Primary Lung Hyalinizing Clear Cell Carcinoma: A Diagnostic Challenge in Biopsy

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Case Report

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Abstract

Introduction: Hyalinizing clear cell carcinomas (HCCCs) are rare, low-grade, malignant tumours. They most commonly involve the minor salivary glands of the head and neck. HCCC that occurs in uncommon locations and examining samples from small biopsy pose a diagnostic challenge for most pathologists.

Case presentation: We herein report a primary pulmonary HCCC diagnosed by small biopsy and summarize its histologic, immunophenotypic, and molecular features along with a review of 11 previously reported cases to emphasize the potential diagnostic pitfalls.

Conclusions: Small biopsy diagnosis of primary pulmonary HCCC is fall from ideal. A collection of mimics needed to be ruled out. Awareness of the key morphologic features of pulmonary HCCC combined with essential immunohistochemistry and molecular tests contributes to the correct diagnosis.

Introduction

Primary pulmonary salivary gland-type cancers are rare, accounting for under 1% of all lung tumours[1]. Along with mucoepidermoid carcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma, primary pulmonary hyalinizing clear cell carcinoma (HCCC), as a new entity, has been included in the 2021 WHO classification of pulmonary tumours[1].

The HCCC is a rare salivary gland tumour. It was first described in 1994 by Milchgrub et al.[2]. It most commonly involves the minor salivary glands of the head and neck, especially the palate and oral base [3]. When it occurs in uncommon locations, such as the bronchus or nasopharynx oropharynx, or when pathologists must examine a small biopsy sample, the diagnostic challenge can be considerable. To date, 11 primary pulmonary HCCC cases from eight articles have been reported[4–11]. However, only one case was diagnosed from a small biopsy [8]. Herein, we report an additional case of primary pulmonary HCCC diagnosed by small biopsy with an emphasis on the potential diagnostic pitfalls.

Case Presentation

Clinical history:

A 57-year-old Asian woman was admitted due to a finding of pulmonary mass in the right lower lobe upon physical examination. The patient, an ex-smoker (10 cigarettes a day × 20 years), had no specific medical history otherwise. The chest computerized tomography (CT) scan (Fig. 1A) revealed a 2.8-cm dorsal segment of the right lower lobe mass. A positron emission tomography scan (PET-CT) showed central hypermetabolic activity only in the right lower lobe, raising suspicions of a neoplastic process (Fig. 1B). Bronchoscopy revealed a dorsal segment of the right lower lobe mass (Fig. 1C), and a biopsy was performed.
Histopathology and ancillary testing:

The hematoxylin and eosin (HE)–stained sections of the biopsy yielded a neoplasm composed of atypical small-to-medium sized epithelioid cells with light eosinophilic to clear cytoplasm and round-to-oval nuclei and inconspicuous nucleoli lacking significant pleomorphism and mitotic activity. The tumour cells were arranged in irregular nests, cords, trabeculae (Fig. 2A) and tubular pattern with a loose myxoid stroma (Fig. 2B). Focally, the tumour cells appeared to connect to the basal layer of the bronchial epithelium and lacked keratinization and in situ carcinoma of the overlying epithelium (Fig. 2C). Immunohistochemistry showed the tumour cells to be positive for CK7 (Fig. 2D); most tumour cells were found to be positive for p40 (Fig. 2E), ck5/6, p63 and negative for PAX8, CD10, RCC, CAIX, TTF1, S100, CDX2, SATB2, CK20, calponin, and SMA. An initial diagnosis of low-grade mucoepidermoid carcinoma with clear cell feathers was rendered. Because mucoepidermoid carcinoma of the lung is rare and involves specific molecular changes \[12\], molecular testing was performed. Fluorescence in situ hybridization (FISH) was negative for MAML2 gene rearrangement (Fig. 3A). These results prompted a histologic re-review of the case, a literature search, and consultation with an outside expert. A focal hyalinized stroma appreciated by Dr. Zhou prompted the potential diagnoses of HCCC or myoepithelial tumours. Subsequently, additional EWSR1 gene rearrangement and EWSR1-ATF1 gene fusion tested by FISH confirmed the presence of the EWSR1 gene rearrangement (Fig. 3B) and EWSR1-ATF1 gene fusion (Fig. 3C). A final diagnosis of HCCC of the lung was ultimately rendered.

A right lower lobectomy with hilar and mediastinal lymphadenectomy was performed. Grossly, a firm, solitary, well-circumscribed, 2.8-cm tan mass, 1.0 cm from the bronchial margin, was identified (Fig. 4A). H&E-stained sections of the mass showed classical HCCC morphology: tumour cells with light eosinophilic to clear cytoplasm and inconspicuous nucleoli lacking significant pleomorphism and mitotic activity. The tumour cells grew in cords, trabeculae, and nests in a hyalinizing acellular stroma (Fig. 4B). They had infiltrated the periphery alveolar tissue and showed aggregates of chronic inflammation in the periphery of the tumour. No angiolymphatic invasion, perineural invasion, pleural involvement, or necrosis were observed. Immunohistochemistry and FISH results were the same as those of the biopsy. The metastatic foci was found in 1 out of 12 lymph nodes. (Fig. 4C). All surgical margins were negative. At the time of this report, the patient was free of any local recurrence. She was free of metastasis at her 3-month follow-up, despite receiving no additional therapy after surgery.

Discussion

To our knowledge, only eleven cases of HCCC arising in the lung have been reported in the literature to date[4–11]. Three cases had biopsy results, and two of them first diagnosed by small biopsy were squamous cell carcinoma[7–8]. Four of the eleven excised specimens were initially diagnosed as squamous cell carcinoma or mucoepidermoid carcinoma \[4–5, 11\]; this indicated that the diagnosis of HCCC was difficult, especially from small biopsy samples. The small biopsy collected from our case showed that the tumour cells had undergone infiltrating growth and lacked significant pleomorphism and mitotic activity, indicating a low-grade carcinoma. Most tumour cells had light eosinophilic cytoplasm,
and a small number of clear cells prompted us to consider several types of salivary gland-type tumours: low-grade mucoepidermoid carcinoma with clear cells[13], myoepithelial tumor[14], HCCC[4] and metastatic clear cell renal cell carcinoma or non-small-cell lung carcinoma. Immunohistochemistry result showed that the tumour cells were only positive for CK7, p40, ck5/6, and p63, which excluded metastatic clear cell renal cell carcinoma and lung adenocarcinoma. The mild cytological atypia and the lack of significant mitotic activity would have been unusual for the primary squamous cell carcinoma of the lung. Additionally, there was no evidence of squamous differentiation or in situ squamous carcinoma of the overlying epithelium; thus, we excluded squamous cell carcinoma. The initial diagnosis was low-grade mucoepidermoid carcinoma with prominent clear cells, given the homogeny of the cell population and the lack of mucous cells. Assessment of MAML2 by break-apart fluorescence in-situ hybridization, a highly sensitive and specific test for mucoepidermoid carcinoma, indicated that the tumour was intact. Based on these results, we excluded low-grade mucoepidermoid carcinoma. Primary myoepithelial tumours in lungs are very rare [14]. They encompass benign myoepithelioma and malignant myoepithelial carcinoma. The distinction between myoepithelioma and myoepithelial carcinoma is largely based on morphologic features. Features that favor carcinoma include cytologic atypia, increased mitotic activity, necrosis, infiltrative growth, and metastatic disease[14, 15]. Myoepithelial tumours of salivary glands and HCCC were part of our diagnostic differentiations. They can have similar tumour cell morphology, growth pattern, and hyalinized, myxoid/hyalinized, or chondroid/hyalinized stroma[14]. Considering the infiltrative growth pattern of our case, we excluded benign myoepithelioma. Other morphologic data and the tumour stroma features indicated that it could be clear cell myoepithelial carcinoma or HCCC. However, myoepithelial carcinoma usually has more pleomorphism and, unlike HCCC, shows true myoepithelial differentiation with the expression of S100, SMA, and sometimes calponin. The EWSR1 rearrangement has been documented in both these types of cancers, but Skálová A et al.[16] found that clear cell myoepithelial carcinoma with EWSR1 rearrangement frequently involved PLAG1 gene fusions but no EWSR1 fusion transcripts, while EWSR1-ATF1 gene fusion has been observed in most cases of HCCC[17]. We used FISH detection on the EWSR1-ATF1 chimeric gene. Results confirmed the presence of EWSR1-ATF1 fusion. Based on the tumour cell morphology and immunohistochemistry and FISH results, we confirmed the diagnosis of HCCC. Because there have been few case reports of HCCCs metastasizing to cervical lymph nodes and the lungs[18], we performed PET-CT evaluation. This confirmed the lungs to be the sole tumour site. Thus, we concluded that the tumour represented salivary-gland-type primary HCCC of the lung. The patient underwent surgery, and the excised specimens showed classical HCCC morphology. Immunohistochemistry and FISH characteristics were consistent with the diagnosis made based on this small biopsy.

In conclusion, it was extremely difficult to diagnose HCCC arising in the lungs by biopsy. It requires careful assessment of the morphology and adequate testing, such as immunohistochemistry and molecular testing.

Abbreviations
HCCC: Hyalinizing clear cell carcinoma; PET-CT: positron emission tomography scan; HE: hematoxylin and eosin; FISH: Fluorescence in situ hybridization.

Declarations

Ethics approval and consent to participate

The research was prospectively reviewed and approved by Anhui Wanbei Coal-Electricity Group General Hospital.

Consent for publication

Not applicable.

Availability of data and materials

Data archiving is not mandated but data will be made available on reasonable request.

Competing interests

All authors declare no conflict of interest.

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Authors’ contributions

All authors contributed to the writing of the manuscript and read and approved the final manuscript.

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Figures

Figure 1
A: Chest CT scan revealed an interval enlargement of a 2.8-cm dorsal segment of the right lower lobe mass (red arrow). B: PET-CT showed central hypermetabolic activity only in the right lower lobe mass (red arrow). C: Bronchoscopy revealed a dorsal segment of the right lower lobe with a possible cancerous mass (red arrow).

Figure 2

A: The tumor cells arranged in irregular nests, cords, trabeculae, and tubular shapes with loose mucinous stroma and focal stroma hyalinized (red arrow) (HEx 40). B: Atypical small-to-medium-sized epithelioid cells with light eosinophilic to clear cytoplasm lacking significant pleomorphism and mitotic activity arranged in irregular nests, cords, trabeculae, and tubular patterns (red arrow) with a loose myxoid stroma. C: (HEx 200). Focally, the tumor cells appeared to be connected to the basal layer of the bronchial epithelium. D: Immunohistochemistry revealed that the tumor cells were positive for CK7. E: Immunohistochemistry revealed that most of the tumor cells were positive for p40.

Figure 3

A: Fluorescence in situ hybridization (FISH) was negative for MAML2 rearrangement (the MAML2 locus is rearranged in 2% of neoplastic cells as characterized by one green, one red, and one fusion signal). B: Fluorescence in situ hybridization (FISH) was positive for EWSR1 gene rearrangement (the EWSR1 locus is rearranged in 25% of neoplastic cells as characterized by one green, one red, and one fusion signal). C: Fluorescence in situ hybridization (FISH) was positive for EWSR1-ATF1 fusion (EWSR1-ATF1 fusion in 32% of neoplastic cells as characterized by one green, one red, and two fusion signal).
Figure 4

A: The cut surface revealed a firm, solitary, well-circumscribed, 2.8-cm tan mass, 1.0 cm from the bronchial margin (red arrow). B: Atypical small-to-medium sized epithelioid cells with light eosinophilic to clear cytoplasm embedded in a hyalinized stroma (the red arrow indicates bronchial cartilage). C: The tumor cells that had metastasized to the lymph nodes showed the same morphology as the primary tumor.