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Case Report

Oral squamous cell carcinoma with prominent clear-cell features: a case report and diagnostic review

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ABSTRACT

Clear-cell variants of oral squamous cell carcinoma (OSCC) are exceedingly rare and present a diagnostic challenge due to their uncommon histomorphological features and overlap with other clear-cell neoplasms. We report a case of a 65-year-old male presenting with a persistent ulceroproliferative lesion in the lateral oropharyngeal wall. Histopathological examination revealed nests of squamous epithelial cells with abundant clear cytoplasm and marked pleomorphism. Periodic acid–Schiff with diastase (PAS-D) staining indicated glycogen accumulation, and immunohistochemistry confirmed epithelial origin via strong pan-cytokeratin expression. These findings supported the diagnosis of the clear-cell variant of OSCC. The differential diagnosis encompassed salivary gland tumors, odontogenic lesions, and metastatic clear-cell malignancies. Accurate identification required a combination of histological, histochemical, and immunohistochemical analyses. Although the World Health Organization has not yet classified this variant formally, its recognition is crucial due to the possibility of a more aggressive clinical course. This case contributes to the limited literature and underscores the importance of comprehensive diagnostic approaches to improve our understanding of this rare entity.

Keywords: Oral squamous cell carcinoma, Clear-cell variant, Glycogen-rich cells, Histopathology, PAS-D staining, Immunohistochemistry, Rare oral malignancy, Head and neck cancer

INTRODUCTION

Head and neck cancers represent about 3% of all malignancies, with oral squamous cell carcinoma (OSCC) comprising the vast majority.[1] OSCCs are typically graded histologically as well, moderately, or poorly differentiated, based on keratinization and cellular atypia.[2] In addition to these common subtypes, less frequent histological variants such as verrucous, spindle cell, adenosquamous, basaloid, and clear cell carcinomas have been identified.[3,4]

Clear-cell squamous cell carcinoma (CCSCC) is an exceptionally rare variant of OSCC, first described by Kuo in 1980, with only a small number of cases reported since.[5,6] The clear-cell phenotype is thought to arise from intracellular accumulation of glycogen, mucin, lipid, or hydropic change. This appearance often creates diagnostic difficulty, as it must be distinguished from salivary gland tumors and metastatic clear-cell lesions.[7,8]

Although CCSCC is not formally recognized in the World Health Organization classification of oral malignancies,

published case reports suggest that clear-cell change may reflect dedifferentiation, possibly signifying more aggressive behavior, early metastasis, and poor prognosis.[9,10]

CASE REPORT

A 65-year-old male presented to the otolaryngology outpatient clinic with complaints of persistent discomfort and a sensation of fullness on the left side of his throat, ongoing for approximately 2.5 months. Clinical examination revealed an ulcero-proliferative lesion in the lateral oropharyngeal wall, with areas of erythema and focal ulceration. No palpable cervical lymphadenopathy was noted at the time of presentation.

A contrast-enhanced computed tomography (CT) scan of the neck demonstrated a heterogeneously enhancing, irregular soft-tissue mass measuring approximately 44×36×32 mm in the lateral pharyngeal wall. An incisional biopsy of the lesion was obtained. Histopathological evaluation revealed sheets and nests of atypical squamous epithelial cells exhibiting marked cellular pleomorphism, prominent nucleoli, and abundant clear cytoplasm infiltrating the surrounding connective tissue.

To determine the origin of the clear-cell change, periodic acid–Schiff with diastase (PAS-D) staining was employed, revealing intense positivity suggestive of glycogen accumulation. Immunohistochemistry using pan-cytokeratin marker confirmed diffuse cytoplasmic positivity in both the dysplastic epithelial islands and the clear-cell population, supporting a diagnosis of clear-cell variant of OSCC (Figure 1a-f).

The primary mode of treatment for OSCC, including its rare variants, is surgical excision with or without adjuvant therapy depending on the stage and histopathological findings. In this case, the patient underwent wide local excision of the lesion with ipsilateral selective neck dissection to ensure clear margins and address potential lymphatic spread. Given the moderately differentiated histology with clear-cell features, the patient was referred for adjuvant radiotherapy to minimize the risk of local recurrence.

Post-treatment surveillance was initiated with regular follow-up every 3 months, including clinical examination and imaging. At the 12-month follow-up, the patient remained disease-free, with no signs of recurrence or metastasis. This favorable outcome emphasizes the importance of timely diagnosis and multidisciplinary management, even in histological variants with potentially aggressive behavior.

While current literature is limited due to the rarity of this variant, accumulating evidence suggests that early detection and a tailored treatment plan, supported by accurate histopathological and immunohistochemical analysis, are key to improving clinical outcomes in patients with clear-cell OSCC. More case reports and longer-term studies are needed to better understand the prognostic implications and define standardized treatment protocols for this unusual entity.

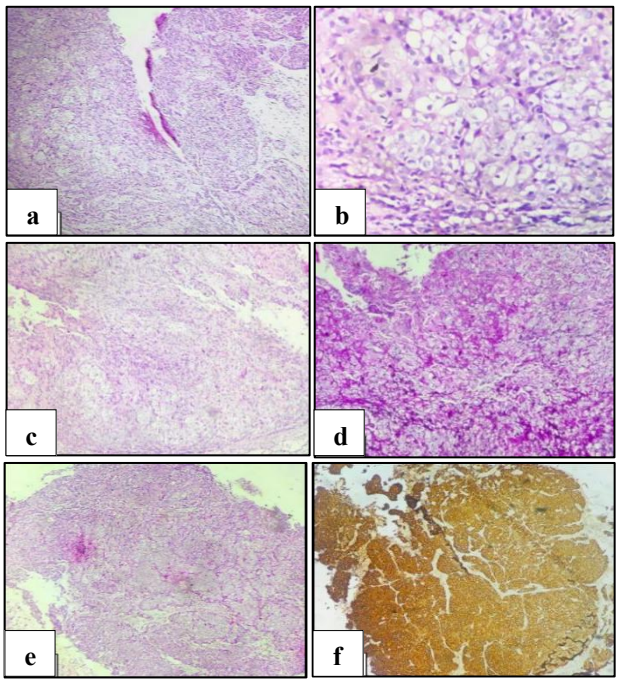

Figure 1: (a) Low-power photomicrograph showing nests and sheets of malignant squamous cells with clear cytoplasm infiltrating the underlying connective tissue, (b) high-power view revealing pleomorphic cells with eccentrically placed hyperchromatic nuclei and abundant clear cytoplasm, (c) histological section demonstrating prominent clear-cell change within tumor islands, (d) periodic acid–schiff with diastase stain highlighting glycogen-rich clear cells with strong cytoplasmic, (e) immunohistochemical staining for pan-cytokeratin showing diffuse and intense positivity in tumor cell clusters, including those with clear-cell morphology, and (f) high-magnification IHC image confirming epithelial origin of clear-cell tumor areas via pan-cytokeratin expression.

DISCUSSION

Clear-cell changes in epithelial malignancies, including squamous cell carcinomas, represent a histological phenomenon often caused by intracellular accumulation of glycogen, lipids, mucin, or hydropic degeneration.[11] In the oral cavity, the presence of clear cells can complicate diagnosis due to overlap with other neoplasms, particularly those of salivary gland, odontogenic, or metastatic origin. Therefore, when encountering clear-cell features in oral lesions, it is critical to undertake a thorough differential diagnosis to distinguish between entities such as mucoepidermoid carcinoma, epithelial–myoepithelial carcinoma, acinic cell carcinoma, clear-cell odontogenic carcinoma, and metastases from renal cell carcinoma.[12]

In our case, the clear-cell morphology was found to be a result of glycogen accumulation, confirmed through PAS-D staining, which ruled out mucinous and lipid-rich etiologies. This histochemical approach, supplemented by immunohistochemical positivity for pan-cytokeratin, confirmed the epithelial and squamous nature of the tumor.[13] Additional immunomarkers like S-100 and smooth muscle actin (SMA) may be helpful to exclude melanocytic and myoepithelial tumors, respectively, though they were not required in this case due to conclusive cytokeratin positivity.

Due to its rarity, the clear-cell variant of OSCC is not yet formally categorized in the WHO classification of head and neck tumors. However, reported cases suggest that this variant may be associated with a more aggressive biological course compared to conventional OSCC. Some authors propose that the clear-cell phenotype may reflect dedifferentiation in tumor progression, correlating with an increased potential for local invasion and distant metastasis.[14]

CONCLUSION

The clear-cell variant of oral squamous cell carcinoma is an exceptionally rare and diagnostically demanding subtype. Its resemblance to other clear-cell neoplasms necessitates careful histopathological, histochemical, and immunohistochemical evaluation for accurate diagnosis. Although not yet officially recognized by the WHO, available literature suggests a potentially aggressive clinical course.

Early detection and a multidisciplinary approach to management, including surgery and adjuvant therapy when indicated, are crucial for achieving favorable outcomes. Continued reporting of such rare variants will help improve diagnostic clarity and guide appropriate treatment strategies in the future.

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