Oncology Treatment Discovery, 2025, Volume 3, Issue 3
http://ojs.bbwpublisher.com/index.php/OTD
Online ISSN: 2981-8079
Print ISSN: 3083-4996

Esophageal Carcinoma with Small-Cell Neuroendocrine Carcinoma Component and Lymph Node Metastasis Mixed with Poorly Differentiated Squamous Cell Carcinoma: A Rare Case Report

Binghui Ding*, Ling Li

Department of Thoracic Surgery II, Guangzhou Institute of Cancer Research, the Affiliated Cancer Hospital, Guangzhou Medical University, Guangzhou, China

**Author to whom correspondence should be addressed.*

Abstract: This study reports a case of a 74-year-old male patient with esophageal carcinoma who presented two months before admission with dysphagia and chest pain during meals. Preoperative imaging and biopsy revealed a mixed esophageal neuroendocrine carcinoma and non-neuroendocrine carcinoma (squamous cell carcinoma, SCC), with small-cell neuroendocrine carcinoma (SCNEC) comprising the predominant component (65%). Based on the preferences of the patient and his family, surgical treatment was performed first. Postoperative pathological examination revealed poorly differentiated SCC as the predominant component (approximately 90%), with SCNEC accounting for about 10% and lymph node metastasis present, indicating that the NEC component exhibited marked aggressiveness. This case highlights the importance of multiple deep preoperative biopsies and calls for a reevaluation of the WHO definition of Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm (MiNEN), particularly the 30% threshold. Further clinical studies are warranted to refine the diagnostic criteria and therapeutic strategies for MiNEN to improve patient outcomes.

Keywords: Esophageal cancer; Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN); Squamous cell carcinoma (SCC); Neuroendocrine carcinoma (NEC); Lymph node metastasis

Online publication: October 17, 2025

1. Introduction

Esophageal neuroendocrine carcinoma (NEC) is an extremely rare tumor, with an incidence of 3.56 per 100,000 in the United States and European countries; smoking and heavy alcohol consumption are the main risk factors [1]. It accounts for only 3.3% of all esophageal malignancies [2]. Globally, squamous cell carcinoma (SCC) is the most common type of esophageal cancer, comprising over 90% of cases, particularly in Asia, East Africa, and South

America [3]. However, mixed tumors containing both NEC and SCC components in the esophagus are even rarer, and their diagnosis and treatment remain highly controversial. Although current treatment strategies include surgery, chemotherapy, radiotherapy, and targeted therapy, no standardized treatment protocol has been established because of the rarity of the disease. Here, we report a case of esophageal carcinoma with mixed NEC and SCC components.

2. Case report

A 74-year-old male presented with a two-week history of dysphagia and retrosternal pain during meals, occasionally accompanied by coughing. He had a 30-year history of smoking approximately 20 cigarettes per day and had quit one year prior to presentation. He also had a 30-year history of alcohol consumption, primarily Chinese liquor (baijiu), averaging 500 mL per day, and had not ceased drinking.

Barium swallow examination showed a narrow, strip-like passage of contrast medium at the level of the eighth to ninth thoracic vertebrae, approximately 5 cm in length, with rigidity of the mid-esophageal wall and poor peristaltic function. Upper abdominal CT (**Figure 1**) demonstrated thickening of the mid-esophageal wall with a maximum thickness of approximately 11 mm and enlarged mediastinal lymph nodes (up to 10 mm × 8 mm) with homogeneous enhancement, raising suspicion of lymph node metastasis.

Endoscopic biopsy (**Figure 2**) revealed a nodular mass located 33–37 cm from the incisors, with an eroded surface, friable texture, and contact bleeding. Histopathological examination with hematoxylin and eosin staining and immunohistochemistry demonstrated features consistent with a mixed neuroendocrine carcinoma–non-neuroendocrine carcinoma, comprising approximately 65% SCNEC and 35% SCC.

On admission, the patient's height was 162.0 cm and weight was 51.5 kg. Because of severe esophageal obstruction that precluded nasogastric feeding, a three-incision (cervical, thoracic, and abdominal) partial esophagectomy with intrathoracic esophagogastrostomy and jejunostomy was performed. Postoperative pathological findings are shown in **Figure 3** and **Figure 4**.

The postoperative clinical course was uneventful, and the patient was discharged without complications. Postoperative follow-up CT is shown in **Figure 1**.

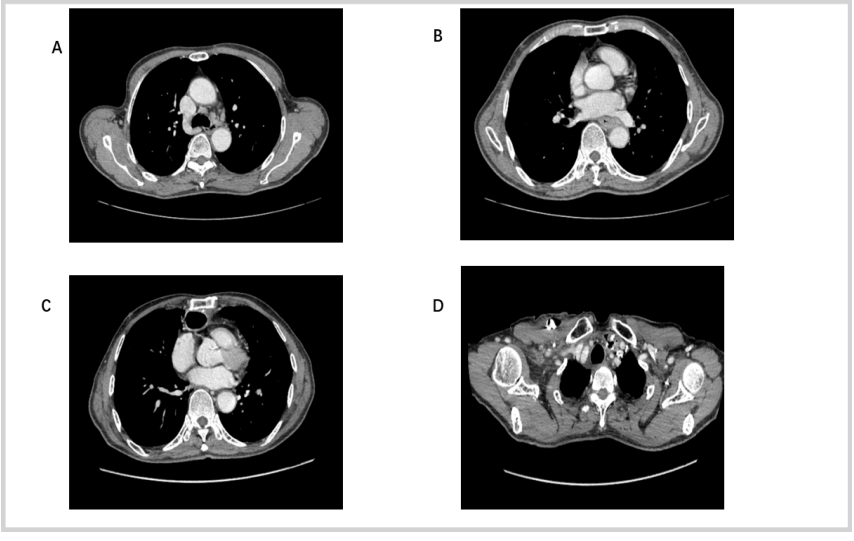

Figure 1. Preoperative and postoperative CT images of the patient.Panels A and B show preoperative CT images, while Panels C and D show postoperative CT images.

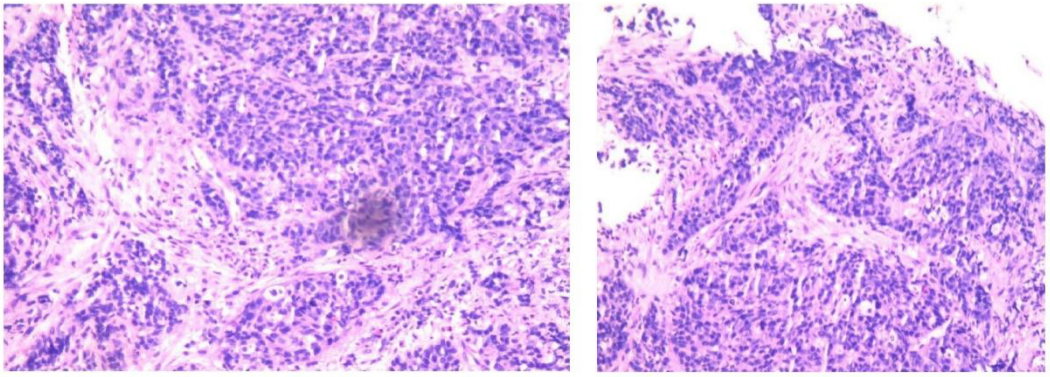

Figure 2. Endoscopic biopsy pathology.

Histopathological section obtained from preoperative endoscopic biopsy of the esophagus showing marked infiltration of atypical cells beneath the squamous epithelium, with some forming nests. Combined with immunohistochemistry, the findings are consistent with a mixed neuroendocrine carcinoma–non-neuroendocrine carcinoma, comprising approximately 65% SCNEC and 35% SCC. The final tumor component ratios will be determined from the postoperative resection specimen. Immunohistochemistry: CK (+), P40 (partial +), P63 (partial +), Synaptophysin (Syn; partial +), Ki-67 (≈75% +), CD56 (partial +), Chromogranin A (CgA; partial +), INSM1 (partial +), CK7 (scattered +), LCA (−), CAM5.2 (−), CK20 (−).

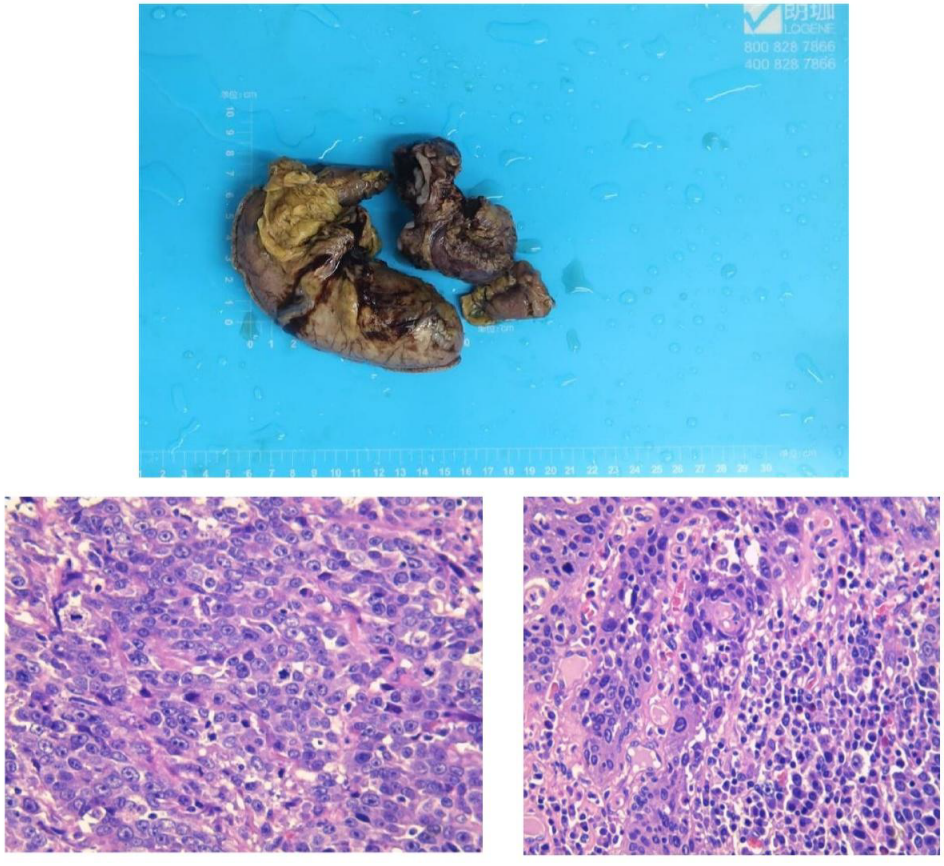

Figure 3. Postoperative specimens of esophageal carcinoma.

Specimens included: paraesophageal lymph nodes of the mid-esophagus, group 7 lymph nodes, proximal margin, distal margin, perigastric lymph nodes near the cardia, lymph nodes along the left gastric artery, esophagus with partial stomach, left supraclavicular lymph nodes, and paraesophageal lymph nodes of the distal esophagus (2 specimens).

Pathological findings: (1) Mid-esophageal paraesophageal lymph nodes: no metastatic carcinoma identified (0/2). (2) Group 7 lymph nodes: no metastatic carcinoma identified (0/6). (3) Proximal resection margin: esophageal tissue free of carcinoma. (4) Distal resection margin: no carcinoma observed in the sampled tissue. (5) Pericardial (cardia) lymph nodes: only fibrous, adipose, and muscular tissue were present; no lymph nodes or carcinoma identified. (6) Lymph nodes along the left gastric artery: no metastatic carcinoma detected (0/1). (7) Esophagus with partial stomach: consistent with a mixed neuroendocrine–non-neuroendocrine carcinoma, comprising approximately 10% SCNEC and 90% poorly differentiated SCC. Tumor infiltrated the full thickness of the esophageal wall into the periesophageal fibroadipose tissue, with suspected intravascular tumor emboli; no definite perineural invasion was observed. Gastric tissue was free of carcinoma. One lymph node identified in the peristomach adipose tissue showed no metastatic carcinoma (0/1). Immunohistochemistry (ID: 148968-018#): CK5/6 (+), P40 (+), Chromogranin A (CgA; −), Synaptophysin (Syn; −), INSM1 (focal +), TTF-1 (−), PD-L1 (22C3; CPS ≈8), PD-L1 (22C3 Neg; −), P53 (~90% +, suggestive of mutant type), Ki-67 (~70% +). (8) Left supraclavicular lymph nodes: no metastatic carcinoma detected (0/2). (9) Paraesophageal lymph nodes of the distal esophagus (2 specimens): no metastatic carcinoma detected (0/2).

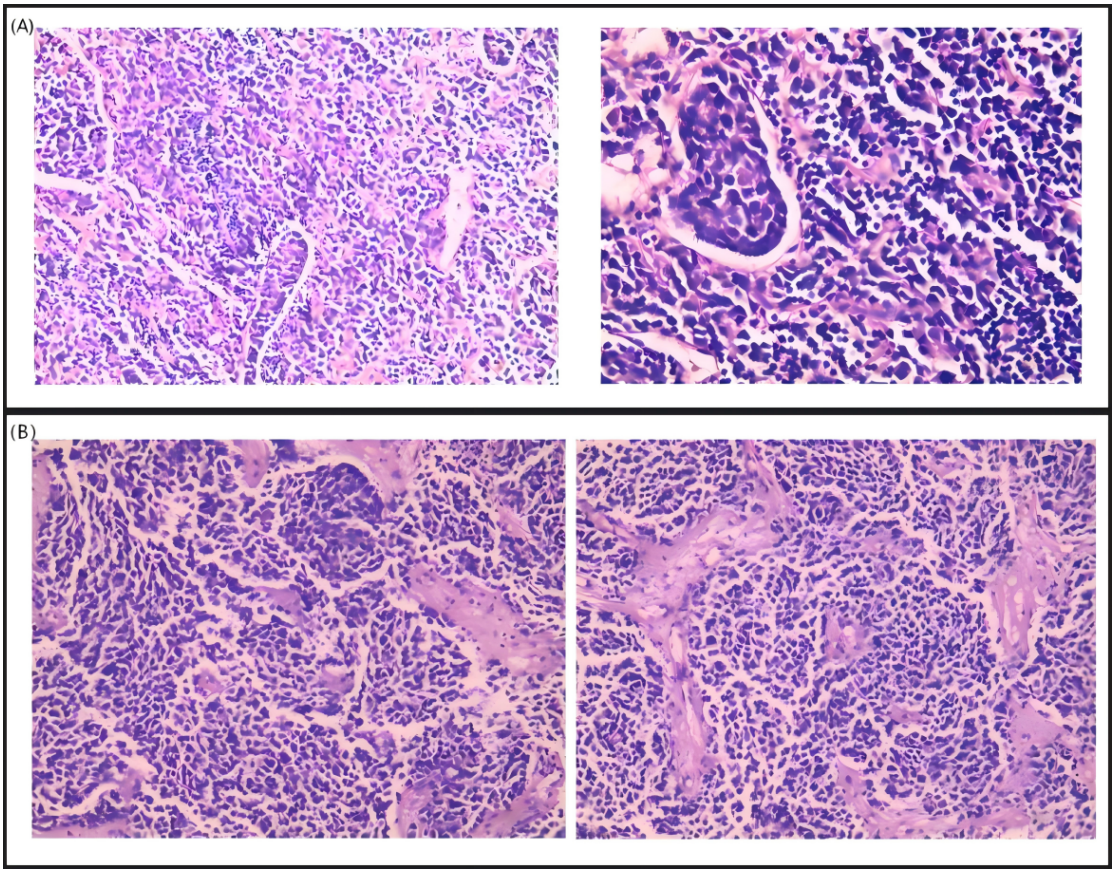

Figure 4. Intraoperative frozen sections. (A) Distal paraesophageal lymph node (intraoperative frozen section). Pathological diagnosis revealed metastatic small cell carcinoma in the examined lymph node (1/1), accompanied by necrosis.(B) Right pararecurrent laryngeal nerve lymph node. Pathological examination revealed metastatic small cell carcinoma in 2 out of 4 examined lymph nodes. Immunohistochemistry showed CK pan (+), Ki-67 (~90%+), Syn (+), and P40 (−).

3. Follow-up and recent examinations

The patient received multiple cycles of adjuvant chemotherapy combined with immunotherapy after surgery. Between November 25, 2023, and February 27, 2024, the patient completed five cycles of cisplatin combined with etoposide and atezolizumab as chemotherapeutic immunotherapy. Subsequently, the patient underwent regular radiotherapy and tolerated treatment well, with no severe adverse reactions observed. Following this, four cycles of albumin-bound paclitaxel chemotherapy were administered on May 29, June 17, July 14, and August 4, 2025, achieving stable disease (SD); all cycles were well tolerated and completed successfully.

Throughout the adjuvant treatment period, the patient remained clinically stable, with no evidence of tumor recurrence or distant metastasis. Repeated imaging studies and clinical follow-up indicated good recovery and a significant improvement in quality of life. During the postoperative and subsequent treatment period, the patient underwent regular imaging and endoscopic follow-up assessments, with findings as follows:

August 2025 follow-up CT (August 4, 2025) of the chest and entire abdomen showed postoperative changes of the esophagus, with no evidence of local tumor recurrence. The anastomosis appeared normal, and no abnormal soft tissue density was observed. Multiple small lymph nodes were seen in the mediastinum and hilar regions, without significant enlargement or signs of metastatic involvement. Chronic inflammatory changes and small pulmonary bullae were noted in both lungs, with no new solid nodules or evidence of metastasis. The liver, gallbladder, spleen, pancreas, and kidneys were unremarkable, and no abnormal fluid collection was observed in the abdominal or pelvic cavities. No evident metastatic lesions were detected in the skeletal system. Overall assessment revealed no evidence of local recurrence or distant metastasis.

July 2024 endoscopy demonstrated a patent anastomosis with well-healed mucosa and no evidence of tumor recurrence. Mucosal congestion and edema were noted in the gastric tube and lumen, suggesting postoperative reflux esophagitis, without stricture, obstruction, or neoplasm. The duodenal bulb mucosa appeared smooth, with no significant abnormalities.

Clinical status and quality of life: According to the most recent hospitalization record (August 2025), the patient reported no significant dysphagia, chest pain, or cough. Nutritional status was stable, body weight was 51 kg, and oral intake was unremarkable, with only occasional reflux symptoms. The patient's mental and physical condition was good, daily activities were independent, vital signs were stable, and overall general condition was satisfactory. Quality of life was significantly improved compared to preoperative status, with normal oral intake and minimal limitations in daily activities. The Karnofsky Performance Status score was estimated at 80–90.

In summary, the patient exhibited good overall recovery during the postoperative and follow-up periods, with no evidence of local recurrence or distant metastasis. Imaging and endoscopic evaluations revealed no tumor progression, nutritional status and quality of life were satisfactory, and the primary complaint was mild reflux symptoms.

4. Discussion

The 2019 World Health Organization (WHO) classification defined mixed neuroendocrine–non-neuroendocrine neoplasms (MiNEN), also referred to as mixed adenoneuroendocrine carcinoma (MANEC), as tumors composed of neuroendocrine (NE) and non-neuroendocrine (non-NE) components, with each component constituting at least 30% of the tumor [4]. However, the 30% threshold is primarily based on the assumption that a minor tumor component (< 30%) is unlikely to significantly affect the patient's biological behavior [5]. It is noteworthy, however,

that this cutoff is arbitrary and not supported by definitive clinical evidence [5]. Therefore, the precise diagnosis of MiNEN remains controversial.

Preoperative biopsy of the patient indicated a mixed neuroendocrine–non-neuroendocrine carcinoma, with small cell neuroendocrine carcinoma comprising approximately 65% and squamous cell carcinoma approximately 35%. Postoperative pathological examination revealed that small cell neuroendocrine carcinoma accounted for only about 10%, whereas poorly differentiated squamous cell carcinoma represented about 90% of the tumor. According to treatment strategies at many centers, MiNEN is often managed using the same approach as pure neuroendocrine carcinoma (NEC) [6], typically involving neoadjuvant chemoradiotherapy followed by surgery. However, given the patient's poor nutritional status and severe obstruction at admission, upfront surgical intervention was considered more beneficial. Considering that poorly differentiated squamous cell carcinoma constituted 90% of the postoperative specimens, neoadjuvant chemoradiotherapy would likely have limited effectiveness in symptom relief, functional improvement, or delaying tumor progression.

This case underscores the importance of performing multiple deep biopsies preoperatively to establish an accurate diagnosis [6]. Furthermore, although postoperative pathology indicated that small cell neuroendocrine carcinoma comprised only 10% of the tumor, metastases were observed intraoperatively in the right pararecurrent laryngeal nerve and distal paraesophageal lymph nodes. These findings demonstrate the biological activity of this minor component and support a diagnosis of MiNEN.

5. Conclusion

The study reported a rare case of esophageal MiNEN, initially diagnosed via preoperative biopsy as a mixed neuroendocrine–non-neuroendocrine neoplasm in which NEC predominated (~65%). Due to severe obstruction and poor nutritional status, the patient underwent upfront surgical treatment. Postoperative pathology revealed that poorly differentiated SCC predominated (~90%), with NEC comprising a minor component (~10%). Although the NEC component was minor, the presence of lymph node metastases indicated its aggressive biological behavior.

This case highlights the importance of thorough, deep, and multi-site biopsies for accurate diagnosis and emphasizes the need to consider the potential impact of even a minor NEC component on MiNEN biological behavior and clinical management. Although the 30% threshold defining MiNEN remains arbitrary and controversial, the presence of metastasis in this case supports the MiNEN diagnosis and suggests that such tumors can exhibit significant biological aggressiveness regardless of the proportion of each component. Further clinical studies are required to refine the diagnostic criteria and treatment strategies for MiNEN, ultimately aiming to improve patient prognosis.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Giannetta E, Guarnotta V, Rota F, et al., 2019, A Rare Rarity: Neuroendocrine Tumor of the Esophagus. Crit Rev Oncol Hematol, 137: 92–107.

[2] Kanakasetty G, Dasappa L, Lakshmaiah K, et al., 2016, Clinicopathological Profile of Pure Neuroendocrine

Neoplasms of the Esophagus: A South Indian Center Experience. J Oncol, 2016: 2402417.

[3] Reichenbach Z, Murray M, Saxena R, et al., 2019, Clinical and Translational Advances in Esophageal Squamous Cell Carcinoma. Adv Cancer Res, 144: 95–135.

[4] Scoazec J, Rindi G, 2019, Oesophageal Neuroendocrine Neoplasms. In: WHO Classification of Tumours Editorial Board, ed. WHO Classification of Tumours of the Digestive System. 5th ed. International Agency for Research on Cancer, Lyon: 56–58.

[5] Rosa S, Sessa F, Uccella S, 2016, Mixed Neuroendocrine-Nonneuroendocrine Neoplasms (MiNENs): Unifying the Concept of a Heterogeneous Group of Neoplasms. Endocr Pathol, 27(4): 284–311.

[6] Sulaiman M, Agarwal S, Mandal A, et al., 2022, High-Grade Mixed Neuroendocrine Non-Neuroendocrine Neoplasm of the Gastroesophageal Junction: A Rare Case Report and Review of Literature. Indian J Pathol Microbiol, 65(4): 918–920.