Oral potentially malignant disorders – More to unfold…

Changes in oral mucosa related to tobacco habits are noticeable and can form a group of pathologies termed as potentially malignant disorders (PMDs).

Oral PMDs as delineated by the World Health Organization include lesions such as leukoplakia, erythroplakia, palatal changes associated with reverse smoking, and also conditions labeled as oral submucous fibrosis (OSMF), oral lichen planus (OLP), and discoid lupus erythematosus.

Even though the reported prevalence for oral PMDs is 1-5% in the general population, little is known about the actual prevalence of oral PMDs. South and East Asia has shown a high prevalence of oral PMDs (Chung et al., 2005 and Ariyawardana et al., 2007), with an average age of clinical presentation being 50-69 years. The latest trend in the age group, at least for 5% cases is under 30 years.

Buccal mucosa is the favored site for oral PMDs followed by gingiva, tongue, and floor of the mouth. These PMDs feature clinically as white and/red lesions.

There are few instances where more than one PMD coexist such as oral leukoplakia with lichen planus or OSMF with leukoplakia or OSMF with lichen planus. Considering the pathogenesis of these combined lesions, is it attributed to the common etiological factor – tobacco?? Then, how do we predict the biologic behavior of such coexistent pathologies? This is another area to be explored well.

Various non-invasive techniques such as vital staining, light-based detection systems, optical diagnostic methods, and use of salivary biomarkers have been tried for clinical detection and diagnosis of oral PMDs. Even though vital staining and light-based techniques are in wide use, optical diagnostics and application of salivary biomarkers demand a good number of long-term prospective studies.

A model for detecting oral PMDs with high risk has been derived and validated in Sri Lankan population. Such models need to be customized and validated at different parts of the world.

A large non-homogeneous suspicious clinical lesion may demand 2-3 biopsies at different sites.

Microscopic evaluation of oral PMDs reveals a spectrum that ranges from simple hyperkeratosis and hyperplastic change to carcinoma in situ.

The histologic grading of oral epithelial dysplasia (OED) is significant from both diagnostic and prognostic perspective. At the same time, pathologic evaluation of OED is carrying a lot of subjectivity and this is well documented. Some pathologists have even graded OED as high- and low-risk types. Despite numerous methods, tools and algorithm being explored, variability is accountable at intra- and inter-observer assessment of OED.

Fractal geometry applied for oral mucosa has shown a gradual increase of fractal dimensions, from normal to dysplastic to neoplastic mucosa. However, the fractals have to be studied further to derive definitive inferences.

Accumulation of genetic and epigenetic changes in a multistep process as evidenced by current scientific explorations has indicated the transition from normal epithelium to premalignant state and then to carcinomatous change. Either overexpression or amplification of transcription factors (c-Jun, Cyclins D and E, D1, p53 – elements of cell cycle control) have been recognized; other molecules which have been studied are epidermal growth factor and its receptors, Ras, Myc, and other oncogenes.

Although cumulative quantitative genetic aberrations (inclusive of aneuploidy) have been implicated in carcinogenesis, it is still an enigma to explain malignant transformation of a simple hyperkeratotic lesion!! No single molecular pathway has been established well as a mainstay for progression of epithelial dysplasia to squamous cell carcinoma.

In addition to altered surface epithelium, the investigators are fascinated by changes observed in the underlying connective tissue. Defense cells, especially mast cells and tissue eosinophils have really caught the attention of pathologists. Mast cells have been studied extensively in oral squamous cell carcinoma and in popular PMDs such as OLP and OSMF. How about the role of tissue eosinophils? Have these eosinophils got to say anything about malignant transformation of oral PMDs? Even though tissue eosinophils have been studied in oral squamous cell carcinoma with conflicting results, the role of tissue eosinophils in oral leukoplakia or in OED is not completely understood. The reported literature claims that mast cell could be responsible for the recruitment of tissue eosinophils. However, this finding has to be confirmed in a larger sample and in different PMDs.

When it comes to the malignant transformation rates of oral PMDs, limited evidence is available. The malignant transformation rate differs for each lesion (leukoplakia – 0.13-2.2%/year, OSMF – 0.5%/year, and OLP - <1%/year), and overall for PMDs is over 2%/year (Napier and Speight, 2008).

In addition to follow-up studies, systematic reviews and meta-analyses are mandatory to know the malignant transformation rates of oral PMDs.

Moreover, clinical parameters, pathological evaluation, morphometric analysis, and molecular markers do help us in understanding the disease process and also in assessing the malignant potential of oral PMDs.
Although numerous treatment modalities (non-surgical and surgical including laser) have been tried for oral PMDs, it is difficult to make definitive recommendations due to the lack of randomized controlled clinical trials and long-term follow-up studies.

Upon digging the English literature, in spite of numerous studies being reported on oral PMDs, we realize that there are numerous questions which have to find satisfactory answers yet. There is a need to conduct randomized controlled trials, more number of prospective studies with a larger sample and long-term follow-up. Hospital-based studies with interdepartmental integrity and interhospital networking are more encouraging in shedding light on actual prevalence and biologic behavior of these oral PMDs. A bench to bedside approach is the need of the hour to understand and tackle with these enigmatic lesions. Furthermore, there is a need to relook at the tobacco cessation and tobacco de-addiction measures.

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