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A Curious Case of Clear Cell Morphology in a Patient with Lung Cancer: Diagnostic Challenges

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Abstract: An 82-year-old woman with COPD presented to the emergency department with cough, increasing sputum production, wheezing, and worsening shortness of breath for two weeks. On imaging studies, the patient was found to have a right upper lobe spiculated nodule and an endobronchial lesion with near total occlusion of the right lower lobe bronchus with sub-segmental atelectasis. Bronchoscopy with EBUS-TBNA of subcarinal and right hilar lymph nodes revealed lung cancer with clear cell phenotype. Given the predominance of clear cell morphology, the diagnosis of metastatic renal or ovarian cancer was entertained. However, there was no evidence of renal or ovarian lesions on the PET-CT scan, ruling out the possibility. Salivary gland type lung cancer (STLC), which is responsible for less than 1% of all lung cancer cases in adults, was also considered. The two distinct STLCs that may have similar morphologic appearances are hyalinizing clear cell carcinoma (HCCC) and mucoepidermoid carcinoma (MEC). The other type of tumour in the lung that demonstrates a clear cell phenotype is perivascular epithelioid cell neoplasms or PEComa, which are mesenchymal in origin. Immunohistochemical staining was strongly positive for p63, CK5/6, CK7, CK-LMW, and negative for TTF-1, Napsin A, p16, and CK20. Additional staining, including HMB-45, S-100, and mucicarmine, were also negative. Next-generation sequencing for the salivary gland fusion panel, including *EWSR1-ATF1* fusion and *EWSR1* gene rearrangement for HCCC and *MAML2* gene rearrangements for MEC, was negative. She was diagnosed with non-small cell lung cancer favouring squamous cell carcinoma with clear cell phenotype, a rare entity.

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Introduction

Lung cancer is the number one cause of cancer mortality in the world (Centers for Disease Control and Prevention, 2022). Extensive research into the molecular biology of lung cancer has contributed to the discovery of driver mutations, leading to the development of many targeted therapies. Moreover, improved patient care, such as improved surgical techniques and high-intensity focused radiation therapy, have improved overall survival in patients with lung cancer (Howlader et al., 2020).

Lung cancers are primarily classified as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with the latter representing the majority of newly diagnosed cases (Duma et al., 2019). The NSCLC is subdivided into adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma. Other types of cancers, including salivary gland tumours, sarcomas, and sarcomatoid carcinomas, can also occur in the lungs.

Despite a remarkable improvement in molecular techniques, phenotypic histopathologic characterization of lung cancer is crucial before a battery of immunohistochemical (IHC) stains can be obtained. Appropriate phenotyping can reduce the number of IHC used and save tissue for additional future studies. A "clear cell phenotype" of lung cancer on microscopy has been a source of

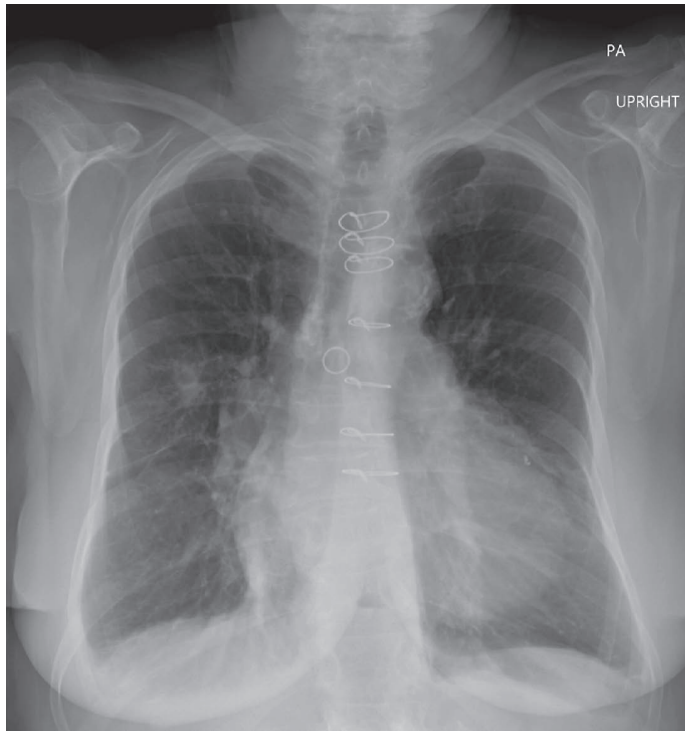

Figure 1 – Posteroanterior chest X-ray showing bilateral hyperinflation with a spiculated right perihilar lung nodule.

confusion for a long time, and a definitive diagnosis of lung cancer type could be challenging. Although initially described as a distinct entity, it is now widely accepted that all lung cancer subtypes can have a clear cell phenotype. Therefore, the 2021 World Health Organization (WHO) classification of thoracic malignancy did not classify "clear cell lung cancer" as a distinct entity. We present the case of an elderly woman with lung cancer for whom a definitive diagnosis of cancer subtype proved challenging due to the presence of "clear cell phenotype".

Case report

An 82-year-old woman presented to the emergency department (ED) with cough, increasing sputum production, wheezing, and worsening shortness of breath for two weeks. The patient was an active smoker with more than a 120-pack-year history. She denied any fever, night sweats, weight loss or loss of appetite. She had no recent history of travel outside the United States and denied any sick contact or any personal history of tuberculosis. Her medical history was significant for chronic obstructive pulmonary disease (COPD), hypertension, and coronary artery disease, for which she had undergone coronary artery bypass graft surgery 20 years ago.

In the ED, she was afebrile with stable blood pressure. However, she was tachycardic, tachypneic, and hypoxemic, requiring 2 l per minute of oxygen to maintain adequate SpO_2. Auscultation of the chest revealed diffuse bilateral wheezing and rhonchi. A chest radiograph revealed bilateral hyperinflated lungs with a spiculated lesion in the right middle lung zone in the peri-hilar area (Figure 1). A computed tomographic angiogram (CTA) of the chest revealed no pulmonary embolism but demonstrated a spiculated nodular lesion in the right upper lobe (RUL) (Figure 2A). An endobronchial lesion with near total occlusion of the right lower lobe (RLL) bronchus with sub-segmental atelectasis was also noted (Figure 2B and C). She was treated with broad spectrum antibiotics

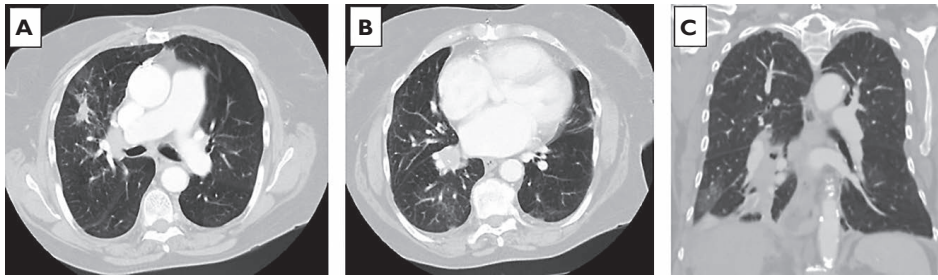

Figure 2 – Axial computed tomography (CT) of the chest showing a spiculated lesion in the right upper lobe (A). Endobronchial lesion nearly occluding the right bronchus intermedius was seen (B). Coronal CT scan showed partial atelectasis of right lower lobe (C).

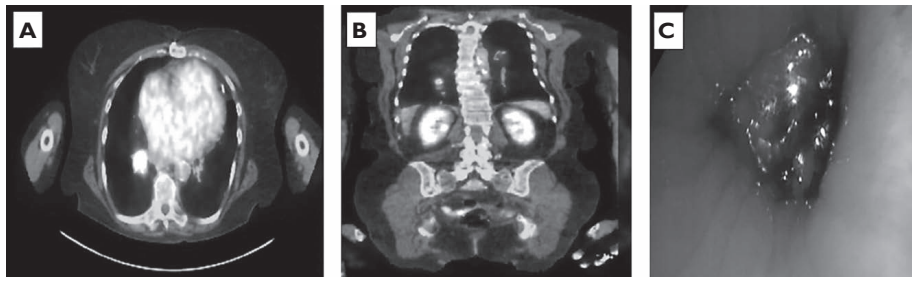

Figure 3 – PET-CT scan showing hypermetabolic endobronchial lesion (A) and right upper lobe lung nodule (B). Bronchoscopy showed fungating endobronchial lesion with near total occlusion of the right lower lobe bronchus and the entrance of the right middle lobe bronchus (C).

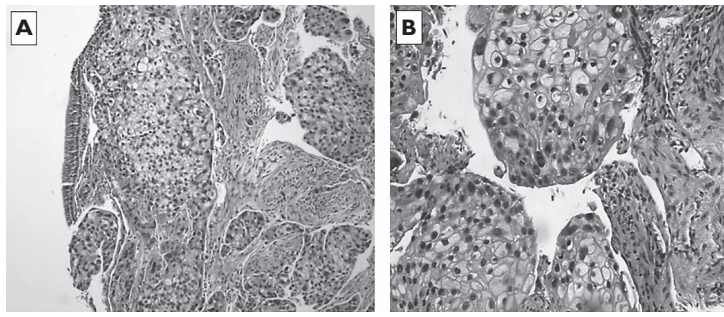

Figure 4 – Hematoxylin and eosin stain of the endobronchial biopsy samples revealed small to moderate sized epithelioid cells arranged in irregular nests and sheets with eosinophilic to clear cytoplasm at 100× (A) and 400× (B) magnification.

and intravenous corticosteroids with clinical improvement and was discharged from the hospital. A subsequent positron emission tomography (PET)-CT scan demonstrated hypermetabolic RLL endobronchial lesion, right hilar lymph node, and equivocal uptake in the subcarinal lymph node. There was no focal extrathoracic fluorodeoxyglucose (FDG) uptake or FDG avidity in the RUL nodule (Figure 3A and B). Bronchoscopic examination revealed an intraluminal polypoid growth in the RLL with near total occlusion of the RLL bronchus and the entrance of the right middle lobe bronchus (Figure 3C). Endobronchial biopsies were obtained from the RLL endobronchial lesion, and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed from stations 7 (subcarinal) and 10R (right hilar). The histopathologic analysis of the endobronchial biopsies showed clear cells arranged in irregular nests and sheets without gland formation or keratinization (Figure 4A and B). TBNA from station 7 demonstrated cells with similar morphology.

Given the predominance of clear cell morphology, the diagnosis of metastatic renal or ovarian cancer was entertained. However, there was no evidence of renal or ovarian lesions on the PET-CT scan, ruling out the possibility. Salivary gland type

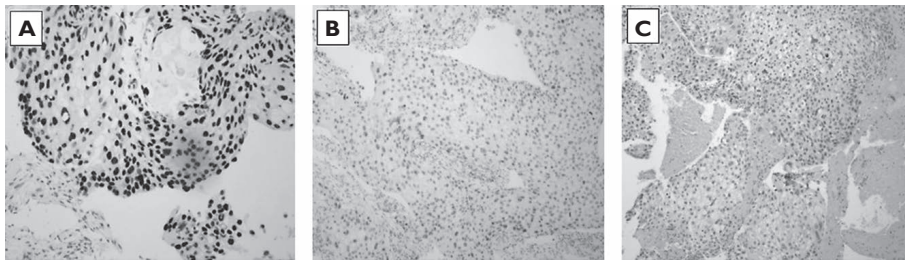

Figure 5 – Immunohistochemical staining showed strong p63 positivity (A), negative TTF-1 (B) and mucin (C) staining.

lung cancer (STLC), which is responsible for less than 1% of all lung cancer cases in adults, was also considered (Macarenco et al., 2008). The two distinct STLCs that may have similar morphologic appearances are hyalinizing clear cell carcinoma (HCCC) and mucoepidermoid carcinoma (MEC). The other type of tumour in the lung that demonstrates a clear cell phenotype is perivascular epithelioid cell neoplasms or PEComa, which are mesenchymal in origin. Immunohistochemical staining was strongly positive for p63, CK5/6, CK7, CK-LMW, and negative for TTF-1, Napsin A, p16, and CK20 (Figure 5). Additional staining, including HMB-45, S-100, and mucicarmine, were negative. The clear cytoplasm of these cells was the result of glycogen deposition, which was periodic acid Schiff (PAS) positive (Figure 6). Immunohistochemistry was performed by MAWD Pathology Group, Columbia, MO, USA (specific details of methods utilized can be obtained by e-mail request to the corresponding author).

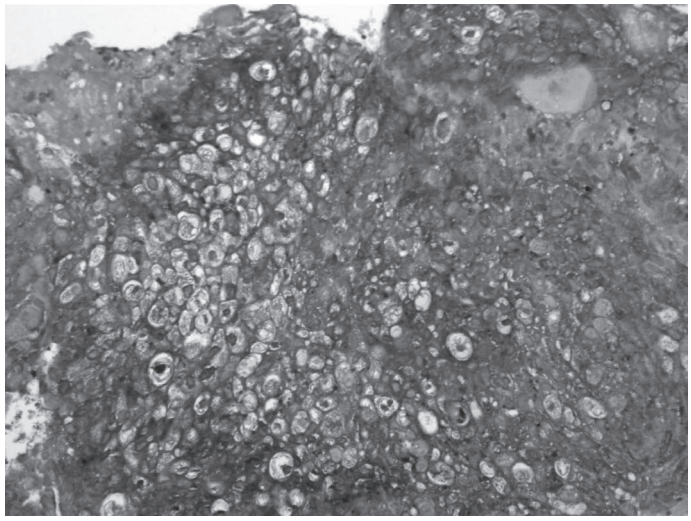

Figure 6 – Periodic acid Schiff (PAS) staining demonstrated strong positivity from the endobronchial biopsy sample (400× magnification).

The RNA-based Next Generation Sequencing (NGS) for salivary gland fusion panel (Neo Genomics), which detects translocations and fusion of a number of specific genes, including *EWSR1-ATF1* fusion and *EWSR1* gene rearrangement for HCCC and *MAML2* gene rearrangements for MEC, was negative. Further review of the slides showed moderate nuclear pleomorphism, with a minority of cancer cells showing giant, highly pleomorphic nuclei, inconsistent with low-grade malignancy, such as HCCC. Given the strong positivity of p63, CK5/6, the patient was diagnosed with NSCLC, favouring SCC, with clear cell type.

Discussion

We have presented a case of NSCLC favouring SCC with clear cell phenotype. SCC with clear cell type is a rare entity that can pose a significant diagnostic challenge. Although a definitive diagnosis of a lung cancer type solely based on morphologic examination could, in some cases, be possible from resected specimens, such confidence is generally lower from small sample biopsies. As approximately 70% of lung cancers are diagnosed at an advanced stage, it is crucial to consider the IHC data for a more definitive diagnosis from small sample biopsies (Travis et al., 2011). Clear cell morphology of lung cancers has been a rare entity and can be a source of confusion among clinicians and pathologists.

Morphologic clear cell pattern can be present in both adenocarcinoma and SCC, and the latest 2021 WHO classification recommends the mention of "clear cell features" in the pathology report while describing this entity (Nicholson et al., 2022). However, SCC with clear cell features typically involves only a part of the tumour histology.

It is crucial to differentiate between adenocarcinoma and SCC of the lung with clear cells, HCCC of lung origin, and metastatic salivary gland tumour to the lung. Additionally, renal cell cancer, ovarian cancer, PEComa, and MEC can have similar histopathology. A PET-CT scan, commonly performed in these patients, can easily identify salivary gland, ovarian and renal neoplasms. IHC plays a crucial role in the exclusion of other competing diagnoses. TTF-1 and Napsin A are markers for adenocarcinoma of lung origin. Markers for epithelial cell lineage, such as CK 5/6 and 7, exclude PEComa and sarcomas, such as clear cell sarcoma. Additionally, PEComas stain positive for HMB-45 and sometimes for S-100 (Zarbis et al., 2007). MEC can have clear cell morphology due to the presence of mucin-impregnated clear cells but can be differentiated by morphologic appearance and mucicarmine stain (Shen and Che, 2014).

Differentiation between SCC and HCCC could prove challenging as the IHC markers are similar. Both SCC and HCCC can have positive p63, P40, and CK5/6, therefore making the diagnosis based on IHC alone difficult (Zhang et al., 2022). In HCCC, histopathologic analysis reveals round to ovoid cells with clear to

eosinophilic cytoplasm and inconspicuous nuclei. The cells are arranged in cords, nests, trabecular and hyalinizing patterns (Wang et al., 2021). Nuclear features of high-grade malignancy are typically absent. The cytoplasm to nuclear ratio is lower in clear cells compared to eosinophilic cells. In contrast, SCC demonstrates a higher degree of nuclear pleomorphism and features suggestive of aggressive malignancy. Molecular studies for *EWSR1* gene rearrangements and *EWSR1-ATF1* gene fusion are diagnostic for HCCC (Takamatsu et al., 2018). Clinically, HCCC appears to have an indolent course, with the majority of reported cases having no evidence of metastatic disease. The HCCC arises from the submucosal minor salivary glands in the airways and, therefore, is commonly endobronchial. Surgical resection could be curative (Shah et al., 2015).

Conclusion

All subtypes of NSCLC can have a clear cell morphology. However, clear cell morphology is extremely rare in patients with squamous cell cancer. Other neoplasms with similar morphologic appearance, such as metastatic ovarian and renal cell cancer, adenocarcinoma of the lung, HCCC, mucoepidermoid carcinoma, and PEComa need to be excluded by immunohistochemistry and molecular testing before reaching the definitive diagnosis.

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