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Case study

Primary pulmonary hyalinizing clear cell carcinoma of bronchial submucosal gland origin

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Summary Hyalinizing clear cell carcinoma (HCCC) has only been described in salivary glands of the head and neck. We report a 38-year-old man with a 2.6-cm lung tumor that was growing in a peribronchial location and had morphologic features of HCCC. The tumor cells expressed cytokeratin 7 and keratin AE1/AE3, and the vast majority of tumor cells marked also with p63 and p40. They were negative for cytokeratin 20, S-100, smooth muscle actin, napsin A, and thyroid transcription factor-1. Fluorescence in situ hybridization revealed *Ewing Sarcoma Breakpoint Region 1 (EWSR1)* rearrangement, and reverse-transcription polymerase chain reaction confirmed the presence of the *EWSR1-Activating Transcription Factor 1 (ATF1)* fusion transcript, which was subsequently sequenced. The morphologic, immunophenotypic, cytogenetic, and molecular findings together with the patient's history and location of the tumor support a diagnosis of primary pulmonary HCCC of bronchial submucosal gland origin. It is our understanding that this is the first report of HCCC arising as a primary tumor outside the head and neck region.
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1. Introduction

Hyalinizing clear cell carcinoma (HCCC) of salivary gland origin has been recognized in the head and neck pathology literature for over 2 decades—most commonly in minor salivary gland locations [1]. It is regarded as a low-grade malignant neoplasm that can locally recur and rarely metastasize. Histopathologically, this tumor is characterized by sheets, cords, small nests, and trabeculae of epithelioid cells with at least a subset exhibiting clear cytoplasm. The neoplastic cells are often set in a background of hyalinized fibrosis. Immunophenotypically, tumor cells show squamous differentiation. More recently, *Ewing Sarcoma Breakpoint Region 1 (EWSR1)* rearrangement was identified in these tumors by fluorescence in situ hybridization (FISH) and a fusion transcript, *EWSR1-Activating Transcription Factor 1 (ATF1)*, by reverse transcription-polymerase chain reaction (RT-PCR) and sequencing [2]. Although this molecular signature is not exclusive to HCCC, together with the histopathologic and immunophenotypic features and location of the tumor, its detection is useful to establish a diagnosis of HCCC of salivary gland origin.

Although rare cases of HCCC of the head and neck have been reported to metastasize to the lung [3,4], to our knowledge, primary pulmonary HCCC has not yet been reported. In fact, HCCC has not been reported outside the head and neck region.

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2. Materials and methods

2.1. Case

A 38-year-old man, nonsmoker, underwent right lower lobectomy for a solitary mass that was being observed for 4 years. The patient had no other pertinent medical history. A computed tomographic (CT) scan revealed a solitary right perihilar mass that measured 3.03 cm in greatest dimension in the vicinity of a large airway (Fig. 1). The mass originally measured 2.19 cm on a CT scan 4 years prior and had increased to 2.76 cm 3 months before resection. The mass had slightly increased in size, when compared with an examination 1 month prior.

2.2. Histochemistry and immunohistochemistry

Slides stained with antibodies against cytokeratin (CK) 7 (clone OV-TL12/30; Cell Marque, Rocklin, CA), CK20 (clone Ks20.8; Cell Marque), cytokeratin cocktail (clones AE1/AE3; Cell Marque), chromogranin (polyclonal; DAKO, Carpinteria, CA), and synaptophysin (clone MRQ-40; Cell Marque) were provided by S. B. J. Consecutive slides were stained with antibodies against p63 (clone BC4A4; Biocare Medical, Concord, CA), p40 (polyclonal; Biocare Medical), napsin A (clone IP64; Leica Microsystems, Buffalo Grove, IL), thyroid transcription factor-1 (clone SPT24; Leica Microsystems), S-100 (polyclonal; DAKO), and smooth muscle actin (SMA) (clone 1A4; DAKO). A mucicarmine stain (Sigma Aldrich, St Louis, MO) was also performed.

2.3. FISH

FISH for *Mastermind-like 2 (MAML2)* rearrangement was performed as previously described using a break-apart probe [5]. FISH for *EWSR1* gene rearrangement was performed on formalin fixed paraffin embedded (FFPE) tumor sections according to standard protocol using a commercially available *Ewing Sarcoma (EWS)* break-apart probe (Abbott Molecular, Des Plaines, IL). Two hundred tumor nuclei were counted. The normal cutoff was less than 7% of tumor cells with 1 5′EWSR1 signal, 1 3′EWSR1 signal, and 1 5′EWSR1/3′EWSR1 fusion signal.

2.4. RT-PCR and Sanger sequencing

RT-PCR amplification was performed to detect *EWSR1* exon 11–*ATF1* exon 3 fusion transcripts (Genbank access no. NM-005243.3 for *EWSR1* and NM-005171.4 for *ATF1*), using a primer set as follows: 5′-TCTAGGCCCACCTGTA-GATCC (forward) and 5′-GTGAGGAGCCTATGCTGTCG (reverse) with PCR product size of 185 base pairs. A housekeeping gene *phosphoglycerokinase* (NM-000291.2) was also amplified to check the sample RNA quality, using a primer set: 5′- CAGTTTGGAGCTCCTGGAAG (forward) and 5′- TGGAGATGCAGAAAATGCTAAG (reverse) with PCR product size of 126 base pairs. An aliquot of PCR product was used for bidirectional Sanger sequencing to confirm the specificity of PCR amplification.

3. Results

3.1. Gross and microscopic findings

A right lower lobectomy specimen revealed a 2.6-cm firm, gray-white, well-circumscribed mass 0.3 cm from the bronchial margin and abutting the pleura. The mass appeared to arise from the bronchial wall and to obstruct the bronchus. Extensive inspissated mucus was noted throughout the specimen.

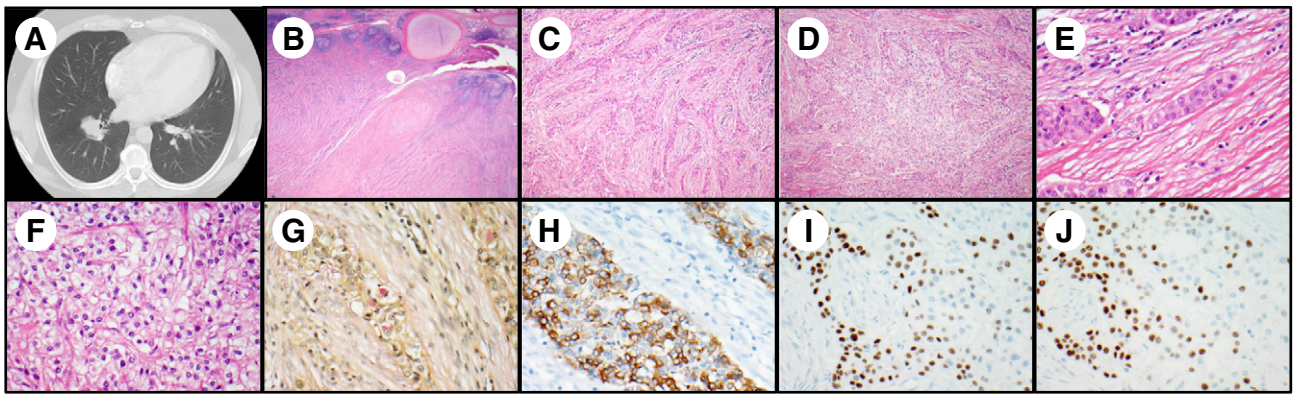

Fig. 1 A, Chest CT scan reveals a circumscribed mass that impinges on a large airway in the perihilar region of the right lung. B, On low power, hematoxylin and eosin-stained slide shows an invasive neoplasm with tumor-associated lymphoid proliferation in the submucosa of a large airway (note cartilage). Intermediate magnification reveals epithelioid tumor cells predominantly arranged in cords (C) and occasional nests (D). C to E, Tumor cells are growing in a background of hyaline fibrosis. Tumor cells have an epithelioid appearance with eosinophilic (E) or clear (F) cytoplasm, open chromatin, and prominent nucleoli. G, Occasional tumor cells have cytoplasmic mucin as highlighted with a mucicarmine stain. H, They express cytokeratin cocktail and CK7 (not shown). The vast majority of neoplastic cells express p63 (I) and p40 (J) in a similar distribution. Original magnification, ×12.5 (B), ×100 (C and D), ×400 (E-J).

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