Cytomorphological assessment of small cell lung carcinoma in a malignant pleural effusion

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Abstract

Malignant pleural effusions are uncommon in small cell lung carcinoma (SCLC). We report a case of this in an elderly female patient. Her previous history of ductal breast carcinoma, ovarian serous carcinoma, and non-small cell lung carcinoma prompted several possible differential diagnoses. We discuss the importance of cytology specimens in the diagnosis of lung carcinomas, and the cytomorphological features of SCLC with their nuances and subtleties.

Keywords Cardiothoracic pathology; cytology; cytomorphology; lung carcinoma; morphology

Case report

A 94-year-old female presented with shortness of breath, cough, and fatigue. She had a history of invasive ductal breast carcinoma, non-small cell lung carcinoma (NSCLC), and ovarian serous carcinoma. On examination, she had a left pleural effusion, which was aspirated and assessed for malignancy.

The effusion consisted of clear yellow fluid and a blood clot. On microscopy, the specimen on Papanicolaou's (PAP) stain was cellular and showed a mixed inflammatory infiltrate, macrophages, and mesothelial cells. Amongst these were groups and singletons of atypical cells with enlarged and hyperchromatic nuclei that displayed nuclear moulding and increased nuclear-cytoplasmic ratio (Figures 1a and 1b). The morphology was that of a malignant small blue cell tumour.

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Immunocytochemistry was positive for the neuroendocrine marker CD56 (Figure 2), TTF1, had a mutant expression profile for p53, and there was dot-like positivity for cytokeratins such as MNF-116 (Figure 2) and CK7. These malignant cells were negative for Napsin A, WT1, PAX8, GATA3, GCDFP-15, ER, AMACR, CA-125, CK20, and CDX2.

The immunomorphological profile was typical of small cell lung carcinoma (SCLC).

The patient was frail and could not tolerate further investigations. The clinical team discussed the findings with the patient and her family, and all agreed that she was for best supportive care and not for invasive treatment.

Discussion

SCLCs are high grade neuroendocrine tumours accounting for 15% of all lung carcinomas diagnosed worldwide. Most SCLCs develop in heavy smokers, although some arise in non-smokers.[1] Genetically, biallelic inactivation of *TP53* and *RB1* is characteristic of SCLC, and most of these tumours have downregulated Notch signalling.[1,2] Known for rapid progression and early metastasis, SCLCs are usually located centrally in major airways and frequently involve mediastinal lymph nodes. Metastatic spread is common at the time of presentation, but malignant pleural effusions (MPEs) are more common in NSCLC than SCLC.[1] National and international studies have shown MPEs were associated with poorer survival, which further worsen the already poor prognosis of SCLCs.[3,4]

In SCLC, cytology specimens often highlight nuclear features better than tissue biopsies with prevalent crush artefacts.[1] Thus, a methodical approach to interpret various cytomorphological features is required for an accurate diagnosis.

Cell groups and cohesion

Initially, assessment of cell cohesion is helpful in the differential diagnosis. In newly developed effusions, cells of SCLC are usually solitary, but recurrent and long-standing effusions show cohesive clustering or spherical proliferation.[1,5]

Cellular arrangement

Neoplastic cells can be seen in papillary-like formations or three-dimensional groups, and rarely monolayers. Papillary arrangements may not represent a true papillary tumour.[5]

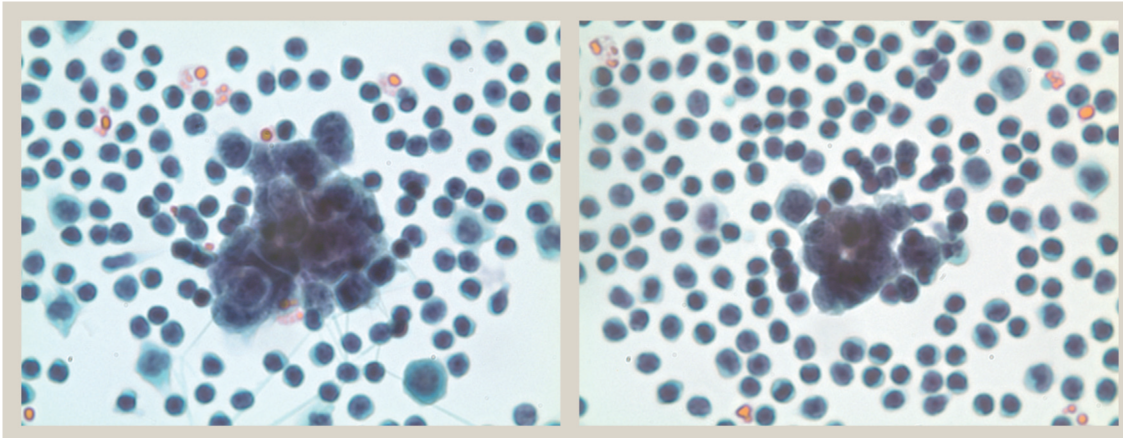

Figure 1 Small cell lung carcinoma. Representative images of neoplastic cells in PAP-stained smears (400X magnification).

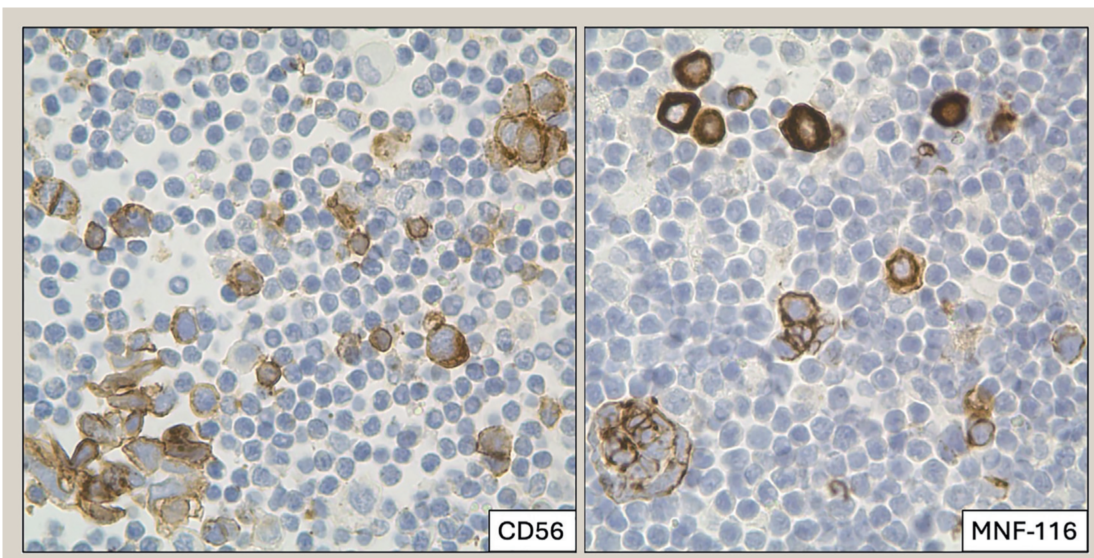

Figure 2 Small cell lung carcinoma. Neoplastic cells expressing immunohistochemical positivity for CD56 and MNF-116 (dot-like) (400X magnification).

Cytoplasm

Cytoplasmic features can be examined better under the Diff-Quik-stained smears (Figure 3). SCLCs often have minimal cytoplasm.[1]

Structures and cytologic features

Unique structures and cytologic features are carefully examined as SCLCs often show characteristics of certain primary tumours. SCLCs can be round to oval, occasionally spindle cells with abundant apoptotic or pyknotic dark nuclei. Mitotic figures are poorly preserved in smears. Usually, a necrotic background is present with prominent chromatin streaking. In alcohol-fixed preparations, the chromatin appears finely or coarsely granular, lacking prominent nucleoli. Nuclear moulding can often be seen.[1,5]

Logistic regression analysis by Sturgis et al. identified nuclear moulding as the most effective criterion for differentiating SCLC from NSCLC, with 3 individual criteria (nuclear moulding, finely granular or "salt-and-pepper" chromatin, and scant delicate cytoplasm) demonstrating over 90% sensitivity and specificity in SCLC.[6]

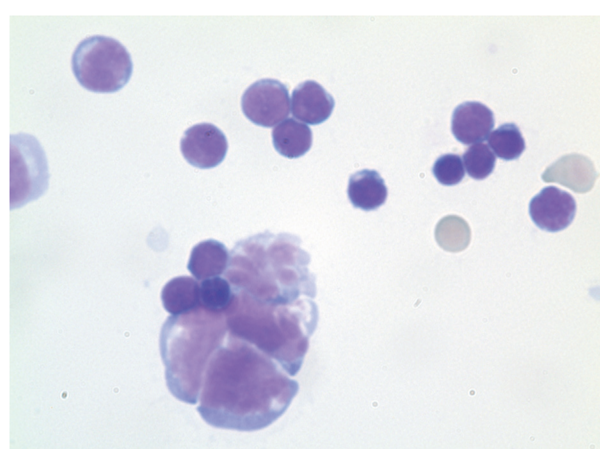

Figure 3 Small cell lung carcinoma. Representative image of neoplastic cells in Diff-Quik-stained smears (400X magnification).

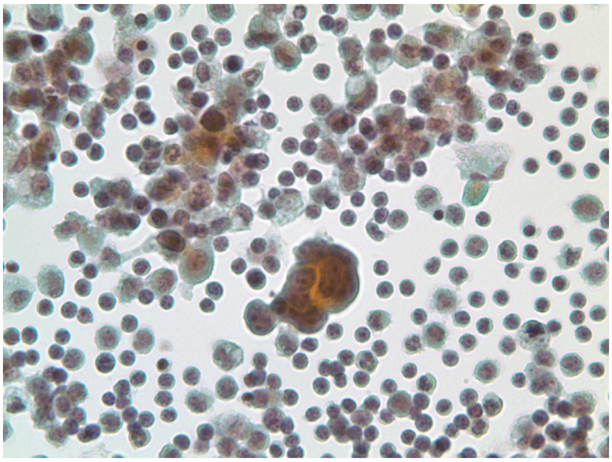

Figure 4 Ovarian serous carcinoma. An example of neoplastic cells (400X magnification).

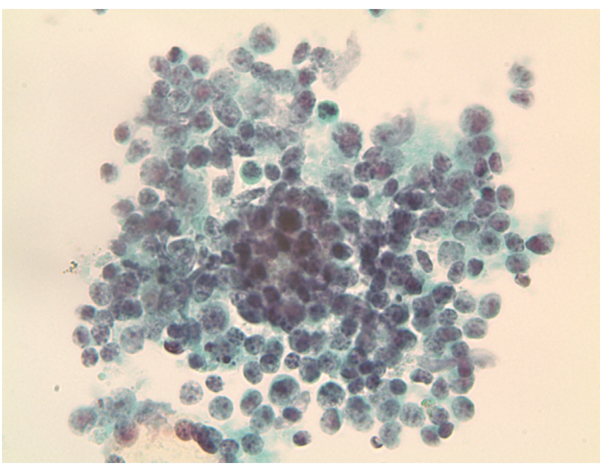

Figure 5 Diffuse large B cell lymphoma. An example of neoplastic cells (200X magnification).

In practice, it is common to encounter cases where findings do not align closely with the literature. There can be nuances in the cytomorphology of SCLC, based on the specimen quality and preservation, which is challenging in cytological evaluation compared to histological examination. In this case report, the cells and nuclei appear large, and the typical features such as a finely granular chromatin and prominent crush artifact are less evident (Figure 1). This leads to difficulties in accurate diagnosis, as the characteristic cytological features of SCLC may be obscured or less pronounced. Additionally, the absence of crush artifact in fluid specimens further complicates the identification of SCLC cells, as this artifact is typically relied upon histologically to aid in the recognition of small round cells.

A differential diagnosis considered was ovarian serous carcinoma given the clinical history and cytomorphology. When deciding for/against this differential, the cytomorphology can appear similar as groups of atypical cells with scant cytoplasm, significant nuclear pleomorphism, prominent nucleoli, and nuclear moulding (Figure 4).

In cases with loss of cell cohesion, the cytomorphology may resemble a lymphoma. Figure 5 is a cytology specimen of a diffuse large B cell lymphoma showing similar morphology to the true diagnosis, including large atypical cells with hyperchromatic nuclei and smooth chromatin, with small indistinct nucleoli. In poorly preserved samples, crushed cells may simulate crush artefact seen in SCLC, and artefactual clustering of cells can mimic nuclear moulding.[7]

The WHO advises that light microscopy is often sufficient for a SCLC diagnosis, and immunostains are not required for confirmation but used to exclude or confirm a differential diagnosis.[1] Our case report exemplifies this diagnostic approach where given the nuances of cytomorphology, despite close interpretation, and complex medical history, warranted the use of immunocytochemistry to confirm the primary tumour and cell lineage.

Conclusion

This case reports a 94-year-old female diagnosed with SCLC on her MPE. The diagnostic approach was discussed in detail, highlighting the importance of cytomorphology in diagnosing SCLCs, as well as their potential subtleties and nuances. To accurately interpret respiratory cytology specimens, one must interpret cytomorphological features with a methodical approach, in the context of the clinical history, relevant radiologic imaging, and if needed, appropriate immunocytochemistry.[5,7] ◆

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Practice points

- In lung malignancy, cytology specimens often highlight nuclear features better than tissue biopsies due to crush artefact
- Classic SCLC cytological features:
  - Small clusters or single round to oval, occasionally spindle cells with minimal cytoplasm
  - Abundant apoptotic or pyknotic dark nuclei with finely or coarsely granular chromatin ("salt-and-pepper"), lacking prominent nucleoli
  - Necrotic background with chromatin streaking or nuclear moulding
- Light microscopy is usually sufficient for diagnosing SCLC, but expect subtleties in the cytomorphology of SCLC in clinical practice. Careful assessment and understanding of these nuances can lead to the correct diagnosis, even without the use of ancillary studies
- Be selective when using immunostains for complex cases to rule out or confirm differentials
- A choice of immunocytochemistry as an adjunct diagnostic tool for SCLCs:
  - Positive: AE1/AE3, CAM5.2, CK7, neuroendocrine markers (e.g. chromogranin, synaptophysin, CD56, INSM1), TTF1 (not specific for pulmonary origin in SCLC)
  - Negative: CD138, CD57, CK20, p63, p40, Napsin A, PAX8
- Differential diagnosis to consider and rule out for SCLC, which requires careful assessment of cytomorphology and appropriate use of immunocytochemistry[1]:
  - Other neuroendocrine tumours, such as large cell neuroendocrine carcinoma and carcinoid tumour
  - Merkel cell carcinoma
  - Basaloid squamous carcinoma
  - SMARCA4-deficient thoracic undifferentiated tumours
  - Small round cell sarcomas, such as Ewing sarcoma, *CIC-DUX4*-rearranged and *BCOR-CCNB3*-rearranged tumours
  - Lymphoma
  - Melanoma

Multiple choice questions

1. Which method is NOT appropriate to differentiate between a SCLC and a carcinoid tumour of the lung?

a. **Ki-67 index**
b. **Morphology**
c. **Cytokeratins**
d. **Number of mitotic figures**
e. **Necrosis**

Correct answer: c

2. Which immunocytochemical profile definitively EXCLUDES a SCLC?

a. **Chromogranin+, Synaptophysin+, CK7+, TTF1-**
b. **Chromogranin+, Synaptophysin+, TTF1+, PAX8+**
c. **INSM+, CK7-, CK20-, TTF1+, Calcitonin-**
d. **INSM+, TTF1+, CK7+, CK20-**
e. **CD56+, Synaptophysin+, TTF1-, CK7+, CK20-, PAX8-**

Correct answer: b

3. Which genetic mutation is most commonly associated with SCLC?

a. **PTEN**
b. **MEN1**
c. **RB1**
d. **MYC**
e. **BRCA1**

Correct answer: c

