Case Report

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Eagles eye for exploration: Field cancerization - a surgeons dilemma

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ABSTRACT

"Field cancerization" was introduced in 1953 to describe histologically abnormal tissues surrounding oral squamous cell carcinoma, particularly in the upper aerodigestive tract, likely related to exposure to carcinogens. Concept now refers to multiple local and distant primary tumors within the upper aerodigestive tract, along with oral premalignant lesions. Tobacco and alcohol are independent risk factors, but when combined, they have a synergistic effect. Earliest lesions are often undetectable by clinical and histologic examination; careful surveillance can detect most tumors in their intraepithelial and microinvasive stage. Early detection improves long-term survival, although multiple resections are often necessary.

Keywords: Field cancerization, Micro invasive stage, Local and distant tumors

INTRODUCTION

The idea of field cancerization was conceived by Slaughter almost a decade prior to introducing the term in 1953. In an earlier publication, he stated that; "cancer does not arise as an isolated cellular phenomenon, but rather as an anaplastic tendency involving many cells at once."4 The term "lateral cancerization" was subsequently used to indicate that the lateral spread of tumors was due to progressive transformation of cells adjacent to a tumor, rather than the spread and destruction of the adjacent epithelium by preexisting cancer cells.5 In a more extensive histopathologic review of 783 oral cancer patients, Slaughter et al. then used the term field cancerization to describe the existence of generalized carcinogen-induced early genetic changes in the epithelium from which multiple independent lesions occur, leading to the development of multifocal tumors. 6 In some cases, multiple contiguous tumor foci coalesce that partly explain the lateral spread of squamous cell cancers. It was also observed that normal-looking cells in close proximity to malignant cells were histologically abnormal and therefore were part of the transformed cells in a particular tumor field, and consequently were responsible for the occurrence of local tumor recurrences. These observations were made at about the era the deoxyribonucleic acid (DNA) double helix was discovered by Watson and Crick, hence, in the absence of modern molecular techniques. More recent studies using various genetic analyses have provided unequivocal evidence in support of the work of Slaughter et al.⁷

CASE REPORT

- Patient 48/M first presented on July 6, 2010, with complaints an ulcer in upper alveolus and retromolar area noticed 6 weeks back. He also complained of difficulty in opening mouth. He gave a history of extraction of last upper molar done 1 week back. History of oral submucous fibrosis since 10 years. History of tobacco use, Gutka (stopped 10-12 years back), smoking (stopped 1 month back) and alcohol intake. After clinical, radiological, and histopathological (biopsy) examination; provisional diagnosis: Cancer of left upper alveolus destroying maxillary sinus floor
- On July 9, 2010, a left maxillectomy with wide excision

of the tumour was done under general anesthesia. Histopathology report: Moderately differentiated keratinizing squamous carcinoma involving the left upper alveolus behind the last molar tooth and the medial surface of molar teeth. Tumour infiltrated the underlying tissues superficially. A dense inflammatory response to the tumor was noted. Lymphatic emboli or perineural invasion were not seen. Cut margins: All mucosal cut margins were free of tumor. Additional report on decal section of the maxilla bone. Tumor reached up to the surface of the maxilla bone but did not infiltrate it diagnosis: Cancer of left upper alveolus Stage II (T2 N0 M0)

On October 10, 2013 clinically a localized swelling soft on palpation associated with left lower second molar was reported. Computed tomography (CT) scan revealed no new lesion; patient was referred to dental dept. and kept under close observation. patient got 2nd molar extracted. On January 10, 2014, the extraction site showed friable tissue suspective for malignancy, a biopsy of the lesion was done, which was reported as benign hyperkeratotic, inflamed, benign squamous mucosa with no evience of malignancy in this material. On February 14, 2014 during follow-up, an unhealing friable tissue at the same site was noted, curretage was done and slides reviewed. Reported as chronically inflamed verrucous proliferation in favor of veruceous hyperplasia. On April 18, 2014 patient again reported with a similar soft

granulation tissue at the socket site. Surgeons opinion: To treat the lesion as verrucous carcinoma a CT scan was advised in May 2014 a marginal mandibulectomy along with wide local excision of the lesion was done. Histopathologically it was reported as veruccous carcinoma of the lower left alveolus, tumor infiltrating the tissues superficially.

DISCUSSION

"Cancer does not arise as an isolated cellular phenomenon, but rather vas an anaplastic tendency involving many cells at once."

Field cancerization in head and neck squamous cell carcinoma has also been addressed using mtDNA markers. Notably, these mutations increased with increasing severity of dysplasia, suggesting acquired mitochondrial genome alterations might drive or indicate disease progression. Normal adjacent mucosas to dysplastic lesions were also analyzed. Identical mtDNA mutations were found in perilesional tissue of 3/8 lesions that had mtDNA alterations. A tumor marker is a substance present in or produced by a tumor or tumors' host in response to the tumor's presence that can be used to differentiate a tumor from normal tissue or determine the presence of a tumor based on measurement in blood or secretions. Salivary biomarkers for oral cancer detection several salivary tumor markers

Table 1: Lesion-directed therapies.

Treatment	Approach	Comments
Excision	Physical ablation	Not a first-line treatment and typically reserved for lesions highly suspicious for invasive SCC
Curettage/ electrodessication	Physical ablation	May be beneficial in hyperkeratotic lesions and in combination with field therapy
Cryosurgery	Physical ablation	Widely used. Approach is not standardized, leading to a wide range of outcomes
Laser	Physical ablation	Wide range of outcomes reported in the literature, possibly due to user-dependent factors
ALA/MAL PDT	Chemical destruction	Used in both lesion- and field-directed therapy

PDT: Photo-dynamic therapy, MAL: Methyl aminolevulinate, ALA: Aminolevulinic acid, SCC: Squamous cell carcinoma

Table 2: Field-directed therapies.

Treatment	Approach	Primary MOA
5-fluorouracil	Chemical destruction	Blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, interfering with the synthesis of DNA and inhibiting the formation of RNA
Diclofenac	Chemical destruction	Cyclooxygenase inhibitor; apoptosis/anti-angiogenic effects
ALA/MAL PDT	Chemical destruction	Protoporphyrin IX selectively accumulates in lesions, stimulating free radical production when exposed to therapeutic light source
Imiquimod	Immunologic destruction	TLR7 agonist, induction of proinflammatory cytokines
Ingenol mebutate	Immunologic destruction	Lesion necrosis/neutrophil-mediated, antibody-dependent cellular cytotoxicity

PDT: Photo-dynamic therapy, MAL: Methyl aminolevulinate, ALA: Aminolevulinic acid, SCC: Squamous cell carcinoma,

MOA: Mechanism of action, DNA: Deoxyribonucleic acid, TLR: Toll-like receptor 7

are found to be significantly increased in the saliva of oral cancer patients. Molecular markers for the diagnosis of oral cancer can be quested in three levels; changes in the cellular DNA which results in altered mRNA transcripts leading to altered protein levels intracellularly, on the cell surface or extracellularly. The term "signed-powers-of-two" was proposed to be allocated for the second tumor that has developed independently from the first tumor. When a second tumor arises from the same field in which a first tumor has developed, it was preferred to designate it as a "second field tumor" (SFT). It is important to make this discrimination because a different etiology may have clinical consequences. SFTs will be followed relatively easily by third and fourth field tumors. Therefore, SFT patients may need a different follow-up, characterized by more frequent and more focused screening.

CONCLUSION

Field cancerization is a well-known and well documented process of malignant transformation. An obvious shortcoming in almost all the studies of field cancerization is the lack of extensive genome-wide scans that will enable early and important genetic changes in tumor evolution to be uncovered. Many studies have relied heavily on known markers associated with a particular tumor. Comprehensive high-throughput analyses for the discovery of early and relevant genetic changes that extend across global networks and represent modular alterations of multiple targets (or surrogates) of terminal histologically differentiated stages of cancer subtypes will be essential for early detection, risk assessment and primary chemoprevention.

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