CASE REPORT

Glycogen-Rich Clear Cell Squamous Cell Carcinoma Originating in the Oral Cavity

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Abstract Clear cell squamous cell carcinoma (CCSCC) is a rare histological subtype of squamous cell carcinoma (SCC) that was originally described in the skin. Here, we report a case of a 66-year-old female patient who presented with a fungating ulcerative mass of the left lateral tongue extending anteriorly to the floor of the mouth, and posteriorly to the left retromolar fossa and the oropharynx. The patient had a history of SCC of the left posterior tongue that was treated with partial glossectomy and adjuvant radiotherapy. Representative biopsies were obtained from the floor of the mouth, tongue and retromolar fossa. The examined biopsies showed various degrees of dysplastic surface epithelium with transition into infiltrating epithelial tumor nests and cords with clear cytoplasm and malignant cellular features. Pancytokeratin, CK5/6, and p63 were all diffusely positive. S-100, Calponin, and smooth muscle actin (SMA) were negative. PAS stain was diffusely positive and diastase labile in the tumor clear cells. Sparse areas of mucicarmine positivity were noted. Based on these findings a

final diagnosis of a glycogen-rich CCSCC was given. This case represents a very rare histological variant of oral SCC, which is significant for the histological differential diagnosis of clear cell tumors of the oral cavity.

Keywords Oral cavity · Squamous cell carcinoma · Clear cell · Glycogen · Prognosis

Introduction

Head and neck cancer is the 6th most common malignancy worldwide, and while its incidence varies by geographical location, it is expected to rise over the coming decades [1, 2]. Squamous cell carcinoma (SCC) is the most common malignancy encountered in the oral cavity [3] with different histological subtypes described in the literature including basaloid, verrucous, spindle cell, papillary, adenosquamous, acantholytic, and canaliculatum variants [4]. Clear cell tumors of the head and neck are rare, whether benign or malignant [5]. The aim of this case report is to present a rare case of a glycogen-rich squamous cell carcinoma of the oral cavity that presented with local aggressive behavior and distant metastasis to the lung.

Case Report

A 66-year-old woman presented with a large painful mass that showed ulcerations of the left lateral tongue extending anteriorly to the floor of the mouth, and posteriorly to the oropharynx and the left retromolar fossa (Fig. 1). The patient had a history of SCC of the left posterior tongue that was treated with partial glossectomy and adjuvant radiation therapy approximately 2 years prior to presentation.

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Fig. 1 Pre-operative T1 MRI imaging. **a** Axial section showing the tumor of the left side of the tongue with its extensions anteriorly to the floor of the mouth, and posteriorly to the left retromolar fossa and

the oropharynx. **b** Coronal section indicating extension into the floor of the mouth and retromolar fossa

Three biopsies were taken from each site of the current ulcerative lesions. All three H & E stained sections demonstrated various degrees of dysplastic stratified squamous epithelium with evidence of transition into invading tumor nests and cords with clear cytoplasm. Clear cells showed squamous differentiation, cellular atypia, and scattered abnormal mitotic figures (Fig. 2). Areas of necrosis and stromal hyalinization were also noted as well as perineural and intramuscular invasion (Fig. 3). Several areas showed connection with overlying dysplastic surface epithelium (Fig. 4). A panel of immunohistochemical stains was negative for myoepithelial markers (S-100, Calponin, smooth muscle actin). PAS was positive, diastase labile in the tumor clear cells indicating the presence of glycogen (Fig. 5). The results of the special stains and the immunohistochemistry are summarized in Table 1. A diagnosis of a glycogen-rich squamous cell carcinoma, clear cell variant, high-grade, was given to all three samples.

Initial re-staging MRI and PET scan did not demonstrate any distant disease. The patient was presented to the multidisciplinary head and neck tumor board with a clinical diagnosis of a recurrent T4N2cM0 SCC (clear cell variant) with recommendation for salvage surgery and consideration for post-operative re-irradiation. The patient underwent subtotal glossectomy, partial pharyngectomy, bilateral neck dissection and simultaneous anterolateral thigh free flap reconstruction. At a follow-up appointment 3 months after salvage surgery, a chest CT scan indicated metastasis to the

left lung (Fig. 6). The patient was scheduled for chemotherapy and a potential clinical trial.

Discussion

In this report we present a rare case of a glycogen-rich, clear cell variant of SCC arising from the epithelium of the oral cavity of a 66-year-old female. Differences in the treatment and prognosis of the various clear cell tumors makes reaching a definitive diagnosis a more challenging task when clear cells predominate in histological sections.

In the presented case, the tumor cells in all three samples exhibited clear cell differentiation and malignant behavior. Intracellular accumulation of water, mucopolysaccharides, glycogen, mucin, lipids, tonofilaments and immature zymogen granules can attribute to the clear appearance of these cells [6, 7]. Phagocytosed foreign materials in the cytoplasm, hydropic degeneration, and a paucity of intracellular organelles are other possible causes [6]. In the oral cavity, such tumors can be categorized into three groups based on their origin: clear cell tumors of salivary glands, clear cell odontogenic tumors, and metastatic clear cell tumors [7], which made it logical to consider a wide differential of malignant clear cell neoplasms that can arise in the oral soft tissues. These consist of clear cell salivary gland tumors; including epithelial myoepithelial carcinoma, clear cell myoepithelial carcinoma, acinic cell carcinoma,

Fig. 2 Clear cytoplasmic features and squamous cell configuration of the CCSCC. **a** H&E stained soft tissue section from the extension of the tumor into the retromolar fossa, showing invading epithelial tumor islands in the form of sheets and strands ($\times 20$, scale bar 2 mm). **b** Tumor cells show a dominating feature of abundant clear cytoplasm and rounded nuclei that are mostly eccentrically placed. **c**

Some tumor nests show central clear cells with peripheral cells showing eosinophilic cytoplasm. **d** Other tumor nests show highly anaplastic cellular features with large bizarre looking nuclei and abnormal mitotic figures. The peritumoral stroma is abundantly inflamed ($\times 80$, 200 μm scale bar)

mucoepidermoid carcinoma, and clear cell adenocarcinoma. Clear cell odontogenic tumors, particularly clear cell odontogenic carcinoma, must also be considered, as should metastatic tumors, especially from the breast and kidney, and other rare tumors like sebaceous carcinoma of the oral cavity and clear cell squamous cell carcinoma.

Epithelial myoepithelial carcinomas present as rare, low-grade tumors with biphasic differentiation of cuboidal to flat ductal cells surrounded by large, clear myoepithelial cells [8]. H&E stained sections of the three samples lacked this particular histological pattern. Clear cell myoepithelial

carcinoma is a rare disease with only few cases that developed in the minor salivary glands of the oral cavity. This malignant tumor exhibits variable histological presentation with clear cells. The immunohistochemical staining pattern for both types of tumors usually reveal positive reactions to myoepithelial markers including smooth muscle actin, calponin, vimentin, S-100, and high molecular weight cytokeratins [9]. Smooth muscle actin, calponin, vimentin, and S-100 were negative in our samples.

Acinic cell carcinoma is a malignant salivary gland tumor with serous acinar cell differentiation where clear

Fig. 3 Tumor shows features of high-grade malignancy. H&E stained soft tissue section showing **a** tumor islands in the form of strands with clear cell component, in a background of hyalinizing stroma. **b**

Area of necrosis. **c** Intramuscular invasion and **d** perineural invasion ($\times 80$, 200 μm scale bar)

cells can be present in 1% of the tumor or as the predominant component [10]. The clear cytoplasm is most probably attributed to fixation artifacts or a reduction in the number of organelles. There is controversy as to the existence of a pure clear cell acinic cell carcinoma [5]. Acinic cell carcinoma typically exhibits PAS positive, diastase resistant zymogen granules in the cytoplasm, which was not the case in our presented tumor.

Mucoepidermoid carcinoma is the most common malignant salivary gland neoplasm. It is mainly composed of epidermoid, mucous, and intermediate cells [5] though clear cells can comprise a large proportion of the tumor [7]. The cytoplasm of mucous cells yields

a prominent reaction to mucicarmine and PAS while the clear cells of the tumor may contain glycogen, mucin, or both [11]. Intermediate cells were not a finding in our case which is required for accurate diagnosis of mucoepidermoid carcinoma, and foci of positive mucicarmine stain were mainly in areas of minor salivary glands infiltrated by tumor cells or areas of residual ducts with retained mucus in the lumen [12]. Although mucicarmine showed scattered positivity in our samples indicating the presence of mucin, it has been argued that in the absence of a glandular structure, adult keratinocytes in squamous cell carcinoma can undergo metaplastic changes to produce mucin [13].

Fig. 4 Tumor shows transition of the overlying dysplastic surface epithelium into invading tumor islands. **a** H&E section showing lesional extension towards retromolar fossa. **b** Lesion extension towards the floor of mouth ($\times 80$, 200 μm scale bar)

Clear cell carcinoma of salivary glands is an uncommon tumor that makes up <1% of primary salivary glands tumors [14]. It occurs most frequently in the minor glands and diagnosis can be made by excluding other salivary gland tumors that present with clear cells [15]. Clear cell carcinoma can be hyalinizing or nonhyalinizing and is invariably positive to pancytokeratin antibodies and immunonegative for myoepithelial markers [16]. The cytoplasm of the clear cells can be PAS positive diastase labile indicating glycogen [8, 17, 18]. In addition, staining with mucicarmine would not reveal intracytoplasmic mucins [12]. In our case, the tumor cells in the examined sections showed squamous and clear cell differentiation and direct connection with overlying dysplastic surface epithelium. Furthermore, positive immunohistochemical staining for p63 and cytokeratin 5/6 in poorly differentiated carcinomas has been linked to squamous epithelial origin [19].

Odontogenic tumors with dominant clear cell component are very uncommon lesions [6]. Calcifying epithelial odontogenic tumor (Pindborg tumor) is characterized by the presence of epithelial islands, amyloid deposits and Liesegang ring calcifications, which were not present in our case [20]. Ameloblastoma can rarely present with a clear cell variant intraosseously or peripherally in the gingiva but our case lacked the ameloblast-like configuration [7, 21]. Clear cell odontogenic carcinoma is an aggressive tumor with a significant clear cell component that arises intraosseously and lacks a connection with surface epithelium [6, 22].

Tumor metastasis to the jaw is also an uncommon occurrence, though the bones of the jaw are affected twice as

common as the oral mucosa, which more often will involve the gingiva and the tongue. The most common primary tumors presenting with metastasis to the oral cavity are lung cancers in men and breast cancers in women [23]. Staining for mammaglobin, a marker for metastatic breast cancer [23], was negative in our case. Metastatic renal clear cell carcinoma demonstrates a prominent sinusoidal vascular network which was also absent in our samples, as was staining with RCC marker and PAX-8, both of which are expressed by metastatic clear cell renal cell carcinoma [5, 24]. Metastatic amelanotic melanoma was excluded based on immunonegative staining to S-100 and HMB-45 [25].

Sebaceous carcinoma is characterized histologically by invading cells showing sebaceous differentiation and sometimes marked squamous differentiation. The tumor cells have abundant vacuolated foamy cytoplasm due to lipid accumulation, a feature not present in our case [26].

Squamous cell carcinoma is the most common malignancy arising in the oral cavity [1–3]. Carcinomas of the oral cavity can present as a non-healing ulcer, red or white patches, or a large mass, with the tongue being the most involved intraoral site [3, 27]. The clear cell histological subtype is now a recognized rare variant of SCC of the skin, first reported by Kuo, where the clear cell appearance is not attributed to the presence of glycogen, mucin or lipids, but rather believed to be due to the accumulation of intracellular fluid and hydropic degeneration [28, 29]. One CCSCC was reported to have arisen in the esophagus, which demonstrated glycogen deposition confirmed by a positive PAS staining digested by diastase [30]. In addition, a CCSCC as a malignant component of carcinoma

Fig. 5 Immunohistochemical and special stain profile of the CCSCC. **a** Tumor cells stain positive for p63. **b** Diffuse cytokeratin 5/6 positivity in islands of tumor cells **c** H&E stained section showing tumor

islands with clear cells positive for PAS. **d** The stain was diastase labile ($\times 80$, 200 μm scale bar)

ex pleomorphic adenoma of the submandibular gland was reported in which the clear cells showed intracellular accumulation of glycogen [31].

To date there are three reported cases of a CCSCC occurring within the mucosa of the oral cavity. The first case as described by Frazier et al. involved a hemorrhagic exophytic mass on the posterior mandibular gingiva. Microscopic examination revealed dysplastic stratified squamous epithelium with infiltrating islands of epithelial cells with clear cytoplasm that stained positive with PAS and were diastase labile [32]. The second reported case by Nainani et al. presented as an ulcerative-proliferative lesion on the left buccal mucosa, which demonstrated sheets of predominantly clear cells with dysplastic features invading the underlying connective tissue. The clear cells were negative for PAS, mucicarmine, and Oil Red O, indicating the

absence of glycogen, mucin and lipids, respectively [33]. The most recent case as described by Kaliamoorthy et al. in 2015, presented as a non-healing ulcer on the left lateral border of the tongue that showed malignant histologic criteria with prominent clear cell changes that were negative for PAS and mucicarmine [34]. Table 2 summarizes previous cases of clear cell squamous cell carcinoma originating from oral surface epithelium.

It is unclear if this rare variant of oral SCC has a worse prognosis than the more common histologic variants, as there is a paucity of literature on such tumors. Regardless of histology, up to 50% of oral SCC will recur (pending initial pathologic stage) and most often at the local site. A worse salvage prognosis depends on numerous factors including; time to recurrence (<6 months), initial tumor depth >10 mm, perineural involvement, extranodal extension and

Table 1 Special stains and antibodies used in all histological sections of the three biopsies

Special stain/antibody	Expression within tumor	Clone	Company	Dilution
Renal cell carcinoma (RCC)	–	PN-15	Cell Marque, Rocklin, CA, USA	Prediluted
Mamaglobin	–	31A5	Cell Marque	1:100
PAX-8	–	Polyclonal	Cell Marque	Prediluted
PAS	+	N/A	Dako Corporation, Carpinteria, CA	N/A
PAS-D	+	N/A	Dako Corporation	N/A
Mucicarmine	±	N/A	Dako Corporation	N/A
Calponin	–	26A11	Leica BOND, Buffalo Grove, IL	Prediluted
HMB45	–	HMB45	Leica BOND	Prediluted
Multi-cytokeratin	++	AE1/AE3	Leica BOND	Prediluted
Myosin heavy chain (smooth muscle)	–	S131	Leica BOND	Prediluted
S-100 (A and B)	–	Polyclonal	Leica BOND	Prediluted
Smooth muscle actin	–	Alpha sm-1	Leica BOND	Prediluted
Vimentin	–	SRL33	Leica BOND	Prediluted
Cytokeratin 5/6	++	D5/16B4	VENTANA, Tucson, AZ	Prediluted
p63	+	4A4	VENTANA	Prediluted

++ diffuse strong positivity, + positive, ± scattered positivity, – negative, N/A non-applicable

Fig. 6 Chest CT scan showing a metastatic mass into the left lung

history of prior adjuvant radiotherapy. Patients who do present with nodal disease often have more advanced regional tumor burden as was seen in this case study (N2b) [35–37].

Some researchers have attributed glycogen accumulation in cancer cells to a hypoxic tumor microenvironment, which will eventually result in the induction of P53-dependent cellular senescence, inhibition of tumor growth, and enhanced tumor cell survival under nutrient stress conditions [38, 39]. Such senescence could have happened as the tumor cells accumulated more glycogen, which will render them resistant to cancer treatment that requires high proliferative index. Moreover, radiation resistant human cancer cell lines have been linked to a radiation-induced increase in intracellular glycogen, with underlying mechanisms particularly involving glycogen synthase kinase (GSK-3) [40]. It is presumed that similar molecular mechanisms might be involved in the intracellular accumulation of glycogen in previously irradiated recurrent oral SCC, which would

Table 2 A summary of previous literature on clear cell squamous cell carcinoma originating from oral surface epithelium

Author	Year	Location	Reason of clear cytoplasm
Frazier et al. [32] Oral Surg Oral Med Oral Pathol Oral Radiol	2012	Mandibular gingiva	Glycogen
Nainani et al. [33] J Clin Diagn Res	2014	Buccal mucosa	–ve to PAS and mucicarmine
Kaliemoorthy et al. [34] J Nat Sci Biol Med	2015	Lateral tongue and lingual vestibule	–ve to PAS and mucicarmine

contribute to a more radioresistant phenotype. Hence, targeting components of glycogen metabolism as a strategy in cancer therapy has been proposed, which could enhance anticancer treatment [39, 40].

In conclusion, this article presents a rare case of a high-grade, glycogen-rich, CCSCC arising within the left side of oral cavity with extensions into the oropharynx. A clear cell histological variant of oral SCC is very rare but should be considered in the histological differential diagnosis of clear cell tumors of the oral cavity.

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Compliance with Ethical Standards

Conflict of interest No conflict of interest to disclose.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of retrospective study formal consent is not required. The tumor tissue and radiographic material included in the manuscript were obtained as part of the standard of care for the patient and retrospectively collected for the case report.

Informed Consent No identifier information is included in the case report, and the study meets the waiver criteria for the institutional review board of University of Maryland Baltimore.

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