), (b) MRCP and (d) T1-weighted sequence after application of gadolinium contrast medium

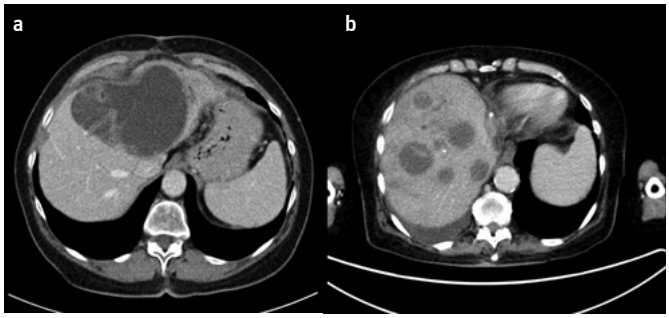

Figure 3. a, b. Biliary cystadenoma (after partial resection in 2010) (a), metastatic cystic foci and infiltration of peritoneal fat during its transformation into cystadenocarcinoma (b)

cystadenomas was performed in six (50%) and liver resection in four (33.3%) patients. In two patients, given the central position of the lesion with involvement of the main vascular and biliary structures, we performed partial resection of the cyst with excochleation and electrocoagulation of the remaining cyst wall attached to the abovementioned structures. In one patient, the biliary tract was reconstructed using a T-drain.

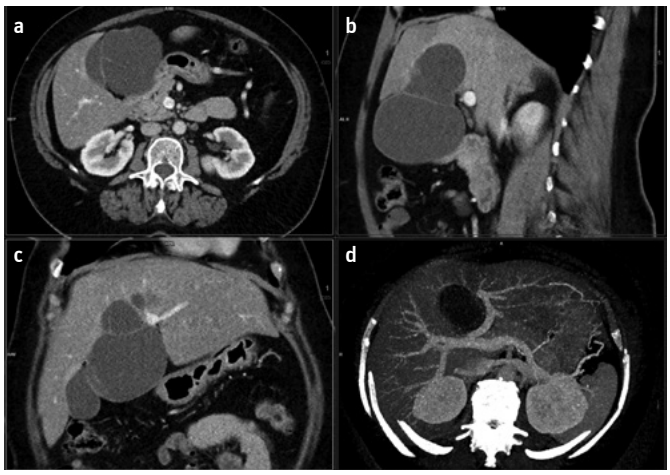

Figure 4. a-d. Cystadenocarcinoma propagating into the subhepatic space—image of topical relationships with the gallbladder, which is pushed laterally and dislocation of the left portal vein branch; (a) axial, (b), sagittal, (c) coronal multiplanar reconstructions (d) portal CT angiography using maximum intensity projection

RESULTS

Preoperatively, serum levels of CA 19-9 and CEA were within normal range. Complications after surgery included two biliary fistulas treated by endoscopic papilosphincterotomy and one subphrenic abscess treated by CT-guided drainage (grade III-a according to the Clavien–Dindo classification). There were seven cases of low-grade, four of intermediate, and one of high-grade intraepithelial dysplasia according to histological classification. The average length of hospitalization was 27 (7–52) days. No patient died within 30 days of surgery. Recurrence of the cystadenoma with transformation into cystadenocarcinoma occurred in two patients with incomplete removal of the original cystadenoma (one with intermediate and one with high-grade intraepithelial neoplasia), whose serum CA 19-9 levels rose and who showed progression on positron emission tomography-CT (PET-CT). In the first patient, complete removal of the tumor was attempted during the second operation. However, given its intimate adherence to the vascular and biliary structures, left-sided R1 hepatectomy had to be performed in the end followed by oncological treatment. Liver transplantation was considered, but was not performed due to rapid disease progression (Figure 3a, b). The patient died 28 months after her first liver surgery. The second patient, whose biliary tract was reconstructed using a T-drain after R1 liver resection, suffered a recurrence of the lesion with malignant transformation 6 months after her initial surgery, with no obstruction of the biliary tract (Figure 4). We considered liver transplantation or oncological treatment. However, the patient repeatedly failed to attend any of her scheduled appointments. The remaining patients are all healthy, with no signs of recurrence.

DISCUSSION

Cystadenomas of the liver are rather rare benign conditions of the liver, with an incidence rate of around 5% of all cystic lesions of the liver. Intrahepatic biliary cystadenoma was first

described in 1887 and the first liver resection was performed in 1892. In 1958, Emre et al. (3) defined cystic adenoma of the liver as a multilocular lesion with an ovarian-like stroma epithelial lining. However, several cystadenomas were later described as lacking an ovarian-like stroma epithelial lining. Devaney et al. (4) suggested that cystadenocarcinomas could be classified into three groups: cystadenocarcinoma originating from benign cystadenoma with an ovarian-like stroma; de novo cystadenocarcinoma occurring only in men; and cystadenocarcinoma occurring only in women, without an ovarian-like stroma. In 2010 (5), the World Health Organization (WHO) defined cystadenomas of the liver as mucinous cystic neoplasms with classification based on the highest degree of cytoarchitectural dysplasia (low-grade, intermediate, and high-grade intraepithelial neoplasia; Figure 5-8).

The causes of cystadenoma development remain unclear. Cystic adenomas occur in both sexes, but predominantly affect females (up to 85% of all lesions). As most cystadenomas develop in women, as confirmed by our group of patients, their development is undoubtedly triggered by female sex hormones. The peak incidence of cystadenomas in women is between the ages of 40 and 50 years, while in men these lesions occur at a later age, which may also be to a certain extent influenced by hormones, as the levels of male sex hormones decrease with age (6,7).

The symptoms of cystadenomas are very ambiguous. Most lesions are discovered accidentally during abdominal radiodiagnostic examinations for a different indication, which is why they are termed as incidental cystic lesions. Symptoms include indeterminate abdominal pain, right upper quadrant mass or discomfort. Obstructive jaundice develops if these lesions compress the biliary tract. Compression of the diaphragm and right hemithorax may cause various breathing difficulties in the patients.

Diagnosis and differential diagnosis of cystadenomas and cystadenocarcinomas are rather challenging (8). On USG images, they often appear as cystic formations, which are further examined with the aid of CT and MRI, often using hepatotropic X-ray contrast media. A characteristic feature of biliary cystadenomas is their cystic appearance, which is the formation of cyst clusters divided by relatively thin septa. Fine calcifications may be present in the wall. The presence of solid masses and thickening of the wall or septa is considered a sign of possible malignant transformation into cystadenocarcinoma. The fundamental imaging method for focal liver processes is USG given its high sensitivity for detecting cystic lesions associated with biliary cystadenomas. However, considering the extent of its field of view, it can be difficult to display intracystic septa, and cystadenoma can thus be mistaken for a large simple cyst. The crucial issue in CT is the intravenous application of iodinated contrast medium in the portal phase of enhancement, where intracystic septa and potential intracystic solid masses

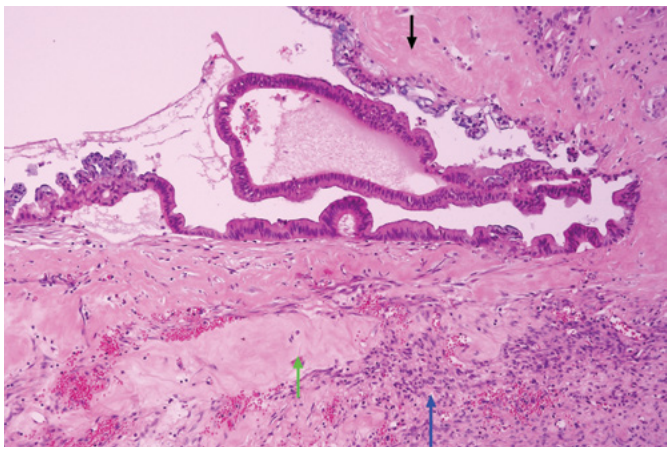

Figure 5. Mucinous cystic neoplasm with high-grade intraepithelial neoplasia. Cavity lined with cuboidal to columnar dysplastic epithelium, beneath which ovarian-like stroma can be found (blue arrow), with focal presence of corpus albicans-like bodies (green arrow). In substantial proportion of the cyst circumference, the ovarian-like stroma was replaced by hyaline due to regressive changes (black arrow) (H&E, 100x)

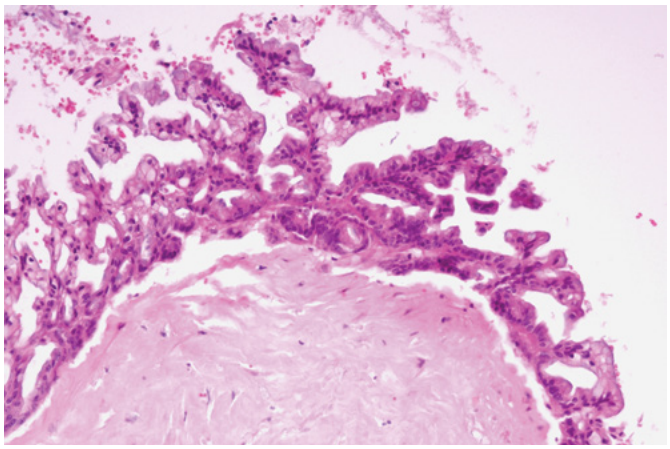

Figure 6. Mucinous cystic neoplasm with high-grade intraepithelial neoplasia. Architectural and cytologic atypia of the lining corresponding to high-grade intraepithelial neoplasia can be found. In this region, the ovarian-like stroma was replaced by hyalinized collagen (H&E, 200x)

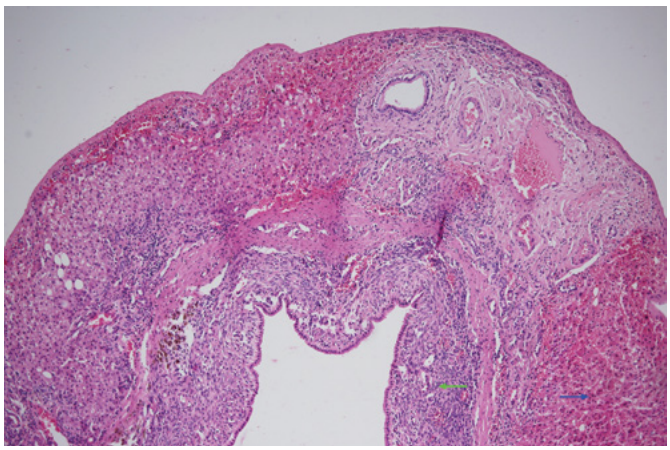

Figure 7. Mucinous cystic neoplasm with low-grade intraepithelial neoplasia. Low magnification shows columnar cyst lining and its wall composed of the inner layer of ovarian-like stroma (green arrow) and outer layer of hepatic parenchyma (blue arrow) (H&E, 100x)

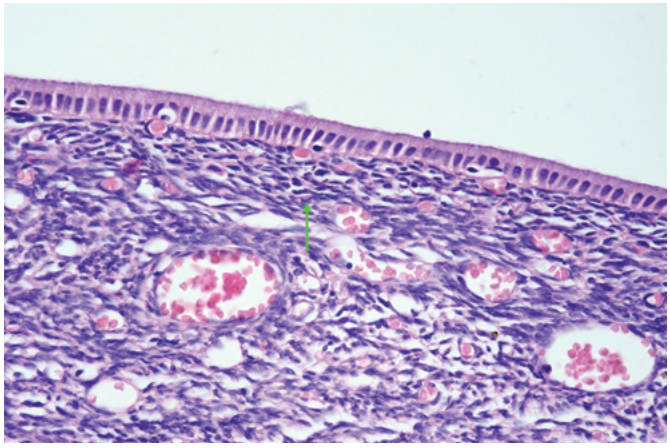

Figure 8. Mucinous cystic neoplasm with low-grade intraepithelial neoplasia. Columnar epithelium shows regular mildly elongated nuclei arranged at the cell base. Beneath the epithelium the characteristic ovarian-like stroma is prominent (H&E, 200x)

are best discernible. Another advantage of CT is the imaging of calcifications. Compared to CT, the advantage of MRI is mainly the perfect imaging of septa-even when these are very fine. Highly T2-weighted images are used in such cases and are remarkable for the high signal from fluids. Imaging is performed in thin sections; yet, the same sequences with background tissue suppression can be used to display the biliary system in magnetic resonance cholangiopancreatography (MRCP). Gadolinium containing contrast media administration is important in the differential diagnosis of cystic lesions. The cyst contents can also be assessed in terms of detecting a thickened "colloid" mucinous content with a higher T1 signal, or in terms of establishing intracystic bleeding into the cystadenoma by detecting hemoglobin degradation products-mainly methemoglobin in T1-weighted gradient echo sequences. Diffusion weighted imaging helps detect restriction of diffusion in the solid sections of such formations in cases when transformation of cystadenoma into cystadenocarcinoma has occurred. Hybrid imaging such as positron emission tomography combined with computed tomography or magnetic resonance imaging (PET-CT or PET-MRI) hybrid imaging combines the advantages of morphological imaging with the assessment of metabolic activity, which is useful in evaluating the possible transformation of cystadenoma into cystadenocarcinoma, since malignant tissues demonstrate typically high uptake of fluorodeoxyglucose. Imaging differential diagnosis can be more difficult mainly in terms of distinguishing cystadenoma and cystadenocarcinoma from echinococcal cysts, metastatic mucinous tumors, cystic metastases, liver abscesses, cystic hemangiomas, lymphangiomas, mesenchymal hamartomas and teratomas and of course congenital cystic lesions. The differentiation of benign cystadenomas from cystadenocarcinomas is crucial for further surgical treatment because the prognosis of cystadenocarcinoma is poor.

To differentiate between cystadenomas and cystadenocarcinomas, some authors recommend determination of CEA and CA 19-9 marker levels, which should be elevated in both the serum and the cystadenocarcinoma fluid (9,10). However, several authors have not described such an increase in marker levels. In general, it is very difficult to use these tumor markers for primarily determining the exact diagnosis of cystadenocarcinoma of the liver (11). However, the increase of serum CA 19-9 levels in our two patients with incomplete resection of the cystadenoma during follow-up was a sign of the malignant transformation of these lesions.

CT- or USG-guided biopsy of the cyst wall lacks any significant histopathological significance and should not be performed mainly given the risk tumor cell dissemination in the case of cystadenocarcinoma affecting both the liver tissue itself and the peritoneum.

Surgical treatment represents the only radical treatment of cystadenomas (12,13). The histological type of lesion involved represents the crucial factor for determining the correct surgical method to be applied. If malignancy is suspected, radical removal of the cyst should be performed, if possible, i.e., radical liver resection (14,15). Enucleation is possible and sufficient in cystadenomas with low-grade intraepithelial neoplasia. However, it is not sufficient in cystadenomas with intermediate or high grade of intraepithelial neoplasia. In some cases of cystadenoma, it is unfortunately technically impossible to perform radical resection of the liver, which was the case in our two patients where the lesions were located centrally with involvement of the main vascular and biliary structures of both liver lobes. In these cases, it is possible to perform partial resection of the cyst. However, there is a great risk of cystadenoma recurrence and subsequent malignant transformation, which was unfortunately the case in our two patients. Treatment of the remaining cyst wall, which is left adhering to the vascular and biliary structures, is basically impossible and insufficient be it by excochleation, argon coagulation, laser, or other thermal ablation methods. Liver transplantation as a treatment modality can be considered in cystadenomas that cannot be completely removed technically, or large cystadenomas taking up a high volume of the liver (16,17). In these cases, a strictly individual approach is necessary, selecting the right treatment modality in line with the patient's preferences (18,19).

Long-term survival of patients with cystadenomas of the liver following their radical surgical removal is the rule. Surgical methods, which leave a part of the benign cystadenoma in the liver due to the above-mentioned technical problems or methods that only enucleate the cystadenocarcinoma with intermediate or high-grade intraepithelial dysplasia have a 90% risk of recurrence or transformation of the originally benign cystadenoma into cystadenocarcinoma.

The study has several limitations, including its retrospective design and the small sample size. However, the findings of this study are significant in comparison with the other published studies.

In conclusion, cystadenomas of the liver are rather rare benign lesions, the etiopathogenesis of which is not quite clear. They represent benign lesions with a high potential of transformation into cystadenocarcinomas. Therefore, they should be radically removed by liver resection or cyst enucleation. Any other minor surgical treatments, such as partial resection, are not indicated. Moreover, irremovable cystadenomas are an exception, requiring subsequent close follow-up or liver transplantation. Due to the frequently complicated differential diagnosis and treatment of these rather rare liver lesions, it is necessary for the patients to be examined and treated in hepatobiliary centers specialized in complex liver and biliary tract surgery.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University Hospital in Pilsen.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - V.T.; Design - V.T., J.F.; Supervision - V.T.; Materials - V.L., J.B.; Data Collection and/or Processing - T.S.; Analysis and/or Interpretation - V.T., O.D.; Literature Review - V.T.; Writer - V.T.

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