



Mixed adenoneuroendocrine carcinoma of the ampulla: Two case reports

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Received: August 2, 2014

Peer-review started: August 4, 2014

First decision: August 27, 2014

Revised: September 22, 2014

Accepted: November 7, 2014

Article in press: November 11, 2014

Published online: February 21, 2015

aged 43 and 60 years, which was confirmed by histology after pancreaticoduodenectomy. These tumors contained neuroendocrine and adenocarcinoma components. The neuroendocrine components were positive for chromogranin A (CgA), synaptophysin (Syn) and CD56 by immunostaining. The adenocarcinoma components were negative for CgA, Syn and CD56. Both cases were T3N0M0 (Stage IIIA). They survived for 15 and 20 mo after surgery, respectively. A brief discussion about the histopathological features, clinical behavior and treatment of MANEC of ampulla, and review of the relevant literature are presented.

Key words: Neuroendocrine tumor; Mixed adenoneuroendocrine carcinoma; Composite carcinoma; Ampulla; Immunohistochemical

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Core tip: The authors report two cases of mixed adenoneuroendocrine carcinoma (MANEC) of the ampulla, which is an extremely rare disease. Both patients received pancreaticoduodenectomy and chemotherapy after surgery. The cases provide a brief discussion about the histopathological features, clinical behavior and treatment of MANEC of the ampulla based on previously published studies.

Huang Z, Xiao WD, Li Y, Huang S, Cai J, Ao J. Mixed adenoneuroendocrine carcinoma of the ampulla: Two case reports. *World J Gastroenterol* 2015; 21(7): 2254-2259 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i7/2254.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i7.2254>

Abstract

Mixed adenoneuroendocrine carcinoma (MANEC) is a malignant tumor with adenocarcinoma and neuroendocrine components, with $\geq 30\%$ of each component required. MANEC of the ampulla is rare. To the best of our knowledge, only 15 cases of MANEC of the ampulla have been reported in the English-language literature. Here, we report two cases of MANEC of the ampulla in two women

INTRODUCTION

According to the 2010 edition of the World Health Organization (WHO) classification of tumors of the dig-

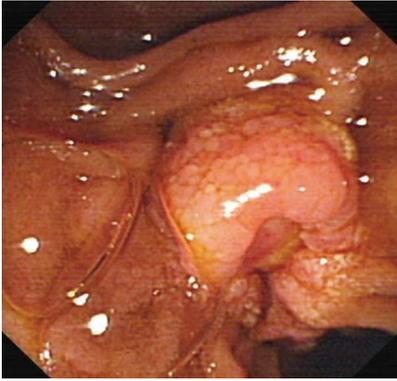


Figure 1 Endoscopic retrograde cholangiopancreatography showing a cauliflower-like mass at the duodenal papilla (Case 1).

estive system, tumors with two malignant components: neuroendocrine and gland-forming epithelial cells, and each component exceeding 30%, are classified as mixed adenoneuroendocrine carcinoma (MANEC)^[1]. These tumors have non-specific symptoms and imaging characteristics, and are mainly diagnosed histopathologically and immunohistochemically after surgery. MANEC can occur in various organs like the gallbladder^[2], bile duct^[3], stomach^[4], colon^[5] and cecum^[6], and location in the ampullary region is rare. To the best of our knowledge, only 15 cases of MANEC of the ampulla have been reported in the English-language literature^[7]. Here, we present two cases of MANEC of the ampulla and review the literature.

CASE REPORT

Case 1

A 43-year-old woman presented with upper abdominal pain in November 2011. Physical examination revealed mild yellow sclera and right upper abdominal tenderness. Laboratory test results included total bilirubin 2.2 mg/dL [normal range (NR): 0.2-1.1 mg/dL], conjugated bilirubin 0.87 mg/dL (NR: 0-0.3 mg/dL), unconjugated bilirubin 1.33 mg/dL (NR: 0.1-1 mg/dL), aspartate aminotransferase 118 U/L (NR: < 35 U/L), alanine aminotransferase 285 U/L (NR: < 35 U/L), alkaline phosphatase 515 U/L (NR: 35-105 U/L). Serum levels of tumor marker carcinoembryonic antigen (CEA), carbohydrate antigen (CA)19-9 and CA12-5 were normal. Magnetic resonance cholangiopancreatography found a soft tissue shadow located in the ampulla region, associated with dilation of the common bile duct. Endoscopic retrograde cholangiopancreatography showed a cauliflower-like mass at the duodenal papilla (Figure 1), and the biopsy showed poorly differentiated adenocarcinoma.

The patient underwent pancreaticoduodenectomy. A cauliflower-like mass at the duodenal papilla measuring 1.5 cm × 2.0 cm in diameter was presented as the

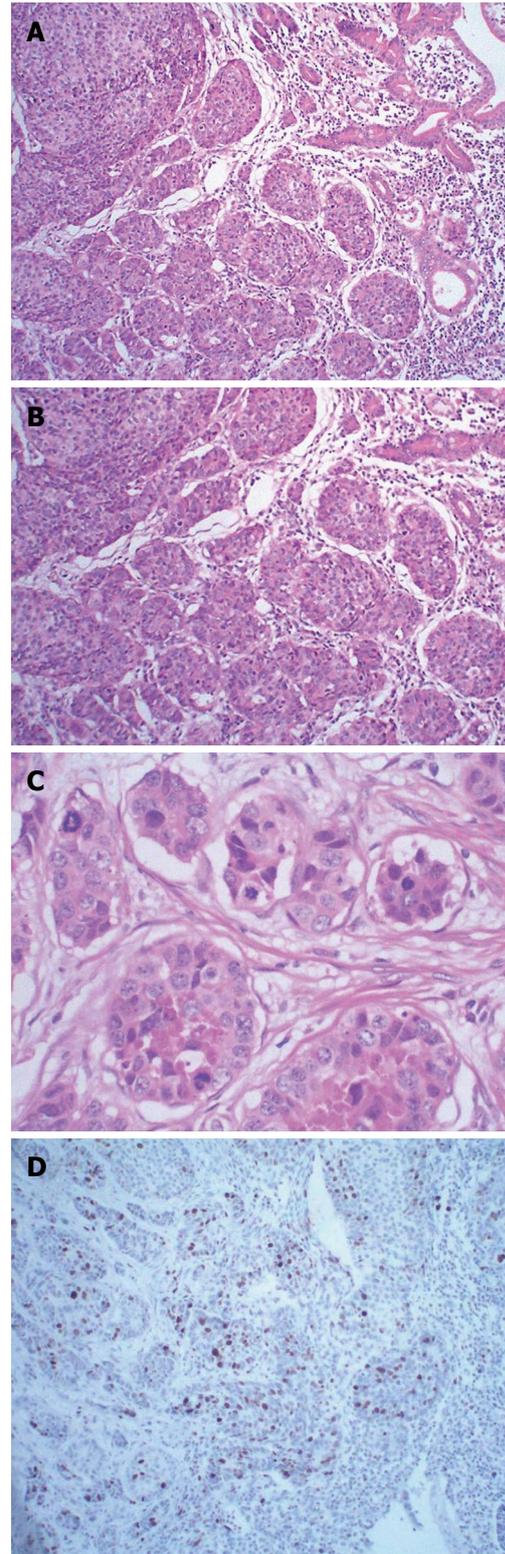


Figure 2 Histological data of Case 1. A: Poorly differentiated adenocarcinoma admixed with neuroendocrine components [hematoxylin and eosin (HE) staining, × 100]; B: The neuroendocrine component was arranged into a nest and the large cells were consistent in size with round nuclei, abundant cytoplasm and coarse chromatin (HE staining, × 100); C: The neuroendocrine carcinoma cells show high mitotic rate (HE staining, × 400); D: Immunohistochemical assay for Ki67 showing high proliferating index (× 100).

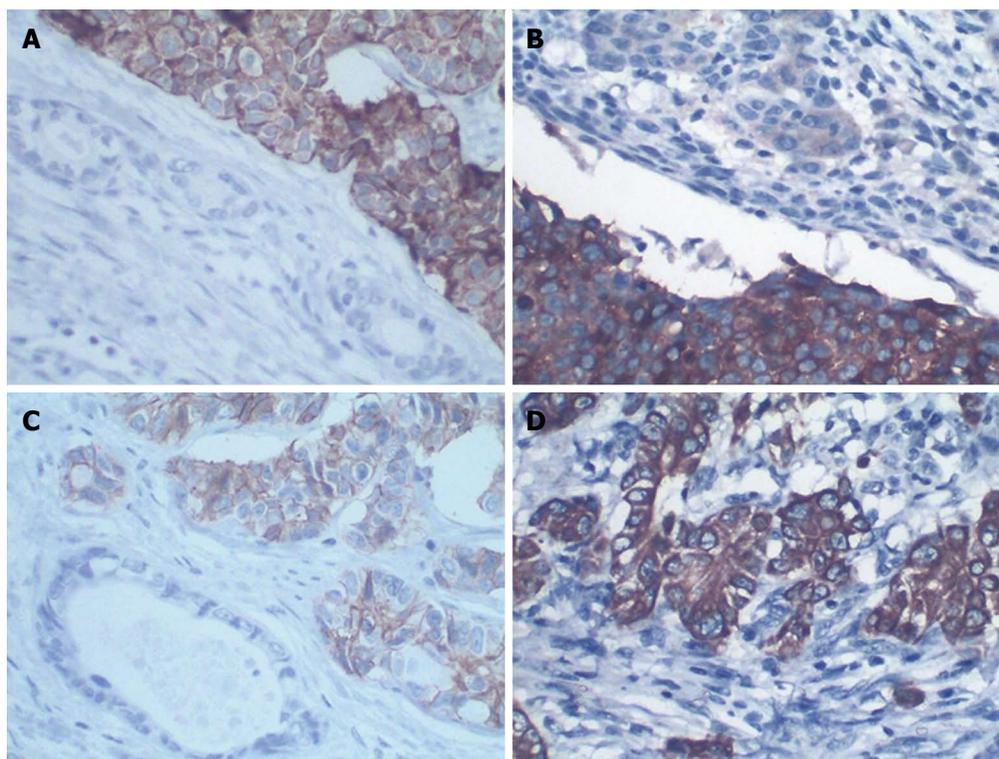


Figure 3 Immunohistochemistry for chromogranin A, synaptophysin, CD56 and CK8 of Case 1. A: Immunohistochemistry staining for chromogranin A: the neuroendocrine carcinoma components show strong and diffuse cytoplasmic positivity ($\times 400$); B: Immunohistochemistry staining for synaptophysin: the neuroendocrine carcinoma components show strong and diffuse cytoplasmic positivity ($\times 400$); C: Immunohistochemistry staining showed the neuroendocrine carcinoma cells were positive for CD56; D: Immunohistochemistry staining for CK8: moderate and diffuse cytoplasmic positivity of adenocarcinoma cells ($\times 400$).

surgical specimen. Histological examination showed that the tumor comprised two cell populations (Figure 2A). One was poorly differentiated tubular adenocarcinoma. The adenocarcinoma cells were arranged into an irregular pattern and accounted for 40% of the whole tumor. The second component was arranged in a nest and the tumor cells were consistent in size, with round nuclei, abundant cytoplasm and coarse chromatin (Figure 2B). The mitotic rate was 30/10 high-powered fields (HPF) (Figure 2C) and the Ki67 labeling index was 25% (Figure 2D). Immunohistochemically, the neuroendocrine components were positive for expression of chromogranin A (CgA), synaptophysin (Syn), and CD56 (Figure 3A-C), but negative for insulin, glucagon, gastrin and somatostatin. The adenocarcinoma cells were immunoactive for cytokeratin (CK)8 (Figure 3D) and CK18, but negative for CgA, Syn and CD56. Altogether, the cytomorphology and immunophenotype were consistent with the diagnosis of MANEC of the ampulla. The serosa and pancreas were infiltrated by the tumor, and the peripheral lymph nodes were free from tumor involvement and without distant metastasis. According to the 7th edition of the TNM system, the patient was T3N0M0 (Stage IIIA). The patient underwent adjuvant chemotherapy after surgery, consisting of a combination of oxaliplatin, calcium folinate and tegafur, and the patient died of tumor recurrence after 20 mo.

Case 2

A 60-year-old woman was admitted to our department in September 2012 with symptoms of abdominal pain, nausea and vomiting for 4 mo, with a background of gastrorrhagia. The findings of physical examination were unremarkable. The laboratory tests showed a hemoglobin level of 6.5 g/dL and hematocrit of 22.5%. The liver function tests and tumor marker (CEA, CA19-9 and CA12-5) levels were normal. Computed tomography (CT) of the abdomen revealed a mass located in the lower common bile duct, with dilation of the intrahepatic and common bile ducts. Gastroduodenoscopy revealed a mass at the duodenal papilla, and biopsy showed poorly differentiated adenocarcinoma.

Pancreaticoduodenectomy was performed. An ulcerating mass at the ampulla of Vater measuring 1.5 cm \times 1.7 cm in diameter was presented as the surgical specimen. Histological examination showed the tumor comprised two elements: poorly differentiated glandular adenocarcinoma and non-adenocarcinoma (Figure 4A). Approximately 55% of the tumor was composed of non-adenocarcinoma components. The adenocarcinoma cells were arranged into an irregular pattern. The non-adenocarcinoma components were arranged in a nest and the cells had abundant cytoplasm and nuclear hyperchromatism (Figure 4B). The mitotic rate was 25/10 HPF (Figure 4C) and the Ki67 index was 40% (Figure 4D). Immunohistochemical staining

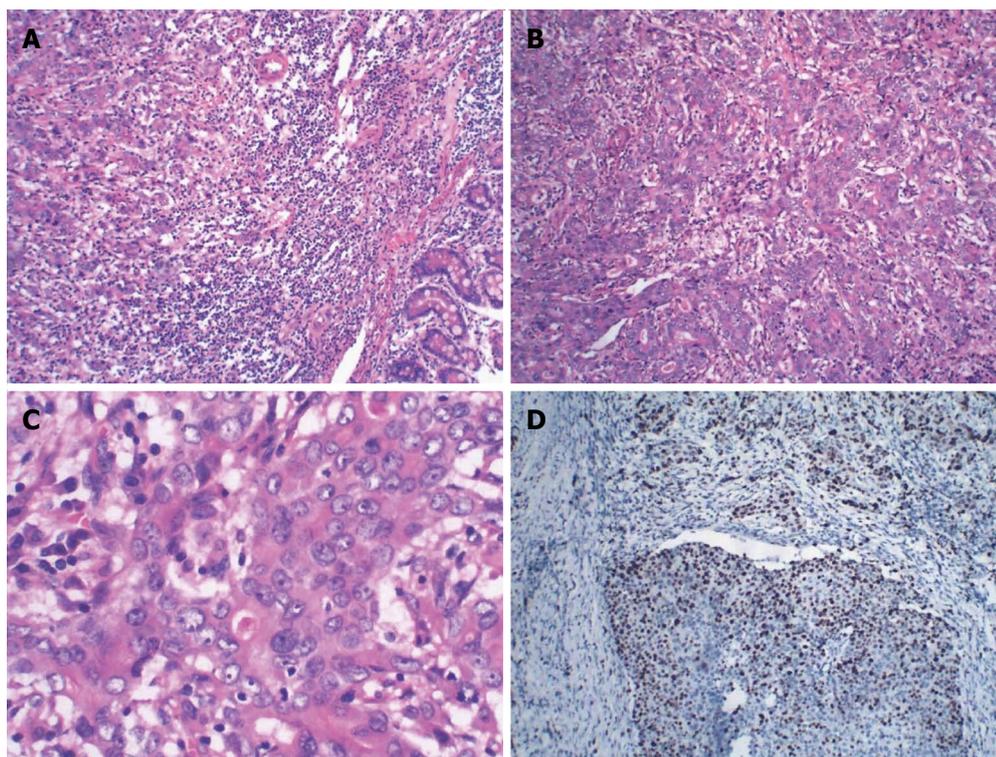


Figure 4 Histological data of Case 2. A: Poorly differentiated adenocarcinoma admixed with neuroendocrine components (HE staining, $\times 100$); B: The neuroendocrine components: large cells were characteristic for abundant cytoplasm and nuclear hyperchromatism (HE staining, $\times 100$); C: The neuroendocrine carcinoma cells show high mitotic rate (HE staining, $\times 400$); D: Immunohistochemical assay for Ki67 showing high proliferating index ($\times 100$).

showed that the adenocarcinoma components were positive for CK8 and CK18, but negative for CgA, Syn and CD56. The non-adenocarcinoma cells were positive for CgA, Syn and CD56, but negative for CD34 and D2-40. Taking the morphological and immunohistochemical features into account, the diagnosis of MANEC of the ampulla was confirmed. The tumor penetrated the serosa and pancreas, but none of the regional lymph nodes showed metastasis and no distant metastasis was detected (T3N0M0, Stage IIIA). The patient underwent adjuvant chemotherapy after surgery, consisting of a combination of oxaliplatin and gemcitabine, and the patient died of tumor recurrence after 15 mo.

DISCUSSION

According to the WHO classification (2010), neuroendocrine neoplasms in the digestive system were categorized into NET G1 (carcinoid, mitotic count of < 2 per 10 HPF and/or $\leq 2\%$ Ki67 index); NET G2 (mitotic count 2-20 per 10 HPF and/or 3%-20% Ki67 index); NET G3 (neuroendocrine carcinoma, mitotic count of > 20 per 10 HPF and/or $> 20\%$ Ki67 index); and MANEC^[1]. MANEC can be divided into three subtypes: composite carcinoma, collision tumor and amphicrine tumor^[8]. According to this subtype scheme, the two cases we presented here were both considered to be a composite carcinoma.

Patients with MANEC of the ampulla often complain of nonspecific symptoms such as abdominal pain, nausea, vomiting, epigastric discomfort, and jaundice. Most of the

patients have no carcinoid syndrome. Examination such as endoscopy, ultrasound, CT and magnetic resonance imaging may provide useful information, but the confirmed diagnosis mainly depends on histopathological and immunohistochemical analysis after surgery. MANEC usually comprises two elements: a variable grade of differentiated adenocarcinoma and a neuroendocrine component. Each component should occupy $\geq 30\%$ of the tumor. The adenocarcinoma components usually include intestinal type, goblet carcinoid, signet ring carcinoma, and acinar cell carcinoma. The neuroendocrine components contain small, intermediate and large neuroendocrine cells. The neuroendocrine cells usually show multifocal necrosis and high proliferation. Immunohistochemically, the neuroendocrine components are usually positive for CgA, Syn and CD56, and are also immunoreactive for neuron-specific enolase (NSE). To confirm the neuroendocrine nature of the tumor, it is recommended to rely on convincing immunoreactivity for at least two markers^[9]. Adenocarcinoma components are usually negative for CgA, Syn, NSE and CD56. Moreover, the endothelial markers such as CD34 and D2-40 are used to confirm whether there is vascular invasion involved in the neuroendocrine tumors. As in our cases, the neuroendocrine components were positive for CgA, Syn and CD56. The Ki67 index was 25% and 40% respectively. The mitotic rates both exceeded 20/10 HPF, which is in accordance with the classification standard of neuroendocrine carcinoma. The adenocarcinoma components were positive for CK8 and CK18, but negative for CgA, Syn and CD56.

The histological origin of MANEC is unclear. The ultra-structural features of both neuroendocrine and glandular differentiation were at the single level, suggesting that the two components of MANEC arise from multipotential stem cells^[2]. Moreover, Kim *et al.*^[10] have proposed that the common genetics of the glandular and neuroendocrine components of mixed tumor differentiation concurrently arise from a single precursor, by analyzing the genome-wide loss of heterozygosity. So, we suggest that the two components of MANEC arise from multipotential stem cells and show bi-phenotypic differentiation after carcinogenesis is initiated. The clinical behavior of this tumor is also still unclear due to the rarity of these tumors. Harada *et al.*^[11] have suggested that the neuroendocrine components more easily infiltrate the stromal, vascular and lymph node than the adenocarcinoma components. Some authors have also proposed that the neuroendocrine components show more aggressive features and influence the prognosis more easily than the adenocarcinoma components^[12,13]. However, Volante *et al.*^[14] have reported that the clinical behavior of those tumors depends on the adenocarcinoma component if the associated endocrine component is well differentiated, and upon the neuroendocrine component if it is poorly differentiated. However, to date, there are no systematic data to illustrate why the percentage of each component of the MAENC is 30%, or whether this value represents the real threshold that somehow influences prognosis^[1].

Pancreaticoduodenectomy is the optimal treatment for carcinoma of the ampulla. However, for patients who are unable to tolerate radical excision, local excision may be a better choice. After radical resection, multimodal treatment with adjuvant radiotherapy and/or chemotherapy should be adopted for patients with carcinoma of the ampulla. MANEC of the ampulla is a rare subtype of ampullary tumor with aggressive behavior and poor prognosis. Lee *et al.*^[4] have proposed that treatment should focus on the more aggressive cells of the tumor since the clinical outcome of this mixed tumor follows that of a more aggressive cell type. Wu *et al.*^[15] have proposed that the postoperative survival rate of neuroendocrine neoplasm significantly affected by tumor diameter, histological grade, lymph node metastasis, distant metastasis, radical surgery and muscular layer invasion. The present two patients underwent pancreaticoduodenectomy with no surgical complications and received adjuvant chemotherapy after surgery, but both died of tumor recurrence within 2 years. MANEC of the ampulla is considered as a highly malignant tumor, and the standardization of its treatment including surgery, chemotherapy and radiotherapy, biological targeted therapy requires further investigations.

abdominal pain, and the other with abdominal pain, nausea and vomiting.

Clinical diagnosis

The physical signs of the two cases were also dissimilar; upon physical examination, one case revealed mild yellow sclera and right upper abdominal tenderness, and the other had no remarkable findings upon physical examination.

Differential diagnosis

Duodenal adenocarcinoma, ampulla carcinoma, and pancreatic cancer. Pathological examination and immunohistochemical staining for chromogranin A (CgA), synaptophysin (Syn) and CD56 are the major methods for differential diagnosis.

Laboratory diagnosis

The first patient showed total bilirubin 2.2 mg/dL, conjugated bilirubin 0.87 mg/dL, unconjugated bilirubin 1.33 mg/dL, aspartate aminotransferase 118 U/L, alanine aminotransferase 285 U/L and alkaline phosphatase 515 U/L. The second patient showed hemoglobin 6.5 g/dL and hematocrit 22.5%, and serum levels of tumor marker carcinoembryonic antigen, carbohydrate antigen (CA)19-9 and CA12-5 were both within NR: limits.

Imaging diagnosis

Imaging of the two patients revealed a space-occupying lesion located in the ampulla area with the bile duct dilating.

Pathological diagnosis

The tumors included neuroendocrine and adenocarcinoma components and each component exceeded 30%; the neuroendocrine components were positive for CgA, Syn and CD56, and the adenocarcinoma components were negative for CgA, Syn and CD56.

Treatment

Both cases underwent pancreaticoduodenectomy and adjuvant chemotherapy after surgery.

Related reports

Mixed adenoneuroendocrine carcinoma of the ampulla, which is a malignant tumor, is rare. The histological and clinical behavior is still not well understood.

Experiences and lessons

Imaging and biopsy may provide some useful diagnostic information, but the diagnoses were all based on histology and immunostaining after surgery.

Peer-review

The presented cases are very rare. The article provides insights into the histopathology of this tumor and introduced the treatment, and can add more data in the treatment of this disease.

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COMMENTS

Case characteristics

The two female patients presented with non-specific symptoms; one with

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P- Reviewer: Behzatoglu K, Gurzu S, Le Bian AZ **S- Editor:** Gou SX
L- Editor: A **E- Editor:** Liu XM





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ISSN 1007-9327

