CASE REPORT

Synchronous oral squamous cell carcinomas with unusual histopathological feature

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ABSTRACT

Patients with head and neck carcinomas have high incidence (2–3% per year) of second primary lesions. Although "field cancerization" was first described in oral squamous cell carcinomas (OSCCs), only few studies have been concentrated on multifocal primary squamous cell carcinomas in the oral cavity. Synchronous carcinomas are defined as second neoplasms at the same time or within 6 months period of primary lesions. After this period, they are considered as metachronous neoplasms. Tumors composed exclusively or in large part of clear cells are rare in salivary glands, jaws and oral mucosa. OSCCs composed of clear cells or clear cell variant are not documented in the English literature. We present an unusual case of synchronous OSCCs composed predominantly of clear cells.

Key words: Clear cell variant, field cancerization, metachronous carcinomas, oral squamous cell carcinomas, synchronous carcinomas

INTRODUCTION

Head and neck squamous cell carcinomas (HNSCCs) are a major cause of death worldwide. Patients with head and neck carcinomas have high incidence (2–3% per year) of second primary lesions.[1] Many authors have described the multifocal occurrence of squamous cell carcinomas of upper aerodigestive tract.[2] Although "field cancerization" was first described in oral squamous cell carcinomas (OSCC),[3] only few studies have been concentrated on multifocal primary squamous cell carcinomas in the oral cavity.[2] Synchronous carcinomas are defined as second neoplasms at the same time or within 6 months period of primary lesions. After this period, they are considered as metachronous neoplasms.[4] The criteria to identify synchronous tumors defined by Warren and Gates and Moertel *et al.*[5] include the following: (1) all the tumors had to be histologically malignant; (2) all had to be distinct masses separated by normal tissue (at least by 2 cm); and (3) the possibility that the tumors could be metastatic had to be excluded histologically. Originally, it was hypothesized that multiple primary carcinomas in oral cavity developed independently after widespread epithelial exposure to carcinogens (field cancerization theory), but the recent molecular studies now support the alternative theory of common clonal origin.[6]

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Histologically, the OSCC is composed of sheets, nests or cords of squamous cells invading the connective tissue. In well-differentiated squamous cell carcinomas, cells resemble obvious origin from squamous epithelium and individual cell keratinization or keratin pearls are characteristic features. The less and poorly differentiated squamous cell carcinoma cells bear little resemblance to their cells of origin. The cells show greater variation in size and shape, increased/abnormal mitotic figures and greater lack of cohesiveness. The cells fail to carryout function of a differentiated squamous cell, i.e. the formation of keratin. Clear cells, as the name suggests, are cells having a clear halo around their nuclei and are characterized microscopically by failure of their cytoplasm to stain with hematoxylin and eosin. Tumors composed exclusively or in large part of clear cells are rare in salivary glands, jaws, and oral mucosa.[7] OSCCs composed of clear cells or clear cell variant are not documented in literatures. We report an unusual case of synchronous oral synchronous OSCCs composed predominantly of clear cells.

CASE REPORT

A 70-year-old female patient reported to the department of oral medicine and radiology with the chief complaint of pain and growth in the upper front teeth region and right lower back teeth region from past 1 month. Both growths were sudden in

onset and increased to present size within 1 month duration. The patient also complained of continuous pain of mild intensity, localized to the lesional area with no aggravating and relieving factors, and was febrile since 20 days. The patient was diabetic and hypertensive since 3 years and was on medication. He gave a history of paan chewing with areca nut, lime and tobacco since 40 years. He used 3–4 paans per day and used to keep paan in the inner side of the right cheek for about 20 minutes and spit it out.

General physical examination revealed a very poor overall general condition of the patient. The patient was malnourished. Pallor and generalized lymphadenopathy were present. The patient was febrile with body temperature of 99.2°F, increased respiratory rate and normal blood pressure.

Extra-oral examination revealed bilateral, palpable, single, firm, mobile and tender submandibular lymph node, whereas intra-oral examination revealed two intra-oral lesions. Lesion 1 shows the growth was at the maxillary anterior region in-between central incisors and was single, lobulated, measuring 35 × 20 × 40 mm with well-defined borders and ulcerated surface [Figure 1]. Lesion 2 shows the growth was at the edentulous area of mandibular right first molar, single and lobulated measuring approximately 15 × 12 mm in diameter anteroposteriorly, and was extending from distal surface of the second premolar to the mesial surface of the second molar. Mediodistally, lesion was on lingual crest of alveolar ridge occupying buccal and lingual vestibule [Figure 2]. The overlying mucosa of both the lesions was normal in color with areas of ulcerations. On palpation, both the swellings were firm, tender, sessile and profuse bleeding was present. Other intra-oral findings included grade III mobility of all mandibular incisors and generalized periodontal pockets.

Intra-oral periapical radiographs, occlusal radiograph, and orthopentamograph [Figures 3 and 4] show ill-defined radiolucency, displacement and resorption of apical parts

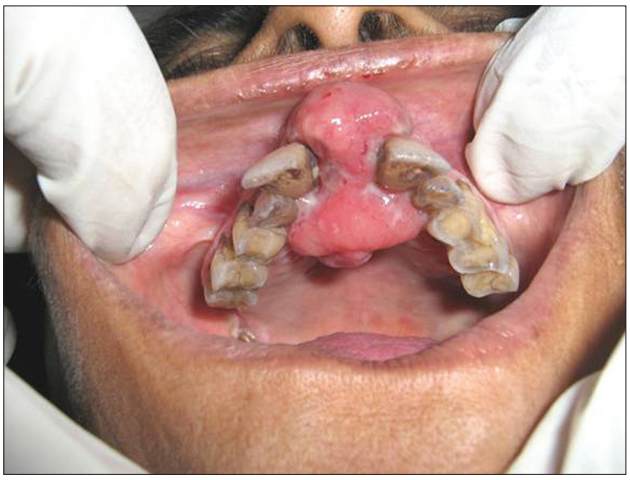

Figure 1: Lesion 1 showing lobulated growth in the maxillary anterior region in between central incisors

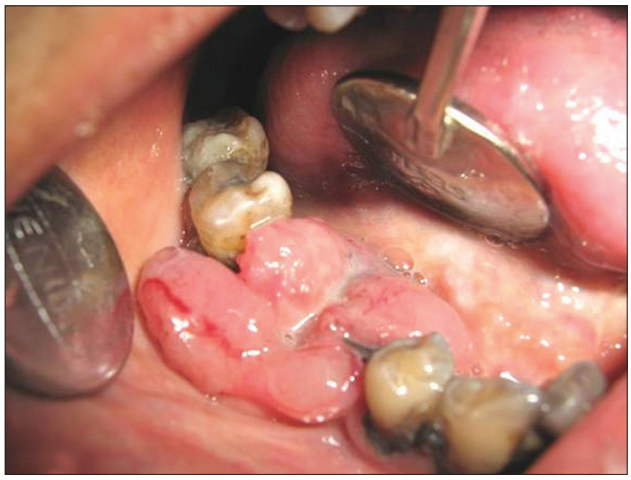

Figure 2: Lesion 2 showing lobulated growth in edentulous area of mandibular right first molar

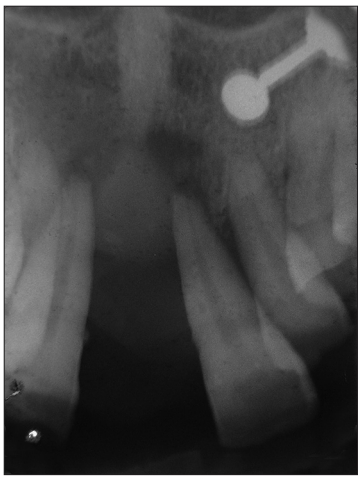

Figure 3: Intra-oral periapical radiographs showing ill-defined radiolucency, displacement and resorption of apical parts of roots of teeth in the areas of lesion 1

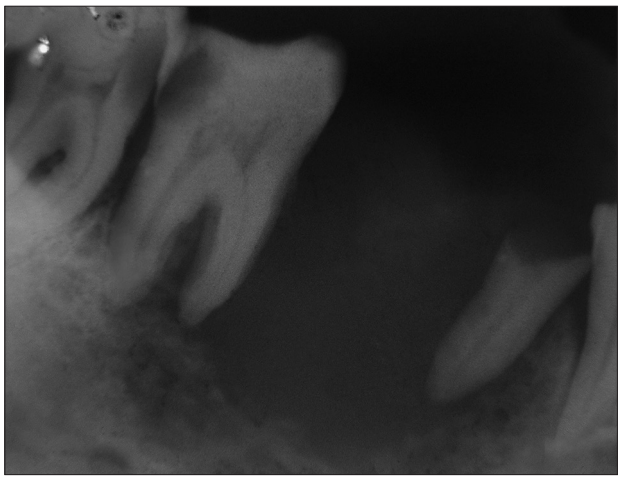

Figure 4: Intra-oral periapical radiographs showing ill-defined radiolucency, displacement and resorption of apical parts of roots of teeth in the areas of lesion 2

of roots of teeth in the lesional areas. Ultrasonography of abdomen and chest radiographs showed no abnormalities ruling out distant metastasis. Blood investigations were within the normal limits except reduced Hb% (9.2 gm%) suggesting anemia. Based on clinical, radiographic and systematic investigation findings, differential diagnosis of pyogenic granuloma, peripheral giant cell granuloma as benign lesions and squamous cell carcinoma, salivary gland tumors and oral soft tissue metastasis as malignant lesions were given. Incisional biopsy of both lesions was performed and submitted for histopathological examination.

Hematoxylin and eosin-stained histopathological sections of both lesions were similar, showing lobules, islands and sheets of predominantly clear cells and few squamous cells invading into connective tissue from severely dysplastic overlying epithelium. The invading clear cells were round to polygonal in shape consisting of clear cytoplasm with numerous mitotic figures (4–5 per high power field). The squamous cells were round to polygonal in shape with abundant eosinophilic cytoplasm. Dysplastic features such as nuclear and cellular pleomorphism, hyperchromatic nucleus and abnormal mitotic figures were frequent suggestive of malignancy [Figures 5 and 6]. The histological sections of both lesions were subjected to histochemical and immunohistochemical analyses to know the origin of tumor cells. The sections were negative for Periodic acid Schiff and mucicarmine stains ruling out the tumor of odontogenic and salivary gland origin. The sections were negative for Vimentin, S-100 and HMB-45, ruling out the malignancy of connective tissue and malignant melanoma. Sections showed strong positive immunoreactivity for epithelial membrane antigen (EMA) and cytokeratins 8 and 18 (CK8 and CK18) [Figure 7] suggesting OSCCs.

The patient underwent a complete excision of primary lesions with bilateral supraomohyoid neck dissection. The excisional biopsy tissues showed similar histopathological and immunohistological features, such as incisional biopsy tissue with all lymph nodes positive for tumor invasion. Based on clinical, radiographical, general and histopathological examination, a final diagnosis of synchronous OSCC with predominant clear cells was made. The patient died within the 2 months of follow-up.

DISCUSSION

The second primary tumors are a major problem in head and neck oncology, because their development has a profound impact on long-term survival, particularly of patients with early disease.[6] To explain the clonal relationship between the multiple primary tumors of the oral cavity, Slaughter *et al*.[3] had proposed the theory of "field cancerization" whereby multiple tumors could originate independently in an area of epithelium pre-conditioned to cancer development by long-term exposure to carcinogens. Initial molecular studies showing discordant p53 mutation between index and second primary tumors in the head and neck seemed to support this theory of independent tumor origins.[8] The alternate theory is that multiple tumors in the head and neck are of common clonal origin, and has

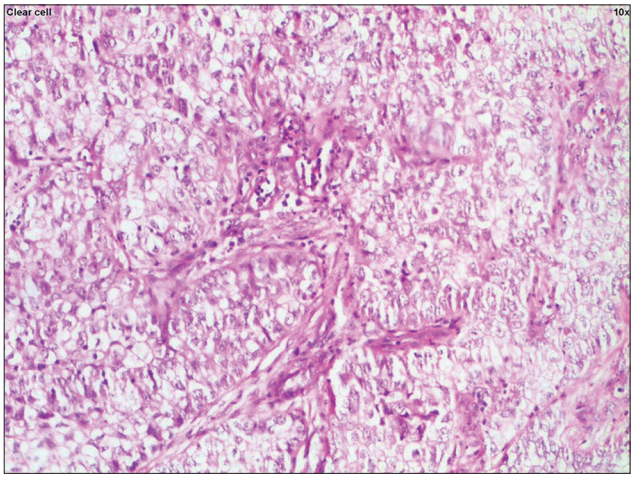

Figure 5: Photomicrograph showing lobules of predominantly clear cells invading the connective tissue (H and E stain, ×40)

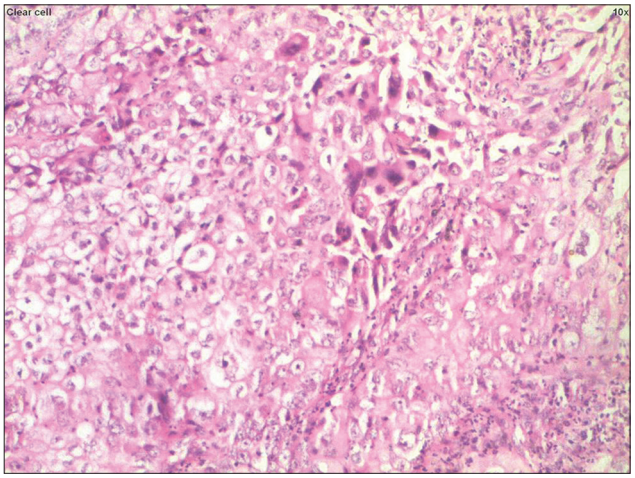

Figure 6: Photomicrograph showing sheets of clear cells and squamous cells showing features of malignancy (H and E stain, ×40)

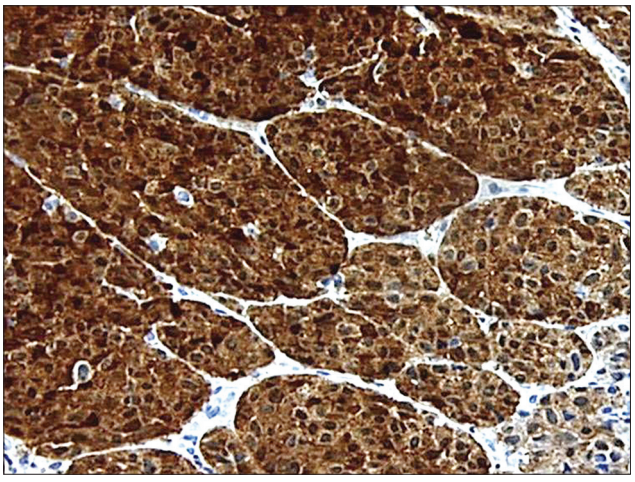

Figure 7: Photomicrograph showing strong positive immunoreactivity for cytokeratins 8 and 18 (CK8 and CK18, ×40)

gained support as a result of the detection of identical genetic alteration in these tumors.[1]

The frequency of developing synchronous and metachronous carcinomas in the head and neck mucosal sites ranges from 8% to 21%.[2] A recent study of patients with HNSCCs showed 100% male predominance of synchronous OSCCs, with no synchronous occurrence in female patients.[5] In contrast, our patient was a female. About 90% of patients with synchronous OSCCs are more than 40 years of age[2] that correlates with our patient's age, who was 70-years old. The most common site of occurrence of synchronous OSCCs is tongue (33.3%) followed by buccal mucosa (26.7%).[2] Our patient had lesions involving gingiva and alveolar mucosa, which is a rare site of involvement.[6]

The histopathology of both lesions was very similar, may be because of possibility of common clonal origin of synchronous OSCCs even if the lesions are >7 cm apart.[5] Both lesions were composed predominantly of highly malignant clear cells and few squamous cells. Clear cells, as the name suggests, are cells having a clear halo around their nuclei and are characterized microscopically by failure of their cytoplasm to stain with hematoxylin and eosin. The cytoplasmic clearing is caused by subcellular changes, such as loss of organelles, accumulation of glycogen, mucin and lipids or may be due to fixation artifacts.[7] Many factors can potentially yield cytoplasmic lucency in formalin-fixed sections that are stained with hematoxylin and eosin. However, the possibility of artifact was ruled out because standard fixation (10% neutral buffered formalin for >24 hour) method and conventional laboratory procedures for processing tissues and staining were followed. Tumors composed exclusively or in large part of clear cells are rare in salivary gland, jaws, and oral mucosa. They represent only 1–2% of all tumors in such locations.[9] In the maxillofacial region, clear cell neoplasms can be schematically subdivided into at least three categories (odontogenic, salivary glands, and metastatic), according to their presumed origin. The neoplasms of other origins composed of clear cells, such as clear cell acanthoma, primary eccrine gland carcinoma, clear cell chondrosarcoma, and malignant melanoma are rarely found in oral cavity.[9]

The clear cell odontogenic carcinoma (CCOC) was considered for differential diagnosis due to nests of clear cells inter-mixed with smaller islands of polygonal cells with eosinophilic cytoplasm that may be finely stippled.[9] Clear cells in the CCOC are negative for mucicarmine, Alcian blue, Congo red and Sudan black but are positive for periodic acid schiff [PAS] due to the presence of glycogen. In our case, clear cells were negative for PAS stain. The clear cell variant of calcifying epithelial odontogenic tumor (Pindborg tumor)[9] was ruled out due the absence of prominent amyloid deposition, calcifications in stroma and moreover, cellular characteristics in our case represented malignant potential.

Clear cell salivary gland tumors considered in our case included epithelial myoepithelial carcinoma, hyalinizing clear cell carcinoma, clear cell acinic cell carcinomas, and clear cell mucoepidermoid carcinoma.[9] The lack of intermediate cells and mucin production excludes mucoepidermoid carcinoma. The absence of intra-cytoplasmic, PAS-positive diastase-resistant secretary granules and S100 protein ruled out acinic cell carcinoma, myoepithelial cell carcinoma, and epithelial myoepithelial carcinoma. Hyalinizing clear cell carcinoma was ruled out due to the absence of dense fibrous stroma. The PAS-positive cytoplasm and cell types showed cellular pleomorphism and high mitotic index.

Metastatic renal cell carcinoma was ruled out due to the absence of prominent intra-tumoral hemorrhage, typical sinusoidal vascularity, and diastase-sensitive PAS-positive cells suggesting the presence of glycogen.[7] The general examination, chest X-ray and ultrasonography ruled out the possibility of other distant metastatic tumors to the oral cavity. Amelanotic melanomas consist of large nests of polygonal, rounded or bluntly spindled cells with clear to weakly eosinophilic cytoplasm. But they show typical immunohistochemical expression of S-100 protein and other melanoma-associated antigen such s HMB-45,[7] which was negative in our case ruling out the possibility. In our case, both lesions showed strong positivity for EMA, CK8, and CK18 suggestive of OSCC.[10]

Based on clinical, histological and immunohistochemical evaluation, we diagnosed the lesion as synchronous OSCC clear cell variant. The patient died within few days of excisional biopsy because many studies show poor survival rate in the synchronous OSCCs compared with single primary OSCCs.[2]

The presence of clear cells or clear cell variant of OSCCs is not documented in the English literature. In our case, the lesions tend to be more aggressive and caused early metastasis leading to shorter survival period. However, more cases with similar histopathological picture need to be documented to determine the biological behavior of synchronous OSCCs with predominant clear cells.

REFERENCES

1. Bedi GC, Westra WH, Gabrielson E, Koch W, Sidransky D. Multiple head and neck tumors: Evidence for a common clonal origin. Cancer Res 1996;56:2484-7.
2. Cianfriglia F, DiGregorio DA, Manieri A. Multiple primary tumours in patients with oral squamous cell carcinoma. Oral Oncol 1999;35:157-63.
3. Slaughter DD, Soathwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953;6:963-8.
4. Schwartz LH, Ozsahin M, Zhang GN, Touboul E, de Vataire F, Andolenko P, *et al*. Synchronous and metachronous head and neck carcinomas. Cancer 1994;74:1933-8.

5. Dissanayaka WL, Jayasooriya PR, Kumarasiri PV, Tilakaratne WM. A histopathologic comparison between synchronous and single primary oral squamous cell carcinomas. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:732-8.
6. Scholes AG, Woolgar JA, Boyle MA, Brown JS, Vaughan ED, Hart CA, *et al*. Synchronous oral carcinomas: independent or common clonal origin? Cancer Res 1998;58:2003-6.
7. Nappi O, Mills SE, Swanson PE, Wick MR. Clear cell tumors of unknown nature and origin: A systematic approach to diagnosis. Semin Diagn Pathol 1997;14:164-74.
8. Chung KY, Mukhopadhyay T, Kim J, Casson A, Ro JY, Goepfert H, *et al*. Discordant p53 gene mutations in primary head and neck cancers and corresponding second primary cancers of the upper aerodigestive tract. Cancer Res 1993;53:1676-83.
9. Maiorano E, Altini M, Favia G. Clear cell tumors of the salivary glands, jaws, and oral mucosa. Semin Diagn Pathol 1997;14:203-12.
10. Fillies T, Jogschies M, Kleinheinz J, Brandt B, Joos U, Buerger H. Cytokeratin alteration in oral leukoplakia and oral squamous cell carcinoma. Oncol Rep 2007;18:639-43.

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Announcement

Faculty development program was organised by the Department of Oral Pathology and Microbiology under the able guidance of the faculty development team of Sri Ramachandra University on August 31st and September 1st 2012 under the aegis of the Indian Association of Oral and Maxillofacial Pathology (IAOMP). It was inaugurated by Dr. K. V. Somasundaram. The Guest of Honour was the Hon. Secretary IAOMP Dr. K. Ranganathan. Dr. N. Malathi, Head of the Oral Pathology Department, SRMU played a major role in conducting the program. The key ingredients in the program were interactive sessions, microteaching sessions and group discussions from topics ranging from student mentoring and motivation to newer concepts in teaching and assessment methods. 20 delegates including senior faculty members enthusiastically attended the program.