Mixed Adenoneuroendocrine Carcinoma at the Gastroesophageal Junction: A Case Report

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Background

- Mixed adenoneuroendocrine carcinomas (MANECs) are a very rare, aggressive, and almost uniformly fatal group of neoplasms that are a type of mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) found in the gastro-entero-pancreatic (GEP) tract.
- The incidence of these neuroendocrine tumors account for 0.04% to 1% of the 4000 cases reported in the literature, E-NENs accounted for 0.03% to 0.05% of all esophageal malignancies.
- Pathogenisis remains theoretical and the three competing theories are as follows;
  1. Merge theory (8).
  2. Pluripotent divergent theory (1).
  3. Molecular instability theory (7).
- Compared to “MANECs”, the term “MiNENs” addresses the heterogeneous spectrum of possible combinations between neuroendocrine and non-neuroendocrine elements more effectively.
- Histologically, the neuroendocrine component is morphologically similar to small or large cell neuroendocrine carcinomas of the lung. The non-neuroendocrine component of high-grade MiNENs can demonstrate tubulovillous or villous adenoma, adenocarcinoma, or more rarely, squamous cell carcinoma.
- Adenomatous and adenocarcinomatous components are typically discovered in the stomach and colon, whereas the squamous cell components are commonly found in the esophageal or anorectal regions.

Case

- An Obese, 56-year-old Caucasian male presented to the emergency department with a two-week history of worsening epigastric abdominal pain and intermittent dysphagia with solids and liquids immediately after ingestion. He described the abdominal pain as sharp and radiating to his back. He described a sensation of food getting stuck at the xiphoid process after consumption. He also reported a 23-pound unintentional weight loss over the past month, a single episode of melena a week prior. Past medical history was significant for hypertension, hyperlipidemia, chronic obstructive pulmonary disorder (COPD), and gastroesophageal reflux disorder (GERD). His family history was significant for lung cancer in a sibling, and his social history was significant for former EtOH and unspecified substance use, and current smoking of approximately one pack per day.
- Physical examination was largely benign. Computed tomography (CT) of the abdomen and pelvic with intravenous (IV) contrast revealed suspicious wall thickening involving the distal esophagus, the gastroesophageal junction (GEJ), and gastric cardia. There was narrowing of the esophageal lumen without evidence of obstruction. The patient underwent esophagogastroduodenoscopy (EGD), which revealed a malignant appearing esophageal stricture at approximately 35-37 centimeters from the incisoral orifice. The scope was retroflexed in the stomach revealing a large, polypoid mass bulging from the GEJ (Figure 1A-1B).

Case Cont.

- Histopathology revealed poorly differentiated adenocarcinoma and high-grade (Grade 3) neuroendocrine differentiation. The neuroendocrine carcinoma and adenocarcinoma components were admixed with no evidence of a collision tumor (Figure 2A-2D). Immunohistochemistry (IHC) demonstrated positivity for AE1/AE3, CK7, CDX2, CK20, and synaptophysin (Figure 3A-3D). The Ki-67 index of the neuroendocrine component was 50%. A diagnosis of MANEC was granted.
- The patient then underwent fluorodeoxyglucose (FDG) positron emission tomography (PET), which confirmed no metastasis of the primary tumor site. Our facility in rural Appalachia does not have access to endoscopic ultrasound (EUS) or have the capability to perform complex esophageal surgical procedures, so the patient was referred to an external facility to discuss surgical intervention. The patient then began treatment with a combination of preoperative neoadjuvant chemoradiation via 3D conformal radiotherapy (*3DCRT*) with image-guided radiation therapy (IGRT) technique followed by laparoscopic Ivor-Lewis esophagectomy.

Figures

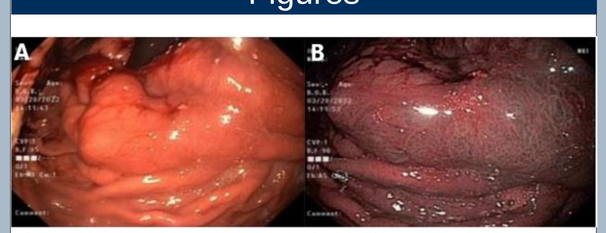

Figure 1: A) Endoscopic image demonstrating the polypoid mass protruding from the gastroesophageal junction into the gastric cardia with the endoscope in retroflection; B) image viewed under narrow band imaging (NBI) technology.

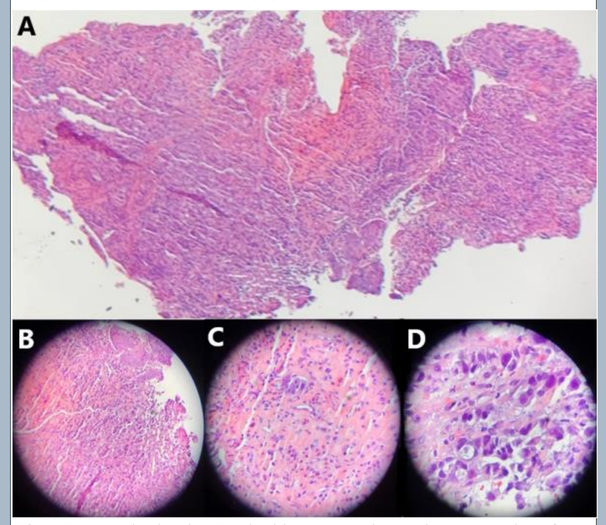

Figure 2: Image showing A) H&E stain of the tumor specimen at the gastroesophageal junction with malignant cells x 20; B) H&E stain of the specimen demonstrating malignant neuroendocrine carcinoma cells adjoining squamous mucosa of the gastroesophageal junction x100; C) H&E stain of the specimen demonstrating poorly differentiated adenocarcinoma components of the tumor, x200; and D) H&E stain of the specimen demonstrating poorly differentiated adenocarcinoma with signet ring features, x400.

Figures Cont.

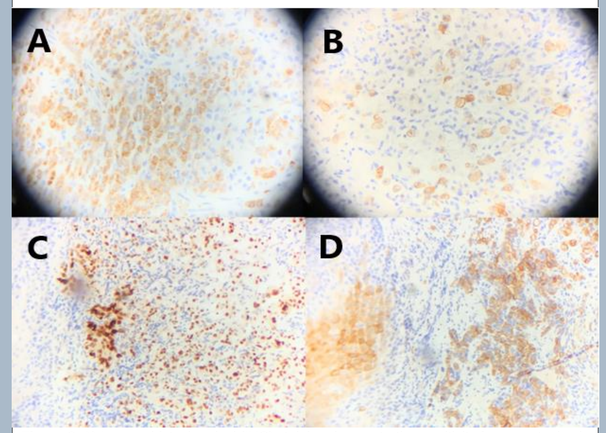

Figure 3: A) Immunohistochemical (IHC) staining demonstrating positivity for synaptophysin in the neuroendocrine carcinoma component of the neoplasm (x400); B) IHC staining demonstrating positivity for CK20 in adenocarcinoma component of the neoplasm (x400); C) IHC staining demonstrating positivity for CDX2 in adenocarcinoma component of the neoplasm (x200); D) IHC staining demonstrating positivity for CK7 in the neuroendocrine carcinoma component (x100).

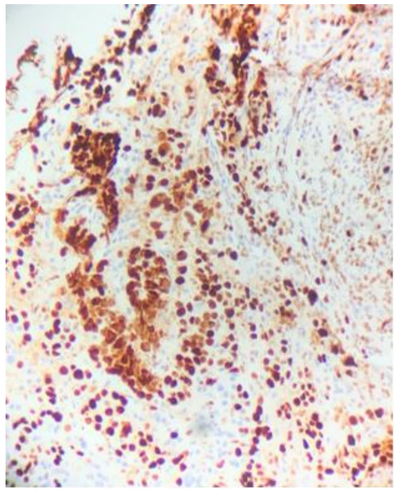

Figure 4: IHC staining demonstrating positivity for Ki-67 in neuroendocrine carcinoma component (x100)

Discussion

- Diagnosis of MANEC occurs primarily through histopathologic analysis and IHC. The present case demonstrates positivity for AE1/AE3, CK7, CDX2, CK20, and synaptophysin. Histologically, the NEC component is morphologically similar to small cell or large cell NEC of the lung, according to the 2010 WHO Classification (4). Immunohistochemically, pure neuroendocrine areas of both small and large cell neuroendocrine components are diffusely positive for synaptophysin and usually for chromogranin A, although to a lesser extent (2).

Discussion Cont.

- Synaptophysin is a mandatory marker for large cell NEC, whereas chromogranin A is variable and may be weak or absent. This is not the case for small cell NEC where both markers must be present (3). CK7, 8, 18, and 19 have also been shown to be significantly higher in large cell NEC in comparison to small cell NEC in tumor of pulmonary origin (6). Milione et al.(4) found the Ki-67 index of the NEC component to be the most important prognostic factor in these cases. MANECs with Ki-67 less than 55% showed better survival compared to pure poorly differentiated NECs with Ki-67 between 21 and 55%.
- Existing treatment recommendations have been based on limited available evidence. For patients with localized disease, a combination of platinum-based chemotherapy (i.e., cisplatin) with local treatment consisting of surgery, radiotherapy, or both offer the greatest likelihood of survival. Surgical intervention is not recommended, however, in cases of debulking, surgical resection of metastasis, or when localized surgical resection is associated with increased mortality due to anatomical location (i.e., esophagus) (3). In this case, the patient’s localized GEJ neoplasm was treated with a combination of neoadjuvant chemoradiation prior to surgical resection.
- In a previous systematic review, Frizziero et al.(1) made several conclusions regarding treatment modalities. In the setting of localized disease, surgical resection was the treatment of choice for nearly all potentially curable cases. Surgery was offered to approximately 25% to 33% of patients with advanced disease for symptom relief or initial curative intention in patients subsequently found to have advanced disease. Survival outcomes for localized disease were found to be largely variable across retrospective studies, ranging from a few months to several years. Median survival times were not reached in the localized setting of this review due to the lack of long-term follow-up data (1).

Conclusion

We report a rare case of MANEC located at the GEJ in a 56-year-old male. This combined neoplasm is highly aggressive and frequently fatal. The amount of evidence available in the medical literature regarding this tumor type is extremely limited. Diagnostic and treatment recommendations are currently based on case reports and large retrospective studies. This patient was treated with a combination of neoadjuvant chemoradiation and surgical resection. Currently, further studies are needed to determine optimal treatment strategies.

References

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