Case Report

Clear Cell Carcinoma of Minor Salivary Gland – Case Report

Irulandy Ponniah,[1]*MDS*, Palani SureshKumar,[1]*MDS, DNB*, Kaliappan Karunakaran,[2]*MDS*

Abstract

Introduction: Clear cell carcinoma is a rare low-grade carcinoma that almost exclusively occurs in the minor salivary glands. This tumour is one of the new additions in the recent World Health Organization (WHO) classification of salivary gland tumours. Clinical Picture: A 50-year-old woman presented with a gradually enlarging painless submucosal mass of 3 months' duration over the left side of the palate. Treatment and Outcome: A preoperative diagnosis of primary clear cell carcinoma of salivary gland with focal surface epithelial dysplasia was rendered after thorough clinical examination to rule out renal origin. The lesions were excised with wide surgical margins and 3 years into the postoperative period, the patient was disease-free. Conclusion: We report a case of clear cell carcinoma of intra-oral minor salivary gland and draw comparisons with metastatic clear cell carcinoma of renal origin.

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Key words: Hyalinising stroma, Renal cell carcinoma

Introduction

Clear cell carcinoma is a rare low-grade carcinoma that occurs almost exclusively in the intra-oral minor salivary glands.[1-11] Occasional cases have been reported in other sites.[3,10-14] Various terms applied to this tumour reflect its histological diversity.[1-3,9] The recognition and consequent reporting of this neoplasm increased significantly after the report by Milchgrub et al.[3] It is of interest to note that this tumour has been included as a distinct entity in the third World Health Organization (WHO) classification.[15] The aim of this article was to report an intra-oral clear cell carcinoma that microscopically closely resembles a clear cell carcinoma of renal origin, making microscopic differentiation difficult.

Case Report

A 50-year-old female presented with a gradual painless mass of 3 months' duration on the left side of the palate. There was no history of bleeding or tumour elsewhere in the body. She denied the consumption of alcohol or smoking but admitted to regular tobacco-chewing (betel net with slaked lime) for almost 10 years. Her dental and medical history was non-contributory. On general examination, she appeared apparently normal with no lymphadenopathy but was slightly anaemic. Intra-oral examination revealed a submucosal mass, measuring 2 x 2.5 cm in size and extending from the midline to the left alveolar gingiva, corresponding to the left maxillary permanent first molar, second molar and the attached gingiva of the second premolar. Secondary ulceration was noted anterolaterally. On palpation, the mass was non-tender and varied in consistency, from soft to firm. Conventional radiographs showed no bony or sinus involvement. Preoperative biopsy of the mass showed trabeculae, cords, nest or solid sheets of optically clear cells without evidence of ductal differentiation. Individual cells were round to polygonal with distinct cell membranes and a centrally placed nucleus. The clear cells were surrounded by a prominent hyaline stroma. Some of the clear cells were attenuated by the extensive hyaline stroma (Fig. 1). No residual salivary gland elements or features typical of other recognised salivary gland neoplasm were evident but atypia and a poorly differentiated focus were appreciated (Fig. 2). The overlying stratified squamous epithelium was stretched by the close approximation of the lesional tissue; in focal areas, it displayed features such as the loss of polarity and orientation, hyperchromatism, increased nuclear/cytoplasmic ratio and prominent nucleoli (Fig. 3).

[1] Department of Oral and Maxillofacial Pathology, Tamil Nadu Government Dental College and Hospital, Chennai, India
[2] Department of Oral and Maxillofacial Pathology, JKK Nataraja Dental College and Hospital, Nammakkal, Tamil Nadu, India
Address for Correspondence: Dr Irulandy Ponniah, Department of Oral and Maxillofacial Pathology, Tamil Nadu Government Dental College and Hospital, Chennai 600003, India.
Email: salivaryduct@yahoo.co.uk

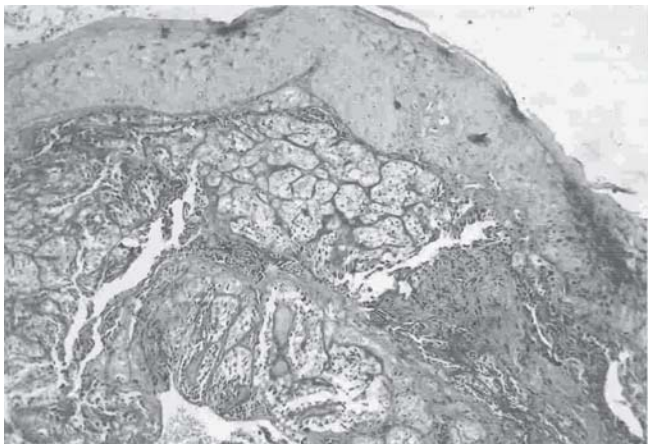

Fig. 1. Islands of clear cells surrounded by PAS-positive hyaline stroma in an organoid pattern and attenuation of clear cells by stromal deposition. Note the close approximation of neoplastic cells with the overlying epithelium (PAS stain, original magnification x100).

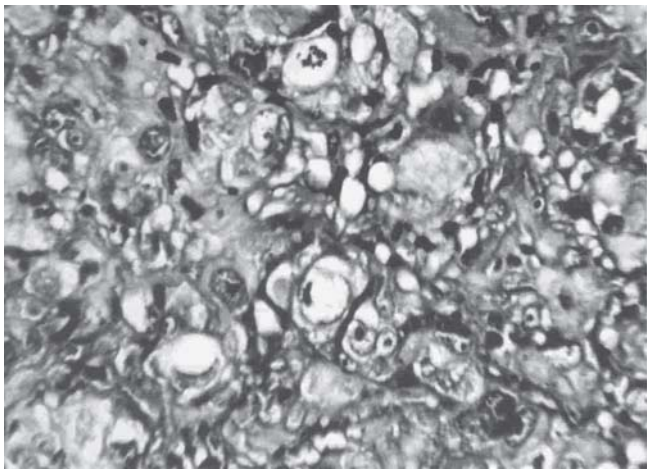

Fig. 2. High-grade cytology mimicking clear cell carcinoma of renal origin (PAS stain, original magnification x400).

Special stains such as mucicarmine, periodic acid-schiff reagent (PAS) or phosphotungstic acid haematoxylin (PTAH) were negative for the clear cells. In contrast, the hyaline stroma stained with PAS but not Congo-red stain. A thorough clinical examination and imaging studies (chest X-ray and renal ultrasonography) were performed to rule out metastasis but they failed to show pathological results. A diagnosis of primary clear cell carcinoma was thus made. The lesion was surgically excised in accordance with the treatment for low-grade carcinoma. Examination of the excised tissue showed very similar histological features to that of the preoperative biopsy. Residual uninvolved minor salivary gland tissue was also noted. Neural or vascular invasion was not found in the sections examined. Additionally, immunohistochemical stains for cytokeratin (AE1/AE3), S100, smooth muscle actin and vimentin were

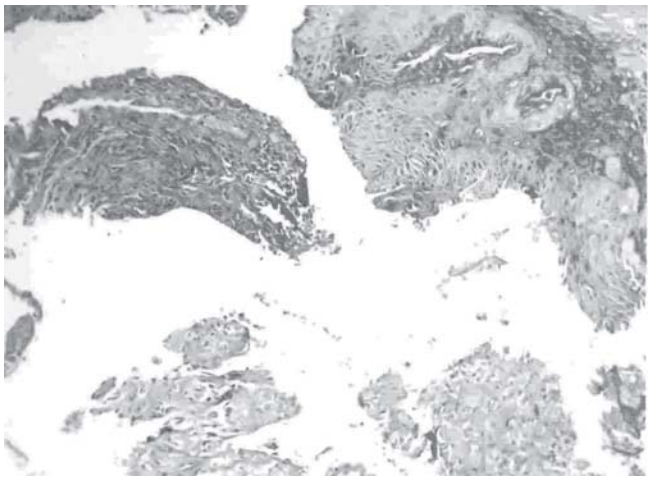

Fig. 3. Features of epithelial dysplasia of the overlying epithelium that is detached from the lesion tissue found at the bottom (PAS stain, original magnification x100).

performed. A negative result was obtained for all the markers except cytokeratin. The patient was free from local or distant disease during the 3 years of follow-up.

Discussion

Primary clear cell tumours of salivary origin fall into 2 distinct lineage restrictions – those that require evidence of myoepithelial differentiation and those that do not. Clear cell carcinoma is a classic and distinct entity that represents the latter differentiation pathway.[11] By definition, clear cell carcinoma contains a significant proportion of clear cells, but it does not fit into any other recognised neoplastic entities.[11] Although non-lipid and non-mucin, but glycogen-rich clear cell tumours in salivary glands have long been recognised,[1-14] they were only recently included in the third WHO classification as a distinct low-grade carcinoma.[15] Most of these tumours have been reported as sporadic cases with the exception of a few well documented series.[3,11] The natural course is an indolent, painless, submucosal mass that occurs predominantly in the minor salivary glands of elderly women.[1-5,7-15]

The microscopic feature of clear cell carcinoma is distinctive. Individual tumour cells are principally characterised by optically clear cytoplasm with well-defined borders and a centrally placed nucleus.[2,3,10] The stroma is typically hyaline although dense fibrous, and loose myxoid or mucoid may be found.[3,4,8,10,11] Because of the characteristic hyaline stroma of the clear cell carcinoma, it is often termed hyalinising clear cell carcinoma,[3] but this is not a constant feature.[11] Some tumours may be relatively solid, and thus may be referred to as clear cell carcinoma.[11] This term is also preferred by the third WHO classification, whether or not there is significant hyalinisation.[15] The hyaline stroma does not represent the basement membrane type of material

found in tumours of myoepithelial lineage.[8] The diagnosis of clear cell carcinoma is usually apparent in H & E sections,[3,12,13] but it is imperative to perform special and immuno stains to exclude other salivary gland tumours with a clear cell component.[2-8,11-14.]

Although clear cells are found in a number of salivary gland tumours, most can be excluded based on other typical cellular or growth phenotypes.[2,3,9,10,13] The distinction from epithelial-myoepithelial carcinoma is, however, quite difficult, especially the solid form without any discernible double-layered cytology.[9] The presence of PAS-positive and Congo-red negative stroma in clear cell carcinoma may help in the differentiation between this and other clear cell tumours.[3]

The cytoplasmic clarity in clear cell carcinoma is due to glycogen; it reacts variably with PAS and is mainly attributed to water.[2] Alternatively, it may result from the loss of organelles, storage of substances or fixation artefacts.[9] Therefore, a negative result for PAS staining does not preclude a diagnosis of clear cell carcinoma,[2,5] unless myoepithelial markers are likewise negative, as found in this case.[2-14] It should be noted that S100 protein, which is one of the markers of myoepithelial cells, is rarely positive in clear cell carcinoma while other markers of myoepithelial lineages are invariably negative.[11]

Since the management of metastatic renal cell carcinoma and primary clear cell carcinoma of salivary origin requires different therapeutic decisions, a comparison of the present lesion with renal cell carcinoma merits attention. A high degree of vascularity and pronounced atypia in addition to the lack of prominent hyaline stroma is generally regarded as the hallmark of renal cell carcinoma.[3,16] Although vascularity was not a striking feature of the present lesion, atypia and a poorly differentiated focus were appreciable. Furthermore, the lack of residual salivary gland structures and the close approximation of lesional tissue with the overlying epithelium in the incisional biopsy warranted the consideration of renal cell carcinoma as one of the prime diagnoses. However, subsequent clinical examination and imaging studies established a primary salivary origin based on the absence of detectable renal pathology.

Though clear cell carcinoma characteristically infiltrates adjacent structures,[2-7,9-14] and even extends to the overlying epithelium,[3] there has been no report of surface epithelial dysplasia as found in this case.

Of the glandular malignancies, changes in the overlying epithelium-like dysplasia and pseudo-epitheliomatous hyperplasia are so far restricted to adenosquamous cell carcinoma and polymorphous low-grade adenocarcinoma respectively. Adenosquamous cell carcinoma is a malignant tumour with the histological features of both adeno-carcinoma and squamous cell carcinoma, but it is not listed as a salivary gland entity in the recent classification.[15] Therefore, except polymorphous low-grade adeno-carcinoma, changes in the overlying epithelium is unusual in salivary gland tumours. This raises the possibility of a common aetiology in the genesis of the present lesion.

In the context of the patient's reported habit of tobacco-chewing, the presence of dysplasia in the overlying epithelium requires no elaboration of its causative role, since it is strongly implicated as one of the causes in this geographical region. However, the significance of dysplasia in the context of a possible common aetiology is difficult and more complex to interpret in a single case in the absence of any molecular studies. The best guess that can be offered is that the dysplastic changes would have evolved as a consequence of the underlying glandular neoplasia. Further, the changes are not found throughout the epithelium but only focally suggest that it is more likely.

Wide excision is the treatment of choice for most clear cell carcinoma,[2-5,7,8,10] although neck dissection and radiotherapy have been performed in a few cases.[3,6,10,12,13] Adverse biologic behaviour ranges from multiple recurrences to local nodal or distant disease.[3,11,12,14] The decision to include node dissection or radiotherapy is generally based on the presence of positive margins, high grade histology, invasion (vascular/neural) or positive neck nodes.[17] While these prognostic factors also apply to clear cell carcinoma, an additional factor correlated with nodal metastasis is the presence of mitotic activity.[2,3,6] Close follow-up is therefore important. Our patient was free from local or distant disease during the 3 years of follow-up.

In conclusion, we report a case of intra-oral clear cell carcinoma with epithelial dysplasia of the surface epithelium, a finding which has not been previously reported. Although focal high-grade histology mimicking clear cell carcinoma of renal origin was observed, a thorough clinical examination helped us to arrive at the right diagnosis.

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