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Case Report

J Med Cases. 2019;10(4):120-122

High Grade and Poorly Differentiated Neuroendocrine Carcinoma: Three Case Reports

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Abstract

Neuroendocrine carcinomas (NECs) of the luminal gastrointestinal tract and pancreas are rare, poorly differentiated neoplasms. There has been difficulty identifying associated risk factors given their very low incidence. Here we present three cases of NEC diagnosed in an 8-month period in a Minneapolis safety-net hospital.

Keywords: High grade; Poorly differentiated; Neuroendocrine; Carcinoma; Rare tumor

Introduction

Neuroendocrine carcinomas (NECs) of the luminal gastrointestinal (GI) tract and pancreas are rare, poorly differentiated neoplasms. The annual incidence in the USA is approximately 3.56 per 100,000 population [1]. The majority of NECs are nonfunctioning tumors and present with abdominal pain [2, 3]. With the less common functional NECs, patients can present with symptoms of glucagonoma such as weight loss and glucose intolerance, insulinoma such as fasting hypoglycemia, VIPoma such as watery diarrhea that persists with fasting and/or gastrinoma such as severe acid-related peptic disease [3]. Nonfunctioning NECs generally present late, with metastatic disease present at the time of diagnosis. When metastatic disease is present, treatment options are limited to palliative chemotherapy [4, 5].

The low incidence of high grade gastroenteropancreatic (GEP) neuroendocrine neoplasias (NENs) leads to difficulty identifying associated risk factors. Some reports note an association with smoking, but it is not as tight an association as with small cell lung cancer [6]. Esophageal NECs may be associated with a history of achalasia, gastroesophageal reflux disease, or Barrett's esophagus [7, 8]. The presence of colonic adenomas or ulcerative colitis has been linked to colorectal NECs [8].

We present three cases of high grade GEP NEN and compare the possible risk factors, presenting symptoms, treatment and outcomes within the three.

Manuscript submitted April 12, 2019, accepted April 22, 2019

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doi: https://doi.org/10.14740/jmc3294

Case Reports

Case 1

A 53-year-old man from Mexico with a history of multiple gastric ulcers, prior *Helicobacter pylori* infection, and hypertension presented to the GI clinic in April 2018 with chronic abdominal pain, five episodes of melena, and anemia. Esophagogastroduodenoscopy (EGD) revealed a medium-sized ulcerated mass in the third portion of the duodenum. Computed tomography (CT) of the abdomen and pelvis confirmed the presence of a mass in the pancreatic head with duodenal invasion and also revealed a second mass in the pancreatic tail as well as an enlarged inguinal lymph node. Pathology from the duodenal biopsy and endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) biopsy of the pancreatic tail lesion both demonstrated high grade poorly differentiated NEC. FNA from the inguinal node confirmed metastatic disease. Patient completed staging workup with a bone scan, brain magnetic resonance imaging (MRI), and chest CT which did not demonstrate additional metastases. With multifocal, metastatic disease, the patient was offered and undertook palliative chemotherapy, which has been well tolerated. Follow-up imaging with CT and endoscopy showed decrease in size of all lesions. Despite this response, life expectancy with this aggressive tumor remains limited.

Case 2

A 72-year-old woman from India with a history of type 2 diabetes mellitus presented to the emergency department in October 2018 with fever, chills, abdominal pain and vomiting; she had acute hypoxic respiratory failure and signs of septic shock. CT of the abdomen revealed a necrotic mass in the transverse colon and distal stomach with a gastrocolic fistula as well as an intrahepatic abscess, mediastinal mass and a lucent lesion in the right femoral head suspicious for metastasis. Patient underwent an EGD with biopsies of the mass. Pathology demonstrated high grade poorly differentiated NEC. The patient

was treated with 3 weeks of antibiotics for her hepatic abscess. Chemotherapy was considered following treatment of the patient's infection; however, due to her frailty and her goals of care, the decision was made to pursue palliative care. She was discharged to hospice.

Case 3

A 40-year-old African American woman with no past medical history presented to the emergency department in March 2018 with intermittent epigastric abdominal pain. Abdominal ultrasound revealed a 4.7-cm gallbladder mass. CT of chest, abdomen, pelvos (CAP) did not show liver involvement or distant metastasis. She was taken to the operating room (OR) for laparoscopic cholecystectomy. Surgical pathology was positive for high grade poorly differentiated NEC with invasion of the peri-muscular connective tissue on the hepatic side but without evidence of hepatic involvement. She returned to the OR for partial liver resection and removal of several lymph nodes. Pathology demonstrated NEC in the resected liver specimen and one out of five portal and hepatic lymph nodes.

The patient completed five of six cycles of etoposide/carboplatin; the last cycle was held due to critically low cell counts.

CT of the abdomen 5 months after diagnosis showed stable postsurgical changes and no evidence of residual or metastatic disease.

Discussion

Three cases of high grade poorly differentiated NEC were diagnosed at Hennepin Healthcare, a safety-net hospital in Minneapolis, between March and October of 2018. Our patients' ages ranged between 40 and 72, two were female and one was male, and nationalities were Mexican, Indian and African American. Our first case had a pancreatic NEC with extension to the duodenum, the second had widely metastatic disease from unknown primary, and the third had a gallbladder NEC with metastasis to the liver and a portal lymph node.

Although all of our patients had metastatic disease at the time of diagnosis, they undertook a diverse set of treatments with different intents. One patient undertook chemotherapy with palliative intent; another pursued curative chemotherapy; the third, due to her extreme frailty and her goals of care, chose to be enrolled in hospice.

All of our patients presented with abdominal pain, the most common presenting symptom in patients with nonfunctioning NECs [2, 3]. Two of our three patients were immigrants and none were Caucasian.

Risk factors for NEC have not been well studied and are not entirely clear. Reports have associated smoking with NEC [6]; however, none of our patients were smokers. There has been no relationship associated between race, nationality or region and NEC. At this time, it is unknown if there might be risk factors or exposures from other geographic locations.

Three patients presenting within 8 months with this type of rare cancer could potentially mean that there is an exposure related to NEC that we are not aware of yet. We could also be missing the diagnosis more often than we think as medical providers or perhaps there is also a rapidly rising prevalence. While none of our patients was Caucasian, this distribution may be more of a reflection of our hospital system's mission and patient base than of a demographic pattern. Further study of cases of NEC to see if there is a relationship between race, nationality or region and these rare carcinomas would be valuable.

The fact that all three of our patients had metastatic disease at the time of diagnosis is not surprising given the most common presenting symptom is abdominal pain which is very nonspecific. If we can come up with knowledge regarding early presentations of NECs this might lead to the construction of an algorithm for when abdominal pain should lead to imaging such as CT scan.

Jan Paul Vandenbroucke, a recognized Belgian epidemiologist who also trained in internal medicine, stated in his 2001 review of case series and case reports that these studies play an important role in medical education and since they have high sensitivity for reporting novelty they are crucial for progress of medical science [9]. Regarding these cases, if we are able to determine risk factors with hopefully larger case series or genomic testing, there might be a better chance of discovering NEC prior to late-stage presentation with metastatic disease.

Conclusions

Despite the fact that poorly differentiated high grade NECs are extremely rare tumors, three patients with this diagnosis were seen within 8 months in our safety-net hospital in Minneapolis. Additional data are needed to clarify risk factors for NECs, possibly including race, exposures and smoking status.

Acknowledgments

We are grateful to Dr. Mark Linzer for comments on an earlier draft of this paper.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained by all patients for this publica-

tion.

Author Contributions

MC is the main author, and drafted original manuscript; RM is the main reviewer of initial draft.

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