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REVIEW ARTICLE **OPEN ACCESS**

OSMF- An Unheeded Condition Having A Malignant Prospective

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ABSTRACT
Oral submucous fibrosis or what we say in short OSMF is the most ordinarily encountered potentially premalignant oral epithelial lesion which is concomitant with munching of betel and areca nuts in one or the different forms.It has a fairly high likelihood of developing into oral squamous cell carcinoma (OSCC), the most prevalent oral cancer with a high fatality rate. The OSMF pathophysiology is quite complex, and as a result, many different processes might cause it to become malignant. It is preferable to diagnose and treat OSMF at an early stage so that the development of malignancy can be properly managed. Numerous theories have been developed to explain the likely mechanism of OSMF's malignant transformation, with new emphasis placed on biomarkers and genes that are crucial in the conversion of OSMF to OSCCs.This ystematic review gives a brief of all the possible mechanisms of malignant transformation of OSMF so that one can understand it in a easiest way.
Keywords: *OSMF, malignancy, OSCC, potential, Biomarkers, Betel nut, Quid*

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INTRODUCATION

The idea of "pre-cancer" was first put up in 1805 by a group of European doctors who hypothesised that certain benign diseases could develop over time into aggressive malignancies (Baillie and Simms, 1806). Oral Potentially Malignant Disorders (OPMDs) are tissue "fields" with more or less distinct clinical appearances at initial assessment, and a proportion within each clinical category has been documented to have subsequently developed cancer during follow-up, i.e. tissues within these categories have boosted malignant potential. This concept was clarified in a report by a 2005 workshop. It is recognised that certain of these clinical abnormalities, particularly red and white patches or mixed patches, co-exist at the edges of overt oral squamous cell carcinomas (OSCCs). Similar morphological and cytological alterations are present in OPMDs [1].

The 2005 workshop's expert opinion, which was later published in 2007, suggested switching to the name OPMD in place of the previously used terminology "pre-cancer," "epithelial precursor lesions," "premalignant," "precancerous," and "intraepithelial lesion." In recognition of the fact that field change typically exists as a result of exposure to environmental carcinogens [2].

For tasks like eating, yawning, singing, etc., a sufficient mouth opening is necessary. The devastating condition known as oral submucous fibrosis (OSMF) affects the mouth opening by thickening the oral mucosa and generating an unusually high fibrous component in the submucosa. The entire oral mucosa, palate, throat, and oesophagus are all affected by this condition, which is classified as an OPMD (Oral Potentially Malignant Disorder).

The reported malignant potential is within 8%. The primary carcinogen in a multifactorial model for the aetiology of OSMF, oral malignancies emerging in OSMF constitute a clinicopathologically distinct condition [2].

A widespread condition known as a precancerous condition, such as submucous fibrosis, lichen planus, etc., is one that associated with a significantly increased risk of cancer . However, it was decided to use "potentially malignant disorders (PMD)" at (WHO) Workshop that was conducted in 2005 since it emphasises that not all disorders covered under this category may develop into cancer [3].

Paymaster was the first to highlight the OSMF's precancerous characteristics in 1956. His sample included 156 biopsy samples, 118 oral submucous patients out of which 81 were men, and 37 were women, ranging in age from 22 to 80 years. Since then, the malignant transformation of OSMF has

generated a lot of debate and scepticism.[4]According to reports, those with OSMF are more likely to develop leukoplakia and OSCC [5].

This article will be reviewed under the following headings:

- Epidemiology
- Percentage of malignant transformation
- Carcinogenic potential of etiological agents like areca nut
- Pathophysiology of the transformation of OSMF from potentially malignant disorder to Malignancy
- Shreds of evidence of premalignant transformation into malignancy.

Epidemiology

According to reports, India's incidence is 0.5% of the population, with a 7.6% chance of developing a malignancy [6].

Percentage Of Malignant Transformation

The development of a rapid increase in number of OSSC, is the primary cause of concern for the entire world with regard to OSMF [7].

According to Pindborg J.J. and Zachariah J. in 1965 among the 100 patients of OSCC, biopsies taken in the vicinity of OSMF cancer, epithelial atypia showed was 71.4%and which were taken far from cancerin areas of oral submucous fibrosis was 11.5% [8].

In a study conducted in 1989 in Kolkata by Gupta PC Bhonsle RB, Murti PR, Daftary DK, Mehta FS, and Pindborg JJ, 12,212 tobacco smokers experienced a transition rate of 7.6 percent over a period of 17 years [9].

According to a review published in 2004 by Nair U, Bartsch H, and Nai J, chewing areca nuts or gutkha has been linked to 30 percent of mouth cancer cases in India and has been proven to have carcinogenic, genotoxic, and clastogenic effects. However, information regarding the OSMF patient's development of malignancy was not given [10].

According to Hazarey V.K., Erlewad D.M., Mundhe K.A., and Ughade S.N., a hospital-based study carried out in Nagpur in 2007 found a transformation rate for epithelial dysplasia with 1000 OSMF patients reported at 5.4 percent with a mean duration of 40 months. Additionally, they noted a 5:1 ratio between the probability of OSMF malignant transformation in men versus women [11, 12]

PTEN expression in OSMF and oral squamous cell carcinoma (OSCC) was examined in 2012 by Angadi PV and Krishnapillai R., who also correlated it with the pathophysiology and malignant transformation of OSMF. A total of 60 patients were examined using PTEN antibody immunohistochemistry, of which 30 had OSMF and 30 had OSCC. As a control, 10 samples of normal oral mucosa (NOM) were also stained. PTEN expression gradually decreased from normal mucosa to OSMF and OSCC. PTEN expression varied significantly between NOM and OSMF, OSMF and OSCC, and both NOM and OSCC [13].

According to a 2013 study by Garg K. N., Raj V., and Shaleen Chandra, out of 141 PMDs, 23% of OSMF patients had a steadily rising percentage of malignant transformation. Additionally, they calculated the relative risk of cancer development for the chewers and found that it was approximately 5.98 percent [14].

The function of MC tryptase and chymase in the aetiology of OSMF and its malignant transformation was assessed by Yadav A, Desai RS, Bhuta BA, Singh JS, Mehta R, and Nehete AP in 2014. The immunohistochemistry expression of MC tryptase and chymase was examined in 20 instances of OSMF, 10 cases of OSCC, and 10 cases of healthy controls. The subepithelial zone of Stages 1 and 2 had higher levels of MCs tryptase than the deep zone of Stages 3 and 4 OSMF. Regardless of distribution locations, OSCC showed a proportionate rise in tryptase and chymase positive MCs [15].

A retrospective study by Chourasia NR, Borle RM, and Vastani A in 2015 sought to determine the prevalence (OSCC) along with oral submucous fibrosis in central India and to link precipitating variables related with OSMF and OSCC. They also sought to investigate the prevalence of OSCC caused by untreated OSF. The study comprised 225 cases of OSCC and 119 cases of OSF in diverse areas of the oral cavity. All of the included patients were histopathologically and clinically diagnosed, and historical data was retrieved. They discovered that 119 OSMF patients, or 97.4% of them, chewed betel nuts regularly. Malignant transition to OSCC was reported to occur at a rate of 4.2%.The incidence of Oral cancer concomitant with OSMF was found to be 25.77%, which was statistically significant. They concluded that the malignant transformation of OSMF is underestimated and further studies with a larger sample size and longer follow-up period should be carried out to reveal the actual malignant potential of the disease [16].

Out of the 1774 cases reported in a study by Mohiuddin S, Fatima N, Hosein S, and Hosein M in Pakistan in 2016 to determine the crucial elements of OSMF malignant transformation [17].

The claimed malignancy rate varies depending on the regional variations in gutka chewing habits. Thus, the oral cancer incidence rate has shifted from the adult age group to younger as a result of the habit of chewing gutkha, which has also increased OSMF prevalence in the younger population.

Carcinogenic Potential Of Etiological Agents Like Areca Nut

The primary cause of OSMF, areca nuts, has been identified as a "group one human carcinogen" according to the second International Agency for Research on Cancer monograph on betel quid. The malignant transformation of potentially malignant disorders (PMDs) begins with single-cell atypia that is susceptible to genetic mutation and/or various carcinogenic factors such as tobacco, betel nut, betel quid, virus, and alcohol [18].

The activity of carcinogens, which first manifests as atypia nadodemalikely a precondition for the development of cancer. This is the first sign that oral squamous cell carcinoma is progressing [19].

The epithelium in OSMF experiences compromised healing and/or repair due to excessive fibrosis, which restricts the supply of nutrients to the epithelium and causes existing vessels to constrict. This compromises the epithelium's ability to heal and/or repair itself [2].

Numerous investigations had been done to identify the several ways that areca nuts and their contents could cause OSMF to convert malignantly [20].

The description of the malignant transformation of OSMF includes a probable genetic predisposition as well as many biochemical pathways. In those with impaired immunity and dietary inadequacies, it might be promoted even more. The main causes of carcinogenesis in OSMF are listed as being arsenic-induced inactivation of tumour suppressor genes (P16), DNA damage from reactive oxygen species (ROS), interactions between the extracellular matrix and the epithelium, arsenic-induced angiogenesis, and aberrant collagen synthesis. Additionally, hypoxia brought on by diminished vascularity encourages malignant transformation even more**.**

Pathophysiology Of The Transformation Of Osmf From Potentially Malignant Disorder To Malignancy

Epithelial cells are repeatedly and continuously exposed to antioxidants, enzymes, and reactive oxygen species which weakens the cellular defence and causes DNA damage. Damaged cells can then mutate into cancer initiation cells, which can then progress and cause malignancy after being promoted by such initiated cells.

According to a study conducted by Chaturvedi P, Vaishampayan SS, Nair S, Nair D, Agarwal JP, et al. in 2013 most malignant transformations occur in younger males[22]and in a study conducted by Mohiuddin S, Fatima N, Hosein S, Hosein M.in 2016 reported 78.4% of females presenting with malignant transformation [17].

Despite high chances of malignancy in males, they have better prognostic features such as thebetter grade of tumor differentiation, lower incidence of nodal metastases, and less extra-capsular [17].

Shreds Of Evidence Of Transformation Of Pre-Malignancy To Malignancy

These shreds of evidence can be further subdivided into the following:

- Clinical
- Histopathological
- Molecular

There can also be an association of non-healing ulcer, growth, or any other dysplastic lesion.

Histopathological evidence

Oral mucosal connective tissue experiences observable alterations, such as epithelial atrophy, dysplasia, hyperplasia, hyperkeratosis, intercellular edoema in the prickle layer, etc., that may affect the malignant transformation process, the progression of the transformation, and its metastasis.Epithelial-mesenchymal transitions (EMT) are the name given to observable changes that take place in the epithelium and connective tissue and appear to be coordinated.[5]The distinctive changes in the epithelium include epithelial atrophy and, on occasion, epithelial hyperplasia with or without dysplasia. Extracellular matrix remodelling in connective tissue causes excessive collagenization and further cross-linking of collagen results in hyalinization, which makes the collagen resistant to proteolysis.Further contributing to the compromised blood supply to the local tissue milieu, or hypoxia, is the constriction of blood vessels in OSMF. This tissue hypoxia will cause angiogenesis, which could lead to OSMF's malignant change in the future [5].

Constant irritation from areca nut and its components causes pro-inflammatory cytokines to be regulated, which further causes juxta-epithelial inflammation. Thus, the OSMF undergoes malignant transformation as a result of these coordinated reactions in the epithelium and connective tissue [18].

Molecular evidence

Sister chromatid exchange

Silver-binding nucleolar organiser area counts and higher rates of spontaneous sister chromatid exchange have recently been discovered to be reliable indicators of malignant transformation in OSMF [24].

p63

It plays a significant part in controlling the proliferation, differentiation, and maturation of keratinocyte cells and belongs to the p53 family of tumour suppressors [2].

AgNOR

The ribosomal DNA loops known as silver stainable nucleolar organiser regions (AgNORs) are found in cellular nuclei that contain rRNA synthesis genes. The AgNOR stain allows for the histological visualisation of AgNORs as black spots. The number of AgNORs, which are cell replicatory markers, declines while the size of the epithelium grows from the bottom to the top in a healthy oral epithelium. AgNOR counts are higher, dispersion is greater, and AgNOR sizes are lower in basal cell hyperplasia areas. A unique profile for the normal epithelium, leukoplakia, and SCC is provided by the AgNOR count and distribution in the oral epithelium [5].

Markers for Assessing the Malignant Transformation Potential

Various markers have a high potential for malignant conversion. Some of them are:

- Myofibroblasts
- Langerhan cells
- Cytokeratin profile
- HIF-1α

CONCLUSION

OSMF is a condition that occurs frequently. It also has a high incidence of oral cancer morbidity. Since there is no effective medical or surgical treatment for this problem. It is preferable that OSMF be identified in its early phases. It should be recommended to stop chewing areca nuts and consider other aspects. The greatest method for limiting the disease process at the community level may turn out to be intervention studies and public health awareness campaigns linked to OSMF conditions & practises. Male individuals and possibly younger patients are more likely to have concurrent OSCC in OSMF. Less lymph node involvement and a well-differentiated histology are present in these tumours. Additionally, it can be argued that the degree of fibrosis may not be a factor in the development of cancer, a higher degree of differentiation, or less nodal metastasis.Despite a wealth of literature, the origins of OSMF remain a mystery. OSMF's start is explained by the chronic physical, chemical, and mechanical damage to vulnerable oral mucosa caused by habitually chewing betel nut, which results in excessive mucosal repair. This theory is supported by the recruitment of myofibroblast to epithelial damage sites in OSMF via a CCL-2 (Chemokine (C-C motif) Ligand 2) based mechanism. The pathophysiology of OSMF as well as its malignant transformation are explained by thinking of OSMF as an overhealing wound. Therefore, OSMF is categorised as a morphologically altered tissue with an external source as the aetiology and malignant transformation in the category of "oral possibly malignant disorders."

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