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Case Report

Rare esophageal large-cell neuroendocrine carcinoma treated with Serplulimab: a case report

Danxia Wen, Xiaoyang Wang, Min Luo, Hengchen Yan

Department of Radiation Oncology, Center for Cancer Prevention and Treatment, Meizhou People's Hospital (Huangtang Hospital), Meizhou Academy of Medical Sciences, Meizhou 514031, Guangdong, China

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Abstract: Esophageal large-cell neuroendocrine carcinoma (LCNEC) is a rare and aggressive malignancy that presents diagnostic and therapeutic challenges. We present the case of a 72-year-old female with LCNEC of the distal esophagus who was initially treated with chemotherapy and radiation therapy, followed by immunotherapy due to disease progression. Diagnostic imaging revealed extensive metastases to the abdominal lymph nodes. Histopathological examination confirmed the diagnosis of LCNEC with high-grade squamous intraepithelial neoplasia. The treatment complexities underscore the necessity of a multidisciplinary approach involving medical oncologists, radiation oncologists, and pathologists. While chemotherapy remains the standard, the role of immunotherapies, such as Slurilizumab in LCNEC management is evolving. Subsequent imaging revealed gradual tumor reduction, and the patient was maintained on immunotherapy. The patient has remained on immunotherapy since then, with a progression-free survival of 1 year and 4 months as of the latest follow-up, approximately 3 years post-diagnosis. This case highlights the potential of combining immunotherapy with conventional treatments for disease control. Further research is crucial to optimizing therapeutic strategies and prognostic factors for esophageal LCNEC to enhance clinical outcomes and patient care.

Keywords: Esophageal large-cell neuroendocrine carcinoma, chemotherapy, immunotherapy, slurilizumab, case report

Introduction

Esophageal neuroendocrine carcinoma (NEC) is a rare malignancy arising from neuroendocrine cells within the esophagus, accounting for less than 2% of all esophageal neoplasm cases [1]. NECs encompass a spectrum of histological subtypes, ranging from well-differentiated to poorly differentiated forms, which complicate patient management and prognostication [2]. Therapeutically, the heterogeneity of NECs necessitates personalized treatment protocols. However, available options are limited, and the rarity of these tumors means that clinical trials are few and often lack the robustness needed to derive conclusive evidence, thereby supporting the development of innovative treatments [3]. Consequently, the management of advanced disease is particularly problematic, with current strategies focusing on symptomatic relief rather than curative outcomes. This underscores the urgent need for multidisciplinary approaches and new therapeutic modalities in this domain [4]. Large-cell NEC (LCNEC) of the esophagus represents an even rarer subtype, characterized by aggressive behavior and poor prognosis [5]. Owing to low incidence and limited treatment options, the management of esophageal LCNEC poses significant challenges in clinical practice. Our study presents the case of a 72-year-old female diagnosed with LCNEC of the distal esophagus, who, after an initial response to chemotherapy and radiation therapy, demonstrated progressive disease necessitating the integration of immunotherapy. The incorporation of slurilizumab into the treatment regimen resulted in a notable progression-free survival of 1 year and 4 months, with tumor regression observed on subsequent imaging. This case underscores the evolving role of immunotherapy in LCNEC management, suggesting that it may serve as an adjunct to

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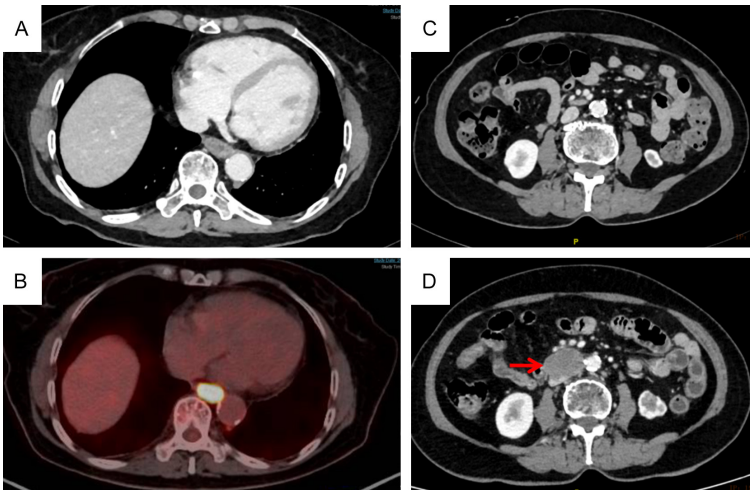

Figure 1. Initial imaging findings of the esophageal large-cell neuroendocrine carcinoma case. A. Enhanced computed tomography (CT) imaging revealed thickening of the distal esophageal wall. B. Positron Emission Tomography (PET)-CT indicated a strip-like area of high metabolic activity in the distal esophagus, corresponding to the vertebrae at thoracic levels 9 and 10. C. Follow-up CT scans showed initial response to chemotherapy and radiotherapy. D. Follow-up CT scans showed disease progression with the development of abdominal lymph node metastases on imaging follow-up 18 months later.

traditional modalities to enhance disease control and improve patient outcomes.

Case presentation

A 72-year-old female presented with a 4-day history of hematemesis and dysphagia, prompting further evaluation. Upon admission, the patient denied any significant medical history, except for a remote history of an intracranial aneurysm treated with endovascular therapy 12 years prior and coronary artery disease managed with coronary artery stenting 10 years ago.

Imaging studies

On August 17, 2021, enhanced computed tomography (CT) imaging revealed thickening of the distal esophageal wall, suggesting primary esophageal malignancy. Several nodular soft tissue lesions were identified adjacent to the gastroesophageal junction and along the lesser curvature of the stomach (**Figure 1A**).

Subsequent brain magnetic resonance imaging on August 19, 2021, showed no evidence of cerebral metastases. Further comprehensive evaluation through Positron Emission Tomography-CT on August 20, 2021, indicated a strip-like area of high metabolic activity in the distal esophagus, corresponding to the vertebrae at the thoracic levels 9 and 10, consistent with esophageal cancer (**Figure 1B**). Additionally, multiple nodular high-metabolic lesions were observed near the abdominal aorta above the celiac trunk, suggesting lymph node metastases. Small lymph nodes with increased metabolism were also observed behind the thoracic aorta, adjacent to the esophagus and portal cavum.

Endoscopic ultrasound performed on August 19, 2021, revealed that the wall layer structure was obliterated at the site of the esophageal lesion, and a hypoechoic lesion with uneven internal echoes was noted, with the thickest part measuring approximately 19.6 mm. The lesion appeared to breach the outer membrane locally; however, its demarcation from the surrounding tissues remained distinct. A hypoechoic nodule measuring approximately 6.5×8.3 mm was detected near the tracheal bulge, approximately 26 cm from the incisors. Around the gastric fundus, three hypoechoic nodules were identified, the largest measuring 16.3×15.4 mm, showing local confluence.

Biopsy and immunohistochemical analysis of the esophageal sample revealed positive staining for synaptophysin and CD56, with a high proliferation index (Ki67) around 70% (**Figure 2**). Minimal cytokeratin 8 positivity was observed, with negative staining for P63, P40, chromogranin A (CgA), and thyroid transcription factor-1. Based on hematoxylin and eosin staining and immunohistochemical profile, the diagnosis was confirmed as large cell neuroendocrine carcinoma of the esophagus, with high-grade squamous intraepithelial neoplasia on the surface epithelium (cT3N2M0, stage III).

Treatment and therapeutic response

Given the advanced stage of the disease and aggressive histology, systemic chemotherapy with etoposide and carboplatin was initiated as first-line therapy for four cycles. After chemo-

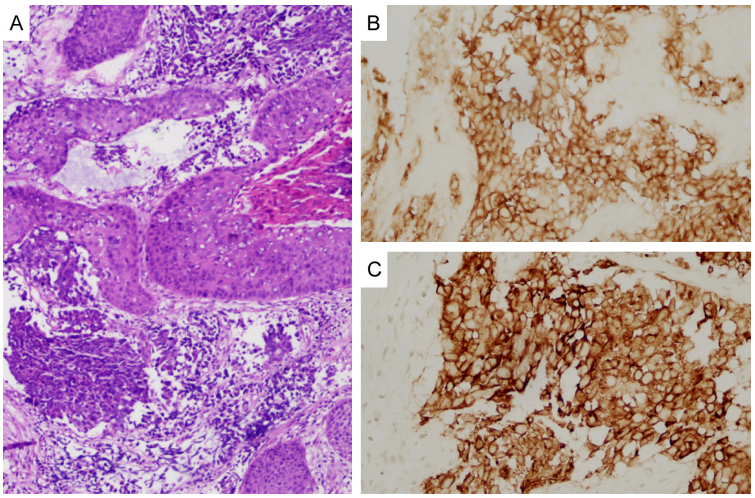

Figure 2. Histopathological examination and immunohistochemical profiling. (A) Large cell neuroendocrine carcinoma (hematoxylin-eosin, original magnification 20×). The tumor cells demonstrate strong and diffuse expression of CD56 (B) and synaptophysin (C) (Immunohistochemical profiling, original magnification 400×).

therapy, the patient underwent intensity-modulated radiation therapy targeting the primary esophageal lesion and regional lymph nodes, with a total dose of 60 Gy in 30 fractions (planning gross tumor volume) and 54 Gy in 30 fractions (planning clinical tumor volume). The treatment protocol was the adjusted to include two additional cycles of etoposide and carboplatin after the completion of radiotherapy. Despite the initial response to chemotherapy and radiotherapy, the patient experienced disease progression with the development of abdominal lymph node metastases on follow-up imaging 18 months later (**Figure 1C** and **1D**). Consequently, immunotherapy with slurilizumab, a programmed death-ligand 1 (PD-L1) inhibitor, was added to the Irinotecan treatment regimen for four cycles. The abdominal lymph nodes decreased in size after two cycles of treatment but enlarged after four cycles (**Figure 3**). Owing to intolerance, the treatment was switched to continue with slurilizumab monotherapy, which continued to date. Additionally, from July 11, 2023, to July 26, 2023, the patient underwent stereotactic body radiotherapy with a dose of 48 Gy in 12 fractions (planning gross tumor volume). Serial imaging assessments demonstrated a partial response to slurilizumab monotherapy, with a reduction in tumor burden (**Figure 4**). At the time of writing, the patient has been diagnosed for nearly 3 years, with a progression-free survival (PFS) of 1 year and 4 months on slurilizumab.

Changes in tumor and blood-related testing

Serial tumor marker assessments revealed significant fluctuations throughout the treatment course. At diagnosis, serum neuron-specific enolase (NSE) was markedly elevated at 48.7 ng/mL (normal range: 0-16.3 ng/mL). Following initial chemotherapy, NSE levels decreased to 22.5 ng/mL, but subsequently rose to 35.8 ng/mL during disease progression. With slurilizumab initiation, the NSE levels gradually declined, reaching 18.2 ng/mL after 6 months of immunotherapy. CgA, initially elevated at 120 ng/mL (normal range: 0-95 ng/mL), showed a similar response pattern, decreasing to 85 ng/mL post-chemotherapy and stabilizing at 78 ng/mL during immunotherapy maintenance.

Hematological parameters demonstrated treatment-related changes. The initial complete blood count showed mild anemia (hemoglobin 10.2 g/dL) and thrombocytosis (platelet count 450×10^9/L). Chemotherapy induced expected cytopenias, with nadir hemoglobin values at 8.5 g/dL, white blood cell count at 2.1×10^9/L, and platelet count at 85×10^9/L. Immunotherapy was associated with stable hematological parameters, with maintenance phase values within normal ranges (hemoglobin 11.8 g/dL, white blood cell count 5.2×10^9/L, platelet count 210×10^9/L). Liver function tests remained stable throughout treatment, with alanine aminotransferase consistently below 40 U/L and alkaline phosphatase ranging from 85-110 U/L.

Discussion

Esophageal LCNEC is a rare and aggressive malignancy associated with poor prognosis and limited treatment options. The management of this disease requires a multidisciplinary approach involving medical oncologists, radiation oncologists, thoracic surgeons, and pathol-

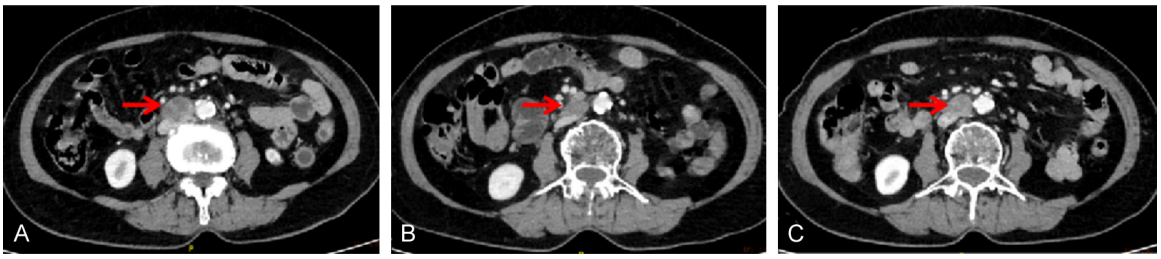

Figure 3. Immunotherapy treatment response in this case. A. computed tomography (CT) scans before slurilizumab and Irinotecan treatment. B. CT scans after 2 cycles of slurilizumab and Irinotecan treatment. C. CT scans after 4 cycles of slurilizumab and Irinotecan treatment.

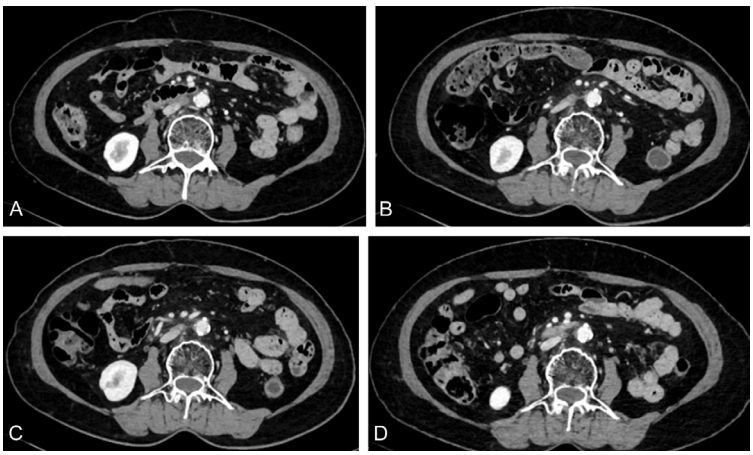

Figure 4. Serial imaging demonstrating treatment response to slurilizumab. A. computed tomography (CT) scan after 4 months of slurilizumab treatment. B. CT scan after 6 months of slurilizumab treatment. C. CT scan after 9 months of Slurilizumab treatment. D. CT scan after 12 months of slurilizumab treatment.

ogists [6]. Chemotherapy remains the cornerstone of treatment for advanced esophageal LCNEC, and platinum-based regimens are commonly used in clinical practice [7]. However, the optimal chemotherapy regimen and the role of targeted therapies in the management of esophageal LCNEC remain poorly defined owing to the scarcity of clinical data. Immunotherapy has emerged as a promising treatment modality for various solid tumors, including esophageal cancer. However, the efficacy in esophageal LCNEC remains uncertain.

This case report presents the clinical course of a patient diagnosed with LCNEC in August of 2021. Initially treated with a regimen of etoposide and carboplatin chemotherapy for four cycles followed by radiotherapy, the treatment protocol was adjusted to an additional two cycles of etoposide and carboplatin after completion of radiotherapy. In February 2023, disease progression was noted on CT scans with abdominal lymph node metastasis, prompting a switch to acombination therapy of slurilizumab and irinotecan for four cycles. While the tumor initially responded with shrinkage after two cycles, subsequent imaging revealed progression after four cycles. Owing to intolerability, the patient was transitioned to single-agent slurilizumab therapy, resulting in gradual tumor reduction. Currently, the patient continues to receive slurilizumab maintenance therapy. Approximately 3 years ago, disease-free survival reached 1 year and 4 months with no evidence of progression under slurilizumab treatment. Our case highlights the potential utility of immunotherapy in combination with chemotherapy and radiotherapy in achieving disease control and improving patient outcomes of esophageal LCNEC.

The literature review of chemoradiotherapy cases (**Table 1**) demonstrates the limited efficacy of conventional treatments for esophageal LCNEC, with a median overall survival (OS) ranging from 8 to 36 months. Platinum-based regimens, particularly cisplatin or carboplatin combined with etoposide, remain the mainstay of treatment, achieving response rates of 60-70% but with limited durability. Our case initially followed this pattern, with disease progression occurring 18 months after completion of chemoradiotherapy. The addition of slurilizumab represented a significant departure

Table 1. Literature review of esophageal large cell neuroendocrine carcinoma cases

Study (Year)	Stage	Treatment Approach	Outcomes (month)
Galanis et al. (2022)	IIB	Adjuvant cisplatin + etoposide	OS: > 36
Nakao et al. (2019)	IVB	Adjuvant docetaxel + fluorouracil	OS: 20
Terada et al. (2011)	NA	Adjuvant chemoradiation	OS: 8
Tustumi et al. (2017)	IIA	Adjuvant irinotecan + cisplatin + radiotherapy	OS: 13
Tomiyama et al. (2018)	IVB	Fluorouracil + cisplatin	OS: 11
Fukuchi et al. (2014)	IVA	Adjuvant chemotherapy	OS: 9

NA, not applicable; OS, Overall survival.

from conventional treatment paradigms. While the reviewed studies focused solely on chemoradiotherapy, our approach of sequential immunotherapy following disease progression resulted in markedly superior outcomes, with the patient achieving more than 36 months of OS and 16 months of PFS on immunotherapy maintenance. This suggests that incorporating immunotherapy, even as a salvage therapy, may substantially improve outcomes in this aggressive malignancy.

In conclusion, comprehensive histopathological and immunohistochemical analysis are essential for an accurate diagnosis. A multimodal treatment approach, including chemotherapy, radiotherapy, and immunotherapy, may be necessary to achieve disease control and improve patient outcomes. Further research is warranted to elucidate optimal treatment strategies and prognostic factors for esophageal LCNEC, ultimately enhancing clinical decision-making and patient care.

Conclusion

This case report provides valuable insights into the clinical course and management of esophageal LCNEC, contributing to the existing literature on this rare disease.

Disclosure of conflict of interest

None.

Address correspondence to: Xiaoyang Wang, Department of Radiation Oncology, Meizhou People's Hospital (Huangtang Hospital), Meizhou Academy of Medical Science, Huangtang Road, Meijiang District, Meizhou 514031, Guangdong, China. E-mail: wangxiaoyang@mzrmyy.com

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