Neuroendocrine carcinoma of the common bile duct associated with congenital bile duct dilatation: A case report

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Case report

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Abstract

Background

Cholangiocarcinoma is frequently seen in patients with congenital bile duct dilatation (CBD). Most cholangiocarcinomas are adenocarcinomas. Other types, especially neuroendocrine carcinomas (NECs), are rare. To the best of our knowledge, this is the third reported case of an NEC of the common bile duct associated with CBD and the first to receive adjuvant chemotherapy for advanced disease.

Case presentation

A 29-year-old woman presented with upper abdominal pain. Preoperative imaging indicated marked dilatation of the common bile duct and a tumor in the middle portion of the common bile duct. She was suspected of having distal cholangiocarcinoma associated with CBD and underwent pylorus-preserving pancreaticoduodenectomy. Pathological and immunohistological findings led to a final diagnosis of large-cell NEC (pT3aN1M0 pStageIIB). The postoperative course was uneventful, and she was administered cisplatin and irinotecan every 4 weeks (four cycles) as adjuvant chemotherapy. She has remained recurrence-free for 14 months.

Conclusion

This presentation is rare, and further reports are necessary.

Background

Congenital bile duct dilatation (CBD) is found in approximately one in 100,000 to 150,000 people, and is frequently observed in Asian patients, including those of Japanese origin [1]. In Japanese patients with CBD, the incidence of cholangiocarcinoma is approximately 15%. The incidence of cholangiocarcinoma after extrahepatic bile duct excision is 0.7%, which is approximately 200 times higher than the incidence of cholangiocarcinoma in the general population in Japan [2, 3]. Cholangiocarcinomas develop frequently in patients with CBD and are usually adenocarcinomas; other types, especially neuroendocrine carcinomas (NEC), are rare[4].

We present a rare case of an NEC of the common bile duct associated with CBD. To the best of our knowledge, this is the third case of an NEC of the common bile duct associated with CBD to be reported [5, 6].

Case Presentation

Chief complaints

A 29-year-old Japanese woman presented to a hospital complaining of upper abdominal pain.

History of present illness

The patient's symptoms commenced 2 months prior and worsened one month before presentation. She subsequently presented to a hospital, where laboratory data revealed liver dysfunction. She was admitted for further examination and was found to have CBD and a tumor in the common bile duct. Consequently, she was referred to our hospital for surgery.

History of past illness

She developed cholecystitis at the age of 15 years and had no relevant family history.

Physical examination

The patient's blood pressure was 93/62 mm Hg, heart rate was 70 beats per minute, respiratory rate was 12 breaths per minute, body temperature was 37.1 °C, and oxygen saturation in room air was 99%. Physical examination revealed slight upper abdominal tenderness, without jaundice, and a positive Murphy's sign and Blumberg's sign.

Laboratory examinations

Blood analysis revealed elevated levels of aspartate aminotransaminase, 309 IU/L (normal, 8–40 IU/L); alanine aminophosphatase, 511 IU/L (normal, 5–35 IU/L); γ-glutamyl transpeptidase, 614 IU/L (normal, 7–50 IU/L); alkaline phosphatase, 822 IU/L (normal, 100–340 IU/L); and carcinoembryonic antigen, 79.7 ng/mL (normal, 0–4.9 ng/mL). All other laboratory data were within normal limits.

The levels of hepatobiliary enzymes and tumor markers were elevated, which implied that the patient might have developed cholangitis due to a cholangial carcinoma.

Imaging examinations

Abdominal dynamic contrast-enhanced computed tomography showed dilatation of the common bile duct and the bilateral intrahepatic bile ducts (which was diagnosed as Todani type IV-A) and a tumor in the middle portion of the common bile duct (Fig. 1A). Endoscopic ultrasonography showed a tumor in the cystic dilated common bile duct (Figs. 1B, 1C), and one centimeter of the common channel continued from the duodenal papilla. Endoscopic retrograde cholangiopancreatography (ERCP) was not performed on the patient due to absence of jaundice, thereby preventing pancreatitis.

Treatment

The patient was suspected of having distal cholangiocarcinoma (cT2N0M0 cStageIB) associated with CBD and underwent pylorus-preserving pancreaticoduodenectomy with modified Child reconstruction. Intraoperative observation of the abdominal cavity did not reveal any feature of tumor dissemination or liver metastasis. The surgery was performed as scheduled.

Macroscopic findings showed a 50-mm sessile irregular lesion protruding into the markedly dilated lower common bile duct (Fig. 2A, 2B). Pathological findings showed solid proliferation of large, atypical cells accompanied by an adenocarcinomatous component (less than 5%) (Fig. 3A, 3B). Metastasis was detected in one of the 31 lymph nodes tested. Immunohistochemical studies revealed that the large, atypical cells were positive for AE1/AE3, E-cadherin, CD56, chromogranin A, and synaptophysin. The Ki-67 labeling index was over 90% in the solid component (Fig. 3C, 3D).

Final Diagnosis

The final diagnosis was large-cell NEC (pT3aN1M0 pStageIIB). The resection margin was negative.

Outcome and Follow-up

The postoperative course was uneventful, and she was discharged on the 14th postoperative day. This was a case of an advanced neuroendocrine carcinoma, and she was scheduled to receive adjuvant chemotherapy to prevent recurrence. However, the standard regimen of adjuvant chemotherapy for neuroendocrine cholangiocarcinoma has not yet been established; therefore, we selected a mixed regimen of cisplatin and irinotecan according to the National Comprehensive Cancer Network (NCCN) guidelines for small cell carcinomas of the lung. The patient received cisplatin at a dose of 60 mg/m^2 on the 1st day and irinotecan at a dose of 60 mg/m^2 on the 1st, 8th, and 15th days. This regimen was repeated every 4 weeks for four cycles as adjuvant chemotherapy. She has been recurrence-free for over 14 months.

Discussion

The most common form of cholangiocarcinomas associated with CBD are adenocarcinomas; NECs are rare. We searched PubMed for English-language reports describing NEC of the common bile duct associated with CBD and only two cases were reported. To the best of our knowledge, this is the third case of an NEC of the common bile duct associated with CBD to be reported. Pathological diagnoses of the previously reported cases were of well-differentiated NECs [5, 6].

Congenital bile duct dilatation

CBD is seen more often in female patients than in male patients (male-to-female ratio, 1:3). CBD is also common in Asian patients. Todani et al., categorized CBD into five main types, and almost all CBDs of types Ia, Ic, and IV-A are associated with pancreaticobiliary maljunction [2].

A proposed etiology of bile duct dilatation is an increase in the bile duct pressure of the narrow segment of the lower bile duct accompanied by pancreaticobiliary maljunction while the bile duct wall is immature, thereby resulting in dilation of the bile duct. Another hypothesis is that the primitive common bile duct proliferates asymmetrically in the early embryonic period, i.e., insufficient epithelial proliferation in the

lower bile duct and excessive proliferation in the upper bile duct leads to stenosis of the lower bile duct and dilatation of the upper bile duct [2].

Pancreaticobiliary maljunction causes mixing and regurgitation of bile and pancreatic juices, which stagnate in the gallbladder and the bile duct, especially in the dilated common bile duct. This increases the cytotoxic potential for damage to the biliary epithelium under conditions of infection, inflammation, biliary stasis, decreased trypsin inhibitor concentrations, and the presence of enterokinase [5, 7, 8]. During repair, multiple alterations of oncogenes and tumor suppressor genes occur, and this could lead to the development of carcinomas through multistage interactions. Hyperplasia of the biliary or gallbladder epithelium is characteristic of pancreaticobiliary maljunction; moreover, mutations of the *K-ras* and *p53* genes and overexpression of the p53 protein are observed in malignant as well as benign lesions of the biliary tract in patients with pancreaticobiliary maljunction. These changes are referred to as the "hyperplasia-carcinoma sequence" [9, 10].

One study reported that the incidence of cholangiocarcinoma was approximately 15% in Japanese patients with CBD. The incidence of cholangiocarcinomas after extrahepatic bile duct excision is 0.7%, although this is approximately 200 times higher than the incidence of cholangiocarcinoma in the general population in Japan [2, 3]. Another study reported that the overall incidence of cholangiocarcinoma with pancreaticobiliary maljunction with both a dilated and a nondilated bile duct, is 10.4%, which is more than 285 times higher than the risk in general population [10]. Furthermore, the average age of patients with cholangiocarcinoma associated with pancreaticobiliary maljunction is 10 years lower than that of the general population [2, 11, 12].

Neuroendocrine carcinoma of the common bile duct

Biliary NEC represents 0.19% of all primary malignant tumors in the extrahepatic bile duct [13]. It is estimated that over 50% of patients with gastroenteropancreatic NEC exhibit distant metastasis during initial diagnosis. Biliary NEC is relatively aggressive. In a review of 22 patients with biliary NEC, distant metastasis occurred in 16 cases on initial admission. Distant metastasis is present in all cases within one year after surgery, even though surgery is the mainstay of treatment for biliary NEC and is regarded as the curative option. Furthermore, the survival outcomes are poorer (in the decreasing order) for NECs that originate in the lungs, gastrointestinal tracts, and hepato-biliary-pancreatic systems [14]. Terashima et al., reported that the response rate to chemotherapy in patients with extrapulmonary NEC was lower than that in patients with pulmonary NEC. In cases of extrapulmonary NEC, the hepato-biliary-pancreatic systems group showed the lowest response rate [15].

In many anatomical sites, neoplasms exist that exhibit both neuroendocrine and non-neuroendocrine elements, which can be present as morphologically distinct cell populations or be more intimately intermixed. The neuroendocrine elements of these "mixed" or "combined" neoplasms are most commonly NECs; the non-neuroendocrine components can be glandular, squamous, or of other lineages [16].

In our case, neuroendocrine components occupied 90% or more of the tumor's invasive area, and few adenocarcinomatous components were found (Fig. 4A). In contrast, early adenocarcinomatous components were found on the mucosa of the tumor surface (Fig. 4B). This suggests that hyperplasia and dysplasia due to chronic inflammation of the bile duct mucosa initially result in adenocarcinomas, which subsequently transforms to NECs; however, in our case, a small extent of hyperplasia or dysplasia was noted on the noncancerous mucosa of the bile duct or gallbladder, differing from typical CBD. However, the concept of cancer stem cells is widely accepted as important in cancer development, with recent studies showing that cancer stem cells play important roles in the carcinogenesis of various types of cancer. In particular, several investigations have demonstrated that the different components of mixed neuroendocrine-non-neuroendocrine neoplasms are monoclonal, although their molecular signature is not identical to that of their relative counterparts when they present as separate neoplasms [17, 18].

Neuroendocrine carcinoma of common bile duct associated with congenital bile duct dilatation

We searched the PubMed database for reports in English language describing neuroendocrine carcinomas of the common bile duct associated with congenital bile duct dilatation and found two cases. One was a 6-year-old girl who underwent extrahepatic duct resection and hilar lymphadenectomy. The pathological diagnosis was a well-differentiated NEC; she was recurrence-free for two years without adjuvant chemotherapy. The other was a 28-year-old woman who underwent pancreaticoduodenectomy. The pathological diagnosis was a well-differentiated NEC (pT1N0M0 stageIA); she was recurrence-free for 3 years without adjuvant chemotherapy. Our patient was a 29-year-old woman who underwent pancreaticoduodenectomy. The pathological diagnosis was a poorly differentiated NEC (pT3aN1M0 stageIIB); she continues to undergo follow-up as an outpatient. In accordance with NCCN guidelines for small cell carcinomas of the lung, she received cisplatin at a dose of 60 mg/m^2 on 1st day and irinotecan at a dose of 60 mg/m^2 on 1st, 8th, and 15th days; administration of both drugs was repeated every 4 weeks for four cycles as adjuvant chemotherapy. She has not experienced recurrence in 14 months. The common feature in all three cases was that the patients were of the same gender. Ours is the only case to receive adjuvant chemotherapy for advanced disease.

In our case, it was probable that the adenocarcinoma first developed in the common bile duct with subsequent neuroendocrine differentiation. In contrast, the two previous reports did not clearly indicate whether their tumor included adenocarcinoma components; thus, NEC may have developed *de novo* in the common bile duct.

Conclusion

We present a rare case of a poorly differentiated NEC of the common bile duct associated with CBD. The association between CBD and NEC is unclear, although CBD has a known risk for carcinogenesis. While it

is uncertain whether similar patients will present in the future, NEC originating in the bile duct is rare, and it is necessary to continue to accumulate such reports.

Abbreviations

CBD
congenital bile duct dilatation
NEC
neuroendocrine carcinoma
ERCP
endoscopic retrograde cholangiopancreatography

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

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

Availability of data and materials

Not applicable

Competing interests

The authors have nothing to declare.

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Authors' contributions

KY and TA made substantial contributions to the conception and design of the study and to data acquisition, analysis, and interpretation. KY and TA drafted the article and made critical revisions related to important intellectual content of the manuscript. NY, TC, OH, NH, AM, YH, NT, OR, and KK contributed to data acquisition, analysis, and interpretation. All authors approved the final version of the manuscript for submission.

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Not applicable

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Figures

Fig.1

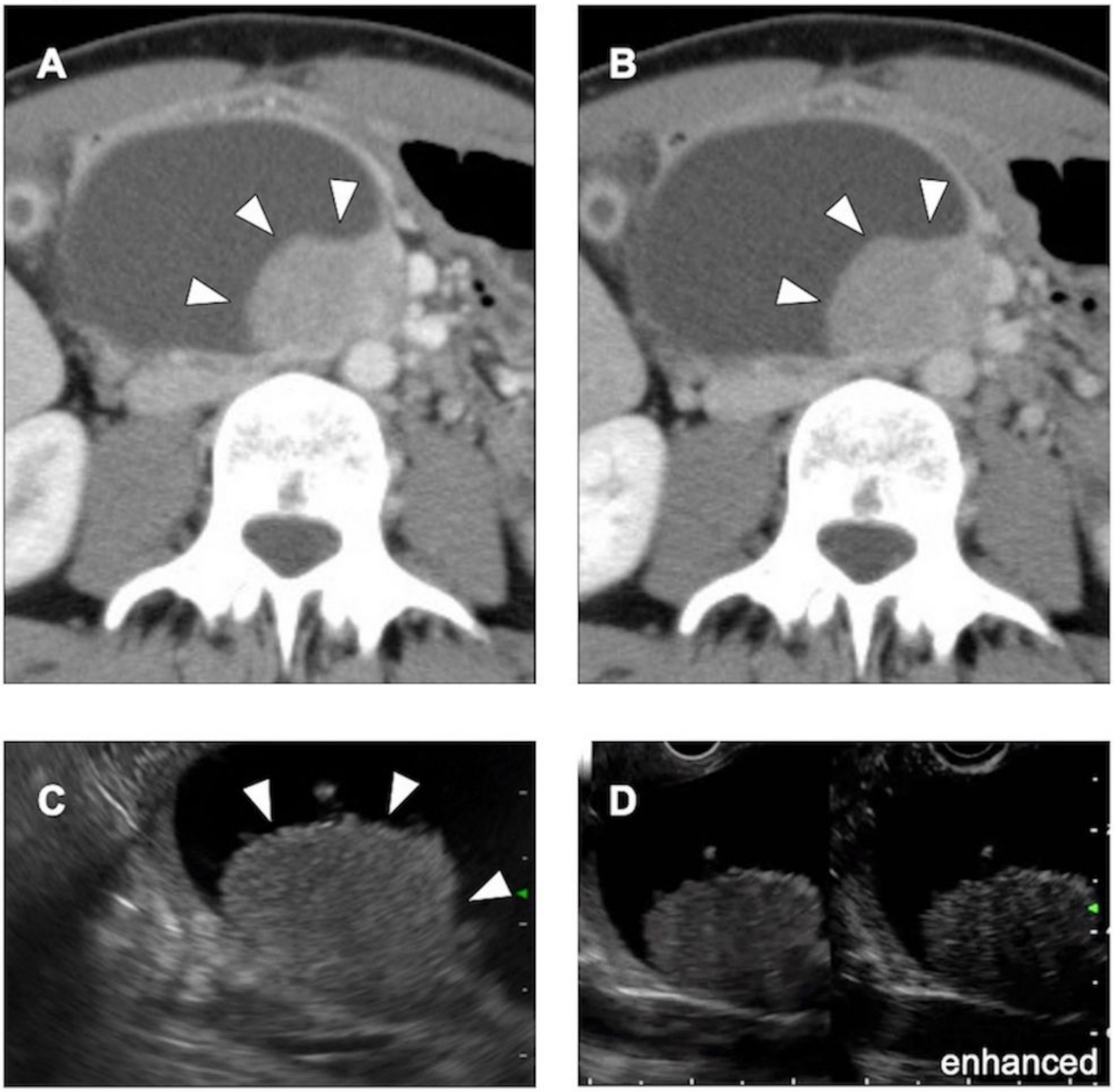

Figure 1

Preoperative imaging (A and B) Arterial phase and delayed phase of abdominal dynamic contrast-enhanced computed tomography. These images show a tumor in the middle portion of the common bile duct and dilatation of the common bile duct and the intrahepatic bile ducts bilaterally; the dilatation is diagnosed as Todani type IV-A. The tumor has enhanced iso-density at arterial phase, and contrast effect was prolonged to delayed phase. (C) Endoscopic ultrasonography showed a tumor in the cystic dilated

common bile duct. (D) Contrast-enhanced endoscopic ultrasonography shows uptake of contrast agent into the tumor

Fig.2

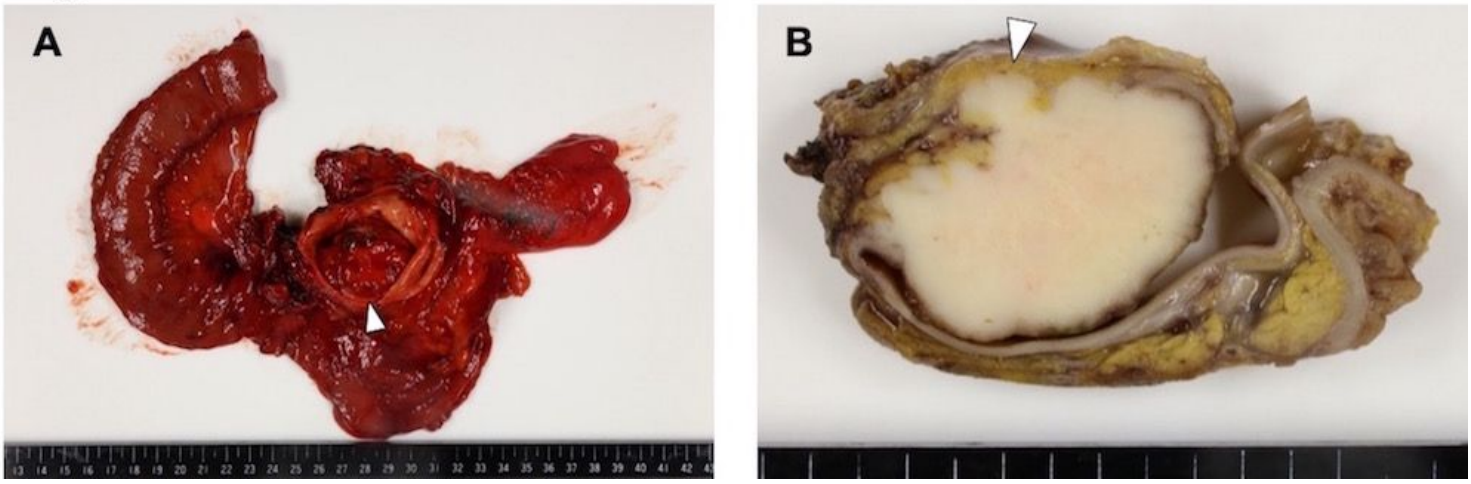

Figure 2

Macroscopic finding (A) A 50-mm sessile irregular lesion protruding into the lower common bile duct is observed. (B) Gross description of the short axis of the common bile duct. Tumor invasion into the pancreas (arrowhead)

Fig.3

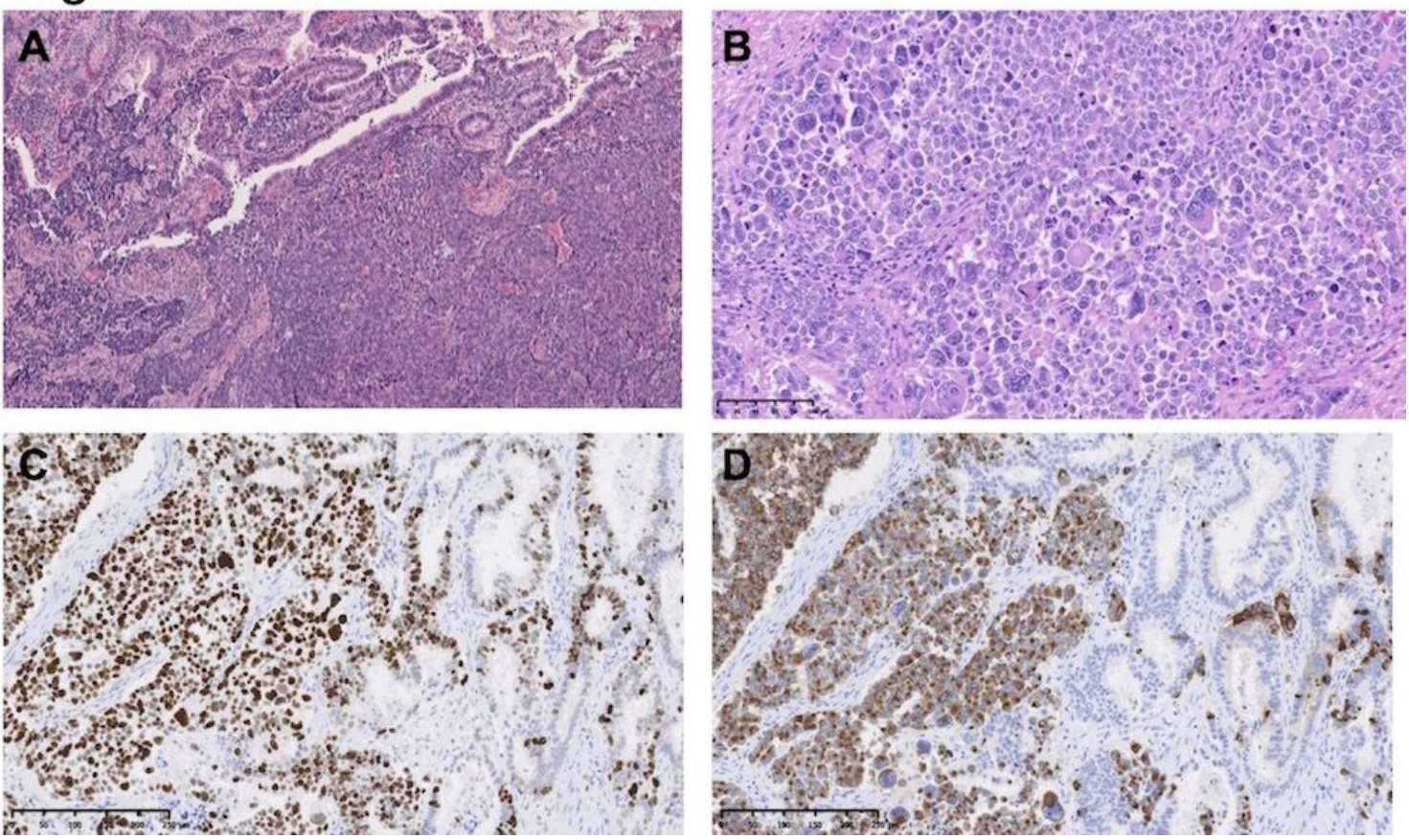

Figure 3

Microscopic findings; hematoxylin and eosin stain and immunohistochemical stain (A) The transition area from adenocarcinoma with a tubulopapillary structure (left upper part) to neuroendocrine carcinoma (NEC) with a solid structure (right lower part). Hematoxylin and eosin stain (H&E, ×60). (B) The area of NEC consisting of large tumor cells with irregular-shaped hyperchromatic nuclei (H&E, ×200). (C) Ki-67 labeling index was over 90% solid component (×100). (D) Tumor cells are positive for chromogranin-A in the solid component, thereby revealing neuroendocrine differentiation (×100)

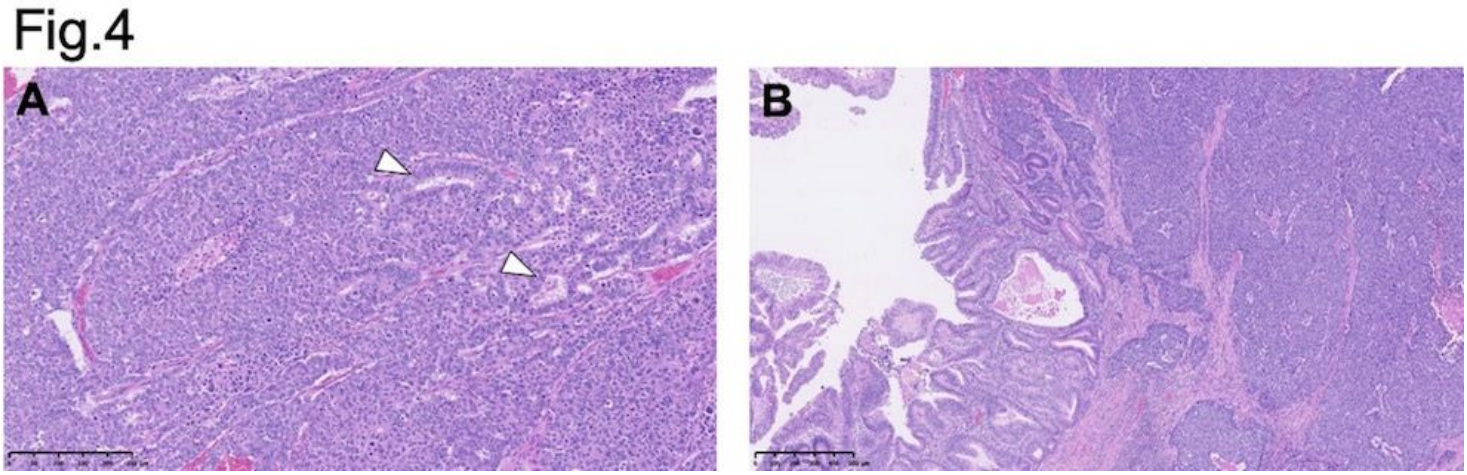

Figure 4

Microscopic findings; neuroendocrine components and adenocarcinomatous components (A) Neuroendocrine components occupy 90% or more of the tumor invasive area, and few adenocarcinoma components are found here (arrowhead) (H&E, ×100). (B) Early adenocarcinoma components spread on the mucosa of the tumor surface (H&E, ×40)