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CASE REPORT

High-Grade Pulmonary Neuroendocrine Carcinoma (NEC) presenting as a Mediastinal Mass: A Morphological and Immunohistochemical Diagnostic Challenge

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Abstract

Background: Pulmonary neuroendocrine tumors (NETs) encompass a wide spectrum, ranging from well-differentiated neuroendocrine tumors (NETs: typical and atypical carcinoids) to poorly differentiated, high-grade neuroendocrine carcinomas (NECs: small cell lung carcinoma [SCLC] and large cell neuroendocrine carcinoma [LCNEC]). Accurate classification is critical for appropriate management. **Case Presentation:** A 75-year-old male with COPD and recurrent cerebrovascular accidents presented with progressive dyspnea, cough with mucoid expectoration, and low-grade fever. Imaging revealed a large mediastinal mass encasing the right pulmonary vessels with metastatic lung changes. CT-guided biopsy showed a malignant neoplasm with necrosis, high mitotic activity, and a Ki-67 index of 62%. Tumor cells expressed TTF-1, synaptophysin, and chromogranin, consistent with high-grade pulmonary NEC. NETs were excluded; morphology favored a differential diagnosis of SCLC versus LCNEC. **Conclusion:** This case highlights the diagnostic challenge of differentiating pulmonary NEC subtypes. Integration of morphology and immunohistochemistry is essential, as therapeutic strategies diverge markedly from those used for NETs.

Keywords: Pulmonary neuroendocrine carcinoma, Small cell lung carcinoma, Large cell neuroendocrine carcinoma, Mediastinal mass, Immunohistochemistry

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Introduction

Pulmonary neuroendocrine neoplasms (NENs) represent approximately 20% of primary lung cancers and are classified into two broad categories:

1. Well-differentiated neuroendocrine tumors (NETs): typical carcinoid and atypical carcinoid.
2. Poorly differentiated neuroendocrine carcinomas (NECs): small cell lung carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNEC) [1,2].

Distinguishing between NETs and NECs is crucial, as prognosis and management differ substantially [3]. While NETs exhibit relatively indolent behavior with low to moderate mitotic activity, NECs are aggressive, high-grade malignancies with rapid progression [4]. Morphology, supported by immunohistochemistry (IHC) and proliferation index (Ki-67), plays a central role in diagnosis, particularly when tissue is limited to small biopsy samples [5].

Case Report

A 75-year-old male, smoker, with COPD and recurrent strokes, presented with two months of cough, expectoration, low-grade fever, and progressive dyspnea (MMRC grade 2 → 4). Examination revealed digital clubbing, SpO_2 92% on room air, and reduced breath sounds on the right side.

Chest X-ray showed a right upper-zone mediastinal opacity with extension into mid and lower zones. Contrast-enhanced CT demonstrated a lobulated, homogeneously enhancing mediastinal mass (6.3 × 13.5 × 15.6 cm) extending into the right lung, encasing the right pulmonary artery and veins, and involving hilar and paratracheal regions. Patchy nodular infiltrates in both lungs suggested metastases. A thin right pleural effusion was present (Figure 1).

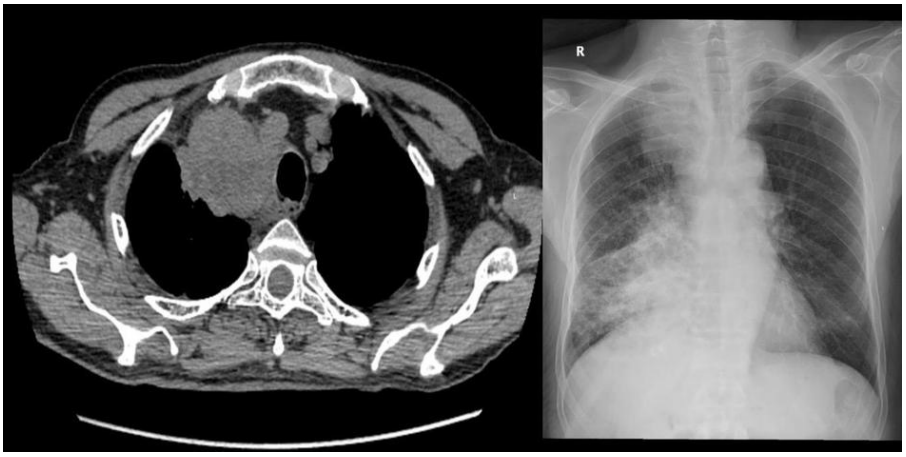

Figure 1. Chest X-ray (PA view) shows homogeneous opacity in the right upper zone extending into the paratracheal region, and a non-homogeneous opacity in the right mid and lower zones with loss of the right cardiac border. CT thorax reveals a lobulated, homogeneously enhancing mediastinal soft-tissue lesion (6.3 × 13.5 × 15.6 cm).

CT-guided biopsy revealed pleomorphic malignant cells in diffuse sheets with scant cytoplasm, hyperchromatic nuclei, frequent mitoses, and necrosis (Figure 2). IHC showed TTF-1 nuclear positivity, synaptophysin and chromogranin cytoplasmic positivity, scattered CK7 positivity, and high Ki-67 (~62%). CK20, LCA, and vimentin were negative; CD56 was non-contributory (Figure 3). Findings were consistent with high-grade pulmonary NEC [4,5]. In this case, the mediastinal involvement represents secondary extension from a centrally located pulmonary neuroendocrine carcinoma rather than a primary mediastinal tumor. This inference is supported by the radiologic pattern of contiguous spread from the right lung, the expression of TTF-1 on IHC—favoring pulmonary origin and the absence of features suggestive of thymic or primary mediastinal neuroendocrine carcinoma.

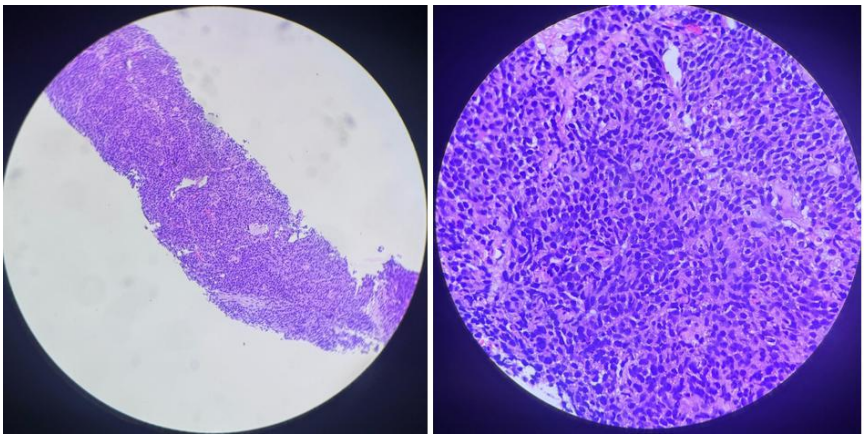

Figure 2. HPE shows diffuse sheets of pleomorphic malignant cells with scant cytoplasm, hyperchromatic nuclei, frequent mitoses, and necrosis.

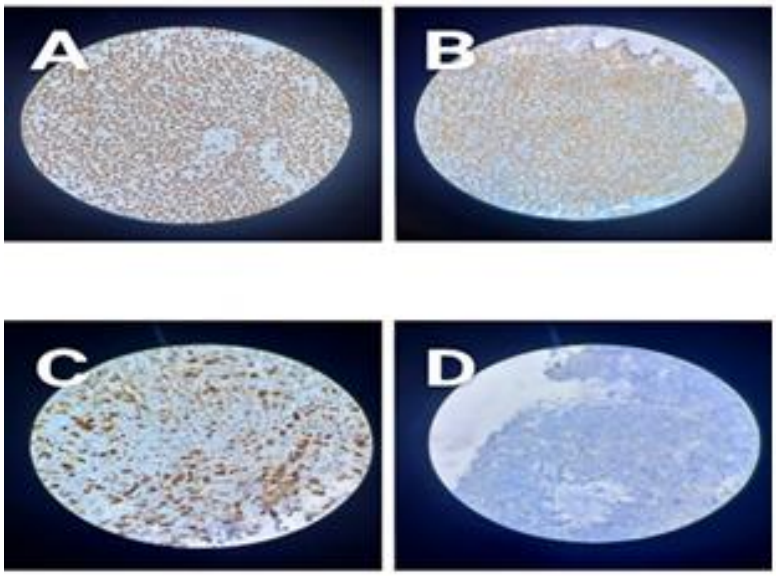

Figure 3. IHC demonstrates TTF-1 nuclear positivity, synaptophysin and chromogranin cytoplasmic positivity, and high Ki-67 (~62%), consistent with high-grade pulmonary neuroendocrine carcinoma.

The patient was diagnosed with stage IV disease and referred for further management to a dedicated Oncology centre and is currently under treatment.

Discussion

Pulmonary NENs are classified into four major histologic categories: typical carcinoid, atypical carcinoid (both NETs), large cell neuroendocrine carcinoma (LCNEC), and small cell lung carcinoma (SCLC) (both NECs) [1].

High-grade tumors (NECs: LCNEC and SCLC) are distinguished from NETs by marked mitotic activity, extensive necrosis, and a high proliferative index [2,5]. In the present case, the high Ki-67 index and positivity for neuroendocrine markers excluded a diagnosis of NET.

Differentiating between the two NEC subtypes—SCLC and LCNEC—remains challenging [3]. SCLC typically consists of small cells with nuclear molding, crush artifact, and scant cytoplasm, whereas LCNEC demonstrates larger polygonal cells, more abundant cytoplasm, and prominent nucleoli [4]. Both entities express neuroendocrine markers and TTF-1 and carry a poor prognosis [2]. However, management diverges: SCLC is generally treated with systemic chemotherapy and immunotherapy, whereas LCNEC, when localized, may be managed along non-small cell lung cancer (NSCLC) protocols [4].

The differential diagnosis in this setting also included thymic carcinoma and lymphoma, both of which can present as large anterior mediastinal masses. Thymic carcinoma typically arises from thymic epithelium, shows positivity for cytokeratin, CD5, and CD117, and lacks TTF-1 expression. In contrast, lymphomas are of lymphoid origin, express CD45 and lineage markers (CD3 or CD20), and are negative for epithelial and neuroendocrine markers. In the present case, the tumor's strong TTF-1 positivity excluded thymic and lymphoid malignancies, confirming pulmonary origin of the tumor.

The unusual presentation as a dominant mediastinal mass further expanded the differential diagnosis to include lymphoma and thymic carcinoma, emphasizing the central role of histopathology and immunohistochemistry in narrowing the diagnosis [1].

Conclusion

Pulmonary neuroendocrine carcinomas (NECs) present significant diagnostic challenges, particularly when they manifest as mediastinal masses. Careful integration of morphology, immunohistochemistry, and proliferative indices is essential to distinguish NECs (SCLC and LCNEC) from well-differentiated neuroendocrine tumors (NETs). Such differentiation is critical, as therapeutic approaches for NECs diverge substantially from those for NETs, and even between SCLC and LCNEC themselves [2,4,5].

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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