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【 CASE REPORT 】

Laterally Spreading Adenocarcinoma Involving the Lower Bile Duct and Duodenum Expressing Heterogeneous Immunohistochemical Phenotypes

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Abstract:

A 70-year-old man was admitted to our hospital due to elevated levels of hepatobiliary and pancreatic enzymes. Computed tomography showed contrast-enhanced mucosal hypertrophy from the duodenal papilla to the distal bile duct. Endoscopic examinations revealed a laterally spreading granular tumor and ampullary swelling. After surgical resection, an examination revealed well-differentiated adenocarcinoma of the ampulla with tubular adenoma spreading from the distal common bile duct to the second part of the duodenum showing both bile duct and duodenal phenotypes. To our knowledge, this is the first case of a tumor spreading from the bile duct to the duodenum that exhibited multiple phenotypes.

Key words: ampullary adenocarcinoma, bile duct, duodenum, different phenotypes, laterally spreading tumor

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Introduction

The ampulla of Vater is the junction of the main pancreatic and the distal bile ducts within the head of the pancreas. The common channel of the ampulla empties into the duodenum through the papilla. This area is surrounded by the parenchyma of the pancreatic head and the duodenum. The area within 2 cm of the ampulla is called the periampullary region (1).

Cancers in the periampullary region account for 5% of all gastrointestinal cancers, among which pancreatic cancer is the most common, followed by distal bile duct cancer. In contrast, cancer of the ampulla is rare; the incidence is <1 per 100,000, and women are less frequently affected (0.45/100,000) than men (0.7/100,000) (2).

The World Health Organization (WHO) classifies adenocarcinoma of the gallbladder and extrahepatic bile ducts into biliary type, gastric foveolar type, intestinal type, clear-cell adenocarcinoma, mucous adenocarcinoma, and signet-ring-cell carcinoma (3). Furthermore, ampullary tumors are clinicopathologically classified into four types (4); however, some cases cannot be so categorized.

We herein report a rare case of an ampullary adenocarcinoma with accompanying adenoma spreading into the bile duct and duodenal mucosa. To our knowledge, no such case has been reported to date.

Case Report

A 70-year-old man was referred to our hospital due to elevated serum levels of hepatobiliary enzymes: total bilirubin, 0.8 mg/dL (normal range, 0.2-1.2); aspartate aminotransferase, 108 IU/L (8-38); alanine aminotransferase,

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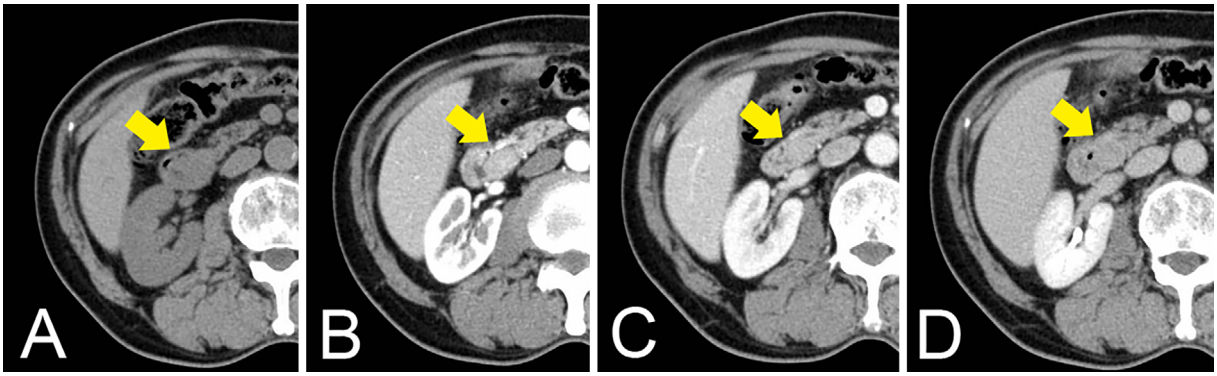

Figure 1. **Computed tomography (CT) showed contrast-enhanced mucosal hypertrophy from the duodenal papilla to the distal bile duct (yellow arrow: A, plain; B, arterial phase; C, portal phase; D, equilibrium phase). The hypertrophy was enhanced in (B) the arterial phase, and (D) the enhancement was washed out in the equilibrium phase.**

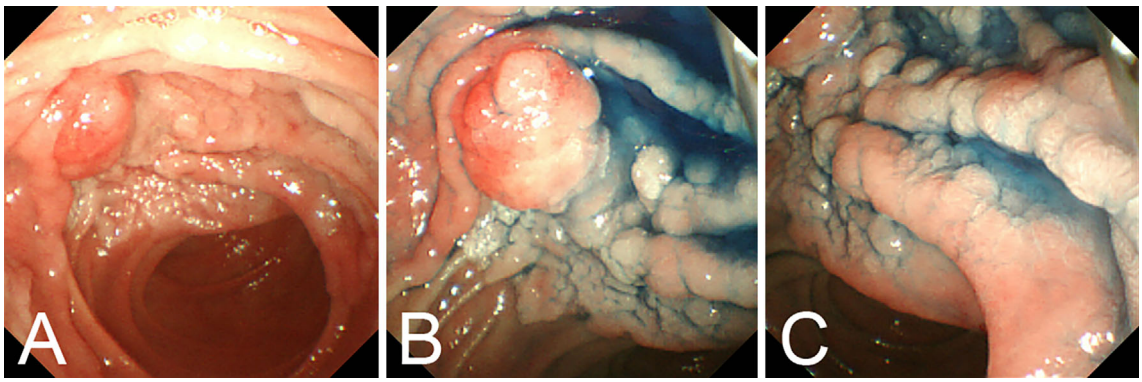

Figure 2. **Upper gastrointestinal endoscopy showed a granulomatous tumor with a circumference around one third that of the lumen, spreading from the duodenal papilla (A, white light; B, indigo carmine staining) to the inferior duodenal angle (C, indigo carmine staining), with reddish swelling of the ampulla.**

282 IU/L (6-43); and lactate dehydrogenase, 243 IU/L (121-245). His medical history showed only an appendectomy. Prior to stopping smoking 2 years ago, he had smoked 15 cigarettes per day. He reported drinking one bottle of beer per day. His mother had pancreatic cancer, and a brother had gastric cancer. He denied having abdominal pain, and neither hepatosplenomegaly nor abdominal tenderness was noted on abdominal palpation. The results of all laboratory tests, including hepatobiliary enzymes, carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9, at the time of admission were within the normal ranges.

Computed tomography (CT) showed contrast-enhanced mucosal hypertrophy from the duodenal papilla to the distal bile duct. The hypertrophy was enhanced in the arterial phase, and the enhancement was washed out in the equilibrium phase, suggesting a spreading tumor (Fig. 1). Upper gastrointestinal endoscopy showed a laterally spreading granular tumor with a circumference around one third of the lumen, spreading from the duodenal papilla to the inferior duodenal angle, with reddish swelling of the ampulla (Fig. 2). Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated a deficit of contrast medium along a 2-cm section of the duodenal papilla to the distal bile duct, with 4-mm dilatation of the main pancreatic duct (Fig. 3A). Per oral cholangioscopy (CHF-240; Olympus, Tokyo, Japan) using a side-view endoscope showed a papillary tumor laterally spreading from the ampulla to the lower bile duct (Fig. 3B).

An ampullary biopsy revealed dense papillary and tubular hyperplasia of atypical glandular epithelium with nuclear enlargement and partially adhesive glands, findings highly suggestive of adenocarcinoma or adenoma with high-grade dysplasia. Therefore, the patient underwent subtotal stomach-preserving pancreatoduodenectomy and was discharged after an uneventful recovery.

A histological analysis revealed well-differentiated adenocarcinoma of the ampulla with sequential infiltration of highly dysplastic tubular adenoma spreading from the distal common bile duct to the second part of the duodenum, which was 4.5 cm in length from the oral to the anal side of the duodenum and 2.5 cm in length from the hilar side of the bile duct to the ampulla (Fig. 4A). The intramucosal tubular adenocarcinoma arose at the ampulla within an extensive, carpet-like adenoma involving most of the second part

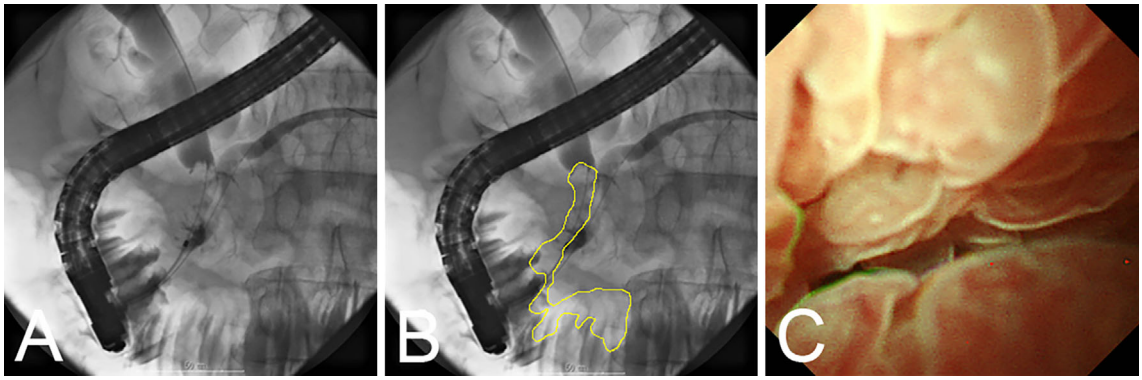

Figure 3. **(A, B) Endoscopic retrograde cholangiopancreatography demonstrated a deficit of contrast medium from the duodenal papilla to the distal bile duct with mild dilatation of the main pancreatic duct. (B) Yellow line, tumor laterally spreading from the distal common bile duct to the second portion of the duodenum. (C) Per oral cholangioscopy using a side-view endoscope showed a laterally spreading papillary tumor from the ampulla to the distal common bile duct.**

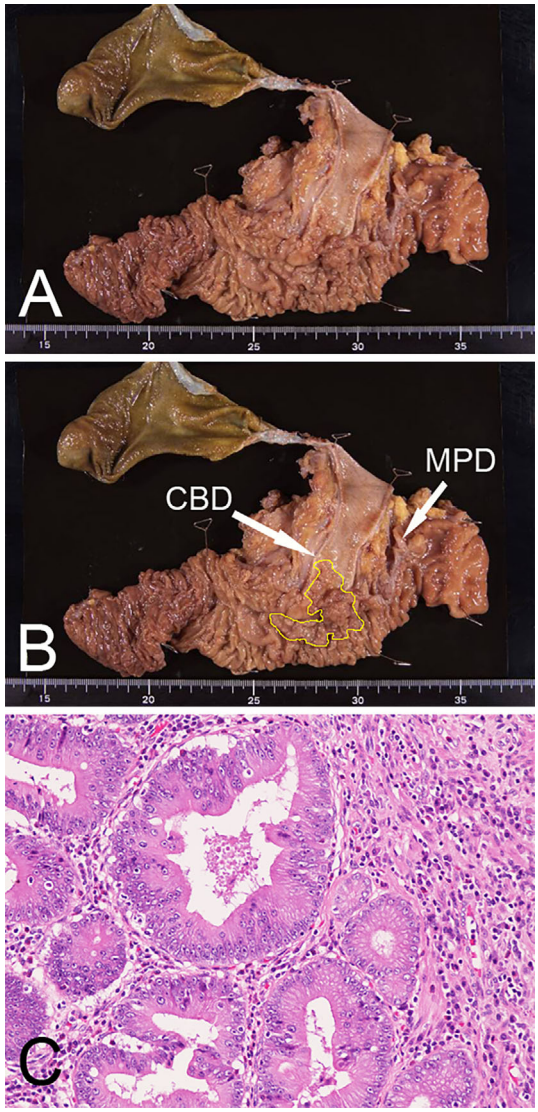

Figure 4. **(A, B) Resected formalin-fixed specimen. (B) Yellow line, tumor laterally spreading from the distal common bile duct to the second portion of the duodenum. (C) Hematoxylin and Eosin staining of the ampulla of Vater. The adenocarcinoma was limited to the mucosa.**

of the duodenum with continuous extension into the distal bile duct. The adenocarcinoma was limited to the mucosa (Fig. 4B); there was neither involvement of the main pancreatic duct nor metastasis in the seven resected lymph nodes (pTisN0M0, stage 0 in UICC TNM classification).

Immunohistochemical staining for cytokeratin (CK) 20 was positive in the whole tumor (Fig. 5G-I): interestingly, CK7 staining was positive in the cytoplasm in the bile duct and ampulla but not in the duodenum (Fig. 5D-F), while caudal homeobox gene transcription factor-2 (CDX2) staining was positive at the side of the duodenum from the ampulla (Fig. 5M-O). Thus, the spreading tumor had CK7-positive epithelium in the bile duct and CK7-negative epithelium in the duodenum, with adenocarcinoma in the middle. In addition, MUC5AC staining was partially positive in a portion of the duodenal epithelium, while MUC1 and MUC2 staining was negative throughout the epithelium (Fig. 5J-L). These results suggested that the tumor was predominantly intestinal-type ampullary adenocarcinoma.

Discussion

Ampullary carcinomas typically show intestinal- or pancreatobiliary-type differentiation, histopathologically resembling carcinomas of the adjacent tissues (duodenum, bile duct, or pancreas) (5). We herein report an exceedingly rare adenoma laterally spreading into the bile duct and duodenum from an *in situ* adenocarcinoma of ampullary origin.

There have been several case reports of synchronous presentation of ampullary adenocarcinoma and common bile duct cancer (6), a collision tumor composed of cancers of the bile duct and the ampulla (7), papillary adenoma of the distal common bile duct with a separate peri-ampullary adenocarcinoma (8), and duodenal adenoma obstructing the ampulla (9). However, no case in which the tumor spread from the bile duct to the duodenum with a different pathologic phenotype in each organ has been reported. The tumor in the present case so completely occupied the ampulla and

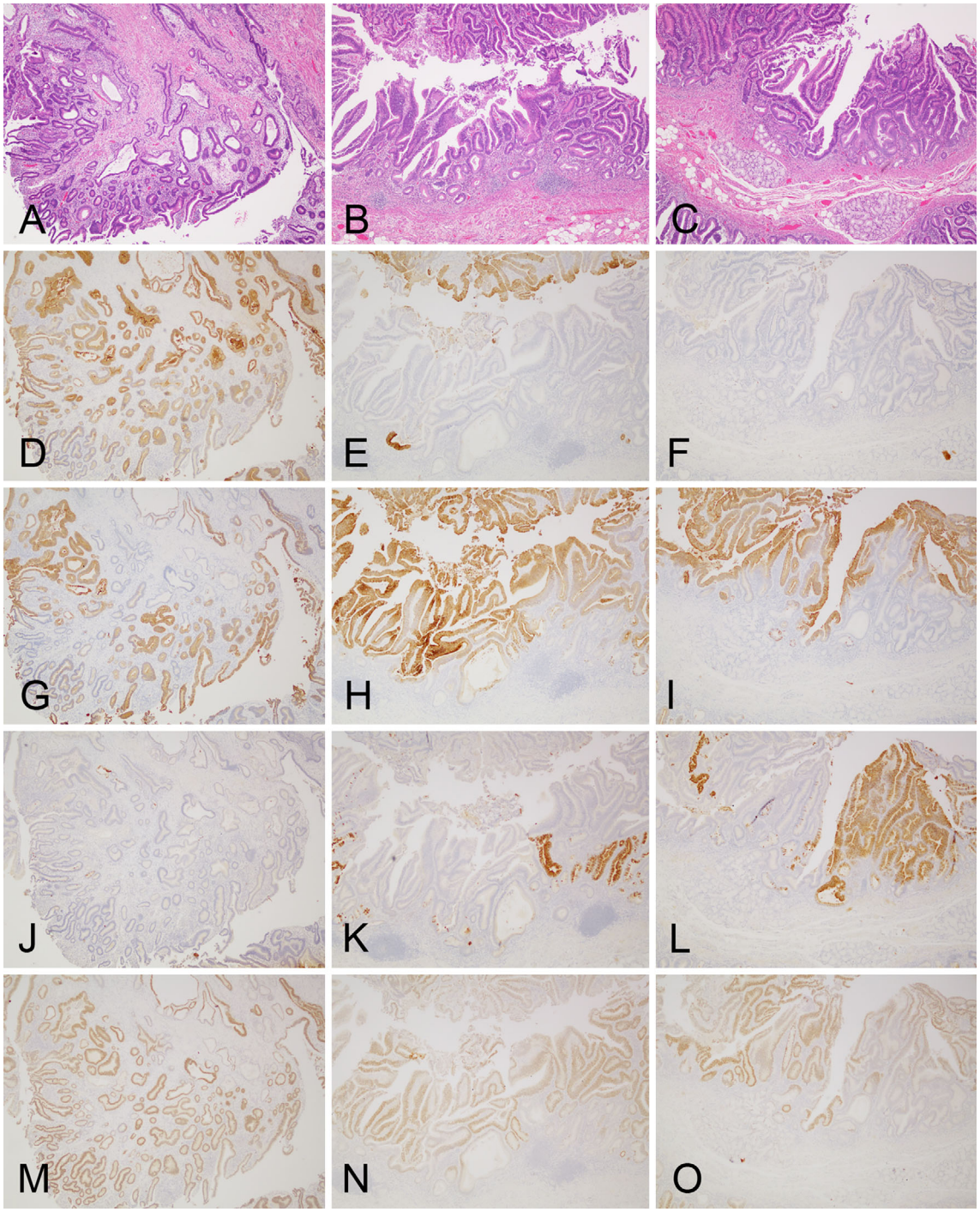

Figure 5. **Representative histological findings of the lateral-spreading tumor. Portions in the bile duct (A, D, G, J, M), ampulla of Vater (B, E, H, K, N), and duodenum (C, F, I, L, O) are indicated by Hematoxylin and Eosin staining (A, B, C), and immunohistochemical staining for CK7 (D, E, F), CK20 (G, H, I), MUC5AC (J, K, L), and CDX2 (M, N, O). Original magnification, ×40.**

terminal segment of the bile duct that dilatations of the common bile duct and the main pancreatic duct were depicted in the fluoroscopic images during ERCP and serum hepatobiliary enzymes were elevated.

Adsay et al. classified ampullary carcinoma into four subtypes (4): intra-ampullary type, which is an invasive carcinoma arising in intra-ampullary papillary-tubular neoplasms with no or minimal duodenal surface involvement; ampullary-ductal type, which shows constrictive, sclerotic, plaque-like thickening of the walls of the common bile duct and/or pancreatic duct, resulting in mucosa-covered, button-like elevations of the papilla into the duodenal lumen; peri-ampullary-duodenal type, involving the growth of massive exophytic, ulcero-fungating tumors into the duodenal lumen that encase the ampullary orifice with only minimal intra-ampullary luminal involvement; and ampullary carcinoma-not otherwise specified, an ulcero-nodular tumor located at the ampulla of Vater. These four clinicopathologic subtypes

are prognostically distinct; the intra-ampullary type has the best prognosis, and the ampullary-ductal type the worst (4).

The present case cannot be attributed to any of the four types in the proposed classification because the study excluded tumors spreading widely into bile duct and/or duodenum, since the origin of the tumor was indistinct (4). Indeed, tumors broadly spreading from the bile duct, pancreatic duct, and duodenum are typically resected, as they are difficult to diagnose as ampullary tumors (4). In our case, however, the tumor was identified as well-differentiated intramucosal tubular adenocarcinoma in a tubular adenoma because the CK7-positive region encompassing half of the lesion precluded its identification as a duodenal tumor; CK7 is typically underexpressed (10), whereas CK7 and CK20 are overexpressed, in more than half of intestinal-type intraampullary papillary-tubular neoplasms (CK7 and CK20: 93% and 63%, respectively) (11). In contrast, bile duct tumors typically express CK7 (10). Furthermore, the lesion at the ampulla was the only site of intramucosal adenocarcinoma, suggesting this lesion to be the origin of the tumor. Our case was also unique in that the tumor showed both bile duct and intestinal phenotypes.

The transition of tumor phenotype indicated that the tumor had developed at the ampulla and spread into the bile duct and duodenum. We speculate that the present tumor initially occurred at the ampulla, and thereafter changed its phenotype (CK7+, CK20++) to one similar to that of the bile duct (CK7++, CK20+) and duodenal neoplasia (CK7-, CK20++) and which spreads along the bile duct and the duodenum, respectively. A collision tumor composed of cancers of the bile duct and duodenal ampulla has previously been reported (7); however, if our case was a collision tumor, its origins would be the bile duct and duodenum with more malignant characteristics than duodenal ampulla alone. Because malignancy was detected only at the duodenal ampulla in the present case, the tumor was unlikely to have been formed by the collision of two tumors.

Mucins and CDX2 are useful markers for diagnosing ampullary adenocarcinoma and particularly for determining the degree of malignancy (12). Most intestinal-type ampullary cancers express CDX2 and MUC2, whereas pancreatobiliary subtype papillae are, at least focally, positive for MUC5AC, and gastric-tubular subtype papillae are, at least focally, positive for MUC1 (3, 11, 13). The immunohistochemical results showed that the tumor in our case comprised intestinal-type ampullary or peri-ampullary adenocarcinoma.

Mucins are also useful markers for predicting the survival. MUC5AC in our case was positive in only part of the duodenal epithelium, not the site of adenocarcinoma *in situ*, as we assume our case was an intraepithelial cancer, not an advanced ampullary adenocarcinoma. Patients with ampullary adenocarcinoma positive for MUC5AC have a worse survival than those negative for MUC5AC (12, 13).

The elevated hepatobiliary enzyme levels recovered over the two-month period between the tests performed at a local clinic and those performed on the day of admission. This is consistent with preliminary intermittent obstructive jaundice, a characteristic symptom of ampullary tumors (14). Ampullary tumors are typically diagnosed by CT, magnetic resonance imaging, ERCP, or endoscopic ultrasound (EUS) (15). As the present tumor completely occupied the ampulla and partially reached the distal bile duct, cholangiography revealed a deficit of contrast medium which thus suggested the presence of a solid tumor in the distal bile duct. Although EUS is more sensitive and specific than CT for ampullary tumors and nodal staging, CT, ERCP, and conventional upper gastrointestinal endoscopy revealed the tumor so distinctly that EUS was not needed to assess its depth.

Forceps biopsies revealed no malignancy; however, a negative biopsy result does not exclude the presence of cancer (15). Therefore, the patient underwent complete resection of the tumor and surrounding organs. Surgical resection is conventionally recommended for the treatment of ampullary carcinoma (2). Endoscopic removal is an alternative modality for ampullary adenoma or early-stage ampullary adenocarcinoma, provided it can be resected completely (2, 16, 17). The first large case series of such tumors was reported in 1993 by Binmoeller et al. (18). However, as the tumor in our case spread from the bile duct to the duodenum, it could not be resected endoscopically. Furthermore, the incidence of complications of duodenal endoscopic resection (e.g., intraoperative perforation, delayed perforation, and delayed bleeding) is high (19). The tumor has not recurred in the three years since its resection.

In conclusion, a tumor spreading from the bile duct to the duodenum from the ampulla of Vater is rare. The tumor in this case showed both bile duct- and intestinal-type spreading. The surgical procedure performed was the current first-line therapy for suspected malignancy, and discrete pre-therapeutic examinations by CT and ERCP were necessary.

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

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