Intraductal papillary neoplasm of the bile duct with infiltrative small cell neuroendocrine carcinoma: A case report

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Abstract

Introduction: We present the case of an intraductal papillary neoplasm of the bile duct (IPNB) accompanying a small cell neuroendocrine carcinoma.

Patient concerns: A 73-year-old male Chinese patient presented with jaundice of unknown origin. A contrast-enhanced computed tomography scan revealed that the wall of the lower common bile duct was thickened and nodular, causing a narrowing in the lumen and upper common bile duct enlargement above the narrow segment.

Diagnosis and interventions: The initial diagnosis based on clinical manifestations was IPNB and pancreatoduodenectomy was performed. Pathological examination of the resected bile duct revealed papillary proliferation of biliary-type cells with nuclear atypia, indicating IPNB. Immunohistochemistry was positive for neuroendocrine markers indicative of infiltration and small cell neuroendocrine cancer.

Outcomes: The patient died on postoperative day 138.

Conclusion: This is the first reported case of its kind, as none has been reported in any published literature so far.

Introduction

An intraductal papillary neoplasm of the bile duct (IPNB) is a rare and special type of biliary system epithelial-derived tumor, manifesting as a papillary or villous mass in the bile duct epithelium. This tumor was first reported and called bile duct papillomatosis by the French surgeon, Chappet in 1894. In 2010, the World Health Organization (WHO) named it IPNB; therefore, this type of tumor can be considered as both an ancient and young disease. It has been reported in literature that 40% -80% of IPNB are invasive cancers, tubular adenocarcinomas, or mucinous adenocarcinomas.[1, 2]

Neoplasms with neuroendocrine differentiation of the extrahepatic bile duct or gallbladder, including neuroendocrine neoplasms and neuroendocrine carcinomas (NEC). According to the 2019 WHO classification criteria, neuroendocrine cancers are divided into large cell and small cell types.

We present a patient with IPNB accompanying a NEC in the extrahepatic bile ducts. This case is the first of its kind to be published.

2. Case Presentation

Clinical course

The patient was a 73-year-old male with no relevant past history. Three weeks before admission, he had upper abdominal cramps after intake of greasy food, accompanied with nausea, vomiting, and jaundice which appeared two weeks before admission. On physical examination, we found: icteric skin and

sclerae, deep tenderness in the right upper abdomen, and a negative Murphy's sign. The liver function tests before admission were: alanine aminotransferase (ALT) 114 U/L，aspartate aminotransferase (AST) 95 U/L，alkaline phosphatase (ALP) 448 U/L，gamma-glutamyl transferase (GGT) 515 U/L，total bilirubin (T-BIL) 194.55 umol/L，direct bilirubin (D-BIL) 114.86 umol/L，Table 1，. The tumor markers were，CA 19-9 59.63 U/ml，carcinoembryonic antigen (CEA) 1.21 ng/mL，and CA 125 8.50 U/ml，Table 2，. On ultrasound, the common bile duct was 3.3 cm wide, and there were several hyperechoic groups in the lower lumen, the largest one being 2.29 x 1.78 cm，Figure 1，. The plain and enhanced abdominal computed tomography (CT) showed a thickened and nodular wall in the lower part of the common bile duct, with a maximum thickness of about 1.3 cm and a CT value of about 47 HU. The arterial phase and portal phase were about 93 HU and 89 HU, respectively. The affected portion of the bile duct was narrowed, while there was an upstream distention with a maximum width of about 4.0 cm. Similar 1.4 x 1.1 cm strengthened nodules were seen in the expanded upper wall of the bile duct. The intrahepatic bile duct was dilated, with local soft rattan-like changes，Figure 2，. The initial diagnosis was IPNB. Pancreatoduodenectomy was performed on August 21, 2019. During the operation, the common bile duct was significantly widened by about 3 cm. After the surgery, the specimens were dissected, and polypoid masses were observed growing around the lower common bile duct, 2 cm from the duodenal papilla with a length of about 2 cm. The tumor reached the common bile duct stenosis, and multiple stones were seen in the narrow segment and its proximal common bile duct. Water intake started on postoperative day 7, and a gradual transitioned to a normal diet was done. Postoperative jaundice gradually subsided, and the liver function tests on postoperative day 12 showed: ALT 25 U/L，AST 25 U/L，T-BIL 32.67 umol/L，and D-BIL 16.10 umol/L，Table 1，. The patient had no fever, no abdominal pain, and the jaundice subsided. Though counseling on the recommended VP-16 (etoposide) + cisplatin chemotherapy was done for the patient, the patient did not give his consent. He developed anorexia, nausea, and vomiting on postoperative day 90, without jaundice. Biochemical tests were performed on postoperative day 97 and were all elevated as follows: ALT 54 U/L, AST 104 U/L, ALP 271 U/L, GGT 391 U/L，T-BIL 10.66 umol/L，D-BIL 3.57 umol/L ，Table 1，，CA 19-9 144.45 U/ml, CEA 12.06 ng/mL, and CA 125 49.91 U/ml，Table 2，. The abdominal ultrasound showed multiple metastatic tumors in the liver. The patient abandoned further treatment. Jaundice occurred on postoperative day 111. On postoperative day 119, ascites developed, and multiple lung metastases were observed on a chest CT scan. An abdominal puncture was done on postoperative day 129, but the ascites was difficult to drain as it was a sticky and jelly-like. The patient died on postoperative day 138.

Table 1
Liver Function Index

	Reference Range	Pre-operation	POD 12	POD 97
ALT (U/L)	9–50	114	25	54
AST (U/L)	15–40	95	25	104
ALP (U/L)	45–125	448		271
γ-GT (U/L)	8–55	515		391
T-Bil (umol/L)	3.42-21.00	194.55	32.67	10.66
D-Bil (umol/L)	0.00-8.60	114.86	16.10	3.57
ALT:, AST:, ALP:, γ-GT:, T-Bil:, D-Bil:, POD: post-operation day				

Table 2
Tumor Bio-markers

	Reference Range	Pre-operation	POD 97
CA199 (U/mL)	0.00–35.00	59.63	144.45
CEA (ng/mL)	0.00–5.00	1.21	12.06
CA125 (U/mL)	0.00–35.00	8.50	49.91

CA199:, CEA:, CA125:

Pathology of the resected bile ducts

Tumors composed of spindle cells were seen in the submucosa of the common bile duct. The epithelial part of the common bile duct was composed of an intraductal papillary neoplasm with high-grade intraepithelial neoplasia. Gross specimens and low-power microscopic sections showed that the tumor had the characteristics of papilloma, and the infiltrating components showed small cell carcinoma with active division（Figure 3）. The tumor penetrated the wall of the bile duct and invaded the pancreatic tissue. No lymph node metastasis was observed. Immunohistochemical results were S-100（+）CK （partially+）CD56（+）Syn（+）CgA（+）Ki-67（80%+）Muc-5AC（-）and Muc-2（-）Figure 4（.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

3. Discussion

IPNB is defined by WHO as "an exogenous papillary mass of bile duct epithelial origin, mainly growing in the bile duct lumen, which can occur in any part of the biliary tract system including the intrahepatic bile

duct and the extrahepatic bile duct. Some tumors have the characteristics of secreting mucus".[3]

Its clinical manifestations are recurrent pain in the right costal region and acute cholangitis signs namely, intermittent jaundice and fever. These clinical manifestations may be related to acute biliary obstruction caused by the fragility of the tumor, or to transient biliary obstruction caused by the secretion of mucus from some tumors. Some patients could be asymptomatic. IPNB can appear single or multiple, benign or malignant. About 35% of IPNB patients have malignant transformation at the time of onset or during follow-up. According to its pathological characteristics, it can be divided into low-grade lesions and high-grade lesions, among which low-grade lesions are often called "papillary adenoma", and high-grade lesions are called "non-invasive papillary carcinoma."[4]

A neuroendocrine tumor (NET) originates from APUD cells and is common in the gastrointestinal tract and respiratory tract. NETs occurring in the biliary tract (BNET) are extremely rare, accounting for 0.2–2% of all gastrointestinal NETs.[5] BNET can occur in any part of the extrahepatic bile duct, of which the hepatic duct and distal bile duct are the most common locations, followed by the middle bile duct, gallbladder duct, and proximal bile duct.[6] Most of these tumors are non-functional, and a few have the function of secreting hormones or vasoactive substances like serotonin, gastrin, insulin, calcitonin, vasoactive intestinal peptide, etc. Only about 9% of them cause carcinoid syndrome.[7] Clinical manifestations of BNET patients are mainly dependent on tumor size, location, invasion of adjacent tissues or distant metastasis, etc. The most common clinical manifestation of BNET patients is jaundice.[8]

Our patient manifested with recurrent pain and discomfort in the right upper abdomen, and jaundice. Later, the patient was treated for ascites. The patient had a viscous and colloid hemorrhagic ascites, which was consistent with IPNB characteristics. Jaundice and bile duct stones were related to the mucus secretion function, while stenosis of the lumen was caused by the tumor itself. The invasive growth and short-term distant metastasis of the tumor may be related to NET characteristics.

The most important imaging features are the communication between the lesion and the dilated bile duct and multiple nodules in the lesion. CT and magnetic resonance imaging (MRI) show that the tumors are mostly located in the dilated part of the intrahepatic bile duct, forming papillary and polyp-like accessory wall nodules, which are significantly strengthened in the early stage. Some tumor cells secrete too much mucus, resulting in bile duct dilatation, sometimes accompanied by dilation of the main pancreatic duct and expansion of the duodenal papilla.[9] The gross pathological features of IPNB are single or multiple, gray or yellow, brittle papillary masses in the bile duct, or diffuse villous masses in the bile duct. Microscopically, papillary proliferation of bile duct epithelial cells manifesting as adenoma or adenocarcinoma can be seen. It is connected to the bile duct wall with a pedicle-like structure composed of a fibrous vascular matrix surrounded by the upper skin.[10] In this case, a 2.5 x 4.5 x 1.5 cm mass in the lumen of the common bile duct, surrounded the wall of the duct and was accompanied by silt-like calculi, visible to the naked eye, which was consistent with the imaging findings of the disease.

NET is difficult to distinguish from other types of cholangiocarcinomas via imaging. Preoperative tumor markers such as AFP, CEA, CA I9-9, and CA 125 are non-specific, and the diagnosis mainly depends on pathology. Immunohistochemical analysis and detection items include Syn and CgA which help in determining the neuroendocrine cell characteristics of tumor cells, and the Ki-67 index which indicates the degree of tumor malignancy.[11] According to the fifth edition of the WHO classification of digestive system tumors, when extrahepatic bile duct papillary tumors progress to invasive cancer, high-grade intraepithelial neoplasia is usually observed, and the invasive components are mostly tubular adenocarcinoma or small cell neuroendocrine carcinoma. In this case, postoperative imaging visualized the tumor in the lower part of the common bile duct and a polypoid growth around the circumference. Under the microscope, the tumor penetrated the common bile duct wall and invaded the adjacent tissues. Immunohistochemical results showed Syn (+), CgA (+), and Ki-67 > 80%. The infiltrating component was consistent with small cell carcinoma, suggesting a poor prognosis.

Both pure intrabiliary papillary tumors and BNETs are rare primary bile duct tumors. Bile duct papillary tumors occurring with NETs are extremely rare. Since both IPNB and NET can cause biliary obstruction, bile duct dilation, and have varying degrees of malignant potential, aggressive surgical resection is the treatment of choice for these two types of tumors. The surgical method should be determined according to the lesion. The basic principle is consistent with that applied during cholangiocarcinoma surgery; that is, in addition to the removal of the primary site of the lesion, regional lymph node dissection should also be performed. If the lesion is located in the liver and is confined to the liver segment, lobe, or hemi-liver, the corresponding liver segmentectomy, lobectomy, or hepatectomy should be performed, and hilar lymph node dissection should be performed. If it is located in the hilar bile duct, radical surgery as is done for hilar cholangiocarcinoma should be performed. If it is located in the extrahepatic bile duct, radical treatment and radical pancreaticoduodenectomy as is done for extrahepatic cholangiocarcinoma should be performed. If the lesion involves one side of the liver and the extrahepatic bile duct, pancreaticoduodenectomy and corresponding hemi-hepatectomy are feasible. Liver transplantation and pancreaticoduodenectomy are theoretically feasible if the lesion involves the intrahepatic bile ducts extensively.[12] For patients with unresectable NETs, arterial embolization chemotherapy and radiofrequency treatment can be considered. Postoperative adjuvant chemotherapy, targeted therapy, local radiotherapy, and somatostatin analogues can be used. These can improve symptoms and extend survival. [7, 13, 14] In this case, the tumor was located in the lower common bile duct, 2 cm from the duodenal papilla; therefore, radical pancreaticoduodenectomy (Whipple operation) was performed. Given that platinum-combined chemotherapy is recommended for small cell carcinomas, we resorted to administer VP-16 chemotherapy to this patient.[15] However, he did not give his consent; therefore, it was impossible to evaluate the effect of chemotherapy on the disease. Due to the low incidence of NETs in the extrahepatic bile duct, there is currently no evidence of high-level evidence-based medicine for postoperative adjuvant therapy. Presently, some clinical studies have reported that sunitinib and everolimus are often used for NETs and can prolong the survival time of patients.[15, 16] However, there is no report on their effectiveness in extrahepatic cholangiocarcinoma. Radiotherapy may be ineffective for cholangiocarcinoma. With the marketing of targeted drugs and tumor immunotherapy drugs in recent

years, future studies can consider conducting gene testing for such patients, and use such treatments if conditions permit to investigate their effectiveness given that no report on this exists as at now.

IPNB progresses relatively slowly, and the prognosis is relatively good. It has been reported that the 5-year postoperative recurrence rate of benign IPNB is about 20%, and the overall 5-year disease-free survival rate (for benign and malignant) can reach 81%.[17] However, primary NETs of the bile duct are often diagnosed late and have a poor prognosis due to tumor spread or metastasis.[17]

Papilloma of the bile duct with small cell neuroendocrine carcinoma is a rare disease, which is difficult to be diagnosed preoperatively. A combination of a perfect clinical examination, careful observation of imaging findings, and full preoperative evaluation help in formulating a reasonable surgical plan, especially in improving outcomes. Histochemistry is useful for diagnosis confirmation. Surgical resection is still the most effective treatment method, and it is currently the only treatment method to obtain potential efficacy and prolong disease-free survival.

Declarations

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Conflict of Interest: The authors declare that they have no conflict of interest.

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Figures

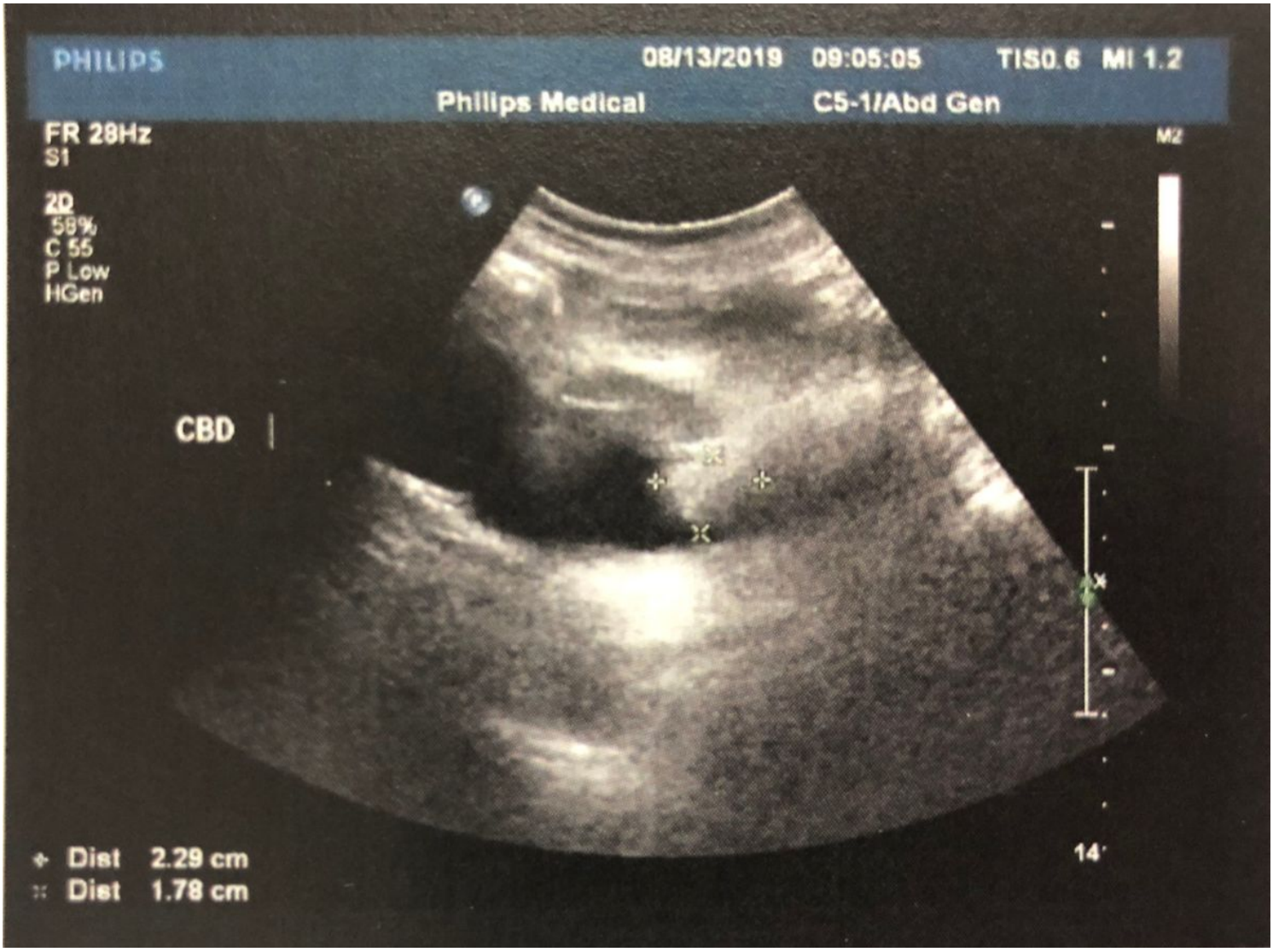

Figure 1

Ultrasound Imaging of the bile duct

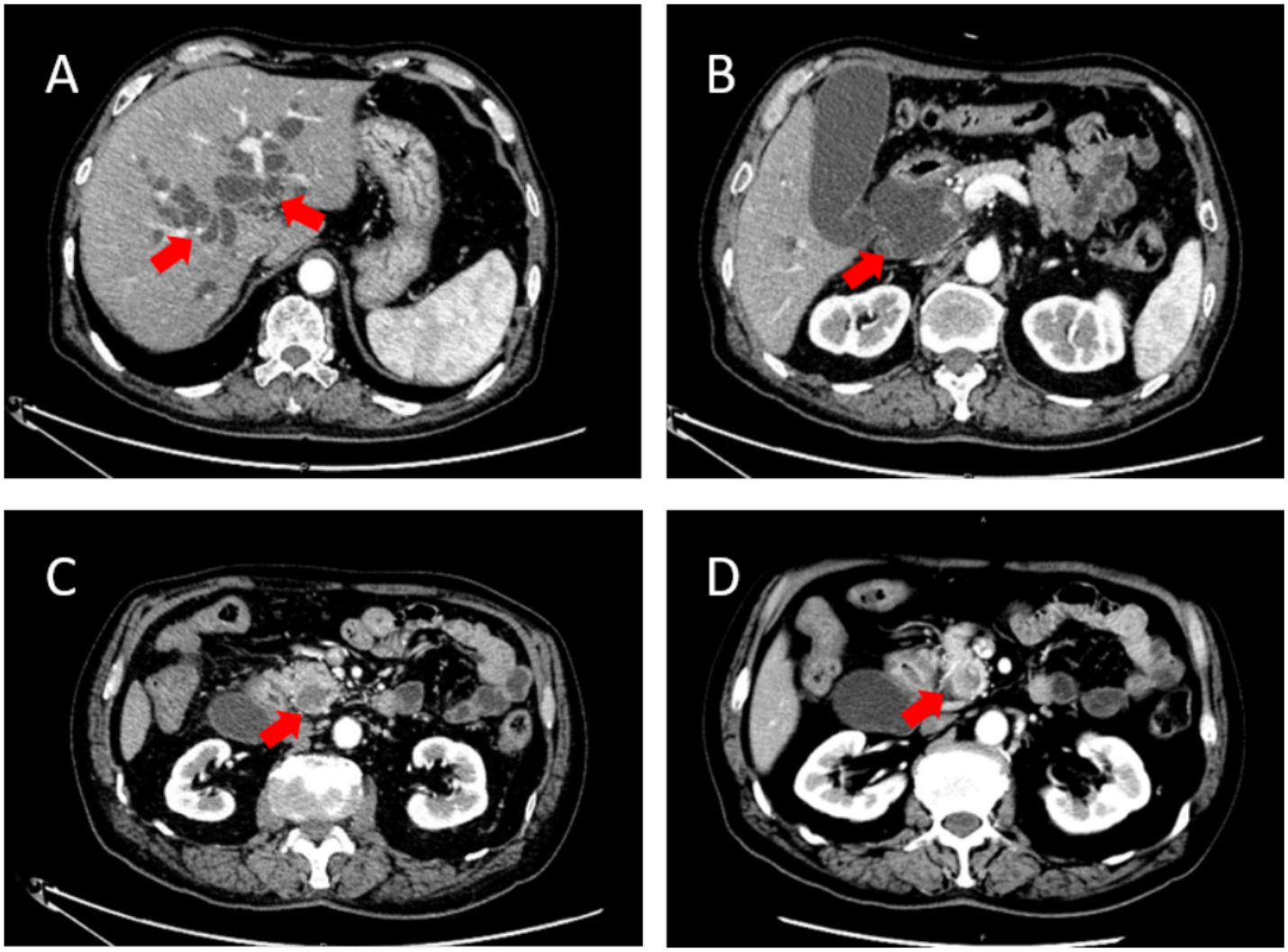

Figure 2

Abdominal enhanced CT scan A. Secondary bile duct dilatation inside the liver B. Secondary bile duct dilatation outside the liver C. Secondary common bile duct dilatation D. Thickening of the wall of the lower common bile duct, with local soft tissue nodules

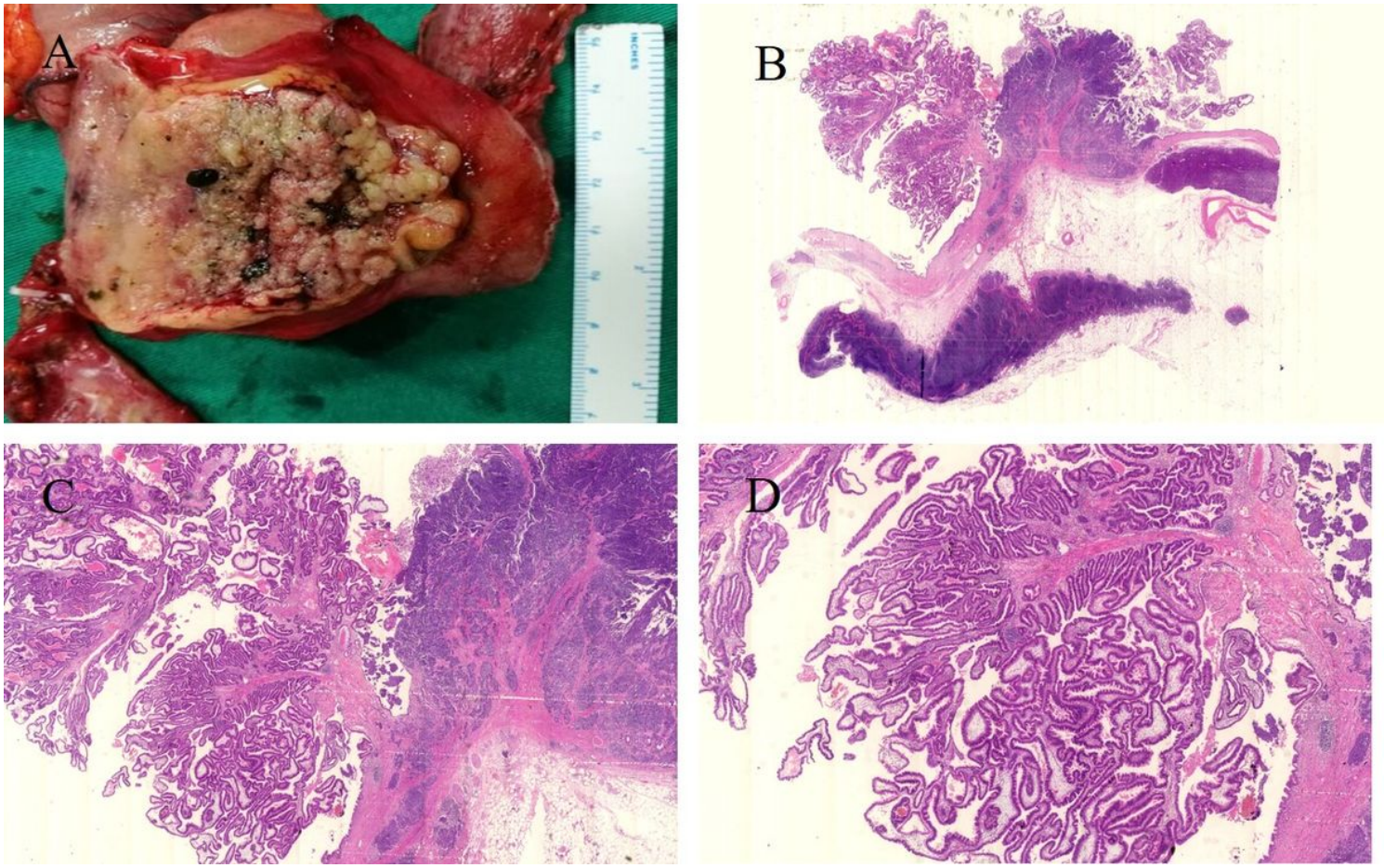

Figure 3

Gross specimen and low power image. The dilated common bile duct is filled with an intraductal papillary neoplasm(A, B). In the same section, papilloma component and small cell carcinoma component exist at the same time. On the left side of the visual field we can see papilloma component with slow division, while on the right side small cell carcinoma component with active mitotic phase can be found(C). The papillary architecture is relatively regular and uniform in appearance, and the tumor cells are arranged along the fibrovascular stalks(D).

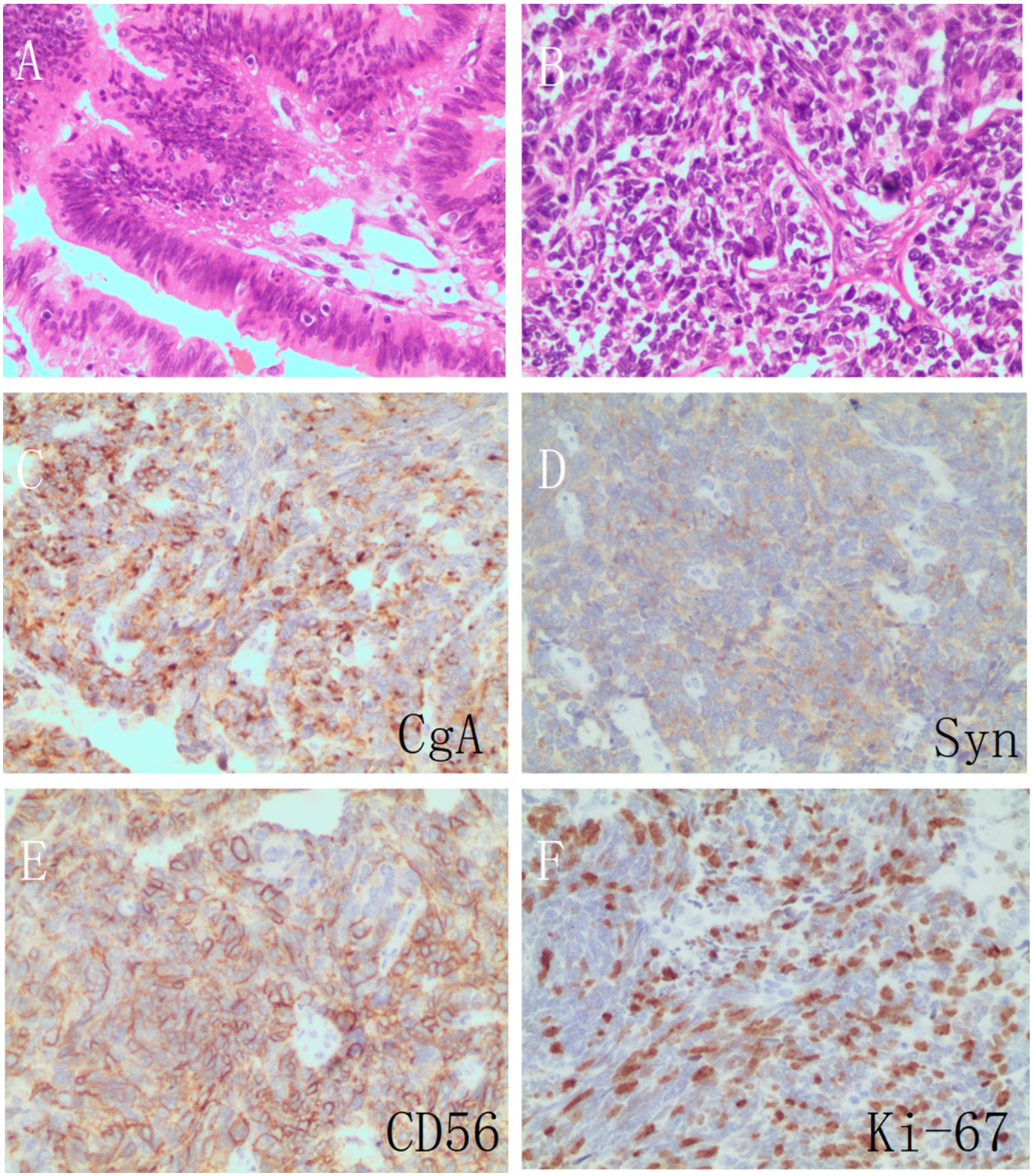

Figure 4

Pathology of the resected bile ducts Hematoxylin and eosin staining showing intraductal papillary tumor of the common bile duct with high-grade intraepithelial neoplasia. The tumor cells are columnar and arranged in a papillary structure. The tumor cells have moderate atypia (A). The cancer cells are nested and diffusely arranged. They are small and oat-like, with little cytoplasm and a high nucleoplasm ratio

(B). Immunohistochemical analysis showed that neoplastic cells were positive for chromogranin A (C), synaptophysin (D), CD56 (E), and Ki-67 (F). The proliferative index (Ki-67) was >80%.