CASE REPORT

Gut and Liver, Vol. 3, No. 3, September 2009, pp. 231-234

A Case of Primary Neuroendocrine Carcinoma of the Gallbladder Associated with Anomalous Union of the Pancreaticobiliary Duct

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Primary neuroendocrine carcinoma of the gallbladder is extremely rare because normal gallbladder mucosa does not contain neuroendocrine cells. Neuroendocrine cells can be detected at sites of intestinal metaplasia induced by chronic inflammation, which may be the initial step in the development of neuroendocrine tumor of the gallbladder. Anomalous union of the pancreaticobiliary duct (AUPBD) is an uncommon congenital anomaly that is frequently associated with choledocholithiasis, cholangitis, pancreatitis, and cancer of the gallbladder or bile duct. In AUPBD, cancers of the gallbladder and bile duct can be induced by chronic inflammation. We report herein a case of large-cell neuroendocrine tumor of the gallbladder associated with AUPBD. **(Gut and Liver 2009;3:231-234)**

Key Words: Anomalous union; Pancreaticobiliary duct; Neuroendocrine tumor; Gallbladder

INTRODUCTION

Although neuroendocrine tumor can be seen frequently in gastrointestinal tract, primary neuroendocrine carcinoma of the gallbladder is rare and among them, large cell neuroendocrine carcinoma is extremely rare.

Anomalous union of pancreaticobiliary duct (AUPBD) is an uncommon congenital anomaly which defined as a junction of the bile duct and pancreatic duct outside the duodenal wall. This anomaly is frequently associated with choledochal cyst and can cause choledocholithiasis, cholangitis, pancreatitis and malignancy of the gallbladder or bile duct.

We report a case of AUPBD associated with large cell neuroendocrine carcinoma of the gallbladder.

CASE REPORT

A 38-year-old woman was admitted to Chonnam National University Hospital with 10 kg-weight loss for 2 months. Physical examination showed an icteric sclera and a tender palpable mass in the right upper quadrant of the abdomen. The blood chemistry were albumin 4.4 g/dL, AST 162 U/L, ALT 189 U/L, alkaline phosphatase 255 U/L, total bilirubin 7.3 mg/dL, direct bilirubin 4.3 mg/dL, gamma glutamyl transpeptidase 1,098 U/L, amylase 30 U/L, and prothrombin time 10.2/129.9/0.89 sec/%/INR. The CA 19-9 was 79.9 U/mL.

The chest X-ray was within normal limit. The abdominal ultrasound demonstrated a 5 cm sized mixed echoic mass in S4 segment of the liver and an 8 cm sized mass in the fundus of the gallbladder. The peripheral bile duct was dilated and the gallbladder was distended. Abdominal computerized tomography (CT) showed a 7.8×6.2 cm sized exophytic necrotizing mass in the fundus of the gallbladder. There were multiple conglomerated necrotizing lymphadenopathies in the hepatic hilum which invade confluent portion of the intrahepatic bile ducts, cystic duct, portal vein and hepatic artery (Fig. 1).

In endoscopic retrograde cholangiopancreatography (ERCP), there was a filling defect in the common hepatic duct. When the radiocontrast dye was injected to proximal portion of the common bile duct (CBD), the pancreatic duct was visualized at the same time and the length of common channel was 30 mm (Fig. 2A). After endoscopic biliary sphincterotomy (EST), the endoscopic nasobiliary drainage (ENBD) catheter was inserted. The ENBD

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Received on March 12, 2009. Accepted on May 30, 2009.

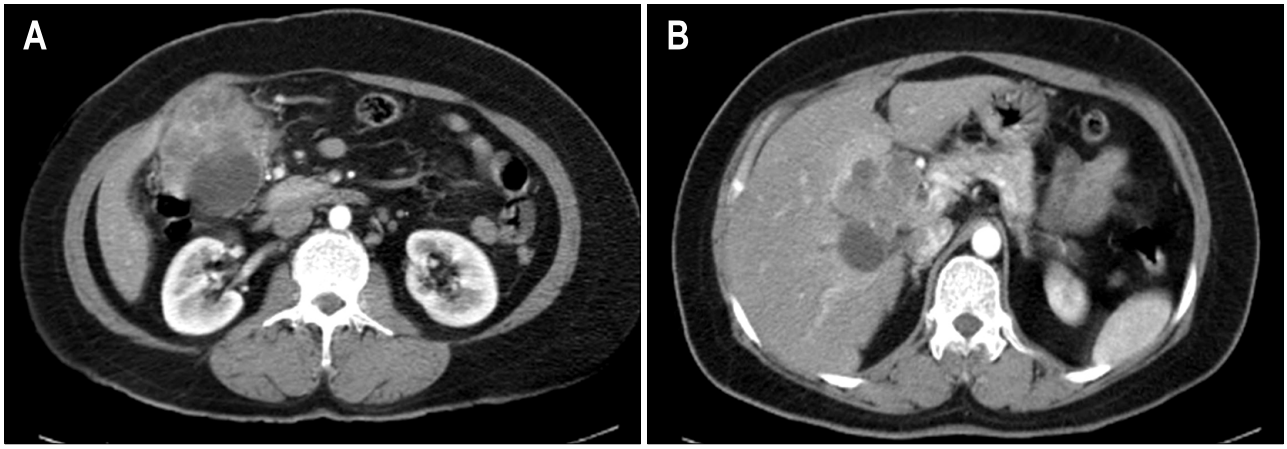

Fig. 1. (A) CT scan showing a 7.8×6.2-cm exophytic necrotizing mass in the fundus of the gallbladder. (B) CT scan showing multiple conglomerated necrotizing lymphadenopathies in the hepatic hilum. The proximal CBD, cystic duct, portal vein, and hepatic artery were invaded.
CT, computerized tomography; CBD, common bile duct.

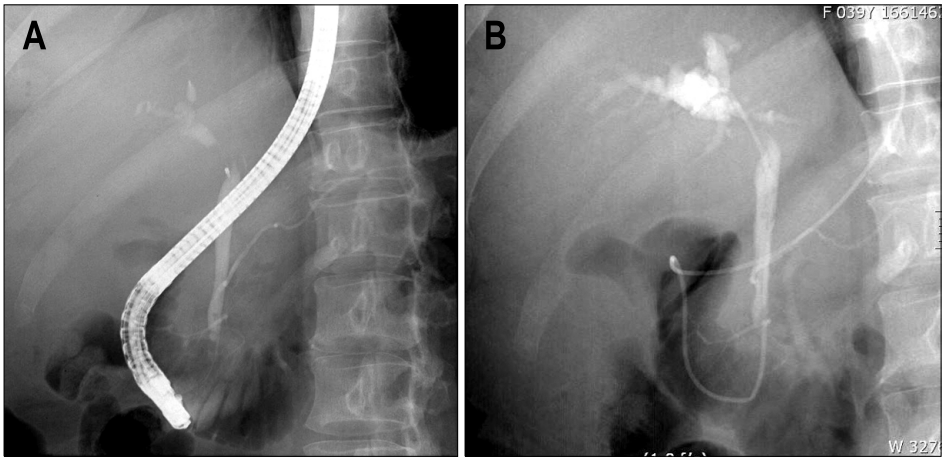

Fig. 2. (A) A filling defect in the common hepatic duct with proximal dilatation was noted on ERCP. The length of the common channel was 30 mm. (B) The ENBD cholangiogram showed a long common channel, and the pancreatic duct was visualized simultaneously with the common bile duct. ERCP, endoscopic retrograde cholangiopancreatography; ENBD, endoscopic nasobiliary drainage.

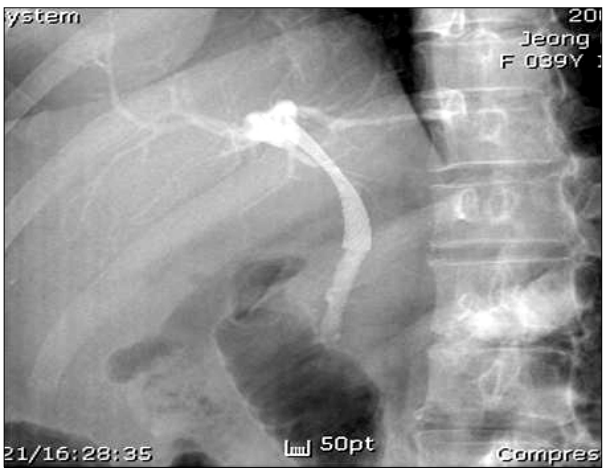

Fig. 3. An endoscopic biliary metal stent was inserted from the first branch of the right intrahepatic bile duct to the mid common bile duct.

cholangiogram (Fig. 2B) showed long common channel (over 20 mm), and pancreatic duct was visualized with CBD at the same time. The analysis of bile juice showed amylase 33,762 U/L, lipase 185,080 U/L, and CA 19-9 18,100 U/mL.

On hospital day 5, she complained abdominal pain and the blood chemistry were amylase 143 U/L and lipase 641 U/L. After conservative treatment, abdominal pain was relieved and the levels of serum amylase and lipase were normalized. On hospital day 12, a biliary stent (10 ×40 mm, covered, Wall stent, Endoprosthesis, Boston scientific, Galway, Ireland) was inserted endoscopically (Fig. 3). Biopsy was performed under the ultrasonographic guidance. The tumor showed a monotonous proliferation of small round cells with hyperchromatic nuclei and scanty cytoplasm, resembling neuroendocrine carcinoma. Immunohistochemical staining for chromogranin

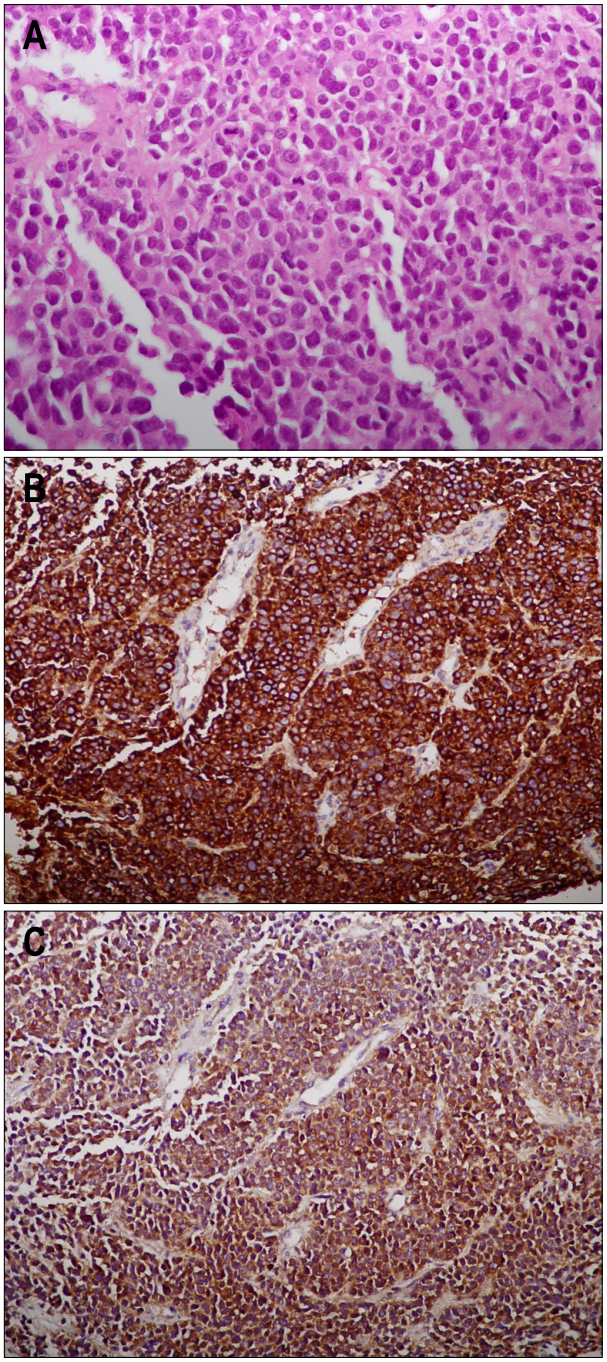

Fig. 4. (A) The tumor showed a monotonous proliferation of small round cells with hyperchromatic nuclei and scanty cytoplasm, resembling neuroendocrine carcinoma. Abundant necrosis and innumerable mitotic figures were seen (H&E stain, ×200). Immunohistochemical staining for chromogranin (B) and synaptophysin (C) disclosed an intense and diffuse positivity in the tumor cells, but a few tumor cells showed a granular cytoplasmic immunoreactivity (Immunohistochemical stain, ×100).

and synaptophysin discloses an intense and diffuse positivity in the tumor cells (Fig. 4). The patient refused chemotherapy and discharged. After all, she died of progressive disease 5 months after initial diagnosis.

DISCUSSION

AUPBD is a congenital anomaly of the union of the pancreatic and bile ducts characterized by abnormally long common channel (>15 mm in adult) on ERCP and can be strongly suggested when the level of amylase in bile is above 10,000 IU/L.[1,2] Chronic inflammation and ulceration in the bile duct can be caused and cancer of the gallbladder and bile duct can be induced.[3] Recurrent pancreatitis can be induced by reflux of bile into the pancreatic duct or increased pressure of the pancreatic duct.[4]

Primary carcinoma of the gallbladder is mostly adenocarcinoma (80-95%) and neuroendocrine tumor of the gallbladder is rare (less than 4%).[5] The origin of neuroendocrine carcinoma of the gallbladder is still unclear. Neuroendocrine tumors can be detected frequently in gastrointestinal tract, especially in appendix, small intestine, rectum and stomach. However, primary neuroendocrine tumor of the gallbladder is rare. Normal gallbladder mucosa does not contain neuroendocrine cells. When intestinal metaplasia of the gallbladder occurs in association with long-standing chronic inflammation due to cholelithiasis and congenital anomalies, neuroendocrine cells can be detected in site of intestinal metaplasia which may be the initial step in the development of neuroendocrine tumors of the gallbladder.[6,7] Interestingly, a recent study reported that heterotopic gastric mucosa in the gallbladder might be one of the causes of gallbladder cancer.[8] And, some studies reported that Helicobacter pylori existed in site of gastric metaplasia in gallbladder.[9,10] The neuroendocrine tumor of gallbladder can be associated with chronic helicobacter pylori infection.

Neuroendocrine tumors can be classified into typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma (SmCC). In one study which analyzes 65 cases of gastrointestinal neuroendocrine tumors, the tumors were classified as 49 TCs, 4 ACs, 6 LCNECs and 6 SmCCs.[11] Only three cases of AUPBD associated with small cell carcinoma of the gallbladder and one case of AUPBD associated with adenocarcinoma with focal small cell and large cell neuroendocrine tumor of the gallbladder has been reported.[5,12-14]

In the present case we could not know the tumor of the gallbladder was purely neuroendocrine tumor or mixture of neuroendocrine tumor, because the mucosa of the gallbladder was not fully evaluated under cholecystectomy. However, the neuroendocrine features suggested

strongly that chronic inflammation of the bile duct by AUPBD might induce intestinal metaplasia and neuroendocrine carcinoma of the gallbladder.

Recently, endoscopic biliary drainage is recommended for unresectable pancreaticobiliary malignancies which the survival is expected to be more than 3 months.[15] In AUPBD, the junction of the bile duct and pancreatic duct is located more proximally than normal population, so the pancreatic duct can be easily obstructed by biliary stent. So the length and location of the biliary stent is important to avoid obstruction of the pancreatic duct.

Recently, diagnostic and therapeutic ERCP is being done actively for pancreaticobiliary diseases, and AUPBD is arising for important cause of pancreatitis and tumors of the gallbladder and bile duct. So in doing ERCP, more attention is needed for detecting AUPBD and active treatment is needed for prevention of complications of AUPBD.

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