Review Article

Candida in malignant transformation of oral leukoplakia: A review

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Abstract

Among the fungi, *Candida albicans* is the most common microorganism to pose a possible risk factor for the malignant transformation (MT) in oral potentially malignant disorders (OPMDs). The presence of candidal infection may increase the risk of a OPMDs malignant potential. Histologically diagnosed fungal infection of the oral mucosa has been shown to exhibit epithelial dysplasia and vice versa. The rate of MT in leukoplakia with candidal infection is higher than that in uninfected leukoplakia. If left untreated, candida leukoplakia has a higher rate of neoplastic changes as compared to non-candida leukoplakia. Strong evidence of the fungal involvement in MT of oral leukoplakia is displayed by this higher rate of conversion. The current article reviews the potential role of candida infection in the MT of oral leukoplakia.

Introduction

Oral precancerous lesions are defined as "a morphologically altered tissue in which cancer is more likely to occur than its normal counterpart."[1] The usage of terms for oral lesions that can have the ability to transform into malignancy has been wide-ranging over the years.[2] The word premalignant is frequently used, but it infers that a particular lesion will invariably become malignant.[2] The idea of "precancer" began in 1805 with a postulation given by a European panel of physicians. The panel implicated that there are benign diseases that will always develop into invasive malignancy if followed for a long period.[3] In 1875, the term "precancer" was first coined by a Romanian physician, Victor Babes.[3] The term "precancer" was changed to oral potentially malignant disorders (OPMDs) by the World Health Organization. The term OPMD indicates that the pathological oral tissue has a mere potential for malignant transformation (MT), but not all OPMDs turn malignant. Further, the term disorder was preferred over the term lesions and conditions as the pathological changes were representations of underlying disorder which could affect any part of the oral cavity exposed to the carcinogen.

The risk of progression of an OPMD is difficult to predict. At present, the clinician makes a judgment based on the assessment of several clinical and histopathological features of the individual case.[2] Various OPMDs observed are oral lichen planus, oral submucous fibrosis, oral leukoplakia, and oral erythroplakia, etc. Among these, oral leukoplakia is the most commonly encountered OPMDs. The clinical significance of OPMDs is their unpredictable ability to transform into oral cancer. MT may be defined as the appearance of oral squamous cell carcinoma (OSCC) at the same site as the pre-existing OPMD. The duration between onset of initial diagnosis and progression to oral malignancy confirmed by histology is the time to MT.[4] About 16–62% of the OSCCs are associated with clinically detectable OPMDs such as OL providing an association for both localized and systemic causes as evident from earlier studies.[5] As there is a dearth of literature on the actual prevalence of OPMDs in the general population, a commonly accepted prevalence of 1–5% has been reported. OPMDs are more prevalent in the age group of 50–69 years, which are 5 years less than the common age group for OSCC. Recently 5% of OPMDs have been detected in persons under the age of 30 years. OPMDs are typically seen on the buccal mucosa, followed by gingiva, tongue, and floor of the mouth.[6]

Oral Candidiasis

It is one of the most commonly occurring fungal infections affecting the oral mucosa.[7] *Candida albicans* are normal oral microflora in around 30–50% people.[7] Candida is regarded

as commensals, but can also cause oral mucosal infections in immunosuppressed states such as old age, infancy, human immunodeficiency virus (HIV) infection, and cancers.[8] The transition of *Candida* species from commensal to pathogenic candida is triggered by a variety of predisposing local factors and systemic factors.[9] Local factors include the use of dentures, corticosteroid inhalers, and xerostomia. Systemic factors include any immunocompromised conditions such as HIV infection, malnutrition, leukemia, weakened immunity secondary to age, and endocrine dysfunction such as diabetes, systemic chemotherapy, radiation therapy, and use of systemic corticosteroids, immunomodulatory drugs, xenogenic drugs, and broad-spectrum antimicrobial drugs.

Candida Species in OPMDs

Among the fungi, *C. albicans* is the most common microorganism associated with MT in OPMDs.[10] Colonization of *Candida* species may cause either a sustained or transient saprophytic relationship with the host or localized infections of oral mucosal surfaces.[11] Different types of *Candida* species in oral leukoplakia play a role in MT. Table 1 summarizes the different types of *Candida* species identified to pose a malignant risk in oral leukoplakia.

Histologically diagnosed fungal infection of the oral mucosa and epithelial dysplasia has a substantially significant association. It is suggested that candida causes OSCC by producing carcinogenic compounds such as nitrosamines.[12] It is stated that the tubular hyphal structure of *C. albicans* plays the part in the entry of nitrosamine products to keratinocytes, potentially initiating the process of carcinogenesis.[12]

The role of various infectious agents in the etiology of OPMD and OSCC which includes human papillomavirus and herpes simplex virus remains largely speculative due to conflicting data. Candida is often found in histological sections of oral leukoplakia. Few of the studies have suggested that the potent carcinogen N-nitroso benzyl methylamine is produced by *Candida* species isolated from oral leukoplakia.[12] Patients with oral epithelial dysplasia or OSCC have a high number of *Candida* species in their oral cavity than patients without any histopathological findings of epithelial dysplasia or neoplasia. It was found that the degree of epithelial dysplasia evident in such patients also correlated with a higher load of candidal species in the oral cavity.[24]

Table 1: Summary of *Candida* species identified in oral leukoplakia

Author	Year	Types of *Candida* species
Daftary *et al.*[13]	1972	*Candida albicans*
Krogh[14]	1990	*Candida albicans, Candida tropicalis, Candida parapsilosis*
Vučković *et al.*[15]	2003	Candida
Chiu *et al.*[16]	2010	*Candida albicans*
Abdulrahim *et al.*[29]	2013	*Candida albicans, Candida glabrata, Candida tropicalis, Candida krusei, Saccharomyces cerevisiae*
Hebbar *et al.*[18]	2013	*Candida* spp.
Wu *et al.*[19]	2013	*Candida albicans*
Bakri *et al.*[20]	2010	*Candida albicans, Candida tropicalis, Candida dubliniensis, Candida glabrata, Candida pintolopesii, Saccharomyces cerevisiae*
Sarkar and Rathod[21]	2014	*Candida albicans*
Hongal *et al.*[22]	2015	*Candida albicans*
Banoczy *et al.*[23]	2019	*Candida albicans*

The role of *Candida* species in alteration of proto-oncogenes was speculated by various experimental models of multistep carcinogenesis cited by Field *et al.*[25] Studies done on the association of candida and oral leukoplakia are dating back since the 1970s. Still, it is unclear if the candida infection resulted in the oral leukoplakia or was the candida a superimposed infection in a pre-existing lesion. Follow-up studies on histologically differentiated chronic hyperplastic candidiasis showed a higher rate of MT to leukoplakia on clinical ground.[25] If left untreated, candida leukoplakia has a higher rate of neoplastic changes as compared to non-candida leukoplakia. Strong evidence of the fungal involvement in MT of oral leukoplakia is displayed by this higher rate of conversion.[25] Infection with *Candida* species is seen in all types of oral leukoplakia, but there is a higher predisposition with non-homogeneous types, particularly the speckled variety, for hyphal invasion, and MT.[25] The specific defects in the individual immune system facilitate the ability of *C. albicans* to colonize, penetrate, and damage host tissues, which depends on the imbalance between virulence factors and host defenses. "Adhesins," type of cell surface proteins identified, which recognize host molecules, adhere to the cell surface, and cause phenotypic switching from the yeast form to hyphae form by the above two mechanisms. Candida can produce the carcinogenic compounds such as nitrosamines, N-nitroso benzyl methylamine through these hyphal structures. Oral lesions with advanced potentially malignant changes were associated with strains having high nitrosation potential.[26] The yeast cells are seen extending from the mucosal surface to the deeper cell layers of the epithelium. This shows that there is the transport of precursors such as nitrosamines to deeper epithelial layer and eventual deposition there. Certain strains of *C. albicans* have shown to play a significant role in the development of epithelial dysplasia.[26,27] In such cases, the carcinogenic compounds were elicited to bind with host cell DNA to form adducts, which, in turn, lead to miscoding or irregularities with DNA replication resulting in oncogene formation and initiating the development of cancer.[26] These findings propound a convincing association between leukoplakia and *Candida* species which was first reported in 1965 by Cernea *et al.*, and Jepsen and Winther.[22]

Colonization of *Candida* species in oral leukoplakia was studied by Sarkar *et al.* by employing direct microscopy and histopathological diagnostic methods to ascertain the statistical correlation between candidal invasion and epithelial dysplasia.

Table 2: Overview of epithelial atypia noted in oral leukoplakia infected with candida

References	Country	Study type	Prevalence of candida infection in oral leukoplakia (n) %	Cellular changes associated with candida (n) %	Method of assessment	Malignant transformation (%)
Renstrup[17]	Denmark	Cohort	(55/235) 23.4%	Epithelial atypia: (31/55) 56.4%	Biopsy	N/A
Roed-Petersen *et al.*[10]	Denmark	Case–control	Biopsy: (30/98) 30.6 Smear: (N/A) 67.0%	Epithelial atypia (biopsy): (12/30) 40.0% Epithelial atypia (smear): (N/A) 67.0%	Biopsy	N/A
Daftary *et al.*[13]	India	Cohort	(49/723) 6.8%	Epithelial atypia: (7/49) 14.3%	Biopsy	N/A
Banoczy and Sugar[23]	Hungary	Cohort	(70/520) 13.5%	Cellular changes: Regressed: (N/A) 38% Progressed:(N/A)53%	Biopsy	28.7%
Krogh[14]	Denmark	Cohort	(12/12) 100.0%	Dysplasia: (5/12) 41.7% Mild: (2/12) 16.7% Moderate:(2/12) 16.7% Severe: (1/12) 8.3%	None	N/A
Vučković *et al.*[15]	Serbia	Cohort	(3/12) 25.0%	Dysplasia: (1/3) 33.3%	Biopsy	N/A
Nakazawa *et al.*[28]	Japan	Case–control	(26/44) 59.1%	Epithelial atypia: (N/A) 25.1% p53 mutation: 30.6% Ki-67 proliferation: 21.5% COX-2 expression: 8.5%	Biopsy	N/A
Chiu *et al.*[16]	Taiwan	Case–control	Multiple OL: (35/73) 47.9%	Dysplasia (MOL): (10/35) 28.6% dysplasia (SOL): (4/20) 20.0%	Biopsy	N/A
Dany *et al.*[27]	India	Case–control	(11/30) 36.7%	Mild dysplasia: (3/11) 27.3% Moderate dysplasia: (6/11) 54.5%	Biopsy	N/A
Abdulrahim *et al.*[29]	Ireland	Case–control	Biopsy: (31/78) 39.7% Oral rinse: (55/78) 70.5% Smear: (50/78) 64.1%	Dysplasia (biopsy): (28/31) 90.3% Mild: (4/31) 12.9% Moderate: (14/31) 45.2% Severe (10/31) 32.3%	Biopsy	6.5%
Hebbar *et al.*[18]	India	Cohort	Non-homogenous: (7/8) 87.5% Homogenous: (N/A)	Non-homogenous: (8/8) 100.0% - Mild dysplasia: (3/8) 37.5% - Moderate dysplasia: (5/8) 62.5% Homogenous: (N/A)	Biopsy	N/A
Wu *et al.*[19]	China	Retrospective	(59/396) 14.9%	Dysplasia: (33/59) 55.9%	Biopsy	N/A
Mohd Bakri *et al.*[20]	Malaysia	Case–control	(10/28) 35.7%	Mild dysplasia: (4/10) 40%	Biopsy	N/A
Sarkar and Rathod[21]	India	Case–control	(19/40) 47.5%	Dysplasia: (15/19) 78.9%	Biopsy	N/A
Hongal *et al.*[22]	India	Cohort	(12/29) 41.4%	Dysplasia: (12/12) 100.0% Mild: (3/3) 100.0% Moderate: (5/5) 100.0% Severe: (3/3) 100.0% Carcinoma-*in situ*: (1/1) 100.0%	Biopsy	N/A
Rodriguez-Archilla and Alcaide-Salamanca.[30]	Brazil	Case–control study	391 OL	41.4% showed severe dysplasia	Biopsy	N/A

N/A: Not available; OL: Oral leukoplakia

It was inferred that non-homogenous oral leukoplakia lesions showed a higher rate of positivity on microscopy and culture than homogenous oral leukoplakia.[21] Epithelial atypia was observed in various studies in MT of oral leukoplakia infected with candida as summarized in Table 2.

Conclusion

C. albicans have been considered a risk factor for OPMDs. *C. albicans* being a normal commensal in the oral cavity, its presence alone cannot be related to the etiology and MT of an OPMD. The incidence of candidal infection in oral leukoplakia

ranged between 6.8% and 100.0%. There is a longstanding discussion on whether candida infection is a cause of leukoplakia or if it is a superimposed infection in a pre-existing lesion. On the other hand, its frequent presence in advanced leukoplakia cases and the ability to produce potent carcinogens should also be considered as evidence for a potential causal inference. Because of the higher rate of MT OPMD lesions associated with candida, such cases must be treated with great caution.

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