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Case Report

Primary Small Cell Neuroendocrine Carcinoma of the Mediastinum: Case Report of a Rare Entity

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Abstract: Small neuroendocrine carcinoma of the mediastinum (SCNCM) is a rare subtype of neuroendocrine malignancy characterized by its aggressive behavior and high rates of recurrence and metastasis. The diagnosis of this carcinoma is challenging, requiring confirmation through histopathological and immunohistochemical analysis, as well as specific imaging studies. This study reports a case of primary SCNCM that resulted in the death of a 59-year-old female patient treated at the Clinical Hospital, School of Medicine, Botucatu. The diagnostic proposal of primary small cell neuroendocrine carcinoma of the mediastinum was confirmed after a detailed analysis of the organs in an autopsy examination.

Keywords: Neuroendocrine Carcinoma; Small Cell; Mediastinum; Autopsy; Primary Tumor; Case Report.

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1. Introduction

Primary neuroendocrine carcinomas of the mediastinum are exceedingly rare, typically associated with the thymus and paraganglionic structures adjacent to major mediastinal vessels. In less common cases, these tumors may also affect retroperitoneal structures, the inferior vena cava, the presacral region, the parathyroid gland, the ovary, as well as the gastrointestinal and biliary systems [1–3]. The etiology of small cell neuroendocrine carcinoma of the mediastinum (SCNCM) remains uncertain, with two main hypotheses: one suggests that the tumor arises from ectopic tissue due to aberrant embryonic migration, while the other proposes an origin from a teratomatous component [2].

The estimated incidence of SCNCM is approximately 1 case per 50 million individuals annually, with no sex predilection, and a mean patient age of around 58 years [4]. Clinically, symptoms include cough, dyspnea, dysphagia, weight loss, fatigue, and fever [1, 3]. For differential diagnosis, it is essential to consider Ewing sarcoma, primitive neuroectodermal tumor (PNET), lymphoma, neuroblastoma, and rhabdomyosarcoma, as well as primary or metastatic basaloid carcinoma [2].

The mortality rate of SCNCM reaches 50% within two years, and only half of the patients show any response to chemotherapy. The estimated median survival is approximately 14 months. Given the severity and rarity of this neoplasm, early diagnosis is crucial, as neoadjuvant therapies may improve survival rates compared to surgical resection alone [3, 5, 6]. Historically, the management of SCNCM has been challenging; therapeutic interventions that initially demonstrate efficacy are frequently followed by tumor recurrence and metastases [1, 3, 5, 7].

Given the relevance of the early diagnosis of this malignant neoplasm, this case report shows histopathological findings from the biopsy at the time of diagnosis and necroscopic findings that confirm its primary presentation. Moreover, we discuss macroscopic and microscopic criteria and immunohistochemistry staining even as differential diagnoses.

2. Case Report

This report describes the case of a 59-year-old female patient, a smoker with a 30-pack-year history, with a family history of bladder cancer (brother) and pneumonia (both parents). She was admitted to the Hospital das Clínicas, Faculty of Medicine of Botucatu (HCFMB) presenting with dysphagia for both solids and liquids, associated with a 10 kg weight loss, dry cough persisting for one month, and worsening symptoms in the previous week, including nocturnal agitation, dyspnea, and epigastric pain. On examination, she appeared pale and dehydrated, with tachycardia (111 bpm), oxygen saturation of 92%, and blood pressure of 110/70 mmHg. Physical examination revealed an increased anteroposterior thoracic diameter, bilaterally diminished vesicular breath sounds, reduced thoracic expansibility, a palpable liver extending 10 cm below the right costal margin, and bilateral lower limb edema (2+/4+).

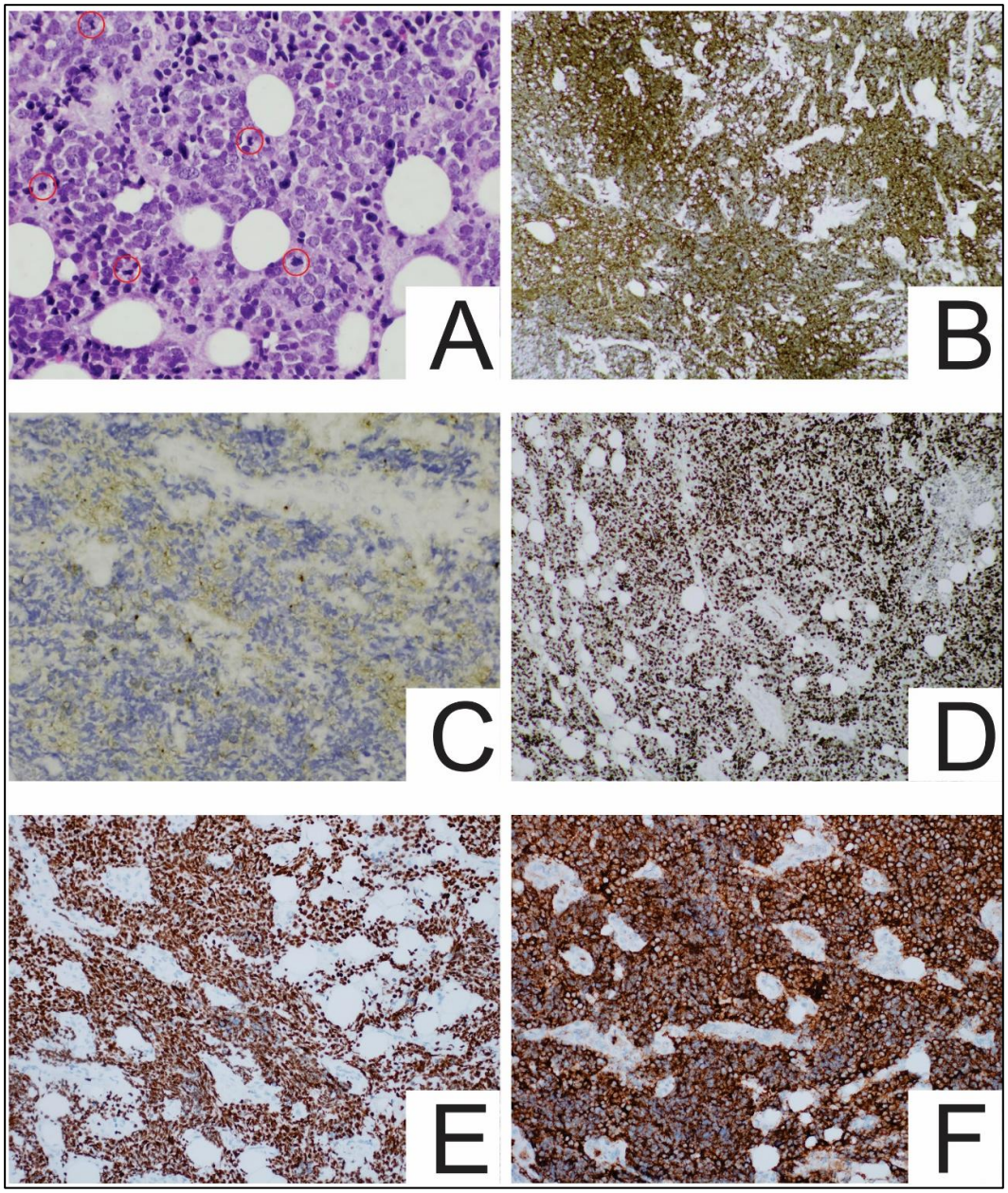
Chest computed tomography (CT) demonstrated a mediastinal mass in close contact with the supra-aortic arterial vessels, causing narrowing of the left subclavian vein, involving the posterior wall of the superior vena cava, and intimately associated with the tracheal carina, right main bronchus, and right pulmonary artery. Additionally, there was left supraclavicular lymphadenopathy measuring 2.3 × 2.1 cm, marked centrilobular and paraseptal pulmonary emphysema bilaterally, and a small right pleural effusion. A mediastinoscopy with a biopsy of the mediastinal mass was performed.

Morphological analysis revealed a lesion composed of small, round, blue, monotonous cells with finely granular chromatin (''salt-and-pepper'' pattern) and slightly prominent nucleoli, exhibiting an organoid growth pattern, a high mitotic index, and areas of necrosis. Immunohistochemical analysis demonstrated immunoreactivity for pan-cytokeratin cocktail (AE1/AE3), chromogranin A (Golgi pattern), and synaptophysin (Golgi pattern), with negativity for hematopoietic markers and a Ki-67 proliferation index exceeding 90%, and positivity for TTF1, and CD56 (Figure 1 A to F). These findings confirmed the histopathological diagnosis of high-grade neuroendocrine carcinoma (Oat cell carcinoma).

Two days after the biopsy, the patient experienced clinical deterioration, developing febrile spikes, tachycardia, anuria, elevated lactate (4.94 mmol/L), poorly perfused extremities, thrombocytopenia, anemia, and shock. She was transferred to the intensive care unit (ICU) for vasopressor support, sedation-analgesia, and antibiotic therapy. On the following day, nine days after admission, despite all instituted medical interventions, the patient exhibited further lactate elevation (12.0 mmol/L), persistent fever, and significant functional decline, ultimately progressing to death. The body was referred for autopsy at the same hospital (HCFMB).

The necropsy revealed a large, ill-defined, firm, fibroelastic, whitish-tan tumor mass involving the major mediastinal vessels, with infiltration of adjacent soft tissues, esophageal compression (Figure 2A), and multiple well-demarcated, whitish, fibroelastic hepatic nodular lesions ($n > 10$), averaging 0.8 cm in diameter (Figure 2C). Samples from the primary tumor mass and hepatic lesions were collected for histopathological examination (Figure 2B, 2D), which confirmed the previous diagnosis and identified the underlying cause of death as high-grade neuroendocrine carcinoma (Oat cell carcinoma) of the mediastinum. The lung was extensively examined, and no lesions were found that suggested primary pulmonary neuroendocrine carcinoma as the main differential diagnosis.

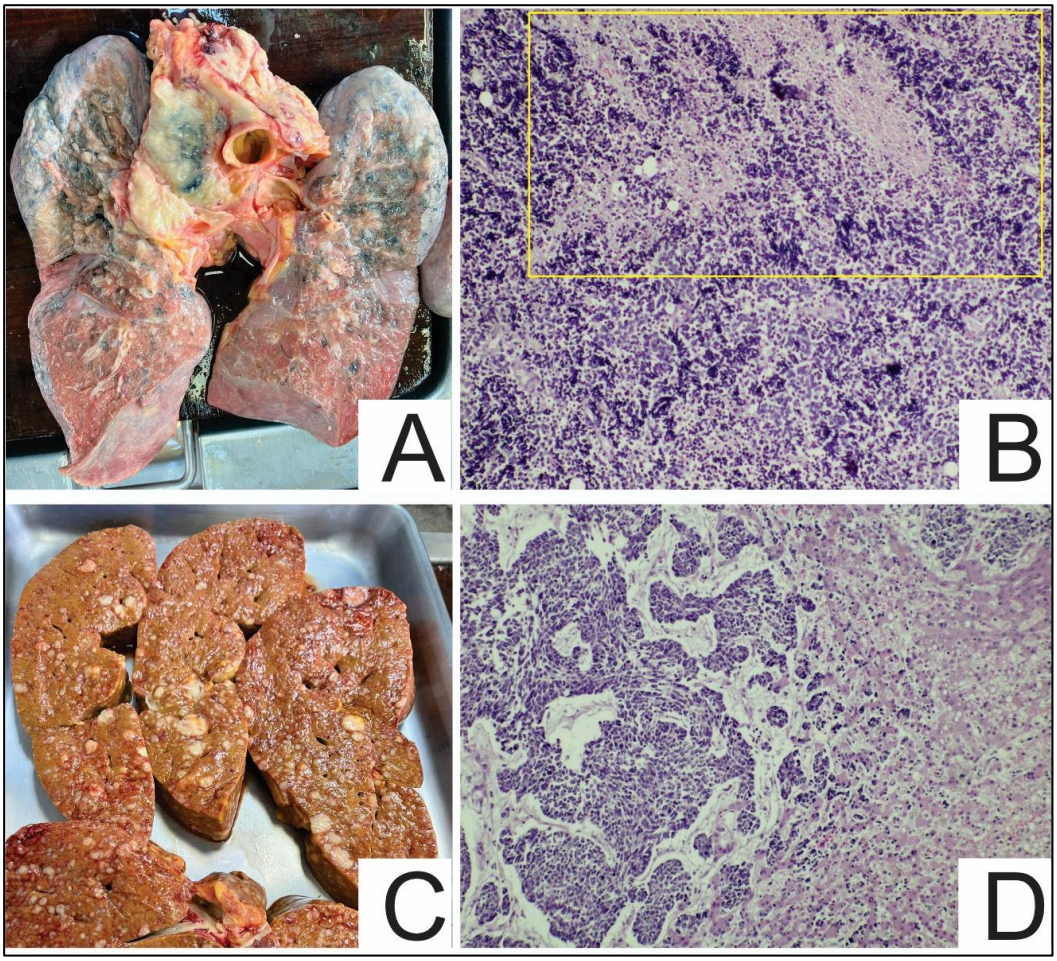
Figure 1. Biopsy of the mediastinal mass: Small, round, blue cells with finely granular chromatin ("salt-and-pepper" pattern) and a high mitotic index, with mitotic figures circled in red (A: 400x, H&E). Immunohistochemical analysis revealed positivity for the pan-cytokeratin cocktail AE1/AE3 (B: 100x), synaptophysin with a Golgi pattern (C: 200x), a high cellular proliferation index (Ki-67), estimated at over 90% (D: 100x), and positivity for thyroid transcription factor 1 (TTF-1) (E: 200 x), and positivity for CD56 (F: 200X).



3. Discussion

A proposed report for this case presents a fatal outcome in a patient with necroscopic findings of primary small-cell neuroendocrine carcinoma of the mediastinum. Small cell neuroendocrine carcinoma of the mediastinum (SCNCM) can be presented clinically like other mediastinal masses, manifesting with compressive symptoms or being incidentally detected on imaging studies. Malignant tumors in this region tend to invade adjacent structures, leading to symptoms such as dyspnea, hoarseness, stridor, or superior vena cava syndrome (SVCS) [8]. In the present case, the patient exhibited dysphagia, cough, and weight loss, symptoms consistent with those reported in the literature.

Figure 2. Autopsy and Histopathological Study: Whitish-tan, ill-defined, fibroelastic tumor mass involving the major mediastinal vessels and infiltrating adjacent soft tissues (A). The tumor component consists of small, round, blue cells with finely granular chromatin ("salt-and-pepper" pattern), an adjacent inflammatory infiltrate, and geographic necrosis highlighted by the yellow rectangle (B: 100x, H&E). Multiple hepatic nodular lesions (C). Hepatic metastasis of high-grade neuroendocrine carcinoma (Oat cell carcinoma) of the mediastinum (D: 100x, H&E).



Diagnosing small cell neuroendocrine carcinoma requires a comprehensive evaluation, integrating histopathological examination, which reveals the characteristic organoid growth pattern, with immunohistochemical analysis. Key diagnostic markers include chromogranin A and synaptophysin. Thus, diagnostic confirmation relies on identifying neuroendocrine morphology and expressing at least one specific marker [1, 9, 10].

In this case, the tumor demonstrated positivity for the pan-cytokeratin cocktail AE1/AE3, chromogranin A, and synaptophysin, findings consistent with literature. AE1/AE3 positive effectively ruled out rhabdomyosarcoma. CD99 immunostaining was also negative. Differential diagnosis includes other small cell neoplasms such as T-lymphoblastic lymphoma or small cell sarcomas (such as the PNET/Ewing tumor). During the autopsy, there was no evidence of thymic involvement, as no residual thymic tissue was identified within the lesion. Similarly, no primary lung neoplasm was identified on the examination of the lung parenchyma. Instead, tumor expansion into adjacent soft tissues and hepatic metastases were observed.

CD56 and TTF-1 markers were also investigated and demonstrated strong positivity. Detection of TTF1 does not prove a primary tumor of the lung but should always prompt close correlation with clinical and radiological findings [11]. Agoff et al. [12] showed that 44% of nonpulmonary small cell carcinoma were also TTF-1 positive. They conclude that

TTF-1 expression is not specific for small cell carcinomas of pulmonary origin and should not be used to distinguish primary from metastatic small cell carcinomas in extrapulmonary sites [9, 12].

At the time of diagnosis, the majority of small neuroendocrine carcinoma cells are in an advanced stage with infiltration of neighboring organs, such as lungs or pericardium, or with distant metastases to the lung, liver, bone or brain [11]. The multiplicity and distribution of small hepatic neuroendocrine lesions favor the metastatic character of neoplastic foci in the liver [13]. This factor points to the high staging and reinforces the reserved prognosis of the patient described in this report.

There are no established treatment guidelines for SCNCM; however, the standard therapeutic approach typically involves surgical resection followed by chemotherapy and radiotherapy, aiming to alleviate symptoms and prolong survival [2]. Chemoradiotherapy is recommended to be the preferred treatment modality for small cell carcinoma with the primary lesions confined to the mediastinum [14]. Nevertheless, the prognosis remains poor due to the high rate of local recurrence and post-excision metastasis, making SCNCM the most aggressive among primary mediastinal tumors, with an estimated median survival of approximately 14 months [7].

4. Conclusion

Mediastinal small-cell neuroendocrine carcinoma is an extremely rare neoplasm with variable clinical presentations and generally poor outcomes. Its diagnosis requires a comprehensive approach, integrating histopathological examination and immunohistochemical analysis. There is no specific treatment protocol for this condition; however, a combination of surgical resection, chemotherapy, and radiotherapy may help alleviate symptoms and improve patient survival. Early diagnosis is crucial for optimizing clinical management. Further studies on this entity are necessary to validate these conclusions and enhance our understanding of the disease.

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