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Review Article

A contemporary narrative review to guide molecular epidemiology of oral submucous fibrosis

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Abstract: Oral submucous Fibrosis (OSMF) is a chronic disease that mainly affects the upper part of the aerodigestive tract. Areca nut and betel quid chewing has been established as the most significant causative factor for this condition. While OSMF is a predominantly Asian disease, the migrant populations from the region have taken the disease across the globe. Additionally, areca nut is now easily accessible in flavors and aggressively marketed. Many research activities have been undertaken for decades to understand the etiopathogenesis and risk factors of OSMF. Although OSMF is a slowly progressing disease, it has the potential to transform to an oral malignancy. This article is an attempt to review the literature and provide an update on its prevalence, etiopthogenesis and its diagnosis. We also highlight certain clinical, histopathological and molecular features that aid in the diagnosis and prognostication of OSMF, highlighting the importance of identifying the possibly high risk OSMF that is prone to malignant transformation. Using this information, future directions can be developed to include treatmentof OSMF through a dynamic gene-specific approach.

Keywords: Oral submucous fibrosis, OSMF, molecular markers, epidemiology, premalignant disorders

Introduction

Oral sub mucous fibrosis (OSMF) is a chronic, insidious and irreversible condition that affects the entire body with majority of the symptoms being present in the head and neck region. It is caused due to the chronic use of areca nut and betel quid, with or without tobacco. The usage of areca nut is indigenous to Southeast Asian countries. Its use is strongly embedded in this region's history, culture rituals and religious practices. Migrant communities from these regions have spread the popularity of areca nut and betel quid use across a diverse population to increase its usage exponentially. Further, the incidence has also increased due to the increased popularity and availability of commercially flavored preparations, leading to a greater diversity of its use. OSMF is often diagnosed clinically and hence many patients present with advanced stages when symptomatic. Additionally, OSMF has been traditionally considered as a potentially malignant lesion for oral cancer, which is a key public health issue in this region. About 90% of the oral cancer arises from premalignant diseases such as OSMF, oral leukoplakia and oral erythroplakia with a few studies identifying the factors predicting transformation. Not all of these cases progress to malignancy-some transform in a short period of time while others remain unchanged for many years. Most recently, studies have attempted to even identify genetic markers to diagnose and predict malignant transformation. This review will discuss the prevalence, etiology and diagnosis, focusing on the histologic and genetic markers of OSMF that can be used to increase the understanding of the disease process and improve epidemiologic accuracy.

Global prevalence

The epidemiology of OSMF differs with ethnicity and region and is closely associated with diet, habits, and culture. OSMF has traditionally been reported to be a disease of the middle age group with peak observed in the second to fourth decade of life. Today with the commercially available preparations and universal popularity among the youth as well, the median age

of incidence is likely to shift towards younger individuals. In most parts endemic of OSMF, males are predominantly impacted but the distribution does vary geographically. The prevalence of OSMF in India has been estimated to range from 0.2-2.3% in males and 1.2-4.6% in females [1]. Interestingly, the ratio of women with OSMF is higher than women with head and neck cancer, as compared to men [1].

The most common site of OSMF is the buccal mucosa and retro molar region. This occurs due to the typical placement of the quid seen in the endemic region between the alveolus (upper and lower) and the buccal mucosa. Due to this, many lesions including oral cancer occur here and the term "gingivobuccal" has been coined for this specific site. As the fibrosis sets in, other parts of the mouth also get affected such as the soft palate, faucial pillars, floor of mouth, tongue, labial mucosa and gingival. It is interesting to note that as the grades of OSMF increases according to the many classifications, the process of fibrosis progresses posteriorly in the mouth to reach the oropharynx. Once involved, there is an advanced symptomology seen for the entire head and neck region, subsequently involving the entire digestive tract.

OSMF is an Asian disease with the India, Sri Lanka, Maldives, Bangladesh, Myanmar, Taiwan and numerous islands in South Pacific contributing to more than half of the global consumption. It is also quite popular in many parts of Thailand, Vietnam, Malaysia, Indonesia, Cambodia, Laos, Philippines and China [2]. The prevalence of OSMF varies with individual reports suggesting 0.9-4.7% in China, 0.62-6.42% in India, 0.15-14.6% in Vietnam, and 0.086-17.6% in Taiwan [2]. Similar prevalence rates have been reported from countries where a high Asian or Indian immigrant rate is present such as the United Kingdom and South Africa. Although OSMF by itself does not lead to any mortality, its malignant transformation rate of up to 23% can have serious consequences [3]. This implies that out of the more than 16 million OSMF patients predicted globally in 2020 by the World Health Organization, more than 3 million could possibly transform into oral cancer, which has a grim prognosis. In fact, a recent study has shown that oral cancer in the background of OSMF is a pathologically distinct entity [4].

Etiopathogenesis

Many mechanisms have been suggested for the etiopathogenesis of OSMF-mainly multifactorial origins such as chewing areca nut in quid with or without tobacco products, chronic nutritional deficiencies and seldom genetic predispositions. The most important of which, areca nut, is an endosperm from the tropical tree Areca Catechu Linnaeus [5]. Its fruit has a psychoactive ability commonly used as a stimulant and for digestion. Commercially available preparations contain of alkaloids, flavonoids and trace elements. They are also available with and without tobacco, indigenously referred to as gutkha, pan masala, mawa, flavored supari, etc. Other than the direct carcinogenesis of tobacco, alkaloids from the areca nut contribute towards classifying areca nut a class I carcinogen [5]. Alkaloids identified in areca nut include arecoline, arecaidine, guvacine and guvacoline. Arecoline, the most potent agent, has a cytotoxic and genotoxic property that mediates this carcinogenesis. It impacts the key proteins that regulate the cell cycle against various stresses such as reactive oxygen species, cyclin-dependent kinase p21 and p27. Another metabolite, αvβ6 integrin, is known to promote tissue fibrosis and carcinoma invasion. Most areca nut formulations have a very high content of copper. This metal is believed to activate several angiogenic factors, such as vascular endothelial growth factors, Tumor Necrosis Factor (TNF)-alpha and Interleukin-1, all of which stimulate activation and proliferation of endothelial cells. These processes are also pivotal in tumor angiogenesis and proliferation [6]. Due to all these effects, areca nut and betel quid are strong and independent risk factors for oral cancer. The main mechanism through which OSMF occurs is the alteration of collagen metabolism by areca nut and its added constituents [7]. The premalignant or malignant changes all occur due to contact carcinogenesis as the quid is placed in a location of the oral cavity, often being constant. The alkaloids and flavonoids are released as the areca nut undergrows metabolism during chewed. Flavonoids initiate collagenase and alkaloids activate fibroblasts to produce collagen, which results in overproduction of collagen formation with decreased degradation [7]. Activation of procollagen genes, elevation of procollagen proteinase levels in procollagen C-proteinase (PCP)/bone morphogenic protein 1 (BMP1) and procollagen

N-proteinase (PNP), result in collagen that is immature and hence even more difficult to break down [2]. Moreover, the copper ion in the preparation increases the activity of lysyl oxidase (LOX) leading to unregulated collagen production [7]. This upregulation of LOX leads to activation of tissue inhibitor of matrix metalloproteinase gene (TIMPs) and plasminogen activator inhibitor (PAI) gene. Recent studies have shown that polymorphisms of collagen-related genes such as the transforming growth factor β-1 (TGFβ-1) gene have a consequential association with OSMF [5]. Association of single nucleotide polymorphisms (SNPs) in the matrix metalloproteinase-3 (MMP-3) promoter region with the 5A alleles has an increased risk for developing the disease while SNPs in the MMP-2 and MMP-9 promoter region is not associated with susceptibility to OSMF [5]. The equilibrium between matrix metalloproteinase and tissue inhibitors of metalloproteinase gets disturbed and ultimately results in increased deposition of extracellular matrix. All these subepithelial changes lead to the clinical presentation of fibrosis [2, 5]. Excessive use of areca nut and its flavored formulations further disturbs the homeostatic equilibrium between synthesis and degeneration of collagen leading to progressive fibrosis and other typical facial features of OSMF. Subsequent production of free radicals and reactive oxygen species are responsible for the high rate of oxidation-peroxidation of polyunsaturated fatty acids. One of the key molecules implicated is TGF-β, a proinflammatory and fibrogenic cytokine generally stimulated in response to arecoline [2, 5-7]. Derangement of iron metabolism has been postulated as a possible etiology of OSMF as well as increasing the risk of cancer [6]. Iron is important in maintaining the general health of oral mucosa and hence many disease states, including cancers, are associated with iron depletion. The epithelium becomes atrophic with increased keratinization and reduced maturation, giving rise to a large amount of immature collagen [6]. Use of areca nut and betel quid also affects the immune system. The levels of transforming growth factor (TGF)-β and interferon (IFN)-γ are lower in mononuclear cells found among OSMF patients [6] (**Table 1**).

Malignant transformation of OSMF

OSMF is widely recognized as condition that precedes oral cancer, rightfully classified as a precancerous. Since its use leads to systemic effects, it is a condition rather than a single lesion or entity in the oral cavity. While OSMF alone causes severe debilitation to oral health and lifestyle, its malignant transformation is the real reason behind its associated mortality. This malignant transformation rate ranges from 1.2 to 23% worldwide [2]. In China, epidemiologic studies have reported the overall transformation rate of 1.2 to 2.2%, while in India is has been reported to be approximately 7.6% [2]. Taiwan has reported some of the highest transformation rates between 3.27% and 23% [2]. This varying malignant transformation rate of OSMF may be due to the differences in age, gender, usage patterns and diagnostic criteria used in the studies. However, all studies shown some percentage of OSMF transforming to oral cancer. Duration of areca nut use has been an important prognostic factor in determining the degree of OSMF. Studies have also shown that the duration of OSMF and the degree of worsening of symptoms directly correlate with the progression to oral cancer. After the diagnosis of OSMF, progression to oral cancer can take place from 3 to 16 years (**Table 2**).

Clinical diagnosis

OSMF is most often diagnosed based on the clinical presentation and history. The most common symptom is restriction in mouth opening while others include dry mouth, pain, taste disorders, restricted tongue mobility, trismus and dysphagia. Since it is a chronic condition, most of the symptoms will be long standing with a slow progression. The soft and pink oral mucosa initially becomes firm and inelastic due to the high collagen content deposited. The fibrosis caused due to constant irritation from the quid and reduced surface vascularity leads to a slightly blanched appearance. Subsequently, the mucosa becomes opaque, with white plaque-like appearance or “papery white”. It becomes tough on palpation, with formation of firm vertical bands along the buccal mucosa at the site the quid is placed most commonly. In more advanced stages, the lips and palate are also involved with lesions occurring bilaterally on one or more subsites. A typical appearance described as “Chewers syndrome” has been described for long standing OSMF and includes gutkha faces, mouth, speech, swallowing and hearing. Patients might also complain of a severe burning sensation, due to the epithelial

Table 1. Factors identified as diagnostic markers in OSMF

Classification	Factor	Interpretation in OSMF	Positivity rates for OSMF
DNA	p16, p14, MGMT and DAPK [21]	Upregulation	57-63.6%
RNA	• TGF Beta R1 and TGF Beta R2 [14, 22]	Upregulation	NA
	• miR-1246 and miR10-b [12, 23]		
	• LncRNA LINC00974 [24]		
	• miR200-b, miR200-c and miR203 [11, 25, 26]	Downregulation	NA
	• LncRNA GAS5-AS1 [27]		
Tissue Protein markers	• Proliferating Cell Nuclear antigen (PCNA) [28]	Upregulation	100% in suprabasal and basal layers, 77% in superficial layer
	• Combination of Ki67 and p16 [16]		NA
	• Beta Catenin [15]		94.4%
	• Alpha-enolase [29]		NA
	• Zinc finger E-box-binding homeobox 1 (ZEB1) [11]		NA
	• ZEB2 [25]		NA
	• Cyclophilin A [30]		47.2%
	• Nuclear Coactivator 7 (NCOA7) [31]		NA
	• Hypoxia-inducible factor 1 (HIF-1) and plasminogen activator inhibitor-1 (PAI-1) [32]		NA
	• CD105 [33]		NA
	• Wnt inhibitory Factor-1 [34]	Downregulation	NA
	• SFRP-1 and SFRP-5 [15]		NA
Serum Markers	• Lactate dehydrogenase [17, 35]	Upregulation	NA
	• Malondialdehyde [36]		NA
	• Serum CEA [37]		NA
	• SCC-Ag [37]		39%
	• Serum Ferritin [37]		19.5%
	• sister chromatid exchange in lymphocytes [38]		53.7%
	• Copper [18]		NA
	• Superoxide dismutase (SOD) and glutathione peroxidase (GPx) [39]	Downregulation	NA
	• Beta carotene [40]		NA
	• Serum proteins and globulins [19]		NA
Salivary markers	• S100A7 [41]	Upregulation	79%
	• Lactate Dehydrogenase [17, 35]		NA
	• 8-hydroxy-2-deoxyguanosine (8-OHdG) and MDA [42]		NA
	• GPx and SOD [43]	Downregulation	
	• vitamin C and vitamin E [42]		

Table 2. Factors indicating malignant transformation of OSMF

FACTOR	INTERPRETATION
O (6)-Methylguanine-DNA [44]	Low levels associated with advanced oral cancer and lymph node metastasis
p53 Mutation [45, 46]	Degree of p53 staining increased with epithelial cell transformation, associated with progression of oral cancer
MDM2-P2 promoter [47]	Elevated levels in dysplastic lesions and oral cancer
C-jun [48]	Chronic stimulation by arecoline leads to oral cancer
HSP 70 [49]	In patients with premalignant lesions, median transition time (premalignancy to malignancy) was significantly shorter in HSP70 overexpression cases
HSP 27 [50]	Increased in betel nut induced oral cancer due to direct action of arecoline
c-MYC, SOX2 and OCT-4 [44]	Downregulation mediates epithelial atrophy, upregulation mediates malignancy
β_1-integrin [44]	In fibroblast-normal levels are antifibrotic, reduced levels promote fibrosis In epithelial cells-decreased levels promote epithelial atrophy, increased levels promote malignancy
ΔNp63α [44]	Downregulation mediates epithelial atrophy, upregulation mediates malignancy
K-5/14 and K-19 [44]	

Abbreviations: OSMF, Oral Submucous Fibrosis; TNF, Tumour Necrosis Factor; PCP, Procollagen C-Proteinase; BMP, Bone Morphogenic Protein; PNP, Procollagen N-Proteinase; LOX, Lysyl Oxidase; PAI, Plasminogen Activator Inhibitor; TIMPs, Tissue Inhibitor of Matrix Metalloproteinase Gene; TGF, Transforming Growth factor; SNP, Single Nucleotide Polymorphisms; MMP, Matrix Metalloproteinase; IFN, Interferon; RNA, Ribonucleic acid; DNA, Deoxyribonucleic acid; SFRP, Secreted Frizzled Related Proteins; LDH, Lactate Dehydrogenase; MDA, Malondialdehyde; RAGEs, Receptors of Advanced glycated End Products; NF-kB, Nuclear factor kappa-light-chain-enhancer of activated B Cells; ROS, Reactive Oxygen Species; HIF, Hypoxia Inducible Factor; IgG, Immunoglobulin G.

atrophy and changes in the mucosal lining of the oral cavity. Due to the limited mouth opening, these patients also have poor oral hygiene with abraded teeth. Some reports suggest poorer wound healing and chronic traumatic ulcerations that might contribute to the increased incidence of oral cancer in these individuals. Diagnosis using autoflorescence spectroscopy, optical coherence tomography and FTIR spectroscopy has also been suggested with a high degree of accuracy.

Histological diagnosis

Pindborg and Sirsat were one of the first to define OSMF based on its clinic-pathologic features as "an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with a juxta-epithelial inflammatory reaction followed by a fibro-elastic change of the lamina propria, with epithelial atrophy leading to stiffness" [8]. Based on this definition, these histologic features can be used to augment the sometimes puzzling clinical diagnosis of OSMF. Most clinicians would not use histopathology to diagnose OSMF, but biopsies are helpful to investigate overlying changes that may look suspicious suggestive of malignant transformation such as ulcers, red/white patches, etc. The sub-epithelium shows fibrosis with chronic inflammatory cells, such as lymphocytes, monocytes, plasma cells, and macrophages. Dense collagen bundles with hyalinization in certain areas are seen with reduced vessel lumen size. At the onset of the disease, tenascin, perlecan, fibronectin and collagen type III are found to be manifested in the lamina propria and submucosa whereas extensive and irregular deposits of elastin are found around muscle fibers in the intermediate stage, along with the above molecules [1]. Collagen type I appears to dominate the ECM in the advanced stages. Their gene expression levels varied with the progression of fibrosis. Difficulty in opening the mouth may be related to loss of various ECM molecules such as elastin and replacement of muscle by collagen type I [1]. While there are a number of clinico-pathological classifications proposed for the diagnosis of OSMF, none accurately predict its malignant transformation and prognosis.

Molecular diagnosis

The most reliable method for diagnosing and predicting malignant transformation of OSMF is by the qualitative and quantitative evaluation of specific molecular markers. Distinct underly-

ing molecular differences and signatures exist between the normal oral mucosa, potentially malignant lesions and frank oral cancer. In the past decade, significant development has been made in determining the biomarkers for prognosticating OSMF through novel techniques that detect cytological features, promoter methylation, polymorphism, mRNAs, microRNA, non-coding RNAs, and protein and trace elements. These signatures have been obtained by evaluating the traditional solid biopsy or in other tissues such as serum and saliva, i.e. liquid biopsy.

DNA and RNA biomarkers

DNA methylation is a physiologic epigenetic process that occurs primarily due to the addition of a methyl group to a CpG dinucleotide in the DNA sequence [9]. Any abnormal methylation affects the physiological stability of cell division and this mechanism has been considered by which environmental risk factors such as areca nut and tobacco can influence the risk of cancer progression [9, 10]. In fact, studies have shown that aberrant methylation secondary to genetic alterations such as deletions, could be one of the earliest molecular changes that can signal disease transformation and progression. Many microRNAs have also been found to have potential effect on malignant transformation of OSMF, especially the downregulation of miR-200c that has been found in the areca nut-associated OSMF through regulation of ZEB1 [11]. Certain RNA biomarkers have also been studied, whose upregulation has been significantly correlated in OSMF. One of the most commonly studied for OSMF is the role of miR-1246, which is not only essential for the maintenance of oral stemness but also vital for the myofibroblast activation. Studies have demonstrated that miR-1246 is positively correlated with the type I collagen, that may act as a downstream effector and lead to fibrosis [12]. TGF-β are another strong stimulator of enhanced collagen production and diminished matrix degradation pathways [13]. Loss of adipose tissue in OSMF can be attributed to TGF-β that cause lipodystrophy. Studies have shown that TGF-β secretion is more during the initial phases of the disease [14]. These patterns may serve as a potential diagnostic biomarker for OSMF progression and monitoring.

Tissue protein biomarkers

Based on the constant developments in the understanding of OSMF's pathogenesis, many tissue protein markers like TGF, beta-catenins, Secreted Frizzled related proteins (SFRP) and Enolases have been studied extensively. In OSMF, uncontrolled signaling of TGF β is postulated as a significant factor in many fibrotic reactions. Early cases of OSMF have been shown to have more intense staining of TGF-β in the epithelium, fibroblast, macrophages and inflammatory cells than the advanced cases [14]. Others have studied the role of SFRPs and their association with beta-catenins for carcinogenesis in OSMF and found that reduced SFRP1 and SFRP5 by promoter methylation could lead to cytoplasmic/nuclear accumulation of β-catenin and eventual tumor progression [15]. The changes of SFRPs and β-catenin localization, as well as its methylation, could be a useful biomarker of malignant progression in OSMF [15]. Other markers such as Ki67, cyclin D1, c-Met and IMP3 show significantly different expressions in normal oral mucosa than that of OSMF. A combination of Ki67 and p16 has been shown to have the highest predictability for detecting OSMF prone for malignant transformation [16].

Serum biomarkers

Serum cell and protein markers like Lactate Dehydrogenase (LDH) and malondialdehyde (MDA) have been studied for prognostication of patients with OSMF. The fibrosis, hypoxia and a shift to anaerobic glycolysis present in the pathogenesis of OSMF lead to increased levels of LDH [17]. Based on this, a study suggests that serum LDH can be used as valuable aid in monitoring treatment outcomes in the OSMF patients [17]. The role of trace elements have also been studied in OSMF. Copper has been considered to play a role in the etiopathogenesis. A study has shown that serum copper levels were significantly increased in OSMF patients with habit history and the levels were shown to gradually enhance with the duration of substance use [18]. The process of carcinogenesis leads to increase in oxidative stress, which in turn causes weakening of antioxidant defense mechanism of the body. This process leads to the destruction of macromolecules like

proteins [19]. A recent study evaluated the serum proteins and globulins levels for their role as potential biomarkers for oral potentially malignant disorders. They observed that the serum protein and globulin levels were significantly decreased in OSMF, oral leukoplakia and nicotine stomatitis [19].

Salivary biomarkers

Many studies have reported the importance of salivary biomarkers to detect and prognosticate OSMF. Research has shown that S100A7 directly binds with receptors of advanced glycated end products (RAGEs) which in turn activates NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) protein complex that leads to enhanced cytokine production. Furthermore, S100A7 helps in the rise of intracellular levels of reactive oxygen species (ROS) in keratinocytes. Thus, S100A7 is essentially both stimulated by ROS and it causes intensification of hypoxia. Salivary immunoglobulins have also been used as salivary markers in OSMF [1]. Elevated levels of major Immunoglobulins were noted in patients with OSMF by Gupta et al. This was one of the first studies of its kind in India [1]. Kallalli et al. further demonstrated the enhanced levels of salivary LDH in patients with OSMF. They found that salivary LDH levels were consistently higher in OSMF and oral cancer, paving it to be a potential biomarker in the future [20].

Discussion

Even though areca nut has been classified as a class I carcinogen, the incidence of OSMF is mostly dictated by the pattern of its use alone or in combinations. One of the reasons that its use is most common in South Asia is that it is locally grown. India alone accounts for 723,000 tones of areca nut production, almost 5 times more than any other country. Another reason is that it being aggressively marketed and sold in eye-catching packaging and flavors that is attracting a considerable increase in the number of people initiating this habit. A lack of differentiation between these products that are sold as "mouth fresheners" and various other tobacco containing products, such as gutkha and paan masala, is present that leads to a false sense of security of health. Further, as smoking is considered a taboo in certain areas of India, majority of the women take to tobacco, areca nut or betel quid chewing.

From an epidemiologist's perspective, determining the prevalence of OSMF should not be difficult as the condition affects the oral cavity which is easily amenable for screening and early detection. While most of the diagnosis is made clinically, the actual number of OSMF cases could be much higher due to the possible lower reporting of patients with minimal symptoms in the early stages that do not seek any medical intervention at the time. Additionally, it is important to identify the possibly high risk OSMF that is prone to transformation. At present, clinical and pathological examination is the mainstay of OSMF diagnosis, but their role as a prognosticator is very limited. Molecular pathology and identification of genetic alterations early can help identify these high risk individuals that can be monitored closely. The most obvious are the changes that arise from the carcinogen areca nut itself. Most of the processes that lead to aggressive behavior arise from the processes of hypoxia, cell cycle alterations, angiogenesis, senescence, alterations in oncosuppressor genes and genetic susceptibility.

While OSMF has a high potential of malignant transformation, it is important to understand that about a quarter of oral cancer occurs without any clinically visible OSMF [51]. While the process of transformation is still unclear, specific biomarkers predicting this premalignant phenotype change needs to be identified. The common biomarkers of advanced OSMF that are common to oral cancer include cysteine proteinase inhibitor, TGF-β1, hypoxia-inducible factor 1α (HIF-1α), DNA damage phenotype, MMP and TIMP and Cytokeratin with elevated serum immunoglobulin G (IgG) [52]. Most of these have been shown to promote tumorigenesis, metastasis and possibly resistance to chemotherapy drugs. MMP is a common biomarker seen upregulated in OSMF and has been shown to be a major factor in cancer progression [53]. Common epigenetic alterations include the hypermethylation of WIF1 and p16, and the expression of long-noncoding RNA HCG22, RP11-397A16.1, LINC00271, CTD-3179P9.1 and ZNF667-AS1 [54]. In-vitro and in-vivo studies have shown that arecoline and other metabolites of areca nut have a direct mutagenic impact on cells leading to carcinogenesis [55]. Their associated processes include chronic inflammation, immature collagen deposition, growth factors and cyto-

kine secretion. Moreover, they are often used in combination with chewed tobacco that has been shown to have a significant relation with oral cancer [55]. Most of the high risk OSMF lie in the promotion phase of carcinogenesis which is lengthy and irreversible. Most of the patients that seek medical intervention are symptomatic and present at this stage which is often in between the dormant premalignant stage and the rampant malignant process. Most therapies delivered at the time with elimination of the carcinogen would interrupt the process of transformation. This could possibly explain the differing malignant transformation rate across the globe ranging up to 30% in areas where access to care and awareness is less. If there is continued exposure to areca nut and tobacco, the transformation to malignancy continues at a rapid pace, often becoming irreversible. Additionally, the immature collagenous tissue could also be a promotor of malignant transformation with thedense fibrotic deposition resulting in capillary lumen occlusion producing a hypoxic environment [56].

The current review presents various factors that can help identify the "high-risk" OSMF population that needs further intervention. Additional biomarker evaluation can further confirm the risk of malignant transformation. While the detection of most biomarker aberrations specific for the diagnosis and malignant transformation may not be feasible at the chairside today, efforts must be made to develop systems by narrowing down on the most relevant markers of significance. We have attempted to review the existing literature on molecular markers in OSMF, with the intent to identify and maximize the use of the potential biomarkers in clinical practice. Since OSMF is prevailing in the developing countries, it is imperative to find a patient-specific approach to management of this debilitating condition that also incorporates affordability, accuracy and efficacy. This will help reduce the burden that advanced disease contributes and thus the strain on the already handicapped health systems in these countries. A collective approach from the concerned network of individuals is needed to achieve this objective, as processing of biomarkers is a technique-sensitive task. A single or multiple biomarkers expressions may be used to develop OSMF staging system for better evaluation of those patients that undergo transformation and prognostication. Treatment for patients with OSMF can thus be individualized based on these molecular markers. Future efforts might also help in gene and targeted therapy for this high-risk population. Targeted therapies implemented early can help in prevention of transformation to OSCC. Although the concept of targeted therapy is still in a nascent stage, an additional approach to develop lines of management based on molecular markers will go a long way to determine the progress and success in the management of this disease.

Disclosure of conflict of interest

None.

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