The Korean Journal of Pathology
2006; 40: 461-5

Undifferentiated Carcinoma Arising in a Choledochal Cyst
- A Case Report -

**Hee Eun Lee · Chang Lim Hyun
You Jeong Lee · Hye Sil Seol
Ja June Jang**

Department of Pathology, Seoul National University College of Medicine, Seoul, Korea

Received : August 8, 2006
Accepted : September 26, 2006

Corresponding Author
Ja June Jang, M.D.
Department of Pathology, Seoul National University College of Medicine, 28 Yongon-dong, Jongno-gu, Seoul 110-799, Korea
Tel: 02-740-8271
Fax: 02-3673-5046
E-mail: tripj@snu.ac.kr

An association between choledochal cyst and carcinoma is well established. Here, we report an extremely rare case of undifferentiated carcinoma exhibiting extensive sarcomatous features arising in a choledochal cyst. The patient in our case had a radiologically confirmed choledochal cyst and anomalous pancreaticobiliary ductal union, and mild wall thickening in the cyst was observed on endoscopic retrograde cholangiopancreatography. The patient underwent common bile duct excision and cholecystectomy. In the choledochal cyst, a nodule measuring 1.5 × 1 cm was detected. The lesion was composed of atypical, spindle-shaped and large, round pleomorphic tumor cells simulating sarcoma. Neither glandular nor squamous differentiation was observed. These cells were immunoreactive for both vimentin and cytokeratin by immunohistochemistry. These histologic and immunohistochemical findings were consistent with undifferentiated carcinoma, spindle and giant cell type, according to the WHO classification.

Key Words : Choledochal cyst; Common bile duct; Carcinoma; Neoplasm

Choledochal cyst is a congenital cystic dilatation of the bile duct. It is a rare entity in Western countries, and most of the reported cases in the world come from Asia. It is well known that choledochal cysts are associated with the occurrence of malignancy. Tumors may develop anywhere within the biliary tree, but more than one-half occur within the cyst itself.[1] Here, we report an extremely rare case of undifferentiated carcinoma arising in a choledochal cyst, in which the majority of the tumor exhibited sarcomatous features.

CASE REPORT

A 70-year-old woman was admitted to the Seoul National University Hospital, presenting with intermittent epigastric pain that occurred during the prior eight years. According to past medical history, she was healthy with no hepatic or biliary disease. No abdominal mass or hepatomegaly was detected on physical examination.

Laboratory tests of peripheral blood revealed normal levels of serum aspartate aminotransferase, alanine aminotranferase, alkaline phosphatase, total bilirubin, and amylase. The white blood cell count ($10.33 \times 10^3/\mu L$) and level of C-reactive protein (3.37 mg/dL) were elevated. Abdominal computed tomography and endoscopic retrograde cholangiopancreatography demonstrated the fusiform dilatation of intra- and extrahepatic bile ducts, and these findings were consistent with the presence of a choledochal cyst, type IVa of the Todani classification.[2] The filling defect of irregular shape was observed in a dilated common bile duct (CBD) (Fig. 1). In addition, anomalous pancreaticobiliary ductal union (APBDU), type C1 of the Komi classification,[3] and gallbladder distention with wall thickening were found. The patient underwent CBD excision and cholecystectomy.

On gross examination, the CBD was found to be fusiformly dilated. The maximal diameter of the cyst was 7.5 cm, and a small, ill-defined nodule measuring 1.5 × 1 cm was observed on the mucosal surface of the cyst (Fig. 2). The nodule had surface erosion, and its cut surface was nodular and homogenously gray-white in color. Microscopically, most of the tumor cells were composed of atypical, spindle-shaped and pleomorphic cells (Fig. 3A-C). The former cells proliferated in a whirled or interlacing pattern simulating a sarcoma, and the latter cells were polygonal

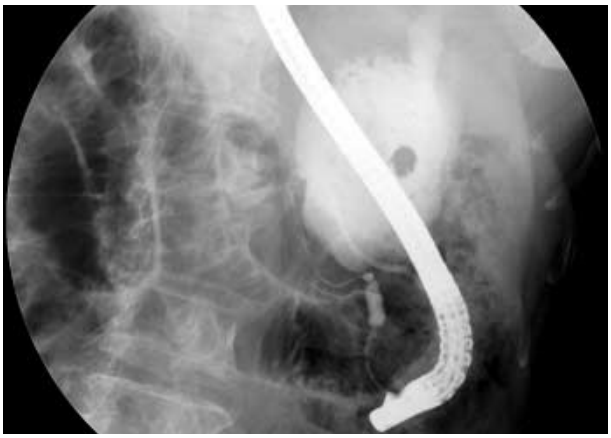

Fig. 1. Endoscopic retrograde cholangiopancreatography demonstrates the fusiform dilatation of common bile duct with irregular filling defect in its wall.

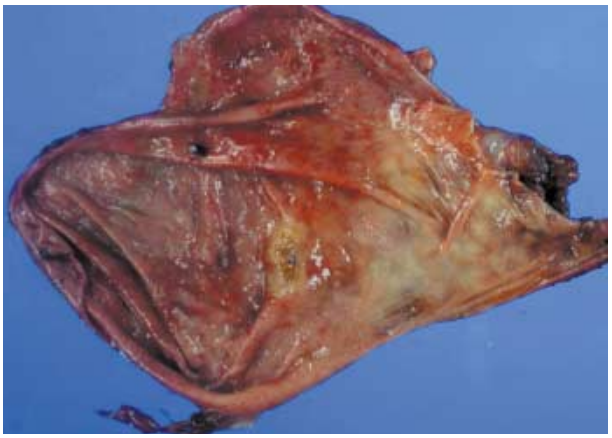

Fig. 2. Common bile duct is fusiformly dilated. An ill-defined small nodule, measuring 1.5 × 1 cm is present on the mucosal surface of the cyst. The surface of nodule is eroded erosion, and its cut surface is nodular and homogenously gray white.

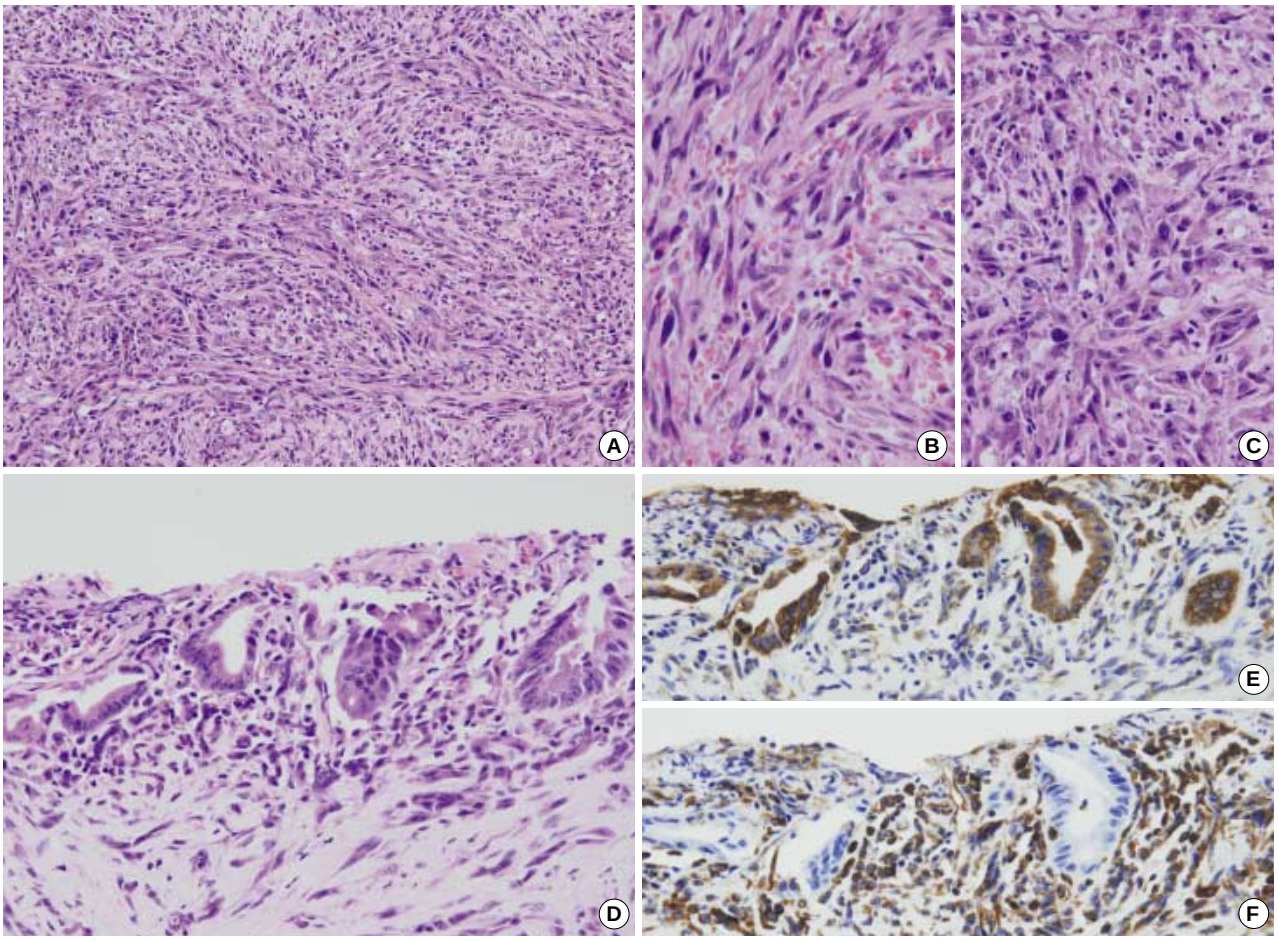

Fig. 3. (A&B) Atypical spindle, Tumor cells are proliferated in a whirled or interlacing pattern simulating a sarcoma. (C) Large round pleomorphic cells are occasionally admixed with mono- and multinucleated giant cells. (D) There is high grade dysplasia of the surface epithelium at the periphery of the eroded surface in small foci. (E&F) Immunohistochemistry for cytokeratin (E) and vimentin (F): Dysplastic epithelia in background of the undifferentiated carcinoma cells are focally immunoreactive for cytokeratin and diffusely immunoreactive for vimentin.

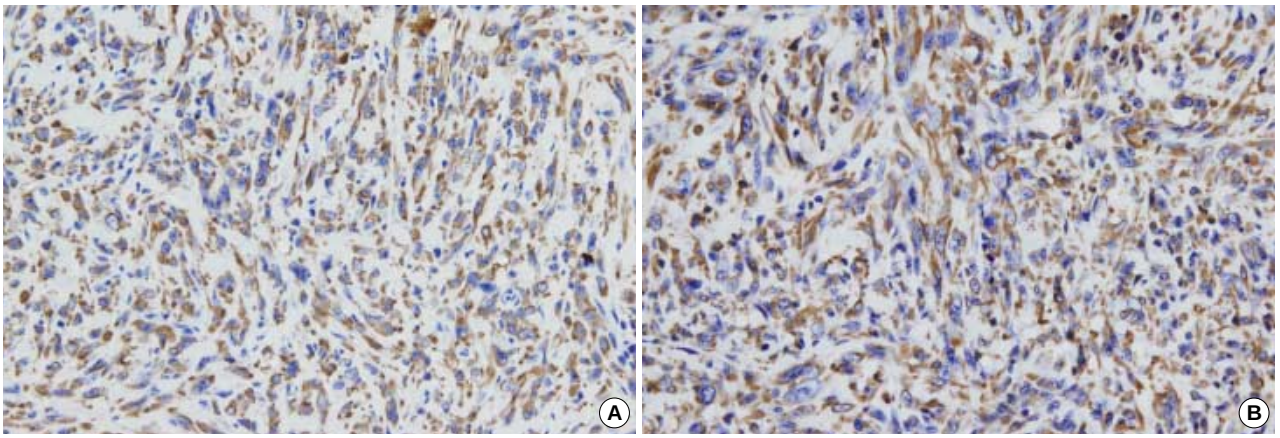

Fig. 4. (A&B) Tumor cells are immunoreactive for cytokeratin 7 (A) and vimentin (B).

or round, and had relatively abundant eosinophilic cytoplasm, large and pleomorphic nuclei, and prominent nucleoli. Some atypical mono- and multinucleated giant cells without osteoclast-like features were observed. Neither glandular nor squamous differentiation of tumor cells was found, but there high grade dysplasia of the surface epithelium at the periphery of the eroded surface was observed in small foci (Fig. 3D-F). Tumor cells were frequently admixed with inflammatory cells and occasionally pooled on myxoid stroma. The mitotic count was 20 per ten high power fields, and focal necrosis was observed. No heterologous component such as a cartilaginous, osseous, or rhabdomyosarcomatous component was found. Tumor cells invaded perifibromuscular connective tissue. Mucosal epithelia of a noncancerous region of the cyst showed multifocal dysplasia of low to high grade. On microscopic examination of the gallbladder, chronic cholecystitis was observed with no gallstone, polyp, dysplasia, or tumor. Immunohistochemical study revealed that the tumor cells were focally immunoreactive for cytokeratin and epithelial membrane antigen, and were diffusely immunoreactive for cytokeratin 7 (Fig. 4A) and vimentin (Fig. 4B). Additionally, the tumor cells showed overexpression of p53 protein and negative immunoreactivity against carcinoembryonic antigen. The Ki-67 labeling index was higher than 80%. According to the above findings, a diagnosis of undifferentiated carcinoma was made.

During a follow-up period of 28 months, the patient remained well with no sign of tumor recurrence.

DISCUSSION

We have described a case of undifferentiated carcinoma arising in a choledochal cyst associated with APBDU. Undifferentiated carcinoma is extremely rare in the biliary tract. According to Albores-Saavedra *et al*.,[4] the incidence of undifferentiated carcinoma is 0.38% (five out of 1,330 cases) of all extrahepatic bile duct cancers. In a study of 196 primary carcinomas associated with choledochal cysts including bile duct, gallbladder, liver, and pancreas cancers in Japanese patients, Todani *et al*.[5] reported that 6.6% were undifferentiated carcinoma. However, no description of the sites or histologic features of those cases was provided in the literature. Additionally, other previous reports documented two cases of undifferentiated carcinoma arising in choledochal cysts, but their histologic features were not described.[6,7] In 1994, Akitaka *et al*.[8] reported a case of adenocarcinoma exhibiting extensive sarcomatous features arising in a choledochal cyst, which corresponded to undifferentiated carcinoma using the World Health Organization (WHO) classification. The case showed similar histologic features to those of our case, and the report was the first to thoroughly describe the clinical and histologic features of undifferentiated carcinoma arising in a choledochal cyst.

According to the WHO classification of tumors of the gallbladder and extrahepatic bile ducts,[9] there are four histologic variants of undifferentiated carcinoma, including spindle and giant cell type, osteoclast-like giant cell type, small cell type, and nodular or lobular type. In our case, the lesion was composed of atypical, spindle-shaped and large, round pleomorphic tumor cells simulating sarcoma, but these cells were immunoreactive for both vimentin and cytokeratin on immunohistochemistry. These histologic and immunohistochemical findings were consistent with undifferentiated carcinoma, spindle and giant cell type, according to the WHO classification.

The prognosis of patients with undifferentiated carcinoma of the gallbladder and intrahepatic bile ducts has been reported to

be poor.[10,11] The outcome of patients with undifferentiated carcinoma of extrahepatic bile ducts with or without choledochal cysts cannot be estimated because of the limited number of cases. In our case, a favorable prognosis is expected because of the small size of the tumor and the lack of invasion to lymphovascular structures or to other organs.

The association between choledochal cyst and carcinoma is well established. In a large-scale study reported in 1985, the risk of malignancy associated with choledochal cyst is 17.5% in Japan.[5] Other reports documented that 2.5-15% of patients with choledochal cysts developed carcinoma in the biliary tract.[4,12] In addition, after the earlier report by Babbit *et al.*[13] about three cases of APBDU with choledochal cysts, a number of studies documented that APBDU was frequently associated with choledochal cyst.[12] In particular, Yamauchi *et al*.[14] reported that 18 out of 24 patients (75%) with APBDU had an associated choledochal cyst. APBDU was defined as a congenital anomaly in which a junction of the pancreatic and bile ducts was detected radiologically and/or anatomically outside the duodenal wall.[12] Recently, it has been documented that APBDU was associated with cancer of the biliary tract. Moreover, it is well documented that malignancy occurs at a higher frequency in choledochal cysts with APBDU than in cysts without APBDU, and several studies have suggested that APBDU may be a more important contributing factor than the choledochal cyst itself. In one report, cancer developed in nine out of 44 cases (20%) of choledochal cyst, and all nine cases had APBDU.[15] Yoshida *et al*.[16] reported that eight out of 35 cases of choledochal cyst developed cholangiocarcinoma, and all eight cases had APBDU.

The mechanism of carcinogenesis in APBDU is thought to be related to reciprocal reflux of pancreatic juice and bile into the biliary tract. Kato *et al*.[17] reported that the mixing of pancreatic juice and bile resulted in the production of various harmful substances, including activated pancreatic enzymes such as trypsin and elastase 1, as well as phospholipase A2, lysolecithin, and some mutagens in the biliary tract, of which mutagens, in particular, were thought to be involved in the development of biliary tract cancer. In addition, it has been demonstrated that epithelia of the gallbladder and bile duct in APBDU frequently show metaplasia or hyperplasia, and sometimes dysplasia, some cases of which progress to carcinoma[17-19] Therefore, it is believed that the risk of malignancy in APBDU-associated choledochal cysts is increased in both the gallbladder and the dilated bile duct, where bile juice containing pancreatic juice accumulates.

Recently, multiple genetic alterations have been demonstrated to be involved in the development of carcinoma associated with APBDU. Among them, the K-*ras* and *p53* gene mutations and the loss of heterozygosity of *p53* are all considered to play an important role in carcinogenesis.[17,19] Indeed, overexpression of p53 protein was identified in our case on immunohistochemistry.

REFERENCES

1. Flanigan DP. Biliary carcinoma associated with biliary cysts. Cancer 1977; 40: 880-3.
2. Todani T, Watanabe Y, Narusue M, Tabuchi K, Okajima K. Congenital bile duct cysts: Classification, operative procedures, and review of thirty-seven cases including cancer arising from choledochal cyst. Am J Surg 1977; 134: 263-9.
3. Komi N, Udaka H, Ikeda N, Kashiwagi Y. Congenital dilatation of the biliary tract: new classification and study with particular reference to anomalous arrangement of the pancreaticobiliary ducts. Gastroenterol Jpn 1977; 12: 293-304.
4. Albores-Saavedra J, Henson DE, Klimstra DS. Tumors of the gallbladder, extrahepatic bile Ducts, and ampulla of Vater, atlas of tumor pathology. Washington, DC: Armed Forces Institute of Pathology, 1998; 195.
5. Todani T, Watanabe Y, Toki A, Urushihara N. Carcinoma related to choledochal cysts with internal drainage operations. Surg Gynecol Obstet 1987; 164: 61-4.
6. Kagawa Y, Kashihara S, Kuramoto S, Maetani S. Carcinoma arising in a congenitally dilated biliary tract. Report of a case and review of the literature. Gastroenterology 1978; 74: 1286-94.
7. Todani T, Tabuchi K, Watanabe Y, Kobayashi T. Carcinoma arising in the wall of congenital bile duct cysts. Cancer 1979; 44: 1134-41.
8. Nonomura A, Mizukami Y, Matsubara F, Ueda H. A case of choledochal cyst associated with adenocarcinoma exhibiting sarcomatous features. J Gastroenterol 1994; 29: 669-75.
9. Hamilton SR, Aaltonen LA. World health organization of tumours, pathology & genetics, Tumours of the digestive system. Lyon: IARC Press, 2000; 209.
10. Guo KJ, Yamaguchi K, Enjoji M. Undifferentiated carcinoma of the gallbladder. A clinicopathologic, histochemical, and immunohistochemical study of 21 patients with a poor prognosis. Cancer 1988; 61: 1872-9.
11. Nakajima T, Tajima Y, Sugano I, Nagao K, Kondo Y, Wada K. Intrahepatic cholangiocarcinoma with sarcomatous change. Clinicopathologic and immunohistochemical evaluation of seven cases. Cancer 1993; 72: 1872-7.
12. Matsumoto Y, Fujii H, Itakura J, Matsuda M, Nobukawa B, Suda K.

Recent advances in pancreaticobiliary maljunction. J Hepatobiliary Pancreat Surg 2002; 9: 45-54.
13. Babbitt DP. Congenital choledochal cysts: new etiological concept based on anomalous relationships of the common bile duct and pancreatic bulb. Ann Radiol (Paris) 1969; 12: 231-40.
14. Yamauchi S, Koga A, Matsumoto S, Tanaka M, Nakayama F. Anomalous junction of pancreaticobiliary duct without congenital choledochal cyst: a possible risk factor for gallbladder cancer. Am J Gastroenterol 1987; 82: 20-4.
15. Song HK, Kim MH, Myung SJ, *et al*. Choledochal cyst associated the with anomalous union of pancreaticobiliary duct (AUPBD) has a more grave clinical course than choledochal cyst alone. Korean J Intern Med 1999; 14: 1-8.
16. Yoshida H, Itai Y, Minami M, Kokubo T, Ohtomo K, Kuroda A. Biliary malignancies occurring in choledochal cysts. Radiology 1989; 173: 389-92.
17. Matsumoto Y, Fujii H, Itakura J, *et al*. Pancreaticobiliary maljunction: pathophysiological and clinical aspects and the impact on biliary carcinogenesis. Langenbecks Arch Surg 2003; 388: 122-31.
18. Jung YS, Lee KJ, Kim H, *et al*. Risk factor for extrahepatic bile duct cancer in patients with anomalous pancreaticobiliary ductal union. Hepatogastroenterology 2004; 51: 946-9.
19. Matsubara T, Sakurai Y, Sasayama Y, *et al*. K-ras point mutations in cancerous and noncancerous biliary epithelium in patients with pancreaticobiliary maljunction. Cancer 1996; 77 (Suppl 8): 1752-7.