Clear cell carcinoma of minor salivary gland: A case of clinical dilemma

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Abstract

Clear cell tumor in oral cavity constitutes an assorted group of lesions, which may be odontogenic, metastatic or of salivary gland origin. Those associated with salivary glands accounts for less than 1% of total cases mainly seen in the major salivary gland. Occurrence of clear cell carcinoma in minor salivary gland is rare and uncommon. Hence, this case of intraoral clear cell carcinoma associated with minor salivary gland of palate in a 57-year-old male patient is being reported.

Keywords: Clear cell carcinoma, immunohistochemistry, maxillary alveolus, minor salivary gland

Introduction

In head and neck region, tumors associated with salivary gland are relatively uncommon, affecting predominantly major salivary glands. Minor salivary gland neoplasm are rare accounting for 9-23% of all salivary gland neoplasms, out of which clear cell carcinoma (CCC) accounts for just 0.2%.[1] Presence of clear cell microscopically creates diagnostic dilemmas and controversies in the classification of salivary gland neoplasm. The aim of this paper was to report a case of histologically diagnosed CCC of minor salivary gland, which clinically appeared to be a malignant carcinoma of maxillary sinus.

Microscopically clear cells are those cells which exhibit clear cytoplasm, well-defined borders and centrally placed nucleus.[2] These cells are found in many different tumors of epithelial, mesenchymal, melanocytic or hematopoietic origin, and thus are seen in various sites including skin, neck, thyroid gland, ears and jaws. Those seen in oral cavity are primarily of either salivary gland or odontogenic origin, although secondary metastatic CCCs and fixation artifacts should also be included in differential diagnosis.[3]

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Case Report

A 52-year-male patient reported to our department with chief complaint of missing teeth in relation to upper left back teeth region since 2 weeks. In history, he reported about a painless mobile tooth in same region since 1 year, which he himself pulled out 2 weeks back leading to development of both intra oral and extra oral swelling. The extra oral swelling was sudden in onset with no change in size, discharge or pain. No reduction in swelling was reported even after medication with antibiotics. No history of nasal discharge or difficulty in breathing was reported by patient. Patient reported a positive history of smoking cigarettes 1pkt/day since 34 years. He appeared apparently normal on general physical examination.

A facial asymmetry was noticed on the left side. Presence of extra oral swelling was diffused over the left middle third of the face, with overlying skin intact [Figure 1]. The swelling was firm and bony hard to palpate, non-tender with no local rise in temperature and with no fixity. Bilateral enlarged submandibular lymph nodes were also noticed on extra oral examination. Intra oral examination revealed a well-defined ulceroproliferative lesion on the edentulous alveolar mucosa of 26 and 27 regions [Figure 2]. Size of the lesion was measuring 2 × 2.5 cm over the crest and extending 2 mm to involve alveolar mucosa on either side. Obliteration of left buccal vestibule was noticed. The lesion was soft to palpate, non-tender and was not associated with any discharge. Grade II mobility 24, 25 and 28 were elicited.

Based on the history, clinical examination a provisional diagnosis of infected alveolar ostitis involving self-extracted 26 and 27 were considered. A differential diagnosis of carcinoma of alveolus and carcinoma of maxillary sinus was also considered with $T_2N_{2c}M_0$ stage.

Radiographic investigation revealed, diffuse clouding of the entire left maxillary sinus in conventional radiograph [Figure 3]. Coronal section in computed tomography (CT) revealed infiltrative soft tissue mass eroding lateral and posterior walls of left maxillary sinus [Figures 4 and 5]. Complete obliteration

of the left maxillary sinus extending to middle and superior concha was also noticed [Figure 6]. Enlargement of level I lymph node bilaterally was demonstrated in CT scan.

Radiological features showed features associated with carcinoma of maxillary. Carcinoma of left posterior maxillary alveolus was also considered in radiographic differential diagnosis. Preoperative incisional biopsy of the lesion was performed, histologically revealing sheets of malignant epithelial cells with clear cell differentiation. The cells were polygon in shape with eosinophilic cytoplasm. Islands and nests of clear cells separated by mature, fibrous connective tissue stroma were demonstrated [Figure 7]. Residual uninvolved minor salivary gland tissue was also noticed. A thorough clinical examination and imaging studies (chest X-ray and renal ultrasonography) were performed to rule out distant metastasis. The lesion was managed surgically in accordance with the treatment for malignant carcinoma [Figure 8]. Hemimaxillectomy of left side with radicular neck dissection was performed followed by obturator placement [Figure 9].

Examination of the excised tissue showed similar histological features to that of the preoperative biopsy. Level I lymph nodes demonstrated infiltration of dysplastic epithelial cells with clear cell differentiation replacing the lymphoid structure. Sections from level II and III were clear with no dysplastic tissue infiltration. Thus, histological impression of CCC $T_2N_{2c}M_0$ was made. Microscopic diagnosis of CCC was challenging because of the spectrum of features overlapping with the other salivary gland tumors that contain clear cells, and thus making diagnosis based on exclusion. Mucoepidermoid carcinoma with clear cell differentiation and clear cell odontogenic carcinoma was considered in differential diagnosis. The patient's progress was monitored for 1 year and there has been no evidence of recurrence of the tumor. Post surgical margins were clear and so radiotherapy was not recommended.

Discussion

The recognition and consequent reporting of CCC increased significantly after it was first reported by Milchgrub *et al*., in 1994 in their series of 11 patients.[4] Earlier it was reported to be primarily seen in the parotid gland,[5] but the literature review suggests that this lesion occurs almost exclusively in the intra-oral minor salivary glands with the prevalence of 0.2%-1%.[1,6,7] It is most commonly found in palate.[1,8,9] Occasional cases have been reported in other sites like tongue,[7,10] buccal mucosa, some rare locations including jaw bones, subglottic larynx, nasopharynx and tonsilar region.[11] In the present reported case, lesion was found on the maxillary alveolar mucosa.

Most of the reported cases occurred in adult patients between fourth and eighth decades, without any absolute predilection for any age group. The mean age reported in literature is 51.7 years.[6-8,11] Similar to intra-oral minor salivary gland tumors, CCC of minor salivary gland also shows increase female predilection with female-to male ratio of 1.4:1.[7,8,12] However, in the present reported case it was seen in male patient of 52 years. Clinical pathology reveals that the lesion, which exhibits itself as a slow progressing painless mass occurs in minor salivary glands and is usually asymptomatic until it reaches a specific dimension. The lesion appears to be locally aggressive with infrequent potential for local or distinct metastases and recurrence. Thus, it is been described as low-grade malignant neoplasm of minor salivary gland.[5,7,9,13,14] Although, most tumors with a major clear cell component are classified as low-grade malignancy tumors, close follow-up is advisable due to the presence of local infiltrative borders microscopically.

The concept of morphogenesis is controversial as this tumor shares common histological features. It is believed that these tumors exhibit two different histomorphogenic linage i.e., its basic cellular differentiation.[7,15] When present in minor component, the nomenclature of the neoplasm is based on the predominant histopathological features but when there are monomorphic populations of clear cells with lack of any characteristic features they are termed as CCC not otherwise specified (CCC-NOS). The term CCC-NOS was officially introduced in the third edition of the World Health Organization classification of salivary tumors in 2005.[16] By definition CCC contains a significant proportion of clear cells, but does not fit into any other recognized neoplastic entities.[14] When clear cells predominate, along with salivary gland tissue, definitive diagnosis may be problematic as the differential diagnosis includes various clear cell variant of primary tumor of salivary gland. The microscopic differential diagnosis of primary CCC of salivary gland includes mucoepidermoid carcinoma, acinic cell carcinoma, myoepithelial carcinoma, epithelial-myoepithelial carcinoma, and oncocytoma.[1,8,16,17] In present reported case due to the presence of clear cells along with trace of minor salivary gland tissues, various other histopathological differential diagnoses such as mucoepidermoid carcinoma and clear cell odontogenic carcinoma were also included. Metastatic carcinomas were ruled out based on systemic and radiological investigations.

Special stainings and immunohistochemical evaluation are essential in distinguishing this tumor from any other possible tumor with clear cell morphology. Immunohistochemical studies are helpful in distinguishing the various epithelial markers expressed by tumor cells. Its sensitivity and specificity is not enough to confirm the diagnosis, However,[18] more than 25 tumor markers have been tested, out of these positive cytokeratin A1/A3, and negative mucin can be used as strong marker of CCC.[10] In present reported case as histopathological report confirmed salivary gland neoplasm, no immunohistochemistry was carried out, and the lesion was treated as malignant lesion of salivary gland.

Being a tumor of low malignant potential, wide surgical excision is the treatment of choice with or without pre/

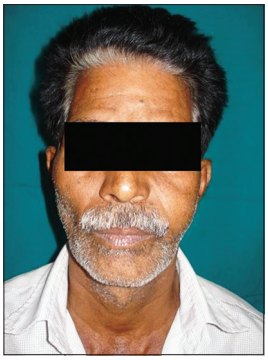

Figure 1: Extraoral examination reveals diffuse swelling on left middle third of face

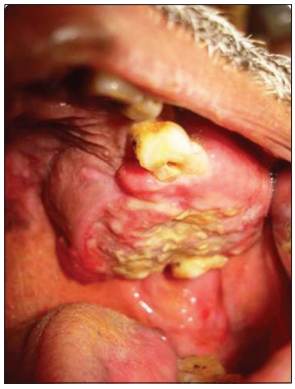

Figure 2: Intraoral examination reveals ulceroproliferative growth on alveolar mucosa of 26 and 27

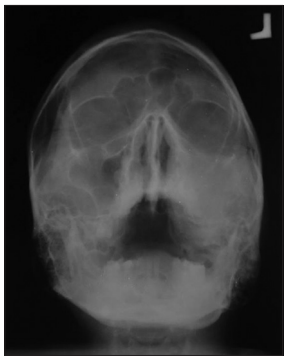

Figure 3: Paranasal sinus view reveals clouding of left maxillary sinus

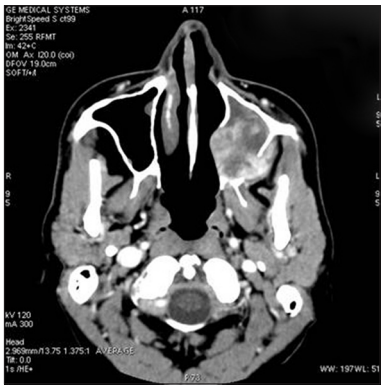

Figure 4: Coronal section of CT scan reveals erosion of mesial, lateral and posterior walls of left maxillary sinus

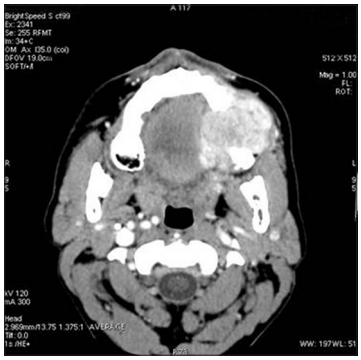

Figure 5: At alveolar bone level, coronal section of CT scan with contrast reveals enhancement of lesion

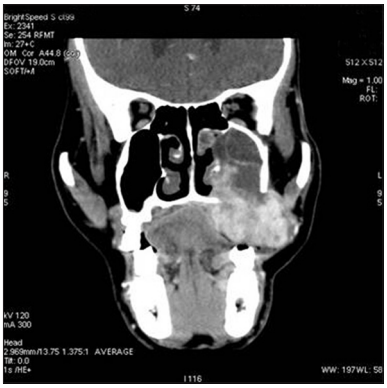

Figure 6: Coronal section of CT scan demonstrates infiltration of lower border of maxillary sinus

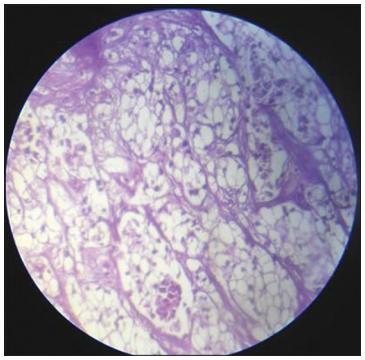

Figure 7: Histopathological examination of the speciman shows nest of clear cells surrounded by strands of fibrous tissue

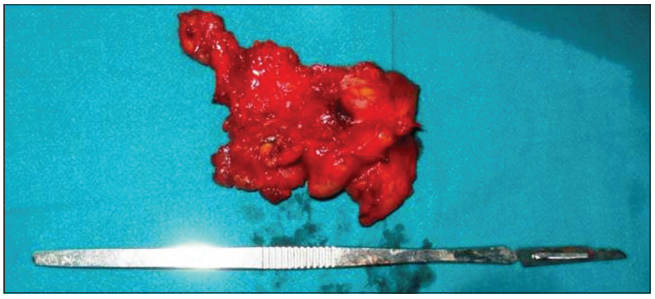

Figure 8: Macroscopic image of tumor mass

Figure 9: Postoperative image with obturator placement

postoperative radiotherapy. The decision to include node dissection or radiotherapy is generally based on the presence of positive margins, high grade histology, vascular or neural invasion, positive neck nodes and mitotic activity [3,12,13,17,19] Low grade malignancy reported by this tumor demands for complete tumor excision for a favorable prognosis. Adverse biological behavior ranges from multiple recurrences to local nodal or distance metastasis thus, a close follow-up is important.

Due to limited number of reported cases and short follow-up the true or relative frequency and their biological behavior is difficult to determine. Reporting of further case series should be conducted aggressively in order to consider CCC as distinct pathological entity. As many tumors of minor salivary gland present similar features, clinical and histopathological differential diagnoses become difficult. Immunohistopathological investigations are thus necessary to distinguish between various forms.

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