Choledochal cystic malignancies

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Summary
Cystic diseases of the bile ducts are rare, but relatively more prevalent in females, and more common in Japan and Asia. Most are diagnosed in children under 10 years of age, with varying patterns of symptoms including right upper quadrant pain, jaundice, and fever. Up to 20% of bile duct cysts are diagnosed in adults, including during pregnancy, in whom the diagnosis can be confounded by associated cholelithiasis, or by abnormalities of the pancreatic junction with pancreatitis.

The risk of malignant transformation increases with age, and is more common in cysts of Alonso-Lej Types I, IV, and V (Caroli’s Disease). Intracystic lithiasis is frequently associated with tumour, and can give similar radiological appearances. Tumours are often first diagnosed at laparotomy, and can already be unresectable.

More than half the tumours are intracystic, but malignant change in cyst mucosa without a tumour mass is often not recognised at surgery. In addition, malignant change in bile duct epithelium can occur after cyst excision, sometimes after many years, and in areas of the biliary tree remote from the cyst, including the gall-bladder. Cyst excision should be attempted at all ages, and patients closely monitored thereafter. Malignancy should be suspected in all adults with bile duct cysts. Hepatectomy, partial or total with transplantation, is the treatment of choice in Caroli’s disease.

Key words: bile duct cyst, Caroli’s disease, diagnosis, malignant transformation.

Introduction
Classification of bile duct cysts
Bile duct cyst is a general term for a cluster of anatomical and pathological variants). The most widely used classification is that of Todani [1], which combines an earlier classification of extrahepatic cysts by Alonso-Lej [2], with the multiple intrahepatic cyst anomalies previously known as Caroli’s disease [3]. A similar classification based on cholangiographic appearance has been proposed, which is helpful in planning surgery and the need for pre-operative biliary drainage [4].

Prevalence of bile duct cysts
Cystic diseases of the bile ducts are rare. Population prevalence estimates range from 1 in 13000 to 1 in 2 million [5]. They are relatively more prevalent in females, and more common in Japan and Asia. Two-thirds of choledochal cysts present before the age of 10 years [6]. In exceptional cases, ultrasound examination results in prenatal diagnosis, with reparative surgery planned for shortly after birth [7]. It is not clear yet whether some of the 20% of bile duct cysts that are diagnosed in adults are late manifestations of congenital cysts, or are acquired lesions resulting from mucosal and cyst wall damage [8].

Malignant transformation
The incidence of malignant transformation increases with age, rising from 0.7% in patients with cysts operated on at below 10 years of age, to 6.6% when operated between 11-20 years, and 14.3% if first treated at > 20 years old [9]. Malignant transformation is the most serious complication, with a prognosis described as poor, or even dismal [8]. In patients whose cancer is found at operation, the 2-year survival rate is < 5% [10].

The Paul Brousse Experience
We reviewed cases referred and admitted to the Hepato-Biliary Centre with cystic disease of the biliary tract in order to determine if there were common factors in the mode of presentation of those who had carcinomas.

Patients and results
Forty eight patients were treated for cystic disease between 1966 and 1998. Six patients had malignancies (12.5%). The distribution of the types of cyst is shown in Table 1, together with the frequency of cyst types reported in the literature. The cases with malignancy are summarised in Table 2.

Table 1: Comparison of the distribution of types of bile duct cysts.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Nagorney [Ref 20]</th>
<th>Paul Brousse series n=48</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency (%) of cysts</td>
<td>Frequency (%) of cysts</td>
</tr>
<tr>
<td>type I</td>
<td>82</td>
<td>46</td>
</tr>
<tr>
<td>type II</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>type III</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>type IV</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>type V</td>
<td>&lt;1</td>
<td>33</td>
</tr>
</tbody>
</table>


Patient 1

A 38 year-old man presented with intermittent right upper quadrant pain, fever and jaundice. Twenty-nine years earlier, he had undergone a loop jejunostomy for a type I cyst. On examination he was icteric, with hepatomegaly, and a large liver with dilated intrahepatic ducts was confirmed by ultrasound and CT scan. Two days later he required intensive care because of severe cholangitis with renal failure. Emergency percutaneous drainage was performed, with no improvement. At laparotomy an inoperable mass was found involving the cyst-jejunostomy, with abscesses in liver metastases. He survived for 1 month.

Patient 2

A 36 year-old man had a 5 month history of upper abdominal pain with weight loss. No masses were palpable. Liver enzyme tests were within reference ranges. Ultrasound and CT scans showed a type I cyst with coeliac adenopathy. At operation an unresectable adenocarcinoma was identified arising in the cyst, and invading the liver with metastasis to celiac nodes. Palliative cyst jejunostomy with gastrojejunostomy was performed. Chemotherapy was initiated two weeks later. The patient died from liver failure with portal hypertension caused by tumour mass, 8 months after surgery.

Patient 3

A 47-year old man underwent cholecystectomy with cyst jejunostomy for a type I cyst. Gallbladder histology revealed an intra-mural adenocarcinoma arising within the cystic duct.

At referral one year later, the patient appeared in good condition, with normal serum liver enzyme activity. Ultrasound, angiography, and CT scan did not show any abnormality.

A complete cyst excision with hepatico-jejunostomy and lymph node curettage was performed. Histological examination of the specimen showed carcinomatous cells inside the cyst wall, without involvement of lymph nodes. This patient was lost to follow-up 12 months later.

Patient 4

A 57 year-old man was referred by a community hospital where he had presented with a history of abdominal pain, jaundice and chills for 1 month. A CT scan and ultrasound revealed Caroli’s disease with intrahepatic stones, and steroid therapy had been prescribed. On examination, the patient was icteric and had hepatomegaly. CT scan and ultrasound showed wide cystic dilatation of all intrahepatic ducts. A Roux-en-Y hepatico-jejunostomy with bile duct clearance was performed. Postoperatively, the patient underwent 5 sessions of percutaneous clearance of residual bile duct stones through the jejunal loop. Cholangiography at 9 months showed the biliary system to be completely free of stones, and the transjejunal catheter was removed. Five months later the patient again complained of upper abdominal pain. Ultrasound and CT scan examination showed a right liver mass with dilated intrahepatic ducts, and stones prevalent in the right side of the liver. At laparotomy an unresectable cholangiocarcinoma of the right liver was discovered, with intrahepatic stones and peritoneal carcinomatosis. Chemotherapy was initiated. The patient died after 6 months.

Patient 5

A 38 year-old man presented with fever and pain in the right upper quadrant. Three years previously he had undergone cholecystectomy. Type V cystic disease had been diagnosed one year earlier on ERCP, and the patient was on regular follow-up. At examination he had hepatomegaly. An ERCP showed cystic dilatation of the intrahepatic ducts with intrahepatic stones. Ultrasound and CT scan revealed dilated intrahepatic ducts with liver abscesses. At laparotomy a cholangiocarcinoma was found, extending into the retroperitoneum, and containing necrotic foci with abscesses. The patient was treated by partial excision with drainage. He died 2 months after the operation.

Patient 6

At 12 years of age, a girl first presented with abdominal pain and jaundice, and a palpable liver mass. Serum liver enzyme activities were elevated. CT scan and angiography showed a type I cyst. Partial cyst excision with hepatico-jejunostomy was performed. The retropancreatic portion of the cyst could not be removed totally because of adhesions to the pancreas. The patient was regularly followed-up. Aged 17-years, she again presented with jaundice. Ultrasound and CT scan showed intrahepatic duct dilatation with multiple liver nodules, and a pancreatic mass with portal vein thrombosis. Biopsy of the mass showed a bile duct adenocarcinoma. Because of the extent of the tumour, no surgery was proposed. Chemotherapy was begun, but the patient died 6 months later from end-stage disease.

Table 2: Characteristics of patients with bile duct cystic malignancies in CHB series.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>Cyst type</th>
<th>Prior cyst surgery</th>
<th>Site of malignancy</th>
<th>Delay from cyst surgery to diagnosis of malignancy</th>
<th>Surgical management of malignancy</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>M</td>
<td>I</td>
<td>cyst jejunostomy at age 9 years</td>
<td>cyst wall, liver metastases</td>
<td>29 years</td>
<td>Palliative cyst jejunostomy with gastrojejunostomy</td>
<td>1</td>
</tr>
<tr>
<td>36</td>
<td>M</td>
<td>I</td>
<td>none</td>
<td>cyst wall with liver metastases</td>
<td>peroperatively</td>
<td>laparotomy</td>
<td>8</td>
</tr>
<tr>
<td>47</td>
<td>M</td>
<td>I</td>
<td>cyst jejunostomy at age 45 years</td>
<td>gallbladder, cystic duct</td>
<td>operative specimen</td>
<td>cyst excision with hepatico-jejunostomy</td>
<td>&gt;12 (lost to follow-up)</td>
</tr>
<tr>
<td>38</td>
<td>M</td>
<td>V</td>
<td>na</td>
<td>cholangio-carcinoma with abscess</td>
<td>peroperatively</td>
<td>partial excision with drainage</td>
<td>2</td>
</tr>
<tr>
<td>57</td>
<td>M</td>
<td>V</td>
<td>hepatico-jejunostomy at age 56 years</td>
<td>cholangio-carcinoma</td>
<td>1 year</td>
<td>laparotomy</td>
<td>6</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>I</td>
<td>cyst excision with hepatico-jejunostomy at age 12 years</td>
<td>head of the pancreas</td>
<td>5 years</td>
<td>laparotomy</td>
<td>12</td>
</tr>
</tbody>
</table>
Discussion

There are many case reports and short series reported in the literature, with which we can compare our observations. The larger series are identified in Table 3, together with information provided on the patients with malignancies.

Cyst types and frequency

The types of cyst with malignancy in our series are consistent with the literature. Malignancies can be associated with any type of bile duct cyst, but the greatest prevalence said to be with type I, type IV and type V [11]. Type II choledochal cysts are associated with a minimal risk of malignant degeneration [12]. In comparison to the occurrence data of Nagorney [13], our population has fewer type I and more type V cysts. This is probably because we see only patients referred because of more complex conditions.

Incidence of malignant change

The larger series give incidences of malignant change that range from 0 % in a short follow-up of only type IV cysts [14], to 28 % in a study of only extrahepatic cysts in adults. The incidence found in any series would be expected to vary with the types of cyst, as described above, the ages of the patients at diagnosis of the cyst, as described by Voyles [9], and the duration of follow-up. Our 12.5% overall incidence is consistent with the literature, as is the 18 % incidence in type I cysts.

Age and other risk factors

Voyles [9] listed factors contributing to malignant change including: prolonged bile stasis and infection, development of carcinogens in stagnant bile, chronic inflammation, a sparse distribution of the protective mucin-secreting glands. Todani also suggested the development of mutagens in bile and stones [1]. Reflux of pancreatic juice to the cyst could contribute to the chronic inflammatory changes in the biliary epithelium [15]. Reovirus [16], genetic factors [6], and oncogenes [17] have also been suggested as risk factors. It is logical to expect some time-dependent effect in the risk of developing carcinoma for any one of these factors. Although Voyles showed the age at cyst diagnosis to be related to the incidence of cancer [9], it is difficult to develop precise risk factors based on age alone. Flanigan [18] reported on patients aged from 17 to 70 years, Rossi [19] on patients between 29 and 64 years, and Nagorney’s ranged from 18 to 62 [20]. Thus malignant change has to be suspected in all patients with a bile duct cyst, at any age.

Table 3: Incidence of malignancy in reviews of bile duct cystic disease.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N° of patients with bile duct cysts</th>
<th>N° of malignancies n (%)</th>
<th>Age (yr) at diagnosis of malignancy mean (range)</th>
<th>Main symptoms of cysts with malignancy</th>
<th>Survival (months) Mean or absolute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flanigan [18]</td>
<td>1975</td>
<td>955</td>
<td>24 (2.5)</td>
<td>32 (17-70)</td>
<td>Biliary obstruction, in advanced cases.</td>
<td>8.5</td>
</tr>
<tr>
<td>Yamaguchi [23]</td>
<td>1980</td>
<td>1433</td>
<td>60 (4.2)</td>
<td>32 (15-66)</td>
<td>Non-specific</td>
<td>na*</td>
</tr>
<tr>
<td>Nagata [26]</td>
<td>1986</td>
<td>27</td>
<td>3 (8.1)</td>
<td>61 (52-71)</td>
<td>Jaundice 2, weight loss 1, pain 1</td>
<td>5, 7, &gt;76</td>
</tr>
<tr>
<td>Rossi [19]</td>
<td>1986</td>
<td>30</td>
<td>6 (20.0)</td>
<td>45 (29-64)</td>
<td>Pain in 6 of 6, weight loss 4 of 6</td>
<td>3.6</td>
</tr>
<tr>
<td>Todani [8]</td>
<td>1987</td>
<td>82</td>
<td>8 (9.7)</td>
<td>35 (15-&gt;50)</td>
<td>na</td>
<td>&lt;60 unless in gallbladder</td>
</tr>
<tr>
<td>Lipsett [5]</td>
<td>1994</td>
<td>42</td>
<td>3 (7.2)</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Scudamore [21]</td>
<td>1994</td>
<td>23</td>
<td>1 (4.3)</td>
<td>na</td>
<td>na</td>
<td>&gt; 33</td>
</tr>
<tr>
<td>Chijiiwa [14]</td>
<td>1994</td>
<td>13</td>
<td>0 (0.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hewitt [27]</td>
<td>1995</td>
<td>14</td>
<td>2 (14.2)</td>
<td>na</td>
<td>na</td>
<td>3, 12</td>
</tr>
<tr>
<td>Stain [28]</td>
<td>1995</td>
<td>27</td>
<td>7 (26.9)</td>
<td>48 (34-60)</td>
<td>na</td>
<td>&lt; 48 in 4 cases</td>
</tr>
<tr>
<td>Lenriot [29]</td>
<td>1998</td>
<td>42</td>
<td>5 (11.9)</td>
<td>39 (29-51)</td>
<td>na</td>
<td>12</td>
</tr>
<tr>
<td>Present series</td>
<td>1998</td>
<td>48</td>
<td>6 (12.5)</td>
<td>39 (17-57)</td>
<td>pain in 4 of 6, jaundice, fever in 3 of 6</td>
<td>&lt; 8 in 5 cases</td>
</tr>
</tbody>
</table>

*na: not available
Presenting symptoms

Few publications deal with the specific clinical presentation of malignancies in bile duct cysts. Nagorney [20] reported weight loss in 4 of 8 cyst patients with malignancy, but only 2 of 21 cases without malignancy. Rossi [10] reported that at initial presentation, 6 of 6 had pain, 4 of 6 weight loss, and 2 of 6 had fever. Pain, jaundice and fever were also noted in this series (Table 3). Only 1 of our 6 patients had a history of weight loss. Only 1 had a palpable mass. All symptoms in these patients, such as fever, jaundice, or pain, are consistent with cholangitis or with cholelithiasis, which frequently occur in bile duct cysts, and can co-exist with malignancy. Abnormalities of the pancreatic duct and common channel are often seen in association with bile-duct cysts, and can co-exist with malignancies. It seems that there are no specific or sensitive clinical indicators of malignant transformation, and that symptoms of obstruction may only develop at a late stage due to the pre-existing cystic dilatation.

Discovery and diagnosis

The co-existence of pathology causing similar symptoms may be the reason why so many malignant transformations are discovered only at operation. In Flanigan’s 1975 series [18], none of the 24 cancers arising in bile duct cysts was diagnosed prior to surgery. In two of our patients also, the malignancy was discovered only at laparotomy. In a third patient, the diagnosis was not made during the operation, but in-situ carcinoma was discovered on histological analysis of the operative specimen. Other cases of post-operative histological diagnosis have been reported, as are cases in which the diagnosis was missed. Nagorney [20] reported 3 of 8 cases which were recognised only because of post-operative complications, including haemobilia and jaundice. Voyles commented in 1983 that the red velvet appearance of pre-malignant mucosa at operation is not dissimilar from that of inflammation [10]. In this series, only 24 of 67 malignancies (33%) were diagnosed at the first operation for symptoms, with a further 15 (22%) in the two years following surgery. Of the 41 patients whose cancers were discovered during surgery or at autopsy, 22 (54%) had had biliary tract surgery in the previous 2 years.

Does the type of surgery have an impact on malignant transformation?

Cyst-enterostomy was for many years the most widely used technique to achieve drainage, but the recognition of the risk of malignant transformation at an average of 10 years after cyst drainage [8] has increased the popularity of cyst excision, where this is possible. Todani thought that increased bile stasis in the by-passed area could lead to malignant change [1]. However, only some 60% of tumours arise in the cyst wall. In Todani’s series of 154 cancers associated with bile duct cysts, 62 were in the gall-bladder, 1 in the liver and 2 in the pancreas. In one of Nagorney’s patients, an intrahepatic ductal sarcoma arose in a patient with a type I cyst. Since malignant change in bile duct epithelium can occur outside the cyst, cystectomy will not completely reduce the risk of subsequent malignancy [21], which can occur late after cyst excision. Nagorney [20] reported another case in which a cholangiocarcinoma arose at the ductal bifurcation 1.8 years after cyst excision. Coyle [22] hypothesised that adenomatous hyperplasia is an early phase of malignant transformation, when reporting a case of cholangiocarcinoma arising 2 years after excision of a type II cyst (the fourth in the literature). Yoshikawa [23] reported a carcinoma in the intrapancreatic terminal bile duct occurring 12 years after primary excision of a giant choledochal cyst. These types of isolated case do not permit an estimate of the true incidence of delayed development of cancer after cyst excision, but they do serve as a reminder that the risk is real. Knowing that malignancy can develop outside the cyst must not reduce the effort at total resection that should be made. When the lower end of the cyst extends into the pancreas, in our recent cases it has been possible to exteriorise the intrapancreatic extension by ultrasonic dissection. In cystic anomalies that involve Wirsung’s duct, it may be necessary to excise the head of the pancreas and the surrounding duodenum. The upper limit of resection can be easily determined when the cyst stops at the confluence. However the limit of resection may be less certain when the upper part of the cyst involves the large branch of the bile duct.

Early detection and prevention

The difficulties in intraoperative detection, and the possibility of cancers remote from the cysts makes it desirable to have some form of early detection of malignant change. In patients in whom cholangiocarcinoma has been diagnosed and resected, Cameron’s group have shown some usefulness of measuring carcinoembryonic antigen in bile [24]. However the practical aspects and limited diagnostic sensitivity make this approach unsuitable for routine use. Prophylaxis is also desirable. In most cyst malignancies today, there is no clear etiology that would allow a prophylactic approach to be developed. In type IVA cysts which are intrahepatic, partial hepatectomy can be performed, removing the principal segments that are affected. The principle of total cyst resection, when applied to Caroli’s disease where the condition is diffuse and malignant degeneration occurs in 100% of cases [11], leads to a policy of total hepatectomy with transplantation. Liver transplantation may also be proposed when a tumour focus has been identified.

Conclusion

There is no characteristic mode of presentation of biliary tract cystic malignancies. Recent weight loss should increase the likelihood that a cancer is present. All patients of any age who have a bile duct cystic condition should be considered as being at risk of existing and future malignant degeneration. Excision is not by itself protection against future development of cancer. Transplantation should be considered for patients with extensive intrahepatic cysts. All patients should have long-term close follow-up. Any patient, and especially any adult, with recurrent symptoms following cyst-related surgery, must be evaluated carefully for malignancies anywhere in the biliary tract.
References


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