Rapidly extensive recurrence of esophageal neuroendocrine carcinoma following complete pathologic response to definitive chemoradiation

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INTRODUCTION

Esophageal neuroendocrine carcinoma (eNEC) is a rare (<3% of US esophageal cancers) and aggressive malignancy (<5% 5-year overall survival [OS]) that lacks treatment guidelines. The timing and nature of relapse after successful treatment is not well characterized. We report a case of rapidly extensive recurrence after complete pathologic response (cPR) to definitive chemoradiation (dCRT) and maintenance therapy (MT).

CASE DESCRIPTION

A 51 year old woman with no medical history presented with 3 weeks of epigastric pain, mild acid reflux, and dysphagia. She denied smoking or alcohol use. Pantoprazole, previously prescribed by her primary care doctor, did not help. Endoscopy revealed a 4 cm, necrotic, mid-esophageal ulcer (*Fig 1*) with NEC histology (*Fig 2*). Staging with endoscopic ultrasound, brain MRI, and PET-CT determined T3N2M0 disease (*Fig 1*).

dCRT (cisplatin/etoposide) was completed in 6 months with symptom resolution. PET-CT revealed resolution of the initial FDG-avid ulcer and lymph nodes (LNs) (*Fig 1*). Endoscopy with esophageal biopsies was normal, confirming cPR (*Fig 1*).

After 3 months of atezolizumab for subsequent MT, chest pain occurred. PET-CT showed FDG-avid masses in the liver, bones, thoracic LNs, and subcutaneous tissue (*Fig 1*). Biopsy of the hepatic lesions confirmed metastatic NEC despite a normal repeat endoscopy (*Fig 1*).

As all the metastatic lesions demonstrated significant uptake on gallium dotatate PET-CT, she has since been on combination salvage therapy with targeted radionuclide (lutetium Lu 177 dotatate) and systemic (capecitabine, temozolomide, lanreotide) treatments.

DISCUSSION

This case is unusual given our patient's **atypical demographic** for esophageal carcinoma. eNEC's median age of diagnosis is 62 years with male preference (73%). About 50% and 25% of patients have a smoking and alcohol abuse history, respectively.

Selecting dCRT over radical esophagectomy maximized our patient's quality of life while accepting a potentially suboptimal OS. Recent data on stage III eNEC patients show a 43 month median OS and 50% 3-year OS for those receiving surgery with neoadjuvant chemotherapy, versus 15 months and 15% for those receiving non-surgical treatment.

Innovative MT was essential given eNEC's risk for relapse and lack of established protocols. Our trial of atezolizumab is the **first reported off-label use of immune checkpoint inhibition in eNEC**. Ongoing phase II trials are studying the efficacy of anti-PD-1 monotherapy and dual anti-PD-1/anti-CTLA-4 therapy in eNEC.

Relapse only 4 months after cPR emphasizes eNEC's **insidious, early metastatic course**. Given eNEC's nature, it is imperative that **empathic, shared decision-making** be an essential component of patient-centered care for this rare malignancy.

FIGURES

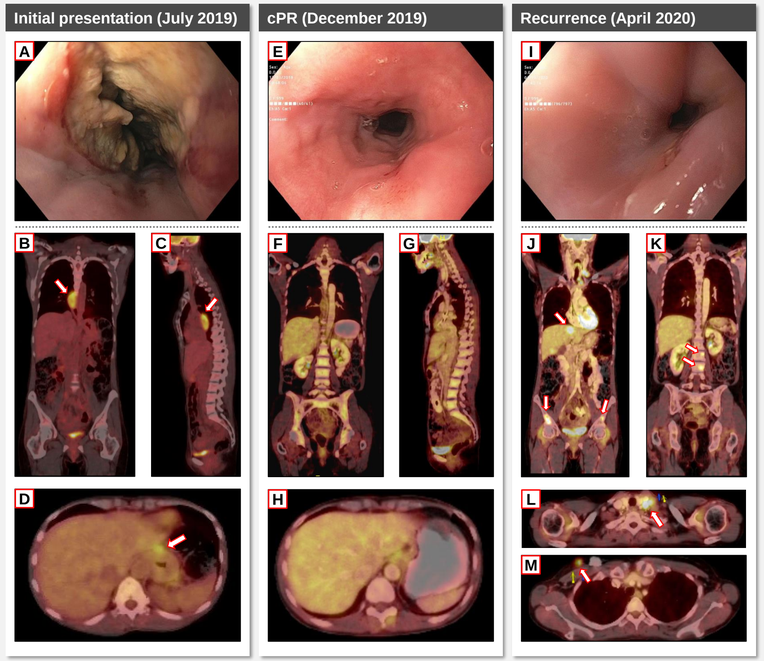

Figure 1

July: 4 cm, necrotic, half-circumferential, cratered ulcer spanning between 28-34 cm from the incisors (A). No distant metastases. Increased FDG activity confined to the mid-esophageal mass (B, C) and gastrohepatic lymph nodes (D).

December: Near complete resolution, with normal biopsies (E). Near complete resolution of abnormal esophageal FDG uptake (F, G), with decreased uptake at the gastrohepatic LNs (H).

April: No significant endoscopic change from December aside from mild re-ulceration of the lesion (~1 cm), and biopsies still normal (I). Interval development of FDG-avid masses within the liver (J), iliac bones (J), L2/L3 vertebral bodies (K), left scapula, right posterior sacrum, thoracic LNs (L), and right chest wall subcutaneous tissue (M).

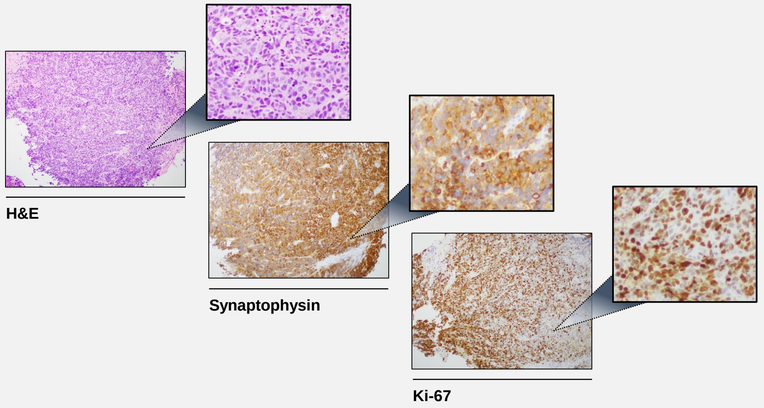

Figure 2

Biopsy histopathology confirming primary eNEC. Homogeneous, small, round, purple/blue cells on H&E staining are characteristic of this high grade, poorly differentiated neuroendocrine malignancy. Positive staining for neuroendocrine markers: synaptophysin, chromogranin, and CD56. Strong Ki-67 positivity reflects the highly proliferative nature of the neoplasm.