Cystadenomas of the liver: a spectrum of disease

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Objectives: To describe the wide variation in presentation of cystadenomas of the liver and to delineate useful tests for diagnosis and effective surgical treatment. Design: A case series. Setting: A university-affiliated hospital. Patients: Four patients (3 women, 1 man) having cystadenoma of the liver, 2 of whom had associated mesenchymal stroma. Main outcome measures: Serum and cyst fluid carcinoembryonic antigen (CEA) and CA19-9 levels, type of surgery, morbidity and recurrence rates. Results: Cyst fluid CEA and CA19-9 levels were elevated. One patient had resection, 2 had complete enucleation and 1 had partial enucleation. There were no deaths. Morbidity included 1 wound infection; there were no biliary fistulas. The patient with partial enucleation had a radiologically confirmed recurrence. Conclusions: Analysis of cyst fluid CEA and CA19-9 is useful for diagnosis; besides hepatic resection, complete enucleation should be considered as a reasonable treatment for patients with this disease.

Cystadenomas of the liver are rare tumours that are infrequently reported. They account for only 5% of reported cystic lesions of the liver.

Most occur in women older than 40 years of age and present either incidentally or from pressure symptoms caused by their large size. Similar lesions occur in the pancreas and ovary. There are 2 distinct classes of liver cystadenomas based on the presence or absence of "mesenchymal stroma."1 All cases with mesenchymal stroma occur in women; there is also a correlation between mesenchymal stroma and the risk of cystadenocarcinoma.2

Recommendations for treatment vary from resection to enucleation.

We present 4 cases of liver cystadenoma that illustrate the spectrum of presentation, anatomic location, pathological features and treatment of these tumours and outline our approach to diagnosis and treatment.

Case reports

Case 1

A 61-year-old man was seen in consultation because of an incidental finding on ultrasonography of a hypodense mass in the right lobe of the liver. The indication for ultrasonography was recurrent renal calculus in the left collecting system. He also had a history of mild asthma but was otherwise medically well. The patient had no symptoms related to the liver mass, no history of jaundice, blood transfusions, hepatitis or any excess alcohol consumption. On physical examination he ap-
peared healthy with no evidence of liver disease or organomegaly. Computed tomography (Fig. 1) showed a hepatic cyst, 3 cm in dimension, with internal septations located in segment VII. The most likely diagnosis was a cystadenoma. Serologic testing for echinococcal disease gave negative results.

The patient underwent a segmental resection of segment VII, which included the lesion and margins of normal tissue of 2 to 3 cm.

Postoperatively the patient had a wound infection that was treated with drainage; otherwise he recovered well. On pathological examination the resected specimen showed a multiloculated cyst with predominantly cuboidal mucinous epithelium without mesenchymal stroma. There was no evidence of malignant disease.

Case 2

A 39-year-old apparently healthy woman presented at another institution with dull, poorly localized upper abdominal pain and pressure sensation. The patient felt there was an expanding mass in the right upper quadrant. There were no other symptoms related to her liver and no evidence of jaundice. Serologic testing for echinococcal disease gave negative results. CT showed a huge multi-septate cyst located centrally within the liver with lateral splaying of the right and left portal veins.

She underwent an operative cystostomy and placement of a drain within the cyst cavity. A biopsy of the cyst wall was reported as “benign nonepithelial cyst with chronic inflammation.”

Subsequently, the cyst drained bile, so endoscopic retrograde cholangiopancreatography (ERCP) with papillotomy and stent placement was performed. This showed communication with the left hepatic duct. The cyst became infected. She was treated with antibiotics intravenously and after a protracted course recovered from the surgery. She was then referred for persistence of her original symptoms. Repeat CT demonstrated that the cyst was unchanged (Fig. 2). Eight months after the initial surgical procedure a repeat laparotomy was performed; the cyst was seen to separate the right and left lateral segments and to extend back to and compress the vena cava. The cyst contained multiple cavities with septations of varying thickness. Fluid in these cavities varied from clear to turbid. The deepest cavity contained bile-stained fluid, and a 0.3-cm opening in the left hepatic duct was found at its base. The cyst was enucleated down toward the opening, where the cyst was found adherent to the glissonian sheaths. The connection to the left hepatic duct was oversewn, and a segment of adherent cyst wall was left; the gallbladder was removed and a T-tube was placed in the common bile duct to decompress the biliary tree. The patient had no postoperative complications, and her symptoms resolved. Two years later a recurrence of the cyst was found on follow-up CT. She returned to work and remained asymptomatic. Her serum CA19-9 level at last follow-up was 11 U/mL (normal <35 U/mL).

Pathological examination showed a cystadenoma with mesenchymal stroma (Fig. 3). There was no evidence of dysplasia or malignant disease.

Case 3

A 61-year-old Chinese woman, who had immigrated to Canada from Hong Kong 12 years previously, presented to her family doctor complaining of swelling in her abdomen over the previous 3 years and mild early satiety over the last 2 years. Her weight had been stable and she had changed her eating habits to smaller more frequent meals. She had no history of liver problems and was otherwise healthy. Physical examination revealed significant enlargement of her abdomen centred in the epigastrium. Palpation revealed a lobulated massively enlarged liver that extended 25 cm below the xiphisternum.

CT showed a multiloculated cystic
mass extending inferiorly from the left lobe of the liver compressing the stomach. Echinococcal serologic testing gave negative results, and CA19-9 and CEA levels were not detectable in her serum. Aspiration of cyst fluid for CEA and CA19-9 determinations was planned, but at ultrasonography the radiologist indicated his findings were compatible with hydatid disease so the aspiration was cancelled.

She was treated with albendazole for 2 weeks preoperatively. At operation the large cystic mass arose inferiorly from segment III on the left side of the porta hepatis. The area around the cyst was packed with hypertonic saline-soaked sponges, and the cyst was aspirated and examined for scolices, but none were found. Frozen-section examination of the cyst wall was compatible with cystadenoma; there was no evidence of dysplasia or malignant disease. The cyst was removed by enucleation. A plane between the portal vein on the right and the liver substance was easily developed. Two possible connections with the secondary biliary radicals were oversewn. Postoperatively, she had no complications, and her symptoms resolved. Histologic examination revealed a benign hepatic cystadenoma with mesenchymal stroma, and cystic fluid analysis revealed a CA19-9 level of 32 450 U/mL and a CEA of 870.5 ng/mL (normal 0–5 ng/mL). Her postoperative serum CA19-9 and CEA levels remained undetectable.

Case 4

A 19-year-old woman presented to the Emergency Department complaining of sharp right upper quadrant abdomen pain that radiated straight through to the back. Also, she had noted that her upper abdomen was distended and that she had a new sense of fullness in the area. These symptoms had been worsening over the preceding 6 weeks; she had been placed on oral analgesics by her family physician. Physical examination revealed a diffuse fullness or mass in the right upper quadrant. Investigations in the Emergency Department included ultrasonography, which demonstrated a large liver cyst.

CT at that time documented a multiloculated mass, 20 cm in dimension, occupying the entire central part of the liver. Serologic testing for echinococcal disease gave negative results. Severe pain was relieved by the insertion of a percutaneous drain into the largest cyst cavity. Straw-coloured fluid was drained; the bilirubin level of the fluid was normal. Cyst fluid analysis revealed a CA19-9 level of
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ence or absence of a "mesenchymal
ations had a recurrence. None of the
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man to a massive cyst presenting
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range and variety of ways that cyst-
Serum and Cyst Fluid Levels in Cystadenoma

<table>
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<th>Series</th>
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</table>

*Normal <5 ng/mL
†Normal <35 U/mL
‡Without mesenchymal stroma

Comment

None of the 4 patients required
intraoperative or postoperative blood
transfusions.

Discussion

These 4 cases demonstrate the
range and variety of ways that cyst-
adenomas can present, from a small
lesion found incidentally in an elderly
man to a massive cyst presenting
acutely with severe pain in a young
woman. One patient presented after a
previous operation failed to correct
her problem. Two cysts had mes-
enchymal stroma and 2 did not. Cyst
fluid levels of CA19-9 and CEA were
loaded but serum levels were not.
Only 1 of the cystadenomas had a
definite communication with the bili-
ary tree. Two of the lesions were suc-
scessfully treated with enucleation, but
the patient with incomplete enuclea-
tion had a recurrence. None of the
cysts showed evidence of malignancy.

There are 2 distinct classes of cy-
standomas, depending on the pre-
ence or absence of a "mesenchymal
stroma" as an intermediate layer in
the cyst wall. This mesenchymal
stroma has a distinctive appearance
(Fig. 3). It is composed of a compact
well-vascularized zone of spindle
cells with ovoid nuclei and promi-
nent nucleoli. It is distinct from the
less cellular outer collagenized con-
nective tissue. These cellular ele-
ments appear similar to primitive
mesenchyme. All cases of cystade-
nomas with mesenchymal stroma oc-
cur in women whereas cystadenomas
without mesenchymal stroma pre-
dominate in men.

Asymptomatic biliary cystadeno-
mas may be found during radiologic
imaging or surgical exploration for
other reasons, as was the case with
our male patient. Patients present-
ing with symptoms generally complain of
abdominal distension or a palpable
mass, or both, with varying degrees
of pain, anorexia, nausea or vomit-
ing. Large cysts may present with
jaundice, cholangitis or steatorrhea
from compression of the common
bile duct. This may be present in up
to 35% of patients. Vena cava ob-
struction and thrombosis have also
been reported. Less common pre-
sentations include painful intracystic
hemorrhage, rupture and fever from
secondary infection. Any patient pre-
senting with recurrence of their liver
cyst after surgical or radiologic treat-
ment should be suspected of having
a cystadenoma (as in Case 2).

Ultrasonography has proven very
useful as an initial investigation in
these patients as it outlines the an-
choic mass with thin internal septa-
tions that are highly echogenic. Some internal echoes may represent
papillary growth instead of septation.
CT demonstrates a smooth thick-
walled cyst with internal septations.
However, septations are often less
well seen on CT than on ultra-
sonography. Magnetic resonance im-
hances the cyst wall, septations and
mural nodules. It is difficult, on pre-
operative imaging, to distinguish
these lesions from cystadenocarcino-
mas; however, a significant solid
component to the wall suggests in-
vase malignant disease. Magnetic
resonance imaging of these lesions
demonstrates the relationship to vas-
cular structures and may be useful in
planning the surgical procedure.

Imaging the intrahepatic bile
ducts with ERCP or intraoperative
cholangiography may be useful if a
communication with the biliary tree
is suspected (arising from major duct
arborization). ERCP is especially
important if the patient is jaundiced.
Core needle biopsy for diagnosis
risks dissemination of tumour cells
and is not recommended. Plain and
contrast roentgenography, liver
scintigraphy and angiography are
rarely necessary.

Analysis of serum CA19-9 may
prove useful in identifying the disease
in some patients, but in no way does
it rule out cystadenoma. Elevated
serum CA19-9 levels have been re-
reported in several cases of cystadenoma with mesenchymal stroma (Table 1). but was not elevated in the 2 patients we tested preoperatively. Thomas and colleagues reported a return of serum CA19-9 to normal after complete resection and suggested it may be useful for long-term follow-up of these patients. However, our patient with recurrence did not have an elevated CA19-9 level. Serum CEA was not useful as it was not elevated in any of the patients studied.

Cyst fluid analysis for CEA and CA19-9 proved more useful than serum analysis (Table 1). Cyst fluid demonstrated marked but variable elevation in CA19-9 and moderate elevation of CEA. These elevated cyst fluid tumour markers give a clear indication of the neoplastic nature and biliary origin of these cysts and distinguish them from simple cysts and echinococcal cysts. Pinto and Kaye reported CEA levels in fluid from 7 simple cysts; these levels were always less than 4 ng/mL. Lee and associates reported CA19-9 levels in 5 simple or polycysts, all levels being less than 11 U/mL. Finally, Thomas and colleagues reported CA19-9 levels in fluid from 5 hydatid cysts; all levels were between 8 and 35 U/mL (normal range).

The level of elevation in no way allows one to differentiate between cystadenomas and cystadenocarcinomas. Indeed, when a cystadenocarcinoma is suspected, one must always weigh the relative risks of needle aspiration and tumour seeding versus proceeding straight to liver resection.

There is a well-established connection between cystadenomas with mesenchymal stroma and cystadenocarcinoma, usually the papillary variant. Devaney and associates found preexisting benign cystadenomas in one-third of patients with cystadenocarcinomas. Sarcomatous transformation of the mesenchymal stroma has also been reported. The relationship between cystadenomas without mesenchymal stroma, as can occur in men, and malignant cystadenocarcinomas is not well established. Although cystadenocarcinomas do occur in men and women with equal frequency, the presence of a benign cystadenoma component is rare, suggesting de novo development. However, cystadenomas in men may also risk malignant transformation; a recent case has been reported showing frankly malignant epithelial cells with some invasion of the cyst wall in a cystadenoma without mesenchymal stroma. Furthermore, several cases of acidophilic cell cystadenoma without mesenchymal stroma have been reported exclusively in men and these have been classified as a semimalignant histologic variant or even a low-grade cancer. Cystadenocarcinomas arising from preexisting cystadenomas tend to have a better prognosis that those arising without this association, as occurs in men.

All cystadenomas in women or men should be excised completely because of their malignant potential and the inability to distinguish a cystadenoma from a cystadenocarcinoma or other malignant cystic tumours on the basis of preoperative investigations. Incomplete excision always results in recurrence, as was the case with our second patient.

We feel that complete enucleation is a reasonable treatment for cystadenoma extending out of the liver. However, care must be taken to inspect and biopsy any suspicious areas of cyst wall, and the specimen must be examined carefully for invasive malignant disease. Deeper lesions not accessible on the surface or lesions that are suspicious for malignancy require resection. Wedge resection or segmentectomy can be used to remove smaller tumours. We do not recommend non-anatomic cystectomy for large tumours, because vital vascular and biliary structures are often found compressed in the liver parenchyma just outside the cyst wall. Cyst drainage or Roux-en-Y cyst-bowel anastomosis is inappropriate and likely to result in complications and recurrence.

Very large, centrally placed cystadenomas are a special problem as they often directly contact hepatic veins and portal glissonian sheaths (as in our cases 2 and 4). Others have reported success with minimal blood loss with complete enucleation. With patience and care a relatively avascular plane can be developed between the cyst wall and liver parenchyma; hepatic veins and glissonian sheaths can also be separated from the cyst atraumatically. A plane for enucleation may have been facilitated by the presence of the mesenchymal stroma, which produces a pseudocapsule. Enucleation was more difficult in our patient with the cystadenoma without mesenchymal stroma. Complete enucleation proved impossible in our patient who had hepatic duct communication, resulting in recurrence. Trisegmentectomy may have been a better option in this patient.

In conclusion, the differential diagnosis of any cystic lesions in the liver should include cystadenoma. When the diagnosis is unclear, serum CA19-9 and cyst fluid analysis for CEA and CA19-9 may prove useful. The prognosis of completely removed cystadenomas is excellent; recurrence is rare. Besides hepatic resection, complete enucleation is a safe and effective treatment.

References