

## Candida in potentially malignant oral disorders

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### ABSTRACT

Oro-pharyngeal cancer is a significant component in the global burden of cancer. A considerable proportion of oral squamous carcinomas develop from preexisting potentially malignant disorder of the oral cavity. The term potentially malignant oral disorders (PMD) were proposed for the precancerous lesions and conditions by World Health Organization in 2007. PMD are considered an in-between clinical state, which showed increased risk for cancer development. Etiology of PMD is multifactorial. Tobacco and alcohol are the major risk factors. In recent years, role of candidal infection is recognized as a significant factor in the development of PMD. There is an enduring discussion whether *Candida* infection can be a cause of PMD or a superimposed infection in a preexisting lesion. This article highlights the association between *Candida* and PMD.

**KEY WORDS:** *Candida*, carcinogen, potentially malignant oral disorders

Oro-pharyngeal cancer is a significant component of the global burden of cancer. The occurrence of oral cancer is particularly high among men and is the eighth most common cancer worldwide.<sup>[1]</sup> A considerable proportion of oral squamous carcinomas develop from preexisting potentially malignant disorder of the oral cavity.<sup>[2]</sup> World Health Organization (WHO) in 2007 proposed the term potentially malignant oral disorders (PMD) for precancerous lesions and conditions.<sup>[3]</sup> Oral precancer is considered intermediate clinical state that showed increased risk for cancer development. If recognized and treated early they show better prognosis.<sup>[4,5]</sup> Etiology of potentially malignant disorders are multifactorial. Tobacco and alcohol are considered a major risk factors but increasingly the role of viral and candidal infection are recognized as being significant in cancer development.<sup>[5]</sup>

*Candida* spp. is normal commensal fungi that are found colonizing the oral mucosa frequently. Oral *Candida* is "opportunistic pathogens". Depending on the host defense mechanisms or local oral microenvironment, *Candida* can

transform from a harmless commensal to the pathogenic organism causing oral mucosal infection.<sup>[6,7]</sup> This article highlights the association between *Candida* and PMD.

### Candida

*Candida* is a yeast-like fungi. *Candida* is derived from Latin word where toga *Candida* was a white robe worn by Roman Senators.<sup>[8]</sup> *Candida* comes under the phylum, Ascomycota and order, Saccharomycetales. It is a pathogenic dimorphic yeast-like fungi. In host tissues or cultures at 37°C, they occur as yeasts. In soil and in culture at 22°C, they appear as molds.<sup>[9]</sup> Currently, there are some 200 organism species within the genus *Candida*. Of the nearly 200 species, six species, *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, and *Candida lusitanae* are the most commonly associated with human infection.<sup>[10]</sup> Diagnosis can be done using methods like microscopic examination, culture methods, proteomic and genomic studies.

Depending on the host defense mechanisms or local oral microenvironment *Candida* can transform from a harmless commensal to the pathogenic organism causing oral mucosal infection. Some conditions in which *Candida* can become pathogenic are old age, smoking, diabetes, malignancies, radiation exposure and immunocompromised states like HIV.

Phenotypic switching of *Candida* is noticed when they become pathogenic and invade the tissues. Yeast cells adhere to both oral and intestinal epithelia and then rapidly switch to

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hyphal growth. Adherence is mediated by a range of cell wall proteins that are expressed on the surface of hyphal cells.<sup>[11]</sup> Two mechanisms are proposed for phenotypic switching. First mechanism is by secretion of degradative enzymes by the fungus-like proteases that might digest epithelial cell surface components. This in turn allows the physical movement of hyphae into/between the host cells. The second mechanism is by the initiation of epithelial cell endocytosis.<sup>[12]</sup>

### Potentially Malignant Oral Disorders

World Health Organization proposed in 1978<sup>[13]</sup> defined precancerous lesions as a morphologically altered tissue in which oral cancer is more likely to occur than in its apparently normal counterpart' and precancerous condition as a generalized state associated with a significantly increased risk of cancer'. Precancerous lesions include leukoplakia, erythroplakia, palatal lesions in reverse smokers.

Precancerous conditions are oral submucous fibrosis (OSMF), lichen planus, discoid lupus erythematosus, sideropenic dysphagia, syphilis, xeroderma pigmentosum, epidermolysis bullosa (WHO 1997).<sup>[14]</sup> WHO collaborating center for oral precancerous lesions in 2007 recommend the term "potentially malignant disorders," as it conveys that not all lesions and conditions described under this term may transform to cancer.<sup>[3]</sup> Among them frequently associated lesions with *Candida* is leukoplakia. Others are erythroplakia, OSMF, and lichen planus.

### Leukoplakia

Leukoplakia means a "white patch", which is derived from Greek words "leucos" means white and "plakia" means patch. It was defined as "a white patch or plaque that cannot be characterized clinically or pathologically as any other disease". Tobacco has been incriminated as a major etiological agent in the development of potentially malignant lesions. The role of *C. albicans* as a possible etiological factor in leukoplakia and its possible role in malignant transformation is still unclear.

Two main clinical types of leukoplakia are homogeneous and nonhomogeneous leukoplakia. Homogeneous lesions are uniformly thin, flat and show shallow cracks on the surface keratin. Nonhomogeneous varieties comprise speckled, nodular and verrucous types.<sup>[3]</sup> The current way for predicting the malignant potential of premalignant lesions is the by looking for the presence and degree of dysplasia.

### Oral submucous fibrosis

Oral submucous fibrosis is an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. It is constantly associated with juxta-epithelial inflammatory reaction followed by fibro-elastic change in lamina propria and epithelial atrophy; which leads to stiffness of the oral mucosa, causing trismus and inability to eat.<sup>[15]</sup>

A multifactorial model for the pathogenesis of OSMF is postulated. Tobacco, lime, betel quid, iron and nutritional

deficiencies, chronic candidiasis, genetic abnormalities, viral infections, autoimmunity etc., are considered to have either direct effect in causing OSMF or an indirect effect by intervening the immune system which is compromised in OSMF.<sup>[16]</sup>

### Lichen planus

Lichen planus is an autoimmune immune disease of unknown etiology. There is the accumulation of T lymphocytes beneath the epithelium of the oral mucosa and increase in the rate of differentiation of stratified squamous epithelium, causing hyperkeratosis and erythema with or without ulceration.<sup>[17]</sup> Clinically it was originally classified into six forms: Reticular, plaque, papular, bullous, atrophic, ulcerative. Role of *Candida* in lichen planus is still unclear.

### Role of *Candida* in Potentially Malignant Oral Disorders

Studies on the association of *Candida* and leukoplakia date back to 1970s. There is a longstanding discussion whether *Candida* infection is a cause of leukoplakia or if it is a superimposed infection in a preexisting lesion. Leukoplakia on clinical ground that were histologically chronic hyperplastic candidiasis showed a higher rate of malignant transformation on follow-up.<sup>[18]</sup> Animal studies have shown that *Candida* can cause epithelial hyperplasia and cellular atypia. It has been shown that, upon treatment, nonhomogeneous *Candida* infected leukoplakia convert into a homogeneous lesion, and some lesions even regressed.<sup>[19]</sup>

Leukoplakia with candidal infection has a higher rate of malignant transformation than uninfected leukoplakia. The ability of *C. albicans* to colonize, penetrate, and damage host tissues depend on the imbalance between *C. albicans* virulence factors and host defenses, often due to specific defects in the immune system.<sup>[20]</sup> Several cell surface proteins called adhesins recognizing host molecules are identified. They adhere to the cell surface and then phenotypic switching from the yeast form to hyphae form occurs by two mechanisms as described above.

*Candida* can then produce carcinogenic compounds, like nitrosamines, N-nitrosobenzylmethylamine. Strains with high nitrosation potential were isolated from lesions with more advanced precancerous changes. The yeast cells in such cases extends from the mucosal surface to the deeper epithelial cell layers representing transport and deposition of precursors like nitrosamines to deeper layers. This showed that certain strains of *C. albicans* play a key role in the development of dysplasia.<sup>[21]</sup>

Carcinogenic compounds then can bind with DNA to form adducts causing miscoding or irregularities with DNA replication. Thus results in oncogene formation and initiating cancer development.<sup>[20,21]</sup> All these findings suggest that there is a strong association between leukoplakia and *Candida* sp.

Few studies relating *Candida* and OSMF showed significantly high oral yeast carriage when compared to normal.<sup>[22]</sup> *Candida dubliniensis* was isolated from oral rinse samples in some studies.<sup>[22]</sup> In the case of lichen planus significant results are not obtained.<sup>[23]</sup>

## Conclusion

Although *Candida* spp. particularly *C. albicans* has been considered an etiologic factor for potentially malignant disorders, the pathogenesis is not clearly understood and is still a field under extensive research. *C. albicans* being a normal commensal in the oral cavity, its presence alone cannot be related to the etiology of PMD. On the other hand, its frequent presence in advanced leukoplakia cases and ability to produce potent carcinogens should also be considered. Thus, PMD lesions associated with *Candida* should be treated with great caution as it shows a higher rate of malignant transformation.

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