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CASE REPORT

Mucinous Carcinoma with Neuroendocrine Differentiation of Salivary Gland Origin

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Abstract Primary mucinous adenocarcinomas of the salivary gland are rare malignancies defined by aggregates of epithelial cells suspended in large pools of extracellular mucin. We report a case of a giant mucinous adenocarcinoma of salivary gland origin, with low-grade cytoarchitectural features and neuroendocrine differentiation arising in the submental region. Grossly, the tumor measured 12.5 × 13.4 × 8.2 cm and replaced the bone and soft tissues of the anterior oral cavity. Microscopically, the neoplasm was composed of large extracellular pools of mucin, which contained papillary and acinar aggregates, and small nodules of ductal type epithelium with minimal nuclear enlargement, powdery chromatin and little pleomorphism. The nodules comprised 20 % of the tumor and showed morphologic and immunohistochemical evidence of neuroendocrine differentiation. Examination revealed histologic features comparable to mammary gland analogues in mucin predominance, ductal type morphology, expression of estrogen and progesterone receptors, and GATA-3 positivity. This is the first case reported of mucin-rich carcinoma of salivary gland origin exhibiting neuroendocrine differentiation.

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Introduction

Mucinous carcinomas, also known as colloid carcinomas, are a subtype of adenocarcinoma infrequently encountered in the breast and colon but are uncommon in the head and neck region. The World Health Organization (WHO) describes mucinous carcinoma as a rare type of salivary gland adenocarcinoma characterized by large pools of extracellular mucin containing suspensions of neoplastic epithelial cells in which the "mucin component usually occupies the bulk of the tumor mass." Yakirevich et al. [1] further stratified mucin-producing carcinomas, defined as having at least 50 % of the tumor mass occupied by extracellular mucin, into colloid carcinomas (CCs), mucinous cystadenocarcinomas (MCAs), mucin-rich salivary duct carcinomas (SDCs) and mucin-rich mucoepidermoid carcinomas (MECs) [2]. Colloid carcinoma lacks an association with other variants of salivary gland carcinoma, though all in this series would meet criteria for the broader WHO 2005 classification of mucinous adenocarcinoma. CC of the salivary glands shows low disease-associated mortality and typically grows in indolent fashion with high rates of local recurrence [3]. Salivary gland mucinous adenocarcinomas of mixed type (MCA, SDC, MEC) have a higher mortality rate, with behavior approximating the grade of the non-mucinous component. We report a case of a massive primary salivary gland mucinous carcinoma with neuroendocrine differentiation arising in the submental region.

Case Report

A 69 year-old male with a distant smoking history presented with a cutaneous lesion in the submentum that progressively enlarged over 14 months (Fig. 1). The patient had visited the emergency room multiple times for intermittent oral cavity bleeding during this period, but failed to follow up for specialist management. The lesion progressively eroded through the anterior mandible into the floor of mouth, causing loss of dentition, dysarthria, mental nerve paresthesias, and marginal mandibular nerve paralysis. He was reduced to a soft food diet, which resulted in a 30-pound weight loss. There was no associated hoarseness, hemoptysis, referred otalgia, stridor, or dyspnea. The other facial nerve branches were functionally intact. No enlarged lymph nodes were palpable on examination.

Magnetic resonance imaging (MRI) demonstrated a heterogeneously enhancing, erosive mass with extensive, bona fide destruction of the anterior mandible. The lesion measured 12.5 × 13.4 × 8.2 cm and extended posteriorly to the level of the second mandibular molars bilaterally (Fig. 2). There was abutment against the ventral tongue and hyoid bone, with possible infiltration into the tongue soft tissues. Positron Emission Tomography/Computed Tomography (PET/CT) showed no evidence of regional or distant metastasis. A punch biopsy demonstrated carcinoma with androgen receptor (AR)-positivity, with the differential diagnosis favoring a low-grade intraductal salivary duct carcinoma. [4, 5]

The patient underwent *en bloc* resection of the tumor, including angle to angle mandibulectomy, floor of mouth resection, and bilateral modified radical neck dissections (Fig. 3). The neck dissections were performed due to the likelihood of microscopic regional metastasis in T3–T4 disease, expected lymphatic drainage patterns, and the working diagnosis at time of surgery. The patient was consented for a possible total glossectomy and total laryngectomy, but the tongue was safely preserved, along with both hypoglossal and lingual nerves bilaterally. A temporary tracheostomy and percutaneous endoscopic gastrostomy (PEG) tube were placed. Reconstruction was performed with a left fibula free flap and anterolateral thigh free flap. After an uneventful postoperative course, the tracheostomy and PEG were removed. He underwent postoperative radiation and total androgen receptor blockade with leuprolide and bicalutamide, and has been free of disease to date after 6 months of surveillance (Fig. 4).

The en bloc pathology specimen was fixed in formalin. Sections from all aspects of the tumor were embedded in 45 blocks, with 15 blocks requiring decalcification. Macroscopically, there was a multinodular appearance of the cut surface with the majority of the tumor demonstrating a mucoid gelatinous texture alternating with fibrous bands, as well as fleshy solid nodules with a red-

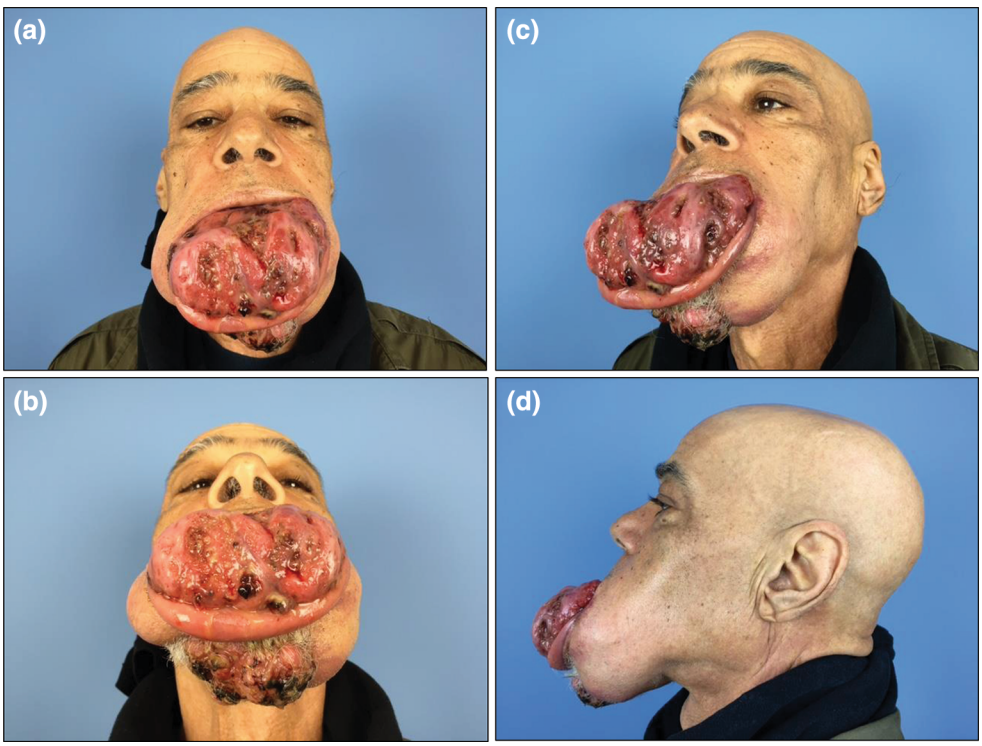

Fig. 1 Preoperative photodocumentation. **a** Frontal view. **b** Base view. **c** Left oblique view. **d** Left lateral view

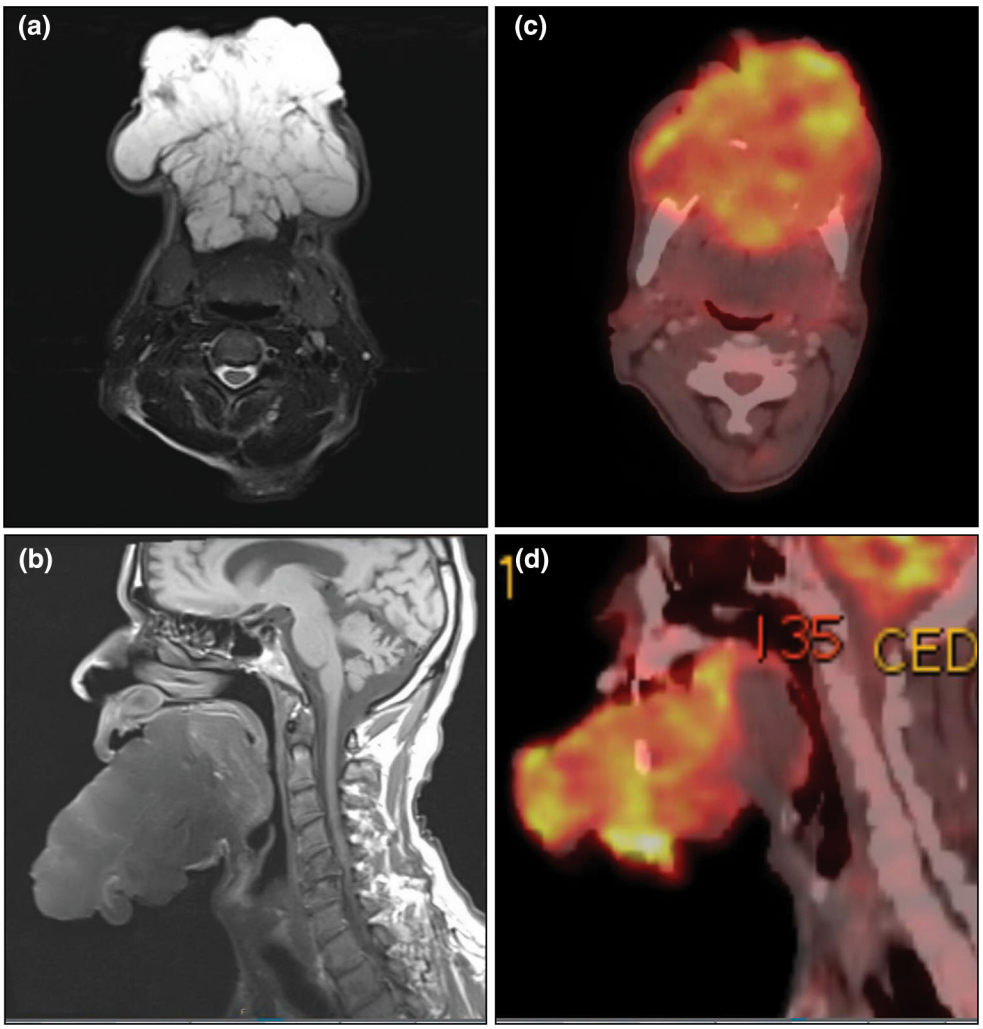

Fig. 2 Preoperative imaging. **a** Axial T2-weighted MRI Neck showing a T2-intense lesion involving the submentum. **b** Sagittal T1-weighted MRI with contrast exhibiting a T1-hypointense lesion involving the floor of mouth and ventral tongue. **c** Axial PET/CT demonstrating a destructive FDG-avid lesion with erosion into the anterior mandible. **d** Sagittal PET/CT exhibiting FDG-avid lesion adjacent to the normal tongue

brown appearance. On histologic examination the specimen was composed of large pools of extracellular mucin accounting for at least 80 % of the tumor. Suspended within the mucin pools were single and branching papillary aggregates of columnar and cuboidal cells with ovoid nuclei, mild nuclear enlargement, and mild to moderate nuclear hyperchromasia and powdery chromatin with minimal pleomorphism (Fig. 5). Other foci contained nodular, loosely cohesive aggregates of epithelioid cells with a more plasmacytoid appearance and finely granular cytoplasm. The mitotic index ranged from 1 to 3 mitotic figures per 10 high power fields. Neither angiolymphatic nor perineural invasion was identified. There was prominent dermal infiltration as well as intraepithelial, cutaneous adnexal, and intraepidermal spread. Extensive sampling and near complete embedding of adjacent tissue was performed. Histological examination of these sections revealed uninvolved bilateral submandibular glands and residual sublingual and minor salivary gland parenchyma, which precluded assignment of a definitive salivary gland primary site. In addition, non-mucinous primary salivary gland neoplasms, such as MCA, intraductal low grade SDC, high grade SDC, or MEC were not identified. Nodal metastasis included two positive lymph nodes out of 45 sampled. All margins were negative. The lesion was staged as T4aN2bM0 [6].

Immunohistochemistry was performed on selected sections from the tumor for further characterization (Table 1). As expected, all components of the tumor both in the ductal and nodular areas exhibited a CK7 positive/CK20 negative immunophenotype. Multiple myoepithelial cell markers, including S100, p63, and smooth muscle myosin were negative. A peripheral myoepithelial area was not observed in any area in contact with stroma, which confirmed the

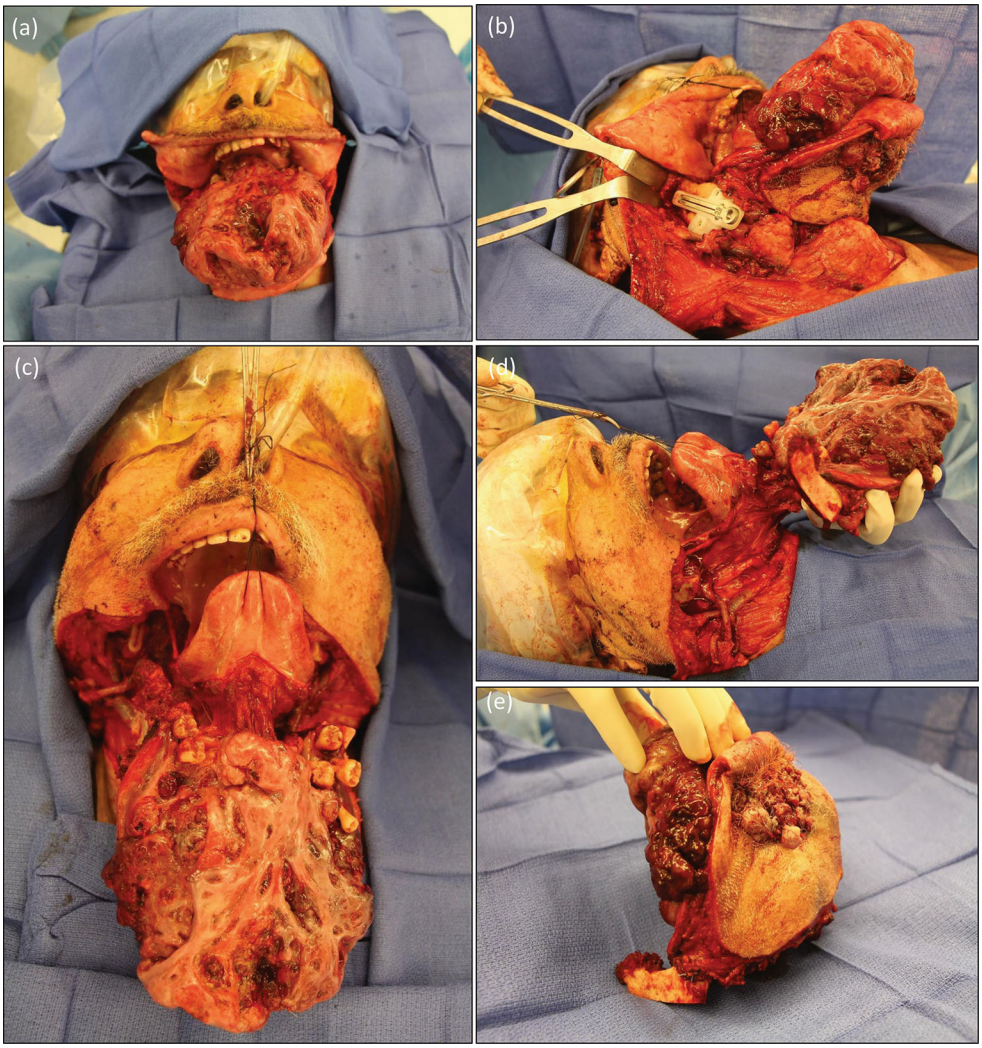

Fig. 3 Intraoperative photodocumentation. **a** Lower lip split. **b** Mandibulectomy cutting guides in place. **c** Tumor release after mandibulectomy. **d** Tumor specimen prior to release at ventral tongue and floor of mouth. **e** En bloc specimen with negative margins

histologic impression that an intraductal component was lacking. A mammary immunophenotype was present in that GATA-3, ER, and PR were all strongly positive (Fig. 5). In addition, androgen receptor was positive to a lesser degree. Immunostains for CD117, PSA, TTF-1 and WT-1 were negative. Interestingly, both chromogranin and synaptophysin were strongly positive in all areas of the tumor but with greater density and strength in the nodules, which comprised <20 % of the specimen.

Discussion

Few verified cases of mucin-rich carcinoma of salivary gland origin have been described in the literature [2, 7–10]. The mean patient age is 57 years, with males more frequently affected than females. The 5-year and 10-year overall survival rates have been reported to be 60 and 44 %, respectively. [10] The most common locations are the palate (35 %) and parotid gland (18 %), with none previously reported in the submental region. Reported tumor size has ranged from 1 to 7.6 cm. Local recurrence, cervical lymph node metastasis, and distant spread of mucin-rich carcinoma occurred in 33, 63, and 29 % of cases, respectively in one series [2]. Clinically, mucin-rich carcinoma evolves slowly (>2 years) with most tumors discovered at advanced stages [7, 11].

In this patient, the predominant pattern (80 %) was the mucin-rich component. However, both morphology and immunohistochemistry confirm ductal differentiation, analogous to that seen in low-grade intraductal SDC and mammary mucinous adenocarcinomas. Furthermore, in this case neuroendocrine differentiation is also demonstrated. Although this combination has been reported in the breast, it has not been described in the salivary gland, perhaps due to the rarity of such lesions at this site.

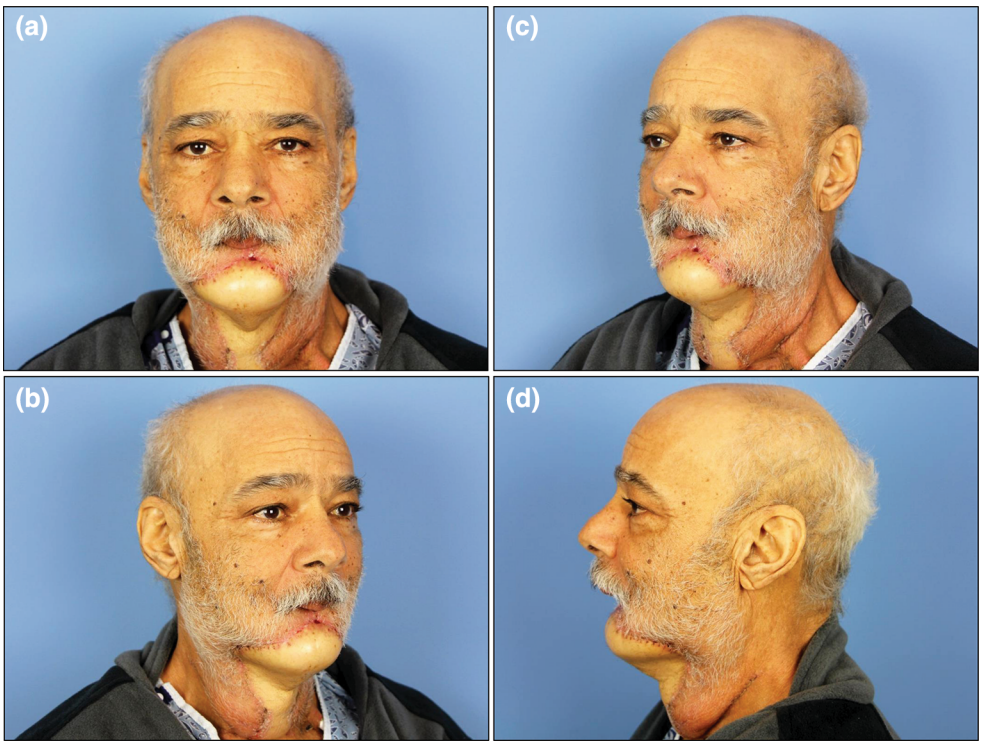

Fig. 4 Postoperative photodocumentation one month after surgery. **a** Frontal view. **b** Right oblique view. **c** Left oblique view. **d** Left lateral view

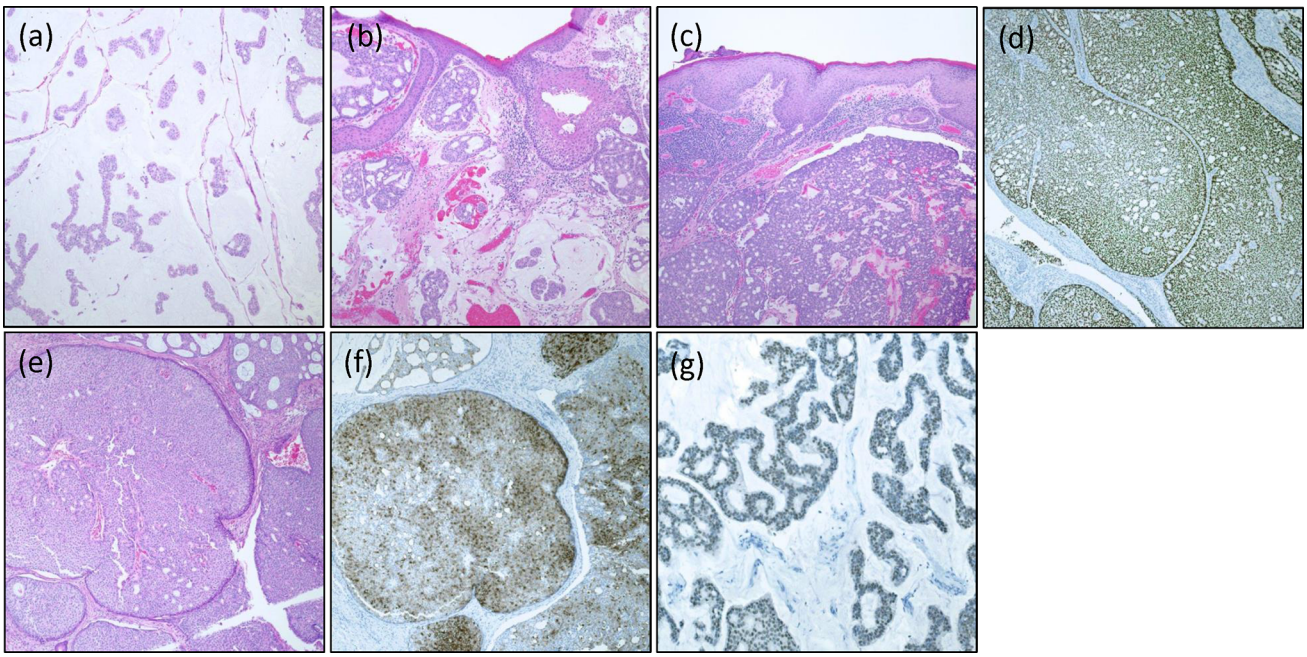

Fig. 5 Pathological staining of mucin-rich carcinoma. **a** Small ductal papillary structures suspended in extracellular mucin, representative of 80 % of overall tumor. **b** Solid areas of carcinoma attached to or emanating from mucosa. **c**. Solid areas of tumor attached to skin with some areas possibly representing intraepidermal spread. **d**. Diffuse and strong nuclear reactivity for estrogen receptor staining. **e** Solid tumor nodules with neuroendocrine cytologic features. **f** Chromogranin positivity within the solid nodules of tumor with reduced intensity in mucinous areas. **g** Strong nuclear reactivity for GATA-3

In the absence of neuroendocrine differentiation, this tumor would have been classified as a mucinous adenocarcinoma [1] and would meet criteria for subtyping as CC. Because of the neuroendocrine marker positivity, lack of definitive primary site within the major salivary glands, and prominent dermal infiltration, we considered the possibility

Table 1 Immunohistochemistry results and conditions

Antibody	Result	Vendor	Dilution	Pretreatment	Detection	Instrument
CK7	Positive	Leica	Predilute	Low pH	LR, DAB	LBIII
CK20	Negative	Ventana	Predilute	High pH	VUV, DAB	VU
CD117	Negative	Dako	1:200	High pH	LR, DAB	LBIII
Chromogranin	Positive	Dako	1:1500	High pH	LR, DAB	LBIII
GATA-3	Positive	Biocare	1:400	High pH	VUV, DAB	VU
ER/PR	3+/3+	DAKO	Predilute	High pH	VUV, DAB	LBIII
Her2neu	Negative	Ventana	Predilute	High pH	VUV, DAB	VU
P63	Negative	Ventana	Predilute	High pH	VUV, DAB	VU
PSA	Negative	Ventana	Predilute	High pH	VUV, DAB	VU
S100	Negative	Dako	1:1500	High pH	LR, DAB	LBIII
Synaptophysin	Positive	Leica	Predilute	Low pH	LR, DAB	LBIII
WT-1	Negative	Dako	1:50	High pH	LR, DAB	LBIII
AR	2+	NA	NA	NA	NA	NA

DAB direct antibody kit, *LR* Leica Refine, *LBIII* Leica Bond III, *VU* Ventana ultra, *VUV* Ventana ultraview, *AR* androgen receptor (performed by Clarient Laboratories, Inc)

of a primary cutaneous endocrine mucin-producing sweat gland carcinoma (EMPSGC), which typically presents as a small cutaneous periocular papule. [12, 13] EMPSGC is uniformly WT-1 positive [14], while selective WT-1 expression has also been reported in pure and mixed mucinous subtypes of breast carcinomas. [15] However, WT-1 expression was negative in this specimen, arguing against an EMPSGC diagnosis.

The described case is unusual in that it exhibits morphologic and immunohistochemical features similar to primary mammary mucinous adenocarcinomas, with neuroendocrine differentiation [16] in its receptor profile and GATA-3 positivity. Studies of chromogranin and synaptophysin are lacking in cases of salivary gland carcinomas, though positivity of neuron-specific enolase and glial fibrillary acid protein has been reported in a mucin-rich salivary gland carcinoma [17]. Given the similarity to mammary mucinous carcinomas with neuroendocrine differentiation, it is possible that this case may exhibit a comparable clinical course, although the large size and anatomic site likely play a significant role in prognosis. The clinical significance of neuroendocrine differentiation is unknown.

Previous studies have described ER, PR, and AR profiles of mucin-rich carcinoma in non-salivary sites. This is especially well-described in mucin-rich carcinoma with a primary breast site [18]. The receptor profiles of mucin-rich carcinoma with a primary salivary gland origin are poorly defined, but the positivity of these markers suggest a role in utilizing hormone receptor targeted therapy. As such, the patient was placed on leuprolide and bicalutamide as adjuvant anti-androgen therapy in conjunction with postoperative radiation.

In summary, we present an unusual case of a giant mucinous adenocarcinoma of salivary gland origin, distinctive for its neuroendocrine differentiation and locally destructive character. Further investigation is warranted to explore its responsiveness to adjuvant treatment, including anti-androgen therapy and radiation.

Compliance with ethical standards

Conflict of interest No conflict of interest to disclose.

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