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CASE REPORT

CLEAR CELL VARIANT OF SQUAMOUS CELL CARCINOMA MASQUERADING AS PYOGENIC GRANULOMA: A DIAGNOSTIC CHALLENGE

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ABSTRACT

Background: Clear cell variant of squamous cell carcinoma (CCSCC) is a rare and aggressive subtype of oral squamous cell carcinoma (OSCC), often difficult to diagnose due to its unusual morphology. This variant can resemble benign lesions, such as pyogenic granuloma, leading to diagnostic delays.

O**bjective**:To highlight the diagnostic challenge presented by the clear cell variant of squamous cell carcinoma and emphasise the importance of histopathological evaluation in distinguishing it from benign gingival growths.

Case Presentation:A 74-year-old male with a painless gingival lesion in the mandibular anterior region presented with a growth that had gradually increased in size and bled upon mastication. Despite clinical features resembling a pyogenic granuloma, the lesion was diagnosed as CCSCC following histopathological evaluation, which revealed clear cell morphology.

Results:Histopathology showed dysplastic stratified squamous epithelium invading connective tissue, with clear cytoplasm and hyperchromatic nuclei. The patient was referred for oncological management, including surgical excision with wide margins and adjuvant therapy.

Keywords: Clear cell carcinoma, Gingival lesion, Oral squamous cell carcinoma, Pyogenic granuloma, Squamous cell carcinoma

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is one of the most common cancers in the oral cavity, accounting for more than 90% of all oral malignancies. The condition primarily affects older adults and is commonly associated with risk factors such as tobacco use, alcohol consumption, and poor oral hygiene [1].

OSCC typically presents as a painless lesion that may bleed, ulcerate, or present with non-healing sores. While the conventional form of OSCC is widely recognised, there are several histopathological variants, with the clear cell variant of squamous cell carcinoma (CCSCC) being one of the rarest and most challenging to diagnose [2].

The clear cell variant of squamous cell carcinoma was first described by Kuo in 1980. It is characterised by the presence of polygonal tumour cells with clear cytoplasm, which gives the tumour its distinctive appearance. These clear cells result from the accumulation of glycogen or lipid-rich material in the cytoplasm, which is a key diagnostic feature. However, this morphological appearance is not exclusive to CCSCC and can be seen in other neoplastic conditions, making the differential diagnosis particularly challenging [3].

Tumours such as mucoepidermoid carcinoma, clear cell odontogenic carcinoma, metastatic renal cell carcinoma, and clear cell salivary carcinoma also exhibit clear cell morphology. As a result, distinguishing CCSCC from these other clear cell neoplasms requires a careful and detailed diagnostic approach, often involving additional histochemical and immunohistochemical studies [4].

CCSCC is clinically significant because it tends to present as a slow-growing, painless lesion, often mimicking benign conditions like pyogenic granuloma, fibroma, or peripheral giant cell granuloma. These reactive lesions, commonly found in the gingiva, can delay the diagnosis of malignancy, especially in elderly patients. Pyogenic granuloma, for instance, is a vascular lesion that frequently occurs in the gingival tissues and is characterised by its red, lobulated appearance. Due to its clinical resemblance to CCSCC, pyogenic granuloma is a common misdiagnosis, leading to delayed treatment and poor patient outcomes if malignancy is not promptly recognised [5].

Histopathological evaluation remains the gold standard for diagnosing OSCC, including its rare variants like the clear cell subtype. Early diagnosis is crucial for improving prognosis and patient survival, as the clear cell variant of OSCC is known to follow an aggressive clinical course. Despite its rarity, the clear cell variant tends to have a poorer prognosis compared to conventional OSCC, often due to the difficulty in detecting it early [7]. Furthermore, CCSCC may be associated with more advanced disease at the time of diagnosis, which can significantly affect the treatment strategy and overall patient outcomes. The presence of clear cells, coupled with other features such as cellular pleomorphism, hyperchromatic nuclei, and increased mitotic activity, should raise suspicion for this rare subtype, especially in patients with risk factors such as smoking and alcohol use [7].

The challenge of distinguishing between benign and malignant gingival lesions emphasises the need for clinicians to maintain a high index of suspicion. Reactive conditions like pyogenic granuloma can present with similar clinical features, but when in doubt, a biopsy and histopathological examination should be performed. This case report aims to illustrate the diagnostic challenges of CCSCC, focusing on a patient who initially presented with a lesion clinically resembling a pyogenic granuloma, but was later diagnosed with the clear cell variant of OSCC through histopathological evaluation [8].

CASE REPORT

A 74-year-old male presented to the outpatient department with a chief complaint of a growth in the mandibular anterior gingiva, which had been progressively enlarging over the past month. The lesion was described as painless, though it frequently bled during mastication. Extraoral examination revealed no significant abnormality (Figure 1).

Figure 1. Extra-Oral Profile

The patient's medical and dental history was non-contributory, and there were no significant systemic conditions. However, his personal history was notable for a history of smoking (7-8 cigarettes per day for the past 20 years) and alcohol consumption (approximately 60 mL daily for the past 40 years).

On clinical examination, the patient’s oral hygiene was assessed as poor (Figure 2). A solitary, sessile, erythematous growth, measuring approximately 3 cm x 2 cm x 1 cm, was noted on the labial gingiva in the region between the distal aspect of tooth 31 and the mesial aspect of tooth 35 (root stump). The overlying mucosa appeared erythematous, with slight blanching inferiorly and posteriorly. The lesion had well-defined but irregular margins (Figure 3).

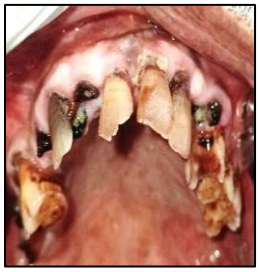

Figure 2. Intra-Oral Examination

Upon palpation, the lesion was soft to firm in consistency, slightly tender, with a smooth to lobulated surface texture. It tended to bleed upon provocation. Mobility of teeth 33, 34, and 36 was noted to be grade III.

Radiographic examination using a panoramic radiograph revealed generalised bone loss, with multiple root stumps and interdental bone loss, specifically between teeth 33 and 34 (Figure 4).

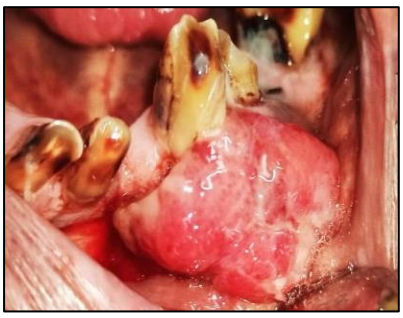

Figure 3. Soft Tissue Growth

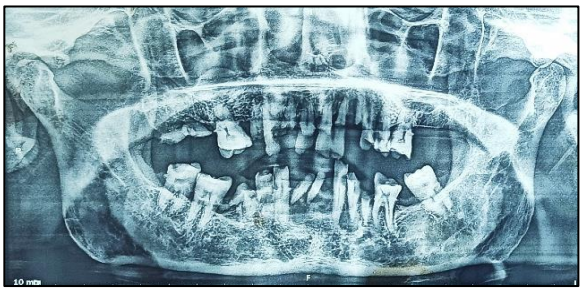

Figure 4. Panoramic Radiograph

Given the clinical features, the provisional diagnosis was pyogenic granuloma, with peripheral ossifying fibroma, peripheral giant cell granuloma, and squamous cell carcinoma considered as differential diagnoses.

Routine haematological investigations were performed and revealed no significant abnormalities. The lesion was surgically excised along with teeth 33, 34, and 35 under local anaesthesia. The excised tissue was submitted for histopathological analysis. (Figure 5).

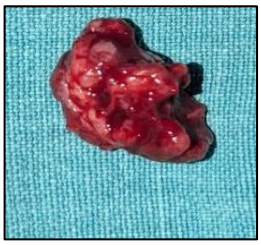

Figure 5. Specimen for Histopathological Examinat

Histopathological findings showed dysplastic squamous surface epithelium showing breach with invasion of epithelial cells into the connective tissue stroma in the form of sheets and islands. Epithelial cells in the connective tissue stroma showed dysplastic features including clear cell cytoplasm with nuclear pleomorphism, hyperchromatism and keratin pearls. The findings were suggestive of - clear cell variant of squamous cell carcinoma.

Following the diagnosis, the patient was referred to a tertiary cancer centre for further oncological management, which included surgical excision with wide margins and adjuvant therapy.

DISCUSSION

Ramani et al. (2021) [9] presented a case report of the clear cell variant of OSCC, describing similar clinical features, including a painless gingival growth with a tendency to bleed, which was misdiagnosed as a benign lesion. Like our case, the diagnosis of CCSCC was confirmed through histopathological examination, which revealed the characteristic clear cell morphology associated with glycogen accumulation. The authors noted that this variant is often underdiagnosed due to its clinical resemblance to more common lesions like pyogenic granuloma. This observation aligns with our case, where the lesion's resemblance to pyogenic granuloma initially led to a provisional diagnosis, underscoring the importance of histopathological evaluation to differentiate between malignant and benign lesions.

Cabral Ramos J et al. (2022) [10] also reported a rare case of CCSCC involving the gingiva. The authors highlighted that, unlike conventional OSCC, CCSCC is often associated with an indolent clinical course initially but can evolve into a more aggressive form. This finding is consistent with the aggressive nature of CCSCC described in our case. While the clinical appearance of the lesion was initially less alarming, its rapid growth and tendency to bleed were indicative of a malignant process. Our case corroborates the need for early recognition of this aggressive variant, as delayed diagnosis can lead to poor prognostic outcomes.

Frazier JJ (2012) [11] seminal study in 1980 first described

the clear cell variant of squamous cell carcinoma. It posited that the clear cytoplasm of the neoplastic cells is due to the accumulation of glycogen, which is confirmed by periodic acid–Schiff (PAS) positivity. Kuo emphasised the diagnostic difficulty in distinguishing CCSCC from other clear cell tumours, such as mucoepidermoid carcinoma or metastatic renal cell carcinoma. Our case highlights the critical role of histochemical and immunohistochemical studies in making an accurate diagnosis, especially in cases where clinical presentation overlaps with benign lesions.

Markopoulos (2012) [12] provided an extensive review of oral squamous cell carcinoma, including its various histopathological subtypes. The study discussed the occurrence of clear cell morphology in different tumours, including OSCC, and emphasised the role of differential diagnosis. The clear cell variant of OSCC, according to the review, is often misdiagnosed as a benign lesion due to its clinical features. Our case aligns with this observation, as the lesion initially appeared to be a pyogenic granuloma, a common benign lesion of the gingiva. Markopoulos' review also noted that clear cell variants of OSCC tend to have a poorer prognosis, which is consistent with the findings in our case, where the lesion's aggressive nature warranted referral for further oncological management.

Sujir N et al. (2019) [13] documented a case of CCSCC where the tumour presented as a non-healing gingival lesion in a middle-aged male with a history of tobacco use. Their report highlighted the importance of considering malignant lesions in the differential diagnosis of gingival growths, particularly in patients with risk factors such as smoking. Similarly, in our case, the patient's history of long-term smoking and alcohol consumption was a significant risk factor, which should have raised suspicion for malignancy. Paul et al. emphasised the importance of early biopsy and histopathological evaluation, which we also advocate, as it was crucial in confirming the diagnosis of CCSCC and preventing a delay in treatment.

According to Ramdas B et al. (2025) [14]. Antibody-drug conjugates (ADCs) offer a promising therapeutic approach for clear cell variant of squamous cell carcinoma (CCSCC) by targeting specific tumor-associated antigens, such as LGALS3BP and integrin beta-6, enabling the selective delivery of cytotoxic agents to tumor cells and thereby improving treatment efficacy and reducing systemic toxicity, with ongoing research necessary to validate these targets and optimize ADC formulations for clinical application.

CONCLUSION

The clear cell variant of squamous cell carcinoma is a rare and aggressive subtype of OSCC that can mimic benign gingival lesions like pyogenic granuloma.

Early recognition and histopathological confirmation are vital to avoid misdiagnosis and ensure timely treatment. Our case corroborates findings from the literature, underscoring the need for clinicians to maintain a high index of suspicion for malignant lesions, particularly in patients with risk factors such as smoking and alcohol consumption. Histopathological examination, including histochemical techniques like PAS staining, plays a crucial role in differentiating CCSCC from other clear cell neoplasms and benign conditions. Further research and clinical awareness are necessary to improve the diagnosis and management of this challenging variant of OSCC.

This case emphasizes the deceptive clinical appearance of CCSCC, which may mimic benign reactive gingival lesions such as pyogenic granuloma. Clinicians should maintain a high index of suspicion and subject all gingival growths to histopathological evaluation. Early and accurate diagnosis is essential for initiating appropriate therapy and improving prognosis in such rare and aggressive variants of oral squamous cell carcinoma.

DECLARATIONS

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Competing Interests
The authors have no competing interests to declare.
Ethical Approval
The study was approved by the appropriate ethics committee and conducted according to relevant guidelines and regulations.
Informed Consent
Not applicable.

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