

## Cholangiocarcinoma arising in choledochal cysts: Case reports

Koledok kistlerinden kaynaklanan kolanjiokarsinom: Olgu sunumları

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Choledochal cysts are congenital dilations of the biliary ducts that may be associated with intermittent biliary obstruction. If the condition goes unrecognized and uncorrected, the impaired bile outflow can lead to chronic hepatic injury, fibrosis, and ultimately, biliary cirrhosis. Although typically diagnosed in the pediatric population, as many as 20-30% of choledochal cysts can be discovered in adulthood. There is a female predominance. Unresected choledochal cyst is clearly associated with increased risk of cholangiocarcinoma. Treatment includes surgical removal of the choledochal cyst and bilioenteric anastomosis. In this article, we report two cases of cholangiocarcinoma occurring in an unresected choledochal cyst.

**Key words:** Cholangiocarcinoma, choledochal cyst, jaundice

### INTRODUCTION

Choledochal cysts are congenital dilations of the biliary ducts, which can cause progressive biliary obstruction and biliary cirrhosis. Cylindrical and spherical cysts of the extrahepatic ducts are the most common types (1). Choledochal cysts are more prevalent in Asia than in Western countries, and approximately 33-50% of reported cases are from Japan. They occur more often in women, with a male to female ratio of 1:3 to 4 (2,3). Cholangitis, rupture, pancreatitis, and gallstones are important complications of choledochal cysts and may occur even in early infancy, whereas chronic cholecystitis and cholangiocarcinoma may be long-term complications if the cyst is not fully removed (4). The incidence of malignant transformation is reported to be 2.5–26%. The malignant change occurs mainly within the choledochal cyst, but may occur in the gallbladder, pancreatic duct, and intrahepatic bile ducts. Multiple malignant transformations are also reported (5).

### CASE REPORTS

**Case 1:** A 49-year-old female presented with a 10-day history of fever, and stomachache. No jaundice or weight loss was reported. The patient had suffered from asthma for the last 10 years. Her surgical history included total abdominal hysterectomy and bilateral oophorectomy performed five years ago. The family history reported the father as having lung cancer. Tenderness on the subcostal area was the only symptom

Koledok kistleri safra kanallarının doğuştan dilatasyonudur ve aralıklı safra tıkanıklığına neden olabilir. Erken tanı ve tedavi edilmediğinde safra akımının bozulmasına; kronik karaciğer hasarı, fibrozis ve sonuçta biliyer siroza neden olabilir. Genellikle pediatrik popülasyonda tanısı konulmasına rağmen, %20-30 oranında erişkin yaş grubunda tespit edilebilir. Kadınlarda daha sık görülmektedir. Rezeke edilmeyen koledok kistlerinde kolanjiyokarsinom riski artmıştır. Tedavi koledok kistinin çıkarılması ve bilioenterik anastomozu içerir. Bu makalede rezeke edilmemiş koledok kistine bağlı gelişen kolanjiyokarsinomlu iki olgu bildirildi.

**Anahtar kelimeler:** Kolanjiokarsinom, koledok kisti, sarılık

discovered in the physical examination. Abnormal blood test results on admission were aspartate aminotransferase (AST) 113 u/L, alanine aminotransferase (ALT) 672 u/L, gamma-glutamyl transpeptidase (GGT) 747 u/L, and alkaline phosphatase (ALP) 355 u/L (see Table 1 for extended test results). Abdominal ultrasonography (USG) showed choledochal cyst. Magnetic resonance cholangiopancreatography (MRCP) showed a 4x5 cm cyst towards the left and right bile ducts in the choledochus. A small polypoid lesion was present on the cystic wall (Figure 1). Endoscopic retrograde cholangio-

Table 1. Laboratory blood results for the cases

	Case 1	Case 2
WBC (4.8-10.8 mm <sup>3</sup> /μL)	10,94	10,21
Hb (12-16g/dL)	14,2	14,9
Plt (130000-400000mm <sup>3</sup> /μL)	211000	189000
AST (0-40 u/L)	133	17
ALT (0-55 u/L)	672	13
GGT (9-36 u/L)	747	17
ALP (40-150 u/L)	355	67
D.Bilirubin (0.2-1.2 mg/dL)	1,1	1,3
Ind. Bilirubin (0-0.5 mg/dL)	0,7	0,4
CEA (<4.7 ng/mL)	0,66	2,09
CA19 9 (0.6-27 U/mL)	15,1	111,04
AFP (0.5-7 IU/mL)	1,46	3
Amilase (25-140 u/L)	38	56
Lipase (8-78 u/L)	25	20

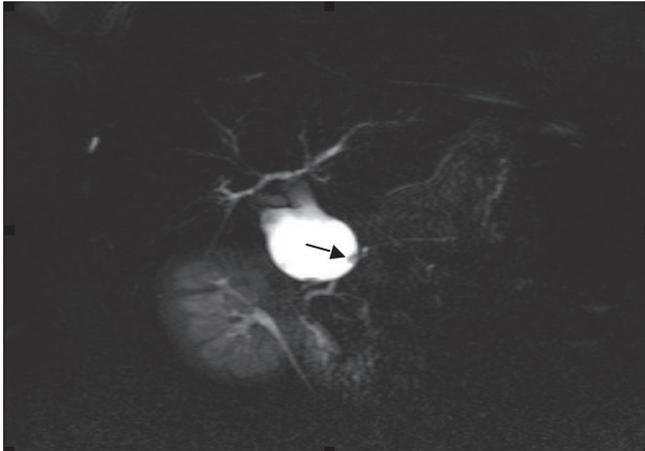


Figure 1. MRCP showing an adjacent mass within the cyst (arrow)

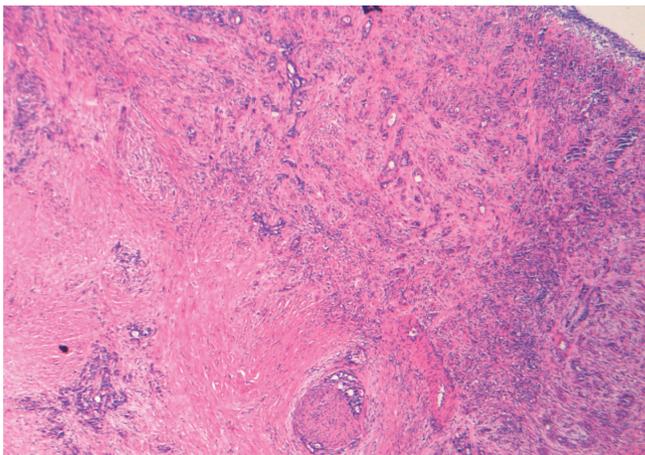


Figure 2. The cyst wall is seen in tumor invasion and perineural lymphatic invasion (hematoxylin-eosin, x 40)

pancreatography (ERCP) demonstrated a cystic dilatation of 4 cm in diameter at the distal choledochus. The cystic fusiform dilatation extended to the proximal choledochus. Possibly due to the polypoid mass, a filling defect of approximately 1 cm was also observed. On the basis of these findings, the diagnosis of type 1 choledochal cyst and probable presence of intracystic cholangiocarcinoma was made. For the treatment, cholecystectomy, choledochus excision and choledochoenterostomy procedures were applied.

On pathological evaluation, the cyst measured 4x5x2 cm. Within the cyst, a lesion covering an area from the cyst wall to the lumen, measuring 1.3x1.2 cm, was observed. Microscopy of this lesion revealed papillary structures lining the fibrovascular core as well as tumoral texture particles consisting of adenoidal structures, compatible with adenocarcinoma. One nodal involvement was indentified in a total of eight resected lymph nodes in addition to the presence of perineural invasion (Figure 2).

Postoperatively, her earlier complaints decreased and liver function test results were within normal range. The patient was referred to the oncology department and diagnosed with Phase III-C cancer. Twenty-eight sessions of chemotherapy were performed, followed by eight sessions of gemcitabine + FUFA treatment. The follow-up survey detected metastasis on the lumbar vertebrae. Radiotherapy was applied to this area. One year after the operation, the patient was diagnosed with ileus, and explorative laparotomy was performed. Eventually, the patient was accepted as inoperable due to widespread acid and peritonitis carcinomatosa.

**Case 2:** A 49-year-old male patient presented with stomach-ache and weight loss. No fever or jaundice was observed, and the patient history was unremarkable apart from heavy smoking for 30 years. Family history indicated that his father had chronic bronchitis. The physical examination revealed upper right quadrant pain. The abnormal blood test results on admission were CA19-9 111.04 U/mL, with bilirubin value just above normal range (see Table 1 for extended test results). Abdominal USG was performed, and the results indicated a distinctive dilation of the choledochus and the presence of a 13 mm gallstone. MRCP verified fusiform dilation of the choledochus channel and the gallstone. In addition, a hypointense mass surrounding the location was discovered on the distal choledochus (Figure 3).

ERCP also confirmed the findings, and revealed the presence of a possible stone with 10x8 mm mobile opacity (Figure 4).

A protruded polypoid lesion was detected in the ampulla, and a biopsy sample was extracted. The pathological examination was non-diagnostic. Eventually, a diagnosis of type 1 choledochal cyst and probable presence of intracystic cholangiocarcinoma was made. The patient was operated. Cholecystectomy and Roux-en-Y choledochojejunostomy were performed. On the pathological sections of the choledochal cyst, tumoral tissue was observed. The tumor consisted gen-

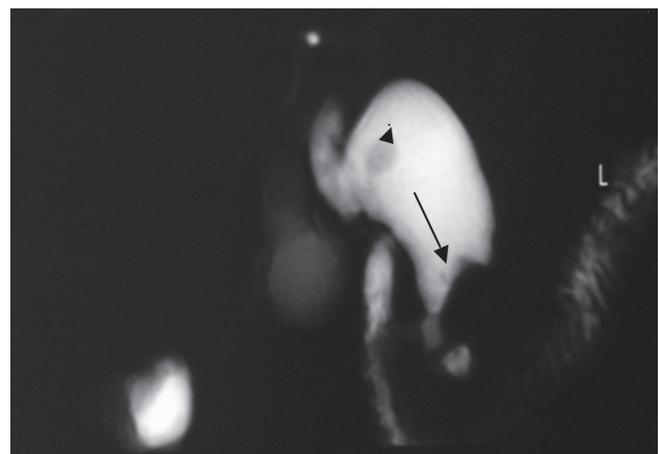


Figure 3. MRCP showing an adjacent mass within the cyst (arrow) and a calculus in the cyst (arrow head).

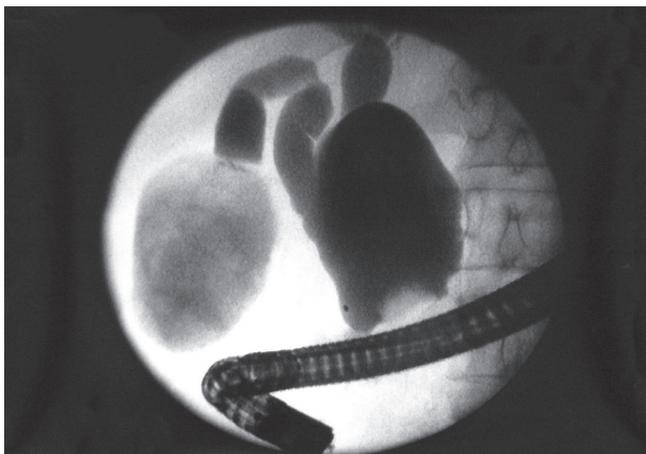


Figure 4. ERCP showing an adjacent mass within the cyst wall.

erally of adenoid structures as well as occasionally separate, malignant in character, atypical signet ring cells. The patient was referred to the oncology department and died three years later.

## DISCUSSION

Choledochal cysts are considered to be rare biliary tract disorders with a high mortality rate due to their late diagnosis. They are defined as congenital anomalies of the biliary tract, characterized by varying degree of cystic dilatation in various segments of the biliary tract, with extrahepatic or intrahepatic divisions (6). Our cases are among the rare examples of choledochal cysts with cholangiocarcinoma resulting in the deaths of the patients due to the late symptoms and treatment, which confirm the findings of the earlier literature. This report intends to document these examples and highlight the importance of early diagnosis and treatment.

Regarding the frequency of choledochal cysts, the disease is observed in about 1 in 15,000 live births in Western countries, while the ratio is as high as 1 in 1000 live births in Japan (7). Unfortunately, the ratio of the disease is not extensively reported in Turkey. These two cases in our hospital were seen between 2006 and 2012. The literature indicates that the disease is typically more common among women, but there has been an increase recently in the number of male patients. Our study included one male and one female.

Extrahepatic bile duct cysts were first classified by Alenso-Lej et al. in 1959, and revised by Todani et al., who described a system of classification of these cysts into five discrete types (Table 2). The most common are types I and IVA, whereas types II and V are generally rare (8,9). The more common type I and type IVA cysts are associated with an abnormal pancreaticobiliary duct junction, and a long common channel, as well as mixing of pancreatic and biliary juice, leading to mucosal breakdown and dilatation. Type I cysts relate to

an abnormal arrangement of the pancreatobiliary ducts, also known as “common channel,” which is seen in up to 92% of the patients with choledochal cysts. This can present in childhood with high grade reflux or later in adulthood with low grade reflux (10-12). Our cases both belong to type I.

Choledochal cysts can be present at any age, and both the pediatric and adult populations presented most commonly with abdominal pain, nausea, vomiting, and jaundice (13). The type of symptoms depends largely on the age at presentation. Abdominal pain has been reported to be the most frequent symptom at presentation and is the main symptom in adults, whereas jaundice is reportedly the main presenting symptom in infants (14).

It should be noted that both of the patients in this study were diagnosed with cholangiocarcinoma after their admission to the hospital with complaints of abdominal pain and weight loss, yet neither of them showed previous symptoms like abdominal pain or jaundice that would indicate choledochal cysts.

Once a preliminary diagnosis is made using ultrasound (US) scanning, other supportive studies may be ordered, including abdominal computed tomography (CT) scans, magnetic resonance imaging (MRI) studies, or MRCP examinations. US has been the imaging modality of choice in children, whereas ERCP was used most commonly in adults. Percutaneous liver biopsy is contraindicated because of the risks of biliary injury and peritonitis (11,15,16).

Treatment of choledochal cysts is complete surgical excision of the cyst mucosa, with a Roux-en-Y choledochojejunostomy proximal to the most distal lesion (17). Each of these drainage techniques retained the wall of the cyst with its abnormal mucosa. Poor drainage leading to stasis and persistent cyst inflammation resulted in stricture formation, biliary lithiasis, and an increased risk of malignant evolution within the cyst wall (18).

Clinically, the common complications of congenital choledochal cyst were recurrent cholangitis, recurrent pancreatitis, rupture, stone formation, and malignant transformation (19,20). Of these, the most serious complication is malignant transformation. Both cases indicated no complication or clinical complaints before the development of the cholangiocar-

Table 2. Classification of biliary tree cysts

Type I: Cystic dilatation of the common bile duct
Type II: True diverticulum of the extrahepatic bile duct
Type III: Choledochoceles (cystic degeneration limited to the intraduodenal portion of the distal common bile duct)
Type IV: Multiple extrahepatic biliary cysts. Type IVA (associated intrahepatic cysts) and type IVB (extrahepatic cysts only)
Type V: Caroli's disease. Cysts of intrahepatic biliary tree, extrahepatic biliary system normal.

cinoma related to choledochal cysts. Although the disease is typically observed in the 5th-7th decades, cases in this study were in their forties. For cholangiocarcinoma patients diagnosed at an early age, primarily ulcerative colitis, and later primary sclerosing cholangitis, parasitic diseases and choledochal cysts should be considered. In both cases, type I choledochal cysts were detected as a risk factor.

Therefore, any patient with a history of a choledochal cyst is a candidate for life-long follow-up. The incidence of malignant transformation is reported as 2.5–26% (21). Cholangiocarcinoma is the second most common primary hepatic malignancy after hepatocellular cancer. Cholangiocarcinoma accounts for approximately 10-25% of all hepatobiliary malignancies. The risk of cholangiocarcinoma increases with age. The malignant change occurs mainly within the choledochal cyst, but may occur in the gallbladder, pancreatic duct, or intrahepatic bile ducts (22). The risk of cholangiocarcinoma remains high when an internal drainage procedure has been performed and the cyst has been partially resected or left unresected (15). Nodular wall thickening and/or an enhancing mass in a choledochal cyst are highly suspicious of malignant change (23,24). In these high-risk patients, fluorodeoxyglucose positron emission tomography/CT (FDG PET/CT) may detect early tumors and reveal unsuspected distant metastases, and thus impact management (25). The typical malignancy is adenocarcinoma of the bile duct or gallbladder, and less commonly squamous cell carcinoma (26-28). Results of the pathological examinations in our cases reported adenocarcinoma on choledochal cysts.

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Cholangiocarcinoma is classified in accordance with the location of the primary lesion, as intrahepatic, hilar, and distal (29). Surgery and radiation therapy are the two most common treatments for cholangiocarcinoma. Palliative resections and aggressive surgical approach in the presence of regional positive lymph nodes have a relevant beneficial impact on the outcome of patients with distal and hilar cholangiocarcinoma. Cholecystectomy and Roux-en-Y choledochojejunostomy and non-surgical stenting are the first choices of palliative biliary drainage for patients with hilar cholangiocarcinoma, and for those with distal cholangiocarcinoma and short life expectancy. In both our cases with lymph invasion, cholecystectomy and Roux-en-Y choledochojejunostomy were applied. The patients were scheduled for chemoradiotherapy later. The prognosis for patients with cholangiocarcinoma arising in choledochal cysts is as grim as that for cholangiocarcinoma in general, with a median survival reported in the range of 6-21 months (30). Our patients in this study died one and three years, respectively, after the diagnosis.

In conclusion, choledochal cysts are rare cystic transformations of the biliary tree. The morbidities associated with choledochal cysts depend on the age of the patient at the time of presentation. Children may develop pancreatitis and cholangitis, whereas adults may develop severe complications, such as cholangiocarcinoma, cirrhosis, and portal hypertension. Early diagnosis and treatment of the disease in such cases would prevent cholangiocarcinoma and reduce the high mortality rate.

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