Mixed Adenoneuroendocrine Duodenal Carcinoma Case Report
Abraham Chacko DO, Edward Jurkovic DO, Thomas Betlej MD
Riverside Medical Center Kankakee, IL

Introduction

MANEC’s are a well recognized entity but not frequently diagnosed thus leading to suboptimal therapy. Diagnosis of MANEC’s require both tissue and immunohistochemical diagnosis. There are various hypotheses regarding etiology. There are no standard guidelines on treatment. Prognosis depends on location of the tumor. Here we report a case of duodenal MANEC where patient underwent surgical resection and subsequent chemotherapy.

Case Description

An 81 year old Caucasian male presents to the hospital with complaints of lightheadedness and dizziness which began as shortness of breath approximately 6 months prior to admission. Additionally the patient had complaints of intermittent dysphagia with solids during this time period. He visited his primary care physician who wanted to refer him to a gastroenterologist with evaluation for endoscopic procedures. His past medical history includes prostate cancer status post external beam radiation, gout, hypercholesterolemia, peripheral vascular disease, coronary artery disease status post coronary angiography and CABG, esophageal strictures status post dilation, and right inguinal herniorrhaphy.

On evaluation in the emergency room, patient was hypotensive with a blood pressure of 98/50 along with orthostatic hypotension, however the rest of his vital signs were stable. In general the patient was non-toxic appearing and in no distress. His mucous membranes were dry. His abdomen was soft, nontender and nondistended with positive bowel sounds. His rectal exam showed normal rectal tone with external hemorrhoids, however there was dark heme positive stool in the rectal vault. Laboratory data showed hemoglobin of 5.9 gm/dL, hematocrit of 19.7% and MCV of 83.5 fl. Patient’s baseline hemoglobin based on prior lab work was between 11 gm/dL and 12 gm/dL. Iron studies showed iron of 35 ug/dL, TIBC of 388 ug/dL, percent transferrin saturation of 9%, and ferritin of 16.3 ng/mL. B12 and folic acid levels were within normal limits.

The patient was set up for an esophagogastroduodenoscopy where a near obstructing ulcerated mass was found in third portion of the duodenum which was not actively bleeding, and multiple biopsies were taken (Figure 1). He had cat scan of the abdomen and pelvis without contrast due to acute kidney injury which revealed focal thickening of the distal duodenum accompanied by abnormal mesenteric lymphadenopathy, stranding of the mesentery and indeterminate liver lesions (Figure 2 and 3). The biopsies returned showing combined neuroendocrine and glandular tumor consisting of sections of conventional tubular adenoma with high grade dysplasia (adenocarcinoma in-situ) and a poorly differentiated neuroendocrine carcinoma. Immunoperoxidase stains performed on the neuroendocrine carcinoma component were positive for cytokeratin (AE1/AE3), synaptophysin and CD 56 and negative for chromogranin. Subsequently the patient underwent a laparotomy with a pancreaticoduodenectomy with Roux-en-y gastrojejunostomy, cholecystojjunostomy, and
pancreaticejunostomy and started on a chemotherapy regimen consisting of carboplatin and VP-16.

Discussion

The first description of a gastrointestinal tumor with an exocrine and a neuroendocrine component was published by Cordier in 1924 (3). Mixed exocrine-neuroendocrine tumors are defined where each neoplastic component represents at least 30% of the lesion (3,4). The most recent World Health Organization (WHO) classification of neoplasms of the gastrointestinal tract calls these neoplasms "mixed adenoneuroendocrine carcinomas" (MANECs). The exocrine and neuroendocrine components can have different morphological features ranging from tubulo-villous or villous adenoma, adenocarcinoma or more rarely, squamous cell carcinoma with varying degrees of differentiation in the exocrine components and well differentiated to poorly differentiated neuroendocrine tumors in the neuroendocrine components. The squamous cell component is most often seen in esophageal and anorectal MANECs while adenomas or adenocarcinomas have been seen in gastric and colorectal MANECs. MANECs are morphologically classified as both gland forming epithelial and neuroendocrine neoplasms and also are defined as carcinomas since both components are histologically malignant.

In some MANECs, the neuroendocrine and exocrine components occur in separate areas of the same lesion which is known as composite or collision neoplasms (1). Other MANECs have both components mixed together known as combined neoplasms. In amphicrine tumors, exocrine and neuroendocrine features are present in the same neoplastic cell which shows a divergent immunophenotype.

Gastrointestinal MANECs are grouped into different prognostic categories according to the grade of malignancy of each component. In 2010, the WHO classified mixed tumors into three groups including high-grade malignant (mixed adenoma/adenocarcinoma-neuroendocrine carcinoma), intermediate-grade malignant (mixed adenocarcinoma G1/G2 neuroendocrine tumor), and low-grade malignant (adenoma-neuroendocrine tumor) (4). It can be a challenge to accurately diagnose a MANEC due to the fact that frequently only one component of the neoplasm may be identified which leads to inferior treatment (3).

A high grade malignant MANEC is comprised of a highly malignant composite or combined neoplasm formed by an adenomatous (villous or tubulo-villous) or carcinomatous (adenocarcinoma or squamous cell carcinoma) component along with a poorly differentiated (small, intermediate or large cell type) neuroendocrine carcinoma. This neoplasm has been seen in the esophagus, stomach, ampullary region, large bowel and anorectal region (3).

High grade malignant MANECs appear as polyoid masses or ulcerating stenotic lesions measuring 0.5 to 14 cm in diameter with a mean size of approximately 5 cm. The neuroendocrine carcinoma component is histologically similar to small cell or large cell NEC of the lung and is equivocal to a grade 3 neuroendocrine neoplasm according to the 2010 WHO classification (3). Both small and large cell neuroendocrine components are diffusely positive for synaptophysin and usually to a lesser extent chromogranin A. Two out of three commonly used neuroendocrine markers must be expressed in high amounts to make a diagnosis of high grade MANEC which includes synaptophysin, chromogranin A or CD56 (3). The Ki67 labeling index is usually very high (60%-90%). The expression of certain hormonal peptides such as somatostatin, adrenocorticotropic hormone (ACTH) or vasoactive intestinal peptide (VIP) have
been detected in a few cases. Previous studies have shown p53 accumulation in gastric, ampullary and colorectal MANECs. Additionally, colorectal MANECs have shown immunoreactivity for CDX2 in neuroendocrine cells of large cell subtypes (3).

There are various hypotheses regarding the pathogenesis of MANECs. Mixed neuroendocrine-glandular tumors may be due to simultaneous proliferation of multiple cell lineages or the proliferation of stem cells that can differentiate along multiple cell lineages. Genetic studies on gastric and colorectal MANECs show that shared loss of heterozygosity at chromosomes 5q, 11q, 17p, and 18q indicates a close genetic relationship and supporting the hypothesis of proliferation from a common precursor lesion (3). Additionally, Furlan et al found a close genetic relationship between the two distinct histologic components of MANECs which supported the hypothesis of a monoclonal mechanism of tumorigenesis (1,2).

The best management strategy of managing a MANEC is unclear due to the rarity of these neoplasms. As a general rule, the more aggressive component of the MANEC should be considered. For example, a MANEC with a well differentiated NEC and an adenocarcinoma component should be treated as adenocarcinomas. On the other hand, a MANEC containing a poorly differentiated NEC component should be treated as NEC (3,4i). Sandri et al described a case of a gastric MANEC which was treated with surgical resection followed by chemotherapy. The optimal chemotherapy regimen consists of cisplatin, doxorubicin and vincristine (4). On the other hand, Pericleous et al states that the chemotherapy regimen should consist of cisplatin and etoposide.

The prognosis of high grade MANECs depends on stage and tumor type. There has been higher survival in patients with loco-regional disease as compared to patients with distant metastases. Overall, patients with gastrointestinal MANECs have higher overall median survival compared to those with pure NECs due to higher stage at time of diagnosis for the latter. Other studies did not show a higher median survival in patients with colorectal MANECs compared to those with pure NECs which may mean that there are clinical differences between NECs and MANECs which are location specific.

**Conclusion**

Gastric MANEC’s are a well recognized entity but not frequently seen. By definition each neoplasm comprises at least 30% of the tumor. Diagnosis is made by biopsy and aided by immunohistochemical staining including synaptophysin, chromogranin A and CD56. The pathogenesis is unclear but studies have shown that these tumors may originate from a single precursor lesion leading to different cell types. Current treatment regimens involves treating the more advanced component of the MANEC including surgical resection followed by chemotherapy based on carboplatin therapy. Localized disease has a better prognosis than those that have metastasized.
1) Furlan D, Cerutti R, Genasetti A. Microallelotyping defines the monoclonal or the polyclonal origin of mixed and collision endocrine-exocrine tumors of the gut. Lab Invest 2003;83:963-971.


FIGURES

Figure 1: 2 mm longitudinal and ulcerated tumor in duodenum

Figure 2: Thickening of the 3rd and 4th portions of the duodenum
Figure 3: Lymph node with stranding of adjacent mesenteric fat