

CASE REPORT

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Hyalinizing clear cell carcinoma of the lung: a case report and literature review

Yu-Ju Su¹, Yun-Shao Wu², Cheng-Hung How^{2*} and Min-Shu Hsieh^{3,4}

Abstract

Background Primary pulmonary hyalinizing clear cell carcinoma (HCCC) is an exceedingly rare tumor with unique clinicopathological features, posing major diagnostic challenges.

Case presentation We present a case of a 74-year-old woman with a lung nodule incidentally detected in the right middle lobe (RML) through ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) imaging. Through comprehensive evaluations by thoracic surgeons, she underwent video-assisted thoracic surgery of RML lobectomy to excise the lung nodule. Subsequent histopathological and immunohistochemical analyses confirmed the nodule as HCCC. She was discharged without any postoperative complications. No recurrence has been observed after two years of follow-up. This case underscored the importance of comprehensive imaging modalities and pathological analysis in the management of primary pulmonary HCCC.

Conclusions This report highlights the critical role of imaging techniques and pathological analysis in diagnosing primary pulmonary HCCC, with this case demonstrating the essential value of ¹⁸F-FDG PET/CT integration.

Keywords ¹⁸F-FDG PET/CT imaging, Diagnosis, Hyalinizing clear cell carcinoma, Immunohistochemistry

Background

Hyalinizing clear cell carcinoma (HCCC) is an exceptionally rare tumor, first documented in the salivary glands, particularly in the palate and tongue [1, 2]. Only a limited number of cases have been reported [1, 3]. It poses significant diagnostic and therapeutic challenges due to its clinical presentation and overlapping features with other lung malignancies [1, 2]. HCCC commonly arises near

bronchial glands and is often discovered incidentally due to its asymptomatic nature [1]. Nevertheless, HCCC has distinct histopathologic features from other lung malignancies that help establish its unique diagnosis early on, such as clear cells within a hyalinized stroma, positivity for CK7 and p63, negativity for TTF-1 and SOX10, and unique EWSR1 rearrangements [1].

Conversely, positron emission tomography (PET) with ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) integrated with computed tomography (¹⁸F-FDG PET/CT) has emerged as a powerful imaging tool for cancer detection [4]. ¹⁸F-FDG PET/CT offers synergistic advantages, including enhanced sensitivity for detecting subtle tumor masses, improved accuracy in differentiating malignancy, as well as detection of distant metastatic tumors [4, 5]. By combining metabolic information from PET with anatomical details from CT, this integrated imaging approach facilitates early detection and precise diagnosis.

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We present a case of primary pulmonary HCCC diagnosed using ^{18}F -FDG PET/CT imaging. The primary objective of this study was to illustrate the diagnostic process, encompassing the utilization of ^{18}F -FDG PET/CT, and to conduct a detailed examination of the clinicopathological characteristics, immunophenotype, and molecular features specific to lung HCCC. With this approach, our goal is to improve the differential diagnosis of pulmonary HCCC and pave the way for future research into the potential relationships between these characteristics and their prognostic implications.

Case report

A 74-year-old non-smoking woman with no chronic systemic diseases, illness and does not take any regular medications was reported. She was a salesperson working in smoke-free environment. Her father had passed away from lung cancer forty years previously. Given her family history of lung cancer, she underwent periodic health assessments, including low-dose computed tomograph (LDCT) screenings in 2014, 2015, 2020, and 2022, with no abnormalities detected by the radiologists. With her own growing concern about hereditary cancer, she proactively underwent an additional PET/CT scan in November 2022. The PET scan indicated mild ^{18}F -FDG hypermetabolism in the right middle lobe (RML) nodule, with a standardized uptake value (SUV) of 1.4 (Fig. 1). No other lesions were detected based on the image results, supporting the RML nodule as an isolated finding. Through comprehensive evaluations by thoracic surgeons, in late 2022, she underwent video-assisted thoracic surgery of RML lobectomy to excise the lung nodule. The specimen was submitted for pathological examination, which revealed histopathological features of a peri/endobronchial tumor with tumor cells containing clear cytoplasm embedded within a hyalinized matrix (Fig. 2).

Immunohistochemistry revealed that the tumor cells displayed positivity for p63 and CK7, while negative for TTF-1 and SOX10 (Fig. 3). Additionally, Ewing Sarcoma breakpoint region 1/EWS RNA binding protein 1 (*EWSR1*) break-apart fluorescence in situ hybridization (FISH) demonstrated break-apart signals, indicating *EWSR1* gene translocation (Fig. 4). These findings conclusively supported the diagnosis of HCCC.

The patient was discharged without any postoperative complications and continued outpatient follow-up. Analgesics were used for about a week post-surgery, with no further medications needed. The patient underwent chest CT scans every six months, along with annual brain MRI and bone scans. Currently, two years post-surgery, there is no evidence of cancer recurrence.

Discussion

HCCC in the literature

HCCC was initially identified in 1994 and is recognized as a low-grade malignant neoplasm with a propensity for local recurrence and rare metastasis [6].

Primary pulmonary HCCC was initially documented in 2015 [7], and it is believed to originate from the bronchial submucosal glands [8]. To date, according to a previous cohort [1], 22 cases have been reported, representing less than 1% of all lung tumors. Among these cases, initial diagnosis accuracy varied, with 12 cases correctly diagnosed upon initial assessment, while others encountered diagnostic challenges [1].

Demographically, primary pulmonary HCCC typically affects middle-aged to older adults, with reports ranging from 32 to 75 years (median: 55 years; average: 53 years) [1, 3]. The ratio of male to female is 9:14 [1, 3], suggesting a slight female predominance. Smoking and familial history may be a risk factor, yet its definite association remains uncertain. Most patients present with non-specific clinical manifestations and lack apparent symptoms, with only a few experiencing respiratory symptoms such as cough and shortness of breath.

Radiologic imaging

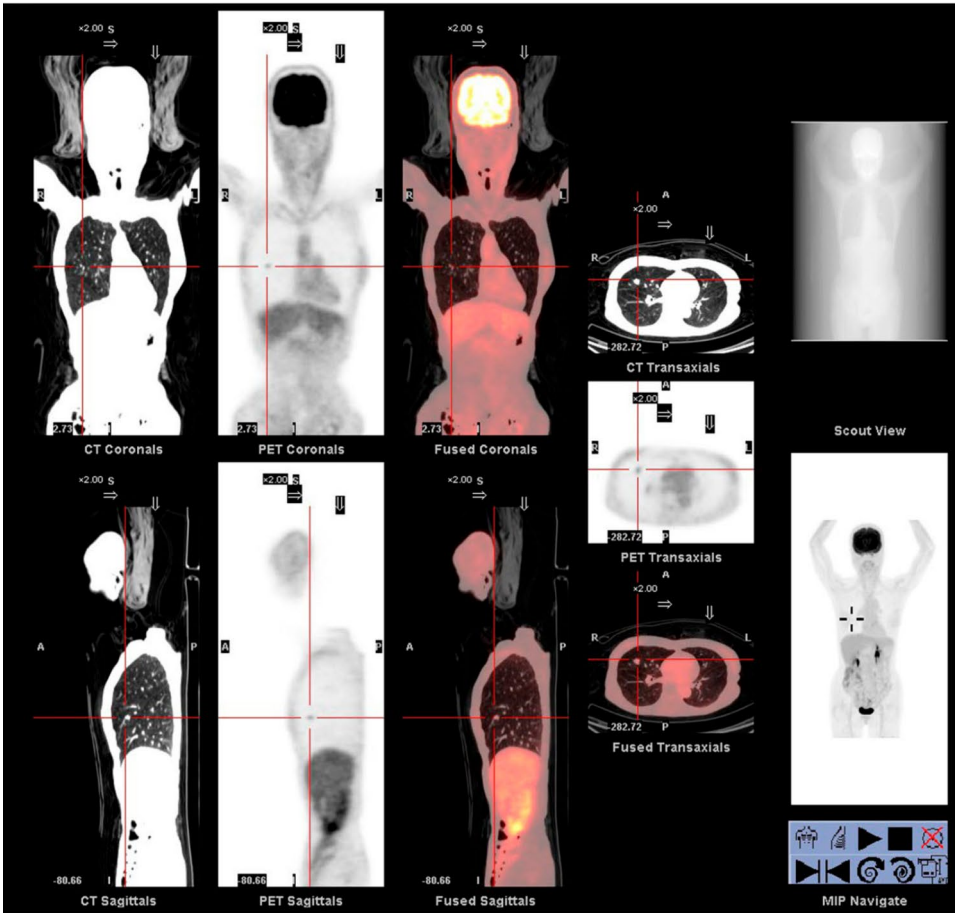
A recent report by Thakur et al. (2023) [9] presents a series of five primary pulmonary HCCC cases. All patients they identified were nonsmokers; three presented with symptoms, while two cases were incidentally detected during routine health screenings. In contrast, our case is distinct due to the proactive use of ^{18}F -FDG PET/CT for diagnosis, prompted by the patient's family history of lung cancer and personal concern despite no symptom.

Unlike early-stage lung adenocarcinoma, particularly those with lepidic morphology, which often present as ground-glass opacities on CT scans, primary pulmonary HCCC typically manifests as a well-defined solid lung nodule on chest CT images. Because HCCC originates from bronchial submucosal glands, the tumor often grows peri/endobronchial, potentially leading to the destruction of the surrounding bronchial tissue. Accordingly, distinguishing the tumor from surrounding bronchial tissue may be challenging based solely on CT imaging, as smaller nodules may resemble normal vascular structures on LDCT, making detection and identification difficult. This was the situation in the present case.

With the development of functional imaging techniques using nuclear medicine, such as ^{18}F Fluoro-deoxy-glucose (^{18}F FDG), physicians have greater confidence in diagnosing indolent malignancies and thus improving decision-making. Using ^{18}F FDG, PET has emerged as a valuable tool for pulmonary malignancy evaluation. Our case echoed that PET/CT has a potential role in early



A



B

Fig. 1 (A) The chest CT imaging; an 8.8 mm solid nodule in RML. (B) The PET/CT scan revealed mild ^{18}F -FDG hypermetabolism with an SUV of 1.4

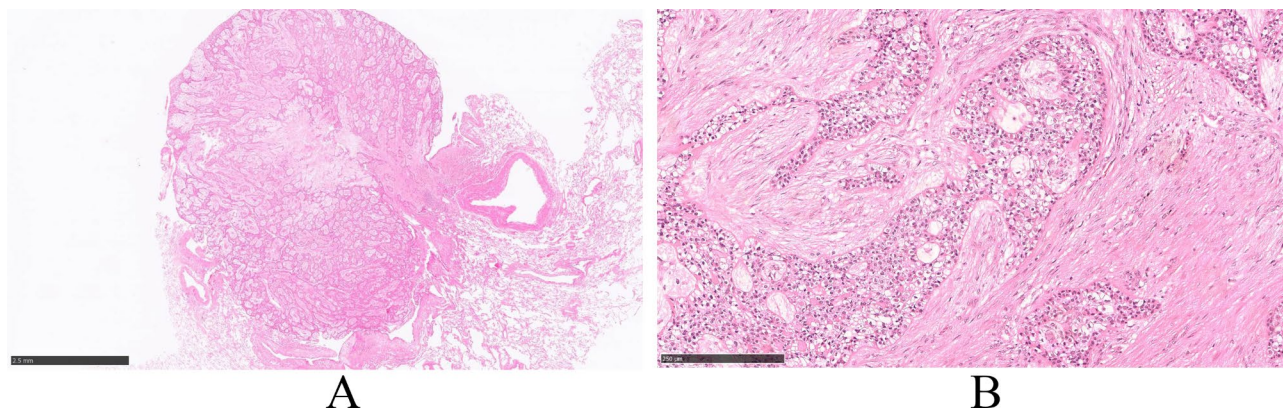


Fig. 2 Histopathologic finding: (A) peri/endobronchial tumor (B) clear tumor cells infiltrating within the hyalinized stroma. Digital image with scale bar in the bottom left corner ((A): scale bar indicating 2.5 mm; (B): scale bar indicating 250 μm)

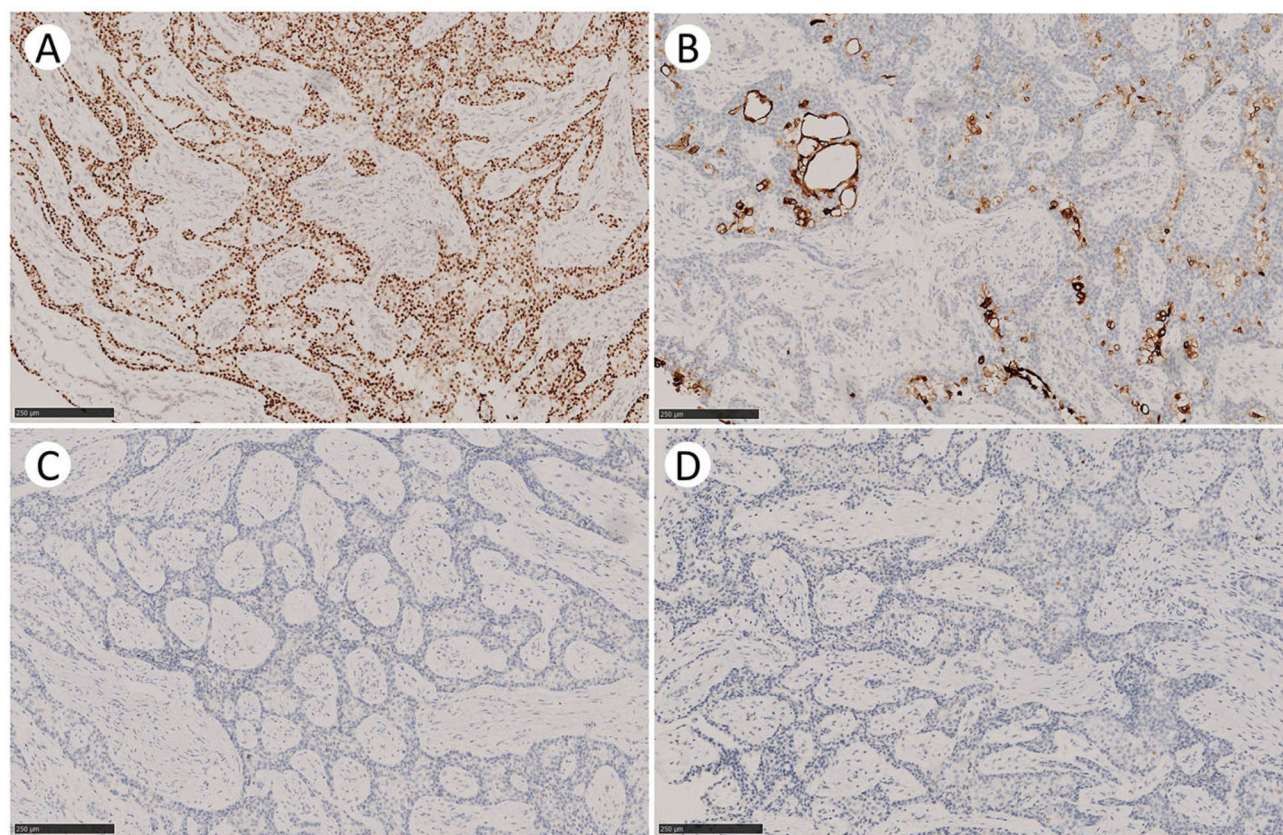


Fig. 3 Immunohistochemical staining displaying positive staining for (A) p63 and (B) CK7, and negative staining for (C) TTF-1 and (D) SOX10. Digital image with scale bar indicating 250 μm in the bottom left corner

detection, early management, and further preventing disease progression.

Histopathological, differential diagnosis, and molecular analysis

HCCC typically comprises cells with clear-to-pale eosinophilic cytoplasm or basaloid cells with scant cytoplasm. The proportion of the characteristic clear cells or hyalinized stroma varies, and sometimes only rare clear cells

can be observed [1, 3, 8]. Its diagnosis is difficult, especially when it develops in organs other than minor salivary gland areas.

Immunohistochemistry commonly reveals positive staining for CK7, p63, p40, and CK5/6 in tumor cells, while staining for TTF-1, napsin A, chromogranin A, synaptophysin, S-100, and SOX10 is typically negative [1, 10, 11]. The Ki67 proliferation index is notably low [1]. In conclusion, HCCC lacks specific immunohistochemical

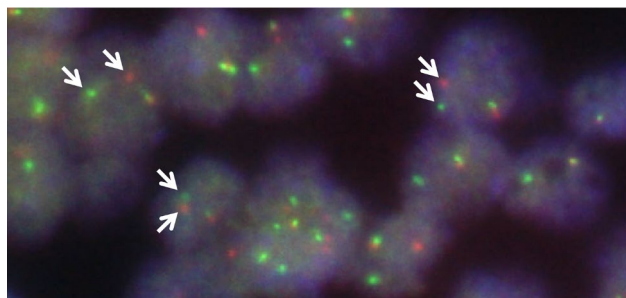


Fig. 4 *EWSR1* break-apart FISH analysis showed *EWSR1* rearrangement, as indicated by the arrows depicting separated red and green signals. Abbreviations CT, computed tomography; PET/CT: positron emission tomography/computed tomography; 18F-FDG: ¹⁸F-fluorodeoxyglucose; SUV: standardized uptake value; RML: right middle lobe; FISH: fluorescence in situ hybridization

markers, leading to immunophenotypic overlapping in differential diagnoses.

The differential diagnosis of primary pulmonary HCCC includes mucoepidermoid carcinoma (MEC), squamous cell carcinoma (SCC), adenocarcinoma with clear cell features, metastatic clear cell renal cell carcinoma, and tumors of myoepithelial differentiation [12].

Recent studies have identified characteristic molecular changes in HCCC, the *EWSR1* gene rearrangements [1, 11]. Although the gene rearrangement of *EWSR1* can occur in both HCCC and myoepithelial carcinoma, the fusion partners are different. In HCCC, *EWSR1::ATF1* fusion was commonly found, followed by *EWSR1::CREM* fusion [1, 13]. Instead, the fusion partners in myoepithelial carcinoma are *POU5F1*, *PBX1*, and rare partners like *ZNF444* [14]. Recently, Wu, Y.L. et al. performed NGS with the 425-gene panel, which revealed an unreported *IRF2::NTRK3* fusion at the DNA level; however, it was not detected at the RNA level via RNA sequencing [1]. A notable distinction from MEC is the absence of Mastermind Like Transcriptional Coactivator 2 (*MAML2*) translocation in HCCC, as *MAML2* rearrangement is typically observed in MEC [15]. SCC has no association with above gene fusions. With the recognition of this specific *EWSR1* rearrangement in HCCC, difficult cases can now be diagnosed through molecular tests.

The report by Thakur et al. [9] also showed uniform positivity for markers such as p63 and p40, negative results for TTF-1 and SOX10, and the presence of *EWSR1* rearrangements in all cases. Feng et al. (2023) [16] describe two cases with distinct histopathologic features—pseudopapillary structures and abundant mucus-filled cysts—highlighting the morphological variability of HCCC and the importance of molecular testing for *EWSR1::ATF1* fusion to secure an accurate diagnosis. Kawachi et al. (2024) [17] highlight the utility of RT-PCR in detecting *EWSR1::ATF1* fusion to distinguish HCCC from similar tumors, emphasizing the importance of

genetic confirmation when histopathology and immunohistochemistry are inconclusive. Additionally, Li et al. (2023) [18] document a unique case of HCCC coexisting with vocal-cord squamous cell carcinoma (SCC), further emphasizing that NGS can be a valuable diagnostic tool in cases where HCCC might be confused with SCC or other malignancies due to overlapping histologic features. Lastly, Wang et al. (2024) [19] conducted a comprehensive literature review on pulmonary HCCC, emphasizing the *EWSR1::ATF1* fusion gene as a critical diagnostic marker and noting surgery as the primary treatment approach due to the tumor's generally indolent nature.

In our case, the immune profile had similar findings to other studies. Further FISH testing demonstrated the recurring *EWSR1* translocation. Together, these findings confirmed the diagnosis of HCCC.

Treatment and prognosis

Pulmonary HCCC demonstrates a great prognosis. Due to its rarity, no standardized treatment approach exists. Depending on the tumor location, surgical resection of the tumor with negative surgical margins is the main treatment of choice. Lobectomy was the most common option in the reported cases [1–3, 11]. Though most are indolent, nodal, lung-to-lung metastasis, or even distant metastatic to bone can still happen [1, 10, 11]. Patients with HCCC are encouraged to have long-term follow-up due to still having risks of delayed local recurrence and metastasis [10, 20].

The absence of recurrence at the 2-year follow-up in our case further supports the favorable prognosis reported in the HCCC literature.

Limitations

This case report highlights significant diagnostic insights for primary pulmonary HCCC, but several limitations should be acknowledged. First, the findings from a single case may not be broadly generalizable to all patients with this tumor type. The rarity of pulmonary HCCC, along with the absence of standardized treatment guidelines, leaves long-term outcomes and recurrence patterns unclear due to limited literature and follow-up data. Continuous reports are necessary to better understand the optimal management and long-term prognosis for this rare tumor.

Conclusions

¹⁸F-FDG PET/CT imaging has enhanced the early detection and diagnostic accuracy of lung malignancies, particularly in those small and subtle nodules, which may be missed in LDCT screens. The immunohistochemical profile and the *EWSR1* gene rearrangement, serve as a cornerstone in HCCC diagnosis. This case emphasized

the significance of integrating ^{18}F -FDG PET/CT imaging for early detection and management of primary pulmonary HCCC.

Abbreviations

HCCC	Hyalinizing clear cell carcinoma
^{18}F -FDG PET/CT 18	F-fluorodeoxyglucose positron emission tomography/computed tomography
LDCT	Low-dose computed tomograph
RML	Right middle lobe
FISH	Fluorescence in situ hybridization

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None.

Author contributions

Conceptualization: Yu-Ju Su, Cheng-Hung How. Data curation: Yu-Ju Su, Cheng-Hung How. Formal Analysis: Min-Shu Hsieh, Investigation: Yu-Ju Su, Min-Shu Hsieh, Methodology: Yu-Ju Su, Min-Shu Hsieh, Project administration: Cheng-Hung How. Resources: Cheng-Hung How. Software: Yu-Ju Su, Yun-Shao WuSupervision: Yu-Ju Su, Min-Shu Hsieh, Validation: Min-Shu Hsieh, Visualization: Yu-Ju Su, Cheng-Hung How, Min-Shu Hsieh, Writing – original draft: Yu-Ju Su, Yun-Shao WuWriting – review & editing: Yu-Ju Su, Cheng-Hung How. All authors approved the final version of manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from the patient in accordance with ethical standards.

Consent for publication

All authors have approved the manuscript and consent to its publication.

Competing interests

The authors declare no competing interests.

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