

KASUISTIK

Congenital bile duct cyst: A premalignant lesion of the biliary tract associated with adenocarcinoma – a case report –

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Summary

The incidence of carcinoma arising in the wall of a congenital bile duct cyst is high and there is no doubt that these lesions represent a precancerous state of the biliary tract. In almost all cases congenital bile duct cysts are related to anomalous arrangements of the pancreaticobiliary duct system which seems to play a crucial role in the development of cystic bile ducts and biliary carcinogenesis. Bile stasis together with reflux of pancreatic juice causing longstanding inflammation and activation of bile acids might be the factors in carcinogenesis of the exposed bile duct epithelium in the cystic wall. In the case of primary or secondary extrahepatic bile duct cysts, primary excision is mandatory because of the high risk to develop biliary cancer with even nowadays poor prognosis despite advantages in biliary surgery during the last years. We report a case of a young woman in which bile duct cancer was found arising in the wall of a congenital bile duct cyst. Despite radical surgery the outcome was poor proving the high malignant potential of bile duct cancer. The question of possible tumor seeding in hepatobiliary surgery is discussed as a way of inducing hepatobiliary metastatic tumors.

Key words: Choledochal cyst – preneoplastic lesion – biliary carcinogenesis – biliary carcinoma – surgical therapy – tumor seeding

Zusammenfassung

(Kongenitale Gallengangszyste: eine prämaligne Läsion der Gallenwege assoziiert mit einem Adenokarzinom)

Die Karzinominzidenz bei kongenitaler zystischer Gallengangspathologie ist hoch, und es steht außer Zweifel, daß diese Pathologie der Gallenwege eine Präkanzerose darstellt. In den meisten Fällen von kongenitalen Gallengangszysten besteht gleichzeitig eine Anomalie der pankreatikobiliären Verbindungsstelle, die für die Zystenentstehung und Karzinogenese eine entscheidende Rolle zu spielen scheint. Lang anhaltende Cholestase sowie Reflux von Pankreassekret mit Aktivierung primärer Gallensäuren werden für die Karzinomentstehung verantwortlich gemacht. Somit besteht bei primär oder sekundär aufgetretenen Gallengangszysten die Indikation zur chirurgischen Exzision, um das Auftreten eines Gallengangkarzinomes mit auch heute noch schlechter Prognose zu verhindern. Wir stellen das Fallbeispiel einer solchen Karzinomentwicklung bei einer jungen Patientin vor, welche trotz radikaler chirurgischer Maßnahmen eine infauste Prognose zeigte. Ferner wird die Frage der Tumoraussaat durch den chirurgischen Eingriff diskutiert.

Schlüsselwörter: Bile duct cyst – biliary carcinogenesis – bile duct cancer

Introduction

Carcinoma of the intra- and extrahepatic biliary tract is a relatively rare disease. In most cases the etiology of these cancers is rather obscure. Depending on the location of the carcinoma there are some risk factors identified, including congenital cystic and dysplastic lesions of the biliary tract. Even if congenital cystic dilatation of the biliary ductal system is a rare abnormality, it is important to be recognized because of its high association with carcinoma arising in the choledochal cyst wall epithelium. For a long time the classical clinical triad of »pain, jaundice and abdominal mass« is not present in most patients, which often causes longterm delay

in diagnosis therefore leading to longstanding inflammation of the biliary epithelium and possible development of carcinoma in the cystic wall. Hence primary radical excision of choledochal cysts is mandatory to prevent development of biliary cancer which has a poor prognosis. We present the case of a biliary carcinoma arising in a choledochal cyst in a young woman with a poor outcome despite extensive radical surgery. Early development of peritoneal and subcutaneous abdominal wall metastases prove the high malignant potential of this lesion.

Case report

A 33-year-old female with an unevenful past history was admitted to our department with a recent history of nausea, vomiting and weight loss of 6 kg in the last month. A palpable abdominal mass in the right upper quadrant with little pain was found on physical examination. An infrahepatic cystic mass in continua-

tion of the hepatoduodenal ligament was demonstrated by abdominal ultrasonography. Intravenous cholangiotomography and abdominal computed tomography revealed a choledochal cyst of 5 x 5 x 5 cm in size (fig. 1 and 2). In accordance to the Todani classification (1) of congenital bile duct cysts the biliary cyst was classified as type 1 a. The lower part of the cystic dilatation showed wall irregularities suspicious for malignant epithelial transformation. Gastroduodenal endoscopy revealed a light compression of the duodenal bulb explaining the clinical symptomatology of nausea and vomiting. ERCP was not performed because there was no doubt about the indication for an operative treatment of this bile duct cyst with suspicion of malignancy. Laboratory blood tests are summarized in tab. 1. Only liver transaminases and bilirubin were slightly elevated indicating cholestasis caused by the bile duct cyst. The tumor marker CEA was at the upper normal limit.

Surgical abdominal exploration was performed and the gallbladder was found to be markedly distended. A large choledochal cyst measuring approximately 6 cm in diameter displacing the duodenum laterally and adhering to the gallbladder and the right side of the transverse colon was found. During exploration and palpation of the cyst, a tumor was found in the distal portion of the choledochal cyst measuring 2 x 2 cm in size causing light stenosis of the distal choledochus. Unfortunately a frozen section of biopsied material from the distal end of the choledochal cyst wall revealed adenocarcinoma. For radical tumor clearance in this young patient we performed an en-bloc partial pancreaticoduodenectomy with excision of the cyst together with the gallbladder and a right hemicolectomy because of the above mentioned suspicious adhesions. The final histological examination (fig. 3) confirmed a moderately differentiated adenocarcinoma of the cystic choledochal wall with invasion of the cystic duct, the papilla of Vater, the pancreatic capsule and the pericolic fatty tissue (stage pT3, pN1, pMO according to UICC) (2). Resection margins were free of tumor and the colon was not infiltrated. After histological examination we considered to have performed a RO-resection.

The postoperative course was uneventful for two months and the patient felt well and regained 2 kg of weight. Two months after the operation and shortly before the first scheduled postoperative follow-up, the patient observed an induration and redness around the right umbilical area. Two weeks later during her first postoperative clinical examination we found a tumor measuring 3 x 3 cm in diameter adherent to the fascia and located at the right of the navel in a site where there was no operative wound or postoperative drainage canal. Additional abdominal computed tomography confirmed a subcutaneous tumor in the abdominal wall suspicious for a metastasis of bile duct cancer (fig. 4). Three months after the first operation the patient underwent surgery again, and the paraumbilical parietal tumor and the adjacent abdominal wall were resected. Unfortunately laparotomy demonstrated diffuse peritoneal metastases in addition to the abdominal wall metastasis confirming a tumor grade 4 B (according to UICC) (2). The abdomen was closed without further intervention. A proposed palliative chemotherapy postoperatively was refused by the patient. She died nine months after the second operation.

Discussion

Bile duct cysts of congenital origin may be intrahepatic or extrahepatic. In the latter location usually solitary and called choled-

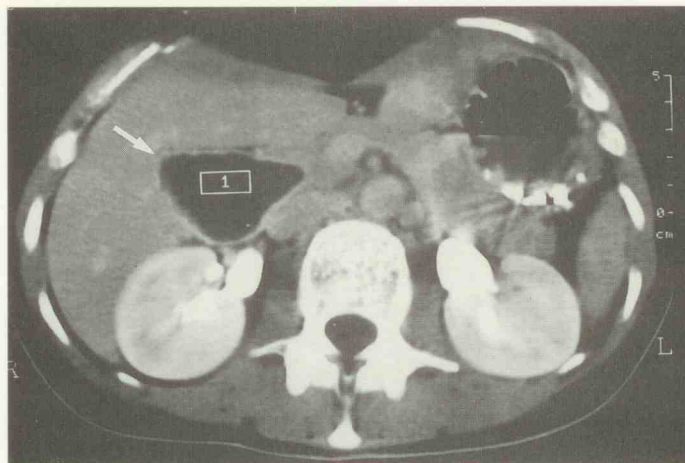


Fig 1: Abdominal computed tomography revealing a huge subhepatic cystic formation measuring 5 x 5 x 5 cm in size (arrow)

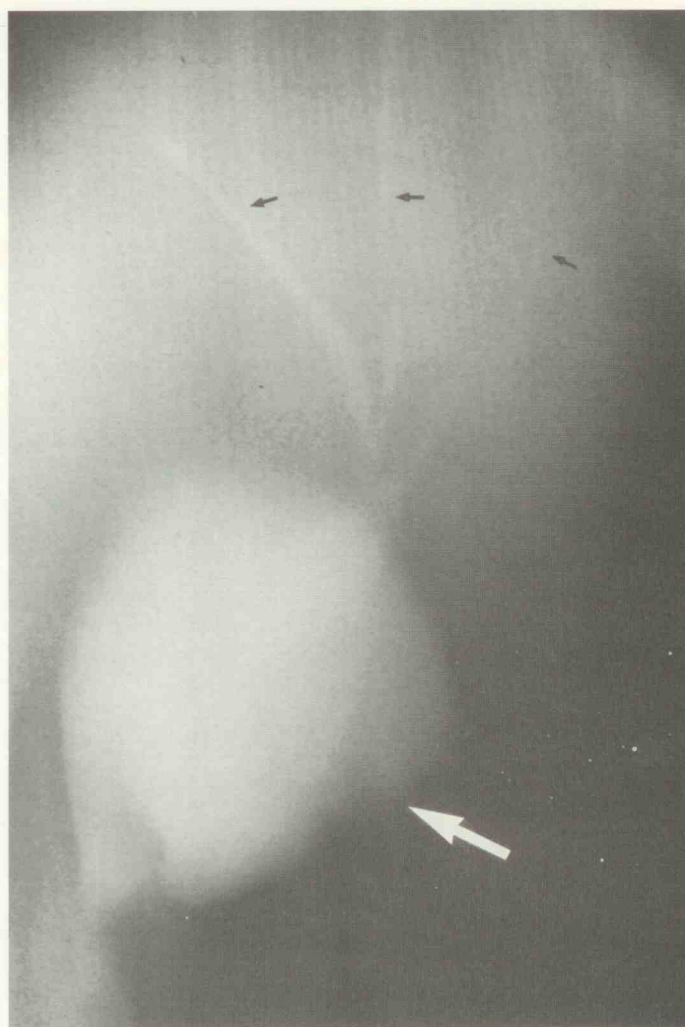


Fig 2: Intravenous cholangiotomography revealing a choledochal cyst type 1 a according to the Todani classification (1, 3) (white arrow). The intrahepatic bile ducts are not dilated (black arrows)

ochal cysts are found. In 1977 Todani et al. (1) reported 37 cases of congenital bile duct cysts and classified them into six different types. Like in our case over 80% of congenital choledochal cysts can be classified as type 1 according to the Todani classification (1, 3). As the cause of choledochal cysts, Babbitt

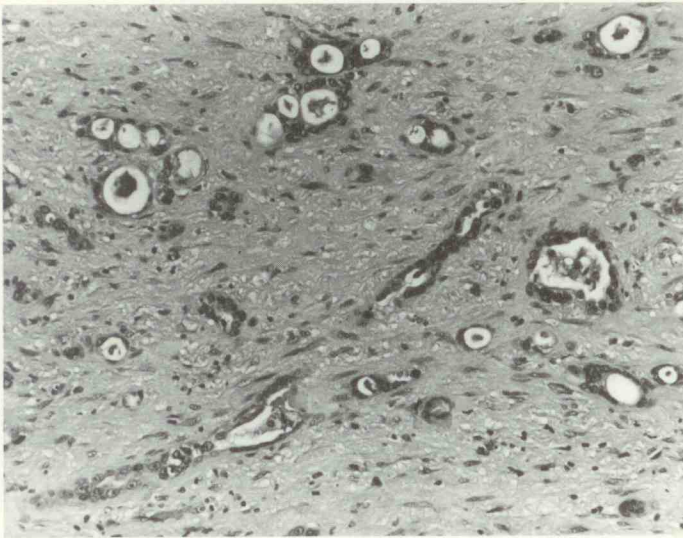


Fig. 3: Histological specimen examination confirming the diagnosis of a moderately differentiated adenocarcinoma with tubular, diffuse and dissociated growth as well as desmoplasia (biliary adenocarcinoma, pT3pN1pMO; x 175)

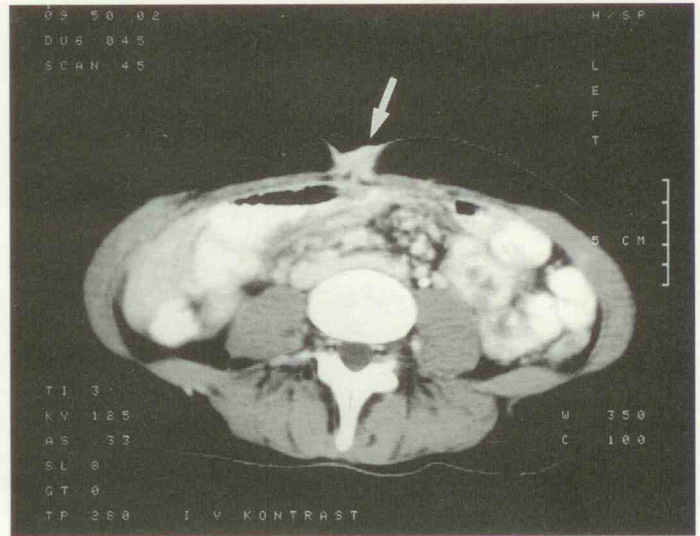


Fig. 4: Abdominal computed tomography ten weeks postoperatively proving a tumor in the abdominal wall located at the right of the navel suspicious for an extraperitoneal metastasis of the biliary adenocarcinoma (arrow)

(4) proposed an abnormal relationship between the common bile duct and the pancreatic duct precluding a sphincteric mechanism at the junction of the common bile and pancreatic duct, a structure present when normal development occurs. Several clinical observations revealed that there is a high association between anomalous arrangement of the pancreaticobiliary ducts and the development of choledochal cysts (4–7), except in patients with intrahepatic bile duct dilatations (Caroli's disease) or choledochoceles where a different etiology is proposed. The anomalous union results in a loss of normal sphincteric mechanism at the pancreaticobiliary junction, permitting reflux of pancreatic juice into the biliary system as indicated by high amylase levels which are found in over 20% of the aspirates from choledochal cysts (6–8).

Iwai et al. (7) and Kimura et al. (9) found an abnormal choledocho-pancreatico-ductal junction in 25 out of 26 and 17 out of 18 patients respectively with congenital choledochal dilatation which strongly supports *Babbitt's* theory. Since we did not perform ERCP in our patient it is unclear whether an anomalous arrangement of pancreaticobiliary ducts existed in our case. The incidence of coexistent bile duct carcinoma arising in choledochal cysts is reported to vary between 2.5% to 15% increasing with the patients age (3, 6, 10, 11). This cancer risk is considerably greater compared to the frequency of extrahepatic bile

duct carcinoma in patients without choledochal cysts which has been confirmed in several autopsy studies to range between 0.012 to 0.48% (12). Furthermore in choledochal cyst carcinoma the incidence is higher compared to the intrahepatic bile duct cysts (13). It was also found that gallbladder carcinoma occurred in 24.6% of cases of anomalous ductal junction in comparison with a 1.9% incidence among consecutive patients proving this fact once more as rather important in this subgroup of biliary tumorigenesis (14). Although there are many possible factors responsible for the carcinogenesis of choledochal cysts it is assumed that the longstanding inflammation of the biliary tract caused by the reflux of pancreatic juice with activation of bile acids and formation of mutagenic bile acids as lithocholic acid might be the important factor producing pathological epithelial changes leading to biliary carcinoma as the last fatal complication (5, 8, 15–17).

Like in our case the most common histological type of cancer is adenocarcinoma. However, squamos-cell carcinoma, anaplastic carcinoma or adenoacanthoma are rarely reported (1, 3, 12, 18). The female to male ratio is reported to be 2.5:1 (3, 12). Whether the higher gallstone incidence in females or some hormonal factors (estrogenes) are related to this ratio remains unclear. As in our case the average age at the time of carcinoma diagnosis in patients with choledochal cysts is 32 years with a range of 15 to 73 years (3, 13). Therefore this cancer subpopulation is several decades younger than the general biliary cancer population indicating that the incidence of carcinoma arising from bile duct cysts is much higher than that of biliary carcinoma without bile duct cysts. Unfortunately there is often a lack of clinical signs so that the diagnosis of congenital bile duct cysts is mostly delayed for years or even decades. If one sign of the »classical triad« of pain, jaundice or abdominal mass (sign of *Courvoisier*) appears in a patient with bile duct cysts the risk of a malignant transformation of the biliary epithelium seems to be elevated.

Diagnostic work-up should include abdominal ultrasonography, intravenous cholangiotomography or PTC, abdominal computed tomography and ERCP with cytological examination. Howev-

Tab. 1: Preoperative laboratory blood tests

Hemoglobin	13.1 g/dl	(12.1–15.4 g/dl)
Leucocytes	7.000/µl	(3.200–9.000/µl)
Thrombocytes	14.700/µl	(12.500–32.000/µl)
ASAT (GOT)*	73 U/l	(11–32 U/l)
ALAT (GPT)*	148 U/l	(9–36 U/l)
Gamma-GT*	79 U/l	(< 39 U/l)
Bilirubin*	24 µmol/l	(< 21 µmol/l)
Alc. Phosphatase	84 U/l	(36–108 U/l)
Amylase	139 U/l	(< 110 U/l)
CEA*	1.5 ng/ml	(- 1.5 ng/ml)

*not within normal range

er, like in our case the correct preoperative diagnosis of biliary cancer is often difficult to establish. Nowadays it is generally agreed on that even asymptomatic bile duct cysts should be treated to prevent complications like ascending cholangitis, formation of gallstones and cancer development as the last fatal complication (1, 3, 5, 13, 17). The extent of surgical treatment of congenital cystic dilatation of the biliary system must be based on the extent of the disease and intraoperative findings. Surgical strategy has changed in the early seventies condemning choledochocysto-duodenostomy and choledochocysto-jejunostomy with Roux-en-Y anastomosis which had been recommended before (19–21) because of the risk of cancer development in the cystic residue several years later (1). Therefore primary excision of the cyst is nowadays mandatory to prevent complications and tumorigenesis. If a cystic carcinoma is found intraoperatively en-bloc resection with partial duodenopancreatectomy and central liver resection if necessary should be performed to obtain a RO-resection which appears to be the only chance for cure. This treatment shows a 5-year survival rate of 10 to 30% with worst prognosis for the proximal bile duct cancer locations (*Klatskin-tumors*) (18).

However, even in cases where a RO-resection can be obtained prognosis is very poor because of the extremely high malignant potential of biliary carcinoma as unfortunately is shown by our case with severe, early peritoneal and extraperitoneal metastases in the abdominal wall after surgery. To our knowledge the appearance of a paraumbilical tumor metastasis in bile duct cancer far away from any incision or abdominal drainage site has not been previously described and it remains unclear, whether this metastatic process has been caused hematogenously via an open umbilical vein or per continuitatem from a near peritoneal metastasis. Nevertheless the influence of surgery itself for tumor seeding in the treatment of biliary cancer is still unknown and not investigated. It is known from other hepatobiliary tumors, notably gallbladder cancer and hepatocellular cancers, that they can be spread by operative treatment, fine needle puncture or laparoscopy (22–25). Therefore the frequency of carcinomatous seeding of gallbladder cancer after surgery into the anterior abdominal wall varies in the literature from 0.7% to 4% (26, 27).

Hamrick et al. (22) have described a distant metastasis to the umbilical region in treated gallbladder cancer. However there are no data about their frequency in bile duct cancer in the literature. Whereas peritoneal implants are frequent, metastases in the abdominal wall seem to occur very rarely. Interestingly only 7% of bile duct carcinomas show peritoneal metastases at operation time and only 6% have other distant organ metastases (18). This very low intraoperative metastatic incidence in combination with a fulminant tumor spreading often seen postoperatively like in our case indicates that surgery could play a crucial role in early tumor seeding in treated biliary cancer. To find an answer referring thereto, further experimental and clinical work should focus on this important question.

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