

# Mixed adenoneuroendocrine carcinoma (MANEC) of the ampulla of Vater in a Chinese patient: A case report

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## Abstract

Mixed adenoneuroendocrine carcinoma (MANEC) is a rare tumour of the gastrointestinal tract with both epithelial and neuroendocrine components. We describe a case of a 57-year-old man who presented with yellow sclera and dark urine. Contrast-enhanced computed tomography (CT) showed enlargement of the intra and extrahepatic bile ducts and a neoplastic lesion at the end of the common bile duct which was indistinguishable from the adjacent head of the pancreas and duodenum. A pancreaticoduodenectomy was performed and histopathological examination of resected samples showed that tumour was a complex lesion with adenocarcinoma and neuroendocrine components positive for neuroendocrine markers (chromogranin A and synaptophysin) with a Ki-67 labelling index of 40%. The patient was diagnosed with MANEC in the ampulla of Vater with a neuroendocrine carcinoma component of approximately 70%. Ampullary MANECs are highly aggressive tumours with a high risk for distant metastases and a poor prognosis. Therefore, establishing a standard therapeutic strategy is crucial.

## Keywords

Mixed adenoneuroendocrine carcinoma (MANEC), mixed tumour, ampulla of Vater, immunohistochemistry

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## Introduction

Classified by the World Health Organization (WHO) in 2010, mixed adenoneuroendocrine carcinoma (MANEC) is a rare gastrointestinal neoplasm with both epithelial and neuroendocrine components, each

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representing at least 30% of the tumour.<sup>1</sup> The tumours are considered to have highly malignant biological behaviour and are associated with a high risk of distant metastases.<sup>2</sup> MANECs have been identified in several organs, such as the bile duct,<sup>3</sup> gallbladder,<sup>4</sup> stomach,<sup>5</sup> pancreas,<sup>2</sup> colon<sup>6</sup> and rectum.<sup>7</sup> According to a retrospective multi-centre study involving 160 cases, MANECs are frequently found in the colon/rectum (58%), stomach (28%) and pancreas (15%).<sup>8</sup> To-date, there have only been a few cases of MANECs located in the ampullary region.<sup>9</sup>

In this report we describe the case of a MANEC located in the ampulla of Vater. The purpose of this article is to expand medical knowledge of this rare condition and disseminate information about its detection, diagnosis and effective treatment strategies.

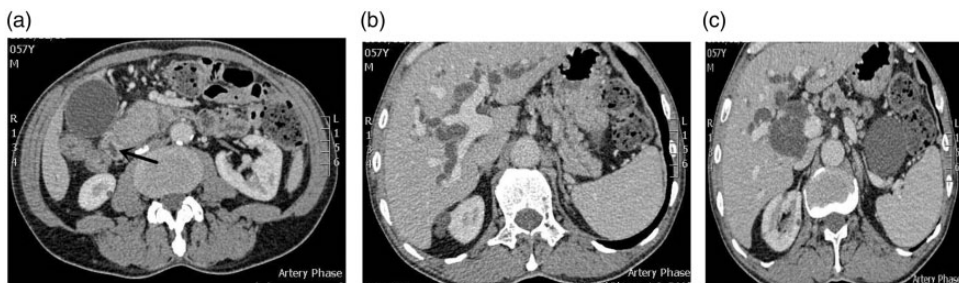
## Case report

A 57-year-old man presented with a 3-week history of yellow sclera and dark urine. He had undergone a 5 kg weight loss over the past three months. Ultrasound examination performed at a local hospital showed enlargement of the intra and extrahepatic bile duct. Contrast-enhanced computed tomography (CT) showed a lesion in the duodenal ampullary region. The patient

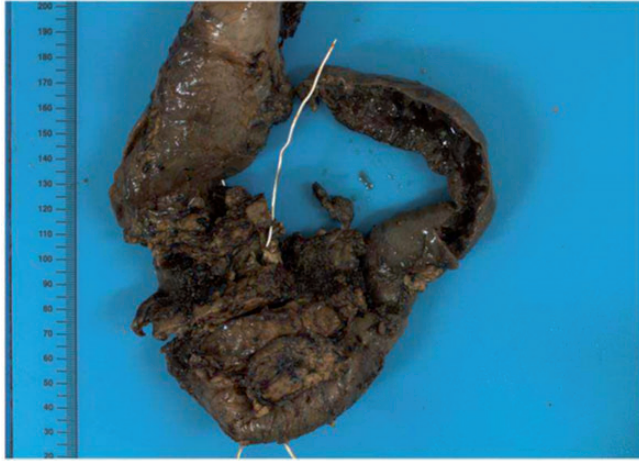
was referred to our hospital for further treatment.

The patient had no family history of cancer but he had been a smoker and drinker for more than 50 years. Physical examination showed mild yellow sclera and upper abdominal tenderness. Laboratory test findings were as follows: total bilirubin, 90.8  $\mu\text{mol/l}$  (normal range 0–21.0  $\mu\text{mol/l}$ ); conjugated bilirubin 81.3  $\mu\text{mol/l}$  (normal range : 0–6.8  $\mu\text{mol/l}$ ); unconjugated bilirubin 9.5  $\mu\text{mol/l}$  (normal range : 5.1–21.4  $\mu\text{mol/l}$ ); aspartate aminotransferase, 111 U/l; (normal range: 13.0–35.0 U/l); alanine aminotransferase, 136 U/l; (normal range: 7.0–40.0 U/l); alkaline phosphatase, 882 U/l (normal range: 50.0–135.0 U/l). The serum levels of several common tumour markers were within normal ranges. Abdominal triple-phase contrast CT showed enlargement of the intra and extrahepatic bile ducts and the presence of a local nodule at the end of the common bile duct which was indistinguishable from the adjacent head of the pancreas and duodenum. There was a strong possibility that the lesion was ampullary carcinoma (Figure 1).

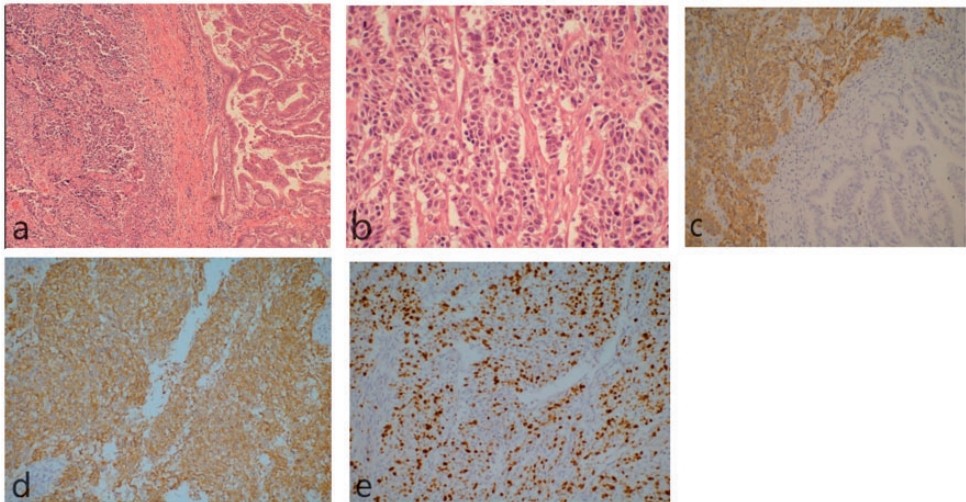
A pancreaticoduodenectomy was performed and a cauliflower-like mass (4 × 5 cm) invading the ampulla of Vater was discovered (Figure 2). An enlarged lymph node, approximately 2 × 2 cm was found beside the left renal artery. Pathology of the resected specimen showed that the tumour had two



**Figure 1.** (a) Contrast-enhanced computed tomography (CT) findings of the neoplastic lesion (arrow). (b) Dilated intrahepatic bile ducts. (c) Dilated extrahepatic bile ducts.



**Figure 2.** Surgical specimen of resected ampullary tumour.



**Figure 3.** Haematoxylin and eosin staining showed coexistent metastatic adenocarcinoma and neuroendocrine carcinoma; original magnification,  $\times 100$ . (a) High magnification of the neuroendocrine component; original magnification,  $\times 400$ . (b) The mitotic rate of the small cell neuroendocrine component was 20 cells per 10 high power fields. (c) Immunohistochemically, the neuroendocrine carcinoma cells were positive for synaptophysin; original magnification,  $\times 200$  and (d) CD 56; original magnification,  $\times 200$ . (e) Immunohistochemical assay for Ki67 showing high proliferating index; original magnification,  $\times 200$ .

elements: Small cell neuroendocrine carcinoma (NEC) was the main component (approximately 70%) and the remainder was a moderately differentiated adenocarcinoma.

(Figure 3a). The mitotic rate of the small cell NEC component was 20 cells per 10 high power fields (Figure 3b). The tumour had infiltrated the duodenum and the

pancreatic parenchyma. Lymphatic and venous but no apparent perineural infiltration was seen. The local mucosal epithelium at the margins of the pancreas and the common hepatic duct showed mild to moderate dysplasia.

Surgical resection margins were free of neoplastic lesion. The small cell NEC components were recognized on standard histology and confirmed with immunohistochemistry by detection of specific endocrine markers (i.e., synaptophysin and CD56) (Figure 3c and d). There was a negative reaction to Chromogranin A (CgA). The Ki-67 labelling index was 40% indicating strong proliferative activity (Figure 3e). The adenocarcinoma neoplastic cells showed positive expression of pan-cytokeratin (CK-pan), but were negative for other neuroendocrine markers such as CD56, CgA and synaptophysin. The tumour was classified as a grade G3 NEC because its mitotic and Ki-67 labelling indices were high and the patient was classified as having a T3N1M0 (Stage IIIB) cancer.<sup>10</sup>

According to the histological findings, the diagnosis of MANEC in the ampulla of Vater was confirmed. The patient refused chemotherapy and died from metastatic disease 14 months after the initial surgery.

## Discussion

MANECs are uncommon neoplasms and presentation in the ampullary region is extremely rare.<sup>9</sup> Furthermore, ampullary MANECs are considered to be highly malignant with a poor prognosis.<sup>9</sup> Therefore, accurate and timely diagnosis is essential. However, preoperative diagnosis of MANECs is difficult because these tumours do not exhibit specific symptoms and they are not associated with characteristic radiological findings or specific serum tumour markers.<sup>11</sup> Accordingly, diagnosis depends on post-operative histopathology and immunohistochemistry. Indeed, the diagnosis of MANEC is mainly based on

tumour immunohistochemical analysis using the three neuroendocrine markers, CgA, synaptophysin, and CD56, combined with markers of non-endocrine differentiation such as cytokeratin (CK) 7, CK 20 and CDX2.<sup>12</sup> At least two out of the three neuroendocrine markers must be abundantly expressed to make a definitive diagnosis of a high grade MANEC.<sup>12</sup> In our present case, the resected tumour sample was positive for synaptophysin, and CD56. It has been suggested by some authors that the prognosis of MANECs is driven by the NEC component which shows high proliferative activity on Ki-67 immunostaining.<sup>8,9</sup> For example, in the case reported here, Ki-67 labelling index was 40%. Therefore, when suspecting a mixed tumour, we suggest that the quantitative assessment of Ki-67 index is important.

It has been suggested that MANECs can be divided into three subtypes: combined tumours; collision tumours; amphicrine tumours.<sup>13</sup> In combined tumours, the two components are intimately and diffusely admixed, whereas, in collision tumours the two components are closely juxtaposed but not admixed. In amphicrine tumours the cell population exhibits both exocrine and endocrine differentiation. According to our morphological and immunohistochemical examinations, the case presented here could be considered a collision tumour.

Due to the rarity of this tumour, the pathogenesis of its biphasic morphology is unclear. The concept of human cancers displaying mixed exocrine-endocrine features has been a matter of debate.<sup>14</sup> Two hypotheses have been suggested.<sup>14</sup> In the first hypothesis, a monoclonal origin for the tumours has been suggested. For example, one study that reported a case of mixed adenoneuroendocrine carcinoma of the pancreas, examined the two different components by immunostaining and found that the tumour protein p53 was positive in both tumour components.<sup>15</sup> This finding



supports the hypothesis that they were derived from a single cancer stem cell. In the second hypothesis, the lesions are thought to develop as two distinct tumours derived from two different precursors. For example, a study using molecular analysis of the TP53 gene found mutation in the two tumour components.<sup>16</sup> Other studies have suggested that MANEC development is affected by hormones, local microenvironment, and preceding chronic inflammation (particularly lithiasis-associated inflammation) which leads to bidirectional or multi-directional differentiation.<sup>17,18</sup> Until a comprehensive molecular characterization of these tumours is available, targeted therapeutic options will be compromised.<sup>14</sup>

Currently, the optimal strategy for managing MANECs is unclear.<sup>9</sup> For an ampullary MANEC, pancreaticoduodenectomy is necessary for curative resection. Since the NEC component in this tumour is involved in vascular infiltration, perineural infiltration, and lymph-node metastases,<sup>18</sup> it is the main prognostic factor.<sup>9</sup> Therefore, adjuvant chemotherapy should target this component. Microscopically, the NEC component is similar to small cell lung cancer, for that reason some investigators have used a combination of adjuvant chemotherapy such as irinotecan and cisplatin.<sup>19</sup> Importantly, a review of 15 separate cases of ampullary MANEC found that recurrence occurred soon after surgery in eight cases.<sup>9</sup> Therefore, we suggest that adjunctive therapy should be strongly recommended, particularly because once metastasized, high-grade digestive NEC has a poor prognosis.<sup>20</sup> In our present case, the patient refused chemotherapy.

In conclusion, ampullary MANECs are highly aggressive tumour types with a high risk for distant metastases and a poor prognosis. Therefore, establishing a standard therapeutic strategy based on an accurate preoperative diagnosis is crucial. Further

research should be undertaken to establish clinical strategies for these rare tumours.


### Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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