Review Article

Correlation of Clinicopathological Features with Prognosis in Oral Squamous Cell Carcinoma with and Without Oral Submucous Fibrosis

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Abstract

Background: Oral Squamous Cell Carcinoma in the background of Oral Sub Mucous Fibrosis (OSCC with OSMF) is one of the most common malignancies in South and South-East Asian countries. The clinical presentation of OSCC is variable, and is related with the site , progression time, association with precancerous lesions and risk factors. Recently, it has been proposed that OSCC with OSMF constitutes a clinicopathologically distinct disease, the differences of which believed to arise from differential mechanisms of areca nut carcinogenesis. The proposed unique nature of OSCC in this altered condition relates to younger age of presentation, better histological grade of differentiation of the tumor, and lesser potential for nodal metastasis. According to the existing knowledge, the prognostic indicators of OSCC with OSMF in context to the clinical presentation of the lesion have not been thoroughly investigated. With this premise in mind this research is designed to provide the basis of clinical presentation of OSCC with OSMF with its early detection and better grade of tumor differentiation. **Objectives:** 1) To assess the clinical presentation in OSCC and OSCC associated with OSMF, 2) To assess the correlation of clinical presentation with clinicopathological features in OSCC and OSCC associated with OSMF, 3) To assess the correlation of clinical presentation with prognosis in OSCC and OSCC associated with OSMF. The data of three hundred twenty clinically and histopathologically diagnosed, surgically operated cases of OSCC were included in the study. Further on the basis of association of OSMF, the OSCC patients were sub grouped into two. Group one includes OSCC without OSMF (166 cases) and group two OSCC associated with OSMF (154 cases). Demographic data and follow-up information for disease free survival of five years was documented in the records. Further detailed information in perspective to clinical presentation of the lesion was recorded. Considering the differential mechanisms of areca nut carcinogenesis in OSCC associated with OSMF, there will be variation in clinical presentations from erythroplakic, erythroleukoplakic, ulcerative, endophyticulceroproliferative to proliferative or exophytic amongst OSCC without OSMF and OSCC associated with OSMF cases. **Conclusion:** The clinical presentations in OSCC associated with OSMF will be supportive of the already suggested unique characteristics with good clinicopathologic profile and better prognosis and oncological outcomes.

Keywords

Oral squamous cell carcinoma; OSMF; Clinical presentation

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Introduction

Background

Oral Squamous Cell Carcinoma (OSCC) is a major cause of morbidity and mortality in the Indian subcontinent. The high prevalence of OSCC is noted in India mainly due to the predominance of habit of chewing smokeless tobacco and areca nut. [1] Areca nut is an independent group-1 human carcinogen in accord with the international agency for research on cancer, World Health Organization (WHO) with respect to its monographs of 1985 and 2004. [2] Areca nut along with the slaked lime and other ingredients leads to a ubiquitous Oral Potentially Malignant Disorder (OPMD) called Oral Sub Mucous Fibrosis (OSMF), which is characterized by progressive fibrosis of the oral mucosa. [3] Upsurge in the popularity of commercially prepared areca nut preparations and increase uptake of this habit by young people due to easy access, effective price changes and marketing strategies has led to rapid increase of the disease. [4] Oral Squamous Cell Carcinoma in the background of Oral SubMucous Fibrosis (OSCC with OSMF) is one of the most common malignancies in South and South-East Asian countries. [5] In this regard, Chourasia et al. reported about 25.77% incidence of concomitant OSMF with OSCC. [6] Recently, it has been proposed that OSCC with OSMF constitutes a clinic pathologically distinct disease, the differences of which believed to arise from differential mechanisms of areca nut carcinogenesis [7-9] The proposed unique nature of OSCC in this altered condition relates to younger age of presentation, better histological grade of differentiation of the tumor, and lesser potential for nodal metastasis.

The clinical presentation of OSCC is variable and is related with the site,progression time, association with precancerous lesions and risk factors. Also in most cases, the lesions areasymptomatic; pain and discomfort appears only when invasion of muscles or nervesare there at advanced phaseof the disease. The varied clinical presentation may be as leukoplakia, erythroplakia or as erythroleukoplakia that in fact has already become malignant, as a necrotic ulcer with irregular raised indurated borders or as a broad based exophytic mass with a surface texture that can be relatively smooth, verrucous or pebbled. [10]

The clinical presentation and behavior in OSCCs arising from OSMF cases is inconsistent. Although exophytic lesions in the background of OSMF are not very unusual, however there is inadequate scientific data from South Asian countries, where OSMF is highly widespread. According to the existing knowledge, the prognostic indicators of OSCC associated with OSMF in context to the clinical presentation of the lesion have not been thoroughly investigated. [11] With this premise in mind this research is designed to provide the basis of clinical presentation of OSCC with OSMF to consider a clinic-pathologically distinct disease as compared to OSCC without OSMF.

Aim

To evaluate the clinical presentations in OSCC without OSMF and OSCC associated with OSMF

Objectives

- To assess the clinical presentation in OSCC without OSMF and OSCC associated with OSMF.
- To assess the correlation of clinical presentation with clinic-pathological features in OSCC without OSMF and OSCC associated with OSMF.
- To assess the correlation of clinical presentation with prognosis in OSCC without OSMF and OSCC associated with OSMF.

This study was a retrospective analysis for which the required protocol was approved by the Institutional Ethical Committee (DMIMS (DU) IEC/Dec-2019/8556-dated-17-12-2019). The data of study population was retrieved from the archival of department of oral and maxillofacial pathology and microbiology, Sharad Pawar dental college and hospital, Wardha, Maharashtra, India from the year 2009 to 2015.

Inclusion and Exclusion Criteria

Clinically and histopathologically diagnosed, surgically operated cases of OSCC were included in the study. Patients with history of multiple primaries, recurrence or metastatic OSCC preoperative chemotherapy or radiotherapy were excluded from the study.

Study Design

In this cross sectional, retrospective cohort study a total three hundred twenty samples will be selected.

Statistical data

Sample size is calculated using the formula: n=(Z2×P×(1-P))/e2

where:

Z: Value from standard normal distribution

Corresponding to desire confidence level (Z=1.96 for 95% CI)

P: Expected true proportion

E: Desired precision (half desired CI width) values

Estimated proportion=0.5

Desired precision of estimate=0.2

Confidence level: 0.95

Population size: N/A

Results: Sample size required for specified inputs=320

Sample selection

Demographic data pertaining to age, gender, detailed history of relevant habit with its dose and duration, site of the lesion of all the study population was retrieved. The clinical staging of patients (tumour node metatstasis) was done in line with the American Joint Committee of Cancer staging system. [12] Hematoxylin and eosin stained tissue sections were obtained from archives of department for histopathological analysis. Three oral pathologists independently performed histopathological grading of all oral cancer cases using broders grading system in a blinded manner. Extent of lymph node metastasis was confirmed by histopathological evaluation of lymph nodes dissected from surgically excised specimens. A pilot study was carried out to appraise inter and intra-observer reliability for scoring of the histopathological parameters. Follow-up information for disease free survival of five years was documented in the records. Further detailed information in perspective to clinical presentation of the lesion was recorded. The clinical presentation of the lesion was categorized into erythroplakic, erythroleukoplakic, ulcerative, endophyticulceroproliferative and proliferative or exophytic. Further while compilation of the patients' data pertaining to history and clinical features, it was observed that many cases of OSCC were associated with one of the most common OPMD that is OSMF. So Further on the basis of association of OSMF, the large cohort of OSCC cases were sub grouped into two. Group one includes OSCC without OSMF (166 cases) and group two OSCC associated with OSMF (154 cases).

Discussion

The prevalence of OSCC and related morbidity and mortality, even though inconsistent across the globe, are elevated in regions where areca nut and tobacco use is high. Moreover the OSCC in the background of OSMF is one of the most common malignancies in South East Asian population, due to injudious use of tobacco and arecanut preparation. In context to the clinical appearance in OSCC associated with OSMF, proliferative, verrucous pattern was more commonly observed as compared to infiltrative and ulcero-infiltrative morphology. [13] Also the Oral Verrucous Hyperplasia (OVH) in patients with OSMF is a relatively common condition among areca nut chewers and has a malignant transformation rate of 7% to 13%. [14]

We will be evaluating all the cases of OSCC with respect to clinicopathological characteristics and treatment outcome. Further we appraise the variation in clinical presentation in OSCC without OSMF and OSCC associated with OSMF. Previous research from our organization had revealed that OSCC associated with OSMF was a distinct clinicopathological entity. The study results support the proposition that the OSCC associated with OSMF lesions takes place through a diverse and specific molecular pathway related to areca nut etiology. This results in the better grade of tumor differentiation, less the chances of nodal metastases along with early detection (early clinical TNM stage) and better prognosis and shows the prevalence in younger males. [9]

Hypothesis

The question that should be addressed in these cases is why the dysplastic epithelium fails to invade the underlying connective tissue but proliferates in an exophytic pattern, unlike in the case of conventional dysplastic lesions. A possible hypothesis is that the exophytic nature of dysplastic epithelium could be a result of abnormal collagen in the connective tissue showing resistance for known invasive mechanisms. Further, normal collagenases may not be able to destroy collagen in OSMF, as there is abnormal cross-linkage. [15] Recent evidence suggests upregulation of the copper-dependent extracellular enzyme lysyl oxidase by fibroblasts in oral submucous fibrosis, leading to excessive cross-linking and accumulation of collagen. [16] Mohammed et al. suggested that a substantial amount of copper released from areca products induces lysyl oxidase activity, upregulating collagen synthesis by fibroblasts, facilitating its crosslinking, and thereby inhibiting its degradation. [17] Although this is not an uncommon clinical scenario, no studies in the literature on this issue have any significant clinical implications. Therefore, systematic investigation of this aspect appears mandatory.

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