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(CASE REPORT)

Large cell neuroendocrine tumor of the lung: Case report of an uncommon tumor and brief literature review

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Abstract

Large cell neuroendocrine carcinoma (LCNEC) of the lung is a rare and aggressive malignancy accounting for approximately 1–3% of all lung cancers. Its rarity, combined with morphologic overlaps with other high-grade thoracic tumors, makes diagnosis and management challenging. We report the case of a 71-year-old male, a heavy smoker with a 45-pack-year history, who presented with a six-week history of progressive dyspnea, productive cough with hemoptysis, and significant weight loss. Imaging identified a 5.0 cm FDG-avid central right upper lobe mass with ipsilateral mediastinal nodal involvement, staged as IIIA disease. Following multidisciplinary tumor board review, the patient underwent right upper lobectomy with mediastinal lymph node dissection. Histopathology confirmed LCNEC with a Ki-67 proliferation index of 75%, and molecular profiling revealed co-mutations of TP53 and STK11 with loss of RB1 expression. The tumor was classified as an NSCLC-like subtype (non-small cell lung carcinoma). He received adjuvant cisplatin and etoposide and remained disease-free for 30 months before developing metastatic recurrence involving the liver, adrenal glands, and cerebellum. Subsequent systemic therapy proved refractory, and the patient died 19 weeks after recurrence, with an overall survival of 39 months. This case illustrates the diagnostic complexity, aggressive biology, and the critical role of multidisciplinary decision-making in managing resectable LCNEC, while underscoring the urgent need for evidence-based therapeutic strategies in this underrepresented tumor type.

Keywords: Pulmonary; Large cell neuroendocrine carcinoma; Immunohistochemistry (IHC); Non-small cell lung cancer-Like; Neuroendocrine cells; Refractory metastatic progression

1. Introduction

Pulmonary LCNEC is a rare neuroendocrine malignancy of the lung, accounting for 1-3% of all lung malignancies. [1] LCNEC typically presents between 65 and 70 years of age and favors males with a heavy smoking history. [2] The clinical presentation begins with nonspecific constitutional symptoms, such as weight loss, hemoptysis, cough, and dyspnea. [1] Diagnosis requires three key features: neuroendocrine morphology, large-cell cytologic features, and a high mitotic rate. [3] Immunohistochemistry (IHC) analysis is positive for synaptophysin, chromogranin A, and CD56 with a high Ki-67 proliferation index. [3] LCNEC has been divided into two subtypes: SCLC-like (Small cell lung carcinoma) and NSCLC-

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like. [4] SCLC-like subtypes are characterized by TP53 and RB1 alterations, whereas NSCLC-like subtypes have TP53 and STK11/KEAP1 mutations. [3]

Emerging evidence suggests that RB1 status can predict chemotherapy responsiveness, with NSCLC types benefiting more from platinum-gemcitabine/taxane regimens and SCLC types favoring Cisplatin-etoposide regimens. [5] Despite multimodal treatment, recurrence rates remain high, particularly in advanced or metastatic cases, with a median survival rate of 7-12 months. [3]

2. Case Presentation

2.1. Clinical Presentation and Initial Investigations

A 71-year-old male with a significant 45-pack-year smoking history presented to the clinic reporting a six-week progression of shortness of breath, productive cough marked by hemoptysis, and unintentional weight loss of 8 kg over the past three months. He also noted new-onset fatigue and right-sided chest discomfort. Medical history was significant for hypertension and type 2 diabetes, both of which were well-controlled. Upon physical examination, breath sounds were diminished in the right upper lobe with associated dullness to percussion, though no palpable lymphadenopathy was detected in the supraclavicular or axillary regions. The patient maintained a good performance status of Eastern Cooperative Oncology Group (ECOG) 1.

Initial laboratory investigations revealed mild normocytic anemia with a hemoglobin of 10.8 g/dL and a mildly elevated LDH. Notably, neuroendocrine markers were significantly high, with serum Chromogranin A and NSE measured at 4.2 and 3.1 times the upper limit of normal, respectively. A paraneoplastic workup for SIADH (syndrome of inappropriate antidiuretic hormone secretion) and catecholamine excess was negative. Diagnostic imaging via chest CT identified a 5.0 cm central mass in the right upper lobe with irregular, spiculated margins, hilar involvement, and ipsilateral mediastinal nodal enlargement. A PET-CT confirmed that the primary mass was intensely FDG-avid, with a SUVmax of 14.6. No distant metastases were identified at baseline, and a brain MRI was unremarkable.

2.2. Multidisciplinary Tumor Board Discussion and Management

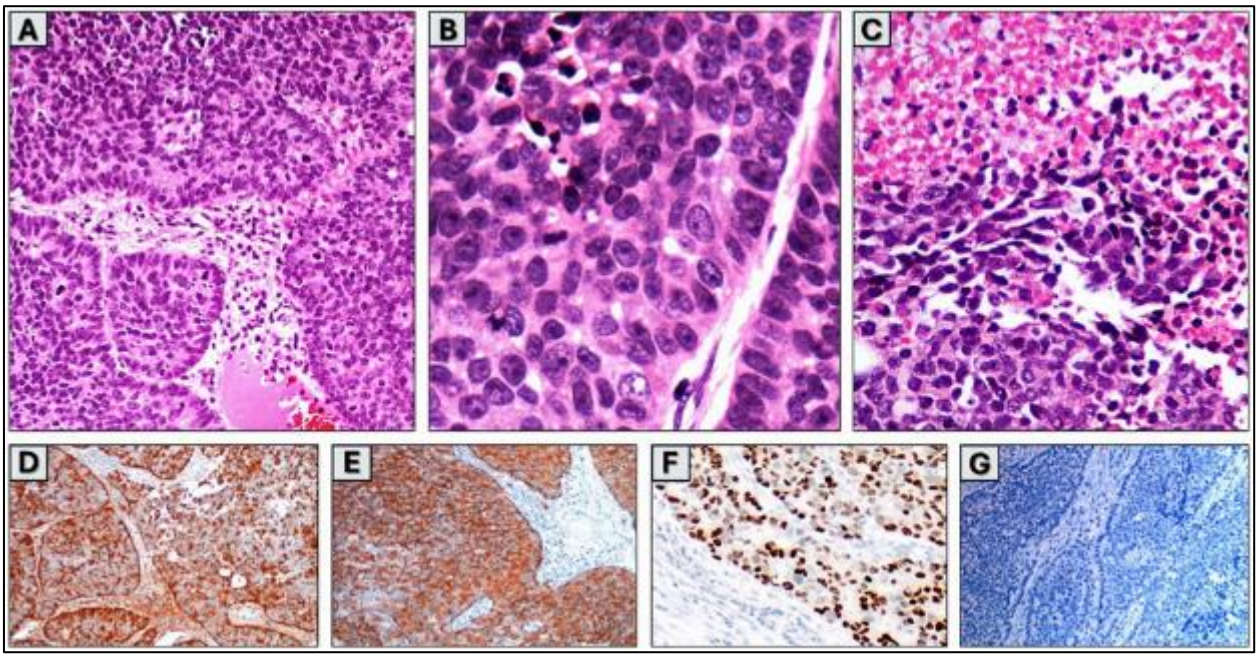
The case was formally reviewed at the multidisciplinary tumor board, which included thoracic surgery, medical oncology, radiation oncology, pulmonology, radiology, and pathology. Two primary management options were debated: preoperative tissue sampling for definitive diagnosis and planning management strategy versus upfront surgical excision. Arguments favoring upfront surgery emphasized the risk of sampling a central, highly vascular mass, the bronchoscopic yield with EBUS versus CT-guided core biopsy, whether IHC from a small biopsy specimen is sufficient to confirm LCNEC histology given its mimics (small cell, and poorly differentiated adenocarcinoma), and whether the molecular profile obtained preoperatively would meaningfully change the surgical decision in a resectable Stage IIIA case. Given the resectable stage IIIA disease, acceptable performance status, and adequate pulmonary reserve on PFTs (FEV_1 68% predicted), the board recommended upfront surgical resection followed by adjuvant platinum-based chemotherapy. Induction concurrent chemoradiation was considered but deferred given surgical candidacy. No clinical trial enrollment was available at the time.

The patient subsequently underwent a right upper lobectomy with mediastinal lymph node dissection. Gross pathology identified a poorly differentiated tumor with central necrosis, while microscopic evaluation revealed large polygonal cells with prominent nucleoli and a high mitotic rate exceeding 11 per 2 mm^2. (**Figure 1 A, B, C**) Immunohistochemistry (IHC) analysis confirmed neuroendocrine differentiation, showing diffuse positivity for Synaptophysin, CD56, and INSM1, with a high Ki-67 proliferation index of 75%. Molecular profiling further identified a co-mutation of TP53 and STK11, along with a loss of RB1 expression. (**Figure 1 D, E, F, G**) The tumor was diagnosed as LCNEC and classified as an NSCLC-like subtype.

The final pathologic stage was pT3 N2 M0. Following surgery, the patient received four cycles of adjuvant cisplatin and etoposide. This regimen was moderately well-tolerated, and the patient entered a period of clinical surveillance. Regular imaging and marker monitoring remained clear for 30 months; however, at the 36-month follow-up, the patient returned with new right upper quadrant pain and night sweats. Restaging via PET-CT revealed a metabolic recurrence involving multiple bilobar hepatic metastases and bilateral adrenal masses. A biopsy of one of the liver masses confirmed metastatic LCNEC, with the Ki-67 index having risen to 88%.

2.3. Follow-Up and Outcome

Despite initiating systemic therapy with carboplatin and etoposide, as well as stereotactic radiosurgery for new cerebellar lesions, the disease proved refractory. After two cycles of treatment, imaging confirmed progressive disease by response evaluation criteria in solid tumors (RECIST 1.1), and the patient's performance status declined to ECOG 3**.** Subsequent second-line therapy with topotecan was complicated by severe neutropenic fever and hepatic decompensation. Following a multidisciplinary discussion regarding goals of care, the patient was transitioned to comfort-focused palliative management. He passed away 19 weeks after the documentation of metastatic recurrence, resulting in an overall survival of 39 months from the time of the initial localized diagnosis.



1A: Intermediate power view showing nests of tumor cells with peripheral palisading (H&E X40); 1B: High power view showing large polygonal cells with prominent nucleoli and a high mitotic rate (H&E X60); 1C: High power view showing prominent tumor necrosis (H&E X40); 1D: Tumor cells positive for synaptophysin; 1E: Tumor cells positive for synaptophysin; 1F: Tumor cells positive for CD56; 1G: Tumor cells negative for P40

Figure 1 Microscopic features and immunohistochemistry of the large lung cell neuroendocrine carcinoma (LCNEC)

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification):

LCNEC is a subtype of lung tumors first described in the early 1990s and now included in the WHO classification of thoracic tumors. [6] These tumors are predominantly found in elderly males who have a heavy lifetime-use history of tobacco products. [5]

Like the other cigarette smoking-associated lung cancers, although the main risk factor for LCNEC is cigarette smoking, exposure to asbestos, radon, or preexisting lung diseases are also known to increase the risk of these tumors. [8] The tumors have genomic characteristics comparable to both small-cell lung and non-small-cell lung cancer, including mutations in TP53 and RB1 in tumor cells. Such mutations also lend themselves to the high-grade phenotype of this tumor. [3]

They can arise in multiple areas of the lungs and are usually diagnosed at an advanced stage. Histologically, such tumors are characterized by a proliferation of large polygonal cells with prominent nucleoli and a high mitotic rate (>10 mitoses/2 mm^2). [6] Furthermore, the neoplastic cells express synaptophysin, chromogranin A, and CD56. LCNEC is classified as a poorly differentiated, high-grade malignant neuroendocrine carcinoma according to the World Health Organization. [6] Patients with LCNEC have a poor prognosis, and there is a clear unmet need for better therapeutic approaches to treat these tumors. [1].

3.2. Pathogenesis, Pathophysiology

LCNEC arises from pulmonary neuroendocrine cells, specialized epithelial cells that regulate airway function by secreting neuropeptides. [6] The development of LCNEC is strongly associated with chronic tobacco exposure, which leads to cumulative DNA damage and increases the risk of malignant transformation. [9,10] At the molecular level, LCNEC is commonly characterized by inactivation of the tumor suppressor genes TP53 and RB1, which disrupt cell cycle regulation and apoptosis, allowing uncontrolled proliferation. [11,12] Additional alterations, including mutations in STK11 and activation of signaling pathways such as PI3K/AKT and MAPK, further enhance tumor growth, metabolic dysregulation, and cellular survival. [8,9]

These molecular changes result in rapid tumor growth, high mitotic activity, and early invasion into surrounding lung parenchyma, with a strong tendency for lymphatic and hematogenous spread. [7,10] Clinically, these processes present as cough, hemoptysis, and dyspnea due to airway obstruction and tumor necrosis, while systemic inflammation contributes to weight loss and fatigue. [7] Histopathologically, LCNEC features large polygonal cells, prominent nucleoli, extensive necrosis, and a high Ki-67 proliferation index, reflecting its aggressive biology. [6] IHC positivity for neuroendocrine markers, such as synaptophysin and CD56, confirms its neuroendocrine origin. [8]

3.3. Comparative Analysis of Our Case with Existing Literature. (Clinical, radiology, pathology, Lab, diagnosis, management, and outcome)

Our patient greatly conforms to this clinical picture of pulmonary large-cell neuroendocrine carcinoma (LCNEC): older heavy smoker symptomatic from cough, dyspnea, hemoptysis, and weight loss with an aggressive central lung mass. This rare form of lung cancer, which accounts for only about 2%–3% of all lung cancers, is now defined as a high-grade neuroendocrine carcinoma with a clinical behavior more similar to small-cell compared with conventional non-small-cell lung cancer. [13,14] The patient's elevated neuroendocrine markers and ECOG 1 status at diagnosis may also correspond to reported patterns of symptomatic yet potentially operable disease. [13]

Despite its size, the centrally located FDG-avid 5 cm right upper lobe mass with associated hilar and mediastinal nodal disease is radiologically consistent with LCNEC; this subtype of lung cancer typically manifests as a large peripheral or central pulmonary lesion with strong PET uptake and early lympho-hematogenous dissemination. [13,15] Baselines without brain metastasis are not uncommon, yet the long-term risk of brain recurrence remains quite high. [15]

Diagnosis in this instance was based on resection pathology and IHC. Criteria for publication focus on large polygonal cells, prominent nucleoli, extensive necrosis, and high mitotic activity, forming major modern pathobiology parameters, along with the expression of neuroendocrine markers such as synaptophysin, CD56, and INSM1. [13,16,17] In particular, the tumor's high Ki-67 index and TP53, RB1, and STK11 co-alteration phenotype fit well with current genomic investigations showing that both SCLC-like and NSCLC-like molecular subsets exist in LCNEC. [7,8]

Lobectomy with mediastinal lymph node dissection followed by adjuvant cisplatin-etoposide is consistent with the literature on resectable stage III disease, which supports surgery plus platinum-based chemotherapy for the best long-term outcomes. [14,18,19] However, recurrence in the liver, adrenal glands, and brain reflects the well-established aggressive biology of LCNEC and its tendency for distant relapse despite apparently successful initial treatment. [15,18] Although this patient achieved an overall survival of 39 months, which is relatively favorable for stage IIIA LCNEC, the disease course remained consistent with previously reported cases of refractory metastatic progression. [14,15]

4. What Have We Learned from This Case?

This case highlights the diagnostic challenges and aggressive clinical course of LCNEC, a rare high-grade lung malignancy. High-grade malignancy should be strongly suspected in patients with rapid symptom progression, unintentional weight loss, and elevated neuroendocrine markers, regardless of resectability. LCNEC shares similar features with other poorly differentiated lung tumors. Therefore, a definitive diagnosis requires thorough histopathologic and IHC evaluation in addition to molecular classification. [8] This requires early collaboration of a multidisciplinary team, which is critical for optimal patient care. Particularly when determining between surgery and systemic therapy. Although surgical resection and chemotherapy remain standard treatments, there is still a high recurrence rate associated with LCNEC. This reflects the tumor's biological aggressiveness and unfavorable long-term prognosis. [7] Molecular alterations in TP53 and RB1 loss may also influence tumor behavior and represent potential therapeutic targets. This case highlights the need for long-term post-treatment surveillance and underscores the importance of more effective, individualized treatment strategies in LCNEC.

Abbreviations:

- Large cell neuroendocrine carcinoma (LCNEC),
- Non-small cell lung cancer-Like (NSCLC-like);
- Immunohistochemistry (IHC);
- Eastern Cooperative Oncology Group (ECOG)

5. Conclusion

Pulmonary LCNEC remains one of the most challenging thoracic malignancies to diagnose and treat. This case underscores key clinical issues that oncologists and thoracic surgeons may face in practice. The diagnosis required integrating histomorphology, a broad IHC panel, and molecular profiling, reflecting the inherent difficulty in distinguishing LCNEC from its morphologic mimics. The multidisciplinary tumor board was central not only to confirming resectability but to navigating the genuine uncertainty surrounding optimal sequencing of surgery, chemotherapy, and radiation in stage IIIA disease, a question the literature has yet to answer definitively.

Despite an encouraging 30-month disease-free interval following curative-intent resection and adjuvant platinum-etoposide chemotherapy, the patient experienced aggressive systemic recurrence with a markedly elevated Ki-67, illustrating the tumor's capacity for clonal evolution and therapeutic escape. The clinical course, from localized, resectable disease to refractory metastatic progression within 3 years, exemplifies the natural history of this entity.

We present this case to contribute to the growing body of clinical experience with LCNEC, a tumor for which prospective trial data remain scarce. It reinforces the value of molecular characterization at diagnosis, the need for close surveillance following resection, and the importance of early goals-of-care discussions when disease recurs. Standardized management protocols and dedicated clinical trials are needed.

Compliance with ethical standards

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All authors make the following declarations:

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- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of informed consent

The patient expired, and all attempts to reach the family members were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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