COMBINED SMALL CELL CARCINOMA AND ADENOCARCINOMA DIAGNOSED ON EBUS-TBNA MATERIAL

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CLINICAL PRESENTATION:

A 64-year-old male patient presented with a 2.5-month history of numbness and severe pain in the arms and legs. He was initially treated with physical therapy, without clinical improvement. A thoracic CT scan revealed a 2 cm, well-circumscribed lesion in the left upper lobe and extensive mediastinal lymphadenopathy, including the left hilar region. EBUS-guided transbronchial needle aspiration (EBUS-TBNA) was performed for diagnostic purposes.

CYTOLOGICAL FINDINGS:

The aspirated material was entirely composed of tumor tissue, exhibiting two distinct neoplastic populations:

- A predominant component composed of small, hyperchromatic cells with evenly dispersed powdery chromatin, scattered paranuclear “blue bodies”, scanty cytoplasm, and nuclear molding with crush artifact, consistent with small cell carcinoma. The background shows apoptotic debris, and some necrosis.
- A second component consisting of cell clusters forming tubular structures, honeycomb-like sheets, and three-dimensional aggregates, with moderate translucent cytoplasm and finely textured chromatin, suggestive of adenocarcinoma.

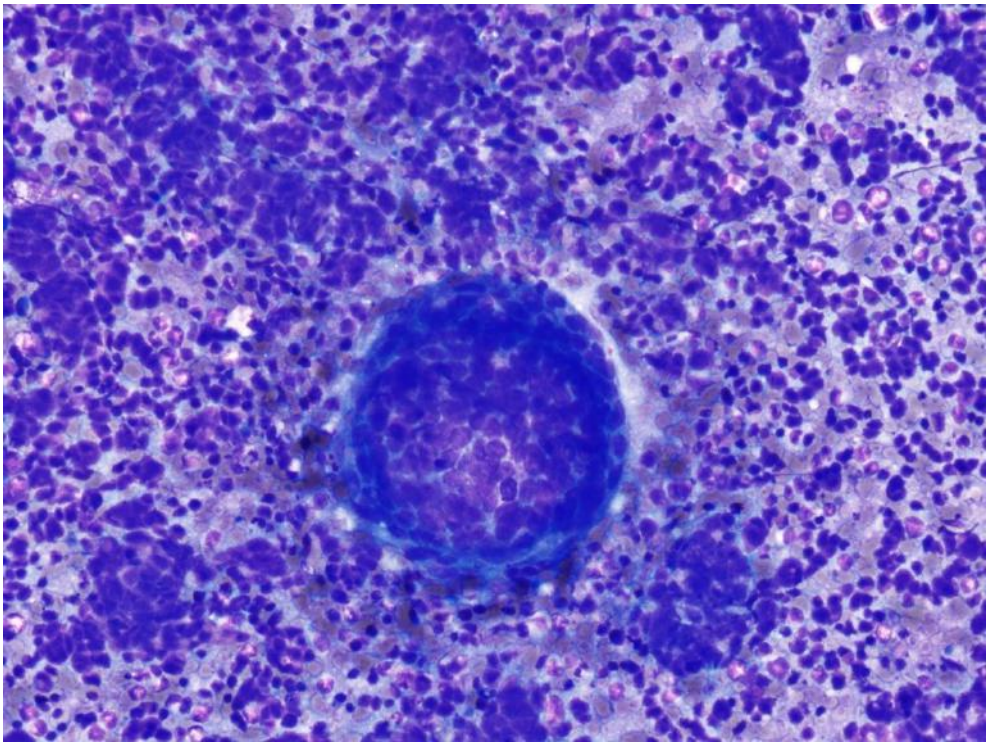


Figure 1 *Dual population: Background shows cytologic features of small cell lung carcinoma, characterized by tightly packed, small cells with scant cytoplasm, finely granular chromatin, and prominent nuclear molding. Within this background, a distinct group of cells forms three-dimensional cohesive clusters ("balls"), displaying features consistent with adenocarcinoma, including moderate cytoplasm and nuclear polarity, suggestive of glandular differentiation.*

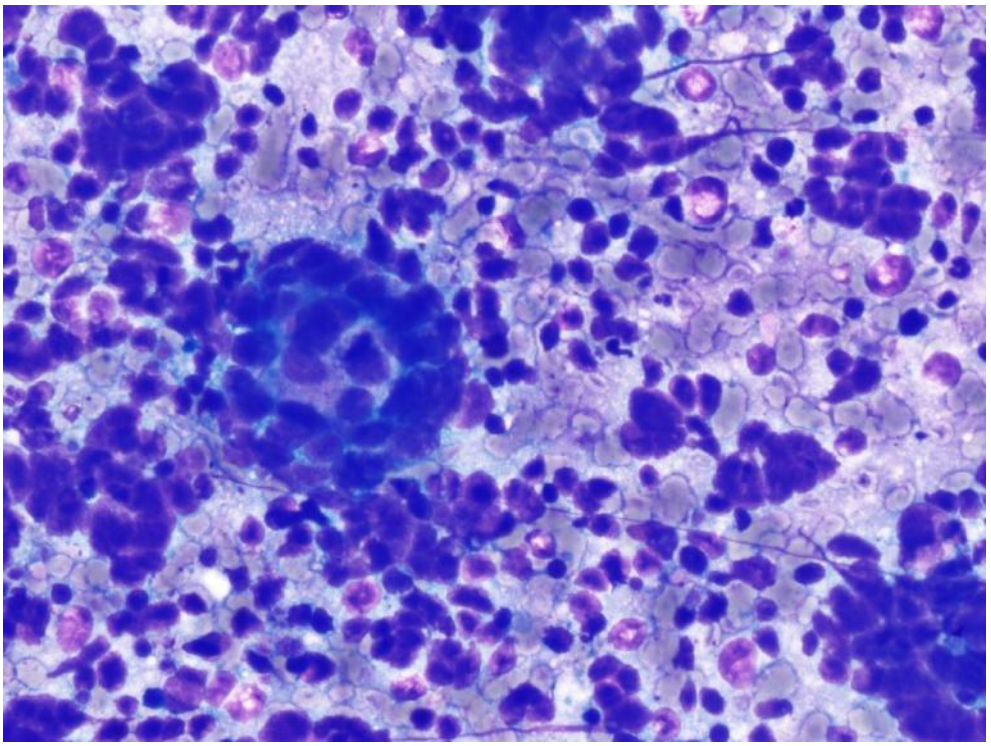


Figure 2 *High-power view of small cell carcinoma showing tightly packed tumor cells with nuclear molding, finely granular chromatin, and scant cytoplasm. 'Blue bodies'—apoptotic debris or crushed*

nuclei—are also noted in the background. Nearby, a 3D cohesive cluster of cells with glandular features suggests an adenocarcinoma component.

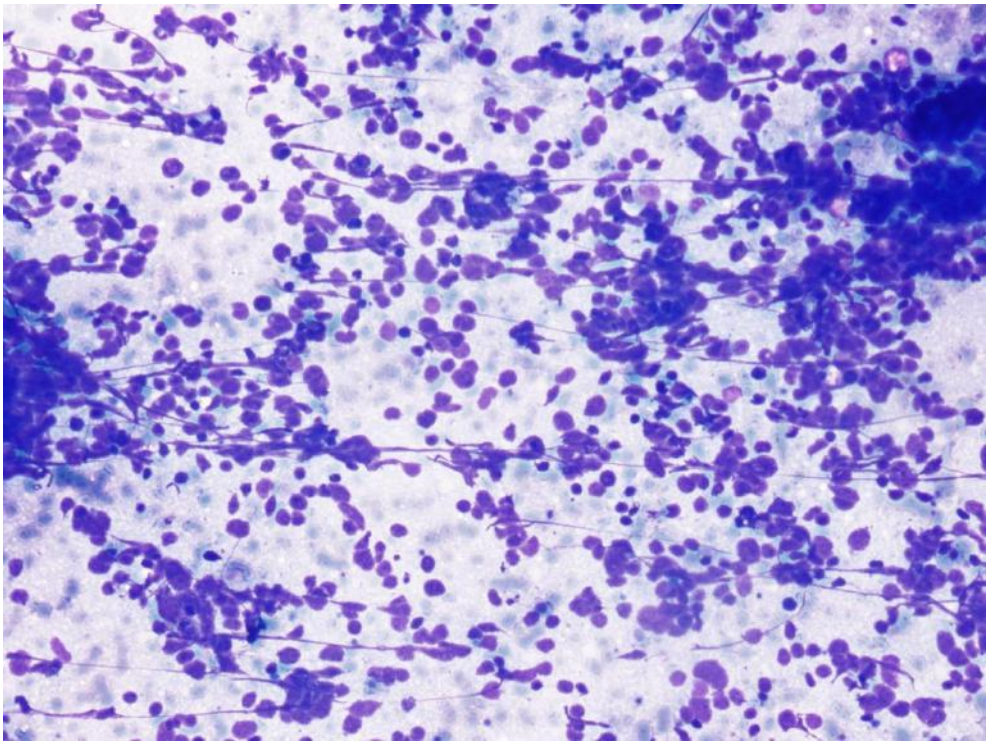


Figure 3 *Low-power view of a smear entirely composed of small cell carcinoma. The sample shows high cellularity with loosely cohesive sheets and single cells. Key cytologic features include nuclear molding, high nuclear-to-cytoplasmic ratio, finely granular chromatin, and focal crush artifact. Minimal apoptotic debris is present.*

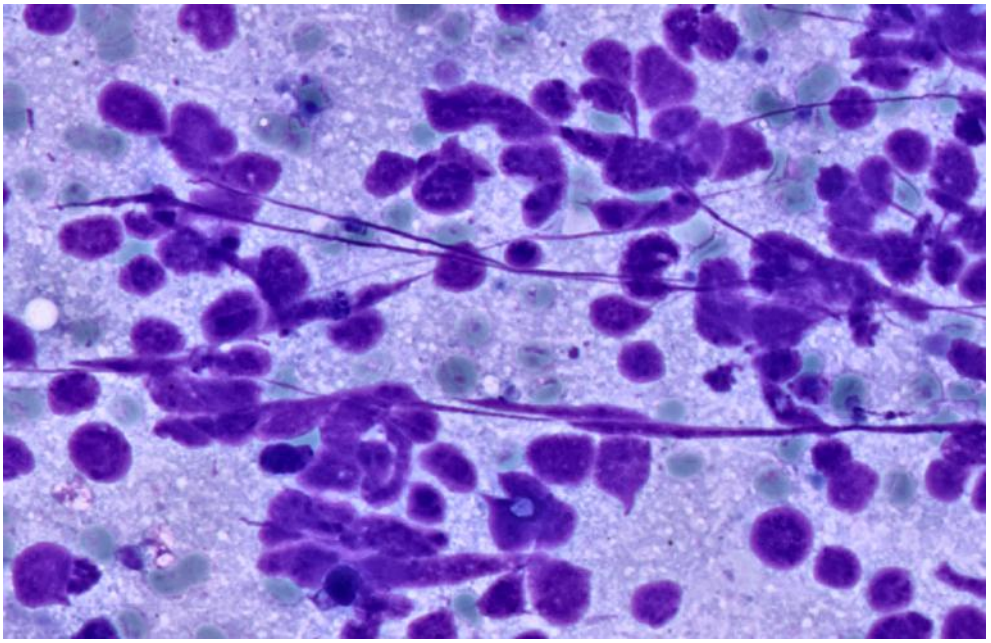


Figure 4 *High-power view of small cell carcinoma showing classic cytologic features: small, round to oval tumor cells with scant cytoplasm, finely granular chromatin, and prominent nuclear molding. Occasional apoptotic bodies and focal crush artifact are also noted.*

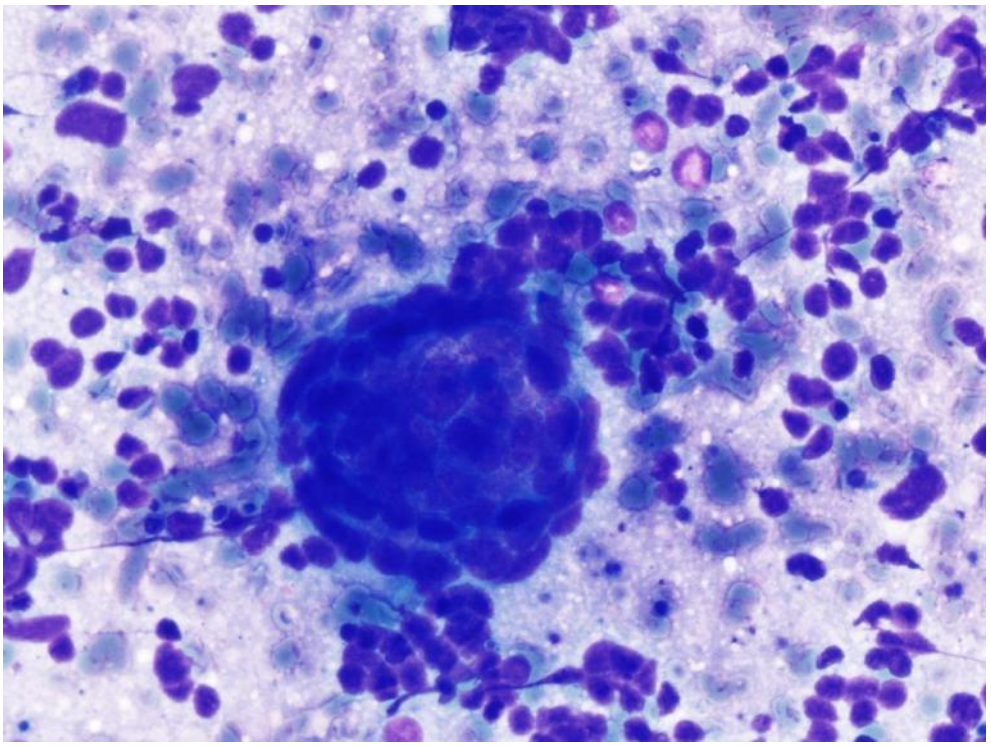


Figure 5 *Prominent three-dimensional glandular cluster consistent with adenocarcinoma stands out in the center, embedded in a background of small cell carcinoma showing nuclear molding and scant cytoplasm.*

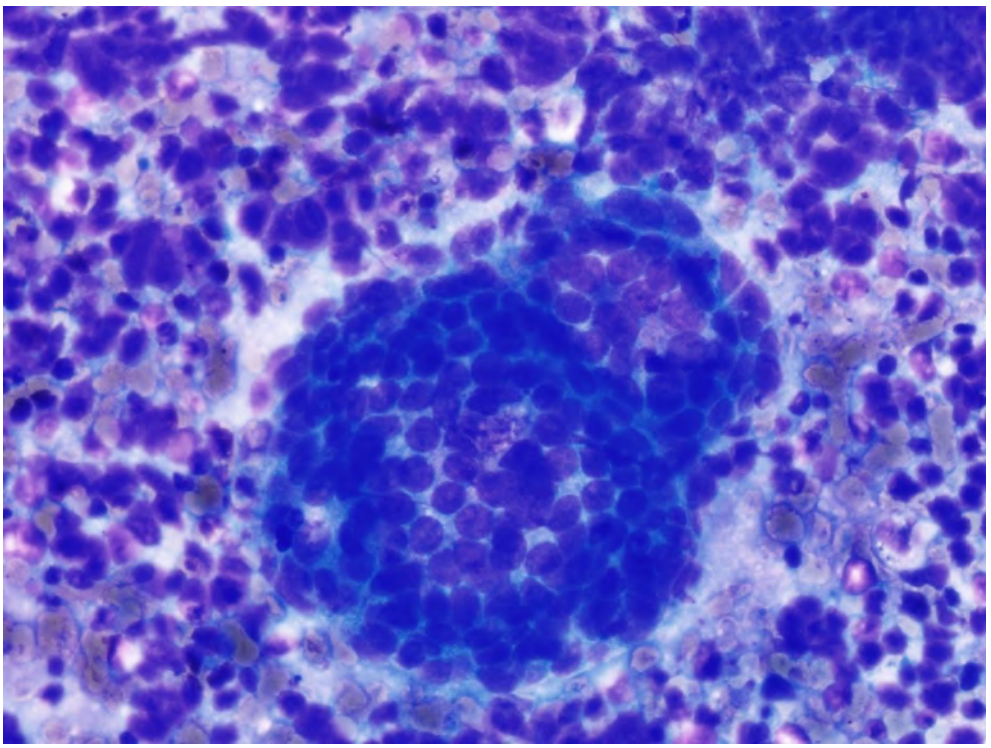


Figure 6 *Two adjacent or bi-lobed three-dimensional clusters of tumor cells exhibiting glandular architecture, prominent nuclear polarity, and moderate amounts of cytoplasm—features characteristic of adenocarcinoma. The cohesive nature and architectural complexity support gland-forming*

differentiation. These clusters are embedded in a background of small cell carcinoma, indicative of combined histology.

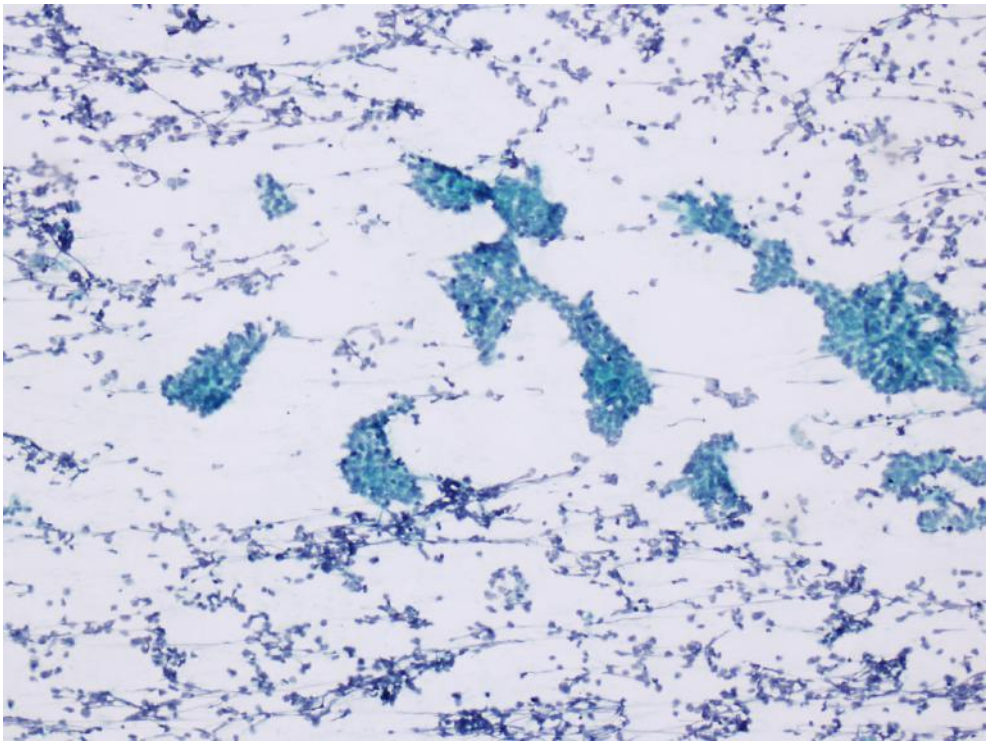


Figure 7 *Low-power Pap-stained smear showing a background of small cell carcinoma with prominent crush artifact and nuclear molding. Centrally, broad flat sheets of cohesive tumor cells with moderate cytoplasm and nuclear polarity are observed, consistent with adenocarcinoma.*

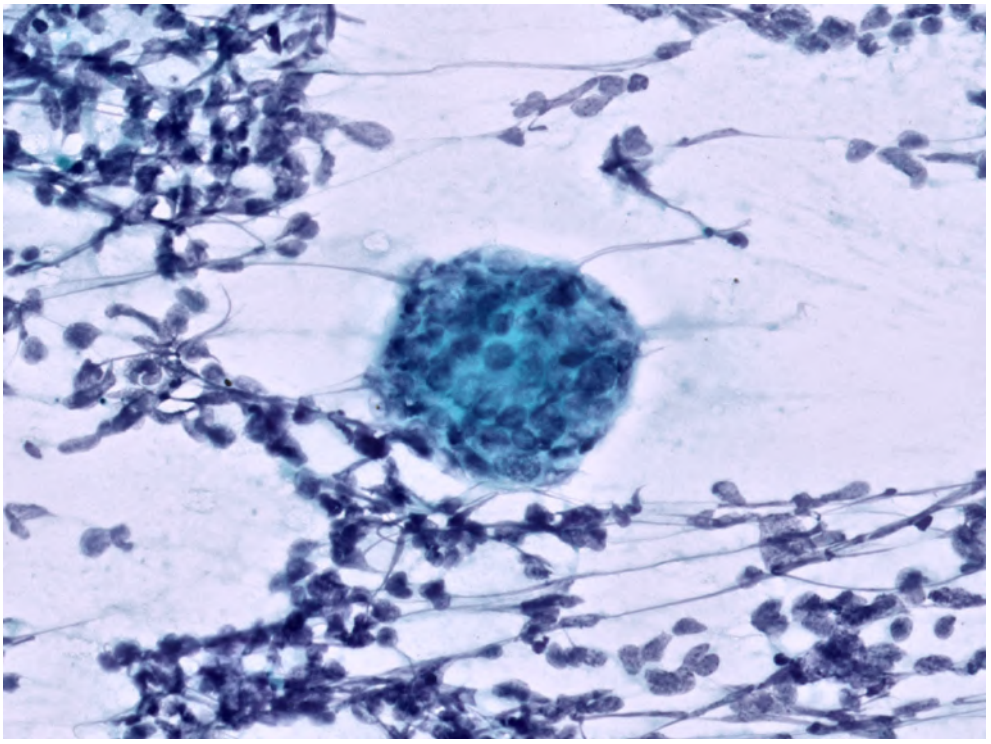


Figure 8 *Low-power Pap-stained smear demonstrating a background of small cell carcinoma with crush artifact and nuclear molding. Centrally located is a well-defined three-dimensional cluster of*

tumor cells showing glandular architecture, distinct nuclear contours, and evident nuclear polarity—features supporting adenocarcinoma morphology.

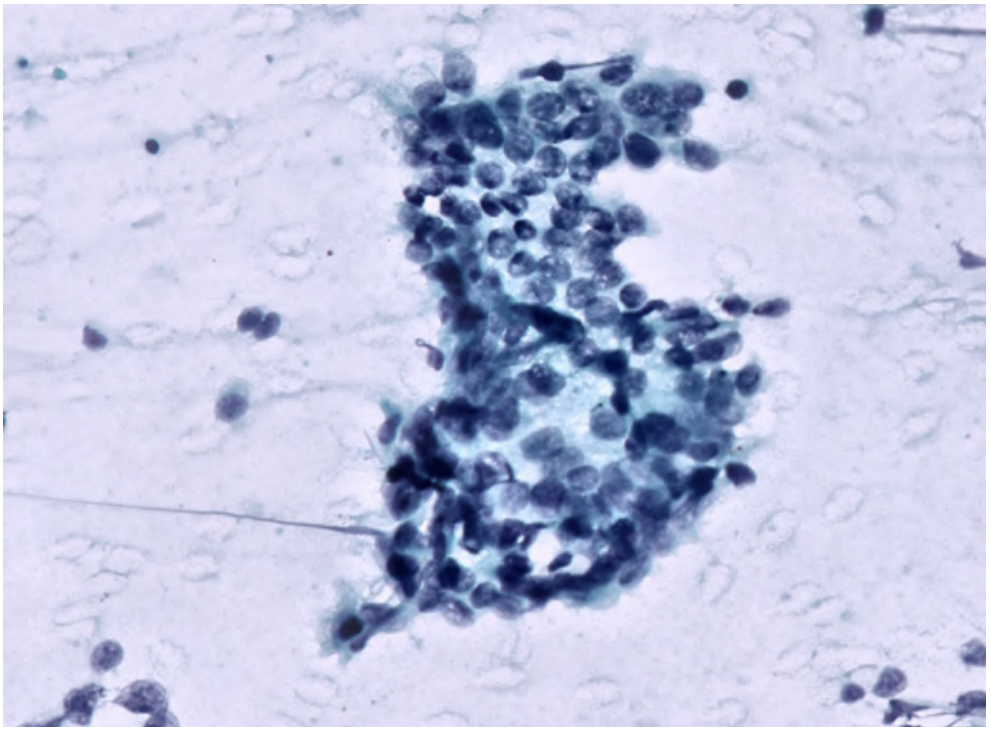


Figure 9 *Low-power Pap-stained smear showing a broad flat sheet of cohesive tumor cells with prominent nuclear atypia, including irregular contours, nuclear enlargement. The background is minimally cellular with only sparse small cell carcinoma elements*

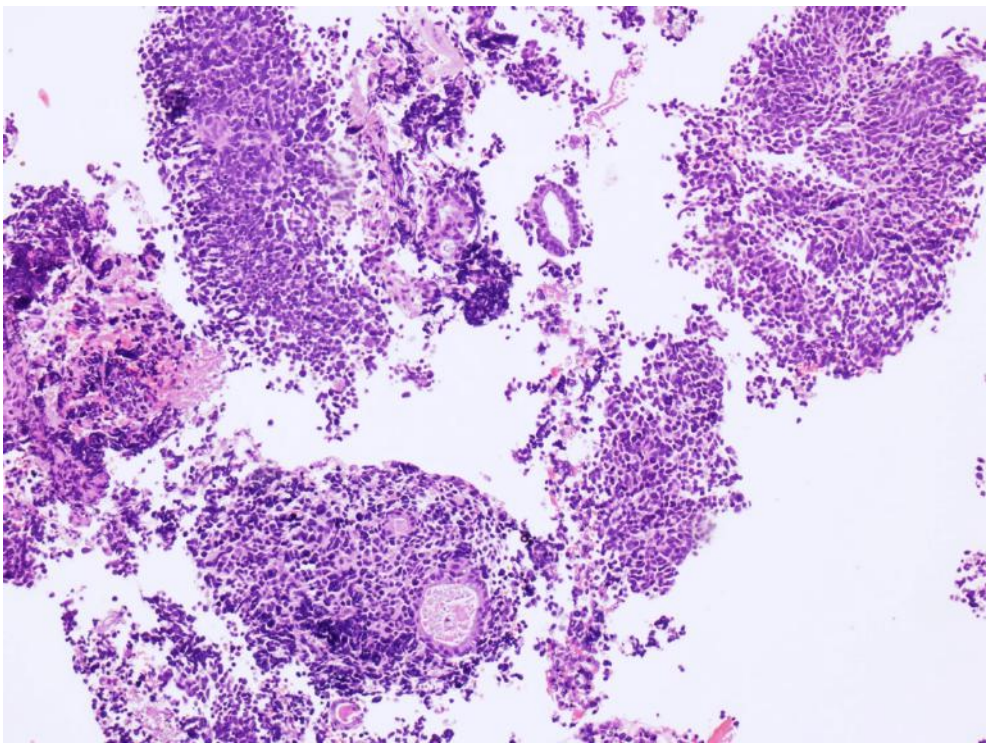


Figure 10 *Low-power view of the cell block showing prominent glandular structures embedded within areas of small cell carcinoma.*

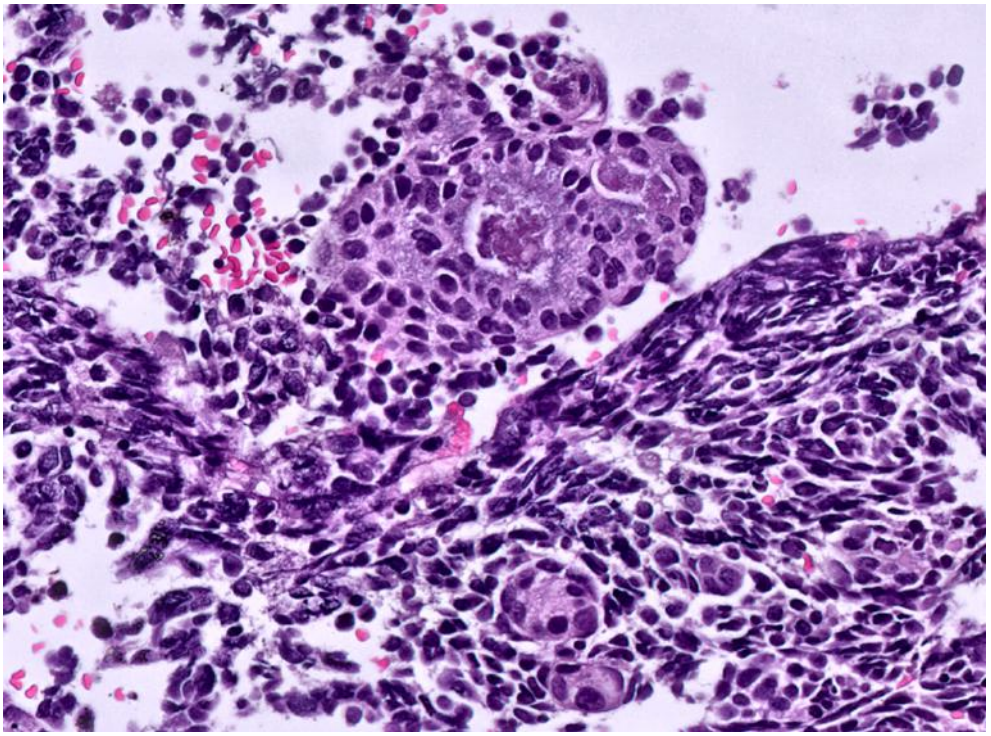


Figure 11*High-power view of cell block showing a cribriform glandular architecture embedded within areas of small cell carcinoma. The glandular structures are composed of crowded epithelial cells with nuclear atypia and complex luminal formations.*

IMMUNOHISTOCHEMISTRY:

Immunostaining was performed on the cell block:

Marker	Small Cell Component	Adenocarcinoma Component
TTF-1	Strongly positive	Focally positive
CD56	Positive	Negative
Pan-Cytokeratin	Dot-like perinuclear	Diffuse cytoplasmic
Rb	Lost	Lost
P40	Negative	Negative

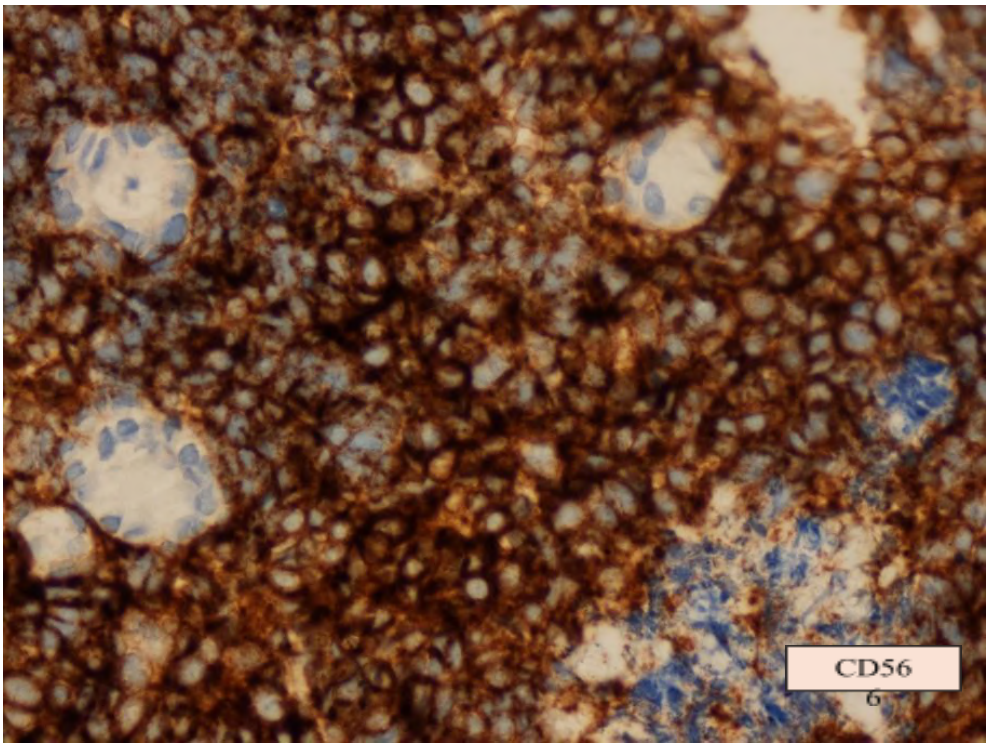


Figure 12 *High-power CD56 immunostain showing diffuse membranous positivity in the small cell carcinoma component, while the adjacent glandular component is negative.*

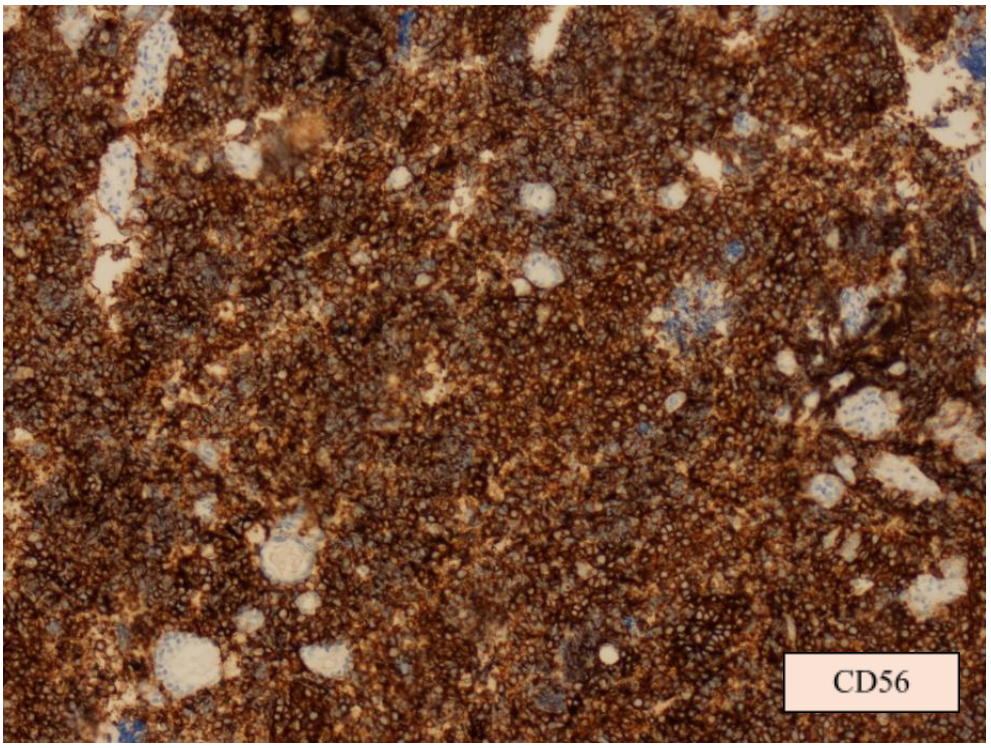
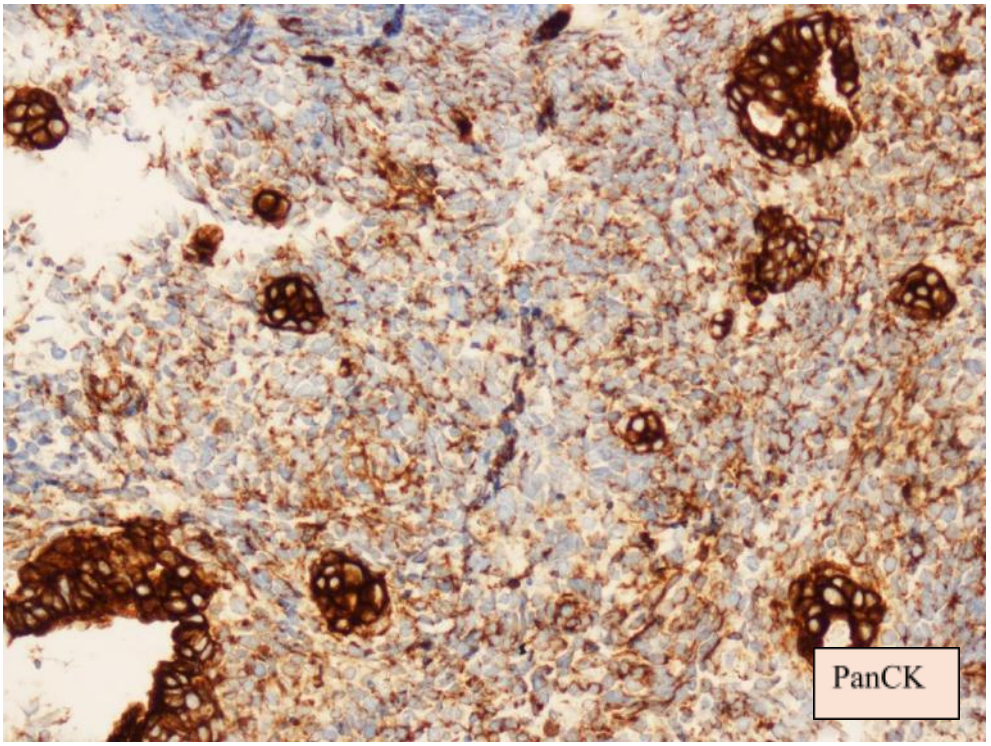


Figure 13 *Low-power CD56 immunostain showing strong positivity in the small cell carcinoma areas, with lack of staining in the glandular component.*



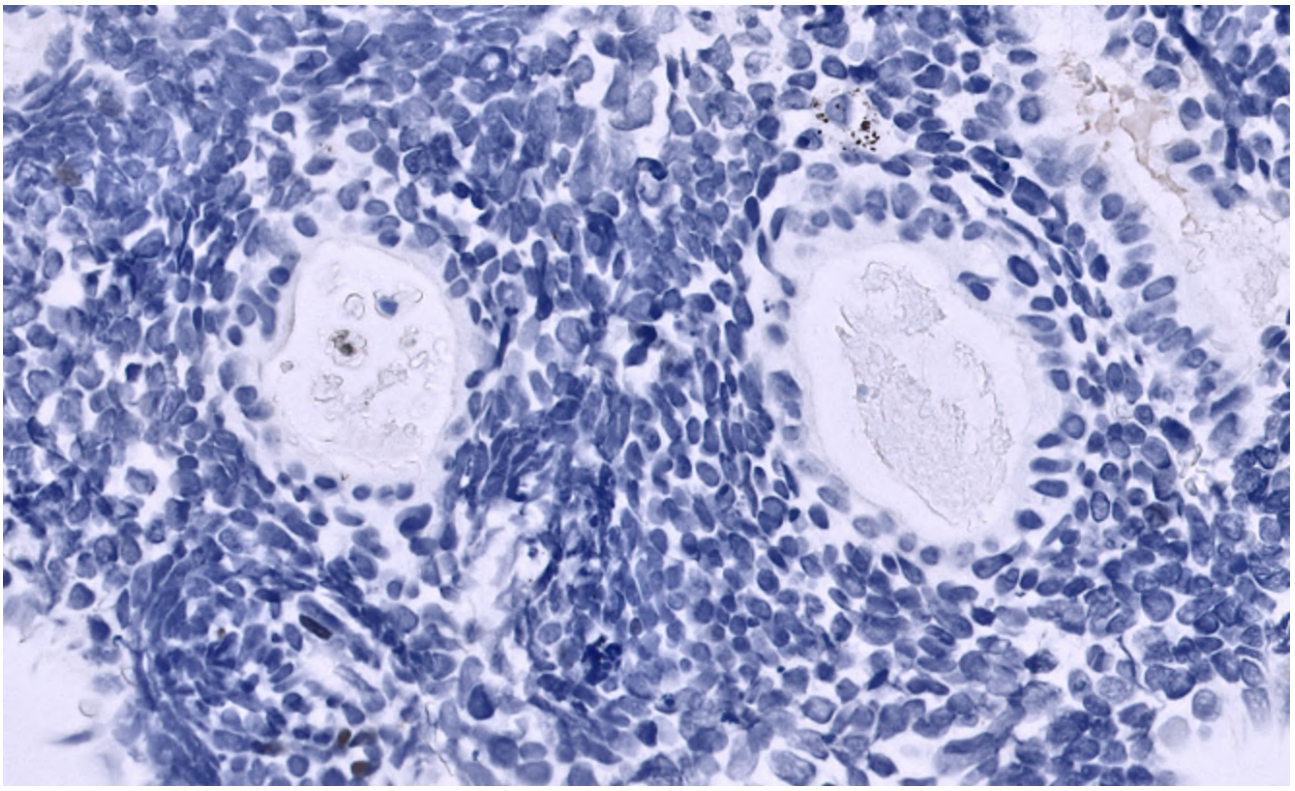


Figure 15 *P40 immunostain shows no staining in either the small cell carcinoma or the glandular component.*

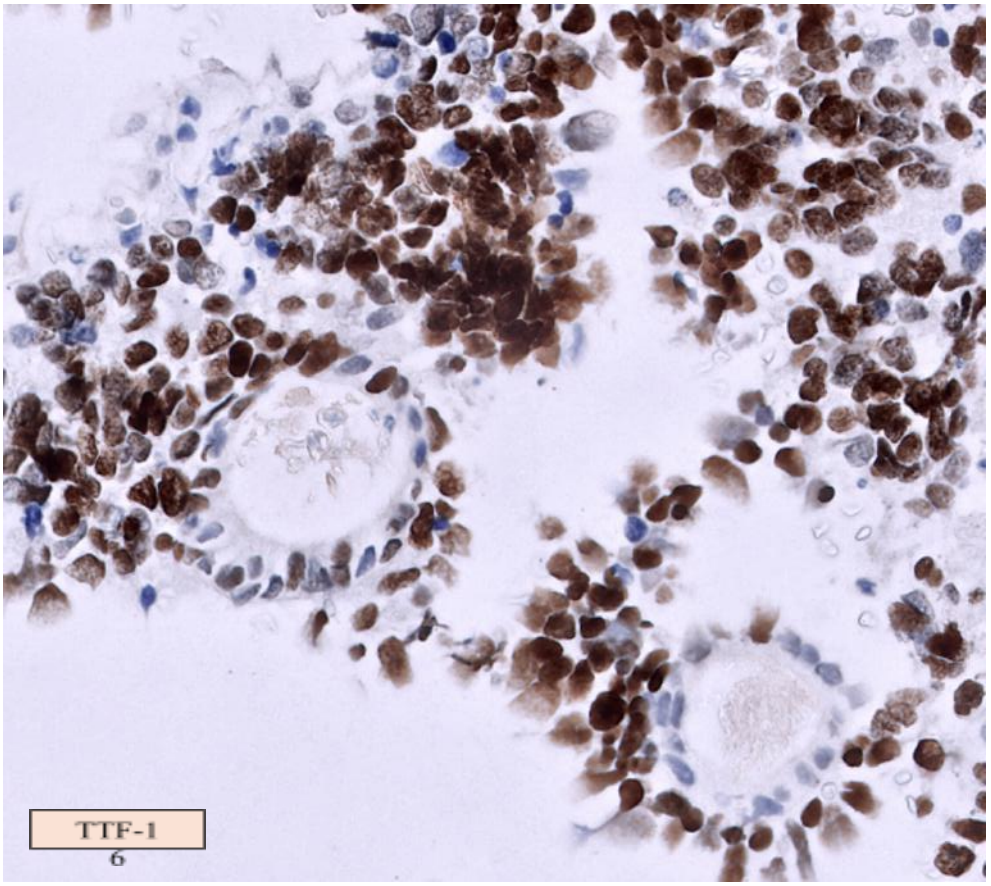


Figure 16 *TTF-1 immunostain shows diffuse nuclear positivity in the small cell carcinoma component and patchy nuclear staining in the glandular component.*

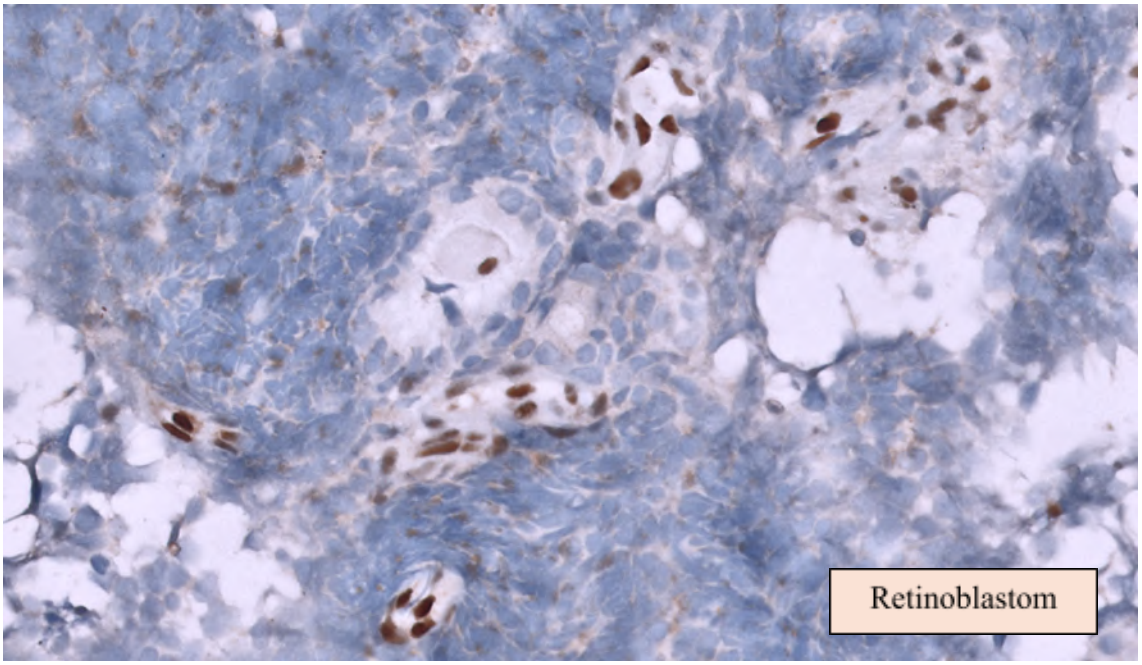


Figure 17 *Retinoblastoma (Rb) immunostain shows loss of nuclear expression in both the small cell carcinoma and glandular components. An intact internal positive control is present in background endothelial cells.*

FINAL DIAGNOSIS:

Combined Small Cell Carcinoma and Adenocarcinoma of the Lung, diagnosed on EBUS-TBNA specimen. The **small cell component was predominant**.

DISCUSSION:

Combined small cell carcinoma (C-SCLC) is a rare lung tumor subtype defined by the coexistence of small cell carcinoma and a non-small cell component, most often adenocarcinoma. Its recognition on small biopsies or cytological specimens can be challenging but is essential for therapeutic planning. In this case, the diagnosis was established on EBUS material, supported by immunohistochemical studies. Loss of Rb expression in both components supports the hypothesis of a common clonal origin[1-2], while the divergent morphology necessitates attention to morphological and immunophenotypic heterogeneity.

Accurate identification of C-SCLC in cytological samples is particularly difficult due to limited tissue, predominance of one component, and crush artifacts obscuring morphological details. Literature suggests that the incidence of C-SCLC is considerably underreported in small biopsy or cytology-based series compared to surgical resections[3]. In fact, up to 45% of surgically resected SCLC cases may harbor a combined histology, whereas cytological or small biopsy specimens frequently fail to capture both components. In a large retrospective study, nearly half of the C-SCLC cases were missed in preoperative cytological or bronchoscopic samples[4]. This underlines the diagnostic limitations of minimal sampling and emphasizes the critical role of cytopathologists in recognizing subtle morphological heterogeneity.

The presence of a non-small cell component not only alters prognosis but also has therapeutic implications. While C-SCLC shares clinical features with pure SCLC, it may exhibit lower response rates to standard chemotherapy and may benefit from surgical resection or targeted therapies in select cases[5]. Therefore, heightened awareness and careful cytomorphological assessment are essential to avoid misclassification and ensure optimal patient management.

KEY LEARNING POINTS:

- **Combined tumors may be under-recognized in small biopsies unless dual populations are suspected and adequately sampled.**
- **Rb loss is a key feature in small cell carcinoma and, when present in both components, suggests a shared pathogenesis.**
- **EBUS-TBNA can provide sufficient material for both diagnosis and immunohistochemical workup, even in complex mixed tumors.**

- **Cytological recognition of combined histology requires attention to subtle morphological differences and careful correlation with immunohistochemistry.**
- **Identification of an adenocarcinoma component in a small cell background may alter therapeutic strategies, including consideration for targeted therapy or surgery.**

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2. *Patrick L. Wagner, Naoki Kitabayashi, Yao-Tseng Chen, Anjali Saqi, Combined Small Cell Lung Carcinomas: Genotypic and Immunophenotypic Analysis of the Separate Morphologic Components,* American Journal of Clinical Pathology*, Volume 131, Issue 3, March 2009, Pages 376–382, https://doi.org/10.1309/AJCPYNPFL56POZQY*
3. *Babakoohi S, Fu P, Yang M, Linden PA, Dowlati A. Combined SCLC clinical and pathologic characteristics. Clin Lung Cancer. 2013 Mar;14(2):113-9. doi: 10.1016/j.cllc.2012.07.002. Epub 2012 Sep 24. PMID: 23010092.*
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5. *Qin J, Lu H. Combined small-cell lung carcinoma. Onco Targets Ther. 2018 Jun 19;11:3505-3511. doi: 10.2147/OTT.S159057. PMID: 29950855; PMCID: PMC6016273.*