Carcinomas Arising in Cystic Conditions of the Bile Ducts

A Clinical and Pathologic Study

RICARDO L. ROSSI, M.D., MARK L. SILVERMAN, M.D., JOHN W. BRAASCH, M.D., J. LAWRENCE MUNSON, M.D., and STEPHEN G. REMINE, M.D.

From the Departments of Surgery and Pathology, Lahey Clinic Medical Center, Burlington, Massachusetts

Thirty patients with cystic disease of the bile ducts operated on between 1965 and 1985 were reviewed. Three patients (10%) had a synchronous adenocarcinoma, and in three patients (10%) a metachronous carcinoma developed for a total incidence of malignancy of 20%. All patients died within 1 year of the diagnosis of malignancy. Of 19 benign cysts available for pathologic examination, one third had proliferative epithelial changes, and in two of these patients a metachronous carcinoma developed. Goblet cell metaplasia was prominent in four patients. This suggests the possibility that dysplastic changes and metaplasia of the epithelium could give rise to carcinoma. Resection of benign cysts of the bile ducts is favored, when feasible, in an attempt to decrease the incidence of malignancy.

TUMORS OF THE BILE DUCT occur infrequently. The number of new occurrences each year in the United States is approximately 4500, and the annual age adjusted frequency per 100,000 men has been estimated at 7.5, 6.5, and 5.4 in Israeli, American Indian, and Japanese populations, respectively.[1,2] These figures contrast with a 2.5–28% reported incidence of bile duct carcinoma in patients with underlying bile duct cysts.

We present six cases of carcinoma arising in cystic conditions of the biliary tract representing 20% of all patients operated on for cystic disease of the bile duct in a 20-year period at our institution. We performed a pathologic study of specimens available from patients who had such operation during this period to determine characteristics of the bile duct epithelium, such as cytologic atypia or metaplastic change, that might predict the development of a carcinoma.

Materials and Methods

The records of all patients treated for cystic conditions of the bile duct at Lahey Clinic between 1965 and 1985 were reviewed. Follow-up information was obtained from hospital records, direct or telephone conversation with the patients' relatives or referring physicians, and autopsy reports if available. All pathologic specimens available for study were evaluated by one of us (M.L.S.). The type of cystic condition present in each case was determined from existing radiologic studies and operative reports and categorized according to a modification[3] of the Alonso-Lej classification as follows: type I refers to a cystic dilatation of the common bile duct, type II cyst is a diverticulum arising from the common bile duct, type III cyst (choledochocele) is a variant in which the terminal intraduodenal portion of the common bile duct is dilated, type IV cyst refers to involvement of both the intrahepatic and extrahepatic bile ducts, and type V cyst involves the intrahepatic ducts exclusively.

Results

Thirty patients with cystic disease of the bile ducts were evaluated and operated on at the Lahey Clinic between 1965 and 1985. Three patients (10%) had a synchronous adenocarcinoma, and in three patients (10%) a metachronous carcinoma developed for a total incidence of malignancy of 20%. These six cases and pathologic studies of 19 specimens from patients operated on for benign cystic conditions of the bile duct are the subject of this review.

Patient 1

A man, 29 years of age when first examined by us, had complained of recurrent pain and jaundice since the age of 18 years. The finding of liver biopsy performed at age 23 was reported to be cholestatic hepatitis. He presented to us with complaint of pain, a palpable right upper ab-

Reprint requests and correspondence: Ricardo L. Rossi, M.D., Department of Surgery, Lahey Clinic Medical Center, 41 Mall Road, Burlington, MA 01805.

Submitted for publication: November 24, 1986.

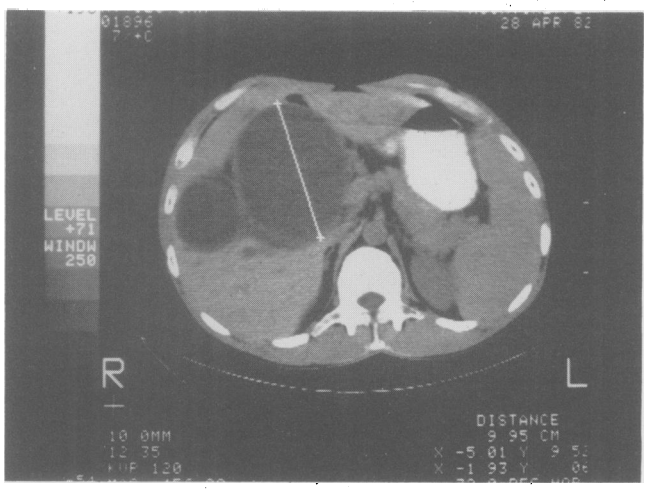

FIG. 1. Choledochal cyst with dilatation of intrahepatic ducts (patient 1).

dominal mass, weight loss, and jaundice. His serum bilirubin level was 4.1 mg/dL (normal: 0–0.3 mg/dL), alkaline phosphatase level was 386 U/L (normal: 20–90 U/L), and aspartate transaminase level was 95 U/mL (normal: 10–40 U/mL). A computed tomographic (CT) scan showed a large cystic abdominal mass with dilatation of intrahepatic ducts (Fig. 1). A percutaneous cholangiogram confirmed a large extrahepatic cyst with intrahepatic ductal dilatation (type IV). He had a cyst resection and a high Roux-en-Y hepaticojejunostomy with removal of stones. Examination of the specimen disclosed severe ulceration of the cyst wall, considerable atypia of the epithelium, and extensive mural fibrosis (Fig. 2). Symptoms resolved, and his liver function returned to normal except for a minimally elevated alkaline phosphatase level. Forty months later at the age of 32 years he had right abdominal pain, chills, and fever. Serum bilirubin level was 0.9 mg/dL, alkaline phosphatase level was 177 U/L, and aspartate transaminase level was 7 U/mL. A CT scan of the abdomen revealed a mass in the porta hepatis and the head of the pancreas. At operation, a partially necrotic, pleomorphic giant cell carcinoma of the hepatic duct bifurcation was noted extending into the retroperitoneum and peripancreatic nodes (Fig. 3). The patient was treated with partial excision of tumor and transhepatic tube drainage. He died 4 months after operation. Autopsy was not performed.

Patient 2

A 64-year-old man had an 8-month history of right upper abdominal pain, back pain, and weight loss. His serum bilirubin level was 1.3 mg/dL, alkaline phosphatase level was 500 U/L, and aspartate transaminase level was 100 U/mL. The history was significant for a truncal vagotomy and pyloroplasty for ulcer disease at the age of 34 and a cholecystectomy at age 59. A CT scan showed a mass in the hilum of the liver (Fig. 4), and retrograde cholangiography revealed a type V cyst involving the right

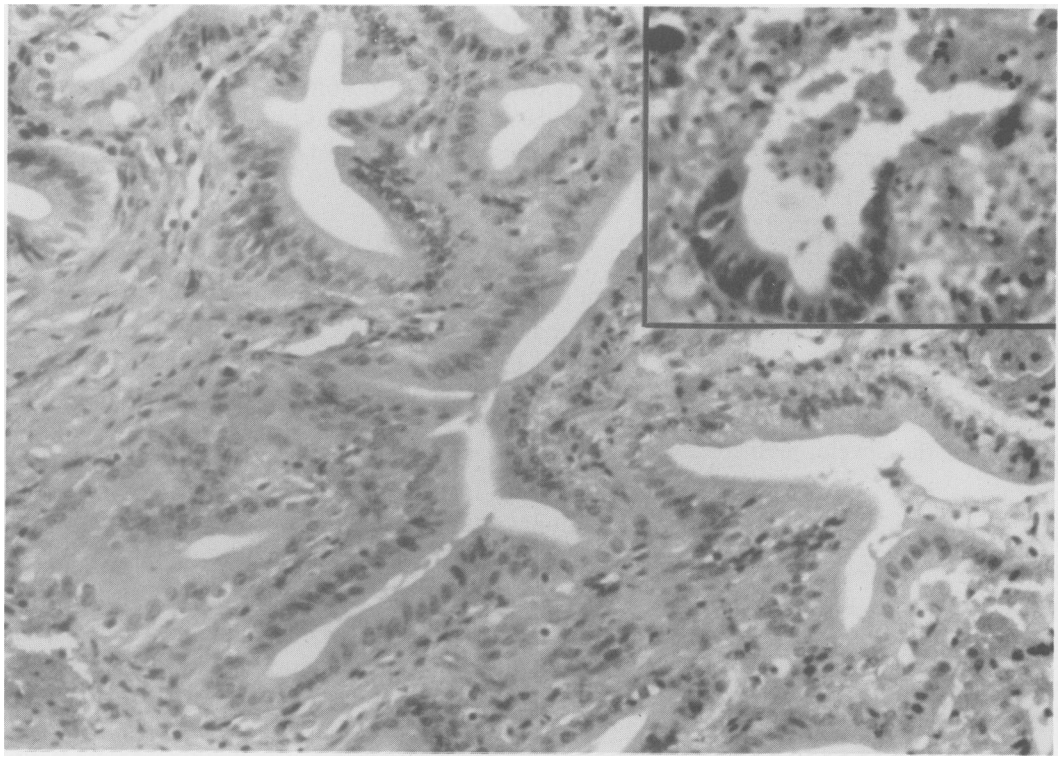

FIG. 2. The epithelium displayed a variety of proliferative changes, including adenomatous hyperplasia as well as degenerated foci with ulceration and cytologic atypia (inset). (Patient 1, hematoxylin and eosin stain, original magnification ×100.)

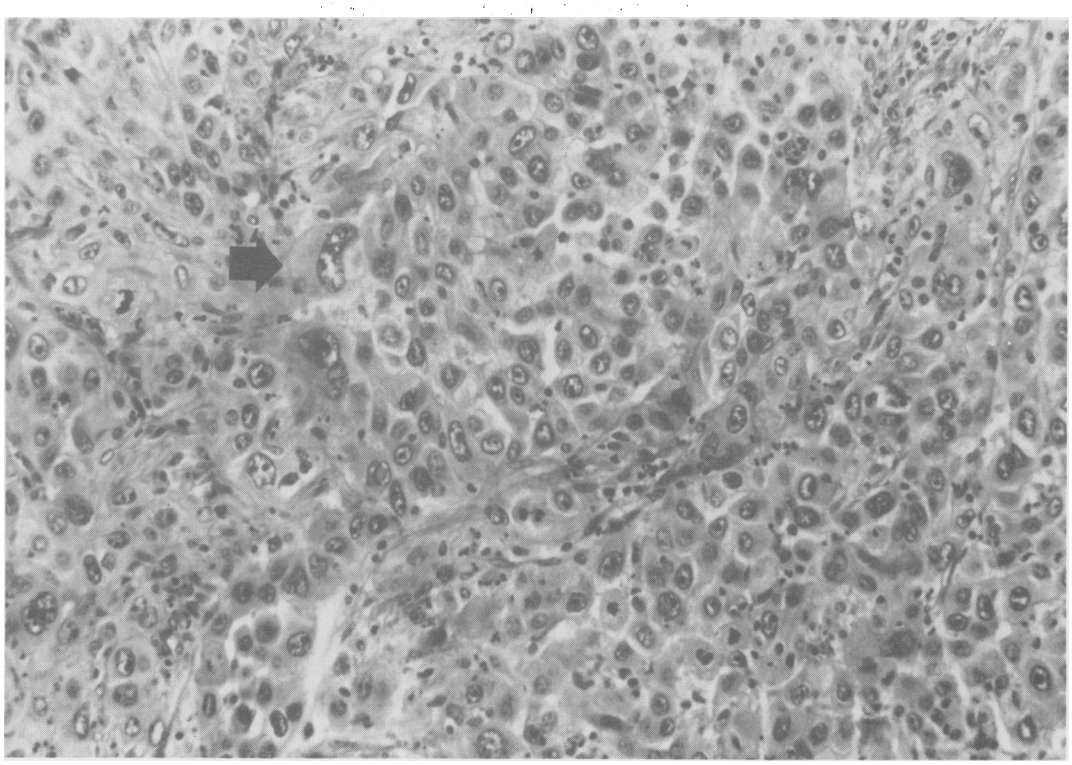

FIG. 3. The tumor comprised a population of pleomorphic large anaplastic cells with occasional giant forms (arrow). Ultrastructural examination showed the presence of well-formed desmosomes and tonofilaments characteristic of squamous cell carcinoma. (Patient 1, hematoxylin and eosin stain, original magnification ×100.)

ductal system (Fig. 5). Incomplete filling of the cyst was suggestive of stones, a tumor, or both. At operation, an adenocarcinoma was found arising in the posterior wall of the cyst with invasion of the liver and metastasis to celiac nodes. The patient was treated with stone extraction, dilatation of the ducts, and transhepatic stenting. Pathologic studies disclosed an adenocarcinoma. He died 4 months later of liver failure and cholangitis. Autopsy was not performed.

Patient 3

A woman, 45 years old when first examined by us, had undergone a cholecystectomy at age 18 and a loop cystojejunostomy for a type I cyst at the age of 40. Five years after the latter operation she presented at the Lahey Clinic with complaints of pain, chills, and fever. Her serum bilirubin, alkaline phosphatase, and aspartate transaminase levels were within the normal ranges. A Roux-en-Y cystojejunostomy with removal of stones was performed at this time. Her symptoms persisted and, for that reason, at age 48 she had partial cyst resection with Roux-en-Y cystojejunostomy. Pathologic examination of the specimen disclosed mural fibrosis and acute and chronic inflammation (Fig. 6). At age 61, she had upper abdominal pain and weight loss. Alkaline phosphatase and aspartate transaminase levels were elevated, but serum bilirubin level was within the normal range. Ultrasound examination and a liver scan showed a large filling defect in the liver. An adenocarcinoma consistent with biliary tract origin was identified by liver biopsy. The patient died 1.5 months later of liver failure. Autopsy was not performed.

Patient 4

A 49-year-old woman had obstructive jaundice and upper abdominal pain. Her serum bilirubin level was 11 mg/dL, alkaline phosphatase level was 25 U/L, and aspartate transaminase level was 98 U/mL. Ultrasound examination showed a dilated common bile duct and intrahepatic duct. A mass with calcification in the hilum of

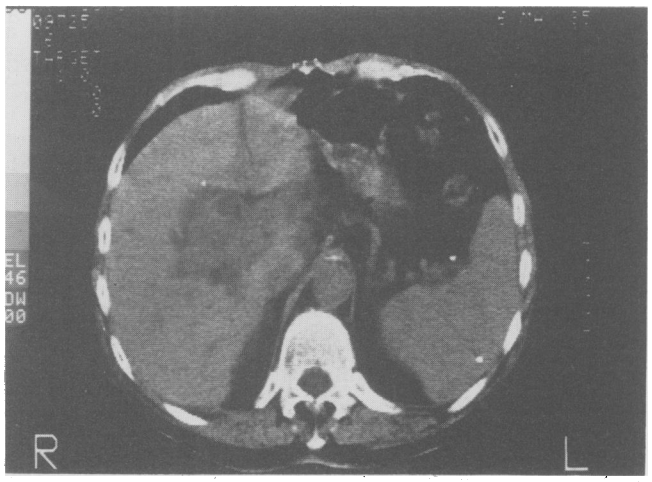

FIG. 4. Hilar mass corresponding to a type V cyst with adenocarcinoma (patient 2).

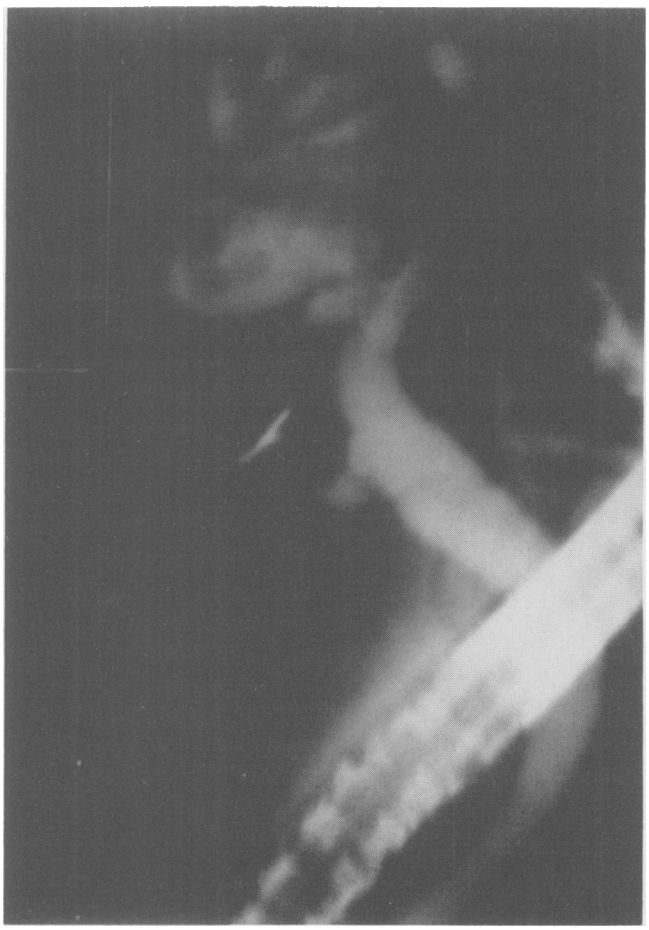

FIG. 5. Retrograde cholangiogram demonstrating a cyst of the right hepatic duct (type V) with a filling defect (patient 2).

the liver was demonstrated by CT scan (Fig. 7). On retrograde cholangiography, a type I choledochal cyst was seen with a proximal filling defect suggestive of tumor, and percutaneous cholangiography showed complete obstruction of the right hepatic duct close to the hilum. An unresectable adenocarcinoma was identified arising in a type I cyst. No stones were present. The patient was treated with segmental ductal dilatation and hepaticojejunostomy, and at pathologic examination, a mucin-producing, poorly differentiated adenocarcinoma was noted (Fig. 8). She died 5 months later.

Patient 5

A 54-year-old woman was referred with a chief complaint of upper abdominal pain for 1 year. The alkaline phosphatase level was elevated, and she was found to have a type I choledochal cyst with an adenocarcinoma arising in the posterior wall and involving the right hepatic duct. Liver metastasis was present but no calculi were present. The patient was treated with ductal dilatation and a loop cystojejunostomy. She died 6 months later.

Patient 6

A 31-year-old woman previously had a cystojejunostomy at age 28 for a type I choledochal cyst and now had a 6-week history of abdominal pain and vomiting. A CT scan showed a mass in the porta hepatis. At laparotomy she was found to have a large mass involving the porta hepatis, the cystojejunostomy, and the duodenal and transverse colon. A gastrojejunostomy and a colostomy were done. At pathologic examination, the lesion was determined to be very poorly differentiated adenocarcinoma (Fig. 9). The patient died 1 month later.

Based on our review of these cases, the main symptoms on presentation were pain in six patients and weight loss in four patients. Two patients had jaundice and one patient had fever, findings that appeared to occur late in the course of the disease. Stones were present in three of the six patients. The median age on presentation with carcinoma in these patients was 52 years (31, 32, 49, 54, 61, and 64 years). All patients died within a few months (1, 1.5, 4 [2 patients], 5, and 6 months) after the diagnosis was made. Four of the carcinomas arose in type I cysts, one in a type IV cyst, and one in a type V cyst.

Of the 19 patients with cystic conditions of the biliary tract in whom pathologic findings were available for review (Table 1), all showed marked inflammatory changes and mural fibrosis. In 17 patients, a cyst lining composed predominantly of a simple columnar epithelium was demonstrated. One third of the patients had proliferative changes of the epithelial lining taking the form of cellular crowding, poor orientation, and often nuclear changes associated with dysplasia. A carcinoma developed in two of these patients with proliferative changes. Four patients exhibited mucosal ulcerations, and focal goblet cell metaplasia was prominent in four cases (Fig. 10).

In two of the six cases reported here, the tumor obliterated any histologic evidence of pre-existing cyst. Two patients had mucinous cancers and two patients had adenocarcinomas resembling the usual ductal carcinoma of typical biliary tract origin. One patient had an undifferentiated giant cell adenocarcinoma with some features of squamous carcinoma, and another patient had a very poorly differentiated adenocarcinoma requiring special immunohistochemical techniques to be characterized.

Four of the six carcinomas were conventional adenocarcinomas with either a ductal or mucinous histopathologic pattern. However, two patients had distinctly unusual histologic characteristics. Patient 1 showed pleomorphic giant cells with squamous features. This form of undifferentiated carcinoma has been well described in the pancreas[4] and to some extent in the gallbladder[5] and probably represents an extreme dedifferentiation of ductal tumor or metaplastic ductal tumor. Patient 6 had a poorly differentiated infiltrating tumor that did not stain for mu-

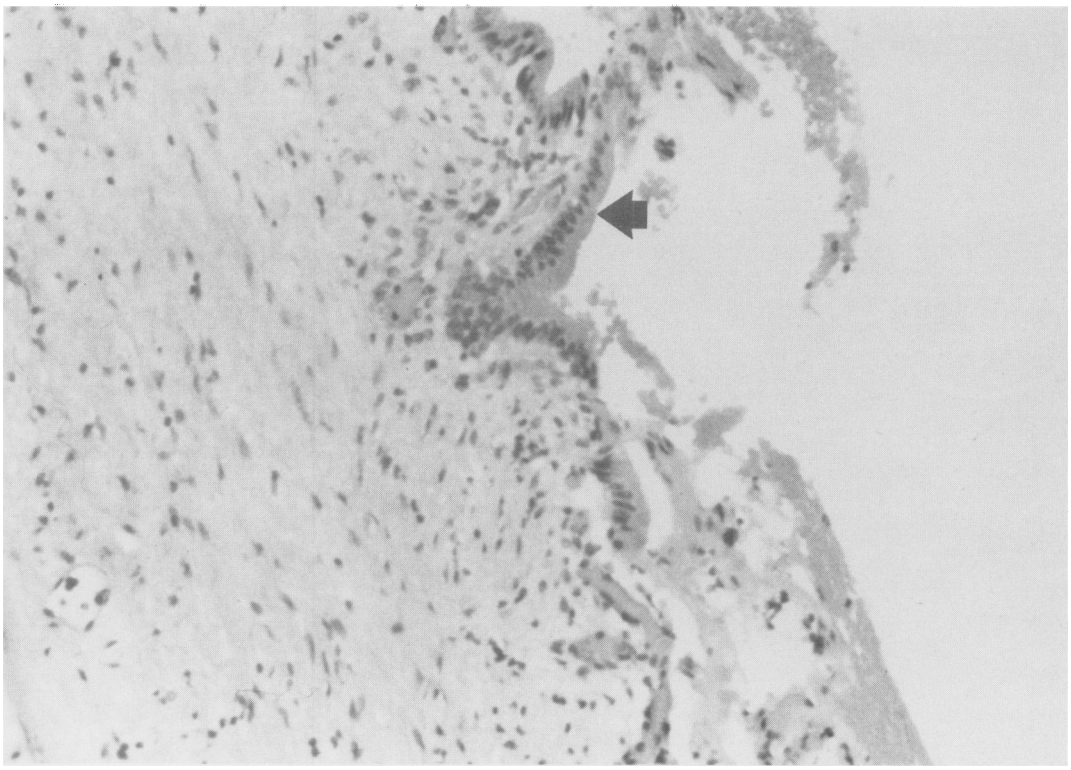

FIG. 6. The "uncomplicated" choledochal cysts found in the majority of the cases examined had simple columnar lining (arrow) overlying a dense fibrous submucosa. Some showed focal ulceration, and all of the nonneoplastic cysts displayed some evidence of chronic inflammation. (Patient 3, hematoxylin and eosin stain, original magnification ×40.)

cin. Immunohistochemical staining showed positivity for keratin and epithelial membrane antigen, and ultrastructural studies lent additional support to epithelial change in the form of tight junctions and a suggestion of a glandular arrangement.

Discussion

In 1944, Irwin and Morison[6] reported on a carcinoma arising in a congenital cyst of the common bile duct. Since then, a 2.5–28% incidence of carcinoma in patients with bile duct cysts has been reported,[7–10] which is higher than that of biliary carcinoma in the general population. In a review of the world literature, Voyles et al.[11] in 1983 reported a total of 67 carcinomas arising in cystic conditions of the bile duct. Their analysis identified a relationship between incidence of carcinoma and the age of initial appearance of symptoms of a choledochal cyst. Children in whom symptoms appeared before 10 years of age had a minimum risk (0.7%) of a carcinoma developing, patients with those symptoms in the second decade of life had a risk of 6.8%, and those whose symptoms appeared after the age of 20 years had a risk of 14.3%. Although 75% of cysts of the biliary tract present in infants and children and only 25% present in adults, 76% of carcinomas have occurred in patients diagnosed as having cystic disease after reaching adulthood. Our incidence of carcinomas (metachronous and synchronous) in patients operated on for cystic conditions of the biliary tract is 20%, which is probably explained by the initial presentation in adulthood of most of our patients and by the referral nature of our practice.

Voyles et al.[11] identified only one patient with carcinoma diagnosed under the age of 20 years. Of 67 patients,

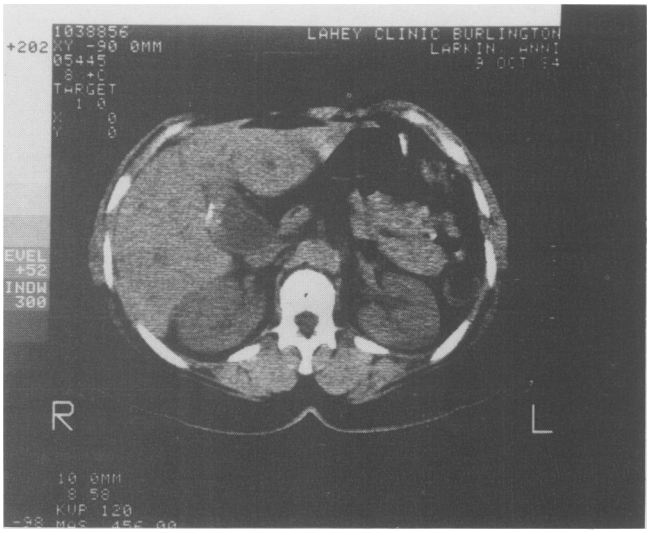

FIG. 7. Hilar mass with calcification corresponding to a carcinoma arising in a type I cyst (patient 4).

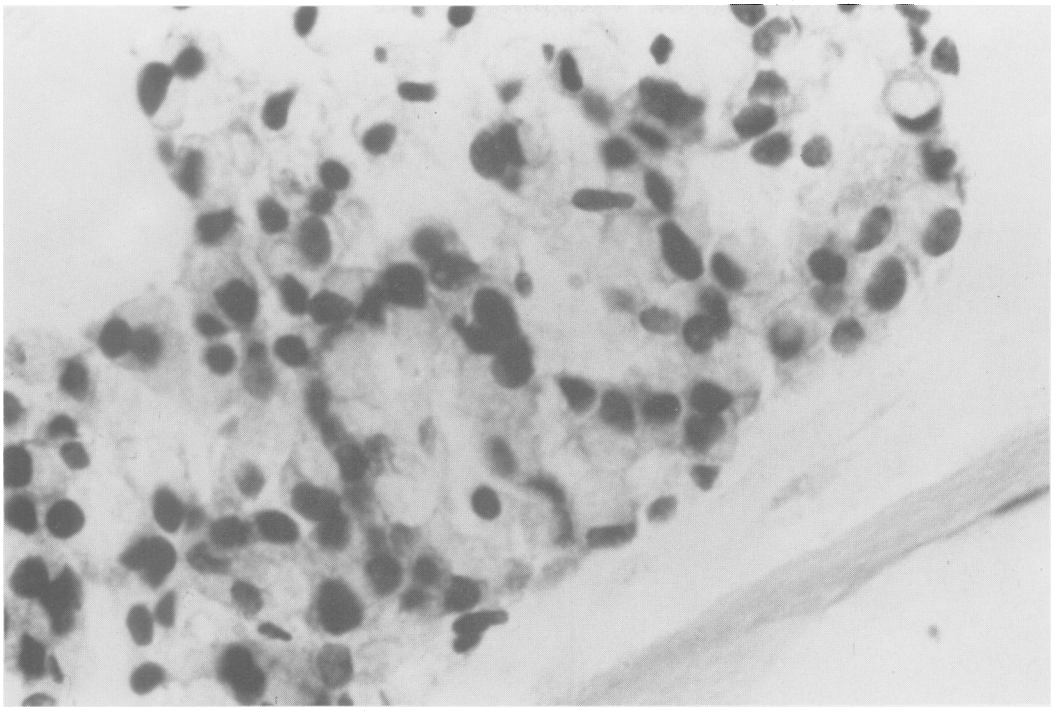

FIG. 8. The tumor consisted of clusters of signet-ring cells lying within pools of mucinous extracellular material. This histologic finding is somewhat less common in biliary adenocarcinomas. (Patient 4, hematoxylin and eosin stain, original magnification ×400.)

24 had carcinoma diagnosed at the initial operation, and carcinoma was discovered within 2 years after operation in 15 patients. Of the 41 patients in whom the malignancy was detected at reoperation or autopsy, 22 patients (54%) had undergone a primary operation of the biliary tract within 2 years previously without the carcinoma being found.

Predisposing factors that have been postulated in the development of carcinoma in these patients include infection, chronic inflammation with development of

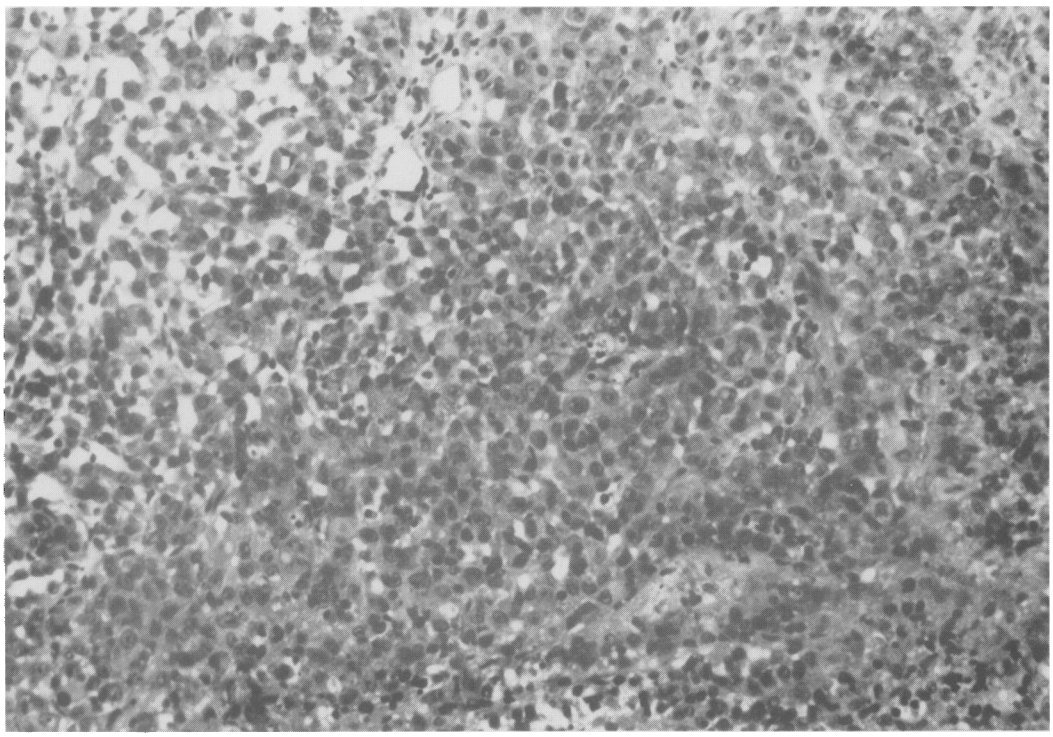

FIG. 9. This tumor showed minimal differentiation. On light microscopy, sheets of undifferentiated, monotonous tumor cells were seen without the presence of glandular arrangement or any suggestion of mucin production. A panel of immunohistochemical reagents confirmed the epithelial origin of the tumor, and the examination by electron microscopy showed abortive lumen formation suggestive of adenocarcinoma. (Patient 6, hematoxylin and eosin stain, original magnification ×100.)

metaplasia, and the carcinogenic effect of chronic exposure to bile and bile products with the development of mutagens in bile and calculi.[8,12,13] A high mutagenic activity has been found in stones extracted from patients with cystic conditions of the biliary tract,[13] which has not been present in gallstones of patients without cystic biliary disease. A possible explanation for this is that the metabolic activity of bacteria in the biliary tract may activate potential carcinogens previously detoxified by the liver. The reflux of pancreatic juice to the cyst could contribute to the chronic inflammatory changes of the biliary epithelium.[14-16]

The most common symptoms on presentation are pain, weight loss, jaundice, and fever. It is not uncommon for the diagnosis of carcinoma to be missed at the time of the primary procedure for a cystic condition of the bile duct.[11] Persistent or recurrent symptoms after operation for a bile duct cyst in the presence of a patent anastomosis should suggest the possibility of a carcinoma.

The prognosis of these lesions is dismal. Only 5% of patients survive 2 years after the diagnosis of carcinoma,[17] and most patients die within a few months. No evidence exists that surgery prolongs survival in these patients. Excision has been proposed[10,18] for benign cystic conditions of the bile ducts, both to achieve a lower recurrence rate of symptoms and cholangitis and also to prevent the development of carcinoma. In one report,[19] 74% of carcinomas in patients with a dilated common bile duct occurred in an extrahepatic cystic dilatation. Nonetheless, such a tumor may arise in any location of the biliary tract, and excision only decreases the likelihood of malignancy developing without fully protecting against it.[10] In patient 1 who had type IV disease, a metachronous tumor occurred at a proximal location in the biliary tract 3 years after excision of a choledochal cyst.

TABLE 1. *Pathologic Findings in 19 Specimens of Benign Choledochal Cysts*

	N
Mural fibrosis and inflammation	19
Simple columnar epithelium	17
Proliferative changes of epithelium*	7†
Mural ulceration	4
Goblet cell metaplasia	4

* Cellular crowding, poor orientation, nuclear changes associated with dysplasia, hyperchromatosis, irregularities of contour.
† Metachronous carcinomas developed in two patients.

Although 80% of carcinomas arise in patients with type I cysts, they have also been described in patients with conditions of types II, III, IV, and V.[9,10,20] The average age at presentation of patients with carcinoma arising in bile duct cysts is 34 years, and 70% of patients are women.

Our review of the specimens of 19 patients revealed proliferative changes of the epithelium in seven patients, and in two of these patients, a carcinoma later developed. Four of the cysts examined showed goblet cell metaplasia. Two patients with carcinoma had mucinous adenocarcinomas, which suggests the possibility that these carcinomas may have arisen from foci of focal goblet cell metaplasia.

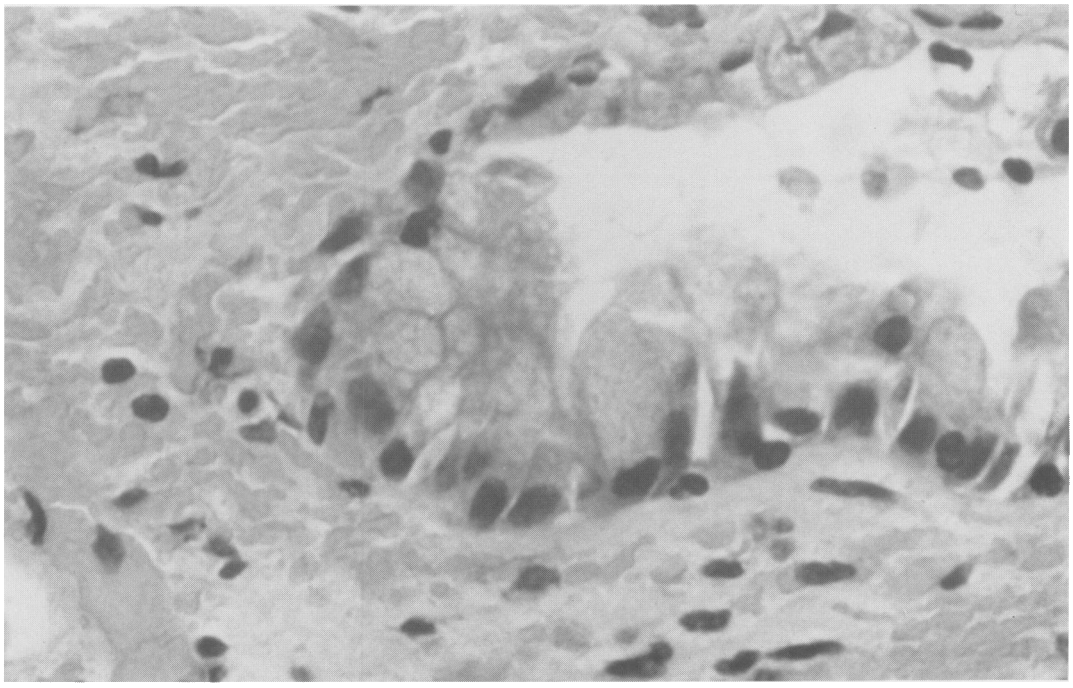

FIG. 10. The cyst lining in four patients showed the presence of goblet cell metaplasia. As the native lining of the biliary tract does not contain an abundance of this type of epithelium, it may represent the source of mucinous-type adenocarcinomas.

Conclusion

We present six cases of carcinoma, three synchronous lesions and three metachronous lesions, arising in cystic conditions of the biliary tract. The six patients represent 20% of all patients treated at Lahey Clinic for cystic conditions of the bile duct in the study period. We believe that excision of benign cystic conditions of the biliary tract when technically feasible achieves better long-term results with regard to cholangitis and jaundice and decreases the likelihood of carcinoma. However, this does not fully protect against development of carcinoma as this occurred in one of our patients. The histopathologic analysis of 19 specimens from patients with cystic conditions of the bile ducts during the 20-year study period showed proliferative changes of the epithelium in seven patients, and in two of these patients, a metachronous carcinoma developed.

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