Hyalinizing Clear Cell Carcinoma of the Lung

Case Report and Review of the Literature

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ABSTRACT

Objectives: *Hyalinizing clear cell carcinoma (HCCC) is common in head and neck sites but extremely rare in the lung. This case report describes an HCCC in the lung of a 54-year-old female patient.*

Methods: *We summarize the histomorphologic, immunophenotypic, and molecular features for our and three previously reported HCCCs of the lung with emphasis on potential diagnostic pitfalls.*

Results: *Sections of a well-circumscribed 3.5-cm lung mass were characterized by a bronchocentric tumor growing in sheets, nests, and cords in a background of hyalinized stroma. Tumor cell appearance was clear to eosinophilic, lacking significant pleomorphism or mitotic activity. By immunohistochemistry, the tumor cells were strongly positive with antibodies to pan-keratin, p63, and CK5/6 while negative for CK7, CK20, thyroid transcription factor 1, napsin A, chromogranin, and synaptophysin. Next-generation sequencing demonstrated an* EWSR1-ATF1 *fusion transcript.*

Conclusions: *Awareness of key morphologic features of pulmonary HCCC is crucial for the recognition of this rare entity in the lung. Ancillary studies, including immunohistochemistry and molecular testing, are essential for the distinction from its mimics.*

Clinical History

A 54-year-old African American woman with a medical history of hypertension, gastroesophageal reflux disease, and intermittent chest pain was referred to our institution with a recently enlarging left upper lobe lung mass. The patient, an ex-smoker (less than one pack per week × 3 years), had been followed with computed tomographic (CT) scans every 3 to 6 months for a lung mass first seen on a chest x-ray 5 years ago. Review of the patient's most recent chest CT scan **Image 1** revealed an interval enlargement of a 3.2-cm left suprahilar mass as well as a slight interval enlargement of a 7-mm noncalcified pulmonary nodule in the lateral left lower lobe. A positron emission tomography scan showed central hypermetabolic activity in the suprahilar mass suspicious for a neoplastic process. No fludeoxyglucose accumulation was seen in the small nodule in the left lower lobe, favoring a benign process. A biopsy of the suspicious mass (performed at an outside institution) was diagnosed as a moderately to poorly differentiated squamous cell carcinoma. Pulmonary function tests performed prior to surgery showed a forced expiratory volume of 2.50 (113% of predicted) and a diffusion capacity of carbon monoxide of 25.8 (86% of predicted). A left upper lobectomy with hilar and mediastinal lymphadenectomy was performed. Grossly, a firm, solitary, well-circumscribed, 3.5-cm tan mass was identified. No pleural involvement was present.

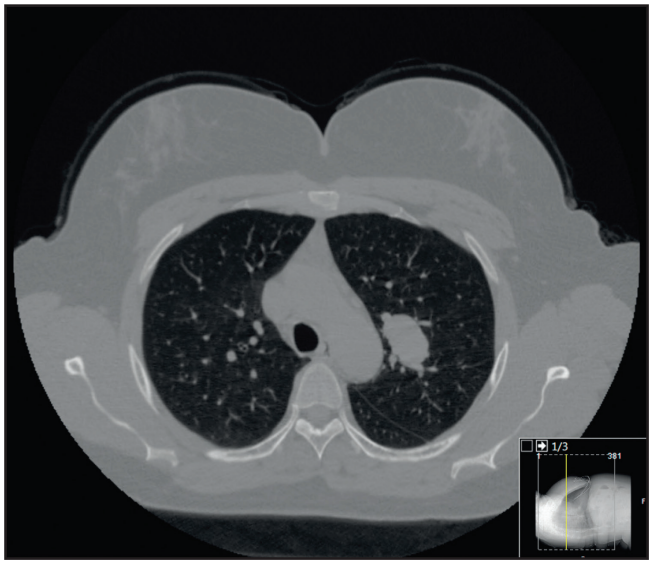

Image 1 Chest computed tomography scan with left upper lobe mass.

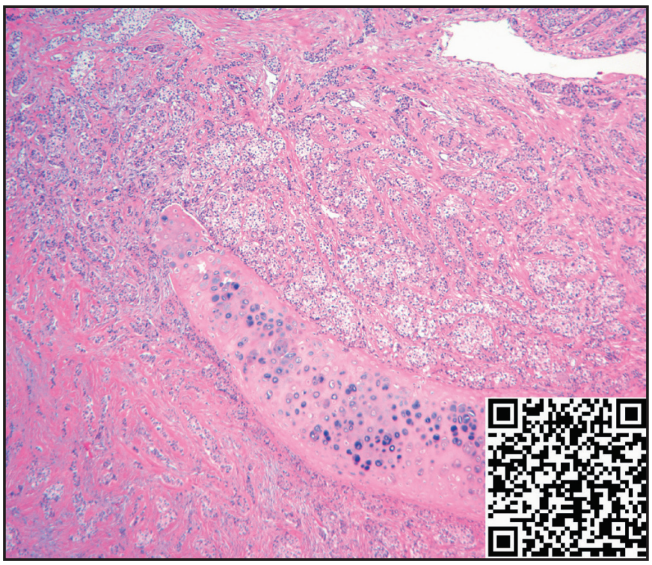

Image 2 Infiltrating neoplastic cells centered on a bronchus (H&E, ×4). (For a whole-slide digital image of this case, scan this QR/barcode with your smartphone or go to http://goo.gl/bLY6f3.)

Histopathology and Ancillary Testing

H&E-stained sections of the mass showed a tumor centered and possibly arising from a major bronchus **Image 2**. Tumor cell growth was predominantly in sheets, nests, and cords in a background of hyalinized stroma **Image 3**. No bona fide glandular or squamous differentiation was appreciated. Stroma-poor regions contained tumor cells with predominantly pale eosinophilic cytoplasm **Image 4** juxtaposed to stroma-rich areas with clear cells **Image 5**. Tumor nuclei were cytologically bland, nucleoli were small or inconspicuous, and chromatin was fine or vesicular **Image 6**. Rare intranuclear pseudoinclusions were identified. There was no evidence of necrosis or nuclear pleomorphism. The periphery of the tumor showed aggregates of chronic inflammation. A prominent plasma cell infiltrate was admixed with the neoplastic cells in more cellular regions of the tumor **Image 7**. A mitotic figure count demonstrated on average one per

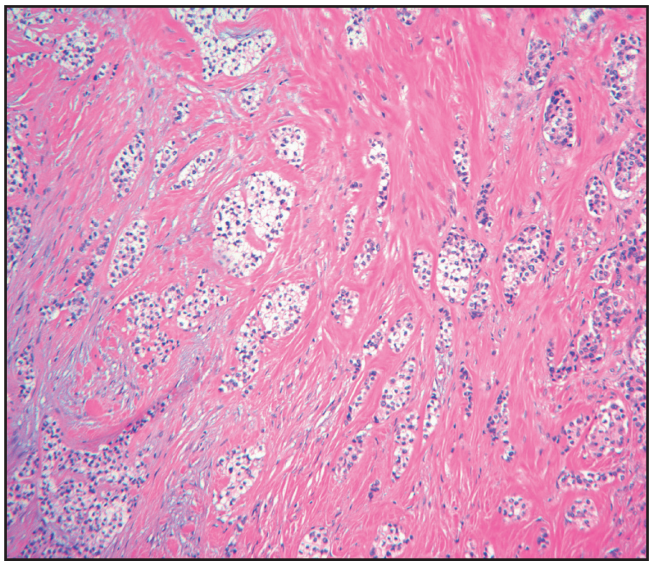

Image 3 Tumor cell growth was predominantly in sheets, nests, and cords in a background of hyalinized stroma (H&E, ×10).

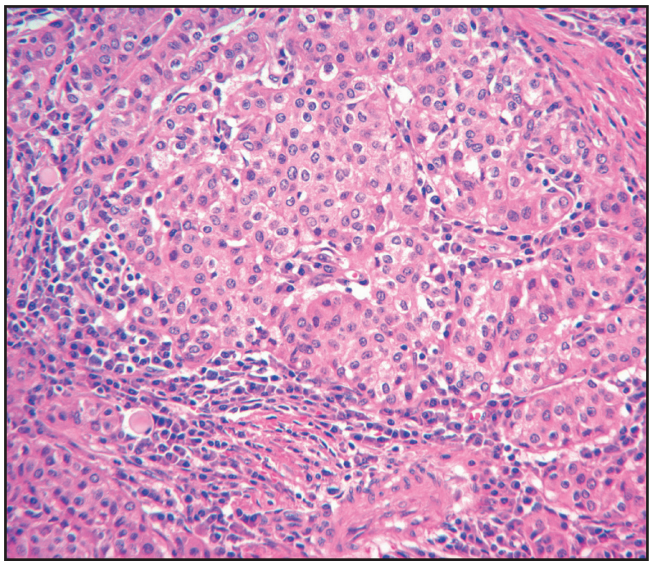

Image 4 Stroma-poor regions contained tumor cells with predominantly pale eosinophilic cytoplasm (H&E, ×20).

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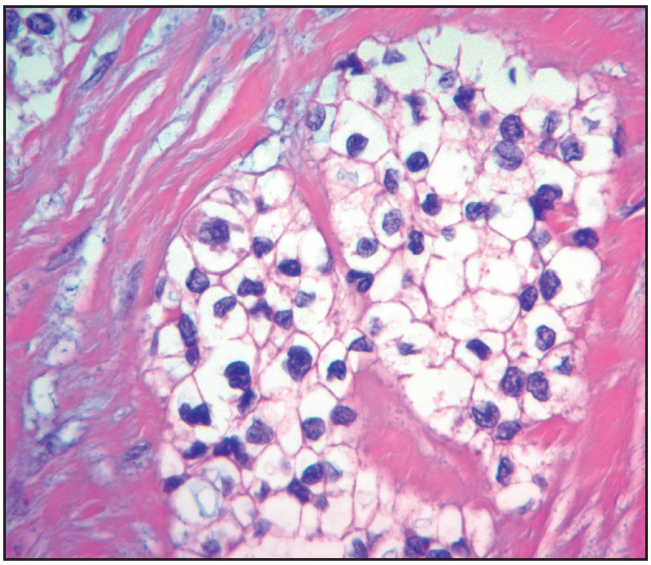

Image 5 Stroma-rich areas with clear cells (H&E, ×100).

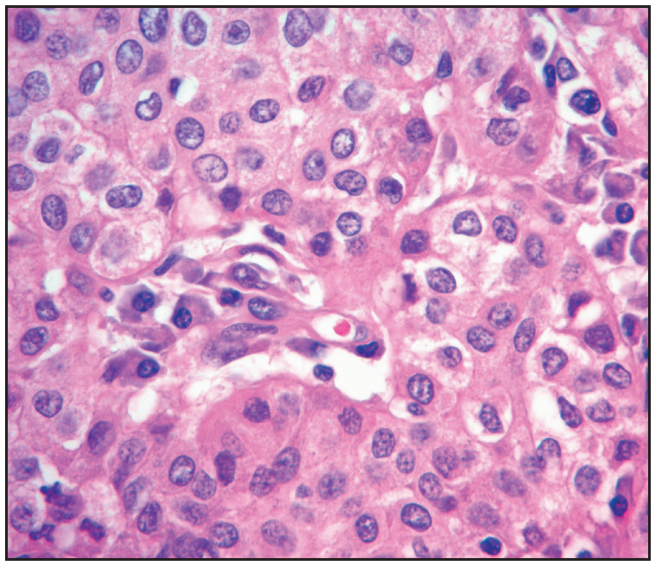

Image 6 Tumor nuclei were cytologically bland, nucleoli were small or inconspicuous, and chromatin was fine or vesicular (H&E, ×100).

10 high-power fields (hpf). By immunohistochemistry, the tumor cells were strongly positive with antibodies to pan-keratin, p63 **Image 8**, and CK5/6 while negative for CK7, CK20, thyroid transcription factor 1 (TTF-1), napsin A, chromogranin, and synaptophysin. For a whole-slide digital image of this case, go to http://goo.gl/bLY6f3 or scan the QR/barcode in Image 2. All 12 lymph nodes were negative for tumor. No pleural involvement or lymphovascular space invasion was present. All surgical margins were negative for tumor. An initial diagnosis of moderately differentiated squamous cell carcinoma (with clear cell change) was rendered, and the tumor was staged as pT2aN0 (stage IB). Due to the patient's light smoking history, molecular testing was ordered by the patient's oncologist. Genomic profiling via hybrid capture–based next-generation sequencing demonstrated a *EWSR1-ATF1* fusion transcript **Figure 1**, prompting a histologic re-review of the case, a literature search, and an outside expert consultative opinion. A final diagnosis of hyalinizing clear cell carcinoma (HCCC) of the lung

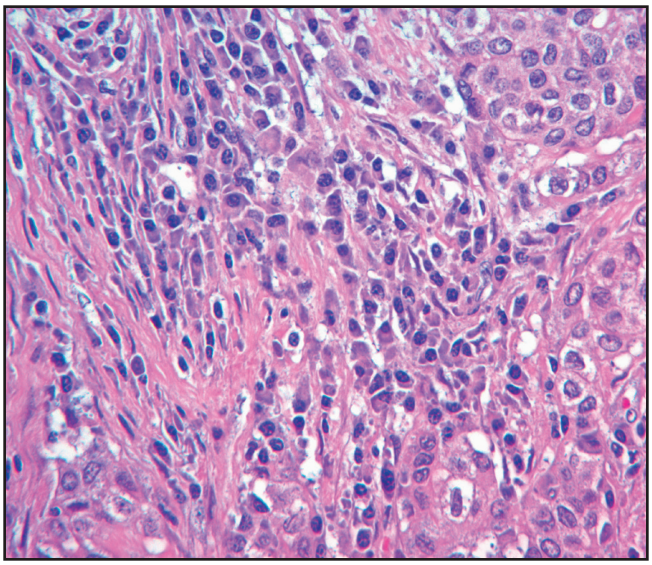

Image 7 A prominent plasma cell infiltrate was admixed with the neoplastic cells in more cellular regions of the tumor (H&E, ×100).

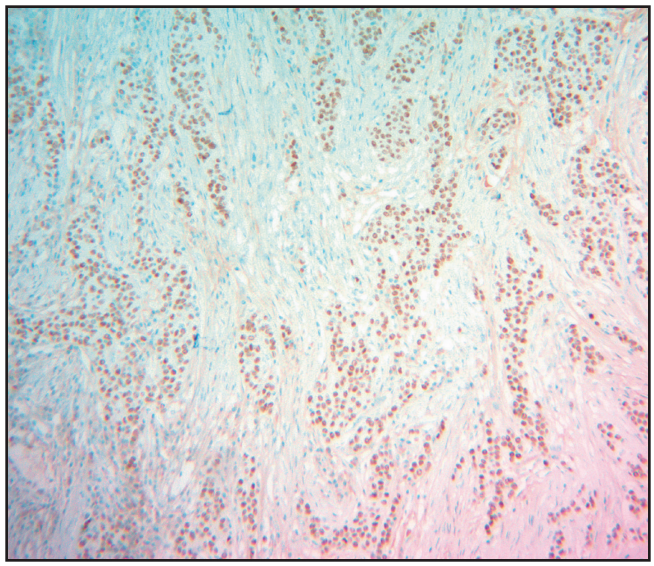

Image 8 By immunohistochemistry, the tumor cells were strongly positive with antibodies to p63 (×10).

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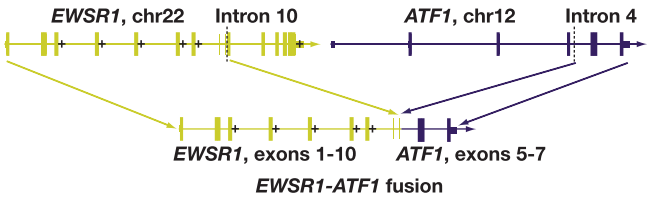

Figure 1 Genomic profiling via hybrid capture–based next-generation sequencing demonstrated an *EWSR1-ATF1* fusion transcript.

(salivary gland type) was ultimately rendered. The patient had no evidence of any lesions or masses in the head and neck region. On clinical follow-up (16 months since surgery), the patient is doing well with no evidence of recurrence or metastatic disease on chest CT.

HCCC

HCCC of the Head and Neck

Most of our knowledge about HCCC stems from the arena of head and neck pathology. HCCC was first described by Milchgrub et al[1] in 1994 as a rare tumor predominantly arising from minor salivary glands in head and neck sites. As of 2014, 136 cases of HCCC of the head and neck have been reported and are summarized in a recent (March 2016) publication by Albergotti and colleagues.[2] The tumor is most commonly discovered as an intraoral, submucosal, and relatively well-circumscribed mass in patients in their fifth or sixth decade of life with a slight female predilection.[3-6] Key histomorphologic features of this low-grade carcinoma include clear cells growing in cords and nests within a hyalinized stroma. Nuclear atypia is minimal, nucleoli are small or inconspicuous, necrosis is absent, and mitotic figures are rare (fewer than one but no more than five mitoses per 10 hpf). Mucinous cells can be seen but are not a defining feature. Of note, only minority of cases show a striking predominance of clear cells; most tumor cells in fact exhibit eosinophilic cytoplasm.[5] Despite a paucity or even lack of clear cells, the characteristic architectural growth patterns (cords, nests, sheets, thin trabeculae) of the tumor cells as well as the background of hyalinized stroma represent helpful clues to the correct diagnosis.[5] Rare cases with high-grade transformation (necrosis, high mitotic index, atypical mitotic figures, nuclear pleomorphism) have been reported.[7] For a more comprehensive review of the morphologic patterns of head and neck HCCC with discussion on ancillary testing and differential diagnosis, the reader is referred to Weinreb's review.[5]

Ancillary Testing

Ultrastructural features, special and immunohistochemical staining profiles, and molecular alterations of HCCC have been exclusively studied in head and neck primaries. HCCC is now recognized to represent a low-grade malignancy with squamous differentiation; use of older terminology such as *clear cell adenocarcinoma* or *clear cell carcinoma not otherwise specified* is discouraged. Ultrastructurally, the presence of desmosomes and tonofilaments supports squamous differentiation.[8] Squamous differentiation is also supported by immunoreactivity for 34βE12 and p63. Other focal or diffusely positive immunoreactivity is seen with antibodies to keratin AE1/AE3, CK5/6, CK7, CK14, CK19, EMA, Cam5.2, and vimentin. Periodic acid–Schiff positivity with sensitivity to diastase is also characteristic, reflecting cytoplasmic glycogen content. Pertinent negative stains include S-100, muscle-specific actin, smooth muscle actin (SMA), and calponin; this immunphenotype helps exclude myoepithelial differentiation.[5,9] While the hyalinized stroma may resemble amyloid, it is actually dense collagen and Congo red negative.

Ewing sarcoma breakpoint region 1 (*EWSR1*) fluorescence in situ hybridization (FISH) is a helpful ancillary test in the diagnosis of HCCC. *EWSR1* is rearranged in 87% to 91% of head and neck HCCCs. The partner gene in this rearrangement is usually activating transcription factor 1 (*ATF1*). By reverse transcription–polymerase chain reaction (RT-PCR) and sequencing, most HCCCs (93%) demonstrate an *EWSR1-ATF1* fusion transcript.[10] Other tumors may also demonstrate an *EWSR1-ATF1* fusion, including clear cell sarcoma of tendons and aponeuroses, angiomatoid fibrous histiocytoma, and several others; these almost always have a very different clinical, histologic, and immunophenotypic appearance from HCCC.[11] Therefore, the presence of this molecular signature in conjunction with the histomorphology and the immunophenotype of HCCC described above allows for the distinction of HCCC from its mimics.[10,12]

HCCC of the Lung

To our knowledge, only three cases of HCCC arising in the lung have been reported in the literature to date.[13,14] Shah et al[13] described two patients with HCCC of the lung in 2014. Both patients were young men (nonsmokers) in their 30s with an incidentally discovered lung mass on a chest CT scan. Both patients underwent lobectomy demonstrating a well-circumscribed, bronchiocentric

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Table 1
Summary of Clinicopathologic Features of All Reported Hyalinizing Clear Cell Carcinomas of the Lung

Patient	Presentation	Size/Location	Surgical Management	IHC/Special Stains	Molecular Testing	Follow-up Time/ Outcome
32-year-old man, nonsmoker[13]	Incidental finding on chest CT scan	1.8 cm/segmental bronchus of left lower lobe	Lobectomy	Positive: pan-cytokeratin, CK7, and p63 Negative: CK20, CD10, PAX-8, chromogranin, synaptophysin, HMB-45, TTF-1, napsin A, S-100, and SMA	Break-apart FISH for *EWSR1*: positive	No recurrence or metastasis after 18 mo
39-year-old man, nonsmoker[13]	Incidental finding on chest CT scan	2.6 cm/bronchial wall of right lower lobe	Lobectomy	Positive: pan-cytokeratin, CK7, and p63 Negative: CK20, CD10, PAX-8, chromogranin, synaptophysin, HMB-45, TTF-1, napsin A, S-100, and SMA	Break-apart FISH for *MAML2*: negative Break-apart FISH for *EWSR1*: positive	No recurrence or metastasis after 18 mo
38-year-old man, nonsmoker[14]	Growing mass on chest CT scan	2.6 cm/bronchial wall of right lower lobe	Lobectomy	Positive: pan-keratin, CK7, p63, p40, and mucicarmine Negative: CK20, chromogranin, synaptophysin, S-100, SMA, TTF-1, and napsin A	Break-apart FISH for *MAML2*: negative Break-apart FISH for *EWSR1*: positive RT-PCR and sequencing: *EWSR1-ATF1* fusion	No recurrence or metastasis after 10 mo
54-year-old woman, ex-smoker (our patient)	Chest pain and growing mass on chest CT scan	3.5 cm/left upper lobe	Lobectomy	Positive: pan-keratin, p63, and CK5/6 Negative: CK7, CK20, TTF-1, napsin A, chromogranin, and synaptophysin	Next-generation sequencing: *EWSR1-ATF1* fusion	No recurrence or metastasis after 16 mo

CT, computed tomography; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; RT-PCR, reverse transcription–polymerase chain reaction; SMA, smooth muscle actin; TTF-1, thyroid transcription factor 1.

tumor with protrusion into the airway. Histomorphologic features were such as described for HCCC of the head and neck. Of note, one of the cases showed small areas of tumor cell necrosis, but nuclear pleomorphism or a high mitotic index (features associated with high-grade transformation) was not mentioned. Surgical margin status or lymph node involvement was not addressed. Ancillary testing included an array of immunohistochemical (IHC) stains with positivity for pan-keratin, CK7, and p63 and negative results for CK20, CD10, PAX-8, chromogranin, synaptophysin, HMB-45, TTF-1, napsin A, S-100, and SMA. Both cases demonstrated *EWSR1* rearrangement by FISH. Of note, no head and neck lesion was identified in either patient, and both were diagnosed as having primary HCCC of the lung (salivary gland type). No adjunct treatment modality was administered, and neither recurrence nor metastatic disease was detected after 1.5 years of follow-up. In the same year (2014) as the case report by Shah et al,[13] García and colleagues[14] published a report of an HCCC of the lung in a 38-year-old nonsmoker who underwent right lower lobectomy for a growing lung mass. The mass was well circumscribed and centered on the bronchus. Histomorphologic features were within the spectrum of those described for HCCC of the head and neck. Necrosis, increased mitotic activity, or nuclear pleomorphism was notably absent. Surgical margin status or lymph node involvement was not addressed. Ancillary testing included an array of IHC stains with positivity for pan-keratin, CK7, p63, and p40 and negative results for CK20, chromogranin, synaptophysin, S-100, SMA, TTF-1, and napsin A. A mucicarmine stain was positive in rare cells. Mastermind-like 2 (*MAML2*) FISH to support a diagnosis of low-grade mucoepidermoid carcinoma was negative. FISH for *EWSR1* showed a rearrangement, and subsequent RT-PCR with sequencing demonstrated the *EWSR1-ATF1* fusion transcript. Given these findings and the absence of a head and neck lesion, the patient was diagnosed with primary HCCC of the lung (salivary gland type). No adjunct treatment modality was administered, and neither recurrence nor metastatic disease was detected after 10 months of follow-up. A summary of the clinicopathologic features for the four reported HCCCs of the lung (including our patient) is provided in **Table 1**. While the reported histologic, immunophenotypic, and

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Table 2
Hyalinizing Clear Cell Carcinoma and Diagnostic Mimics: Key Histopathologic Features and Ancillary Tests

Characteristic	Hyalinizing Clear Cell Carcinoma	Squamous Cell Carcinoma With Clear Cell Change	Low-Grade Mucoepidermoid Carcinoma	Thoracic Myoepithelial Tumors	Metastatic Tumors With Clear Cells
Morphology	Cords, nests, hyalinized stroma	Keratinization and intercellular bridges	Mixture of mucus, epidermoid, and intermediate cells	Nests, sheets,hyalinized or myxoid stroma	Variable depending on primary site
Nuclear pleomorphism	Minimal, ± small nucleoli and rare intranuclear pseudoinclusions	Moderate to marked	Variable	Mild to moderate	Variable
Clear cells	Present (but can be scant)	Present	Present (variable)	Present (common)	Present
Mucinous cells	None to rare	None to rare	Present (rare in mucin-depleted variant)	None	None
Mitotic index	Low (<1-5 per 10 hpf)	High	Low	Low	High
Necrosis	None to very focal	Frequent	Variable	Frequent	Frequent
Ancillary stains	Positive: keratin AE1/AE3, 34βE12, CK7, CK14, CK19, EMA, Cam5.2, p63, p40, CK5/6, vimentin, and PAS-D, mucicarmine (if rare mucin cells are present) Negative: S-100, HMB-45, MSA, SMA, calponin, TTF-1, napsin A, chromogranin, synaptophysin, PAX-8, and Congo red (stroma)	Positive[a]: keratin AE1/AE3, CK7 (variable), p63, p40, and CK5/6	Positive[a]: HMWK, p63, and mucicarmine (mucin cells) Negative: SMA, calponin, and S-100	Positive: HMWK, EMA, p63, SMA, calponin, and S-100	Positive: PAX-8 for metastatic clear cell carcinoma from renal or gynecologic primary
Molecular features	*ESWR1-ATF1*	*FGFR1*, *DDR2*, *PIK3CA*	*MECT1-MAML2*	*EWSR1-PBX1EWSR1-ZNF444FUS-KLF17*	—
Comment	Younger patient(light to never smoker)Must clinically exclude HCCC metastasis from head and neck primary Presence of high mitotic rate, necrosis, and marked pleomorphism is associated with high-grade transformation	Patient age (older), significant smoking history, tumor morphology, and lack of *EWSR1-ATF1* aid distinction from HCCC	Molecular testing aids distinction of mucin-depleted variant from HCCC	IHC and molecular profile both aid distinction from HCCC	Correlation with clinical history and imaging studies is essential

EMA, epithelial membrane antigen; HCCC, hyalinizing clear cell carcinoma; HMWK, high-molecular-weight keratin; hpf, high-power field; IHC, immunohistochemistry; MSA, muscle-specific actin; PAS-D, periodic acid–Schiff–diastase; SMA, smooth muscle actin; TTF-1, thyroid transcription factor 1.
[a]No key IHC stains aid in distinction from HCCC.

molecular characteristics of pulmonary HCCCs mirror those of HCCC occurring in the head and neck, it is noted that all of the three previously reported lung HCCCs occurred in men in their 30s (Table 1). Our case differs in age and sex distribution and is more in line with patient characteristics of HCCC of the head and neck. To our knowledge, our case is the first example of a primary pulmonary HCCC reported in a female patient.

As illustrated in our case, the rarity of HCCC in the lung, paucity of clear cells, and squamous immunophenotype present a potential pitfall for misclassification of this low-grade malignancy. On histologic grounds alone, major diagnostic differential considerations include but are not limited to squamous cell carcinoma with clear cell change, salivary gland tumors involving the lung (eg, "mucin-depleted" low-grade mucoepidermoid carcinoma), myoepithelial tumors, or metastatic carcinomas with clear cells such as metastatic renal cell carcinoma **Table 2**. Close attention to the above-described growth pattern and hyalinized stroma is

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required to entertain the rare diagnosis of HCCC of the lung. Despite positivity for p63, CK5/6, and differential keratins, the overall bland histomorphologic features, low mitotic index, and absence of keratinization argue against the diagnosis of a squamous cell carcinoma with clear cell change. Separation of HCCC from a mucin-depleted low-grade mucoepidermoid carcinoma can be challenging as HCCC can exhibit rare mucin-positive cells. In difficult cases, breakapart FISH for *MAML2* and *EWSR1* may be a helpful ancillary testing strategy to allow diagnostic distinction. Tumors with myoepithelial differentiation also enter the differential diagnosis, particularly thoracic myoepithelial tumors that are nested and solid, composed of clear cells, and associated with a hyalinized stroma.[15] While frequently positive for keratins and p63, these tumors also coexpress S100 and/or myogenic markers (SMA or calponin), aiding in the immunophenotypic distinction from HCCC. Similar to HCCC, thoracic myoepithelial tumors can show *EWSR1* rearrangements, but fusion partners differ, including *PBX-1* and *ZNF444*.[15] Finally, the lung is a common site of metastatic disease. Given the proclivity of HCCC for the head and neck, correlation with a clinical history or referral to an ear, nose, and throat specialist is prudent to exclude a metastatic process to the lung from a salivary gland primary site. In addition, other metastatic malignancies with clear cells must be excluded, certainly by correlation with clinical presentation, history, and/or aid of immunohistochemistry (eg, PAX-8 for renal cell carcinoma).

Treatment and Prognosis

Due to the rare nature of the tumor, no standardized treatment approach exists. Depending on tumor location, surgical resection of the tumor with negative surgical margins is the main treatment of choice. Outcome of lung HCCC (Table 1) after lobectomy has been excellent (no reports of regional lymph node involvement, distant metastasis, or local recurrence), but meaningful conclusions are limited by the paucity of reported cases. Outcome of head and neck HCCC is reportedly good to excellent. Local recurrence rates range from 11% to 20%; metastatic disease is rare.[1,2,6,7,10,16-18] Particularly, lymph node involvement, positive surgical margin status, and tumor cell necrosis are associated with an increased risk for recurrence, which is highest within the first 2 years and years 5 to 7. HCCCs with high-grade features (necrosis, nuclear pleomorphism, high mitotic index, atypical mitotic figures) naturally have a more guarded prognosis. For the most comprehensive literature review of HCCCs of the head and neck with emphasis on clinical outcome, the reader is referred to the publication by Albergotti et al.[2]

Final Remarks

Hyalinizing clear cell carcinoma is a rare and rather indolent low-grade malignancy with predilection for the head and neck. Only three cases of HCCC of the lung have been reported prior to the current case. Our case adds to the sparse but growing literature on this topic, and to our knowledge, it is the first reported case of pulmonary HCCC in a female patient. Pulmonary HCCCs share the histologic, immunophenotypic, and molecular characteristics of head and neck HCCCs. Awareness of key morphologic features is crucial for the recognition of this rare entity in the lung. As was evident in our case, tumors lacking a predominance of clear cells combined with immunophenotypic evidence of squamous differentiation (p63, CK5/6) can lead to misclassification as squamous cell carcinoma. Clinical features that differ from typical non–small cell lung cancer include a relatively young age at diagnosis and a lack of significant smoking history. However, molecular testing for the characteristic *EWSR1-ATF1* fusion transcript is an extremely helpful ancillary test to support the proper diagnosis.

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