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Case Report

Adenocarcinoma, Not Otherwise Specified, Of the Minor Buccal Salivary Glands Initially Suspected to Be an Oral Metastasis from Lung Adenocarcinoma: A Case Report

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Abstract:

Adenocarcinoma, not otherwise specified (NOS), is a malignant salivary gland tumor characterized by formation of ducts and epithelial differentiation without defining features of other specific tumors. Tumors arising from minor salivary glands of the buccal mucosa are rare. We report an 83-year-old man who had undergone resection of a lung adenocarcinoma who was found to have adenocarcinoma, NOS of the minor buccal salivary glands during a postoperative follow-up. Cytological and histological findings showed a mucin-producing adenocarcinoma, suggesting metastatic lung adenocarcinoma. However, immunohistochemical analysis was negative for thyroid transcription factor-1 (TTF-1), napsin A, and hepatocyte nuclear factor-4α (HNF-4α) expression, and the same biomarkers were positive in the resected lung adenocarcinoma, making metastatic disease unlikely. The buccal tumor was surgically excised. Histopathological and immunohistochemical evaluations supported a diagnosis of adenocarcinoma, NOS arising from minor salivary glands. The patient has remained disease-free 5 years post-surgery. This case highlights the importance of careful clinicopathological and immunohistochemical evaluations for distinguishing primary salivary gland adenocarcinomas from metastatic disease in patients with a history of malignancy.

Key words: adenocarcinoma, nos; minor salivary gland tumor; buccal mucosa; lung adenocarcinoma; oral metastasis; differential diagnosis; immunohistochemistry

Introduction

Adenocarcinoma, not otherwise specified (NOS) is a malignant salivary gland tumor characterized by formation of ducts and epithelial differentiation, and lacking the specific histopathological features required for the diagnosis of other defined tumor types [1]. It most commonly arises in the parotid gland [2, 3]. Among minor salivary gland tumors, the palate represents the most frequent site [2, 3], whereas tumors arising in the buccal mucosa are uncommon. Because adenocarcinoma, NOS is a diagnosis of exclusion, distinguishing it from other salivary gland tumors is essential [4], and differentiation from metastatic adenocarcinoma is particularly important [5]. Metastatic tumors to the oral and maxillofacial region account for only 1%–3% of all oral malignancies [6, 7]. The lung is the most frequent primary source of metastases to the oral region [8-11], and adenocarcinoma is the most common histological type of primary tumor [8-11]. Here, we report a rare case of adenocarcinoma, NOS arising from the minor salivary glands of the buccal mucosa, which was initially suspected to be a metastasis from a primary lung adenocarcinoma. The adenocarcinoma, NOS was detected during a postoperative follow-up after lung cancer surgery. The purpose of this report is to describe a rare case of adenocarcinoma, NOS of the minor buccal salivary glands mimicking metastatic lung adenocarcinoma and to emphasize the importance of clinicopathological and immunohistochemical evaluation in differential diagnosis.

Case Presentation

An 83-year-old man presented with a mass in the right buccal mucosa. He first visited our department in November 2019. The patient had a medical history of angina pectoris, cerebral aneurysm, and lung cancer. In September 2017, he underwent right lower lobectomy and lymph node

dissection for lung adenocarcinoma (pT2bN0M0, stage IIA). During postoperative follow-up, 18F-2-deoxy-2-fluoro-glucose positron emission tomography/computed tomography (18FDG-PET/CT) in September 2019 revealed abnormal uptake (SUVmax 6.53) in the right buccal region. A local dentist also detected a buccal mass, and cytology from another hospital was thought to be adenocarcinoma.

The patient was then referred to our department. General examination showed a well nourished man without cervical lymphadenopathy. An intraoral examination revealed a 26 × 22-mm firm mobile painless mass in the right buccal mucosa (Figure. 1).

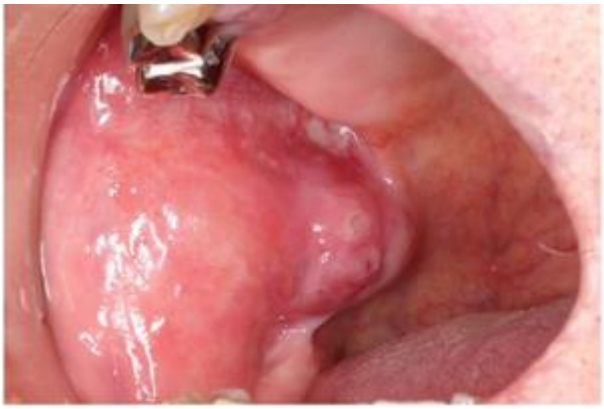


Figure 1: Intraoral findings at the first visit. A painless, slightly firm elastic mass measuring 26 × 22 mm was observed in the submucosa of the right buccal region.

The surface mucosa was normal except for a small ulcer presumed to be the site of the previous cytology. Contrast-enhanced CT revealed a 28 × 20-mm heterogeneously enhancing mass (Figure. 2A).

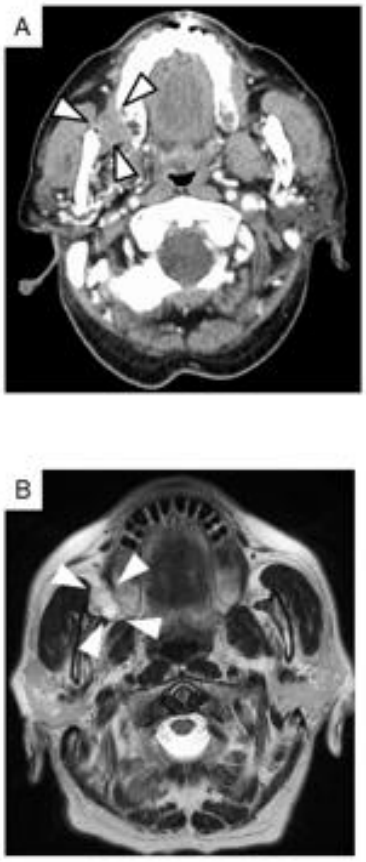


Figure 2: Imaging findings.
(A) Contrast-enhanced computed tomography revealed a 28 × 20-mm mass with heterogeneous internal enhancement in the right buccal region.
(B) Contrast-enhanced magnetic resonance imaging demonstrated a well circumscribed, submucosal lobulated mass with high signal intensity on T2-weighted images. The lesion showed low cellularity, an internal reticular pattern, and marked contrast enhancement.

Magnetic resonance imaging (MRI) demonstrated a strongly enhancing, well defined, lobulated T2-hyperintense lesion with an internal reticular pattern (Figure. 2B). ^{18}FDG-PET /CT showed focal uptake in the buccal lesion only (Figure. 3).

Figure 3

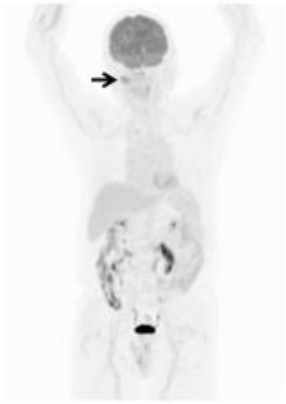
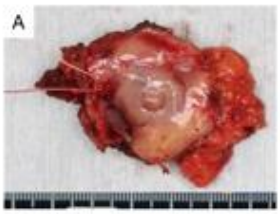


Figure 3: FDG-PET/CT images.

^{18}FDG-PET/CT at the initial visit to our department in 2019 demonstrated abnormal ^{18}FDG uptake in the right buccal region (SUV_{max} 6.53), with no abnormal uptake elsewhere.

Atypical epithelial cells with a mucinous background were found on cytology, which suggested adenocarcinoma. An incisional biopsy was performed for the definitive diagnosis, including the possibility of metastasis. Histopathological examination showed mucin lakes containing floating clusters of tumor cells resembling the previously resected lung adenocarcinoma. However, immunohistochemistry revealed that the biomarkers TTF-1, napsin A, and HNF-4α [12-14], which were expressed in the lung adenocarcinoma, were all negative in the buccal lesion, ruling out metastasis from the lung. In December 2019, the patient was placed under general anesthesia to undergo surgery for the buccal lesion. A wide local excision was performed to produce a specimen with ≥10 mm margins, which included parts of the buccinator and medial pterygoid muscles. The surgical defect was repaired with the use of a polyglycolic acid sheet and fibrin glue. Gross examination of the excised specimen revealed a 24 × 20 × 18-mm well circumscribed, whitish, lobulated submucosal mass (Figure. 4A).

Figure 4



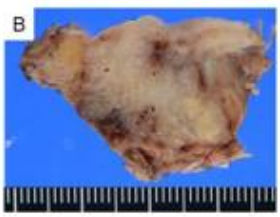


Figure 4: Resected specimen.

(A) Gross appearance of the surgically excised tumor specimen.
(B) Cut surface revealed a well demarcated, whitish, lobulated mass located in the submucosal layer.

The cut surface confirmed a clearly demarcated lesion (Figure. 4B).

Histopathologically, the tumor was partly encapsulated with cystic spaces filled with abundant mucin. Adenocarcinoma cells proliferated in cribriform and papillary patterns. The tumor cells exhibited enlarged round nuclei and clear cytoplasm that contained mucin, with occasional signet-ring–like cells (Figure. 5A).

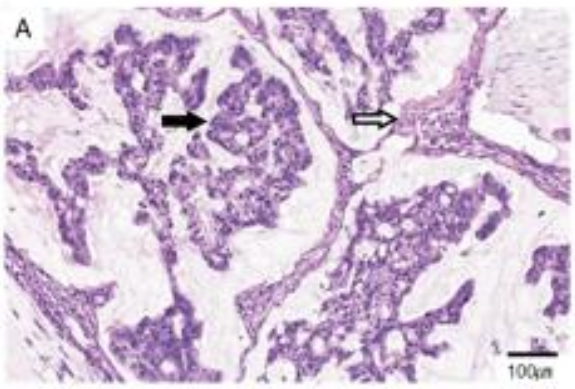
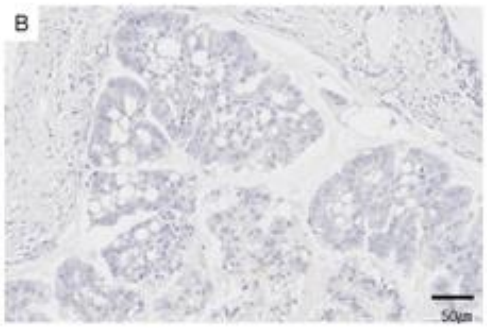


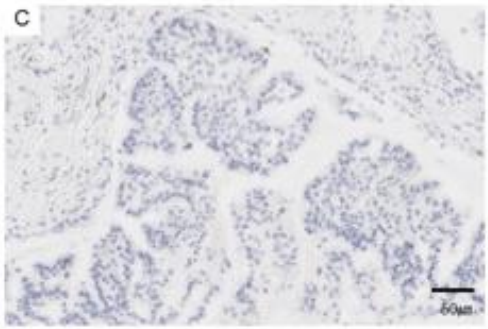
Figure 5: Histopathological and immunohistochemical findings.

(A) Hematoxylin-and-eosin staining showed accumulations of abundant mucin, which contain adenocarcinoma cells proliferating in cribriform nests (black arrow) and papillary structures (white arrow).

Immunohistochemical analysis showed focal positivity for vimentin and GCDFP-15, and negativity for alpha-smooth muscle actin (α-SMA), S-100, tumor protein p63, human epidermal growth factor receptor 2 (HER2), and the androgen receptor. Immunohistochemistry showed negativity for TTF-1, Napsin A, and HNF-4α expression (Fig. 5B), focal positivity for vimentin and GCDFP-15, and negativity for alpha smooth muscle actin (α-SMA), S-100, tumor protein p63, human epidermal growth factor receptor 2 (HER2), and androgen receptor (Figure. 5C).

Figure 5





(B) Immunohistochemical staining of the oral tumor specimen was negative for both TTF-1 (B) and Napsin A supporting the exclusion of metastatic lung cancer.

(C) Immunohistochemical staining of an oral tumor specimen was negative for both androgen receptor (C) and HER2 expression, supporting exclusion of the diagnosis of salivary duct carcinoma.

The patient's postoperative course was uneventful. At the 5-year postoperative follow-up, there was no evidence of recurrence, local metastatic disease involving the cervical lymph nodes, or distant metastases.

Final diagnosis: Adenocarcinoma, NOS of the minor salivary glands.

Discussion

Malignant tumors of the salivary glands account for approximately 3% of all head and neck malignancies, and tumors arising from the minor salivary glands reportedly constitute about 22% of these cases [15]. Tumors originating from the buccal mucosa are relatively uncommon among malignancies of the minor salivary glands [16]. Adenocarcinoma, NOS represents approximately 8%–17% of all salivary gland malignancies [1], whereas its incidence among tumors of the minor salivary glands is low [17, 18]. Adenocarcinoma, NOS is defined as a malignant salivary gland tumor showing ductal formation and glandular epithelial differentiation without the characteristic histologic features of other defined tumor entities [1]. The definition of adenocarcinoma NOS has been refined in recent World Health Organization (WHO) classifications, with micro secretory adenocarcinoma being separated as an independent entity in the 2022 Fifth Edition [19]. These changes highlight the heterogeneous nature of tumors currently classified as adenocarcinoma, NOS. Because adenocarcinoma NOS is diagnosed primarily by exclusion, careful differentiation from metastatic adenocarcinoma is essential [4, 5]. Metastatic tumors to the oral and maxillofacial region are rare, accounting for approximately 1%–3% of all oral malignancies [6, 7]. The lung is the most frequent primary site of oral metastases, and adenocarcinoma is the most common histological type [8–11]. In the present case, the lesion was detected as a buccal mass with abnormal ^{18}FDG uptake during postoperative follow-up after lung adenocarcinoma surgery, and cytologic findings suggested a mucin-producing adenocarcinoma, raising suspicion of metastatic disease. Zegarelli et al. proposed diagnostic criteria for oral metastatic tumors, including confirmation of the primary tumor, histological similarity between primary and metastatic lesions, absence of a previous tumor at the metastatic site, and exclusion of direct invasion [20]. Several of these criteria were considered to be fulfilled in the present case, further supporting the initial clinical suspicion of oral metastasis. Histologically, the biopsy specimen demonstrated abundant mucin production and morphologic features resembling those of the previously resected invasive mucinous lung adenocarcinoma. Therefore, immunohistochemical analysis was performed as an adjunct to the morphological evaluation. While the lung adenocarcinoma showed positivity for TTF-1, napsin A, and HNF-4α, all of these markers were negative in the buccal lesion. Taken together with the clinical presentation and histological findings, these results suggested that metastatic lung adenocarcinoma was unlikely and supported an origin in a primary salivary gland. The resected tumor showed abundant mucin production with papillary and cribriform architectures, which overlaps morphologically with the cytology of salivary duct carcinomas and cystadenocarcinomas. However, negativity for the myoepithelial markers (SMA, S-100, and p63), as well as the absence of androgen receptor and HER2 expression, argued against these entities. Based on the combined morphological and immunohistochemical findings, a diagnosis of adenocarcinoma, NOS was considered appropriate [1]. Recently, immunohistochemical markers such as DOG1 and SOX10 have been reported to be useful in the differential diagnosis of salivary gland neoplasms [21, 22]. These markers are particularly helpful in cases where acinic cell carcinoma or secretory carcinoma is suspected. Surgical excision remains the mainstay of treatment for adenocarcinoma, NOS. Although radiotherapy alone has been reported to provide inferior local control compared to surgery combined with radiotherapy, it may be considered in selected cases depending on tumor grade or margin status [23]. Systemic chemotherapy is generally reserved for recurrent or metastatic disease, and no standard regimen has been established. Combination chemotherapy using cisplatin and docetaxel has been reported [24], as well as taxane-based regimens combined with carboplatin [25-27]. In addition, clinical responses to the epidermal growth factor receptor inhibitor cetuximab have been described in selected cases [28]. Biomarker-driven therapeutic strategies are now also being explored. Androgen deprivation therapy has shown activity against androgen receptor-positive salivary gland carcinomas [29,30], while HER2-targeted therapies, including trastuzumab emtansine and pertuzumab, have been reported effective for HER2-positive tumors [31,32]. Immune checkpoint inhibitors such as pembrolizumab have demonstrated efficacy in tumors with high mutational burdens [33]. Although these approaches are not specific to adenocarcinoma, NOS, they may represent therapeutic options for advanced or refractory cases.

In conclusion, this case demonstrates the importance of careful clinicopathological and immunohistochemical evaluation in distinguishing primary tumors from metastatic tumors, particularly in patients with a history of malignancy. Awareness of this diagnostic pitfall may help prevent misclassification and inappropriate treatment.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The patient was informed that personal information would be anonymized and that every effort would be made to ensure confidentiality.

Declaration of Competing Interests

The authors declare no conflicts of interest.

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