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

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 x 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. 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 aminotransferase, alkaline phosphatase, total bilirubin, and amylase. The white blood cell count (10.33 x 10^3/μL) 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. 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, 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 x 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.
Undifferentiated Carcinoma Arising in a Choledochal Cyst

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 non-cancerous 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., 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. 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. In 1994, Akitaka et al. 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, 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.\cite{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.\cite{5} Other reports documented that 2.5-15% of patients with choledochal cysts developed carcinoma in the biliary tract.\cite{12,13} In addition, after the earlier report by Babbit et al.\cite{14} about three cases of APBDU with choledochal cysts, a number of studies documented that APBDU was frequently associated with choledochal cyst.\cite{15}

In particular, Yamauchi et al.\cite{16} 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.\cite{17} 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.\cite{18}

Kohno et al.\cite{19} 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.\cite{20} 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.\cite{21,22} 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.\cite{17,19} Indeed, overexpression of p53 protein was identified in our case on immunohistochemistry.

REFERENCES


