Using Pleomorphic Adenoma Gene 1 (*PLAG1*) to Distinguish Carcinoma of the Parotid Gland From Primary Lung Cancer: A Case Study

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Author's disclosure of conflict of interest is found at the end of this article.

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Abstract

A 40-year-old female never-smoker with no significant medical history presented with right-side facial swelling and 3 months of progressive, radiating otalgia. This article reviews the case of a young woman with carcinoma ex pleomorphic adenoma (CXPA) and the pathway to arrive at the diagnosis.

CASE STUDY

A 40-year-old female never-smoker with no significant medical history presented with right-side facial swelling worsening over the course of 3 months, with progressive discomfort emanating from her right cheek and radiating to her right ear. An MRI of the skull base with and without contrast showed three distinct right-side parotid lesions (1 cm, 1.5 cm, and 1.6 cm). A CT chest scan with contrast demonstrated a 2.4-cm right hilar lymph node and a suspicious right paratracheal lymph node, as well as a soft tissue mass in peri hilum measuring 2.6 cm. A fine-needle aspiration (FNA) of the right parotid mass was performed. Results were consistent with a carcinoma with squamous features within a specimen of scant cellularity.

The initial FNA was difficult to interpret given scant cellularity. Immunohistochemistry (IHC) was positive for p40, CK5, and p16; human papillomavirus (HPV) RNA in situ hybridization (ISH) was negative. A repeat of FNA of the right parotid showed adequate cellularity with positive p40, desmoglein 3, CK5, and p16. The tissue was negative for S100, Sox10, synaptophysin, TTF-1, Napsin A, and ISH HPV. PD-L1 was identified as focally positive with a combined positive score (CPS) of 1%.

She then underwent a right hilar endobronchial ultrasound-guided FNA. Cytology revealed cohesive sheets of malignant squamous cells

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showing an increased nucleus:cytoplasm (N:C) ratio and hyperchromatic irregular nuclei. Immunohistochemistry was again positive for p40 and p16 as well as CK903, and negative for *GATA3*, nuclear protein in testis (*NUT*), androgen receptor (AR), and Epstein-Barr encoding region (*EBER*). In an additional study, pleomorphic adenoma gene 1 (*PLAG1*) ISH was performed on the specimen of pulmonary origin and was positive.

PLAG1 dual-color break-apart probe 8q12.1 was performed through Empire Genomics. Fifty cells were analyzed. Normal cells showed green and orange signals in juxtaposition, whereas translocated cells showed both juxtaposed green and orange signals, and separate green and orange signals. One hundred percent of the cells analyzed were positive for translocation. Controls for positivity included 10% or more required to show translocation pattern (Figure 1).

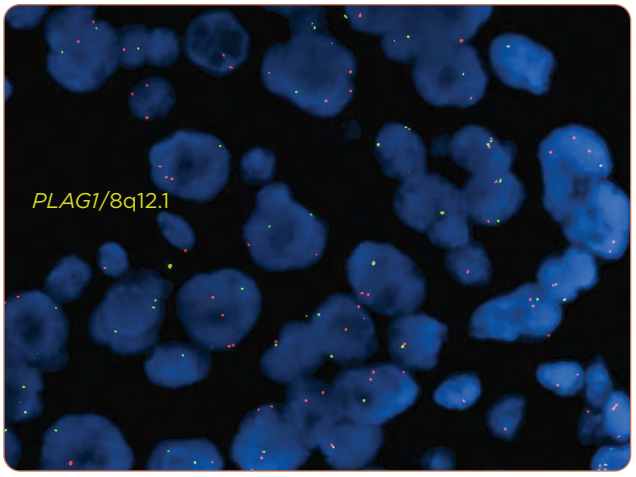

Figure 1. *PLAG1* dual-color break-apart probe 8q12.1.

PLAG1 ISH was performed on previous aspirates of the parotid specimens as well, with strong positivity. Based on this finding, her case was felt to be pathologically consistent with carcinoma ex pleomorphic adenoma.

Pleomorphic adenomas (PAs) are the most common benign salivary gland tumors, representing up to 70% of salivary tumors. The malignant transformation of PA is roughly 10% after 15 years (Key et al., 2022). To diagnose a PA or carcinoma ex pleomorphic adenoma (CXPA), a fine-needle aspiration (FNA) must be performed. A core biopsy is not recommended because the location of the parotid gland is highly innervated and considered a high-risk region.

Distinguishing a benign tumor from a malignant one can be complex due to variability in sample size and technique (Taniuchi et al., 2021). In cases of limited cellularity or sample artifact, immunohistochemistry (IHC) can provide significant insight. Squamous cells are typically IHC-positive for p40, CK5/6, and p63 biomarkers (Chen et al., 2022).

Due to their glandular nature, salivary cells are typically adenoid and not squamoid, making the likelihood of squamous carcinoma of the salivary gland highly improbable (Nakamori et al., 2009; Liu et al., 2021). In the case presented herein, the squamous features confound the picture, delaying the time to final diagnosis.

DISCUSSION

In the case study, a 40-year-old woman with no smoking history presented with right-side parotid swelling and radiographically distant disease involving a paratracheal node and central hilum. Cytology was consistent with carcinoma with squamous features. Her case was reviewed at an internal tumor board where pathologic and radiographic results were felt to be consistent with squamous cell carcinoma of the lung. However, there were clinical concerns associated with this diagnosis. Clinical features, such as her history of never smoking and the parotid gland as a site of metastatic involvement, were felt to be incongruous with primary squamous cell lung cancer.

PLAG1 in situ hybridization (ISH) was then performed on pulmonary specimens and found to be positive for translocation. Cytology from the parotid mass was subsequently analyzed and found to be positive for *PLAG1* translocations as well. *PLAG1* was first identified in 1997 and has excellent sensitivity within pleomorphic adenoma (96%); furthermore, ISH was found to be more sensitive than IHC in detecting *PLAG1* anomalies in CXPA (Katabi et al., 2018).

Carcinoma ex pleomorphic adenoma has been rising in the past decade and, although rare, analyses have identified distant disease, lymph node involvement, and > 4-cm primary tumors as adverse prognostic features (Gupta et al., 2019). In this young woman's case, *PLAG1* positivity distinguished primary lung cancer from primary salivary gland cancer.

Of note, next-generation sequencing (NGS) through Oncomine assay developed at the University of Pittsburgh Medical Center revealed a *MYC* amplification (8q24.21 gain 23.5), 12q region amplification (212q15 gain 21.9;12q14.1 gain 21.9), 11q region amplification (11q13.3 gain 6.6), microsatellite-stable (MSS), and 6.9 mutations/Mb.

Treatment in the case presented herein included combined chemoimmunotherapy (carboplatin AUC 6, paclitaxel 200 mg/m^2, and pembrolizumab [Keytruda] 200 mg every 21 days) with an excellent early clinical response, complete resolution of visible mass, and reduction in perceived pain after a single cycle of therapy. Distant and primary disease were stable after three cycles.

CONCLUSION

PLAG1 is a useful biomarker when CXPA is in the diagnostic differential. Tumor board, expert pathological evaluation, and clinical judgment remain cornerstones of management in these rare tumor types.

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Disclosure

The author has no conflicts of interest to disclose.

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