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Case Report

A Case of Gallbladder Carcinoma Associated With Occult Pancreatobiliary Reflux in the Absence of Pancreaticobiliary Maljunction

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A short title: gallbladder carcinoma with pancreatobiliary reflux

Key words: gallbladder carcinoma, pancreatobiliary maljunction, pancreatobiliary reflux

Abstract

We herein report a case of gallbladder carcinoma associated with occult pancreatobiliary reflux (PR) in the absence of pancreatobiliary maljunction. A 67-year-old woman was referred to our hospital for the evaluation and treatment of a gallbladder tumor. Ultrasonography and computed tomography showed a nodular lesion in the fundus of the gallbladder, indicating the possibility of a gallbladder carcinoma. Endoscopic retrograde ultrasonography showed the tumor in the fundus of the gallbladder and thickness of the surrounding epithelium. Endoscopic retrograde cholangiopancreatography revealed a normal pancreaticobiliary junction without the common channel and a mild dilatation of the common bile duct (15 mm in the diameter). An open cholecystectomy and partial resection of the liver bed of the gallbladder with regional lymphadenectomy were performed. A C-tube was inserted from the cut end of the cystic duct into the common bile duct to prevent the bile stasis. Biliary amylase and lipase levels sampled in the gallbladder were 2,604 IU/l and 775 IU/l, respectively. Biliary amylase level in the bile collected from the C-tube in the common bile duct was 119,550 IU/l on postoperative day (POD) 6 and 22,265 IU/ on POD 12. These observations suggested that PR was present in this patient. The histopathological findings of the resected specimen showed a well differentiated adenocarcinoma of the gallbladder with invasion to the muscle layer and no metastasis of the resected lymph nodes. A high index of the nuclear staining for MIB-I in the cancer cells (about 10%) was exhibited, and a few cells of the normal epithelium also stained positive.

Introduction

Pancreaticobiliary maljunction (PBM) is an anomalous condition in which the pancreatic duct and bile duct merge outside the wall of the duodenum, which causes continuous pancreatobiliary reflux (PR) (1). A range of secondary bile acids and activated pancreatic enzymes are then generated, including amylase, which damages the biliary mucosa. The biliary mucosa hence may undergo a variety of histological changes that frequent result in conditions for carcinogenesis in the biliary tract (2, 3). The presence of PBM without the bile duct dilatation is significant risk factor for gallbladder cancer (4). However, there have been recent reports that PR can occur and play an important role in gallbladder carcinogenesis, not only in patients with PBM but also in those with a normal pancreaticobiliary junction (5 - 9). In this report, we describe a patient who had gallbladder carcinoma probably associated with PR in the absence of PBM.

Case report

A 67-year-old woman presented with epigastric pain and vomiting. She had no past history related to biliary or pancreatic diseases. Abdominal ultrasonography (US) detected gallbladder tumor and she was referred to our hospital for the evaluation and treatment of the tumor. Physical examination indicated no abnormal findings. The laboratory examinations, including liver function tests, amylase, lipase, carcinoembryonic antigen, and carbohydrate antigen 19-9, were within normal ranges. Computed tomography (CT) (Figure 1A) showed the enhanced lesion in the fundus of the gallbladder, thus indicating the possibility of gallbladder carcinoma. There were no signs that the tumor had invaded the liver. Endoscopic ultrasonography (EUS)

showed the nodular tumor and thickness of the surrounding epithelium (Figure 1B and C). The tube of endoscopic retrograde cholangiopancreatography (ERCP) could be easily inserted into the common bile duct (CBD). During the early phase of cholangiography, we detected biliopancreatic reflux (BR). It revealed a normal pancreaticobiliary junction without the common channel and a mild dilatation of the CBD (15 mm in the diameter) (Figure 2). And periampullary diverticulum was detected but the biliary amylase level in the CBD was not measured. An open cholecystectomy and partial resection of the liver bed of the gallbladder with regional lymphadenectomy were performed. The cut end of the cystic duct was pathologically examined by frozen section during the operation. The extrahepatic bile duct was not resected because there were no findings of the tumor extension. A C-tube was inserted from the cut end of the cystic duct into the CBD to prevent the bile stasis. Biliary amylase and lipase levels sampled in the gallbladder were 2,604 IU/l and 775 IU/l, respectively. The biliary amylase levels in the bile collected from the C-tube in the collecting bottle were 119,550 IU/l on postoperative day (POD) 6 and 22,265 IU/ on POD 12. These data suggest PR in this patient. The macroscopic findings of the resected gallbladder showed multiple nodular lesions in the fundus that were not independent tumor, confirmed by histopathology. The histopathological findings of the resected specimen showed a well differentiated adenocarcinoma of the gallbladder with invasion to the muscle layer and no metastasis of the resected lymph nodes (Figure 4A and C). The lesion for EUS showed the wall thickness was the continuous neoplastic epithelium, but the epithelium in the neck showed no dysplasia or hyperplasia. A high index of the nuclear staining for MIB-I was exhibited in the cancer cells (about 10%), and a few cells of the normal epithelial cells (less than 1%)

(Figure 4B and D). The patient made an uneventful recovery, and has been in good health without any signs of recurrence or metastasis for one year.

Discussion

Under normal conditions, the pancreatobiliary junction is controlled by the function of the sphincter of Oddi, which prevents PR or BR. When PR or BR occurs, various pathological conditions in the biliary tract and the pancreas, including chronic pancreatitis, chronic cholecystitis, choledocholithiasis (5), and periampullary diverticulum (10). Itokawa et al. reported the biliary amylase level (72 – 1,199 IU/l) of the CBD during ERCP to be elevated in 22 cases (26%) of the patients with pancratobiliary diseases, particularly in elderly patients and those with a dilated bile duct or choledocholithiasis. They thus concluded that PR without PBM could cause biliary diseases (6). PR can be assessed by measuring the amylase levels of the bile, collected by ERCP, surgery, and from a T-tube. BR can also be confirmed by operative or postoperative cholangiography, CT with drip infusion cholangiograpy, histological detection of gallbladder cancer cells in the main pancreatic duct, and reflux of bile on the cut surface of the pancreas (5). However, the criteria for PR or BR have not yet clearly been determined yet. Sai JK et al. (11) performed secretin-enhanced magnetic resonance cholangiopancreatography in 108 patients who exhibited gallbladder wall thickness on US or CT, and reported that PR similar to PBM occurred in 16 cases (15%) who had a normal pancreatobiliary junction. These results (10, 11) suggested that PR may not be a rare in the patients with pancratobiliary diseases.

PBM is often associated with biliary tract carcinoma (2, 3). Recently, Sai JK et al. (7 - 9) showed that PR without PBM could be associated with precancerous mucosal

changes in the gallbladder including epithelial hyperplasia, dysplasia with increased cellular proliferation, and gallbladder carcinoma. They suggested that prophylactic cholecystectomy should be considered in cases that have extremely high biliary amylase levels. Itoi T et al. have reported that both the Ki-67 labeling index and COX-2 expression are significantly higher in high biliary amylase level groups without PBM at the non-cancerous epithelium of the gallbladder (12). However, in this case, the MIB-I labeling index was significantly higher at the cancer epithelium (about 10%), with even a few cells of the non-cancerous epithelium (less than 1%) showing positive staining.

We could not find any reports that had investigated the incidence of PR or BR without PBM in a large scale study with healthy volunteers. A few reports descried the mean amylase level of the CBD to be three to four times the upper normal limit of serum amylase level in patients with gallbladder cholesterol polyps who are considered to have normal papillary function (10, 13). Moreover, we do not understand the precise mechanism of PR or BP without PBM, particularly with respect to its relation to the dysfunction of the sphincter of Oddi. There is one possibility that duodenal juice containing pancreatic juice refluxes into the bile duct in some cases. The risk of gallbladder carcinoma associated with PR in the absence of PBM should be further clarified.

Figure legends

Figure 1. Computed tomography (A) shows the enhanced lesion in the fundus of the gallbladder, thus indicating the possibility of gallbladder carcinoma. There were no signs that the tumor invaded to liver. Endoscopic retrograde ultrasonography (B and C) showed the nodular tumor and thickness of the surrounding epithelium.

Figure 2. Endoscopic retrograde cholangiopancreatograpy reveals a normal pancreaticobiliary junction without the common channel (shown in the circle). The arrow shows the tumor in the gallbladder. There was no dilatation of the common bile duct (about 15 mm in the diameter).

Figure 3. The macroscopic findings of the resected gallbladder show multiple nodular lesions in the fundus.

Figure 4. The histopathological findings of the tumor (A, C) and normal epithelium (B, D) of the resected gallbladder. A high index of the nuclear staining for MIB-I in the cancer cells is exhibited, while a few cells of the normal epithelium also stain positive (B and D). A and C; Hematoxylin-Eosin staining, X100. B and D; MIB-I staining, X 100

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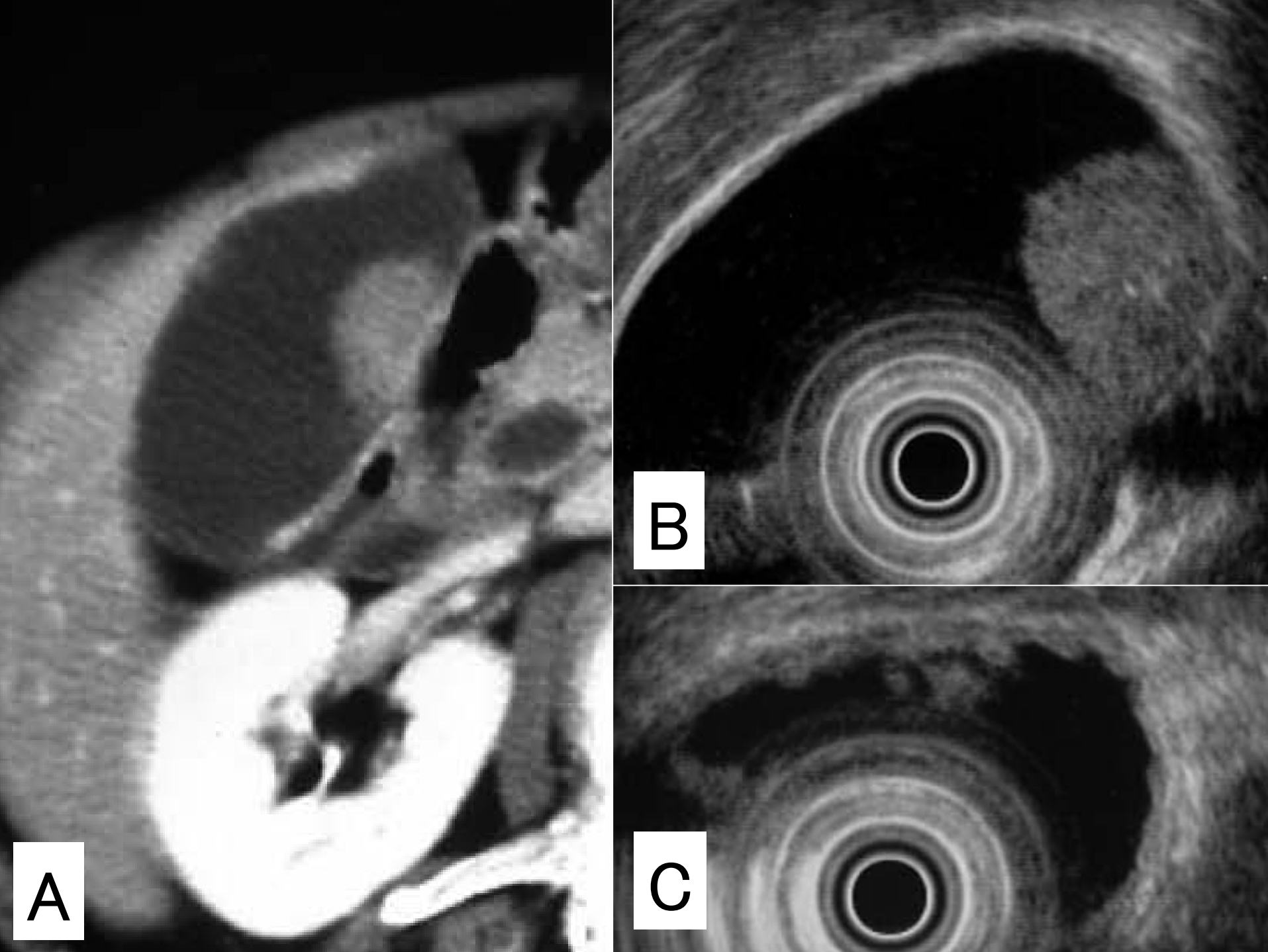
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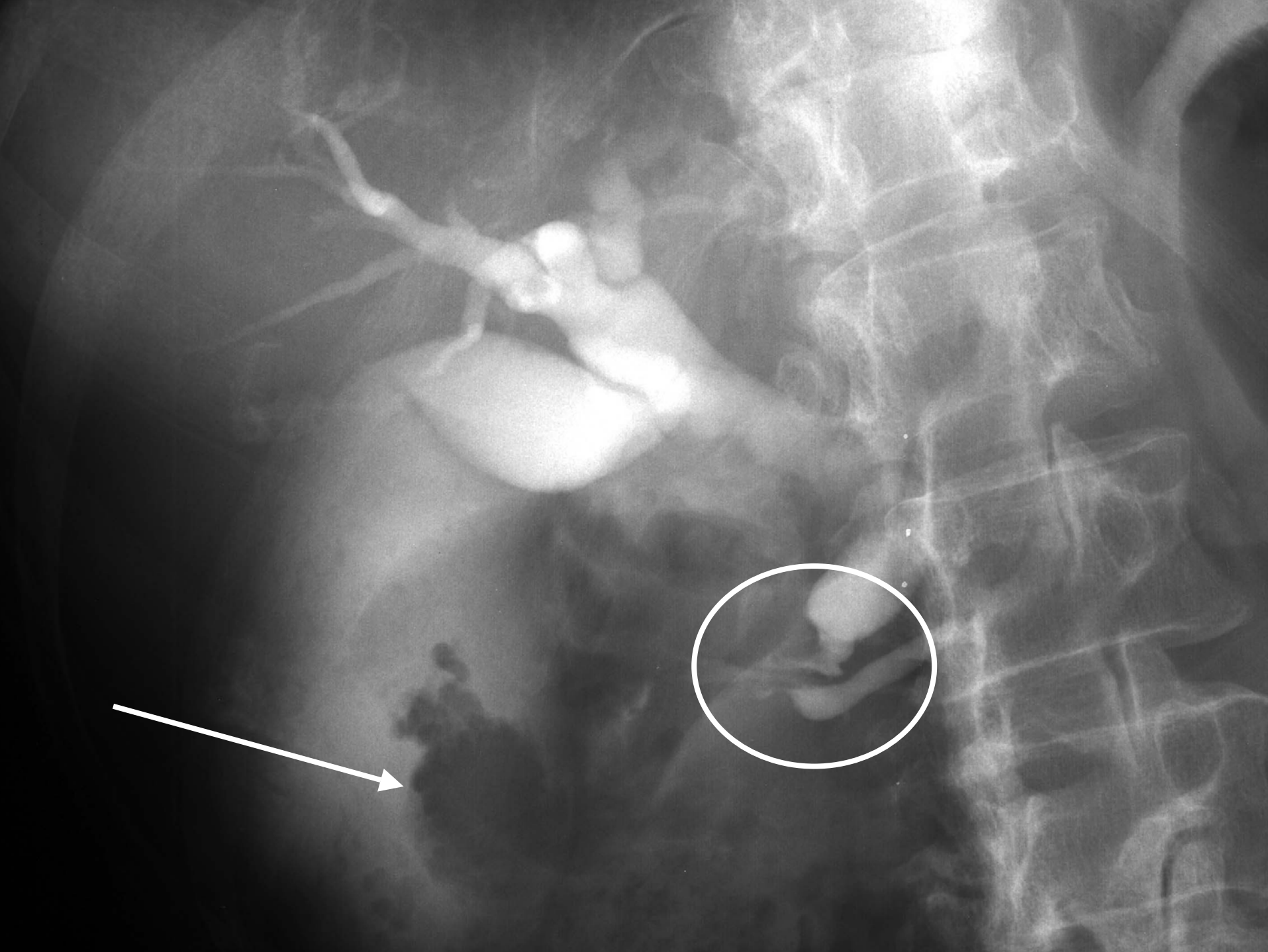

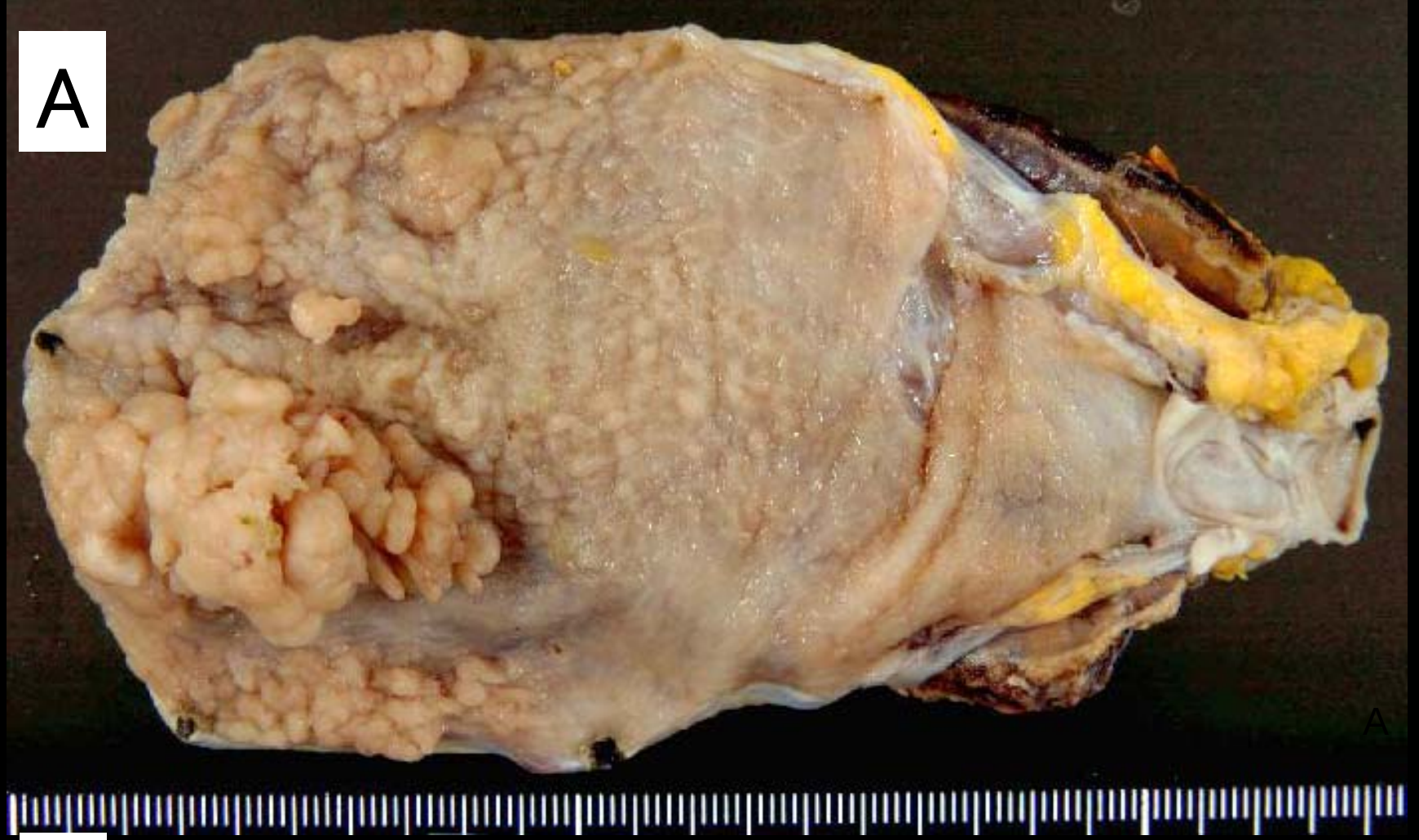
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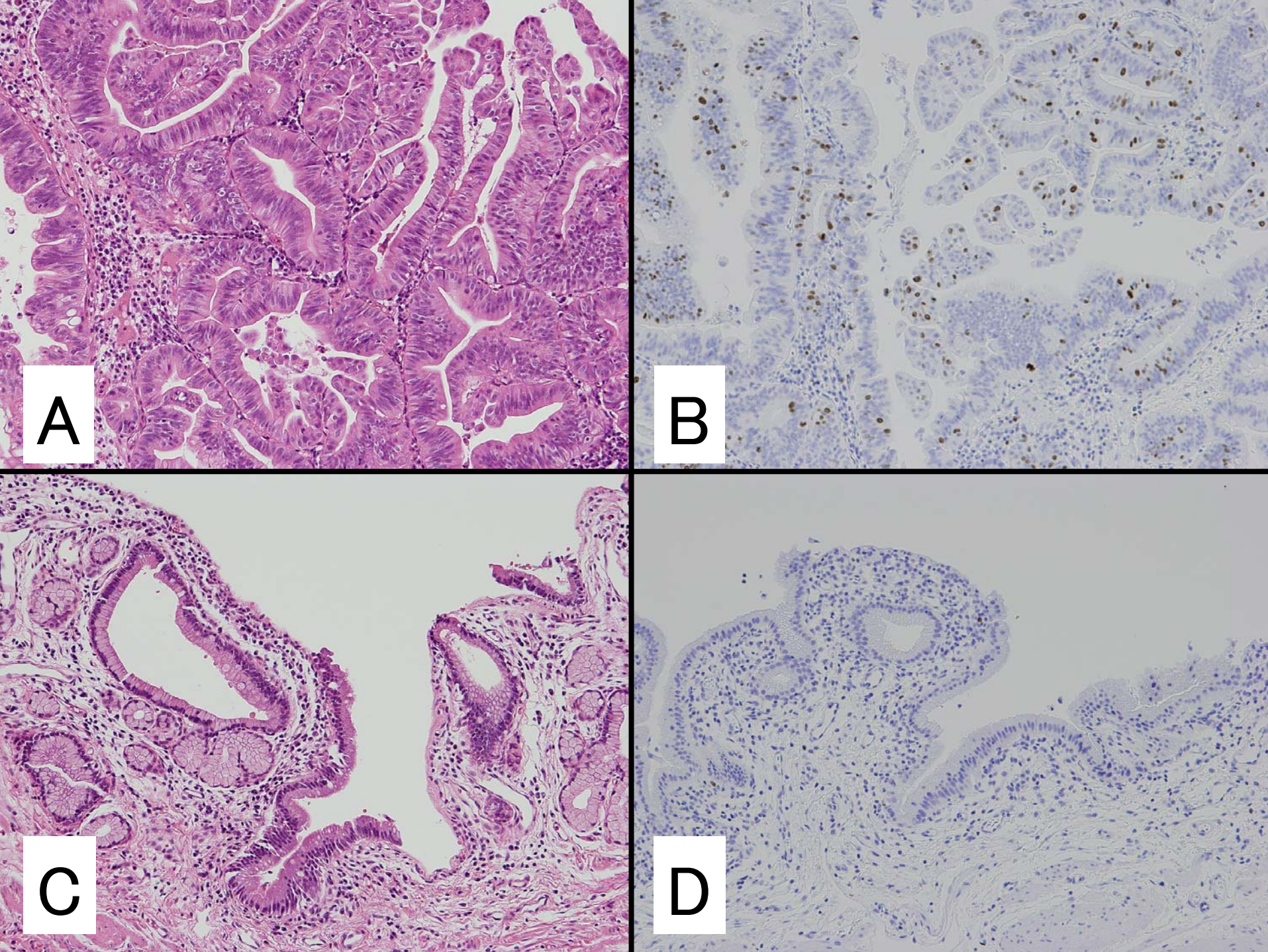
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