ACG CASE REPORTS JOURNAL

CASE REPORT | ESOPHAGUS

A Poorly Differentiated Esophageal Neuroendocrine Carcinoma With Brain Metastasis

Muhammed Yaman Swied, MBBS[1], Yahia Al Turk, MD[2], and Ramprasad Jegadeesan, MD[2]

[1]*Alfaisal University, Riyadh, Saudi Arabia*
[2]*Southern Illinois University School of Medicine, Springfield, IL*

ABSTRACT

Esophageal neuroendocrine carcinomas (NECs) are a rare type of esophageal neoplasm that can initially present with vague signs and symptoms. Gastrointestinal manifestations, such as dysphagia and abdominal discomfort, are the most common symptoms of neuroendocrine neoplasms. Although there is a potential for distant metastases because of esophageal NEC, few cases of brain metastasis have been reported. We report a rare case of an esophageal NEC metastasizing to the brain region.

KEYWORDS: esophageal neuroendocrine carcinoma; brain metastasis; neuroendocrine neoplasms

INTRODUCTION

Esophageal neuroendocrine carcinomas (NECs) are a rare type of esophageal neoplasm, representing 0.04%–4.6% of all gastro-enteropancreatic neuroendocrine tumors (NETs)[1] and 0.4%–2% of all esophageal neoplasms.[2,3] As a result of improved diagnostic techniques, the incidence and prevalence of neuroendocrine neoplasms (NENs) have increased.[4] Gastrointestinal symptoms, such as dysphagia and abdominal discomfort, are the most common manifestations of esophageal NENs.[5] Although esophageal NECs may be capable of distant metastasis, only a few cases of brain metastasis originating from a primary esophageal NEC have been reported. We report a rare case of an esophageal NEC with metastasis to the brain.

CASE REPORT

A 52-year-old man with a medical history of gastroesophageal reflux disease presented to the hospital with a complaint of constipation. At that time, an abdominal computed tomography (CT) scan showed retroperitoneal lymphadenopathy. Approximately 2 months later, a CT-guided retroperitoneal lymph node biopsy was performed. Three days after the retroperitoneal lymph node biopsy, he presented to the emergency department with decreased spatial awareness on the left side, dullness to sensation on the left, headaches, and intermittent confusion. A head CT scan revealed an approximately 4-cm partially calcified mass centered in the right parietal lobe, with a large amount of surrounding vasogenic edema in the right cerebral hemisphere and a 1.6-cm mass centered in the left parietal cortex (Figure 1). He was admitted to the hospital and was treated with dexamethasone. Magnetic resonance imaging of the brain revealed a bilobed enhancing mass within the medial aspect of the posterior right and left parietal lobe that appeared to span the midline (Figure 1). After head imaging was obtained, the results of the retroperitoneal lymph node biopsy were reviewed. Immunohistochemical stains from the biopsy showed neoplastic cells positive for CK8/18 and synaptophysin, focally positive for CKAE1/AE3, and negative for INSM1 and chromogranin (Figure 2) with a high ki67 proliferation index of about 90% (Figure 3). This staining with the morphological features suggested the diagnosis of NEC of unknown primary origin. Image-guided craniotomy with resection of the right occipital lesion was performed, given the mass effect and the surrounding edema. Immunohistochemical stains were performed and showed tumor cells positive for CKAE1/3, CK8/18, synaptophysin, CDX2 (focal), and SATB2 (scattered) and negative for chromogranin, INSM1, TTF1, S100, and GFAP with a high ki67 labeling index >90%. The histological features with this immune profile were consistent with NEC with brain metastasis. The patient got referred to oncology and was started on systemic chemotherapy with etoposide and carboplatin regimen. He also underwent postoperative stereotactic radiotherapy for bilateral parietal lobe lesions. The patient underwent a CT of the chest, abdomen, and pelvis to assess the response to systemic chemotherapy. CT revealed enlarged

ACG Case Rep J 2023;10:e01156. doi:10.14309/crj.0000000000001156. Published online: September 23, 2023

Correspondence: Yahia Al Turk, MD (yalturk74@siumed.edu).

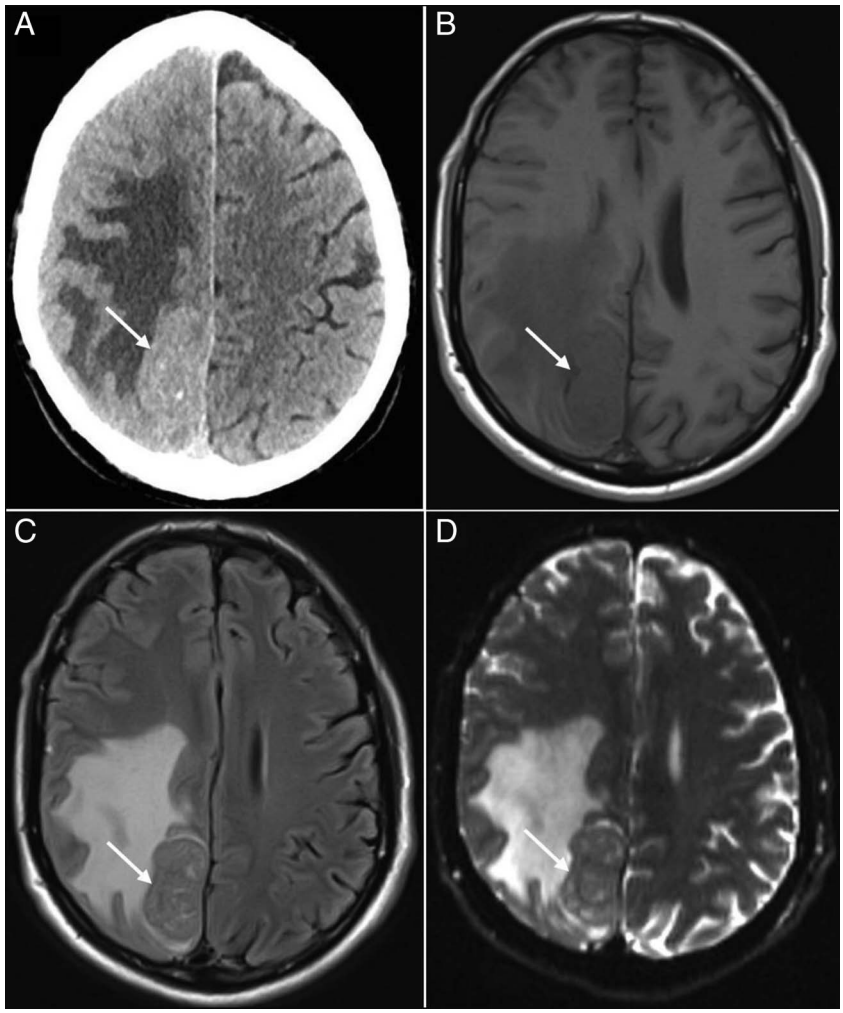

Figure 1. (A) Axial section of the head CT without contrast showing an approximately 4-cm partially calcified mass centered in the right parietal lobe (white arrow). Axial sections of head (B) MRI T1, (C) MRI T2, and (D) MRI DWI showing an enhancing mass within the medial aspect of the posterior right parietal lobe (white arrow). CT, computed tomography; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging.

cervical, mediastinal, and abdominal retroperitoneal lymphadenopathy (Figure 4). In addition, the CT showed rectal wall thickening. He was finally referred to gastroenterology after 4 months of diagnosis to undergo upper endoscopy for further evaluation of intermittent dysphagia to solids and liquids associated with postprandial epigastric pain along with colonoscopy for follow-up of rectal wall thickening noted on the CT scan. Esophagogastroduodenoscopy (EGD) revealed esophageal mucosal changes classified as Barrett's esophagus (C6-M6 [from 31 to 37 cm from the incisors] per Prague criteria) present in the middle and lower third of the esophagus. A large deep circumferential ulcerated tumor occupying at least half of the esophageal lumen was noted 34–37 cm from the incisors with associated esophageal narrowing concerning for primary esophageal cancer in the setting of Barrett's esophagus (Figure 5). Multiple biopsies were obtained from the esophageal ulcerations for pathology. Colonoscopy was normal. Immunohistochemical stains showed neoplastic cells positive for CK8/18 and synaptophysin, focally positive for CDX2, and negative for AE1/3 and chromogranin with a high ki67 proliferation index of about 90%. This staining supported the diagnosis of primary esophageal NEC. The patient completed 6 cycles of systemic chemotherapy with etoposide and carboplatin regimen with improvement in his dysphagia and epigastric pain symptoms as well as response noted on surveillance imaging of the head, chest, and abdomen.

DISCUSSION

The 2 most common types of esophageal tumors are squamous cell carcinoma and adenocarcinoma, accounting for more than 95% of esophageal tumors. Esophageal NENs are uncommon, given that the neuroendocrine system is not well developed in the esophagus.[6] NENs are classified into 2 types: NETs and neuroendocrine cancers (NECs). NETs are well-differentiated NENs that can be labeled by grade as G1, G2, and G3, whereas NECs are poorly differentiated NENs that are high grade by definition.[7] In our patient, there was a delay of 4 months for diagnosing the primary esophageal NET. This suggests the importance of undergoing EGD and colonoscopy to identify the primary source of cancer when imaging shows mediastinal and retroperitoneal adenopathy.

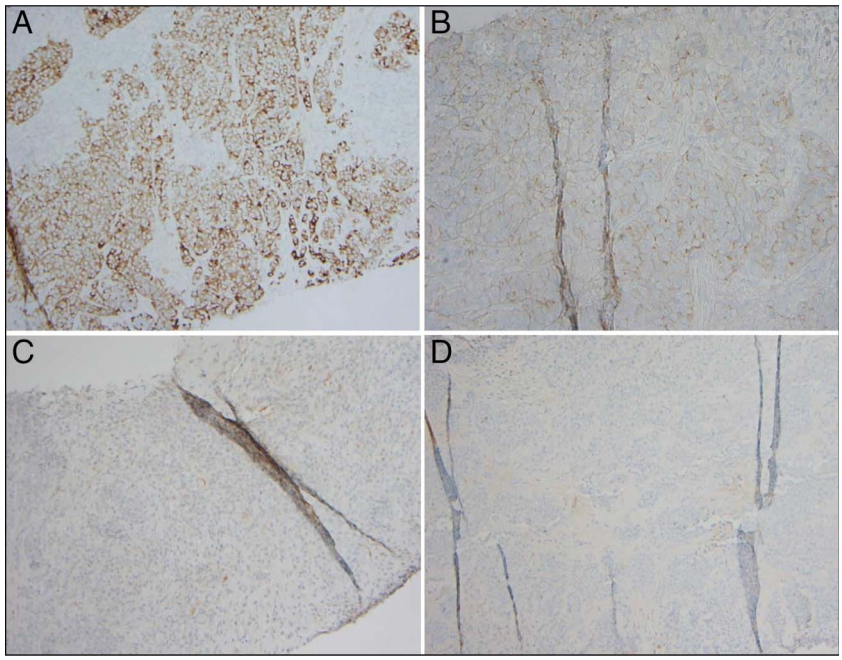

Figure 2. Immunohistochemical stains showing neoplastic cells positive for CK8/18 (A) and synaptophysin (B) and negative for INSM1 (C) and chromogranin (D).

For NENs diagnosis, it is necessary to confirm the presence of neuroendocrine differentiation in conjunction with appropriate morphology, which can be achieved by using immunohistochemical stains for antibodies such as INSM1, synaptophysin, and chromogranin.[7] INSM1 and synaptophysin are the most sensitive in identifying NENs, although they may also stain other lesions.[7] Chromogranin, on the other hand, is typically strongly positive in NETs but only focal and weak to absent in most NECs.[8,9] It is now standard of care to perform Ki67 on all NENs, which is important for tumor grading.[7] The Ki67 proliferation index is usually low in NETs, whereas it is high (typically >55%) in NECs.[7] In our case, immunohistochemical stains showed neoplastic cells positive for synaptophysin and negative for chromogranin with a high ki67 proliferation index of about 90%, consistent with the diagnosis of NEC.

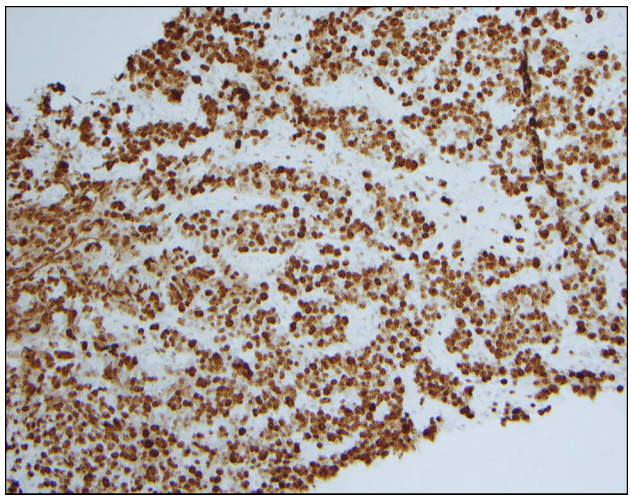

Figure 3. Immunohistochemical stains showing neoplastic cells with a high ki67 proliferation index.

Like other types of esophageal tumors, patients with NECs can present with vague symptoms. Although dysphagia is the most common presentation,[2,5] other symptoms include fever, weight loss, chest discomfort, and odynophagia.[6] Furthermore, esophageal NECs might be discovered incidentally during endoscopic examinations.[2]

Esophageal tumors can be divided based on their locations into upper (15–24 cm from the incisor), middle (24–32 cm from the incisor), and lower (32–40 cm from the incisor).[10] One study found that esophageal NECs are mostly found in the lower esophagus.[3] It is also common for NECs to develop in the midesophagus, which can be due to the larger number of Merkel cells.[2] Therefore, clinicians should be aware of NECs when encountering lesions in the middle and lower esophagus. Endoscopic gross futures of NECs can be divided into ulcerated, flat, and elevated polypoid or nodular types.[10] In a single study of 53 cases of primary esophageal NECs, the ulcerated gross appearance was the most frequent type.[10] In our case, EGD showed a deep ulcerated tumor in the distal esophagus (34–37 cm from the incisor).

When NENs are discovered in the brain first, further diagnostic imaging often reveals the presence of an extracranial primary tumor.[11] Although esophageal tumors have the potential for distant metastasis to the brain with a rate of 1.61%,[12] there have been only a few reports of brain metastasis from a primary esophageal NEN. In addition, NENs make up only 1.4% of

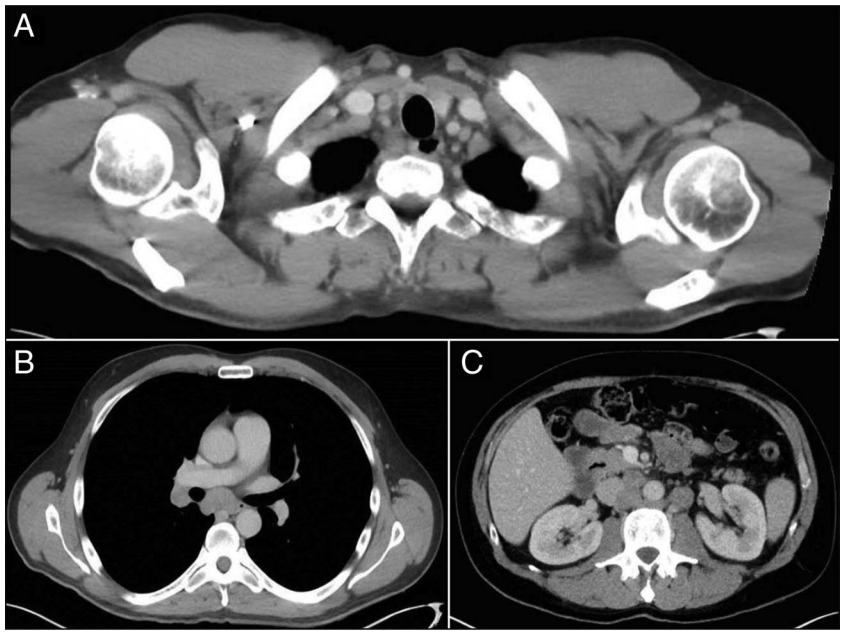

Figure 4. (A) Axial section of the chest CT showing cervical lymphadenopathy. (B) Axial section of the chest CT showing mediastinal lymphadenopathy. (C) Axial section of the abdominal and pelvic CT showing abdominal lymphadenopathy. CT, computed tomography.

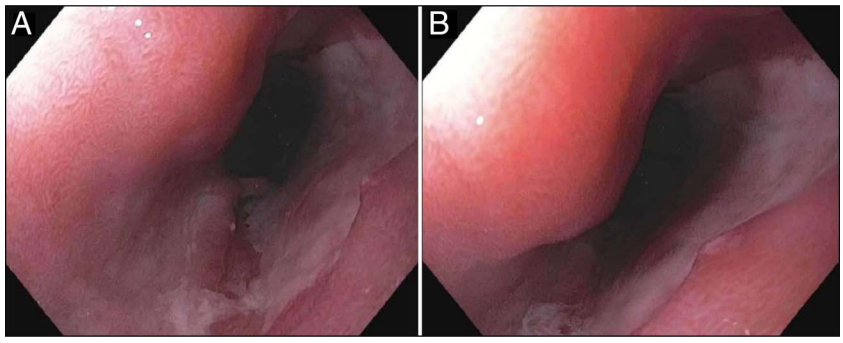

Figure 5. (A) Esophagogastroduodenoscopy showing a deep circumferential ulcerated tumor occupying at least half of the esophageal lumen extending 34–37 cm from the incisors. (B) Extrinsic compression at 34 cm from the incisors.

metastatic brain tumors, with the majority originating from primary tumors in the lung.[11]

In conclusion, we report a rare case of a poorly differentiated esophageal NEC with brain metastasis. Our case suggests that patients with esophageal NECs can initially present with vague signs and symptoms delaying the diagnosis. Awareness of early signs and symptoms is essential for prompt diagnosis and management of esophageal NECs.

DISCLOSURES

Author contributions: MY Swied was involved in the care of the patient, wrote the first draft of the manuscript, and wrote final version after receiving input from the other authors. YA Turk was involved in the care of the patient, edited and reviewed first and second drafts of the manuscript, and is the article guarantor. R. Jegadeesan performed diagnostic EGD on the patient, provided pictures and captions of EGD images, supervised, edited, and reviewed the final draft of the manuscript, and approved final draft of the manuscript.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received June 5, 2023; Accepted August 22, 2023

REFERENCES

1. Giannetta E, Guarnotta V, Rota F, et al. A rare rarity: Neuroendocrine tumor of the esophagus. *Crit Rev Oncol Hematol*. 2019;137:92–107.
2. Awada H, Hajj Ali A, Bakhshwin A, Daw H. High-grade large cell neuroendocrine carcinoma of the esophagus: A case report and review of the literature. *J Med Case Rep*. 2023;17(1):144.
3. Chen C, Hu H, Zheng Z, et al. Clinical characteristics, prognostic factors, and survival trends in esophageal neuroendocrine carcinomas: A population-based study. *Cancer Med*. 2022;11(24):4935–45.

4. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol*. 2008;9(1):61–72.
5. Lee CG, Lim YJ, Park SJ, et al. The clinical features and treatment modality of esophageal neuroendocrine tumors: A multicenter study in Korea. *BMC Cancer*. 2014;14:569.
6. Kuriry H, Swied AM. Large-cell neuroendocrine carcinoma of the esophagus: A case from Saudi Arabia. *Case Rep Gastroenterol*. 2015;9(3):327–34.
7. Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocr Pathol*. 2022;33(1):115–54.
8. Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: An International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol*. 2018;31(12):1770–86.
9. Rindi G, Wiedenmann B. Neuroendocrine neoplasia of the gastrointestinal tract revisited: Towards precision medicine. *Nat Rev Endocrinol*. 2020; 16(10):590–607.
10. Ye L, Lu H, Wu L, et al. The clinicopathologic features and prognosis of esophageal neuroendocrine carcinomas: A single-center study of 53 resection cases. *BMC Cancer*. 2019;19(1):1234.
11. Reed CT, Duma N, Halfdanarson T, Buckner J. Primary neuroendocrine carcinoma of the brain. *BMJ Case Rep*. 2019;12(9):e230582.
12. Song Z, Lin B, Shao L, Zhang Y. Brain metastases from esophageal cancer: Clinical review of 26 cases. *World Neurosurg*. 2014;81(1):131–5.