Mixed adenoneuroendocrine carcinoma of the ampulla of Vater: A case report

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Abstract. Mixed adenoneuroendocrine carcinomas (MANECs) are rare biphasic tumour types, which are morphologically recognisable as both gland-forming and neuroendocrine neoplasms. Within the gastrointestinal tract, MANECs occur predominantly in the stomach or colorectum. The present study described a case of a MANEC originating from the ampullary region. The patient presented with widespread metastatic disease. Biopsy samples obtained from the ampullary primary tumour disclosed a complex lesion with adenocarcinoma and neuroendocrine small cell carcinoma components, positive for the intestinal transcription factor caudal type homeobox-2 and for neuroendocrine markers, including chromogranin A, synaptophysin, cluster of differentiation 56/neural cell adhesion molecule. By contrast, biopsy samples obtained from metastatic tissue revealed pure neuroendocrine carcinoma. As exemplified by this true mixed tumour, tumour heterogeneity evolves as the major challenge in oncology today, with potentially severe implications for the choice of chemotherapy. The assessment of metastatic sites may render valuable diagnostic information that is crucial for clinical decision-making and patient management.

Introduction

Ampullary carcinomas represent 0.5% of all gastrointestinal malignancies. They are more common in men compared with in women, and are normally diagnosed in patients between 60 and 80-years old (1).

The vast majority of lesions reveal a glandular growth pattern. Among these, two predominant subtypes of adenocarcinoma have been identified, which show either pancreaticobiliary (15-20%) or intestinal differentiation (50-80%) (2,3). Subclassification is clinically relevant, since in addition to advanced tumour stage and poor differentiation, the pancreaticobiliary subtype has been identified as an adverse prognostic factor (2,4-6). Tumours with neuroendocrine differentiation, including neuroendocrine tumours and neuroendocrine carcinomas (NECs) are only rarely observed at this site (4,7,8).

Mixed adenoneuroendocrine carcinomas (MANECs) are rare biphasic tumour types, which have only anecdotally been reported in the ampullary region (7,9-12). The current report described a patient with ampullary MANEC, presenting with widespread metastatic dissemination. Both primary and metastatic tissues are assessed by histology, which has not been previously well-described.

Case report

Clinical presentation. A 66-year-old female presented with painless jaundice for 2 days, unspecific abdominal pain and weight loss of 5 kg within the last three months, and was admitted to the Department of Surgery, General Hospital (Linz, Austria). Laboratory analysis revealed pathological liver function tests, with predominant cholestatic profile, including hyperbilirubinemia.

Upon endoscopy, an irregular tumour mass was detected in the ampullary region, measuring ~4 cm in the largest diameter (Fig. 1). Whole-body 18F-fluorodeoxyglucose positron emission tomography was performed, which revealed multiple metastases to liver, spine, retroperitoneal lymph nodes and lungs (Fig. 2).

Histopathological analysis. Biopsy material of the ampullary lesion disclosed a complex malignant epithelial lesion with a non-invasive adenoma component progressing into invasive intestinal-type adenocarcinoma. Other parts of the lesion consisted of typical neuroendocrine small cell carcinoma with diffuse growth pattern, composed of small to medium sized cells with minimal cytoplasm and fusiform nuclei with finely granular chromatin and inconspicuous nucleoli (Fig. 3). The mitotic rate was high and necrosis occurred frequently. Upon immunohistochemical staining, the tumour was positive for neuroendocrine markers, including chromogranin A, synaptophysin and cluster of differentiation (CD)56/neural cell adhesion molecule (NCAM). The intestinal transcription factor, caudal type homeobox (CDX)-2, was positive for both...
Based upon these findings, a diagnosis of MANEC of the ampulla was made. Histology obtained from a liver lesion revealed pure neuroendocrine small cell cancer, which was positive for neuroendocrine markers and for CDX-2, thereby proving its gastrointestinal/ampullary origin (Fig. 4).

**Discussion**

The first description of a gastrointestinal tumour exhibiting both exocrine and neuroendocrine differentiation was published in 1924 by Cordier (13). The widespread use of immunohistochemical techniques in the last decades has led to the recognition that neuroendocrine cells are present rather frequently in exocrine malignancies of the gastrointestinal tract (14). True mixed tumour types, including MANECs, are relatively uncommon, occurring predominantly in the stomach and colorectum.

According to the World Health Organisation definition, MANECs are morphologically recognisable as both gland-forming and neuroendocrine neoplasms with an arbitrary requirement of at least 30% of either component (15). They are defined as carcinomas since both components are histologically malignant. MANECs must be differentiated from collision tumour types (16) or so-called amphicrine tumour types (17), which are characterized by usually monomorphic growth of cells exhibiting both exocrine and endocrine differentiation.

Patients with gastrointestinal MANECs appear to exhibit an improved median overall survival compared with patients with pure NECs, and this finding may be associated with the higher stage at the time of diagnosis of the latter (14). In a previous investigation of colorectal MANECs, no different patient survival was observed between NECs and MANECs (18), suggesting that certain clinical differences between NECs and MANECs may be site-associated (19). In general, MANECs are highly aggressive tumour types with a high risk for distant metastasis, and prognosis is often dismal. It is largely unclear whether the glandular or the neuroendocrine component is the major driving force of disease progression and thus crucial for metastatic cancer spread (11,20,21).

In oncological practice, distant metastases are not normally assessed by histology, when the responsible primary tumour is known (22). The presented case exhibited widespread dissemination of the neuroendocrine small cell carcinoma, however, not of the adenocarcinoma component with potentially severe implications for the choice of chemotherapy. The present study determined that the time has come to reconsider the indication for testing metastatic sites in standard oncology practice.
In conclusion, the present report presented a rare case of a MANEC originating from the ampulla of Vater. The tumour tissue from the present patient was biopsied and assessed at both primary and metastatic sites, proving discordant results.
As exemplified by this true mixed tumour type, tumour heterogeneity evolves as the major challenge in oncology today. The assessment of metastatic sites may render valuable diagnostic information that is crucial for clinical decision-making and patient management.

References


