Cause and Effect Relationship between Candida Spp. and Oral Premalignant Conditions: A Review

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ABSTRACT

Oro-pharyngeal malignancy is a critical part of the worldwide weight of disease. The occurrence of oral malignancy is especially high among men and is the eighth most common cancer around the world. A significant extent of oral squamous carcinomas creates from prior potentially malignant disorder of the oral cavity. Etiology of potentially malignant disorders is multifactorial. Tobacco and liquor are viewed as a noteworthy hazard factors however progressively the role of viral and candidal infection are perceived as being huge in cancer development. Candida spp. is typical commensal fungi that are found colonizing the oral mucosa much of the time. Oral Candida is "“opportunistic pathogens”. Candida can switch from a innocuous commensal to the pathogenic organism which causes oral mucosal infection depending on the host defense mechanisms or local oral microenvironment. This article highlights the relationship among Candida and oral cancer/PMD.

Keywords: Candidiasis, Oral Cancer, Potentially Malignant Disorders (PMD), Fungus

INTRODUCTION

Oral pre-malignancies and carcinomas are basic epithelial pathologies brought about by an assortment of etiological components. In the oral cavity, candidiasis is the most incessant opportunistic fungal infection. Since the underlying reports of a relationship between candidiasis with oral pre-cancer and cancer, different hypotheses have been discussed in regards to the role of candida being developed and change of oral pre-malignancies.[1]

Cancer is representing a noteworthy danger to general health in the developed world as is expanding in the developing world. The burden of infection related cancers is still underestimated worldwide, due to the use of conservative population, prevalence and risk ratio estimates. Overall, oropharyngeal cancers were reported to be responsible for 529,500 occurrences and 292,300 deaths in 2012, accounting for about 3.8% of all cancer cases and 3.6% of cancer deaths and 18% of all malignancies were estimated to be due to infectious agents in 2002. The ability of some albican strains to increase neoplastic changes and deliver saliva nitrosamines that cause cancer has highlighted the potential role of candida in malignant transformation.[2,3,4]

The literature on etiological relationship between fungal infection and malignancy are less, despite the fact that for a long time Candida species have been involved in different epithelial cancers. Candidal infection does not give off an impression of being a hazard factor for dysplastic cervical lesions or cervical carcinoma and most enthusiasm for Candida and carcinogenesis is identified with oral and esophageal carcinoma. The conceivable relationship between Candida species and oral neoplasia was first announced during the 1960s with later reports recommending a link between the presence of Candida albicans in the oral cavity and the development of oral squamous cell carcinoma. In reality epithelial dysplasia improves after disposal of Candida species from infected tissue also supports this contributory association.[5]

There is significant association between histologically determine fungal infection of the oral mucosa and epithelial dysplasia. Candida may instigate oral squamous cell carcinoma (OSCC) by directly creating cancer-causing compounds like nitrosamines.[6]

What is Candidiasis??

Candida is a fungus, first isolated from a tuberculosis patient's sputum in 1844. They are non-photosynthetic, eukaryotic organisms with a cell wall that lies external to the plasma membrane. Within the nuclear membrane there is a nuclear pore complex. The plasma membrane contains huge amounts of sterols, usually ergosterol.[7,8]

Candida albicans are one of the components of normal oral microflora and this species is borne by about 30% to 50% of people. The carriage rate increases with the patient's age. 60% of the mouth of the dentate patient recovers candida albicans beyond age of 60 years. There are numerous kinds of Candida species, which are found in the oral cavity. Types of oral Candida are: C. albicans, C. glabrata, C. guillermondii, C. krusei, C. parapsilosis, C. pseudotropicalis, C. stellatoidea, C. tropicalis.[9]

Certain fungal cell wall components such as mannose, C3d receptors, mannoprotein and saccharins facilitate the adhesion of candida to epithelial cell walls, an important step in the initiation of infection. Different variables embroiled are germ tube formation, presence of mycelia, persistence within epithelial cells, endotoxins, induction of tumor

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necrosis factor and proteinases. Phenotypic switching which is the which is the capacity of specific strains of C. albicans to change between different morphologic phenotypes has also been implicated.[10,11]

Factors Affecting Adhesion of Yeasts

A. Factors related to yeast cells

1. Medium/cultivation.
2. Phenotype.
3. Germ tubes/hyphae.
4. Extra-cellular polymeric material (EP).
5. Floccular/fibrillar surface layers.
6. Mannan.
7. Chitin.
8. Hydrophobicity.
9. Cellular lipids.

B. Factors related to host cells

1. Cell source.
2. Mucosal cell size and viability.
3. Fibronectin.
4. Fibrin.
5. Sex hormones.
6. Yeast carriers vs. patients with overt candidosis.

C. Environmental factors affecting adhesion

1. Cations.
2. pH.
3. Sugars.
4. Saliva.
5. Humoral antibody and serum.
6. Antibacterial drugs.
7. Bacteria Lectins.

Enzymes of Candida

Candida certainly has the ability to produce phospholipases. Phospholipases are aggregated at the tips of fungal hyphae and localized in the region of host cell compartments where dynamic intrusion is happening. These enzymes were found in generally C. albicans strains but not in living beings known to be less virulent than C. albicans, for example, C. glabrata, C. tropicalis, and C. parapsilosis. Extracellular proteinases have likewise been ensnared in the pathogenicity of C. albicans. Proteinase-inadequate strains are noninvasive and the pattern of adherence also reflects the expression of secretory proteinase. Salivary proteins, including IgA, can be almost completely degraded by acidic proteinases of Candida particularly under low pH conditions.[12]

Oral cancer and candidiasis

Oral cancer is a multifactorial disease and along with numerous potentially malignant disorders, chronic oral Candidiasis is seldom yet can move into oral cancer. An imbalance between Candida albicans, virulence factors and host defenses frequently because of explicit imperfections in the resistant/immune system allows Candida albicans to colonize, penetrate and harm host tissues.

There are two proposed mechanisms by which C. albicans can invade keratinocytes. These mechanisms are:

First Mechanism

This mechanism involves the secretion of degrading enzymes by the fungus, primarily aspartic proteases that digest epithelial cell surface components and thus permit the physical movement of hyphae into or between host cells.

Second Mechanism

It involves the E-cadherin pathway in which Candida albicans stimulates keratinocytes to induce epithelial cell endocytosis to produce pseudopod-like structures that encircle the fungus and depict it in a process in the cell. Candida has the ability to induce oral cancer by producing cancer compounds directly, such as nitrosamines. Such a carcinogen may bind DNA to form baseline adducts, phosphate residues and/or hydrogen binding sites that contribute to DNA replication miscoding or irregularities. The resulting point mutations will activate the particular oncogenes and cause oral cancer to develop.

Krogh et al. stated some Candida species isolated from leukoplakia lesions could produce potent N-nitrosobenzylmethylamine (NBMA) carcinogen. Candida albican's tubular hyphal may be significant because its structure allows the entry of precursors from saliva and the discharge of the nitrosamine material into keratinocytes, which may be the initiator of oral cancer.[13,14,15]

Role of Candida in Potentially Malignant Oral Disorders

Leukoplakia with candidal infection has a higher rate of malignant transformation than uninfected leukoplakia. The capacity of C. albicans to colonize, infiltrate, and harm host tissues rely upon the imbalance between C. albicans virulence factors and host defenses, regularly because of explicit deformities in the immune system. A few cell surface proteins called adhesins perceiving host molecules are distinguished. They adhere to the surface of the cell and then phenotypic change from the form of the yeast to the form of the hyphae occurs through two mechanisms as described above. Then Candida may produce cancer-causing compounds such as nitrosamines, N-nitrosobenzylmethylamine. Strains with high nitrosation potential were isolated from lesions with more advanced precancerous changes. In such cases, the yeast cells extend from the mucosal surface to the deeper epithelial cell layers representing transportation and deposition to deeper layers of precursors such as nitrosamines.

This demonstrated certain strains of C. albicans assume a key role in the development of dysplasia. Cancer-causing compounds then can tie with DNA to frame adducts causing miscoding or anomalies with DNA replication. In this way results in oncogene formation and starting development of cancer. Every one of these discoveries propose that there is a solid relationship among leukoplakia and Candida sp.[4,15,16]

Diagnostic Methods of Oral Candidiasis

Smear

Smears are taken from the infected oral mucosa with wooden spatulas and fixed immediately in ether/alcohol 1:1 or with spray fix. Dry preparations examined by Gram stain method and periodic acid Schiff (PAS) method.

Swabs

Swabs are seeded on Sabouraud's agar at 25ºC or room

temperature, on blood agar at 35ºC, on Pagano-Levin medium at 35ºC or on Littmann's substrate at 25ºC. Incubation is performed at 25ºC to ensure recovery of species growing badly at 35ºC.

Biopsy

Biopsy specimen should be sent for histopathological examination when chronic hyperplastic candidosis is suspected.

Imprint culture technique

Sterile, square (2.2 × 2.5 cm), plastic foam pads are immersed in peptone water and put for 30-60 seconds in the restricted area under analysis. The pad is then placed directly on the agar of Pagano-Levin or Sabouraud, left in situ at 37ºC for the first eight hours of 48 hours of incubation. Then, the candidal density at each site is determined by a Gallenkamp colony counter and expressed as colony forming units per mm^2 (CFU mm^{-2}).

Impression culture technique

Take the alginate impression of both maxilla and mandible and then transport them to the laboratory and casting in 6% fortified agar with incorporated Sabouraud's dextrose broth. The agar models are then incubated for 48-72 hours at 37ºC in a wide necked, sterile, screw-topped jar to estimate yeast CFU.

Saliva

Ask patient to expectorate 2 ml of mixed unstimulated saliva into a sterile, universal container and vibrate it for 30 seconds. The count of Candida expressed as CFU/ml of saliva is estimated by counting the resultant growth on Sabouraud's agar with the help of spiral plating or Miles and Misra surface viable counting technique. Patients with clinical signs of oral candidiasis usually have more than 400 CFU/mL.

Paper Points

An absorbable sterile point is placed into the pocket depth and left there for 10 sec and then the points are moved to a 2 ml vial containing the transport medium of Moller's VMGA III.

Commercial diagnostic kits

The Microstix-candida (MC) system contains a plastic strip that affixed a dry culture area (10 mm × 10 mm) of modified Nickerson medium (Nickerson, 1953) and a plasticpouch for incubation. The O Yeast-I dent system is basedon the use of chromogenic substances to measure enzymeactivities. Ricult-N dip slide technique is similar to MC system but of higher sensitivity.

Histological identification

Demonstration of fungi in specimens of biopsy may require the cutting of several serial sections. The specific fungal stains that are widely used for demonstrating fungi in the tissues are PAS stain, Grocott-Gomori's methenamine silver (GMS) and Gridley stains.

Physiological tests

Determining their ability to assimilate and ferment individual carbon and nitrogen sources is used in the definitive identification of Candida species.

Phenotypic methods

Serotyping

Serotyping is limited to the two serotypes (A and B), a fact that makes it inadequate as an epidemiologic tool. Recently, it has been shown that the results obtained with different methods of serotyping can differ widely.

Yeast 'Killer Toxin' typing

Initially, these researchers used nine killer strains to build a triplet code to distinguish between 100 strains of C. albicans and found 25 killer- sensitive types. This approach was extended through the use of 30 killer strains and three antifungal agents, which seemed to differentiate between sufficient numbers of strains of C. albicans.

Morphotyping

This method has been used in a study of the morphotypes of 446 strains of *C. albicans* isolated from various clinical specimens.

Biotyping

Biotyping consisted of three tests the APIZYM system, the API 20C system and a plate test for resistance to boric acid. This system was found to distinguish a possible 234 biotypes, of which 33 were found among the 1430 isolates of C. albicans taken from oral, genital and skin sites.

Protein typing

Non-lethal mutations of proteins during the yeast cell cycle yield proteins of differing physical properties between strains, which may be distinguishable by one or two dimensional gel electrophoresis.

Genetic methods

In arbitrarily primed polymerase chain reaction (AP-PCR) analysis, the genomic DNA is used as a template and amplified at a low annealing temperature using a single short primer (9 to 10 bases) of an arbitrary sequence.

Serological tests

Serological tests for invasive candidiasis

1. Detection of antibodies.
2. Slide agglutination.
3. Immunodiffusion.
4. Phytohemagglutination.
5. Coelectosynersis.
6. Immunoprecipitation.
7. A and B immunofluorescence.
8. Nonspecific Candida Antigens.
9. Latex agglutination.
10. Immunobloting.
11. Cell Wall Components.
12. Cell Wall Mannoprotein (CWMP).
13. b-(1,3)-D-glucan.
14. Candida Enolase Antigen testing.

Immunodiagnosis

The use of specific antibodies labeled with fluorescent stain permits causative organisms to be diagnosed accurately

	Dosage form/strength	Indication
1	Miconazole cream 2% (OTC)	Angular cheilitis
2	Clotrimazole cream 1% (OTC) (prescription)	Angular cheilitis
3	Ketoconazole cream 2% (Prescription)	Angular cheilitis
4	Nystatin ointment 100,000 units/gram (prescription)	Angular cheilitis
5	Nystatin topical powder 100,000 units/gram (prescription)	Denture stomatitis
6	Nystatin oral suspension 100,000 units/gram (prescription)	Intraoral candidiasis
7	Betamethasone dipropionate clotrimazole cream (prescription)	Intraoral candidiasis
8	Clotrimazole troches 10 mg (prescription)	Intraoral candidiasis
9	Amphotericin B 100 mg/ml (prescription)	Intraoral candidiasis

Table-1: Topical antifungal medications

	Generic name	Formulation
1	Amphotericin B	100 mg/ml oral suspension
2	Clotrimazole	10 mg troche
3	Fluconazole	100 mg tablet 10 mg/ml oral suspension 40 mg/ml oral suspension
4	Itraconazole	100 mg capsule 10 mg/ml oral suspension
5	Ketoconazole	200 mg tablet
6	Nystatin	100,000 units/ml oral suspension 200,000 units/ml pastille 500,000 units/ml tablet 100,000 units/ml vaginal table

Table-2: Systemic antifungal medications

within minutes.[17] However, the preparation of specific antisera and purified polyclonal or monoclonal antibodies entails a much more extensive technical outlay, so the application of these reagents need only be considered when a very precise diagnosis is of therapeutic consequence.

Treatment modalities of oral candidiasis

Assessment of predisposing factor plays a crucial role in the management of candidal infection. Mostly the infection is simply and effectively treated with topical application of antifungal ointments. However in chronic mucocutaneous candidiasis with immunosuppression, topical agents may not be effective. In such instances systemic administration of medications is required (Table:1 and 2).[18]

CONCLUSION

Fungal infections caused by Candida species, in particular, Candida albicans has been implicated in the pathogenesis of oral premalignant lesions. There is evidence that Candida possesses necessary enzymes from dietary substances to produce nitrosamines and chemicals that have been implicated in carcinogenesis. The more advanced precancerous leukoplakia lesions yield more rarely occurring biotypes of C. albicans, suggesting a causal role for these biotypes in the malignant transformation. However continued research and scientific studies are required to substantiate the claims of role of Candida albicans in the pathogenesis of oral premalignant lesions and oral cancer.

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