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Cytological-Pathologic Correlation

Primary pulmonary mucoepidermoid carcinoma: Cyto-histologic correlation and review of the literature

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ABSTRACT

Preoperative fine needle aspiration diagnosis and cyto-histologic correlation of primary pulmonary mucoepidermoid carcinoma have rarely been described in detail in the literature. A 26-year old male presented at our institution with cough, bloody sputum, and a 4.3 cm left lower lobe lung mass. He was accurately diagnosed with pulmonary mucoepidermoid carcinoma on preoperative aspiration cytology. The patient subsequently proceeded to left lower lobectomy, confirming the diagnosis. In this article, we present a detailed report of primary pulmonary mucoepidermoid carcinoma describing the cytologic and histologic morphologic features, its differential diagnosis with review of the literature.

1. Introduction

Primary pulmonary mucoepidermoid carcinoma is a rare type of lung cancer with only a few reported cases (accounting for less than 1% of all lung cancers). The most common location in the lung is in the central bronchial region [1,2]. This tumor is classified into low-grade and high-grade. The low-grade mucoepidermoid carcinoma has an excellent prognosis after surgical treatment, while the high-grade tumor is a more aggressive form of malignancy which behaves as other non-small cell carcinomas of the lung [3,4].

To our knowledge, there are no studies describing detailed cytologic-histologic correlation for primary pulmonary mucoepidermoid carcinomas. Herein, we present a detailed report of a patient diagnosed with primary pulmonary mucoepidermoid carcinoma on preoperative cytology with subsequent confirmation of the diagnosis on histopathological and molecular studies.

2. Case summary

A 26-year old male with no known prior medical history presented to an urgent care clinic of the Froedtert & the Medical College of Wisconsin regional hospital in 2019 with a cough associated with bloody sputum. The symptoms resolved by themselves and the patient was sent back home. The patient remained symptomless until the following year when he presented with a new episode of hemoptysis. A review of symptoms was noncontributory, and a physical examination was unremarkable. A chest X-ray revealed the presence of approximately 5 cm retrocardiac oval mass-like opacity. A chest CT scan with contrast demonstrated a 4.3 cm left lower lobe lung mass. The mass was seen to be abutting the left hilum and partially extending into the left lower lobe bronchus. A single mildly enlarged pretracheal lymph node was also noted.

The patient was subsequently referred to a pulmonologist for further evaluation. A follow-up flexible bronchoscopy demonstrated a white exophytic endoluminal mass originating in the anteromedial segment of the left lower lobe. The mass did not appear to be infiltrating into the adjacent mucosa or invading through the airway wall. Severe extrinsic compression of the other left lower lobe basilar segments was noted. The pedunculated lesion was removed by snare and sent to histology. Endobronchial ultrasound-guided transbronchial fine needle aspiration (EBUS-TBFNA) of the endobronchial mass was performed and specimens were sent to cytology. EBUS-TBFNA was also performed for lymph node stations 4R and 7 using BSCI 22g Expect needles (Boston Scientific, USA).

2.1. Cytology findings

The cytologic smear slides stained with Papanicolaou and DiffQuik stains as well as cell blocks were prepared at the cytology laboratory. Microscopic evaluation of the stations 4R and 7 lymph nodes revealed lymphocytes along with bland bronchial epithelial cells and blood; no significant acute inflammation or granulomatous inflammation was seen, and there was no evidence of malignancy. The FNA smears of the

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left lower lobe mass were cellular with a mucinous background (Fig. 1). There were numerous flat sheets of uniform cells that were devoid of cilia, exhibited high nuclear to cytoplasmic ratio, mild nuclear atypia and scant cytoplasm, consistent with so-called intermediate cells. Within these cellular groups, cuboidal mucous cells were seen scattered singly and in small clusters. The mucocytes had intracytoplasmic red, granular mucin droplets, while intermediate cells had a central nucleus with scant light pink-purple cytoplasm. No obvious squamous cells were identified. Immunostains were performed on the cell block preparations and showed that the tumor cells were positive for p40 and negative for SOX-10, synaptophysin, and chromogranin. The mucicarmine special stain highlighted the scattered mucous cells. The overall cytomorphologic and immunohistochemical features were consistent with a low-grade mucoepidermoid carcinoma.

The patient subsequently proceeded to left lower lobectomy with mediastinal lymphadenectomy.

2.2. Histologic findings

Gross examination of the left lower lobe mass revealed a firm yellow-tan mass (4.5 cm) that was endobronchial in location (Fig. 2).

Histopathological evaluation showed a mixture of neoplastic ovoid vacuolated mucous, scattered polygonal squamous, and large polygonal intermediate cells arranged in cysts (about 30%) and solid components (Fig. 3). Mild to moderate nuclear atypia and rare mitoses were seen. Tumor cells were positive for p40 and CK7 while negative for TTF-1, PD-L1, synaptophysin, and chromogranin. The histological features confirmed a low-grade mucoepidermoid carcinoma.

2.3. Molecular analysis

Additionally, molecular test *MAML2* (11q21) FISH (performed by Mayo Clinic, Rochester, Minnesota) for mucoepidermoid carcinoma confirmed rearrangement of the mastermind-like gene family *MAML2* (exons 2–5 of the gene at 11q21).

3. Discussion

An annual incidence of mucoepidermoid carcinoma is 0.44 per 100,000 people, and it is the most common malignancy of the salivary glands [5]. Mucoepidermoid carcinoma can be seen at any age but is most commonly found at the age of 35–65, and approximately 60% of the cases occur in women. Approximately 53%–56% of the tumors involve the major salivary glands (85–88% in the parotid glands, 8–13% in the submandibular glands, and 2–4% in the sublingual glands). Mucoepidermoid carcinoma of the minor salivary glands most frequently arises on the palate but also can be found in the tongue, the floor of the mouth, the lips, the buccal mucosa, and the retromolar area. Very rarely (~1%) it also may arise from the lacrimal glands, nose, paranasal sinuses, larynx, breast, trachea, and lung [6].

The main clinical symptoms of the primary pulmonary mucoepidermoid carcinoma are related to the level of bronchial obstruction and include shortness of breath and cough with mucous or bloody sputum. This tumor can have metastases in approximately 20% of cases, mainly in the subcutaneous tissues, the liver, and the bone. On bronchoscopy, mucoepidermoid carcinoma in the lung is covered by bronchial mucosa with a smooth surface or can be focally ulcerative. The most common localization is the proximal bronchi or the trachea. It presents radiologically as a centrally located well-circumscribed homogeneous or lobulated mass, sometimes with cystic features or calcification; additionally, parenchymal consolidation may be seen. This tumor typically has an increased uptake on a positron emission tomography scan [7,8].

Histologic grade is an important prognostic indicator in mucoepidermoid carcinomas. Multiple studies have shown that the survival rate for high-grade mucoepidermoid carcinoma is significantly reduced compared to that for low-grade counterpart (high-grade tumor is 10 times more likely than low-grade tumor to metastasize to lymph nodes). Five-year disease-specific survival rates for low-grade and high-grade mucoepidermoid carcinomas are 98.8% and 67.0%, respectively [9,10].

On gross examination, the low-grade tumor appears as a grey-white to pink-tan solid or cystic mass filled with mucus, usually well-circumscribed and unencapsulated or partially encapsulated. The high-grade tumor is poorly circumscribed solid mass with infiltrative borders, commonly with areas of necrosis and hemorrhages. The

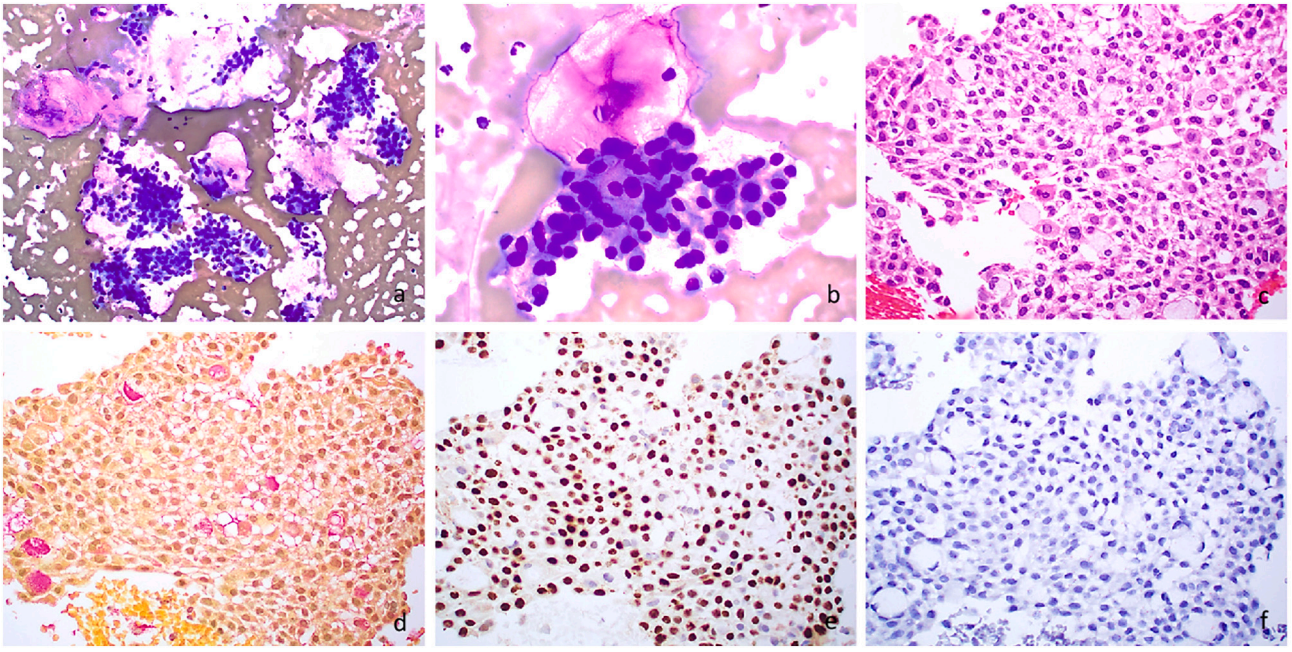

Fig. 1. Small uniform cells with round to ovoid hyperchromatic nuclei, homogenous chromatin, inconspicuous nucleoli, and small amount of cytoplasm (Diff-Quik, a. 200×, b. 600×). Cell block shows sheets of intermediate cells admixed with mucous cells (Hematoxylin-Eosin, c). Mucicarmine highlights scattered mucous cells (d). p40 highlights intermediate cells (e). Tumor cells show no staining with SOX-10 (f).

Fig. 2. Pulmonary mucoepidermoid carcinoma, firm yellow-tan endobronchial mass. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

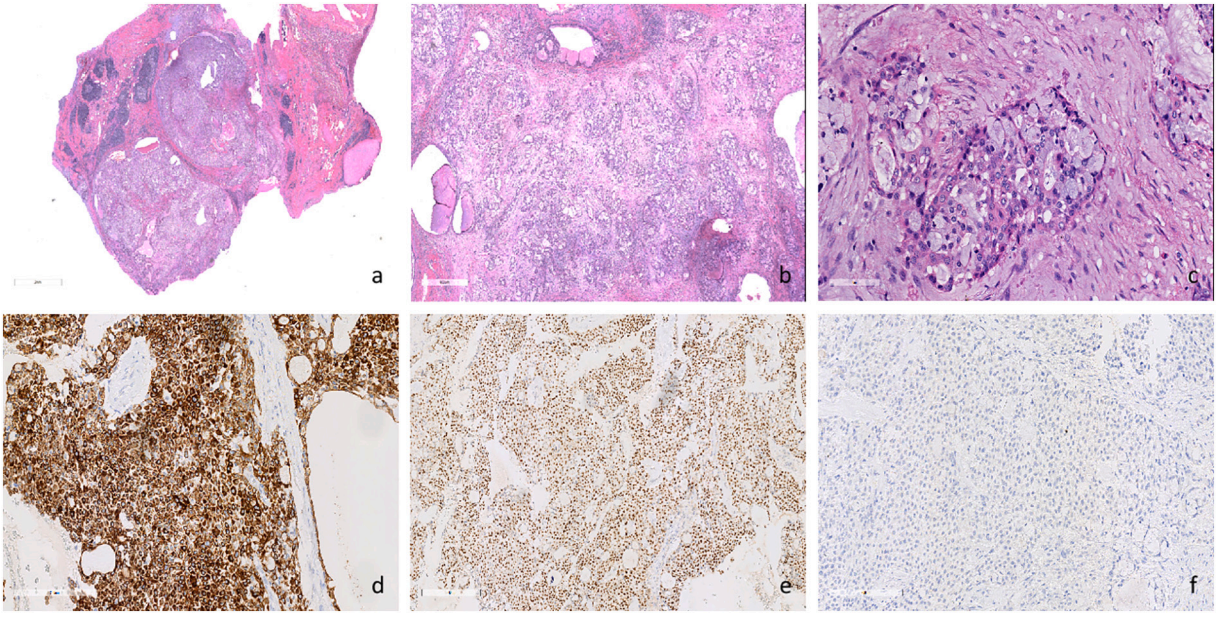

Fig. 3. Left lower lobectomy specimen shows a mixture of neoplastic mucous, squamous, and intermediate cells, creating a vague cribriform structure in a fibrotic background (Hematoxylin-Eosin, a. 20×, b. 40×, c. 200×). The tumor cells showing positive staining with CK7 (d), and p40 (nuclear) (e). The tumor cells are negative for TTF1 (f).

pulmonary tissue distal to the tumor may show obstructive pneumonia or secondary bronchiectasis [11,12].

Microscopically, low-grade tumor is well-differentiated and primarily has mucous cells and squamoid epithelial cells with rare mitoses. Mucous cells are columnar with basally located nuclei and mucin-rich cytoplasm. Squamoid cells are polygonal with smooth cell borders and dense cytoplasm. Occasionally mucin can spill into the pulmonary stroma, and this may have an association with a granulomatous reaction. High-grade tumors are poorly differentiated and show a predominance of squamous epithelial cells with cytologic atypia, nuclear pleomorphism, high mitotic counts, areas of necrosis, and hemorrhage. The stroma of the tumor may be fibrotic, sometimes with calcifications or lymphocytic infiltrates [13].

AFIP (the Armed Forces Institute of Pathology) and Brandwein systems are most used for histological grading of mucoepidermoid carcinomas, both 3-tiered (low-, intermediate-, and high-grade). The former is based on five features: intracystic component, neural invasion, necrosis, mitotic activity, and anaplasia. However, the prognostic utility of AFIP system was shown to be applicable only for parotid and minor salivary gland tumors, and less relevant for tumors of other sites. Brandwein modified the AFIP system by including additional criteria such as lymphovascular and bony invasion, as well as architectural patterns of invasion [14].

Cytologic grading of mucoepidermoid carcinomas, on the other

hand, is two-tiered, with low grade lesions frequently demonstrating sheets of bland intermediate cells, with admixed mucous cells, while high-grade neoplasms show greater cytologic atypia, with less apparent mucous component, having an appearance of a poorly differentiated non-keratinizing squamous cell carcinoma.

Pulmonary mucoepidermoid carcinoma shows positivity for pan-cytokeratin, CK7, CK14, p40, p63, mucicarmine stains and is negative for CK20, TTF-1, SOX10, and Napsin A. This tumor is associated with t (11;19)(q21–22;p13) chromosomal translocation resulting in mucoepidermoid carcinoma translocation 1 (*MECT1*) (exon 1 of gene at 19p13) with mastermind-like gene family (*MAML2*) (exons 2–5 of gene at 11q21) fusion. Gene *CRTC1-MAML2* represents a diagnostic marker for low-grade mucoepidermoid carcinomas and can be evaluated by using a fluorescence hybridization in situ [15,16].

The preoperative cytology diagnosis of primary mucoepidermoid carcinoma may cause diagnostic difficulties due to sampling limitations. The main differential diagnosis in cytology specimens depending on the grade of the tumor includes mucinous adenocarcinoma, adenosquamous carcinoma, and non-keratinizing squamous cell carcinoma.

Mucinous adenocarcinoma typically presents as a solitary peripheral mass in the lung and simulates lobar consolidation. Tumor cells show columnar or goblet cell morphology with basally located nuclei and atypia; there is a lepidic pattern of growth, mucinous epithelium arises from alveolar walls and alveoli are filled with mucin. On cytology bland columnar cells in a drunken honeycomb with extracellular mucin in the background are seen. Mucinous adenocarcinoma is CK7 and CK20 positive, commonly TTF-1 and Napsin A negative, and associated with somatic KRAS or NKX2-1 mutations.

Adenosquamous carcinoma often presents as exophytic, polypoid mass with ulceration. They show a combination of squamous cell carcinoma and adenocarcinoma, with each component being at least 10%. Cytologic specimens are limited in nature for diagnosing adenosquamous carcinoma as one of the two components might be preferentially sampled. A high-grade mucoepidermoid carcinoma is difficult to differentiate from it. Some features that may be helpful are lack of keratinization and squamous pearl formation, characteristic areas showing a low-grade mucoepidermoid carcinoma, absence of overlying squamous cell carcinoma in situ and lack of TTF-1 staining. Identification of a MAML2 translocation can help in difficult cases.

Non-keratinizing squamous cell carcinoma originates from the central airways and appears as a polypoid mass with peripheral projections. Tumor cells are polygonal forming sheets or nests with intercellular bridges but without keratin pearls; there are large nuclei with one or multiple nucleoli, coarsely granular chromatin and numerous mitoses. Non-keratinizing squamous cell carcinoma shows positivity for pan-cytokeratin, CK5/6, p16, p40, p63, Napsin A, and is CK20 negative.

In summary, primary mucoepidermoid carcinoma is a rare type of cancer when presenting as a lung mass. To our knowledge, there are no prior case reports in the literature in which the correlation between cytology and histology was described. Our case describes the cytomorphologic features on lung aspirate cytology that correlated well with the histologic diagnosis on the subsequent lobectomy specimen. Awareness of these features will help the cytopathologists to correctly identify pulmonary mucoepidermoid carcinoma and order the appropriate ancillary tests.

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Declaration of competing interest

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