Case Report

Pulmonary squamous cell carcinoma with a lepidic-pagetoid growth pattern

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Summary
We report a rare case of a peripheral squamous cell carcinoma (SCC) of the lung in which most of the tumor displayed a “lepidic” growth pattern. The tumor cells also appeared to grow along the alveolar walls between the overlying pneumocytes and underlying basement membrane, a form reminiscent of the “pagetoid” mode of spread. The neoplastic cells were positive for the squamous markers p63 and p40. TTF-1 and CK7 highlighted residual non-neoplastic pneumocytes, which either covered the lepidic tumor cells or lined pseudoglandular formations created by the filling of alveolar spaces by the tumor. CK7 also stained the tumor cells, albeit focally and weakly, a not uncommon finding in peripheral lung SCC. The tumor cells were negative for TTF-1 (clone 8G7G3/1), but did show focal weak reactivity with the less specific clone SPT24. The invasive area measured 2.5 mm while the overall size of the tumor including the lepidic-pagetoid component was 9.0 mm. Even though the invasive component was < 0.5 cm, the only option according to existing staging criteria was to stage it as pT1a. Since the current staging system does not account for the non-invasive lepidic component of pulmonary SCC, the increasing awareness of this variant may require its inclusion within the classification and pathological staging of lung carcinoma.

Key words: lepidic spread, pagetoid spread, squamous carcinoma, lung carcinoma

Introduction

Squamous cell carcinomas (SCC) of the lung have been traditionally divided into central and peripheral types according to whether they arise from the lining of a major bronchus (i.e., true bronchogenic carcinoma) through a well-documented dysplasia-carcinoma sequence, or if they develop from the more distal order of bronchi where the dysplasia-carcinoma sequence has not been fully established. Interestingly, peripheral lung SCC may demonstrate various patterns of growth alternate to the classic destructive invasion with its irregular nests set in a desmoplastic stroma. These alternate growth patterns include alveolar space filling (ASF) type where the tumor cells fill the alveolar spaces without altering the alveolar framework, and the lepidic pattern where the cells grow along the alveolar walls, often between the overlying pneumocytes and the underlying alveolar basement membrane.

We present a case of peripheral lung SCC with a predominant lepidic growth pattern and argue that additional research may be warranted to determine whether we need an expanded classification and staging system of pulmonary SCC that accounts for the presence of this and other non-invasive components.
Case report

We present a case of a 68-year-old male with a history of orthotopic heart transplant in 2014 currently on tacrolimus and everolimus, with hypertension, type II diabetes, deep vein thrombosis, subdural hematoma, and a resected left cheek melanoma, who presented for evaluation of an incidental lung nodule on a computed tomography (CT) scan of the chest. The patient denied any fever, cough, dyspnea, chest pain, hemoptysis, unintentional weight loss, or night sweats. He has a 2-pack-year smoking history and quit 30 years ago. He had no known allergies and no pertinent family history. There were no significant pulmonary findings on physical exam; however, 1+ lower extremity edema was noted. CT of the chest showed a 0.7 x 0.8 cm left upper lobe nodule with spiculated contours. A short-term follow-up CT chest 3 months later showed increase in size of the nodule to 1.1 x 0.8 cm. He underwent electromagnetic navigational bronchoscopy which was non-diagnostic for malignancy. A positron emission tomography (PET) scan 8 months after initial chest CT showed a 1.0 x 0.8 cm left upper lobe lung nodule with 2.9 standardized uptake value (SUV). The patient was subsequently referred to thoracic surgery for further evaluation and underwent a left upper lobe wedge resection with lymph node sampling. His postoperative course was uncomplicated.

Pathologic findings

The pulmonary wedge resection specimen measured 15 x 5 x 3.5 cm and contained a 1.2 cm firm mass seen at 1.3 cm from the parenchymal margin and 0.8 cm beneath the pleural surface. An intraoperative frozen section revealed a thin layer of malignant epithelial cells lining thickened septal walls and was interpreted as “at least adenocarcinoma in situ.” On histological examination of the formalin-fixed specimen, the pulmonary mass demonstrated a scar with a 2.5 mm focus of invasive carcinoma as well as non-invasive tumor with lepidic and focal ASF patterns in the immediate surrounding lung parenchyma (Fig. 1A-C). The invasive component revealed a proliferation of atypical squamoid cells with focal dyskeratotic cells and occasional mitoses. The malignant cells were positive for the squamous markers p63 and p40, and negative for napsin-A (Fig. 2A). Focal and weak staining for thyroid transcription factor-1 (TTF-1, SPT24 clone) and cytokeratin 7 (CK7) was noted in 20% and < 10% of the tumor cells, respectively (Fig. 2B). However, the tumor cells were completely negative for TTF-1 after additional staining with the more specific 8G7G3/1 clone, which ultimately supported a diagnosis of SCC (Fig. 2C). At the periphery of the scar, tumor cells grew into alveolar spaces and extended centrifugally along alveolar walls in a lepidic fashion. Close examination revealed that many of the tumor cells grew beneath native pneumocytes in a pagetoid fashion and spread up to 2 mm away from the scar (Fig. 2D). A CK7 immuno-nostain highlighted the attenuated layer of non-neoplastic pneumocytes which were pushed towards the lumen by the invading CK7-negative tumor cells (Fig. 2E). The periphery also revealed intra-alveolar growth of tumor cells consistent with ASF (Fig. 3A). Several tumor nests displayed glandular-like spaces composed of a central ring of non-atypical pneumocytes, which were strongly CK7 and TTF-1 positive, thus qualifying them as entrapped alveolar epitheli-um with pseudoglandular features (Fig. 3B-D). The same pseudoglandular feature was found in alveoli with subtotal ASF. The tumor was diagnosed as a moderately differentiated invasive SCC with pseudoglandular features and a lepidic growth pattern associated with a scar. The invasive component was 2.5 mm, while the additional areas of lepidic and ASF growth patterns resulted in a total size of 9 mm. Four station 7 lymph nodes were sampled and found to be negative for tumor. Pathologic stage was pT1a pN0. If this case were an adenocarcinoma, it would have been staged as pT1mi, but being squamous, the only option was to stage it as pT1a. The tumor expressed PD-L1 with a score of 2-3%.

Discussion

In 1990, Tokuda described a series of 28 peripheral SCCs of the lung in which 5 cases demonstrated a lepidic (“lining type”) growth pattern at the tumor’s advancing edge. He also documented other patterns such as “alveolar space filling” pattern and a “protruding growth type” which contained trapped alveolar epithelium that sometimes formed a central pseudoglandular cavity. Funai et al. described 55 cases of peripheral lung SCC with an ASF pattern as well as a pseudoglandular morphology but made no mention of the lepidic growth pattern. Kawabata et al. and Yousem suggested that these often-coexisting patterns were steps in the evolution of the advancing edge of peripheral squamous carcinomas. It may be assumed that the lepidic growth pattern may be an early phase of the so-called ASF pattern of spread in peripheral lung SCC. An intermediate phase may include pseudoglandular formations due to preservation.
of an inner layer of pneumocytes after they become completely encircled by multiple layers of tumor cells growing beneath them (Fig. 4).

The lepidic pattern of growth of squamous lung carcinomas is not a recent discovery. For instance, in 1986, Dingemans and Mooi described the ultrastructural findings at the periphery of such tumors and found that the leading tumor cells grew along the alveolar basement membrane while undermining the non-neoplastic alveolar epithelium. This growth pattern was

Figure 1. (A) Invasive squamous cell carcinoma (SCC) arising in a scar (arrow) with lepidic growth pattern at its periphery (open arrows) (H&E, 40 x). (B) High power of irregular invasive nests of SCC (H&E, 200 x). (C) Malignant epithelial cells lining thickened septal walls. (H&E, 100 x).
also recognized by Pääkkö et al. in 1990 who noted that it could be found in all types of lung carcinomas. Since then, there have been many case reports of peripheral lung SCC demonstrating a lepidic growth pattern (Tab. I). Some have attempted a radio-
logic-pathological correlation and found that areas of ground glass opacity in CT scans of such tumors correspond to the areas of non-invasive intra-alveolar spread. The term “lepidic” has been classically applied to

Figure 2. Lepidic growth pattern of SCC at the tumor’s edge. (A) Lepidic tumor cells reveal strong nuclear staining for p40 (H&E, 400 x). (B) TTF-1 clone SPT24 weakly stains a few tumor cells (arrow), while strong staining is seen in residual pneumocytes (open arrow). (C) Tumor cells are completely negative with the more specific TTF-1 clone 8G7G3/1. (D) The malignant cells grew along the basement membrane and lifted the overlying alveolar epithelium. This pattern of spread is more akin to a pagetoid pattern of spread. (E) CK7 immunostain highlights the attenuated layer of CK7-positive non-neoplastic pneumocytes pushed towards the lumen by the invading CK7-negative tumor cells.
lung adenocarcinomas and pertains to the manner of spread most often seen in the previously called bronchioloalveolar carcinomas. In this growth pattern, the tumor cells replace the alveolar lining cells without destroying the alveolar framework. This can also occur in lung squamous carcinomas, but the more common scenario, as seen in our case, is that of carcinoma cells growing between intact pneumocytes and the alveolar basement membrane, a pattern more akin to the so-called “pagetoid” manner of spread.

The pseudoglandular pattern has been previously described in the non-invasive component at the lead-
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It has also been reported in invasive tumors with entrapped pneumocytes in areas of desmoplasia adjacent to and within the tumor, a feature that may interfere with the accurate classification of a lung tumor.

The case presented herein reinforces the need for a small immunohistochemical panel for certain lung tumors since confusing morphologic features may lead to incorrect histological classification of the neoplasm. Our case was initially thought to be adenocarcinoma in-situ since it demonstrated a lepideric growth on frozen sections and the diagnosis of adenocarcinoma was further suggested by the pseudoglandular pattern on permanent sections. Indeed, one previously reported case of SCC with a lepideric

Table I. Reported cases of lepidic spread of pulmonary squamous cell carcinoma.

| Reference | Age | Sex | Smoking history | Site of lung involvement | Size in cm of the tumor | Stage | % of lepidic component | Positive IHC markers | Follow-up |
|-----------|-----|-----|-----------------|--------------------------|-------------------------|-------|------------------------|---------------------|-----------|
| Pääkkö (1990) 8 | 64 | M | --- | RUL | 2.5 | --- | --- | --- | NED ? y |
| Nakanishi (1996) 7 | 68 | M | Yes | RUL | 10.5 | --- | 40% | --- | DOD 0.6 y |
| Nakanishi (1996) 7 | 69 | M | Yes | RML | 3.0 | --- | 30% | --- | NED 3.5 y |
| Kimura (2002) 9 | 65 | M | Yes | LLL | c2.2 | cT1N0 | > 60% | --- | n.a. |
| Kobayashi (2006) 9 | 54 | M | Yes | RUL | 2.5 | cT1N0 | --- | --- | NED 3.0 y |
| Durra (2012) 10 | 62 | M | Yes | RML | 4.9 | --- | --- | p63,CK5 | n.a. |
| Atsumi (2013) 11,12 | 61 | F | No | LLL | 1.5 | pTisN0 | 100% | p63,CK5 | NED 0.5 y |
| Sakaizawa (2015) 13 | 68 | F | No | RUL | 4.3 | --- | --- | p40,CK5 | NED 4.0 y |
| Del Gobbo (2016) 14 | 73 | M | Yes | LUL | 1.3 | --- | > 50% | p40,p63,CK5 | n.a. |
| Terada (2017) 15 | 77 | M | Yes | RLL | c2.4 | pT1aN0 | --- | p40 | NED 1.6 y |
| Iguchi (2021) 16 | 70 | M | Yes | RLL | 2.5 | cT1cN0 | 70% | p40 | NED 1.0 y |
| current case | 68 | M | Yes | LUL | 0.9 | pT1aN0 | 70% | p40,p63 | recent |

IHC = immunohistochemistry; F = female; M = male; RUL = right upper lobe; RML = right middle lobe; RLL = right lower lobe; LUL = left upper lobe; LLL = left lower lobe; c = clinical; p = pathologic; NED = no evidence of disease; DOD = died of disease; y = years; n.a. = not available.
component was believed to be a glandular lesion and called “atypical adenomatous hyperplasia” on frozen section 11. The non-invasive variant of growth called ASF has been recently studied in a large group of patients. 18. The authors found that in univariate analysis, both maximum diameter of invasive area of ≤ 10 mm and ASF ratio of ≥ 70% of the tumor had a statistically significant positive influence on disease-free survival. However, only ASF ≥ 70% was significant in a multivariate analysis. The authors thus suggested that such tumors may represent micro-invasive carcinomas. They also proposed that peripheral lung SCC with an ASF ratio of 100% could be classified as non-invasive carcinoma. Funai et al. found that peripheral SCC with a pure (100%) alveolar space-filling growth had a better survival, while tumors with any percentage of invasive tumor did not 2. Omori et al. noted that small peripheral lung SCC with an ASF component ≥ 30% had lower frequencies of lymphovascular invasion, and those with an alveolar space-destructive (ASD) growth ≤ 1 cm2 had a significantly higher overall 5-year survival than those with ASD > 1 cm2 19.

At present, there are no precise guidelines on how to classify and stage pulmonary SCC with a lepidic component. This is reflected in the terminology used in the literature to describe some of these tumors, which have included squamous dysplasia and SCC-in situ in the case of purely lepidic SCC. We advocate for large studies of peripheral SCC of the lung with a lepidic growth pattern to see if they should be classified in a similar fashion as pulmonary adenocarcinoma with a lepidic component; that is, as “minimally invasive” carcinoma (pTmi) when the invasive component is ≤ 0.5 cm and the lepidic growth pattern is ≤ 3.0 cm, and as “non-invasive” (pTis) if the lepidic pattern comprises 100% of the lesion.

When stained with the adenocarcinoma markers CK7, TTF-1 and napsin-A, our tumor demonstrated weak staining for CK7 in occasional (< 10%) tumor cells, no staining with napsin-A, and weak staining in 20% of the tumor with TTF-1 (clone SPT24). The TTF-1 staining of the tumor cells was significantly weaker than the non-neoplastic pneumocytes and bronchial epithelium. These results are not a complete surprise since TTF-1 has been detected in up to 16% of pulmonary SCC, especially with the SPT24 monoclonal antibody but less so with the 8G7G3/1 clone 20. When TTF-1 was repeated using the more specific 8G7G3/1 clone, no staining of the tumor cells was detected in our case. The co-expression of squamous and adenocarcinoma markers has lent support to those who believe that peripheral SCCs of the lung have glandular cell characteristics when compared to central lung SCCs. In fact, Saijo et al. found CK7 immunoreactivity, albeit focal and weak to moderate, in 40% of peripheral SCCs. It is unclear how much of this was due to entrapped pneumocytes. They also detected TTF-1 (clone 8G7G3/1) with a low staining score in 5% of tumors 21. Sung et al found that 50% of peripheral SCCs are CK7-positive 22. Hayashi et al. found that 53% of peripheral SCCs were positive for CK7 and 7% showed a weak reaction for TTF-1 23. Likewise, Zhang et al found “any staining” for CK7 and TTF-1 (clone 8G7G3/1) in 35% and 14% of peripheral SCC, respectively 24. These studies confirm the low but significant expression of “adenocarcinoma markers” in peripheral SCC. The results in our case are consonant with these studies, except that TTF-1 was no longer detected with the more specific 8G7G3/1 clone. These instances of seemingly dual-positivity mainly demonstrated no more than weak staining for TTF-1 and, thus, differ from those rare biphenotypic cases where there is strong and diffuse co-expression of both p40 and TTF-1 within the same tumor cells, cases that may represent a not fully recognized variant of “non-small cell lung carcinoma, favor adenocarcinoma” 25.

In summary, it is unclear if the clinical behavior of low-stage peripheral SCC of the lung varies if adjusted for the presence of a lepidic growth pattern. Just like for the ASF pattern of spread of pulmonary SCC, larger series may determine whether the lepidic growth pattern is clinically significant and warrants its representation within future pulmonary tumor classification and staging systems.

Conflicts of interest
The authors declare no conflict of interest.

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Ethical consideration
No ethical considerations were necessary as there was no confidential breach.

Author contributions
All authors contributed to the preparation of the manuscript.

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