Clear Cell Variant of Oral Squamous Cell Carcinoma: An Uncommon Presentation

[1] Dr. Aastha Visavadiya, [2] Dr. Shylaja Attur,
[3] Dr. Niharika Sarathy, [4] Dr. Norin Patel,
[1&4] PG student, Narsinhbhai Patel Dental College and Hospital, Sankalchand Patel University, Visnagar
[2] Professor and Head, Narsinhbhai Patel Dental College and Hospital, Sankalchand Patel University, Visnagar
[3] Reader, Narsinhbhai Patel Dental College and Hospital, Sankalchand Patel University, Visnagar
Corresponding Author: **Dr. Aastha Visavadiya**
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Abstract

The clear cell variant of Oral Squamous Cell Carcinoma (OSCC) is a rare histological subtype, in the oral cavity. This case involves a 40-year-old male patient who presented with a growth on the right lateral border of the tongue. Histopathological analysis showed proliferating surface epithelium over a cellular stroma. The epithelium exhibited dysplastic features and clear cells extended deep into the muscular layer, suggesting well-differentiated oral squamous cell carcinoma. Periodic Acid-Schiff (PAS) staining showed negative in clear cells. Immunohistochemistry for cytokeratin (AE1/AE3) was positive in both clear and other epithelial cells, while Vimentin showed a strong positive reaction only in the tumour stroma. Based on these special stains and IHC markers, the diagnosis of clear cell variant of OSCC was confirmed. This rare variant is known to be aggressive and presents diagnostic challenges, underscoring the need for more cases to be reported to better understand its biological behaviour and prognosis.

Key Words*: Clear cells, oral squamous cell carcinoma, tongue, immune histo chemistry, tumor stroma.*

Introduction

OSCC is the eighth most common cancer worldwide and the leading head and neck cancer, making up 96% of oral malignancies. Its main aetiology is smoking, smokeless tobacco, and alcohol use.[1]
OSCC can be well, moderately, or poorly differentiated, with 10%-15% of cases being conventional OSCC, which includes subtypes like basaloid, verrucous, spindle, adenoid, adenosquamous, and lymphoepithelioma. [1]

The rare Clear Cell variant of OSCC (CCOSCC) was first described by Kuo in 1980 in the skin. [2] CCOSCC is a rare subtype of squamous cell carcinoma. We present a rare instance in a 40-year-old male.

Case Report

A 40-year-old male presented with burning sensation on the right side of his tongue when consuming spicy foods for the past three months, with no harmful oral habits. Examination revealed a 3x4 cm growth on the lateral border of the tongue, extending to the retromolar region, restricting movement, bled on palpation and had an indurated base (Fig. 1). A stony hard, tender, fixed right submandibular lymph node and decayed tooth 36 was noted. A provisional diagnosis of tongue carcinoma was made.

An incisional biopsy was performed under local anaesthesia. A 2.3 x 1 cm, greyish-white, firm tissue sample was sent for histopathological examination. (Fig. 2 a, b, c).

H&E staining showed proliferating surface epithelium over a cellular stroma. Dysplastic features included acanthosis, basal cell hyperplasia, increased nuclear-cytoplasmic ratio, and clear cells with individual keratinization. The stroma showed thick collagen bundles, spindle fibroblasts, and chronic inflammation. Dysplastic epithelial islands with clear cells extended to the muscular layer and throughout the tissue specimen. (Fig. 3 a, b, c)

The diagnosis of well-differentiated squamous cell carcinoma was made. Periodic Acid Schiff (PAS) staining of the clear cells was negative. (Fig.3d, e).

Immunochemistry with Pan-cytokeratin (AE1/AE3) (Fig.4 a, b) showed strong positive staining in dysplastic epithelial islands, keratin pearls, and clear cells (cell membrane staining), indicating malignancy of epithelial origin. Vimentin was intensely positive in the tumor stroma but negative in neoplastic cells. (Fig.4c, d).

The final diagnosis was clear cell variant of squamous cell carcinoma. The patient was referred to a cancer centre for treatment, but further follow-up was lost.

Discussion

Clear cell variants of OSCC (CCOSCC) are rare, and can beclassified into physiologic and pathologic types. The clearing results from accumulated intracytoplasmic structures, hydropic degeneration or fixation artifacts. [1]CCOSCC is sometimes called hydropic squamous cell carcinoma due to extensive hydropic degeneration and intracellular fluid accumulation in the neoplastic cells. [3, 4]

The aetiology remains unclear; with cases involving patients without harmful habits like tobacco or alcohol use as was noted in the present case. Potential links include immune suppression, arsenic exposure, radiation, and chronic ulceration. [2,5]

CCOSCC usually affects the mandible, but in this case involvedthe posterolateral border of the tongue, marking the fourth instance in this location. [1] It typically appears as a nodule or mass, sometimes ulcerated,[5]but in this case, it presented as a growth.

Khoury Z et al. (2017) linked PAS-positive clear cells and glycogen accumulation to hypoxia, which helps cancer cells survive under stress and resist treatments. Radiation-resistant cells also show increased glycogen, with GSK-3 playing a key role. Targeting glycogen metabolism could improve treatment effectiveness.[4]Kuo classified Clear Cell Squamous Cell Carcinoma (SCC) into three types: Type I (keratinizing) Type II (non-keratinizing) and Type III (pleomorphic).[5] All types were negative for PAS and mucin, indicating the absence of glycogen and mucin.

Premalatha et al. categorized clear cell tumors in the head and neck as odontogenic (e.g., clear odontogenic ghost cell tumors and clear cell odontogenic carcinoma), salivary gland (e.g., clear cell myoepithelial carcinoma, acinic cell carcinoma, mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma, and hyalinizing clear-cell carcinoma), or metastatic lesions (e.g., originate from the kidney, lung, liver, or breast). [1,2] These should be considered as potential differential diagnoses for CCOSCC. [2]

Kaliamoorthy S. et al. found that neoplastic lobules strongly stained for cytokeratin AE1/AE3 (Fig.4), while Vimentin was negative in cells but positive in the stroma. Smooth muscle actin and homatropine bromide-45 were negative in both.[3]

Clear cells in clear-cell odontogenic carcinoma are negative for mucicarmine, Alcian blue, Congo red, and Sudan Black, but positive for PAS due to glycogen. In this case, PAS negativity excluded an odontogenic origin (Fig.3 d,e). [2]

Mucous cells in mucoepidermoid carcinoma (MEC) strongly react to mucicarmine and PAS, while clear cells may contain glycogen, mucin, or both. Clear cells in MEC test positive for PAS and mucicarmine, and show immunoreactivity to calponin, S100, and vimentin, ruling out MEC.[2,3]

There is debate over the existence of a pure clear cell variant of acinic cell carcinoma, which typically shows PAS-positive, diastase-resistant zymogen granules, not observed in present case.Clear cell myoepithelial carcinoma, a rare tumor in minor salivary glands, typically tests positive for myoepithelial markers. However, this case was negative for smooth muscle actin, calponin, vimentin, and S-100.[4]

Oral amelanotic melanoma accounts for 1% of primary oral melanomas and is positive for S-100 and HMB45, with oral cavity metastases being very rare.[2]

Renal cell carcinoma (RCC) often metastasize to the head and neck, with 15% of cases showing multiple metastases. [2] RCC typically has a sinusoidal vascular network, absent in our samples. The clear cells contain

glycogen (PAS positive), and stain positive for RCC marker and PAX-8, seen in metastatic clear cell RCC. [4]
Ramani et al. suggested that clear-cell differentiation in tumors may indicate distinct clonal evolution and a poor prognosis.[2]
The pathophysiology of CCOSCC is not well understood, emphasizing the need for further molecular research to fully comprehend its biological, clinical, and histopathological aspects.

Conclusion

CCOSCC is aggressive and requires comprehensive treatment, with long-term follow-up to monitor for recurrences. The pathophysiology is not well understood, emphasizing the need for further research. Molecular studies are crucial to fully understand its biological, clinical, and histopathological implications.

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