Cytology of Primary Salivary Gland-Type Tumors of the Lower Respiratory Tract: Report of 15 Cases and Review of the Literature

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Primary pulmonary salivary gland-type tumors are rare neoplasms arising from the seromucinous submucosal glands of the lower respiratory tract (LRT), the most common of which are mucoepidermoid carcinoma (MEC) and adenoid cystic carcinoma. They are morphologically indistinguishable from their salivary gland counterpart and recognizing them is a challenge, especially on cytological specimens. We analyzed 15 cases of histologically proven primary salivary gland tumors of the LRT to identify cytomorphological features and define potential diagnostic clues that might assist cytopathologists in the preoperative diagnosis of these neoplasias. Three out of the four cases of adenoid cystic carcinomas showed the characteristic tridimensional cell clusters and hyaline globules, whereas the last one did not show malignant cells; only two cases of MEC presented the three characteristic cell types (i.e., squamous, intermediate, and mucin secreting) on cytology. Since these neoplasms are rare and do not have a completely specific set of cytological features, it is important for practicing cytopathologists to be aware of the possibility of encountering them, in specimens from patients with LRT masses, in order to render the correct diagnosis.

Keywords: cytology, lung, salivary gland-type tumors, mucoepidermoid carcinoma, adenoid cystic carcinoma

INTRODUCTION

Primary salivary gland-type tumors (PSGT) arising from the seromucinous submucosal glands of the lower respiratory tract (LRT) (which includes trachea, bronchus and lung) account for <1% of central airway carcinomas (1). They are rare neoplasms morphologically indistinguishable from their salivary gland counterpart; therefore, recognizing them is a challenge, especially on cytology. Even though any type of salivary gland tumor that has been described in pathology textbooks can potentially arise in the LRT, published data show that the most commonly encountered primary salivary gland-type tumors in this anatomical site are malignant mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (AdCC), and epithelial-myoepithelial carcinoma (2–5). In fact, as opposed to the head and neck region, where the vast majority of salivary gland primaries are benign—with pleomorphic adenoma (PA) being the most common type—the contrary applies to LRT primaries (1).

Cytological examination of fine-needle aspiration (FNA), bronchial aspiration (BA) or brushing (BB), bronchoalveolar lavage (BAL), or even sputum has been shown to be a powerful tool for
the diagnosis of lung cancer, particularly when it presents as an endobronchial growth. Moreover, in recent years, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has emerged as the standard of care for the diagnosis and staging of lung cancer and has been successfully implemented into daily clinical practice. EBUS-TBNA is minimally invasive, safe, cost-effective, and particularly useful in diagnosing centrally located lung lesions (6).

All the aforementioned cytological procedures are useful for collecting material for cytological examination, immunocytochemistry (ICC), fluorescent in situ hybridization (FISH), or molecular analyses, which may be relevant for diagnosis and targeted therapy. Moreover, in 30% of cases, cytological material is the only material available for pulmonary malignancies and proper classification of the lesions, often with subtyping, is fundamental for adequate patient management.

We describe 15 cases of histologically proven PSGT of the LRT; all but two were misdiagnosed on preoperative cytology. We have tried to identify cytomorphological features that could point to a correct cytological diagnosis. To the best of our knowledge, this is the largest cytological series of PSGT of the LRT ever published.

MATERIALS AND METHODS

Case Selection

Nineteen cases of surgically resected PSGT originating from the trachea, main bronchi, and lung with corresponding preoperative cytology were identified by searching the databases of our institutions (Service of Clinical Pathology, Lausanne University Hospital; Department of Pathology, Geneva University Hospital; Section of Anatomic Pathology, San Luigi Hospital, Orbassano, Turin) over a period of 21 years (1995–2015). Cytological and histological specimens of each case were retrieved from the archives to be reviewed for adequacy. Three cases were excluded because slides were no longer available for revision, and one case was excluded because it originated from the larynx and not from the LRT. The database was also investigated to exclude the presence of primary salivary gland tumors that could have metastasized to the LRT.

The study cohort of the present work was thus composed of 15 cases. Clinical, radiological, and pathological reports for each patient were analyzed to collect pertinent information, including age, gender, alcohol and smoking history, presenting symptoms and signs, radiological findings, tumor size, and original preoperative cytological diagnosis.

Cytomorphological Features

All cytological smears were reviewed by an expert cytopathologist (Massimo Bongiovanni) to evaluate the presence of cytomorphological features that could have pointed to a correct preoperative diagnosis, namely: the presence of mucin and the three different neoplastic cellular components (mucin secreting, squamous, and intermediate) characteristic of MEC (3); organoid cell clusters, hyaline globules, cellular uniformity, and granular cytoplasm distinguishing AdCC (7). Particular attention was paid to look either cytologically or histologically for some of the newly described entities of salivary gland tumors, namely the mammary analog secretory carcinoma (MASC), the cribriform adenocarcinoma of the tongue, and minor salivary gland (CATS) that so far have never been described in the LRT (8).

RESULTS

Clinicopathological Findings

A summary of all relevant clinical, radiological, and pathological data of the patients are presented in Table 1. Patients ranged in age from 16 to 87 years (mean 59.6 ± 18.6 years); there were nine males and six females. From histology, 11 cases were diagnosed as MEC (5 low grade and 6 high grade), and the remaining four cases were diagnosed as AdCC according to the histological criteria defined by the current WHO classification (3, 4).

The cytological slides that were revised included: 12 BA, 7 BB, 5 BAL, and 1 FNA. More than one type of cytological sample was available for 6 out of the 15 cases (Table 1). The smears were either alcohol-fixed, Papanicolaou (PAP) stained or air dried, May-Grünwald-Giemsa (MGG) stained. Neither FISH analysis nor molecular studies were originally performed.

Tumors were all centrally located and ranged in size from 1.7 to 5.0 cm (mean 4.4 ± 1.2 cm). Only one AdCC and one MEC were somehow identified preoperatively: the AdCC was diagnosed as a salivary gland-type neoplasia and the MEC as a non-small cell lung carcinoma, consistent with MEC. Five preoperative cytological cases were originally reported as negative for malignant cells (33.3%) (1 AdCC and 4 MEC), and this diagnosis was confirmed after revision of the slides in four out of five cases. Revised cytological diagnosis of the fifth case was that of an adenocarcinoma (concerning the BA specimen only). Interestingly, one AdCC was misdiagnosed as a metastatic breast carcinoma (due to the previous history of ductal breast carcinoma in the patient). During revision of the slides, all three diagnostic cases of AdCC showed the characteristic tridimensional cell clusters and hyalineglobules that permit the cytological diagnosis of this entity, whereas only two cases of MEC presented the three characteristic cell types (i.e., squamous, intermediate, and mucin secreting) on cytology.

DISCUSSION

Cytology has proven to be a powerful tool for the diagnosis of primary lung cancer. A summary of all published cases of PSGT of the LRT for which a cytological diagnosis is available in the literature is provided in Table 2. Exfoliative cytology, in particular bronchial brushing, aspiration, and washing, is especially useful for tumors with endobronchial growth. PSGT of the LRT, because of their origin from the submucosal bronchial glands, mainly present as endobronchial masses (1), and therefore, they are considered as accessible for cytological sampling and diagnosis. However, as previously reported by other authors, primary pulmonary AdCCs and MECs are usually covered by intact respiratory epithelium; therefore, FNA may be more effective than exfoliative cytology in diagnosis for some of such cases (9, 10). The results from our study confirm that when using exfoliative cytology only, a significant proportion of PSGT of the LRT cases (33%) do not yield diagnostic tumor cells.
| No. | Sex | Age  | Alcohol/smoking | Relevant clinical findings | Radiology/bronchoscopy findings | Site                      | Lesion size (cm) | Preoperative cytology | Histologic diagnosis | Revised cytological diagnosis |
|-----|-----|------|-----------------|---------------------------|--------------------------------|-----------------------------|------------------|-----------------------|----------------------|-------------------------|
| 1   | F   | 64   | NA/NA           | NA                        | Distal carinal stenosis      | Carina                     | 2.5              | Salivary gland-type neoplasia | NP                  | NP                      | AdCC                  | AdCC                   |
| 2   | F   | 74   | NA/NA           | History of breast ductal carcinoma | Bronchial polypoid mass      | Right main bronchus         | 4.5              | Metastatic breast carcinoma | NP                  | AdCC                   | AdCC                  |
| 3   | M   | 70   | NA/no           | NA                        | Lung mass                    | Right superior lobe        | 1.7              | Absence of malignant cells  | NP                  | NP                      | AdCC                  | Absence of malignant cells |
| 4   | F   | 75   | NA/NA           | Weakness, non-productive cough | NA                           | NA (biotic material only)   | NA               | Suspicious for carcinoma | NP                  | NP                      | AdCC                  | AdCC                   |
| 5   | M   | 87   | No/no           | Fall with costal fracture, hemorrhagic pleural effusion | Mass lesion with bronchial stenosis and atelectasis | Right lung                 | 2.0              | PDC                   | NP                  | MEC (low-grade)         | PDC                   |
| 6   | F   | 49   | Yes/yes         | Weight loss, dyspnea, retrosternal pain | Lung mass                   | Left upper lobe            | 3.5              | Atypical squamous cells    | NP                  | MEC (low-grade)         | PDC                   |
| 7   | F   | 65   | No/no           | Weakness, productive cough, hemoptysis | Parahilar mass with atelectasis | Left upper lobe            | 2.6              | PDC                   | NP                  | MEC (high-grade)        | PDC                   |
| 8   | M   | 75   | No/yes          | Progressive dyspnea, non-productive cough | Bronchial stenosis           | Left main bronchus         | 4.0              | Suspicious for carcinoma | NP                  | MEC (high-grade)        | PDC                   |
| 9   | M   | 60   | Yes/yes         | Ongoing cough               | Peribronchial mass lesion    | Left inferior lobe bronchus | 5.0              | NP                    | Adenocarcinoma         | NP                      | MEC (high-grade)        | PDC                   |
| 10  | M   | 57   | NA/NA           | NA                         | Lung nodule                  | Medium lobe                | 2.0              | Absence of malignant cells | NP                  | MEC (low-grade)         | Adenocarcinoma (for the BA specimen only) |
| 11  | M   | 35   | NA/NA           | NA                         | Extrinsic bronchial compression | Apical bronchus of right superior lobe | 5.0              | NP                    | Absence of malignant cells | MEC (high-grade)        | Absence of malignant cells |
| 12  | M   | 37   | NA/NA           | NA                         | Lung mass                    | Segmental bronchus of right superior lobe | 2.0              | NP                    | NSCLC, compatible with MEC | MEC (high-grade)        | NSCLC, compatible with MEC |
| 13  | M   | 76   | NA/yes          | NA                         | Apical nodule hypermetabolic at PET scan | Left inferior lobe         | 2.5              | Absence of malignant cells | NP                  | MEC (high-grade)        | Absence of malignant cells |
| 14  | M   | 16   | No/no           | Progressive dyspnea, cough  | NA                          | NA (biotic material only)   | NA               | Absence of malignant cells | NP                  | MEC (low-grade)         | Absence of malignant cells |
| 15  | F   | 54   | NA/NA           | Pleural effusion            | NA                          | NA (biotic material only)   | NA               | Suspicious for carcinoma, NOS | NP                  | MEC (low-grade)         | NSCLC, compatible with MEC |

AdCC, adenoid cystic carcinoma; MEC, mucoepidermoid carcinoma; BA, bronchial aspiration; BB, bronchial brushing; BAL, bronchoalveolar lavage; PDC, poorly differentiated carcinoma; NSCLC, non-small cell lung cancer; NA, not available; NP, not performed.
| Reference | Sex | Age | Presentation | Radiology findings | Bronchoscopy findings | Site | Lesion size (cm) | Preoperative cytology | Frozen section | Histologic diagnosis |
|-----------|-----|-----|--------------|-------------------|----------------------|------|----------------|----------------------|---------------|---------------------|
| Tao and Robertson (9) pt no. 1 | F | 46 | Cough, shortness of breath, decreased energy | Well-circumscribed, round lesion (CT) | Mass occluding the right upper lobe bronchus | Right hilum | 3 | MEC | NA | NA | NA | Negative for malignancy | NA | MEC |
| Tao and Robertson (9) pt no. 2 | F | 54 | Incidental finding on chest X-ray | Coin lesion (chest X-ray) | Polyoid friable tumor | Left main stem bronchus, carinal level | NA | NA | NS | Negative for malignancy | AdCC | AdCC | AdCC |
| Lozowski et al. (10) pt no. 1 | F | 40 | Productive cough, fever, chills, headache, lethargy | Consolidative pneumonitis of left lower lobe | Tracheal carina + stem bronchi | NA | NA | NA | NA | NA | AdCC | NA | AdCC |
| Nguyen (11) pt no. 1 | M | 50 | Cough, hemoptysis | NA | Left stem bronchus | NA | NA | AdCC | NA | Positive for malignancy | NA | AdCC |
| Nguyen (11) pt no. 2 | F | 36 | Cough, hemoptysis | NA | Tracheal carina + stem bronchi | NA | NA | MEC | Negative for malignancy | NA | MEC |
| Nguyen (11) pt no. 3 | M | 48 | Persistent cough | NA | Left stem bronchus | NA | NA | MEC (low-grade) | Negative for malignancy | NA | MEC (low-grade) |
| Nguyen (11) pt no. 4 | F | 29 | Persistent cough | NA | Left stem bronchus | NA | NA | MEC (low-grade) | Negative for malignancy | NA | MEC (low-grade) |
| Nguyen (11) pt no. 5 | M | 80 | Cough, hemoptysis, weight loss | NA | Right upper lobe bronchus | NA | NA | Adeno-squamous carcinoma | Negative for malignancy | NA | Negative for malignancy |
| Buchanan et al. (12) pt no. 1 | M | 23 | Subternal discomfort, choking sensation, wheezing, productive cough | Normal chest X-ray | Obstructing tumor | Trachea | NA | NA | AdCC | NA | AdCC |
| Buchanan et al. (12) pt no. 2 | F | 51 | Cough, wheezing, intermittent breathing difficulties | Spherical mass | NA | Trachea | 1 | NA | NA | AdCC | Negative for malignancy | NA | AdCC |
| Gupta and McHutchison (13) pt no. 1 | F | 85 | Increasing shortness of breath, productive cough | NA | Endotracheal tumor | Midtrachea | NA | NA | NA | AdCC | NA | AdCC |
| Brooks and Baandrup (14) pt no. 1 | M | 66 | Incidental finding on chest X-ray | Peripheral lung mass | Tumor at the carina extending in the bronchi | Carina + adjacent stem bronchi | NA | NA | NA | AdCC | NA | AdCC |
| Radhika et al. (15) pt no. 1 | M | 45 | Progressive breathlessness, productive cough | Collapse of the right lung | Right lower lobe | NA | NA | NA | MEC | NA | MEC |
| Segletes et al. (16) pt no. 1 | M | 47 | Chronic pneumonia, increasing cough | Central right upper lobe mass | Right upper lobe | NA | MEC | NA | NA | NA | NA | MEC |
| Segletes et al. (16) pt no. 2 | M | 72 | Incidental finding on chest X-ray | Left lung mass extending into the chest wall | Left lung | NA | Consistent with MEC | NA | NA | NA | NA | MEC |
| Segletes et al. (16) pt no. 3 | M | 16 | Pneumonia, cough, earache, weight loss | Mediastinal mass with enlarged lymph nodes | Right main stem bronchus | NA | NA | NA | NA | NA | MEC |

(Continued)
| Reference                  | Sex | Age | Presentation                                      | Radiology findings                        | Bronchoscopy findings                  | Site                        | Lesion size (cm) | Preoperative cytology | Frozen section | Histologic diagnosis |
|----------------------------|-----|-----|--------------------------------------------------|-------------------------------------------|----------------------------------------|----------------------------|------------------|----------------------|------------------|----------------------|
| Segletes et al. (16) pt no. 4 | F   | 25  | NA                                               | NA                                        | Tumor in the bronchial lumen          | Upper left lobe bronchus   | NA               | NA                   | NA               | AdCC                 |
| Delpiano et al. (17) pt no. 1 | M   | 52  | Cough, hemoptysis                                | Coin lesion upper lobe of left lung       | Reddish cauliflower-like lesion       | Upper left lobe bronchus   | NA               | NA                   | NA               | Papillary mucous gland adenoma |
| Romagosa et al. (18) pt no. 1 | F   | 33  | Cough, fever, mucopurulent expectoration, shortness of breath | NA                                        | Intrabronchial polypoid mass          | Left main bronchus         | NA               | Cells with bland nuclei, wide cytoplasm, and intranuclear inclusions; minor population of mucus-secreting cells | NA               | Negative for malignancy | MEC (low-grade) |
| Romagosa et al. (18) pt no. 2 | F   | 39  | Incidental finding on chest X-ray                | Right lower lobe mass                     | Right lower lobe                      | NA                         | Cells with bland nuclei, wide cytoplasm, and intranuclear inclusions; minor population of mucus-secreting cells | NA               | Negative for malignancy | MEC (low-grade) |
| Qiu et al. (19) pt no. 1    | M   | 51  | Left chest and shoulder pain, fever, leg swelling | NA                                        | Atelectasis of left upper lobe mass    | Left upper lobe bronchus    | 1                | AdCC                 | NA               | AdCC                 |
| Florentine et al. (20) pt no. 1 | F   | 85  | Obstructing tumor                                | NA                                        | Obstructing tumor                     | Left main bronchus         | NA               | NA                   | NA               | NA                   | AdCC |
| Chuah et al. (21) pt no. 1  | M   | 44  | Throat irritation, persistent cough              | Mass lesion                               | Polypoid tumor in bronchial lumen     | Left hilum                 | NA               | NA                   | NA               | Carcinoid tumor or AdCC |
| Daneshbod et al. (22) pt no. 1 | F   | 55  | Increasing shortness of breath, productive cough | Mass lesion                               | Left lower lobe                       | NA                         | NA               | NA                   | NA               | Carcinoma consistent with AdCC |

(Continued)
| Reference            | Sex | Age  | Presentation                                                                 | Radiology findings                                                                 | Bronchoscopy findings                        | Site                                                                 | Lesion size (cm) | Preoperative cytology | Frozen section | Histologic diagnosis |
|----------------------|-----|------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------|------------------|---------------------|------------------|---------------------|
| Daneshbod et al. (22) pt no. 2 | M   | 65   | Progressive breathlessness, productive cough                                  | Collapse of the right lung                                                       | Carinal tumor extending in major bronchi     | Carina + adjacent stem bronchi                                     | NA               | NA                  | NA               | Negative for malignancy  |
| Özkara and Turan (23) pt no. 1 | M   | 54   | Cough, expectoration, hemoptysis, chest pain, and weight loss                 | Opacity of left upper lobe (X-ray)                                              | Shiny, sessile, polypoid mass               | Left mainstem bronchus                                             | 4                | NA                  | NA               | AdCC, other than classical type |
| Chon et al. (24) pt no. 1 | F   | 46   | Incidental finding on chest X-ray                                            | NA                                                                               | Endobronchial mass lesion (CT)              | Right upper lobe                                                  | NA               | NA                  | NA               | Negative for malignancy  |
| Dyhdalo and Chen (25) pt no. 1 | F   | 45   | Productive cough                                                            | Right lower lobe bronchus                                                        | NA                                            | NA                                                                  | NA               | NA                  | NA               | AdCC, solid variant  |
| Kim et al. (7) pt no. 1 | M   | 42   | NA                                                                           | Bronchial narrowing                                                             | NA                                            | NA                                                                  | NA               | NA                  | NA               | Metastatic carcinoma from trachea |
| Kim et al. (7) pt no. 2 | F   | 47   | NA                                                                           | Endobronchial tumor infiltration                                                 | NA                                            | NA                                                                  | NA               | NA                  | NA               | Positive for malignant cells |
| Kim et al. (7) pt no. 3 | M   | 52   | NA                                                                           | Bronchial obstruction                                                            | NA                                            | NA                                                                  | NA               | Metastatic AdCC from lung | NA               | Metastatic AdCC from lung |
| Kim et al. (7) pt no. 4 | F   | 61   | NA                                                                           | NA                                                                               | Trachea                                       | NA                                                                  | NA               | NA                  | NA               | AdCC  |
| Kim et al. (7) pt no. 5 | M   | 57   | NA                                                                           | Bronchial obstructing mass                                                       | NA                                            | NA                                                                  | NA               | NA                  | A nest of atypical cells |
| Kim et al. (7) pt no. 6 | M   | 65   | NA                                                                           | Tracheal obstruction                                                             | NA                                            | NA                                                                  | NA               | NA                  | Atypical cells |
| Kim et al. (7) pt no. 7 | F   | 75   | NA                                                                           | Bronchial narrowing                                                              | NA                                            | NA                                                                  | NA               | NA                  | Suspicious for malignancy |
| Kim et al. (7) pt no. 8 | M   | 60   | NA                                                                           | Bronchial obstruction                                                            | NA                                            | NA                                                                  | NA               | NA                  | Suspicious for malignancy |
| Kim et al. (7) pt no. 9 | M   | 53   | NA                                                                           | Tracheal mass                                                                    | NA                                            | NA                                                                  | NA               | NA                  | AdCC  |

(Continued)
Mucoepidermoid carcinoma is the most common type of primary PSGT and it accounts for only 0.1–0.2% of all lung cancers (2, 28). In the majority of cases, it develops as an endobronchial lesion located in the central airways, namely trachea, carina, and main stem bronchi; less than 6% of patients present with a peripheral lung nodule (3, 28, 29). Prognosis of pulmonary MEC is significantly better than that of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Five-year survival of these three entities is 88, 21 and <5%, respectively (30). When they are divided into high-grade and low-grade tumors, bronchial MEC show a 5-year survival of 31 and 80%, respectively (31). The cytological features of LRT MEC, which can be diagnosed by FNA, BB, BA, BW, and BAL, overlap those of their salivary gland counterpart. Three cell types should be identified from MEC histology: mucin-secreting, squamous, and intermediate cells, which can be organized in different architectural patterns (32). Low-grade tumors show cystic zones consisting of cytologically bland mucin-secreting cells and solid areas composed of squamous or intermediate cells. Mitoses and necrosis are rare. High-grade tumors mainly consist of atypical squamous and intermediate cells, accompanied by variable numbers of mucin-secreting cells; necrosis; and mitoses are frequent (Figures 1A,B) (3). On cytological specimens, various combinations of mucin-producing, squamous, and intermediate cells have been observed according to tumor grade, with the characteristic admixture of all three cell types being helpful for recognition of this entity (Figures 1C–F) (9, 14, 25): typical non-keratinized squamous cells show round nuclei and moderate cytoplasm; mucinous cells are variable in shape, have small uniform nuclei and prominent nucleoli, and may contain a single vacuole that displaces the nucleus; intermediate cells have well-defined homogeneous cytoplasm and small round nuclei with small nucleoli (25). Published cytological literature concerning primary pulmonary MEC shows that only Tao and Robertson and Brooks et al. have reported the presence of three distinct cell types (9, 14); all of the other authors described at best only two different cellular populations (Table 3) (11, 16, 18, 25). Other features encountered on MEC histology, such as the presence of intranuclear inclusions and clear cell change, have been occasionally described on cytology (18).

Adenoid cystic carcinoma also generally arises as an endobronchial tumor in central airways (Figures 2A,B); only sporadically is it reported in a peripheral lung location (4). Primary pulmonary AdCC is composed of two main cell types, ductal and modified myoepithelial cells, and can present three main architectural patterns, in keeping with salivary AdCC: cribriform, and modified myoepithelial cells, and can present three main architectural patterns (1, 4). Cytological findings include cohesive clusters of repetitive medium-sized cells, with scant cytoplasm and uniform, small, hyperchromatic nuclei containing a finely granular, evenly distributed chromatin (Figures 2C–F). Tumor cells are often arranged around a central core of homogeneous myxoid material, or form three-dimensional, “ball-like” clusters (Table 4) (10–13, 15, 19–22, 24, 26, 33). All of these features that recapitulate the histopathology of AdCC are helpful in correctly orienting the cytological diagnosis of this neoplasm. Sometimes, isolated hyaline globules can be observed (7, 20, 24, 26); singly dispersed cells are present on some smears (11, 26). The basement membrane material, forming globules that have a light blue
appearance on PAP stain and bright magenta on MGG stain, is the characteristic feature of AdCC; diagnostic difficulties arise when they are not present on cytological material, as the pattern could mimic carcinoid tumor, SCLC, NSCLC, and reserve cell hyperplasia (19).

Retrospectively, a correct preoperative diagnosis of all AdCC could have been rendered, because characteristic tridimensional clusters and hyaline globules were present on the smears; the hyaline globules were confused with a metastatic breast carcinoma in the original diagnosis of one case and considered suspicious for carcinoma, NOS, in the other. Considering MEC, only one additional case could have been identified. The cytological diagnosis of MEC was possible since all the three diagnostic cellular components were present with features of malignancy (i.e., squamous, glandular, and intermediate cells). When looking carefully at the smears, it was possible to identify aggregates of medium-sized cells that were bigger than basal and reserve bronchial cells. In the original cytological diagnosis, these intermediate cells were considered as suspicious for a carcinoma, NOS. Of note, in this case, an Alcian Blue staining was performed to identify glandular neoplastic cells, but only normal bronchial mucous cells were seen. Retrospective analysis revealed that the cells defined as “normal bronchial cells,” which stained positive for Blue-Alcian, were actually atypical. This allowed the retrospective diagnosis of MEC. In the remaining cases, the criteria for MEC were not fulfilled and only a poorly differentiated carcinoma could be diagnosed.

Immunocytochemistry is of limited value in diagnosing PSGT of the LRT. If these histological subtypes are not considered, only traditional markers of NSCLC subtyping are used. While epithelial cells of MEC and ductal cells of AdCC are positive for common epithelial markers (such as CK7 and CK 5/6) and
p63 and p40 are expressed in all the intermediate and squamous cell component of MEC, myoepithelial cells of AdCC are usually positive for smooth muscle actin, vimentin, myosin, S-100, and for p63. Thus, CK7, CK5/6, p63, and p40 are potentially misleading markers as they are also part of the immunocyto/histochemical panel used to classify lung carcinomas. Their positivity would lead to a diagnosis of primary lung squamous cell carcinoma, rather than pointing to the presence of a squamous cell component in MEC or to the myoepithelial differentiation typical of AdCC (34, 35).

Besides these more common entities, other rarer PSGT of the LRT include acinic cell carcinoma, PA with its malignant counterpart carcinoma ex PA, myoepithelioma and myoepithelial carcinoma, mucous gland adenoma, and oncocytoma (1, 33, 36, 37). No cytological description of such lesions in the LRT has been reported. Recently, a case of a primary pulmonary mucinous-rich variant of salivary duct carcinoma with preoperative cytology was published: BAL revealed cytoplasmic atypia, and the right upper lobe bronchial brushing was positive for carcinoma. However, ICC was not performed due to the paucity of diagnostic material and a conclusive diagnosis was not reached on cytological material (38). MASC, a rare salivary gland tumor first described in 2010, has never been described as a primary lung neoplasm (39). While reviewing the cytological and histological slides for our study, we paid particular attention to the identification of features that could point to a diagnosis of MASC, which we did not observe. No features resembling acinic cell carcinomas, that could have warranted (on cytological as well as on histological material) an immunocytochemical analysis for mammaglobin or FISH/molecular analysis for ETV6-NTRK3 translocation or ETV6 break, were seen (40, 41). ETV6-NTRK3 translocation or ETV6 breaks are present in up to 80 and 99% of MASC cases, respectively, and are quite specific for this entity (8).

In recent years, in addition to this molecular feature characteristic of MASC, other diagnostic molecular signatures have been described for salivary gland tumors, even the ones developing in the LRT, and some with a high prevalence and discrete specificity (8, 34, 35, 42). With respect to MEC, specific translocations involving the CRTC1 gene and MAML2 or CRTC3 and MAML2 have been described, with frequencies up to 80 and 6% respectively (8, 43, 44). AdCC is characterized by a specific translocation, namely MYB/NFIB, present in up 90% of cases (8, 45). This translocation results in MYB protein overexpression that can be detected using IHC (46, 47). This test can be particularly useful to confirm the diagnosis of AdCC, especially when combined with c-KIT (CD117) positivity, and can be applied on cytological smears. However, immunohistochemical staining for CD117 cannot be used alone in differential diagnosis of salivary gland neoplasms, because AdCC, PA, polymorphous low-grade adenocarcinoma, and monomorphic adenoma have all been

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**Table 3: Cytomorphological features of primary pulmonary mucoepidermoid carcinoma (MEC) reported in the literature.**

| Reference         | Architecture | Background | Cell shape                  | Cytoplasm                      | Nuclei    | Chromatin         | Nucleoli          |
|-------------------|--------------|------------|-----------------------------|--------------------------------|-----------|-------------------|-------------------|
| Tao and Robertson (9) | Tissue fragments with connective tissue core | ND         | Spindle cells               | Scanty                         | Ovoid     | Finely granular, evenly distributed | Conspicuous in some cells |
|                   |              |            | Epidermoid cells            | Apparent but not abundant      | Round     | Finely granular, evenly distributed | Conspicuous, prominent |
|                   |              |            | Mucus-secreting cells       | Containing a large mucous vacuole | Round     | ND                | ND                |
| Nguyen (11)       | Single cells or small aggregates | Basophilic mucus-like material | Squamous cells (highly atypical) | ND       | Large, vacuolated | ND                | Prominent |
| Brooks and Baandrup (14) | Small tissue fragments with papillary projections | Occasional groups with fibrovascular core | Polygonal cells | ND | Round or ovoid | Finely dispersed | Not prominent |
|                   |              |            | Mucinous cells               | Foamy, clear                   | ND        | ND                | ND                |
| Segletes et al. (16) | ND          | Clean      | Glandular cells              | Delicate                        | ND        | Eccentrical       | ND                |
|                   |              |            | Squamoid/intermediate cells  | Dense                          | Central   | ND                | ND                |
| Romagosa et al. (18) | Slightly mucinous | Slightly mucinous | Epidermoid cells (with clear cell change) | Wide, loose, poorly defined | Round, intranuclear inclusions | Finely granular | ND |
|                   |              |            | Mucus-secreting cells        | ND                             | ND        | ND                | ND                |
| Dyhdalo and Chen (29) | Tight clusters | Extracellular mucus material | Small, bland cells            | ND         | Central, round, uniform | ND                | Small |
|                   |              |            | Glandular cells              | Vacuoles with mucin            | ND        | ND                | ND                |

ND, not described.
found to be positive, to differing degrees, for CD117. The use of a panel of immunomarkers including MYB, CD117, and the zinc finger protein PLAG1 (PA gene 1), quite specific for PA, is more judicious and very effective (46–48). A search for the EGFR mutations was performed on the resected specimens of only one of our AdCC cases, which gave a negative result. Usually these tumors do not have EGFR mutations (49), although one case of AdCC with EGFR mutations has recently been reported (50). In our series (MEC and AdCC), molecular techniques could have been applied on cytological material in the case of diagnostic doubt, in order to detect these specific molecular alterations. However, apart the search for the EGFR mutation that has been done for therapeutic reasons, no molecular test was originally performed, not even for more recent cases. This supports the hypothesis that a diagnosis of primary PSGT was not considered.

CONCLUSION

An awareness of the possibility of encountering primary PSGT in the cytological specimens of patients investigated for LRT masses is fundamental to establishing a correct diagnosis. This is particularly relevant for AdCC, as all cases reported in literature showed characteristic cytological features that could have allowed a correct preoperative diagnosis. As far as MEC is concerned, its preoperative diagnosis is more difficult, as the three different cellular components (i.e., squamous, intermediate, and mucin-secreting cells) were not always reported to be present on cytol- ogy specimens. In cases that raise suspicion of AdCC or MEC, additional immunohistochemical (MYB, c-kit) or molecular techniques (e.g., FISH) could be applied to cytological smears to refine the diagnosis.
| Reference                        | Architecture                                                                 | Background              | Cell shape        | Cytoplasm          | Nuclei              | Chromatin                | Nucleoli                |
|---------------------------------|-------------------------------------------------------------------------------|-------------------------|-------------------|--------------------|---------------------|--------------------------|--------------------------|
| Lozowski et al. (10)            | Cyst-like structures filled with dense, pink-staining, amorphous material (rarely) | Pinkish-staining, mucous, granular background | ND                | ND                 | Uniform, small, ovoid | Finely granular, evenly distributed | ND                       |
| Buchanan et al. (12)            | Cohesive clusters of cells with central cystic spaces filled with amorphous, hyaline material Three-dimensional, ball-like formations | ND                      | ND                | Minimal            | Uniform, small, ovoid | Finely granular, bland | ND                       |
| Nguyen (11)                     | Single and clustered tumor cells Gland-like spaces filled with pinkish mucus-like material | ND                      | Cuboidal          | Scanty             | Round, hyperchromatic | ND                       | ND                       |
| Gupta and McHutchison (13)      | Cohesive three-dimensional clusters of cells; cystic spaces containing cyanophilic amorphous material | ND                      | Uniform           | Minimal            | Uniform, small, ovoid | Finely granular           | ND                       |
| Radhika et al. (15)             | Mucoid globules surrounded by malignant cells Solid clusters of cells | ND                      | Cylindroid/ tubular | Scanty             | Hyperchromatic       | ND                       | ND                       |
| Segletes et al. (16)            | Tightly cohesive aggregates Clusters of cells including central acellular spheres of dense, homogeneous material | Clean                   | Small, uniform    | Scant, delicate, non-vacuolated | Ovoid, high nuclear/cytoplasmic ration | Finely granular, evenly distributed | ND                       |
| Özkara and Turan (23)           | Three-dimensional clusters of neoplastic basaloid cells associated with hyaline basement membrane material | Bloody                  | Homogeneous, small | Modest, eosinophilic | Small, hyperchromatic | ND                       | ND                       |
| Qiu et al. (19)                 | Three-dimensional clusters of neoplastic basaloid cells associated with hyaline material forming cylinders or spheres Aggregates of neoplastic basaloid cells with scanty or no amorphous material | ND                      | ND                | ND                 | ND                  | ND                       | ND                       |
| Florentine et al. (20)          | Scattered sheets and ball-like clusters of tumor cells Hyaline globules at times surrounded by neoplastic cells | ND                      | Small, basaloid   | Scanty             | Round               | ND                       | ND                       |
| Chuah et al. (21)               | Solid sheets and gland-like spaces associated with mucoid material Tight, branching clusters with tubular appearance | ND                      | Monomorphic       | ND                 | ND                  | ND                       | ND                       |
| Daneshbod et al. (22)           | Cell clusters associated with myxoid, hyaline material | ND                      | Dimorphic appearance of tumor cells | ND                 | ND                  | ND                       | ND                       |
| Chon et al. (24)                | Tight clusters, globules of acellular mucoid material                         | ND                      | Monomorphic, basloid | ND                 | Round to oval        | Fine granular            | Indistinct               |
| Bhalara et al. (26)             | Poorly cohesive clusters and complex sheets Homogeneous hyaline globules Singly dispersed cells | ND                      | ND                | Scanty             | Monomorphic, bland, hyperchromatic | ND                       | ND                       |
| Kim et al. (7)                  | Organoid clusters Sheet formation Hyaline globules                              | ND                      | Small, uniform, hyperchromatic | Granular           | ND                  | ND                       | Distinct                 |

ND, not described.
ETHICS STATEMENT

The study protocol was approved by the regional ethical commission on research and human beings (CER-VD, 2016-00224). Informed consent was not necessary according to the art. 34 of the Federal Act on Research involving Human Beings (Human Research Act, HRA); data concerning study participants were anonymized.

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AUTHOR CONTRIBUTIONS

MB conceived the idea of the project. MB, MV, GG, and MP contributed to identification of cases and data curation. CS and MB prepared the manuscript. SLR, IL, MP, and MB reviewed the manuscript. All authors edited the manuscript before its submission.
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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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