【 CASE REPORT 】

Early Detection of High-grade Biliary Intraepithelial Neoplasia (BilIN-3) in the Cystic Duct Visualized by SpyGlass DS Cholangioscopy

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Abstract:
An 84-year-old man was admitted with epigastralgia. Computed tomography showed contrast-enhanced wall thickness in the cystic duct. An endoscopic examination revealed short irregular stricture in the cystic duct, and per-oral cholangioscopy revealed a reddish papillary tumor at the stricture site. Surgical resection revealed high-grade biliary intraepithelial neoplasia (BilIN) at the stricture site of the cystic duct. To our knowledge, this is the first case of a solitary high-grade BilIN epithelium in the cystic duct detected by per-oral cholangioscopy.

Key words: cystic duct tumor, cystic duct, cholangioscopy, BilIN-3, high-grade biliary intraepithelial neoplasia

(Intern Med 60: 47-52, 2021)
(DOI: 10.2169/internalmedicine.5072-20)

Introduction

Primary cystic duct carcinoma is a relative rare disease initially reported in 1941 (1). Since then, the strict criteria of Farrar (2) have been used to diagnose the disease, as follows: (a) the growth is restricted to the cystic duct; (b) neoplasia are absent from the gallbladder, hepatic ducts, and common bile duct; and (c) the presence of carcinoma cells is histologically confirmed. Since the cystic duct is a short structure, and its carcinoma can easily invade adjacent organs, Farrar's strict criteria do not apply to all cases of cystic carcinoma, particularly advanced cystic duct carcinoma. Therefore, a more inclusive alternative definition has been suggested: a diagnosis of cystic duct carcinoma can be made in cases where the center of the tumor mass is located in the cystic duct (3, 4).

The cystic duct is a very small organ, and symptoms caused by its cancer at the early stage are very rare. Therefore, detecting early-stage primary cystic duct carcinoma is very challenging, and only a few cases have been reported thus far. Prompt surgery with en bloc resection of gallbladder, cystic duct, common bile duct, and regional lymphadenectomy is the general treatment. Recently, advances in digital per-oral cholangioscopy have allowed us to make a precise and early diagnosis of bile duct tumors, and this approach may also be able to be used for the diagnosis of cystic duct carcinoma, even at early stage.

We herein report a rare case of solitary *in situ* carcinoma of the cystic duct that was able to be detected using per-oral cholangioscopy. To our knowledge, no such case has been reported to date.

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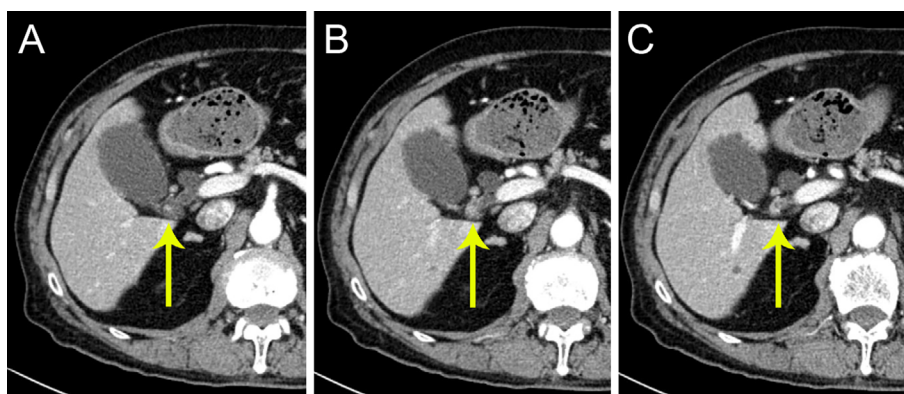
Figure 1. Computed tomography showed contrast-enhanced wall thickness indicating stricture of the cystic duct, as well as swelling of a lymph node above the stricture (yellow arrow; A-C are sequential images of the arterial phase).

Case Report

An 84-year-old man visited the emergency department of our hospital after experiencing postprandial epigastralgia over the past 4 days. The pain usually receded within an hour of onset. However, he experienced unremitting pain after dinner on the day of admission and was admitted to our hospital after an emergency call was made. His medical history included hyperlipidemia, diabetes mellitus, renal dysfunction with hyperuricemia, benign prostate hypertrophy and transurethral resection of the prostate, and angina pectoris following placement of a coronary stent. He had smoked 15 cigarettes a day before ceasing smoking 2 years earlier and did not drink alcohol. His daughter had died of breast cancer. Abdominal palpation revealed epigastric pain and tenderness despite the absence of peritoneal irritation, abnormal bowel sounds, and hepatosplenomegaly. Most laboratory tests performed on samples taken at the time of admission revealed normal values, including hepatobiliary enzymes, carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9). Serum glucose was slightly elevated at 140 mg/dL.

Computed tomography (CT) revealed swelling of the gallbladder and a very tiny area of contrast-enhanced wall hypertrophy in the middle of the cystic duct, with mild swelling of the surrounding lymph nodes (Fig. 1). T2-weighted magnetic resonance cholangiopancreatography (MRCP) revealed swelling of the gallbladder, stricture of the cystic duct, an irregular defect, and mild swelling of the lymph node around the cystic duct (Fig. 2). Endoscopic retrograde cholangiography (ERC) showed a short irregular stricture in the cystic duct (Fig. 3A). Endoscopic ultrasound revealed a low-echoic lesion (8.1 mm in length and 4.8 mm in height) in the middle of the cystic duct (Fig. 3B). As a guidewire was smoothly passed through the stricture of the cystic duct, an intraductal ultrasound probe was inserted into the cystic duct using the guidewire and revealed hypertrophy of the cystic duct wall (3 mm), a well-maintained high-echoic

outer layer (Fig. 3C), and normal wall thickness in the common bile duct. Subsequent per-oral cholangioscopy (Spy-Glass DS; Boston Scientific, Marlborough, USA) with side-view endoscopy revealed a reddish granular mucosa and dilated tortuous vessels on the mucosa at the stricture (Fig. 3D, E) with normal mucosa in the common bile duct, although it could not be passed through the stricture and did not allow us to observe the inside of gallbladder and a part of the cystic duct beyond the stricture. These findings suggested that a small tumor lesion in the cystic duct had caused the patient's initial symptoms.

The cytology specimens obtained from the cystic duct showed no malignancy. Considering the significant radiographic and endoscopic findings, however, cystic duct adenocarcinoma was suspected. Therefore, the patient underwent cholecystectomy and bile duct resection with hepatojejunostomy, after which he was discharged and had an uneventful recovery.

A histological analysis revealed atypical epithelium showing partial loss of polarity, consistent with high-grade biliary intraepithelial neoplasia (BilIN). The length of the entire BilIN mucosa was 15 mm (Fig. 4). No metastases were found in any of the resected lymph nodes (pTisN0M0, stage 0 in the UICC TNM classification). The patient has been alive for three years since the surgery without recurrence.

Discussion

The present case satisfied all of the criteria proposed for a definite diagnosis of early-stage cystic duct cancer (2-6). Due to recent advances in radiological and endoscopic procedures some cases of cystic duct carcinoma can be diagnosed at an early stage (7-11). In an initial report, early-stage cystic duct carcinoma was an incidental finding in a patient with cholelithiasis and choledocholithiasis (11). A case of cystic duct carcinoma was reportedly observed by endoscopic ultrasound (9), and three others were observed using cholangioscopy (7-9). A tumor of the cystic duct was successfully diagnosed pathologically based on a specimen
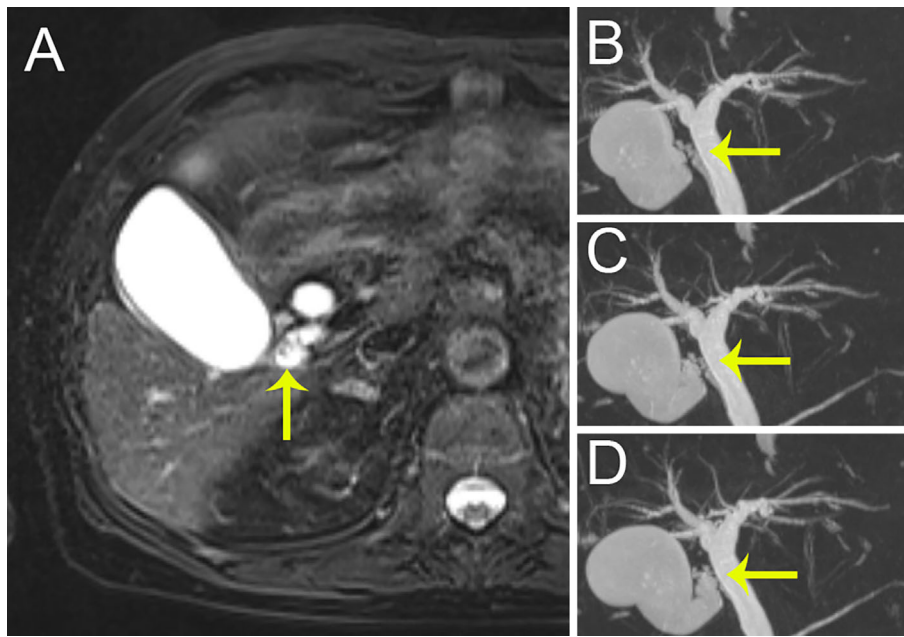
Figure 2. Axial magnetic resonance cholangiopancreatography image (A) and sequential images of maximum intensity projection (B-D) revealed swelling of the gallbladder and stricture of the cystic duct, an irregular defect, and mild swelling of a lymph node above the cystic duct (yellow arrow, T2-weighted images).
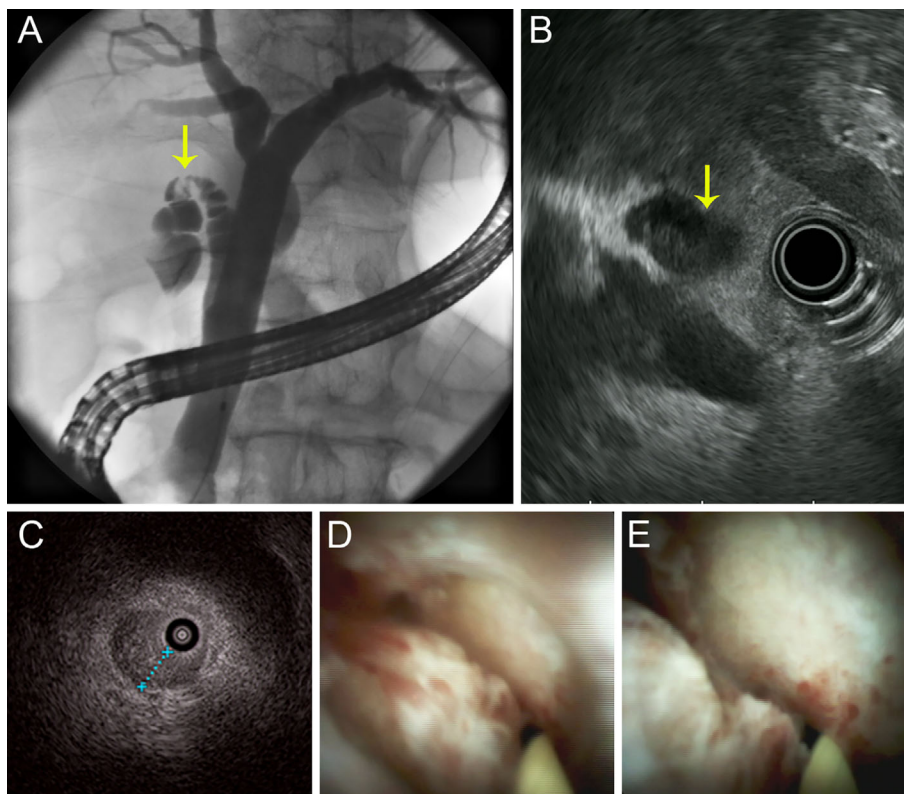

Figure 3. (A) A short, irregular stricture of the cystic duct shown by endoscopic retrograde cholangiography (yellow arrow). (B) A low-echoic lesion (8.1 mm in length and 4.8 mm in height) in the middle of the cystic duct by endoscopic ultrasound (yellow arrow). (C) An area of wall hypertrophy (3 mm in length); the high-echoic outer layer is shown by an intraductal ultrasound probe inserted into the cystic duct. (D, E) a reddish granular mucosa and dilated tortuous vessels on the mucosa at the stricture visualized by per-oral cholangioscopy.
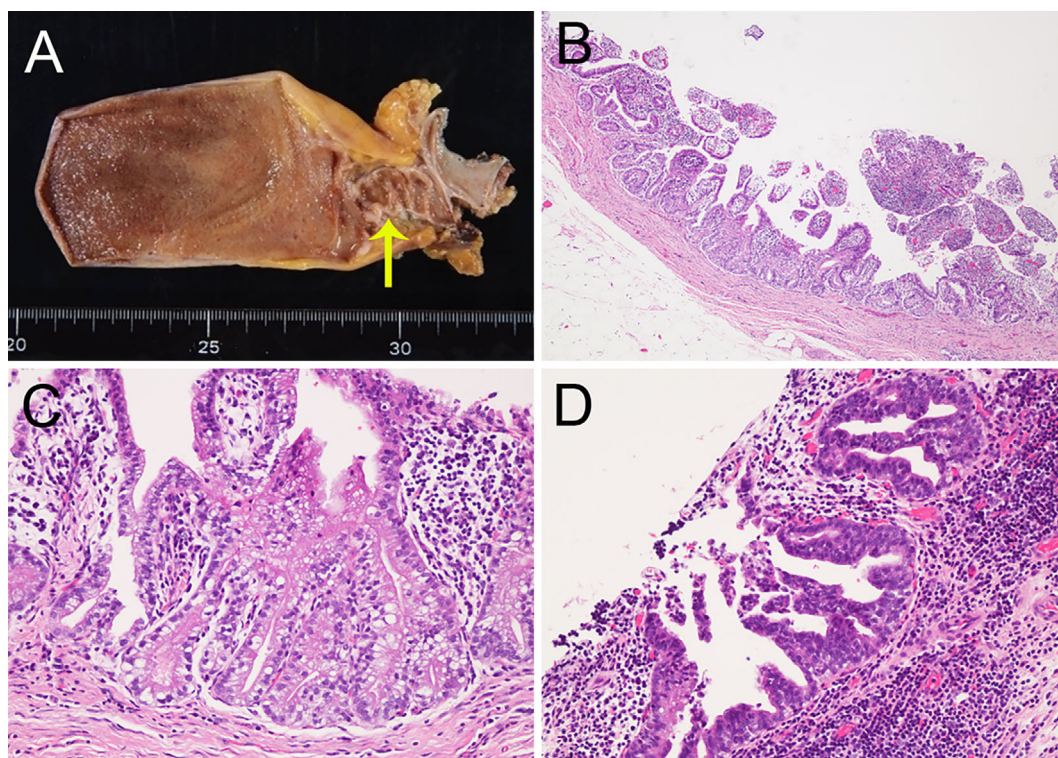
Figure 4. (A) A resected specimen fixed by formalin. The yellow arrow depicts the stricture in the cystic duct. (B) Hematoxylin and Eosin staining of part of the stricture site. Original magnification ×10. (C, D) An image of high-grade biliary intraepithelial neoplasia (BilIN) epithelium. Original magnification ×40.

obtained by SpyGlass-directed biopsies (8).

For the diagnosis of malignancy, the sensitivity and specificity in a pooled analysis with visual impression using a SpyGlass device were 84.5% and 82.6%, respectively (12), and additional SpyGlass-directed biopsies confer higher specificity (12). However in our case, SpyGlass-directed biopsies were not performed for the following reasons: 1) as radiological images of CT and MRCP in addition to fluoroscopic images of ERC showed the stricture was not completely obstructed, the lesion on the epithelium was so thin and small that forceps may have caused a perforation at the site; 2) the cystic duct wall is generally smaller and thinner than the common bile duct wall and can be easily perforated when forceps biopsies are performed; 3) perforation of the cystic duct in cases of malignancy can cause peritoneal dissemination of the cancer; and 4) the treatment strategy, which was surgery in the present case, can be determined without the need for a biopsy as long as the visual characteristics using SpyGlass indicate malignancy (13). Furthermore, no prospective studies have been performed to assess the accuracy or safety of cholangioscope-directed biopsies in the cystic duct, so further studies will be necessary.

In our case, the results of brush cytology at the stricture of the cystic duct were negative. However, a pooled analysis reported that brushing cytology of the bile duct for the diagnosis of malignancy has low sensitivity and high specificity (45% and 99%, respectively) (14), and neoplasms of the cystic duct should be suspected in patients presenting with a distended gallbladder (likely due to cystic duct obstruction) without evidence of stone impaction in the cystic duct and with cystic duct stricture on contrast-enhanced CT. Some reports have suggested the benefit of bile cytology via endoscopic transpapillary gallbladder drainage tube. However, the lesion in our case was located only in the cystic duct, where bile containing cytologic specimens is difficult to obtain through a nasobiliary tube (15, 16).

In our case, high-grade BilIN epithelium in the cystic duct was detected by surgery. This case shows that the symptoms of cystic duct carcinoma may develop earlier than those of gallbladder cancer. Clinicians should pay close attention to strictures of the cystic duct in cases of gallbladder swelling without gallstones or tumors in the neck of the gallbladder.

BilIN was initially described in 2005 (17) It consists of non-invasive, flat, or papillary lesions that are confined to the gallbladder lumen or bile ducts, including the cystic duct (18). BilIN was previously classified as BilIN-1, BilIN-2, or BilIN-3 based on the degree of atypia and polarization of the epithelium (19). Recently, the World Health Organization (WHO) proposed that BilIN instead be classified as low or high grade (18, 20). Low-grade BilIN, corresponding to BilIn-1 and BilIn-2, is characterized by mild cytoarchitectural atypia, a high N:C ratio, hyperchromasia, and prominent nucleoli (18, 20). High-grade BilIN, corresponding to BilIN-3, is categorized as Tis (carcinoma *in situ*) (21) and is characterized by the complete loss of polarity, marked nu-

clear atypia, and frequent mitoses resembling micropapillae or tall papillae (18). According to the new classification, the present case met the criteria for a diagnosis of high-grade BilIN consistent with carcinoma *in situ*.

Direct visualization of the stricture using a cholangioscope may be one of the most reliable methods for determining whether or not surgery is indicated. Cholangioscopy enables an accurate diagnosis, even if the lesion is located in the cystic duct. Although several adenomas, high-grade dysplasias, and *in situ* adenocarcinomas arising from the cystic duct have been reported (11, 22-29), in no case was a cholangioscope used to detect and observe the lesion. Since we were able to initially diagnose the stricture based on radiological images alone, we performed ERC and then inserted a cholangioscope to examine the lesion. The findings allowed us to determine the most appropriate surgical treatment, although the lesion was too thin to perform a forceps biopsy to confirm the pathology.

The recommended treatment for BilIN is radical surgery consisting of cholecystectomy with non-anatomical gallbladder fossa resection and excision of the extrahepatic bile duct with regional lymphadenectomy (3, 6). The average survival time is 27.2 months, versus just 5.8 months for gallbladder carcinoma and 3.2-11.4 months for other extrahepatic biliary duct cancers (6, 30) This is consistent with the finding that symptoms of cystic duct cancer may develop earlier than those of gallbladder cancer (31).

In summary, we have presented the first case report of a high-grade BilIN lesion in the cystic duct in a patient with postprandial epigastralgia, in which CT and ERCP findings revealed stricture of the cystic duct and swelling of the gallbladder. We were able to diagnose the patient through direct visualization of the tiny lesion with a SpyGlass cholangioscope. This case demonstrates that early-stage cancer of the cystic duct can cause epigastralgia.

The authors state that they have no Conflict of Interest (COI).

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