CASE REPORT

Neuroendocrine Carcinoma with an Adenocarcinoma Component on the Ampulla of Vater Causing Acute Pancreatitis: A Case Report

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ABSTRACT

We encountered a rare case in which a 14 mm ampullary tumor had both components of neuroendocrine carcinoma and adenocarcinoma, which caused acute pancreatitis. A Sixty-one-year-old woman was referred to our hospital for evaluation and treatment of pancreatitis due to an unknown cause. After various imaging examinations, the cause of pancreatitis was found to be a duodenal papillary tumor. We performed endoscopic retrograde pancreatic duct drainage by inserting a drainage tube; subsequently, her abdominal pain was relieved, and the pancreatic enzyme levels normalized. As the pathological findings showed poorly differentiated neuroendocrine carcinoma, pancreaticoduodenectomy was performed. As liver and lymph node metastases were found 3 months postoperatively, she underwent chemotherapy. Although she achieved complete remission once, metastases relapsed and she died of progressive disease 28 months postoperatively. Histological examination showed that the tumor comprised two elements: the main component (99.5%) was neuroendocrine carcinoma, and the minor component was adenocarcinoma. The adenocarcinoma component was observed only in the mucosal layer, whereas the neuroendocrine component invaded the submucosa or deeper layer. It is speculated that adenocarcinoma had arisen first from the epithelium, and then it acquired neuroendocrine differentiation capabilities during growth. Although some reports have proposed that neuroendocrine components have more aggressive features than adenocarcinoma components, it is still unclear whether the neuroendocrine or adenocarcinoma component is the main driving force of disease progression. Neuroendocrine carcinoma with an adenocarcinoma component is highly aggressive and associated with a high risk for distant metastasis and a poor prognosis, as in the present case.

INTRODUCTION

Neuroendocrine carcinomas (NECs) with an adenocarcinoma component on the ampulla of Vater are very rare. The 2010 edition of the World Health Organization classification of tumors of the digestive system proposed a concept called mixed adenoneuroendocrine carcinomas (MANECs); MANECs are defined as having two malignant components, neuroendocrine and gland-forming epithelial cells, and each component exceeds 30% of the tumor [1]. The case we discuss herein had neuroendocrine and adenocarcinoma components, although the neuroendocrine component occupied 99.5% of the whole tumor. Even if a tumor does not meet the criteria, an ampullary tumor with both NEC and adenocarcinoma components is rare.

The common symptom of malignancy on the ampulla of Vater is painless jaundice or abdominal pain [2]. We found that NEC with an adenocarcinoma component triggered acute pancreatitis in our patient. It is relatively rare for a duodenal papillary tumor to cause acute pancreatitis [3]. Herein, we describe our experience with a rare patient with a 14 mm ampullary tumor that had both components of NEC and adenocarcinoma, which caused acute pancreatitis.

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Abbreviations MANECs mixed adenoneuroendocrine carcinomas; NECs neuroendocrine carcinomas
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CASE REPORT

A Sixty-year-old woman was referred to our hospital for evaluation of acute pancreatitis. She had presented to the referring hospital with severe, continuous abdominal pain. Results of initial laboratory tests showed increased amylase (783 IU/L) and lipase (1540 U/L) levels, as

well as increased total bilirubin (1.3 mg/dL), aspartate aminotransferase (61 IU/L), alanine aminotransferase (81 IU/L), alkaline phosphatase (727 IU/L), and C-reactive protein levels (2.13 mg/dL). Initial serum tumor markers showed a normal serum level of carcinoembryonic antigen (CEA; 1.9 ng/L), pro-gastrin-releasing peptide (Pro-GRP; 64.4 pg/mL), slightly elevated neuron-specific enolase (NSE; 10.8ng/mL), and elevated carbohydrate antigen 19-9 (CA19-9; 153.4 U/mL). The dynamic contrast-enhanced computed tomography (CT) scan showed pancreatic swelling with slight peripancreatic fluid effusion. The CT scan also showed a hypervascular lesion located in the ampullary region, with dilation of the common bile duct (CBD) and main pancreatic duct (MPD) **(Figure 1ab)**. The endoscopic ultrasonogram showed a 14 mm × 10-mm low echoic mass in the ampullary lesion, which was round and well-defined **(Figure 2)**. Upper gastrointestinal endoscopy showed the reddish, swollen papilla with an irregular surface and easy-touch bleeding **(Figure 3ab)**. The endoscopic retrograde cholangiopancreatogram showed that the CBD and MPD were markedly dilated **(Figure 4)**; therefore, we presumed that the tumor of the ampulla of Vater caused obstructive jaundice and acute pancreatitis. Thus, an endoscopic retrograde bile duct drainage (ERBD) tube and endoscopic retrograde pancreatic duct drainage (ERPD) tube were inserted. After ERPD insertion, her abdominal pain was relieved, and the pancreatic enzyme levels normalized. Pathological findings of the endoscopic biopsy of the ampulla showed poorly differentiated NEC. Immunohistochemically, the tumor stained positive for chromogranin A and synaptophysin. The 18F-fluorodeoxyglucose (FDG)-positron emission tomography combined with CT scan showed 18F-FDG accumulation in the ampulla mass (maximum standardized uptake value, 4.3) with no metastases. Following the preoperative diagnosis of NEC, pancreaticoduodenectomy was performed. A cross-section of the resected specimen showed that the tumor was a well-circumscribed, whitish-yellow solid mass occupying the ampulla, which was suspected to have generated from the common channel since the tumor was localized around the ampullary orifice **(Figure 5)**. The histological examination showed that the tumor comprised two elements **(Figure 6a)**: 1) the main component (99.5%) was NEC arranged in a nest, and each cell had abundant cytoplasm and nuclear hyperchromatism **(Figure 6b)**; and 2) the minor component (0.5%) was the well-differentiated adenocarcinoma **(Figure 6c)**, and the adenocarcinoma component was also found in the epithelium of ampullary duodenal (Ad) area **(Figure 6d)**. The tumor was localized mainly at Ad area, and a part of tumor spread to the common channel area **(Figure 7a)**. The adenocarcinoma component was found to be slightly exceeded submucosal layer of Ad area **(Figure 7b)**. However, there was no superficial extension of tumor to ampullary bile duct (Ab) area and no invasion to the duodenum and pancreatic parenchyma. The epithelium at Ab area was found to have hyperplastic change and it was thought to be the reactive epithelial hyperplasia due to ERBD placement **(Figure 7c)**. Results of immunohistochemical staining showed that the neuroendocrine component was positive for chromogranin A, synaptophysin, and CD56, and the Ki-67 index was 63% **(Figures 8abcd)**; the adenocarcinoma component was negative for these aforementioned tumor markers. The stage of the tumor was classified as pT1N0M0, stage IA based on the TNM classification (Union for International Cancer Control, 8th ed). Three months postoperatively, multiple liver metastases and lymph node metastases were found, despite performing resection at an early stage. The patient had been undergoing chemotherapy consisting of a combination of cisplatin and etoposide (VP16). Although she achieved complete remission, which was attributed to the first regimen, the liver metastases relapsed 12 months later. Then, she received carboplatin plus VP16 as the second regimen, irinotecan as the third, and amrubicin as the fourth. She died of progressive disease 28 months postoperatively.

DISCUSSION

In the present case, a tumor of the ampulla of Vater was detected as the cause of acute pancreatitis. The coexistence of acute pancreatitis and malignancies of the duodenal papilla is rare [3]. The common presentation of a malignancy of the duodenal papilla is painless jaundice. Regarding neuroendocrine tumors of the ampulla of Vater, including

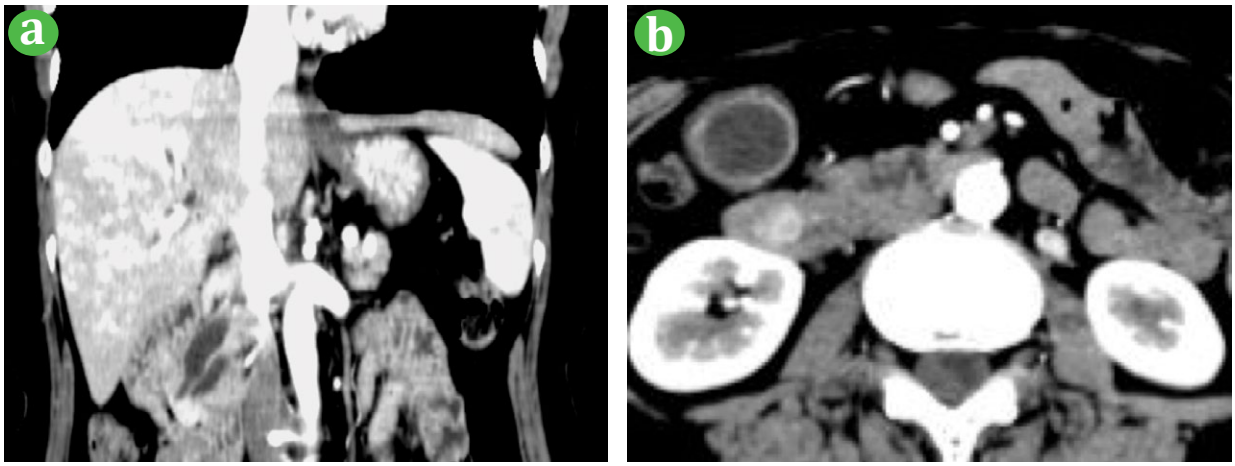

Figure 1. Contrast-enhanced computed tomography scan showing **(a).** a hypervascular lesion located in the ampullary region **(b).** with dilation of the common bile duct and main pancreatic duct.

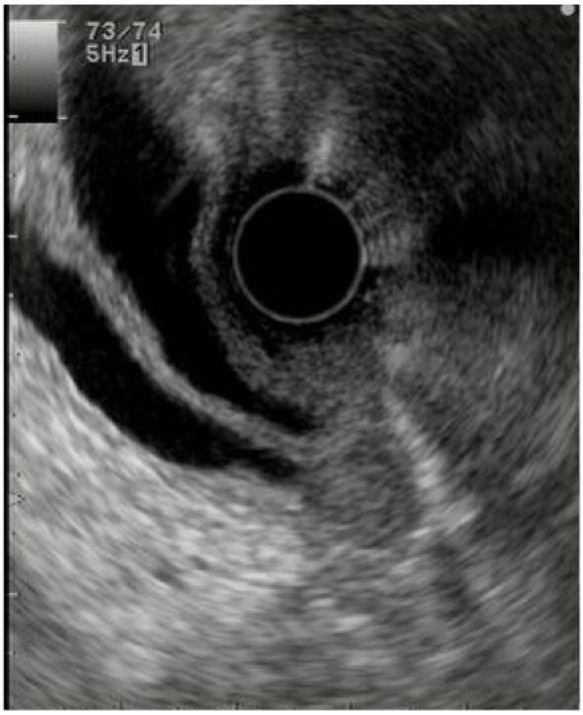

Figure 2. Endoscopic ultrasonogram showing a 14 × 10-mm low echoic mass in the ampullary lesion.

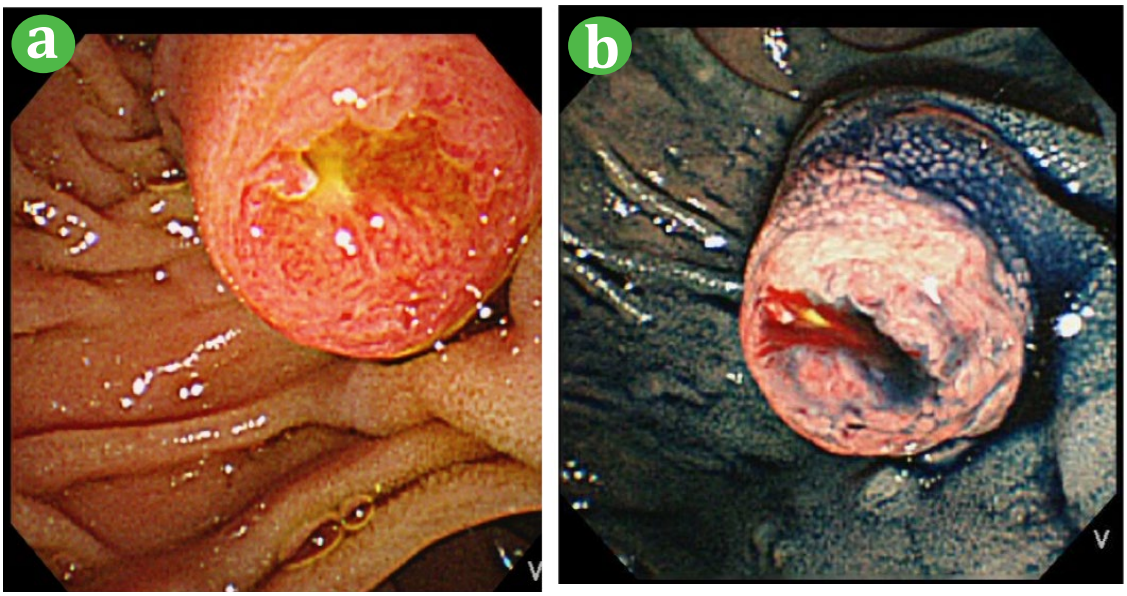

Figure 3. (a, b). Upper gastrointestinal endoscopic image showing the reddish, swollen papilla with an irregular surface and easy-touch bleeding.

composite neuroendocrine and adenomatous carcinoma, jaundice (60%) and abdominal pain (40%) are the most frequent symptoms [2]. The patient described in this article presented with pancreatitis because of obstruction of the pancreatic duct by the tumor, and then ERPD insertion was very effective. When the cause of pancreatitis is unclear, a tumor of the duodenal papilla should be considered as one of the differential pathogeneses.

Regarding the development of each neuroendocrine or adenocarcinoma component, the widely accepted theory is that the adenocarcinoma component exists mainly in the mucosal surface layer, whereas the component of NEC is often located deeper than the mucosal layer [4]. Harada *et al*. also reported that they experienced the cases of MANEC that the adenocarcinoma components were predominately located at the surface of the tumors, whereas the majority of stromal and vascular invasion and lymph node metastasis involved neuroendocrine components [5]. The present patient had the same invasive pattern as aforementioned. Therefore, we speculated that the adenocarcinoma had arisen first from the epithelium around the common channel of the papilla, and then it acquired neuroendocrine differentiation capabilities during growth. However, it is unclear which component arose first and whether both components will originate from common cells. Woischke *et al*. investigated genetic data on colorectal NECs, and found evidence for a common clonal origin of colorectal NECs and adjacent glandular tumor components. Moreover, they suggested the possibility of early separation of glandular and neuroendocrine components during malignant transformation with subsequent independent mutational evolution [6]. Their findings also support our hypothesis.

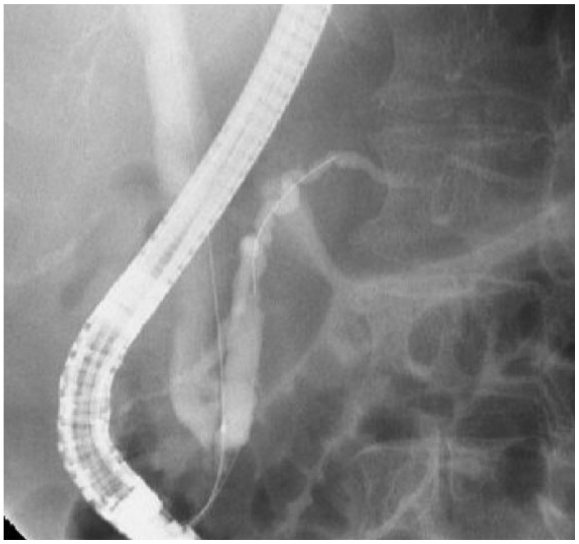

Figure 4. Endoscopic retrograde cholangiopancreatogram showing that the common bile duct and main pancreatic duct are markedly dilated.

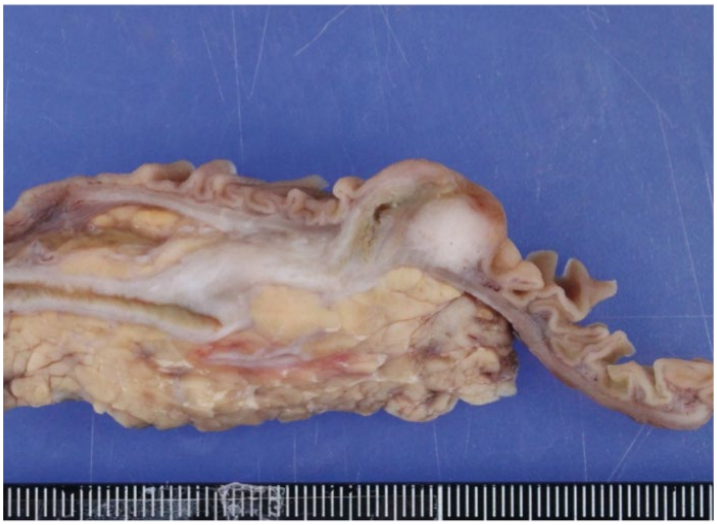

Figure 5. Cross-section of the resected specimen showing that the tumor is a well-circumscribed, whitish-yellow solid mass occupying the ampulla.

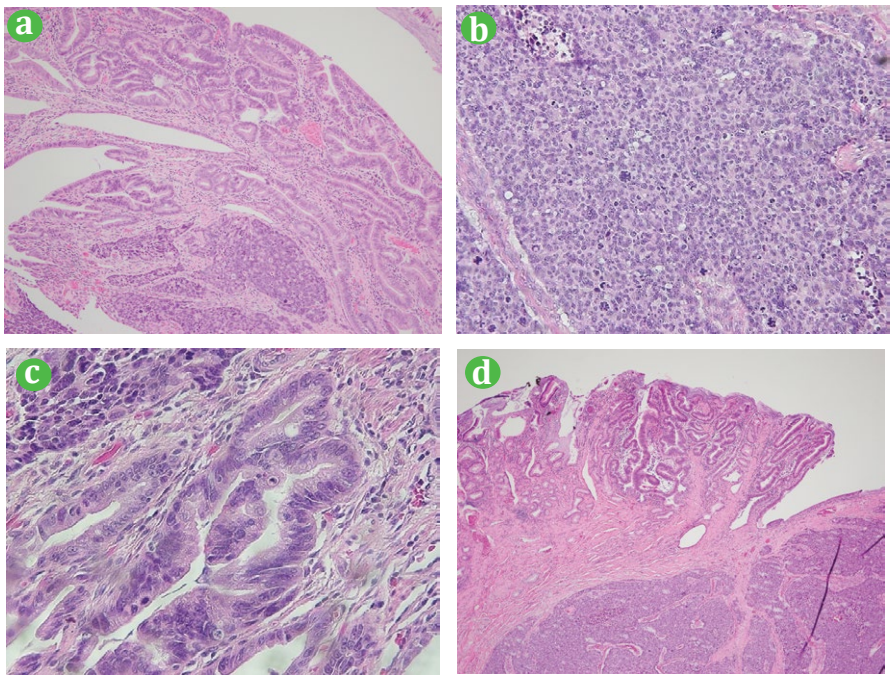

Figure 6. Histological examination showing that **(a).** the tumor comprises two elements: neuroendocrine carcinoma (NEC) and adenocarcinoma. **(b).** The main component is NEC arranged in a nest, and each cell has abundant cytoplasm and nuclear hyperchromatism; and **(c).** the minor component is the well-differentiated adenocarcinoma. **(d).** The adenocarcinoma component is also found in the epithelium of ampullary duodenal (Ad) area.

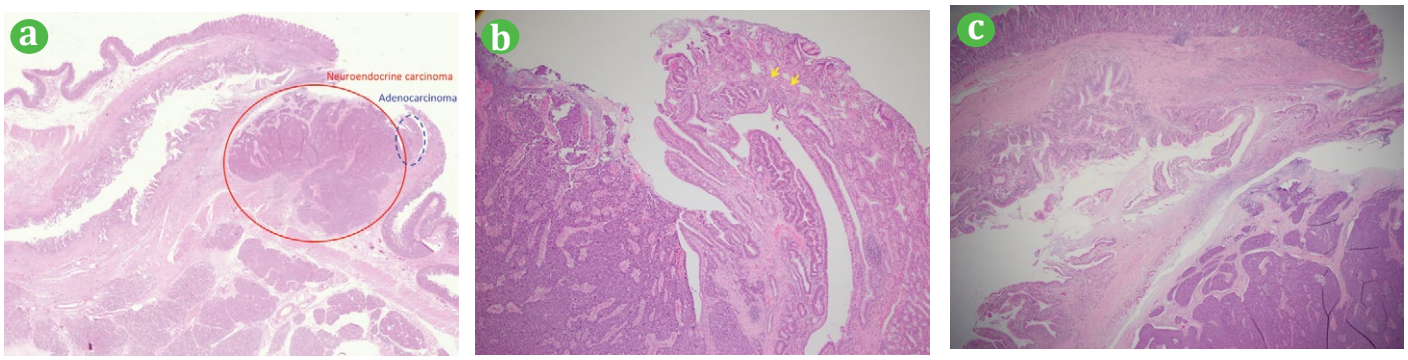

Figure 7. The tumor is localized mainly at ampullary duodenal Ad area, and **(a).** a part of tumor spread to the common channel area. Yellow arrow shows submucosal layer of Ad area, **(b).** and the adenocarcinoma component is found to be slightly exceeded submucosal layer of Ad area. The epithelium of ampullary bile duct (Ab) area is found to have hyperplastic change, and **(c).** there is no superficial extension of tumor to Ab area.

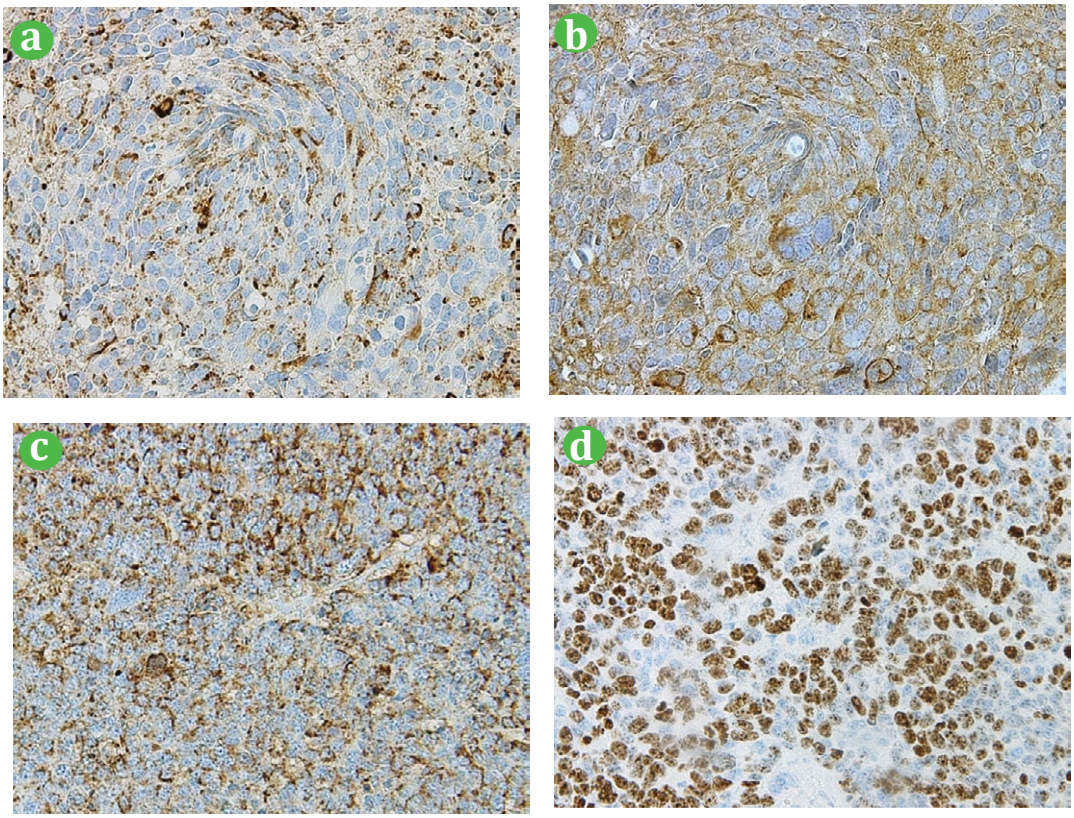

Figure 8. Images of immunohistochemical staining of the resected specimen showing that the neuroendocrine component is positive for **(a).** chromogranin A, **(b).** synaptophysin, and **(c).** CD56. The **(d).** Ki-67 index is 63%.

It is also still unclear whether the NEC or adenocarcinoma component is the main driving force of disease progression. There are several conflicting reports that one of these components, the neuroendocrine component [5,7] or adenocarcinoma component, initiates tumor progression [8]. Yet, Volante *et al*. reported that the clinical behavior of these tumors depends on the adenocarcinoma component if the associated endocrine component is well-differentiated, whereas the prognosis depends on the neuroendocrine component if it is poorly differentiated [9]. However, there are no systematic data to indicate which component affects the prognosis and which treatment is effective.

Generally, NEC and MANECs on the ampulla of Vater are highly aggressive tumors associated with a high risk for distant metastasis and a poor prognosis [3, 10]. Thus, establishment of multidisciplinary treatment, including operation, chemotherapy and radiotherapy, and biological targeted therapy, requires further investigations.

CONCLUSION

In conclusion, we reported has proposed that neuroendocrine components have more aggressive features than adenocarcinoma components, it is still unclear whether the neuroendocrine or adenocarcinoma component is the main driving force of disease progression. Neuroendocrine carcinoma with an adenocarcinoma component is highly aggressive and associated with a high risk for distant metastasis and a poor prognosis, as in the present case.

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Conflict of Interests

The authors declare no conflict of interest and no financial arrangement with any company.

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