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Extrahepatic Biliary Cystadenomas and Cystadenocarcinoma

Report of Seven Cases and Review of the Literature

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Objective
The aim of this investigation was to describe the clinical features, diagnosis, pathologic characteristics, and optimal surgical management for patients with extrahepatic biliary cystadenomas.

Summary Background Data
Extrahepatic biliary cystadenomas are rare epithelial neoplasms. The clinical features and optimal surgical management for these lesions have not been defined clearly. The usual presenting symptom is jaundice. These lesions should be considered premalignant and necessitate resection. Sporadic case studies have reported instances of recurrence with local excision. To the authors' knowledge, this study represents the largest collected single series of extrahepatic biliary cystadenomas and reviews previously reported cases.

Methods
The authors reviewed and reported their institutional experience from 1950 to 1993 in treating seven patients with extrahepatic biliary cystadenomas as well as 19 previously reported cases in the literature.

Results
A strong female predominance (96.3% of patients reviewed) was associated with extrahepatic biliary cystadenomas. Obstructive jaundice was the most common presenting symptom (85%). Abdominal pain occurred in 50% of patients; other symptoms included fever and hemobilia. The most common site of occurrence was the common hepatic duct (32%). Papillary cystadenoma with foci of invasive adenocarcinoma, thus supporting the malignant potential of cystadenomas, occurred in one patient. Local excision from the wall of the bile duct was performed in 18 patients and was associated with 50% recurrence within a mean follow-up of 13 months (range, 4–24 months). No recurrence was reported after formal sleeve resection and bilioenteric reconstruction.

Conclusions
Extrahepatic biliary cystadenomas can become malignant, and in this study, local surgical excision was associated with a 50% local recurrence rate. Sleeve resection with negative histologic resection margins followed by bilioenteric reconstruction, therefore, is recommended.

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Extrahepatic biliary cystadenomas are rare cystic neoplasms. These lesions are much less common than intrahepatic biliary cystadenomas and present differently. Sporadic case studies have shown the potential for local

recurrence after surgical excision, although the incidence and factors associated with recurrence have not been described. Several authors have postulated that intrahepatic biliary cystadenomas remain *in situ* for extended periods of time and can become malignant. It is unclear, however, whether this hypothesis also applies to extrahepatic cystadenomas. The clinical features and the optimal surgical management of these lesions has not been defined clearly. The purpose of this paper was to describe the clinical features, diagnosis, pathologic characteristics, and surgical management of extrahepatic biliary cystadenomas.

METHODS

Case reports of histologically proven extrahepatic biliary cystadenomas resected by surgeons at the Mayo Clinic in Rochester, Minnesota, between January 1950 and August 1993 were reviewed retrospectively. Seven cases of extrahepatic biliary cystadenomas were identified. Review of the literature revealed 19 previously published single case reports. Our patient data base included demographics, clinical presentation, physical findings, liver function tests, radiologic evaluation, pathologic diagnosis, and surgical treatment. The histopathologic findings of all cystadenomas from all patients in our series was reviewed by the same pathologist. Follow-up data at the time of this writing or until death were obtained for each patient.

RESULTS

Our current review included 26 patients with extrahepatic biliary cystadenomas. Seven patients treated at the Mayo Clinic are described in detail in Table 1. The 19 previously reported cases are summarized in Table 2. The average age of patients at presentation was 47 years (range, 20–67 years). There was a strong female predominance (96.3%). All 7 patients in our series were women, as were all but 1 of the 19 patients described in the literature. The most common presenting symptom was jaundice (85%); consequently, variable degrees of cholestasis was the most common laboratory finding. Other symptoms included abdominal pain (50%), fever (7.7%), and hemobilia (7.7%).

Extrahepatic biliary cystadenomas can occur anywhere along the extrahepatic bile ducts, including in the cystic duct. Site of origin is equally distributed throughout the extrahepatic bile ducts except for the cystic duct (Table 3). Imaging varied widely due to the period of study. Recent findings suggested that cholangiography is the most accurate diagnostic imaging procedure for this condition. The most striking finding in our review was a 50% recurrence rate if these lesions were treated by local excision from the wall of the bile duct. Nine of 18 locally excised extrahepatic biliary cystadenomas, including 1 of our 7 cases, recurred within a mean time of 13 months (range, 4–24 months) (Table 4). In contrast, there were no reported recurrences of this tumor with formal resection and bilioenteric reconstruction.

LITERATURE REVIEW

Cystadenomas of the extrahepatic bile ducts are rare neoplasms. The estimated incidence of all benign extrahepatic biliary neoplasms is less than 0.1%. In an autopsy study of 25,000 patients conducted in 1931, Shapiro and Lifvendah reported 3 benign and 12 malignant extrahepatic biliary neoplasms.[1] On review, one of the benign lesions was found to be a congenital biliary dilatation. In 1932, Marshall reported four benign bile duct tumors in 20,000 consecutive operations on the biliary tract.[2] Burhans and Myers reported four benign tumors of the extrahepatic biliary ducts from 4000 consecutive operations on the biliary tract.[3] The incidence of benign tumors of the extrahepatic biliary ducts was 0.1% of all patients who underwent surgery of the biliary and accounted for 6% of all tumors of the extrahepatic biliary tract.

The most common extrahepatic cystic lesion of the bile ducts is congenital biliary dilatation. According to Geist, cystadenomas account for 4.6% of all hepatic cysts of bile duct origin.[4] The majority of biliary cystadenomas are intrahepatic. Less than 10% of reported cases of biliary cystadenomas are extrahepatic in origin.[3,5] Four cases of cystadenoma of the gallbladder have been described in the literature.[5–8] In Burhans and Myers' review of 84 cases of benign neoplasms of the extrahepatic bile ducts, 41 were papilloma; 39, adenoma; 4, granular cell myoblastoma; and 1 each, fibroma, neuroma, leiomyoma, and harmatoma.[3] Adenomas of the extrahepatic biliary tract can be subclassified as solid, cystic, or mixed. Cystadenoma of the bile ducts is the least common subtype of extrahepatic adenoma. The earliest reported case of extrahepatic cystadenoma appeared in 1929 in Kaufman's *Pathology*; in which he credited Barberio in 1913 for the first description of a cystadenoma of the hepatic duct.[9]

The earliest formal case was presented by Rogers in 1943, who described a papillary cystadenoma excised from the common hepatic duct of a 46-year-old woman.[10] Between 1943 and 1993, nineteen cases of extrahepatic biliary cystadenoma have been described in the literature and are summarized in Table 2.

DISCUSSION

The most significant finding of our study is that extrahepatic biliary cystadenomas have an extremely high incidence of local recurrence if treated with local excision

Table 1. REVIEW OF CASE REPORTS OF EXTRAHEPATIC BILIARY CYSTADENOMAS AT THE MAYO CLINIC 1950–1993

Case	Year	Age	Sex	Presentation	Radiologic Procedure	Location	Surgical Procedure	Followup
20	1961	61	F	RUQ pain	Oral cholecystogram	Cystic duct	Cholecystectomy	33 yrs no recurrence
21	1968	20	F	Jaundice	Oral cholecystogram and IV cholangiogram	LHD, CBD	Excision, resection hepaticojejunostomy after recurrence	Recurrence at 4 mos 15 yrs no recurrence
22	1964	37	F	RUQ pain, fever, hemobilia	—	LHD	Resection and hepaticojejunostomy	8 yrs no recurrence
23	1964	67	F	RUQ pain, jaundice	—	LHD, RHD, CHD	Curretage (foci of cystadenocarcinoma)	Died postop, sepsis
24	1982	54	F	Jaundice	U/S, Hida scan	CBD	Resection and hepaticojejunostomy	10 yrs no recurrence
25	1991	64	F	Jaundice	U/S, CT, ERCP	LHD	Resection and hepaticojejunostomy	8 months no recurrence
26	1993	27	F	RUQ pain	U/S	RHD, CHD	Resection and hepaticojejunostomy	8 months no recurrence

RUQ = right upper quadrant; IV: intravenous; LHD = left hepatic duct; CBD = common bile duct; RHD = right hepatic duct; CHD = common hepatic duct; U/S = utltrasonography; CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography.

from the wall of the bile duct, compared with sleeve resection and bilioenteric reconstruction. We have further confirmed a marked female prevalence and have identified the most common presenting symptoms—jaundice and abdominal pain. Our findings support the hypothesis that extrahepatic biliary cystadenomas may be premalignant. We recommend sleeve or segmental resection of bile ducts with negative histologic margins followed by bilioenteric reconstruction as the treatment of choice for patients with extrahepatic biliary cystadenomas.

Selection of the appropriate surgical procedure is important for identification of the definitive treatment of cystadenomas. Table 4 demonstrates the high recurrence rate if these tumors are treated by local excision from the wall of the bile duct. Nine of 18 patients treated initially with local excision had tumor recurrence within a mean time of 13 months (range, 4 to 24 months). For three of the patients (Patients 8, 11, and 12), the tumor recurred a second time at 19, 60, and 72 months, respectively, after repeated local excision. Six patients who were treated initially with a formal sleeve resection and reconstruction by a hepaticojejunostomy. In contrast, have had no recurrences, with a mean follow-up in four of these six patients of 4.9 years. These collective data demonstrate the association between local surgical excision and an exceedingly high rate of local recurrence. Local resection has been defined variably; in most cases, it entailed choledochotomy and excision of the tumor from the wall of the bile duct. Despite the various definitions, however, local excision was accomplished by either sharp dissection or curettage. Likewise, sleeve resection has not been defined clearly in most cases. The histologic findings of the resection margins has not been reported, thus ideal extent of ductal resection remains unknown. However, reports suggest that sleeve resection followed by histologic confirmation of negative resection margins by frozen section and bilioenteric reconstruction could reduce the local recurrence rate.

The clinical presentation of extrahepatic biliary cystadenoma is similar to that of other diseases that cause biliary tract obstruction. The most common presenting symptom in this series was jaundice. Eighty-one percent of patients presented with either intermittent or persistent jaundice. In contrast, 90% of patients with intrahepatic cystadenomas present with abdominal swelling or an abdominal mass.[5] Ten of the 26 patients in the current review had associated right upper quadrant or epigastric pain. Two patients presented with hemobilia. The mechanism by which these tumors cause hemobilia remains unclear. Although uncommon, extrahepatic cystadenoma should be considered in the differential diagnosis of hemobilia, particularly if there is no history of trauma or radiologic or surgical procedures to the hepatobiliary tract.

The pathologic characteristics of these lesions were defined by Wheeler and Edmondson,[11] who found on gross examination that the tumors were multilobular and cystic, often with thin, glistening, multiloculated, bile-stained walls. On microscopic examination, they found the cysts to be lined with a single layer of cuboidal-to-tall columnar, nonciliated, mucin-secreting epithelium resting on a basement membrane. The cysts often contain serous or mucinous fluid and may have a moderately to densely cellular stroma.[11] Cystadenomas of the bile ducts resemble pancreatic cystadenomas and, sim-

Table 2. CASE REPORT REVIEW OF LITERATURE

Case	Author	Year	Age	Sex	Presentation	Radiologic Findings	Pathology	Procedure	Followup
1	Rogers	1946	58	F	Pain, fever, normal jaundice	Abdomen x-ray	CHD, papillary cystadenoma	Local excision	9 months recurrence died cholangitis and hepatic abscess
2	Moore	1952	44	F	Jaundice, pain		LHD, initial path fibroadenoma	Local excision	2 years recurrence LHD
3	Barber	1960	43	F	Jaundice, pain	Normal oral cholecystogram UGI mass effect	RHD, multiocular cystadenoma	Local excision	4 years recurrence 7 years later asymtomatic
4	Dowdy	1962	38	F	Jaundice	Normal oral cholecystogram	CHD mucinous cystadenoma, glandular polyp	Local excision	25 months recurrence, 24 months later no recurrence
5	Burhans	1971	40	F	Pain, jaundice, hemobilia	Normal oral cholecystogram UGI mass effect	CHD, multilocular cystadenoma	Local excision	9 years no recurrence
6	Short	1971	55	F	Jaundice	Liver scan mass at porta hepatis obstruction CHD	CHD mutliocular cystadenoma	Local excision, choledochoduodenostomy	2 years no recurrence
7	Hossack	1972	53	M	Jaundice, weight loss, pruritis	PTC obstruction CBD	CBD, papillary cystadenoma	Local excision	9 months no recurrence
8	Ishak	1977	48	F	Jaundice, pain	^{131}T rose bengal obstruction CBD	CBD, multiocular mucinous cystadenoma	Local excision	1 year recurrence
9	Udoff	1979	48	F	Jaundice	PTC, mass CHD	CHD, multiocular mucinous cystadenoma	Resection, hepaticojejunostomy	Not available
10	Austin	1981	49	F	Jaundice, pain	Normal oral cholecystogram U/S cystic mass, CT confirms	LHD, multiocular cystadenoma	Local excision, T-tube,	2 weeks later reoperation for biliary obstruction
11	Waki	1983	58	F	Jaundice	PTC, mass RHD	RHD, multiocular cystadenoma	Sleeve resection	Not available
12	van steenbergn	1984	57	F	Jaundice	U/S, CT, ERCP mass and biliary obstruction	LHD, multioculated cystadenoma	Resection, hepaticojejunostomy	Not available
13	Thomsen	1984	26	F	Jaundice, cirrhosis	PTC, U/S cystic mass CBD	CBD, mucinous multiocular cystadenoma	Local excision	Died post op variceal hemorrhage

14	Okamura	1987	45	F	Pain, jaundice	US 6 cm cystic mass CHD	CHD, multioculated cystadenoma	Local excision	Not available
15	O'Shea	1987	47	F	Jaundice	ERCP CHD obstruction PTC and brain	Multiocular polypoid cystadenoma	Local excision	1 year recurrence, local excision, 5 year recurrence resection & hepaticojejunostomy, radiation, 3 years later no recurrence
16	Smith	1989	60	F	Jaundice, anorexia	ERCP proximal CBD obstruction	Sessile mucinous cystadenoma	Local excision choledochoduodenostomy	1 year no recurrence
17	Byrne	1989	37	F	Pain	Cholangiogram cystic mass in CBD	CHD, LD, RH, multiocular cystadenoma	Excision	Not available
18	Coulter	1989	61	F	Jaundice, pain	U/S, ERCP	CBD, multiocular cystadenoma areas of carcinoma insitu	Resection hepaticojejunostomy	1 year no recurrence
19	Hodgson	1991	56	F	Epigastric pain	U/S, CT angiogram	LHD, multiocular cystadenoma	Local excision, T-tube	Not available

LHD = left hepatic duct; CBD = common bile duct; RHD = right hepatic duct; CHD = common hepatic duct; U/S = ultrasonography; CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; UGI = upper gastrointestinal.

Table 3. LOCATION OF EXTRAHEPATIC BILIARY CYSTADENOMAS

Duct	Number (%)
Right hepatic	4 (14.3)
Left hepatic	8 (28.6)
Common hepatic	9 (32.1)
Common bile	6 (21.4)
Cystic	1 (3.6)

ilarly, may be subclassified into multilocular and papillary variants, the former being the most common. The pathologic similarities between biliary and pancreatic cystadenomas were described by Thompson and Wolff.[12]

Several authors believe that cystadenomas of the bile ducts can become malignant and thus should be considered premalignant lesions.[5,11,13] Evidence supporting this contention has been found in benign and malignant components within pathologic specimens of cystadenocarcinomas. Of the 10 published cases of intrahepatic cystadenocarcinoma, all but 1 showed evidence of both benign and malignant elements.[5] In 1981, Woods reported a patient with an intrahepatic cystadenoma who was followed with serial biopsies and whose tumor eventually underwent malignant transformation. Papillary proliferation of the epithelium may be a precursor to malignant transformation.[14] The mean age of patients with intrahepatic cystadenocarcinoma is 17 years older than that of the benign group. No malignancy has occurred in patients younger than 50 years of age.[11] In 1989, Coulter and Baxter described an extrahepatic cystadenoma that had been misdiagnosed as a choledochal cyst 15 years previously and that had been left *in situ*.[15] Histopathologic findings of the resected tumor demonstrated areas of carcinoma *in situ* within the specimen. In our current series, one patient had an extrahepatic biliary papillary cystadenoma with foci of grade 2 cystadenocarcinoma. These two cases demonstrate that malignant transformation can occur in extrahepatic as well as in intrahepatic biliary cystadenomas.

The origin of extrahepatic biliary cystadenomas remains unclear. The most widely proposed theory is that cystadenomas are congenital and are thought to develop from either aberrant harmatomatous bile ducts or ectopic rests of embryonal gallbladder.[5,11] Other investigators believe that cystadenomas are acquired neoplastic lesions because of their multilocular nature along with dense their cellular walls and copious secretions.[16]

Roentgenographic characteristics have revealed differentiation among extrahepatic biliary cystadenomas, parasitic cysts, and other cystic lesions of the biliary tract. In numerous earlier cases reviewed, the diagnosis

Table 4. RECURRENCE AFTER LOCAL EXCISION

Case	Author	Pathology	Initial Surgery	Recurrence	Treatment of Recurrence	Follow-Up After Surgery
1	Rodgers	Papillary cystandenoma CHD	Local excision	9 months	Refused surgery	Died of cholangitis secondary to obstruction of CBD due to recurrence
2	Moore	Multiocular cystadenoma LHD	Local excision	24 months	Re-excision	2-½ years no recurrence
3	Dowdy	Multiocular cystadenoma CHD	Local excision	14 months	Re-excision	2 years no recurrence
4	Border	Multiocular mucinous cystadenoma RHD	Local excision	13 months	Re-excision	Died 7 years post-reexcision, no recurrence
8	Ishak	Multiocular cystadenoma CBD	Local excision	15 and 19 months	Re-excision	3 years no recurrence
14	O'Shea	Multiocular cystadenoma	Local excision	12 and 60 months	Re-excision (12 m) hepaticojejunostomy (60 m)	3 years no recurrence
18	Coulter	Multiocular cystadenoma	Local excision	12 months	Resection and hepaticojejunostomy	1 year followup no recurrence
19	Davies	Multiocular cystadenoma	Local excision	4 months	Re-excision	18 years followup no recurrence
21	Davies	Multiocular cystadenoma	Local excision	12 and 24 months	Resection and hepatiocojejunostomy	10 years no recurrence

LHD = left hepatic duct; CBD = common bile duct; RHD = right hepatic duct; CHD = common hepatic duct.

was confused with or mistaken for congenital biliary dilatation. Radiologic diagnosis of extrahepatic cystadenoma can be made before surgery with use of a combination of several imaging modalities. Endoscopic retrograde cholangiography and percutaneous transhepatic cholangiography typically demonstrate an intraluminal obstructing lesion. The lesion may appear as a single, smooth lesion or as a multilobulated mass. Transhepatic cholangiography or endoscopic retrograde cholangiography usually does not reveal opacification of the cyst, because there is no direct communication between the cyst lumen and the biliary tree. The usual appearance on ultrasonography is of a globular or ovoid, thick-walled mass with fluid or low-level echoes within the cyst. The ultrasound results appear similar to cystadenomas or cystadenocarcinomas of pancreatic or ovarian origin.[16] Ultrasound and computerized axial tomography may demonstrate a cystic mass that contains multiple septations and occasional papillary projections. Mural nodules also may be present. Septations are diagnostically important because they allow distinction between extrahepatic biliary cystadenomas and choledochal cysts or cystic dilatation of the bile duct proximal to benign polyps.[17] Cystadenomas are hypovascular lesions angiographically, through occasional contrast accumulation within the cyst cavity on delayed images has been found.[18] The finding of a cystic mass with multiple septations on computerized axial tomography or ultrasound in association with nonopacification of an intraluminal mass on cholangiography is characteristic of an extrahepatic biliary cystadenoma.[17,19,20]

In summary, extrahepatic biliary cystadenomas are rare tumors, almost exclusively found in middle-aged women. They most commonly present with obstructive jaundice and associated abdominal pain, but may rarely present with hemobilia. Radiologic evaluation should include computerized axial tomography and cholangiography. Extrahepatic biliary cystadenomas have distinct roentgenographic characteristics that allow differentiation from other cystic lesions of the bile ducts. These benign tumors are at risk for malignant transformation and should be considered premalignant. The risk for malignant transformation appears to be related to the amount of time that the tumor remains *in situ*. Local surgical excision from the wall of the bile duct is associated with a 50% recurrence rate and, therefore, sleeve resection with negative histologic margins followed by bilioenteric reconstruction is recommended.

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