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Bronchial Brushing Cytologic Finding of Primary Pulmonary Adenoid Cystic Carcinoma Misinterpretated as Small Cell Carcinoma – A Case Report with Literature Review –

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An adenoid cystic carcinoma is a very rare primary pulmonary neoplasm. Bronchial washing and brushing cytological findings of pulmonary adenoid cystic carcinoma have rarely been described. Here, we report the bronchial brushing cytological findings of an adenoid cystic carcinoma, finally diagnosed in a 71-year-old female patient. The low-power view showed moderate cellularity and cohesive clusters of small to medium-sized cells. The high-power view revealed distinct nuclear moldings, a coarse chromatin pattern, and inconspicuous nucleoli, which was favorable to a diagnosis of small cell carcinoma. However, apoptotic bodies, nuclear debris, and mitoses were not seen frequently. The bronchial biopsy showed solid, trabecular, and cribriform patterns in small cells. Periodic acid Schiff staining disclosed globular basement membrane-like materials, and the immunohistochemical staining revealed the presence of myoepithelial cell components, strongly suggestive of a salivary gland type tumor, compatible with an adenoid cystic carcinoma. In this report, we describe the exfoliative cytological features of a pulmonary adenoid cystic carcinoma with emphasis on some diagnostic pitfalls.

Key Words: Carcinoma, adenoid cystic; Lung; Bronchial brushing

An adenoid cystic carcinoma (ACC) of the lung is a malignant tumor that arises in ducts of bronchial submucosal mucous glands. ACC of the lower respiratory tract constitutes ≤0.2% of all primary pulmonary tumors.[1] A diagnosis of ACC on cytology is uncommon even on exfoliative cytology,[2-4] as well as fine needle aspiration cytology.[5,6] To the best of our knowledge, this is the second case of bronchial brushing cytology of a pulmonary ACC in Korea.[4]

CASE REPORT

A 71-year-old woman presented with a complaint of dyspnea, which had started 3 years ago and was recently aggravated. A chest X-ray in the emergency room showed multiple nodules in the right lower lung field. Chest computed tomography findings revealed multiple nodular masses in the right lower lobe, partially involving the middle lobe and right chest wall, right atrium, and pulmonary artery, suggestive of advanced lung cancer (Fig. 1A). Bronchoscopic findings disclosed an intraluminal protruding mass (Fig. 1B). Bronchial washing and brushing cytology and a biopsy were performed. The low-power view of the bronchial brushing cytology showed moderate cellularity and cohesive clusters of small to medium-sized cells (Fig. 2A). The high-power view revealed distinct nuclear moldings, a coarse chromatin pattern, and inconspicuous nucleoli, which was favorable to a diagnosis of small cell carcinoma (Fig. 2B). The initial cytological diagnosis was "consistent with small cell carcinoma;" however, apoptotic bodies, nuclear debris, and mitoses were not seen frequently. The bronchial biopsy showed a submucosal lesion composed of solid, trabecular, and cribriform patterns of small tumor cells (Fig 3A). The high-power view revealed more distinct patterns and two components of tumor cells, ductal and myoepithelial cells (Fig 3B). Periodic acid Schiff (PAS) staining disclosed globular basement membrane-like materials (PAS stain) (Fig. 3C) and the immunohistochemical staining revealed the presence of myoepithelial cell components (S-100 immunostain) (Fig. 3D), strongly suggestive of a

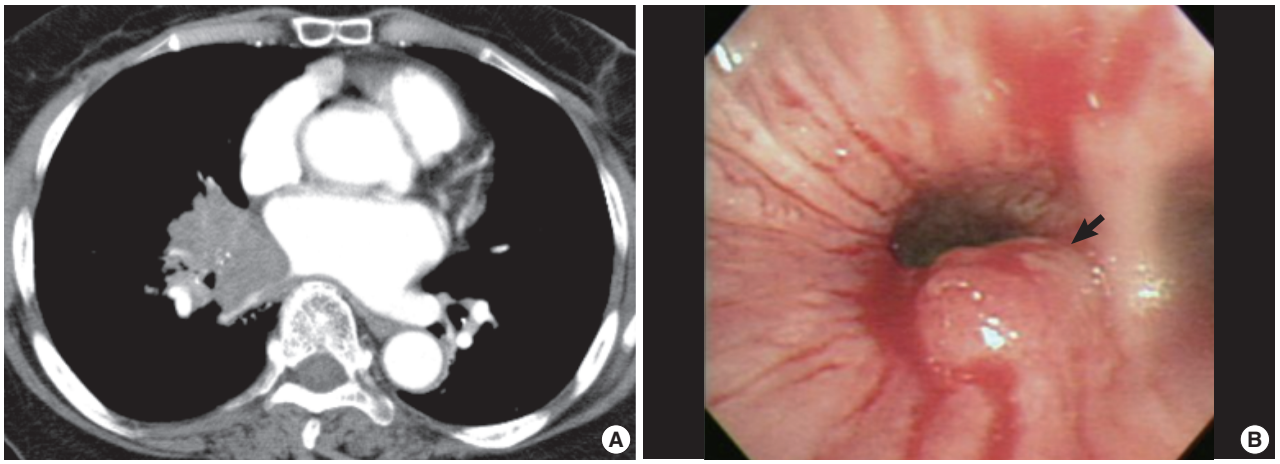

Fig. 1. (A) Chest computed tomography scan reveals an infiltrative mass in the right lower lobe involving the right atrium and pulmonary artery. (B) Bronchoscopy of the right lower bronchus discloses a protruding nodular mass with intact mucosa.

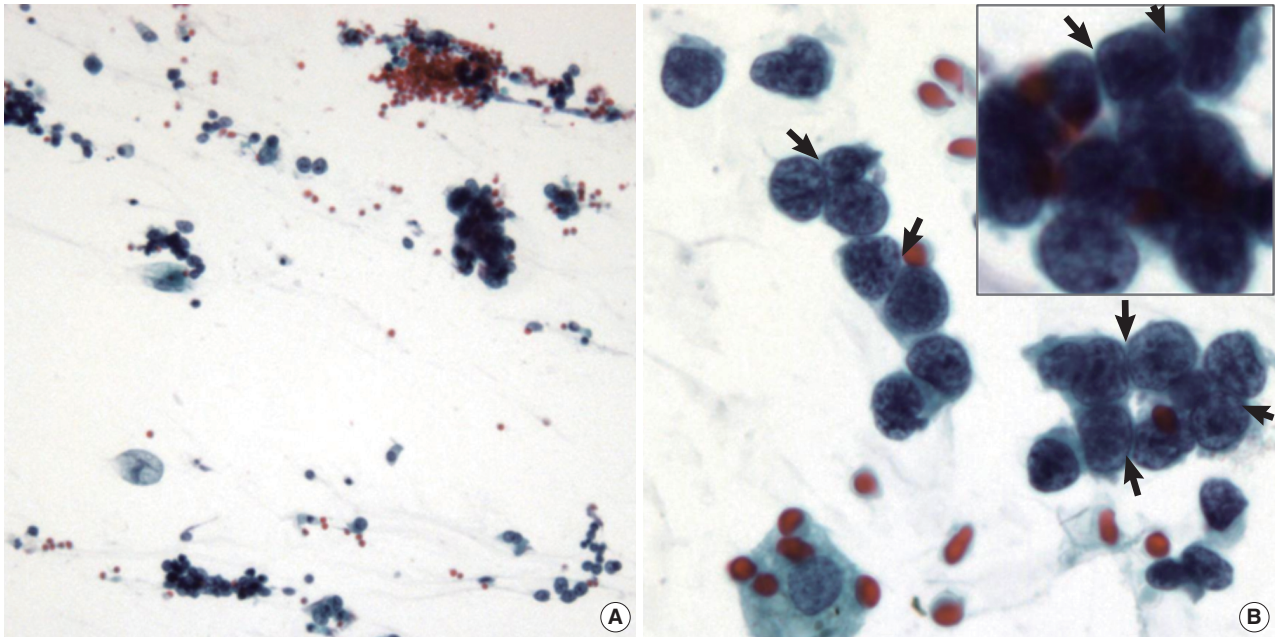

Fig. 2. (A) Low-power view of bronchial brushing cytology shows moderate cellularity and cohesive clusters of small to medium-sized cells in a clean background (Papanicolaou stain). (B) High-power view of tumor cells reveals a few distinct nuclear moldings (arrows), a coarse chromatin pattern, and inconspicuous nucleoli, reminiscent of small cell carcinoma (Papanicolaou stain).

salivary gland type tumor and compatible with ACC. Epithelial membrane antigen immunostaining was also positive in myoepithelial cells. C-kit was diffusely and strongly positive in both tumor cell components. All neuroendocrine markers (CD56, synaptophysin, and chromogranin) and thyroid transcription factor-1 were negative in tumor cells. Retrospectively, the cytologic clusters showed sieve-like structures (Fig. 3E) with globular basement membrane- like materials (PAS stain) (Fig 3F). The patient was lost to clinical follow-up after the pathological diagnosis.

DISCUSSION

ACC is an infiltrative, malignant, epithelial neoplasm with a distinct histological pattern of growth consisting of cribriform or glandular arrays and tubules surrounding central spaces filled with mucin and solid foci. The rarity of this tumor with intact

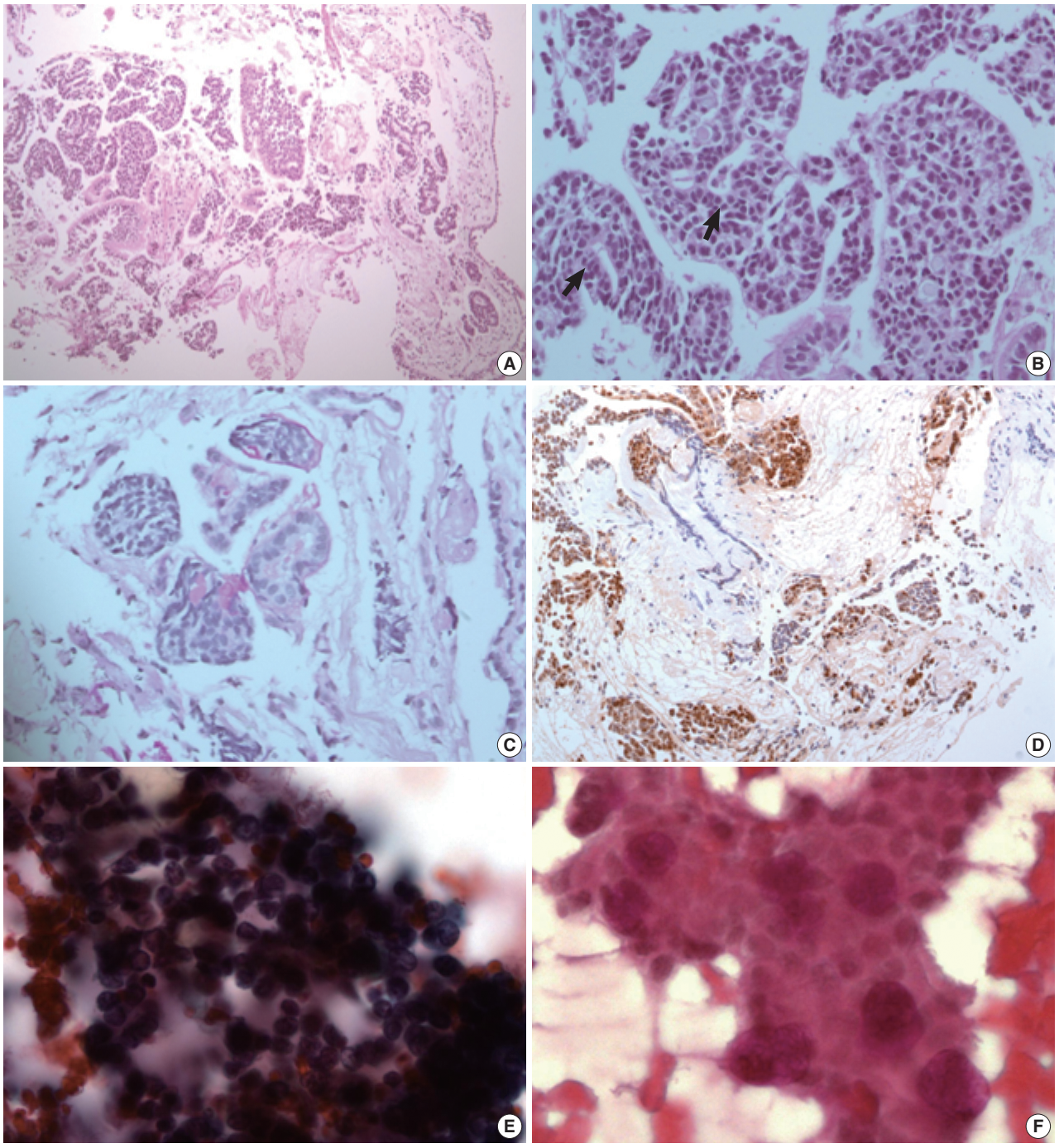

Fig. 3. (A) The subsequent bronchial biopsy shows a submucosal lesion, composed of solid, trabecular,and cribriform patterns of small tumor cells. (B) The high-power view distinctively discloses two tumor cell components. Arrows indicate myoepithelial cells. (C) Periodic acid Shiff (PAS) staining reveals oval globular material in a cribiform pattern. (D) S-100 immunostaining indicates the myoepithelial cells around luminal cells. (E) A retrospective cytologic review discloses a cluster of oval cells containing globular basement membrane-like materials, filled in a sieve-like structure (Papanicolaou stain). (F) PAS staining of a cytological smear also shows a characteristic globular materials.

overlying mucosa increases the false negativity of the exfoliative cytological diagnosis. The other diagnostic pitfall is a misdiagnosis as a small cell carcinoma, similar to our case, because of relatively small monotonous tumor cells with scanty cytoplasm and occasional nuclear moldings.

Cytological evidence of ACC in the salivary gland is well described. Several reports of aspiration cytological diagnosis of ACC indicated that the ACC metastasized to the lung.[7] How-

ever, an exfoliative diagnosis of this tumor is very rare.[2-4] Including our case, there are 13 reports of a cytological diagnosis of primary pulmonary ACC in the English literature; four cases were based on fine needle aspiration and nine on exfoliative cytology. The only other exfoliative cytology report of pulmonary ACC in Korea described the classic features of the tumor, but did not indicate similarity to a small cell carcinoma.[4]

As in our case, pulmonary ACC usually presents as a polypoid lesion on bronchoscopy, causing thickening of the airway submucosa. Although no endobronchial component of the tumor was seen on computed tomography in the present case, a polypoid mass was observed within the bronchial lumen on bronchoscopy. If the tumor is located mainly in the submucosal layer, it is difficult to obtain representative exfoliative cytological material. If exfoliative cytological material is obtained following a bronchial biopsy and disrupts the integrity of the overlying mucosa, the tumor is easily exposed, resulting in successful exfoliation of tumor cells.[3]

The cytology of this neoplasm was round oval tumor cells with scanty cytoplasms, a high nuclear/cytoplasmic ratio, smooth nuclear contours, and no prominent nucleoli. The chromatin was usually compact. The cribriform or sieve-like pattern contained hyaline globules. The formation of tight, branching, tubular clusters of cells, impacting a cylindroids or tubular appearance, is a helpful feature in the diagnosis. However, a diagnosis of the solid variant of ACC may pose a problem, as the tumor may show only tissue fragments containing small cells in a three-dimensional arrangement. Similar to mucoid or basement membrane-like material, this inclusion is positive for PAS and Alcian blue stains but negative for mucicarmine.

Before making a diagnosis of primary ACC of the lung, metastatic ACC from other primary sites must be excluded.[7]

The main differential diagnoses are reserve cell hyperplasia, typical/atypical carcinoid, small cell carcinoma, and well differentiated adenocarcinoma.[2] In reserve cell hyperplasia, sheets of compactly arranged, small cells with scant cytoplasm are evident, with round nuclei and high nuclear/cytoplasmic ratios. The presence of cilia and attached columnar cells are helpful findings of reserve cells. However, the findings of cribriform and tubular structures do not favor a diagnosis of reserve cell hyperplasia. The tumor cells in carcinoids usually display uniform, small cells with rounded nuclei and a stippled chromatin with marked cell dissociation. A small cell carcinoma is composed of small cells with nuclear moldings, stippled chromatin, traumatic nuclear streaking, and scant cytoplasm, but acellular balls of basement membrane-like materials within the cell clusters are not seen in small cell carcinoma. The nuclear molding phenomenon has been described as representative of small cell carcinoma. However, it has also been described in the cytological findings of pulmonary as well as salivary ACC.[2] The lack of apoptotic bodies, nuclear debris, frequent mitoses, and the Azzopardi effect is a good distinguishing point. Well differentiated adenocarcinomas, whether primary or secondary, enter the differential diagnosis if they present with tubular or glandular spaces. However, a globular arrangement of cells cannot be found in a typical adenocarcinoma.

In summary, the nuclear molding and the composition of small sized, monotonous tumor cells with inconspicuous nucleoli in respiratory exfoliative cytology are not directly indicative of small cell carcinoma, particularly in a clinical setting of a submucosal mass epicentered in the bronchus. A differential diagnosis of ACC should be considered on one occasion; a recognition of characteristic globular basement membrane-like material in sieve-like clusters is very important. If possible, PAS staining of the cytology specimen is helpful for hidden globular basement membrane-like material.

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