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Esophageal Large Cell Neuroendocrine Carcinoma: A brief Pathology Review of the Rare Tumor

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Abstract:

Esophageal Large Cell Neuroendocrine Carcinoma (LCNEC) is an exceedingly rare and aggressive neuroendocrine neoplasm (NEN) that originates in the esophagus. This review article aims to provide a concise yet comprehensive overview of LCNEC, touching upon its epidemiology, clinical presentation, diagnostic challenges, histological and molecular characteristics, and current approaches to treatment. LCNEC is marked by rapid progression and a poor prognosis, setting it apart from other esophageal cancers with its unique cellular morphology and neuroendocrine differentiation. Despite its rarity, understanding the pathology, clinical implications, and potential treatment strategies for LCNEC is crucial for improving patient outcomes. This review synthesizes current knowledge, highlighting the importance of accurate diagnosis and the need for further research to develop targeted therapies.

KeyWords: Esophageal Large Cell Neuroendocrine Carcinoma, LCNEC, neuroendocrine neoplasms, NENs esophageal cancer, pathology review, diagnosis, treatment strategies, molecular characteristics.

Introduction

Esophageal Large Cell Neuroendocrine Carcinoma (LCNEC) represents a particularly rare and highly aggressive form of neuroendocrine neoplasms (NENs) that arise within the esophagus. Characterized by its rapid progression and poor prognosis, LCNEC is distinguished from other esophageal cancers by its unique cellular morphology and neuroendocrine differentiation. The incidence of this malignancy is notably low, contributing to a limited understanding and challenges in both diagnosis and treatment. This pathology review aims to provide an in-depth exploration of esophageal LCNEC, encompassing its clinical presentation, histological features, molecular characteristics, and feasible therapeutic strategies. By examining the disease from these multifaceted perspectives, we seek to shed light on the complexity of LCNEC and the ongoing research efforts to improve patient outcomes.

I. Epidemiology and classification:

Esophageal LCNEC is an exceedingly uncommon malignancy, and only few cases have been described in the literature[1, 2]. WHO (5th ed.) classified NENs into 3 types based on the cell differentiation: well-differentiated neuroendocrine tumors (NETs), poorly differentiated neuroendocrine carcinomas (NECs), and mixed neuroendocrine-non neuroendocrine neoplasms (MiNENs). LCNEC and small cell neuroendocrine carcinoma (SCNEC) are under the classification of NECs which account for >90% of all esophageal NENs[3]. Although esophageal LCNEC shares some characteristics with small cell lung carcinoma (SCLC) like brisk mitosis, they are distinct entities with differences in pathology, clinical presentation, and treatment response.

II. Clinical Presentation:

The clinical presentation of patients with Esophageal Large Cell Neuroendocrine Carcinoma (LCNEC) typically involves the middle or lower segments of the esophagus[4]. The patients usually present with advanced-stage disease due to the rapid progression and nonspecific symptoms. Common clinical manifestations reported in patients with esophageal LCNEC include dysphagia, which is difficulty swallowing, often described as a feeling that food is stuck in the chest area. Weight loss, which may be significant and unintended, is another prevalent symptom, reflecting the systemic impact of this tumor. Both symptoms are common to be seen in other

types of esophageal cancer. Chest pain, another nonspecific but distressing symptom, can also occur, alongside gastrointestinal bleeding, which may manifest as vomiting blood or black, tarry stools indicating potential esophageal or gastrointestinal hemorrhage[5]. The diagnosis is challenging, and the tumor is frequently discovered incidentally during endoscopic examinations or imaging studies. Further pathology confirmation including histology, immunochemistry, and molecular test may be required for diagnosis.

III. Histopathological Features:

A. Microscopic Examination:

Histologically, esophageal LCNEC is characterized by medium-sized to large cells with abundant cytoplasm, low nuclear/cytoplasm ration, prominent nucleoli, and a high mitotic rate. The tumor cells may exhibit a nested, trabecular growth pattern or acinar structures[6], resembling other high-grade neuroendocrine tumors.

Immunohistochemical staining is crucial for confirming the neuroendocrine nature of the tumor, with markers such as chromogranin A (about 60% positive), TTF1 (about 70%) and more consistent synaptophysin being commonly positive[7].

B. Differential Diagnosis:

Esophageal LCNEC must be differentiated from other esophageal neoplasms, including small cell carcinoma, squamous cell carcinoma, and adenocarcinoma[8]. This necessitates a thorough histopathological examination along with immunohistochemical profiling to establish an accurate diagnosis.

IV. Molecular Pathogenesis:

Limited data are available on the molecular alterations driving esophageal LCNEC. Hypothesis: Like other NETs, mutations in genes such as TP53, PDGFRA and KIT could be involved in the pathogenesis[9, 10]. Comprehensive genomic profiling may offer insights into potential therapeutic targets and guide treatment decisions in the future.

V. Staging and Prognosis:

Due to the rarity of esophageal LCNEC, there is a lack of standardized staging systems specific to this subtype, and no TNM staging system for esophageal NET. NEC and MiNEN are often staged using guidelines designed for other esophageal carcinomas. Prognosis is generally poor, with a high propensity for lymph node metastasis and distant spread[8]. Early diagnosis and aggressive management are crucial for improving outcomes.

VI. Treatment Strategies:

Surgical resection is the mainstay of treatment for localized esophageal LCNEC. However, given the aggressive nature of the tumor, the role of surgery may be limited in advanced cases. Chemotherapy, typically platinum-based regimens similar to those used for small cell lung carcinoma, constitutes the primary systemic treatment for esophageal LCNEC. The response to chemotherapy is variable[11], and combination regimens are often employed to improve efficacy. The role of radiotherapy in esophageal LCNEC is not well-defined, but it may be considered as part of multimodal therapy, especially in cases where surgery is not feasible.

VII. Future Directions:

Research into esophageal LCNEC is still in its infancy, and further studies are needed to unravel the underlying molecular mechanisms and identify potential therapeutic targets. The development of targeted therapies and immunotherapies may open new avenues for more effective and personalized treatment strategies.

Conclusion:

Esophageal Large Cell Neuroendocrine Carcinoma poses a diagnostic and therapeutic challenge due to its rarity and aggressive nature. A multidisciplinary approach involving pathologists, oncologists, and surgeons is essential for accurate diagnosis and optimal management. Continued research efforts are warranted to enhance our understanding of the molecular basis of esophageal LCNEC and improve treatment outcomes for affected individuals.

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