

Pulmonary Lymphangitic Carcinomatosis of Small Cell Lung Carcinoma: An Autopsy Case Report

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Abstract: Pulmonary lymphangitic carcinomatosis is characterized by the involvement of pulmonary lymphatic vessels by tumor cells. This work reports the autopsy findings of a 53-year-old woman who presented with subacute constitutional symptoms and presence of numerous nodules throughout the body. Chest CT revealed heterogeneous posterior mediastinal mass involving thoracic structures and pulmonary findings suggestive of lymphangitic spread. Before further diagnostic evaluation could be performed, the patient suffered from rapid clinical deterioration, which resulted in her death. Autopsy revealed a posterior mediastinal mass with marked pulmonary lymphatic involvement by neoplastic cells. Immunohistochemical analysis demonstrated positivity for CAM5.6, CD56 and Ki67, consistent with a high-grade neuroendocrine tumor. Metastatic involvement was also observed in the heart, adrenal, pancreas, duodenum and bone marrow. The final autopsy diagnosis was pulmonary thromboembolism as the immediate cause of death, in the context of a highly aggressive small lung cell carcinoma with pulmonary lymphangitic spread.

Keywords: Lymphangitic Carcinomatosis; Neuroendocrine Carcinoma; Lymphatic Metastasis; Lymphangitis.

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1. Introduction

Pulmonary lymphangitic carcinomatosis (PLC) is characterized by the presence of tumor cells in the lymphatic vessels (peri-vascular, peribronchial and interlobar septa), as well as in the pulmonary interstitium and subpleural lymphatics [1]. It is secondary to the metastatic spread of malignancy from a primary site and occurs in only 6 to 8% of cases of pulmonary metastasis [2, 3]. It usually occurs due to hematogenous dissemination of the primary neoplasm, with capillary extension into the lymphatic vessels. However, retrograde dissemination from mediastinal and hilar lymph nodes towards the lung tissue is also possible [1]. Among the primary sites of neoplasia that metastasize and cause pulmonary lymphangitic carcinomatosis, the most common ones are breast, stomach, lungs, pancreas, prostate, cervix, and colon [4]. Pulmonary lymphangitic carcinomatosis usually represents an end-stage malignancy with poor life expectancy, with a median survival of 3–6 months from diagnosis [5].

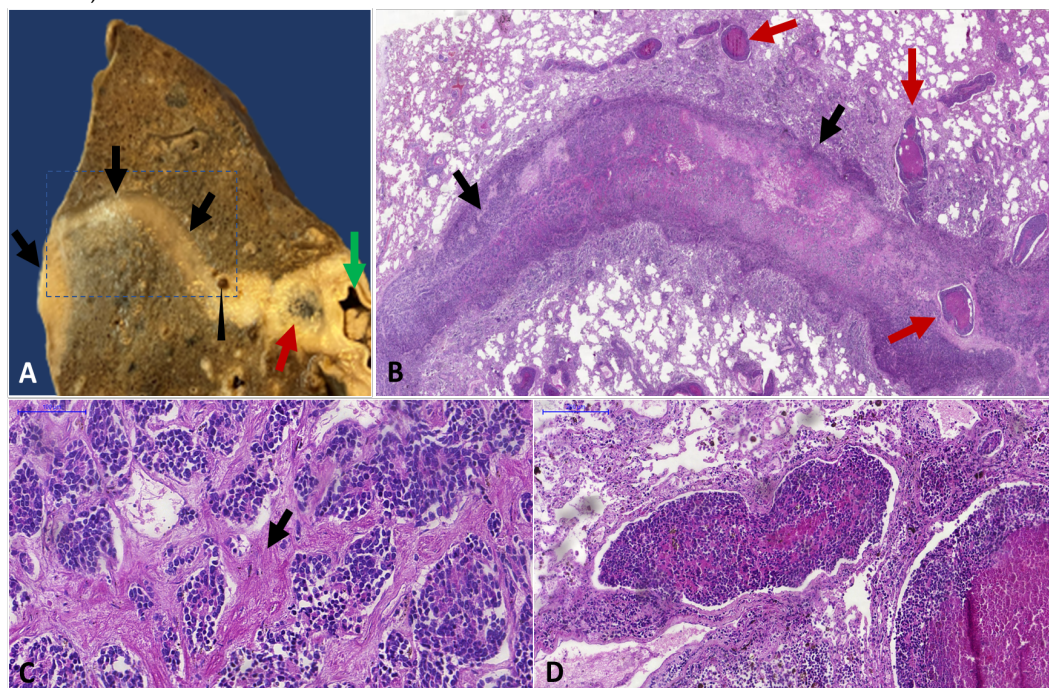
2. Case Report

A 53-year-old female patient was admitted to the emergency department with subacute constitutional symptoms, including fever, anorexia and malaise, along with the

presence of nodules throughout the body. On admission, CT of the chest and abdomen revealed the presence of a heterogeneous lesion centered in the posterior mediastinum, circumferentially involving the thoracic esophagus, trachea and thoracic aorta, in addition to subcutaneous implants suggestive of secondary involvement. Pulmonary parenchyma showed presence of multiple nodules and diffuse thickening of the interlobular septa and of the bilateral peribronchovascular bundle. The patient's clinical condition worsened, not allowing further diagnostic investigations before her death. Autopsy examination revealed an extensive mass in the posterior region of the mediastinum in close contact with trachea, esophagus and thoracic aorta.

The pulmonary cut surface showed whitish thickening of the interlobular septa and of the bilateral peribronchovascular bundle, sometimes forming nodular outlines (Figure 1A). In addition, generalized lymphadenopathy and subcutaneous nodules were identified. The microscopic examination showed marked lymphatic invasion by neoplastic cells in peribronchial and perivascular lymphatic vessels, consistent with pulmonary lymphangitic carcinomatosis. Intravenous tumoral emboli was also identified (Figure 1B to 1D). At higher magnification, it was observed sheets of round to oval blue small neoplastic cells with minimal cytoplasm and hyperchromatic nuclei, sometimes with finely dispersed chromatin and no distinct nucleoli. Necrosis and apoptosis were also seen. Complementary immunohistochemical tests showed positivity for CAM5.6, CD56 and Ki67 (60%) and negativity for CD45, compatible with a high-grade neuroendocrine carcinoma. The mediastinal location of a dominant mass, combined with the histological features, supported the conclusion of small cell carcinoma, most likely of pulmonary origin.

Figure 1. A. Surgical specimen: Macroscopic view of the lung showing interlobular septa and subpleural space with a whitish and thickened aspect (black arrows), lymphatic vessel with neoplastic thrombus (arrowhead), metastasis in an anthracotic lymph node (red arrow) and in the perivascular space with pulmonary embolism (green arrow). B-D. Optimal microscopy of surgical specimen: The microscope image corresponding to the area shown in the blue square in A. B. Extensive infiltration of the interlobular septa (black arrow) and lymphatic vessels by neoplastic cells with necrosis (red arrows), compatible with pulmonary lymphangitic carcinomatosis. C. Nested/trabecular pattern of interstitial infiltration in the interlobular septa, inducing desmoplastic interstitial fibrosis (arrow). D. Blocks of neoplastic cells, with central necrosis in a “comedo type necrosis” pattern within lymphatic vessels, surrounding the interlobular septa. Magnifications: B-panoramic view, C-100x, D-200x.



3. Discussion

Pulmonary lymphangitic carcinomatosis (PLC) represents a rare but clinically severe manifestation of metastatic disease, most often associated with advanced carcinomas of the lung, stomach, breast, or pancreas. Its occurrence as the initial clinical manifestation of a high-grade neuroendocrine carcinoma is exceptionally rare [1-3]. The present case is noteworthy because PLC was the first and only clinical presentation of a fulminant small cell lung carcinoma (SCLC), leading to death within only a few days of hospitalization.

Neuroendocrine tumors comprise a heterogeneous group that differ significantly in prognosis and histological appearance. Some are well differentiated, with slow growth and hormonal secretion, often allowing recognition of the primary site based on morphology and immunohistochemistry [6]. Others, such as small cell carcinoma, are extremely aggressive and usually present at an advanced stage. Cancer of unknown primary site accounts for approximately 2% of all invasive cancers, and neuroendocrine neoplasms represent less than 5% of these cases [7]. Poorly differentiated neuroendocrine carcinomas with an unknown primary site often manifest with widespread metastases, with the liver, bone, lung, and brain being the most commonly affected organs [6, 7].

In this case, the tumor was centered in the mediastinum, forming a dominant mass with extensive pulmonary lymphangitic spread, strongly suggesting a pulmonary origin. Histologically, the tumor consisted of small cells with scant cytoplasm, nuclear molding, necrosis, and a high mitotic rate. The Ki-67 proliferation index was 60%, consistent with SCLC, as poorly differentiated NETs often show levels above 50% [8, 9]. Immunohistochemistry was performed, including TTF-1 and GATA3, both of which were negative. TTF-1 negativity does not exclude pulmonary origin, as up to one-third of extrapulmonary small cell carcinoma and a minority of pulmonary SCLCs lack TTF-1 expression [10]. GATA3 negativity argued against breast or urothelial origin [11-13]. Neuroendocrine markers such as synaptophysin and chromogranin A were not performed, which represents a limitation of the diagnostic panel, which could have further supported the diagnosis. Nevertheless, morphology and Ki-67 supported the diagnosis of SCLC over large cell neuroendocrine carcinoma [8, 9, 14, 15].

Pulmonary lymphangitic carcinomatosis incidence is difficult to establish, as diagnosis is frequently made post-mortem. In many autopsy series, a significant proportion of patients with metastatic disease show lymphangitic spread, most often from gastric or pulmonary primaries. In a recent retrospective study from 2024, among 7,521 autopsies, 255 malignancies were identified, of which 16.9% of patients had pulmonary metastases, and 51% of those demonstrated histologically confirmed PLC. The most frequent primaries were gastric and pulmonary carcinomas (40.9%) [16]. The pathogenesis involves tumor cells reaching the pulmonary lymphatics through venous circulation, lymphatic spread, or occasionally transdiaphragmatic passage. After gaining access to blood or lymphatic vessels - often via direct invasion of adjacent vasculature - tumor cells become trapped in pulmonary lymphatics, leading to obstruction, fluid accumulation, peribronchovascular and septal thickening, and sometimes local nodular growth. Pulmonary vessels are usually spared, which explains the low incidence of pulmonary hypertension as a clinical manifestation [2, 17].

Clinically, its manifestations are usually nonspecific, most commonly presenting as progressive and subacute dyspnea. Other symptoms, such as pleuritic pain, weight loss, fatigue, cough, and hemoptysis, may also occur [2]. Radiological diagnosis of lymphangitic carcinomatosis is also challenging. In early stages, up to half of patients may present with normal imaging, despite the presence of histologic disease [1]. In more advanced phases, CT may reveal peribronchovascular thickening, septal involvement, and peritumoral uptake, but the findings remain nonspecific [1]. PET-CT can provide better diagnostic yield, but the gold standard for diagnosis continues to be histological evaluation of tissue samples [18].

Therapeutic options for lymphangitic carcinomatosis are limited, as it usually reflects advanced disease [1]. Treatment is directed toward the primary tumor and may include

surgery, systemic chemotherapy, or radiotherapy, but in most cases only supportive care is feasible [19]. Prognosis remains poor, with median survival ranging from a few weeks to months after diagnosis [20].

4. Conclusion

This case highlights the diagnostic challenges posed by aggressive neuroendocrine carcinomas, particularly when the clinical presentation is rapidly progressive, and underscores the value of autopsy in providing definitive pathological confirmation. For clinicians and pathologists, it reinforces the importance of considering lymphangitic carcinomatosis in the differential diagnosis of acute and unexplained respiratory failure and recognizing the limitations of imaging and immunohistochemistry in determining the exact primary site in advanced cases.

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