ALK-Rearranged Lung Cancer
Adenosquamous Lung Cancer Masquerading as Pure Squamous Carcinoma

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CASE REPORT
A 58-year-old man with a <1 pack-year smoking history presented with left cervical lymphadenopathy. Excisional lymph node (LN) biopsy revealed a squamous-cell carcinoma (SqCC) (Figure 1). Positron emission tomography scan revealed FDG-avid mediastinal and supraclavicular LNs and a right upper lobe (RUL) lesion with ground glass appearance on computed tomography. Needle aspirate of the RUL lesion was not reviewed at our institution. The outside report stated no malignant cells were present. Other studies did not reveal a primary.

With a presumed diagnosis of lung SqCC, the patient was treated with chemotherapy with marked response followed by a lobectomy and mediastinal LN dissection. Pathologic evaluation identified a 2.9-cm, moderately differentiated, Thyroid Transcription Factor 1 (TTF1)+/p63−/CK5/6− adenocarcinoma (AD) of the RUL (Figure 2). Mediastinal LNs and intrapulmonary lymphatics were extensively involved with TTF1−/p63+/CK5/6+ SqCC. A lung parenchyma SqCC was not identified. Molecular studies on the AD revealed wild-type epidermal growth factor receptor (EGFR) and KRAS. Fluorescence in situ hybridization detected rearrangement of anaplastic lymphoma kinase (ALK).

Approximately 2 years after surgery, the patient had progressive disease in the lung and LNs. A repeat biopsy was not performed. He was treated with crizotinib and had prolonged overall tumor shrinkage lasting 13 months. The lung lesions shrank significantly whereas the LNs remained stable in size. After progression on crizotinib, rebiopsy of a supraclavicular LN revealed a TTF1−/p63+/CK5/6+ SqCC. Cytogenetics confirmed persistence of an ALK-rearrangement (Figure 3).

This case illustrates an adenosquamous carcinoma (AD-SqCC) in which the primary and metastases have different histologies. Although the ability of AD-SqCC to metastasize as a single histology is well documented,1 a remarkable feature of this case is that despite a thorough search, biphasic histology could not be documented in the primary tumor. The finding of the ALK rearrangement in both confirms that the

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Figure 1

Figure 2

FIGURE 1. Squamous histology in cervical lymph node metastasis.

FIGURE 2. Adenocarcinoma histology in the resected primary tumor. Abundant extracellular mucin and focal signet-ring cells are the features typical of ALK-rearranged adenocarcinoma.
primary and metastatic tumors are clonally related. There is one similar case of a patient with a resected primary tumor composed entirely of SqCC and an AD metastasis, both with the same EGFR mutation. We hypothesize that these primary tumors have a minor component with distinct histology that is not represented in histologic sections, but which has an enhanced metastatic potential, and is thus solely represented at the metastatic sites.

This case challenges the principle of histology-based triage for molecular testing. In the last decade, advances have been made in the identification of therapeutically relevant genetic alterations in EGFR, KRAS, and ALK. These events occur almost exclusively in AD but not in SqCC. Unlike in pure SqCC, in AD-SqCC mutations in EGFR and ALK do occur at a rate similar to AD. AD-SqCC are rare, and their diagnosis is difficult because of incomplete sampling on biopsy or predominance of a single histology, as illustrated in this case. We have reported a series of patients in whom AD-SqCC was the underlying cause of samples diagnosed as “SqCC” harboring EGFR or KRAS mutations. This case expands those observations to carcinomas with ALK rearrangements.

Currently, no molecular testing is recommended for SqCC of the lung. In patients who have a minimal tobacco history and a small biopsy or metastatectomy that is diagnosed as SqCC we suggest thorough histological examination for a component of AD, and to consider molecular testing. This approach could identify a mutation for which there is a targeted therapy with proven efficacy.

REFERENCES