Case Report

Decoding Small Cell Lung Cancer: Biology, Biomarkers, and Novel Therapeutic Strategies

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International Archives of Integrated Medicine, Vol. 13, Issue 5, May, 2026.
Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 15-5-2026 **Accepted on:** 27-5-2026
Source of support: Nil **Conflict of interest:** None declared.
Article is under Creative Common Attribution 4.0 International
DOI: **10.5281/zenodo.20541776**

How to cite this article: Alisha Khan, Banka Sai Swetha, Divya Donepudi, Gunvanti Rathod. Decoding Small Cell Lung Cancer: Biology, Biomarkers, and Novel Therapeutic Strategies. Int. Arch. Integr. Med., 2026; 13(5): 62-67.

Abstract

Small cell lung carcinoma (SCLC) is a highly aggressive form of cancer with neuroendocrine differentiation, accounting for about 15% of all lung cancer cases. Although SCLC is highly sensitive to chemotherapy and radiation therapy at the initial stages of treatment, recurrence is common within a year or two, with poor outcomes for patients. Here, we present a case of a 69-year-old male with a history of significant smoking who complained of cough, fever, and shortness of breath. After undergoing various investigations, which showed a mass in the right lung, the patient was diagnosed with SCLC based on the results of a bronchoscopic biopsy. The patient underwent chemotherapy with platinum and etoposide along with thoracic radiation therapy, which resulted in partial remission. In the following paragraphs, the difficulties in diagnosing SCLC, its histopathological characteristics, advances in its treatment, and its prognostic factors with recent developments in immunotherapy and target therapy will be discussed.

Key words

Small cell lung carcinoma, Neuroendocrine tumor, Histopathology, Chemotherapy, Immunotherapy.

Introduction

Lung cancer is a major cause of cancer-related deaths globally. Lung cancer is divided into two

types based on histopathological characteristics: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). SCLC accounts for about 15% of all lung cancer cases. SCLC is known to be strongly linked with tobacco smoking [1]. SCLC is included in the pulmonary neuroendocrine tumor family. SCLC is marked by high proliferative activity, early metastasis, and a poor clinical course. The major clinical presentation of SCLC includes respiratory signs such as coughing, hemoptysis, shortness of breath, and thoracic pain. Systemic signs such as anorexia, weight loss, and fatigue are also common. Paraneoplastic syndromes also occur commonly with SCLC owing to the production of ectopic hormones. The paraneoplastic syndromes can take the form of syndrome of inappropriate antidiuretic hormone secretion (SIADH), Cushing's syndrome, or Lambert-Eaton myasthenic syndrome [2].

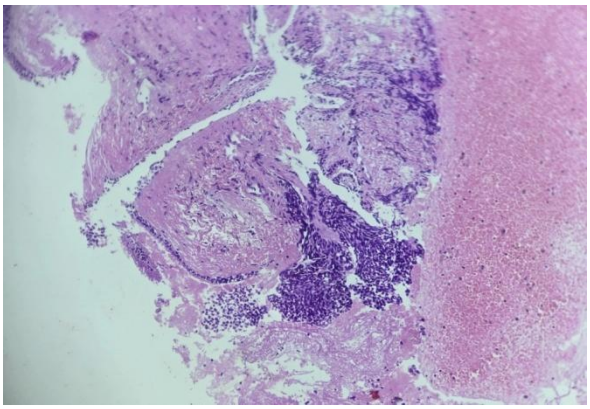
The gold standard for diagnosing SCLC is histopathological examination. The tumor cells in SCLC are small with scant cytoplasm, a high nuclear-to-cytoplasmic ratio, molding of nuclei, and necrosis. Immunohistochemistry is helpful, with tumor markers such as synaptophysin, chromogranin A, CD56, and thyroid transcription factor-1 (TTF-1) aiding in the diagnosis. Although the incidence of SCLC has been decreasing over the past several decades, the overall prognosis is very poor [3]. Most of the patients are diagnosed at an advanced extensive stage with a 5-year survival rate of less than 10 percent. Even with advances in systemic treatment and the addition of immune inhibitors, SCLC remains a treatment challenge [4].

Case Report

The patient, a 69-year-old chronic smoker with a 50-pack-year history, presented to the outpatient department with complaints of productive cough, dyspnea, and low-grade fever for 15 days. He also complained of increasing fatigue and weight loss for two months. There was no history of hemoptysis, chest trauma, or previous tuberculosis treatment. The patient's past medical history revealed chronic obstructive pulmonary disease and hypertension. Physical examination revealed a cachectic patient in a state of mild respiratory distress. Vital signs revealed tachypnea of 24 breaths per minute and oxygen saturation of 90% on room air. Physical examination of the chest revealed decreased breath sounds in the right lower chest with associated wheezes. There was no palpable lymphadenopathy. Neurological examination was normal.

The chest X-ray revealed a right hilar mass with associated mediastinal widening. Contrast-enhanced CT of the thorax revealed a 5.2 x 4.6 cm irregular mass in the right hilar region encasing the right intermediate bronchus. There was associated mediastinal lymphadenopathy and post-obstructive pneumonia. Hypodense lesions in the liver suggestive of metastasis. The flexible bronchoscopy showed an endobronchial mass causing obstruction of the right intermediate bronchus. Biopsy samples were taken. Microscopic examination of the sample showed pseudostratified columnar epithelium with tumor infiltration in a trabecular pattern. The tumor cells were monomorphic with scant cytoplasm, high nuclear/cytoplasmic ratio, finely granular chromatin, nuclear molding, and crush artifacts. Necrosis was also seen in the tumor sample (**Figure - 1, 2, 3**).

Figure – 1: Section shows lung tissue infiltrated by tumor cells arranged in trabecular and nesting pattern with areas of necrosis (H&E Stain).



The tumor was classified as an extensive-stage SCLC with a T3N2M1b classification due to metastasis to the liver. After a team meeting, the patient was started on chemotherapy with carboplatin and etoposide. After four cycles of chemotherapy, a repeat CT scan showed a partial response with tumor size reduction of the primary tumor and the liver metastases. Consolidative radiotherapy was done. Prophylactic cranial irradiation was not done due to patient preference. At six months of follow-up, the patient remained stable with improvement of his clinical condition.

Figure – 2: Section shows fragments of respiratory mucosa infiltrated by sheets, nests, and trabeculae of small, round to oval tumor cells with extensive crushing artefacts (H&E Stain).

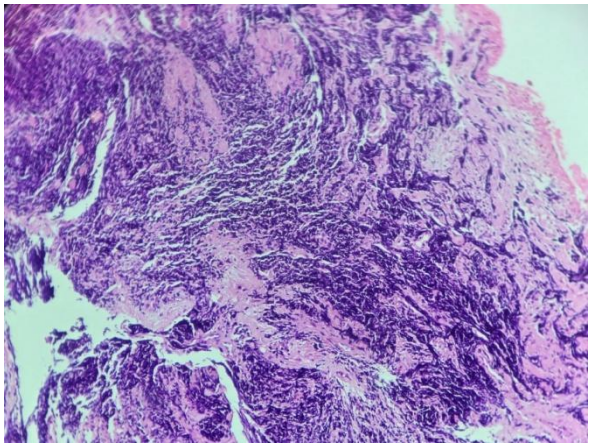
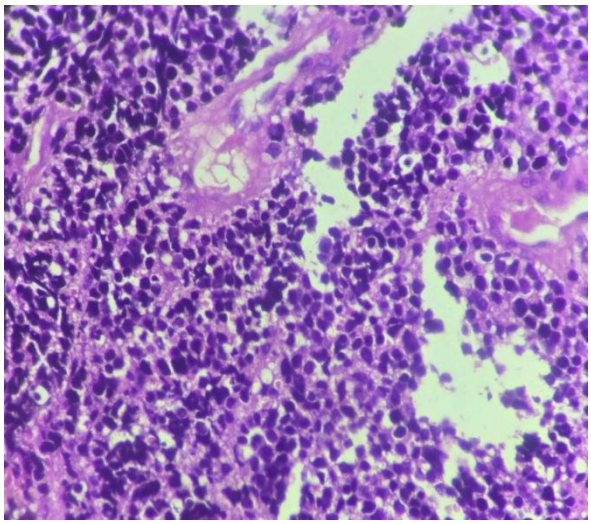


Figure – 3: Section shows tumor cells with scanty cytoplasm, high nuclear-to-cytoplasmic ratio, hyperchromatic nuclei with finely granular ("salt-and-pepper") chromatin (H&E Stain).



Discussion

Small cell lung carcinoma (SCLC) is a highly aggressive neuroendocrine cancer with rapid growth rates, early metastasis, and a high propensity for recurrence even with initial successful treatment. The clinical course in the above patient is a classic presentation of the aforementioned features of SCLC. It is imperative that the clinical presentation and the challenges in the clinical course of the aforementioned cancer are well understood in order to effectively manage the treatment and prognosis of the cancer [5].

Clinical Presentation and Diagnostic Challenges

Small cell lung carcinoma (SCLC) is a highly aggressive form of lung cancer with rapid growth rates and a high propensity for early metastasis. The clinical presentation of the majority of the patients with SCLC is nonspecific respiratory symptoms such as cough, dyspnea, or chest pain, as was the case with the above patient. Systemic manifestations of the cancer include weight loss, fatigue, and fever. Due to the central airway involvement of the cancer, the clinical presentation of SCLC may resemble infectious or obstructive respiratory diseases. From the radiological point of view, SCLC is often seen as a central mass with hilar involvement and associated mediastinal lymphadenopathy, as seen in the present case. However, it is not possible to distinguish SCLC from other undifferentiated tumors based on radiological findings alone. Thus, histopathological examination with Immunohistochemistry (IHC) is indispensable for arriving at a diagnosis. Presence of small cell morphology with scant cytoplasm, nuclear molding, high mitotic count, and extensive necrosis is suggestive of SCLC. Presence of neuroendocrine markers such as Synaptophysin, Chromogranin, CD56, and TTF-1 positivity is indicative of pulmonary origin [6, 7]. Problems arise in distinguishing SCLC from lymphoma or metastatic neuroendocrine tumors or basaloid carcinomas in the presence of crush artifacts.

Therapeutic Approach: Current Standards and Advancements

The treatment of SCLC is largely stage and performance status-dependent. Extensive-stage SCLC, as in the present case, is treated with Platinum + Etoposide chemotherapy. Although initial response is encouraging with a high rate of objective responses, patients relapse within months [8]. The addition of immune checkpoint inhibitors, for example, atezolizumab or durvalumab, to first-line chemotherapy has resulted in a slight improvement in outcomes, which is now the standard approach. Our patient received atezolizumab with good initial tumor regression, which is in accordance with the results from the pivotal studies showing improved survival with the addition of chemo-immunotherapy combinations [9, 10]. Radiotherapy is used as a complementary treatment. Consolidative thoracic radiotherapy (cTRT) for responders in extensive-stage SCLC improves local control, which may translate to survival advantages. Prophylactic cranial irradiation (PCI) reduces the occurrence of brain metastases. However, the approach to PCI has become individualized in the past few years, considering the potential for neurotoxicity as well as patient preference and the use of MRI surveillance. In the second-line setting, Lurbinectedin is a recently approved agent showing improved response rates. However, the aggressive nature of the relapse and the poor response to treatment for the recurrent SCLC, as seen in the patient, emphasize the pressing need for improved therapies [11, 12].

Prognostic Factors and Disease Course

The factors that affect the prognosis of SCLC include stage at diagnosis, performance status, presence of metastatic disease, and response to therapy. The extensive stage SCLC has a poor prognosis with a median survival of only 8-13 months with the best possible therapy [13, 14]. The high Ki-67 index of more than 80 percent, presence of multiple metastases, particularly to the liver, and deteriorating performance status were consistent with an unfortunate but predictable rapid disease progression. The disease course with initial partial response followed by recurrence within a year is consistent with the classic biphasic course of SCLC: initial chemosensitivity followed by chemoresistant rapid tumor regrowth. The presence of bone and brain metastases is common in the late stage of SCLC and has a major effect on quality of life and survival.

Evolving Research and Future Directions

In spite of decades of intense research into small cell lung carcinoma (SCLC), significant advances in therapy for SCLC have been meager compared with other thoracic cancers. The highly aggressive nature of SCLC with its rapid doubling time, early metastasis, and inevitable chemoresistance contribute to its poor outcome [15]. More recently, a notable shift in SCLC research has been towards an understanding of the molecular heterogeneity of SCLC rather than considering it a single entity [16, 17]. This has been achieved through genomic and transcriptomic analyses, which have helped in the identification of different molecular subtypes of SCLC based on dominant transcription factors ASCL1, NEUROD1, POU2F3, and YAP1, each of which has been associated with different biological characteristics, therapeutic vulnerabilities, and prognostic potential [18, 19]. This has led to new ways of precision oncology in SCLC, where therapies can be matched to the specific molecular profiles of SCLC. Another promising area of SCLC therapy is through newly emerging therapeutic modalities, which are believed to be able to counteract the intrinsic resistance of SCLC [20]. This new class of therapy represents a paradigm shift in SCLC therapy from a general approach of systemic therapy to a more targeted approach of subtype-specific therapy, which enhances immunotherapy. Although many of them are still in development, they represent a notable move towards overcoming a disease which has been considered refractory to therapy.

Conclusion

This case emphasizes the aggressive nature of SCLC. It also underscores the need for early detection, histopathological confirmation, and a multidisciplinary approach. Despite advances in systemic therapy and immunotherapy, prognosis for SCLC remains poor. Further research on SCLC needs to be done to improve prognosis.

List of Abbreviations

SCLC – Small Cell Lung Carcinoma
NSCLC – Non-Small Cell Lung Cancer
SIADH – Syndrome of Inappropriate Antidiuretic Hormone Secretion
TTF-1 – Thyroid Transcription Factor-1
cTRT – Consolidative Thoracic Radiotherapy
PCI – Prophylactic Cranial Irradiation
ICI – Immune Checkpoint Inhibitor

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