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Oral Field Cancerization: A Review with Case Reports

Review Article

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Author Details

Simran Naresh Verma[1] and Deepa Das Achath[2]*

[1]*Dr. G.D. Pol Foundations YMT Dental College and Hospital, India*

[2]*Department of Oral Medicine and Maxillofacial Radiology, India*

*Corresponding author

Simran Naresh Verma, Dr. G.D. Pol Foundations YMT Dental College and Hospital, India

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Abstract

The concept of field cancerization was proposed by Slaughter et al. in 1953. Field cancerization of the mucosa of aerodigestive tract frequently develops on account of tobacco and alcohol usage. The oral cavity is one of the predominant and prevalent sites of development of potential malignancies, therefore, it comes into direct contact with many carcinogens. All of the epithelium beyond the boundaries of tumour can undergo histological changes and may have more than one independent area of malignancy. The mucosa undergoes a change, perhaps due to carcinogen exposure and is therefore more susceptible to the development of many foci of malignant transformation. This explains the high incidence of recurrence of oral cancer, the rate being 32.7%, despite excision of tumour or other therapies. So, diagnosis and treatment of oral cancer should not only be focused on the lesion, but also on the field from which it developed. In this article, we emphasize on the concept of field cancerization, highlight the carcinogenic influence of tobacco and alcohol in the development of multiple primary tumours in the oral cavity by presenting clinical cases.

Keywords: Field cancerization; Squamous cell carcinoma; Metastasis; Second primary tumours; Synchronous/ Metachronous tumours**3.**

Introduction

Head and Neck Squamous Cell Carcinoma (HNSCC) is the sixth most common cancer affecting men worldwide and 50% of malignant tumours affecting southeast Asian population [1]. Oral Squamous Cell Carcinomas (OSCC) are the eight most common cancer according to GLOBOCAN 2020 [2], with an average survival rate of 5 years. The recurrence rate reported is 32.7%. The recurrence time has been found to range from 2 to 96 months, with a median of 14 months [3]. The development of recurrences and second primary tumours, even when surgical margins are histopathologically tumour free corroborates the concept of field cancerization [4, 5]. The term "field cancerization" was introduced by Slaughter in 1953 [6]. It refers to that, oral cancer does not arise as an isolated cellular phenomenon, but rather as an anaplastic tendency involving many cells at once that results into a multifocal development process of carcinoma at various rates within the entire field in response to a carcinogen, such as tobacco.4 Multifocal areas of precancerous alterations may trigger independent mutations without involving the particular individual cell which becomes malignant. Tumour recurrence is most often due to changes in the preconditioned epithelium, now more prone to cancer, which is located next to the suture line or has healed over the site of a tumour eliminated by radiation therapy [7].

Criteria used to Diagnose Multiple Carcinomas

Warren and Gates [8] initially formulated a set of criteria to diagnose multiple primary carcinomas which were modified later by Hong et al. [9]. The criteria to be met are as follows:

1. The neoplasm must be distinct and anatomically separate. A multi-centric primary neoplasm is diagnosed when a dysplastic mucosa is present next to it
2. A potential second primary carcinoma which represents a metastasis, or a local relapse should be excluded [4,8,9].

Theories of Field Cancerization

Two theories have been postulated to explain the occurrence of carcinomas in specific sites. One theory state that multiple squamous cell lesions occur independently of each other. This is due to the exposure

of the oral cavity to carcinogens in at the same time leading to multiple genetic abnormalities in the entire area [10]. An alternative theory states that multiple lesions arise due to the migration of dysplastic and altered cells with two different patterns

a. Migration of malignant cells through the saliva- micro metastasis (Figure 1)

b. Intra- epithelial migration of the progeny of initially transformed malignant cell [11,12].

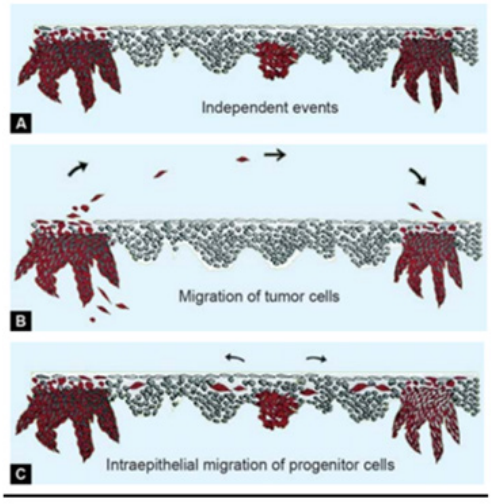

Figure 1: a. Multifocal tumours developing independently b. Micro metastasis through saliva c. Intraepithelial migration.

Origin of Field Cancerization

Cellular Basis: The polyclonal origin, mutations occur in multiple sites of the epithelium due to continuous carcinogen exposure and thereby lead to multi- focal carcinomas/ lesions of independent origin [13].

Genetic Basis: Mutations in YAP1, WWTR1, p75NTR, NFKB2, POLR2A [14,15] in a single cell was considered to be initial step that triggers the process, the mutant cell then proliferates into a clonal unit and then into a patch of mutated cells. This field eventually replaces the normal tissues.

Second Primry Tumors (SPT)

Second primary tumours when occur simultaneously or within 6 months of index (primary) tumour are termed as synchronous primaries and those SPT's which occur after 6 months of index tumour are named as metachronous primaries. The incidence of second primaries synchronous/ metachronous tumour is increasing and reported as high as 10%. The SPT is usually more aggressive, more treatment resistant and metastasizes early, requiring a more aggressive treatment strategy. True second primaries would be those lesions that did not share any genetic similarity and therefore likely arose as a result of independent events [16].

Distant Second Lesions

Because of the common conduit connecting the oral cavity, lungs and oesophagus, there is a similar exposure pathway to the mucosa from environmental carcinogens. Slaughters observation of frequent synchronous/ metachronous tumours in the aero- digestive tract is expected, based on elevated risk from carcinogen exposure alone. The distance between two malignancies does not necessarily predict clonality. As a general rule, distant, peripheral, solitary, squamous lung lesions in conjunction with HNSCC are thought to be metastases and concurrent oesophageal tumours are thought to be separate primary tumours [16].

Detection of Second Primaries

Despite the molecular methods, the specialized radiography like CT, MRI & PET plays an important role in detection of SPT's and metastatic lesions. Simran et al. [17] discussed FDG PET/ CT has a good diagnostic accuracy for identifying metastatic nodes, especially subcentimeter metastatic nodes that appear morphologically normal on CT images [17].

Therapeutic Implications for Field Cancerization

The presence of altered fields of mucosa remaining beyond the limits of resection has been shown both histologically and on a molecular basis. P53 mutations have been demonstrated histologically normal margins in initial studies. The issue of whether those with an extensive, visible mucosal field defect are more likely to benefit from chemotherapy, radiotherapy or chemoprevention is a complex one. Current management is often site- specific. Recurrent oral premalignant disease is often treated by surgical excision, whereas diffuse high- grade premalignant changes in the laryngeal mucosa are frequently treated with radiotherapy. Determination of the role for these and other treatment modalities for clinically occult, clonally altered patches of epithelium is likely to be a difficult issue, since treatment of mucosa with widespread visible alterations is already challenging. Further studies need to be performed to elucidate the mechanisms behind clonal spread [16].

Case Report 1

A 40-year-old male patient presented to the department of Oral Medicine and Oral Radiology with a complaint of multiple white patches in his oral cavity since 3 months. The patches were insidious in onset and gradually increased to the present size. Patient had severe burning sensation on consumption of hot and spicy food. Past dental and medical histories were non-contributory even though he reported some weight loss. The patient had the habit of chewing raw tobacco with lime 50 times a day along with smoking 10 cigarettes in a day and alcohol consumption for the past 15 years.

On extraoral examination, there was no gross facial asymmetry. Single submandibular lymph node was palpable bilaterally measuring 1.5cm in size and mobile, non- tender and was firm in consistency. Intraorally, on left buccal mucosa (Figure 2) there was an elevated bright red patch with whitish specks on its surface at the level of maxillary second and third molars measuring approximately 2 X 1.5cm in size and was non- scrapable and tender on palpation.

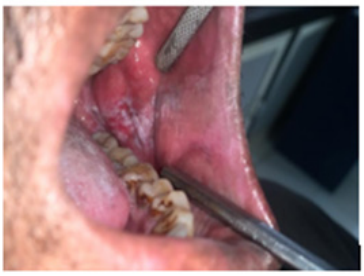

Figure 2: Left buccal mucosa.

On the right buccal mucosa (Figure 3) there was a diffuse mixed red and white lesion- erythematous areas enclosed by white striations along with linear keratotic whit papules in the periphery measuring approximately 1 X 1cm in size along the occlusal level.

Right lateral border of the tongue (Figure 4) showed raised whitish

wrinkled linear lesion measuring approximately 4 X 1 cm in size extending from the middle third of the tongue till the posterior third. The dorsum of the tongue (Figure 5) presented with shallow fissures, multiple scattered white plaques measuring 0.5 X 0.5 cm in size. The lesion was non- tender and non- scrapable on palpation.

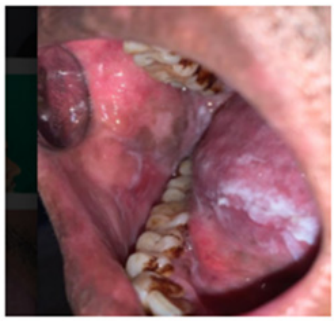

Figure 3: Right buccal mucosa.

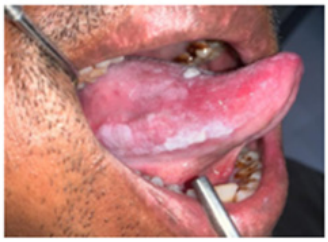

Figure 4: Right lateral border of the tongue.

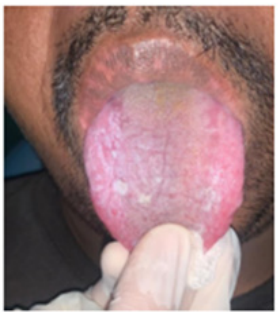

Figure 5: Dorsum of the tongue.

Based on the above clinical presentation a provisional diagnosis of Erythroplakia in relation to left buccal mucosa, homogenous leukoplakia in relation to right lateral border of the tongue, erosive lichen planus in relation to right buccal mucosa ad plaque type lichen planus in relation to dorsal surface of the tongue were made. To establish a definitive diagnosis incisional biopsy was done after toluidine blue staining. The histopathological report confirmed the diagnosis of Erythroplakia in relation to left buccal mucosa, early invasive squamous cell carcinoma in relation to right buccal mucosa and moderate epithelial dysplasia in relation to right lateral border of the tongue. Wide excision of the lesion on the right buccal mucosa and right lateral border of the tongue and modified radical neck dissection with reconstruction using pectoralis major myocutaneous flap was performed. Patient is currently undergoing radiotherapy and is under regular follow up to detect any local relapse or formation of any secondary primary tumours.

Case Report 2

A 44-year-old male patient presented to the department of Oral Medicine and Oral Radiology with a complaint of pain in the lower left posterior region of the jaw since 1 month. The pain was sudden in onset, continuous in nature and gradually increased in intensity. Past dental and medical histories were non- contributory. The patient had the habit of chewing tobacco with lime 15 times a day along with alcohol consumption for the past 12 years. There was history of weight loss since 2 months, change in voice since 1.5 months and reduced tongue protrusion since 2 months (Figure 6).

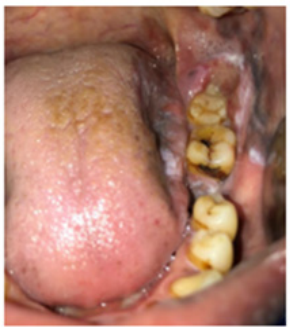

Figure 6: Left retromolar trigone.

On extraoral examination, there was no gross facial asymmetry. A solitary submandibular lymph node was palpable on the left side measuring 1.5cm in size, mobile, non- tender and was firm in consistency. Intraorally, an ulcerative lesion was evident on the left retromolar area (Figure 7), measuring 2 X 2cm in size. It was irregular in shape with everted margins. The centre of the lesion was composed of whitish yellow slough. The lesion was tender on palpation with indurated base.

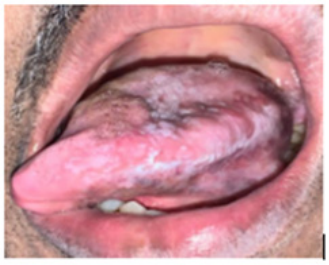

Figure 7: Left lateral border of the tongue.

Along the left lateral and ventral surface of the tongue (Figure 7 & 8) an elevated white patch was present measuring 4 X 2cm n size. The lesion was non- tender and non- scrapable on palpation.

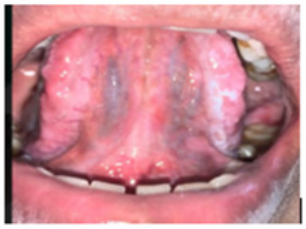

Figure 8: Left ventral surface of the tongue.

Based on the above clinical presentation a provisional diagnosis of squamous cell carcinoma of left retromolar trigone (T1N1M0) and homogenous leukoplakia of left lateral and ventral surfaces of the tongue were made. To establish a definitive diagnosis incisional biopsy was done after toluidine blue staining. The histopathological report confirmed the diagnosis of moderately differentiated squamous cell carcinoma in relation to left retromolar trigone area and hyperkeratosis in relation to left lateral border of the tongue. Wide excision of the lesion on the left retromolar trigone and hemi glossectomy of left lateral border of the tongue and modified radical neck dissection with reconstruction using pectoralis major myocutaneous flap was performed. Patient is under regular follow up for any local relapse or formation of any secondary primary tumours.

Discussion

In field cancerization, an area of epithelium has been preconditioned by long term exposure to carcinogens. In this preconditioned epithelium, multifocal carcinomas can develop as a result of independent mutations [18]. Thus, the carcinoma occurs from multifocal areas of precancerous change and not from one cell that suddenly becomes malignant. It is well accepted that the progression from normal to cancer cell is a multistep process in carcinogenesis [19,20]. Studies on the epidemiology of HNSCC have identified tobacco and alcohol in the developed countries and chewing of betel quid in Southeast Asia as risk factors for development of such multiple lesions. Subjects with multiple lesions are a distinct group with respect to the genetic susceptibility and may have weakened DNA repair capabilities in comparison to other individuals who have normal DNA repair capabilities. Tobacco chewing was associated with the strongest increase in the risk of multiple oral premalignant lesions and may be the major source of field cancerization of the oral cavity in the Indian population. There is risk of genetic alterations such as chromosome aberrations, cytokeratin expression, focal overexpression of p53 as well as increased proliferation with tobacco exposure. The major carcinogens identified in chewing tobacco include tobacco specific N-nitrosamines such as N-Nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [21].

Although tobacco and alcohol use are independent risk factors, when combined, they have a synergistic effect. The actual mechanism for the synergistic effect is unclear. However, the present view is that alcohol enhances the effects of carcinogens found in tobacco. The alcohol dehydrates mucosa and permits nitrosamines and hydrocarbons to penetrate the mucosa easily. Alcohol affects liver function and increases acetaldehyde content in tissues exposed to the carcinogens in tobacco. Alcohol consumption leads to nutritional deficiencies and an immunocompromised state of health by reducing the absorption of nutrients from the intestines. The more the duration and intensity of smoking the greater the risk of developing second primary cancers. All our patients had tobacco associated habits for a very long duration of more than 20 years. Majority of them had a combination of tobacco smoking, and alcoholism [21]. Many recent studies have been conducted to explain the molecular basis of concept of field cancerization. Nieburgs et al. [22] reported malignancy associated changes within smear cells of normal buccal mucosa in patients with malignant disease [22]. Incze et al. [23] showed altered nuclear to cytoplasmic area ratio and suggested that tobacco might play a role in this alteration [23]. Bartkova et al. [24] observed the foci of cyclin D1 expression in the sections of the normal mucosa adjacent to head and neck squamous cell carcinoma which were not observed in the sections of the normal mucosa of healthy individuals. Several studies have shown increased number of proliferating epithelial cells, increased expression of Epidermal Growth Factor Receptor (EGFR) and presence of cytokeratin's 7, 8, 13, 16, and 19 in tumour-associated normal mucosa [24].

Epidemiological data suggest that the risk of developing second primary HNSCCs is higher in smokers/drinkers than in non-smokers/non-drinkers and this risk decreases when the patient quits smoking and stops abusing alcohol. All of these field changes seen in multicentric carcinomas in patients seem to be induced by tobacco habits and alcohol. Therefore, additional research is required to assess whether field changes depicted by these molecular markers have actual carcinogenetic influence or not. Recently, oncogenic Human Papilloma Virus (HPV) has emerged as a distinct risk factor for oropharyngeal Head and Neck Squamous Cell Carcinoma (HNSCC), differing from classic tobacco/alcohol associated HNSCC, suggesting that there also may be distinct patterns of synchronous second primary tumours. Tumour markers are helpful in the early detection of cancer. But in field cancerization identification of molecular markers in the genetically transformed but histologically normal cells will have excellent utility in monitoring the tumour progression and in preventing transformation of pre-malignant lesions into invasive cancer [21].

Conclusion

The presence of a field with genetically altered cells in HNSCC has become an important clinical issue because of the increasing incidence of SPTs in head and neck cancer and profound negative impact of such tumours on long-term survival of patients. Usage of alcohol and tobacco increases likelihood of concurrent or future disease in patients with head and neck cancer. Therefore, these patients should be advised to quit the habits to reduce the risk of the development of multiple primary tumours. Therefore, this calls for frequent oral examination with histological studies and molecular testing be made mandatory for patients after surgery, especially for those at high risk of developing malignancies. Though numerous markers have been identified to help determine the field effect, the entire process is still controversial, therefore further investigations are still in progress to gain a better understanding of carcinogenesis and to use the biomarkers foreseen in this concept for cancer prevention purposes [4,21].

Consent

Not applicable (no identifying information is present in the case report).

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable (no identifying information is present in the case report).

Availability of Data and Materials

Not applicable.

Competing Interests

None.

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None.

Authors' Contributions

All authors contributed to preparation of this manuscript with most writing done by first and second authors.

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