Role of *Candida* Species in Oral Lichen Planus

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**Abstract**

*Candida albicans* is the most common fungal pathogen in humans, although other *Candida* species can also cause candidiasis. Patients with symptomatic or erythematous oral lichen planus (OLP) have commonly been associated with these. In recent times, however, there has been a notable shift in the incidence of non-*Candida albicans* (NCA) species which is gaining prominence due to significant differences in their susceptibility to antifungal drugs. Studies showed that *C. glabrata* and *C. tropicalis* were the most common NCA species isolated in OLP. Treatment failure is common among NCA species in OLP due to its intrinsic resistant or low susceptibility to commonly used antifungal agents. This article reviews the role of *Candida* species in etiology, pathogenesis, clinical features, diagnosis, and management of OLP.

**Keywords:** Oral cancer, Plaque, Potentially malignant disease

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**Introduction**

*Candida* is a yeast-like fungus that exists in three forms, namely, pseudo-hyphae, yeast, and chlamydospore. They are found in the gastrointestinal tract, vagina, and oral cavity.¹ The predominant species of *Candida* isolated from its oral cavity is *Candida albicans* (CA). Apart from CA, there are other non-*Candida albicans* (NCA) such as *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. glabrata*, and *C. dubliniensis* that are frequently found in oral cavity. Oral lichen planus (OLP) is shown to be associated with both types of species.² OLP is a T-cell-mediated chronic mucocutaneous disease affecting 2.2% of the world’s population. OLP presents in a bilaterally symmetrical manner in the oral cavity.³ *Candida* isolates alone or together with other factors may exaggerate the development and advancement of OLP. The oral microenvironment may change by the development of OLP and helping in better adaptation allowing the *Candida* to grow vigorously, thus establishing an interconnected relationship between the pathogenesis and the progression of OLP. Studies have also shown that there is a varying capability of both the strains to promote dysplasia.⁴⁻⁵ NCA has low virulence factors when compared to CA isolates and are known to be more resistant to commonly used antifungal agents.⁶ This emphasizes a need for identification of the different phenotypic variants of *Candida* species and their role in OLP.

**Common Candida Species in Oral Cavity**

*Candida albicans* is the commensal in the oral cavity of normal and diseased individuals (17–75%).² The principal *Candida* isolates from normal oral flora are given in Flowchart 1.¹

**Clinical Presentation of Candida Species in OLP**

Colonization of *Candida* species in the absence of clinical signs and symptoms may not be indicative of the lesion but at same time can be associated with its progression. All *Candida* species show similar symptoms of mucositis. However, the invasiveness varies considerably among different species.⁸ This may also increase the antifungal susceptibilities among species. The role of NCA has become increasingly important, especially in high-risk patients.⁹

Flowchart 1: Principal *Candida* isolates from normal oral flora

- **Principal Candida species**
- **Among all species, approximately 90% of infections are caused by:**
  - *Candida albicans*
  - *Candida glabrata* remains the most commonly isolate but in decreasing relative to the other species.

- **Non-Candida albicans**
  - Eg: *Candida glabrata*
  - *Candida tropicalis*
  - *Candida parapsilosis*
  - *Candida krusei*

The increases incidence of *Candida glabrata* is related to its susceptibility to azole drugs.

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both inherently or acquire resistance to commonly used antifungal drugs.9

Prevalence of Candida Species in OLP and in Healthy Individuals

A single general estimate of the world prevalence of CA and NCA species in OLP is difficult to determine. But there is limited data on the actual prevalence of the various NCA species in OLP. Table 1 is a review of some studies on the prevalence of the various CA and NCA species in patients with OLP. All studies showed that the prevalence of CA was higher than NCA in OLP patients. Thus, although less virulent in nature, NCA need to be differentiated and identified to emphasize the initiation of adequate and appropriate therapeutic modalities in treating OLP cases. As there are significant differences in their susceptibility to antifungal drugs, identification of different Candida species maybe the need of the hour.

Pathogenesis

Candida species present in many parts of the body, including the oral cavity, as a normal commensal, but its growth is prevented by innate immune system of the body.20 The pathogenicity of Candida species depends upon two major factors, including the immune status of the host and virulence of the pathogen which are also responsible for the conversion of Candida spp. from normal commensal to potent pathogen. The virulence factor includes adherence to buccal epithelial cell (ABEC), hemolytic activity, biofilm formation, and production of extracellular hydrolytic enzymes (coagulase, phospholipase, and proteinase) (Table 2). In comparison to CA, NCA lacks many of the virulence factors such as ability to form hyphae and phenotypic switching. They have low capacity of adherence to buccal epithelial cell as well as vascular endothelial surfaces and secrete less proteinases. Biofilm formation in Candida spp. is implicated as an important virulence attribute, as it increases the significant resistance to antifungal therapy and also ability to resist the host defense response.9 This prompted researchers to identify and differentiate CA from NCA for better therapeutic management in cases of OLP due to considerable variations in their susceptibility to antifungal drugs.

Risk Factors

Risk factors that are responsible for increased Candida carriage in OLP are advanced age, female gender, wearing of dentures, immune suppression, iron deficiency, steroid treatment, poor oral hygiene, systemic diseases (e.g., diabetes mellitus), and tobacco usage (Table 3).24

Laboratory Identification

Identification of CA and NCA is of utmost importance owing to difference in their susceptibility to antifungal drugs. A number of laboratory techniques are used to identify Candida species in oral tissues which includes direct (Table 4) and indirect microscopic examination (conventional and molecular diagnostic techniques) (Table 5). All methods are enlisted in Flowchart 2. However, conventional techniques stay the mainstay of Candida species identification in most clinical microbiology laboratories.22,27,28

Table 1: Summary of studies

| Author                  | Total no of cases | Positive cases of Candida | No of Candida albicans | No of non-Candida albicans |
|-------------------------|-------------------|---------------------------|------------------------|---------------------------|
|                         | OLP patients      | Healthy individuals       | OLP patients           | Healthy individuals       | OLP patients | Healthy individuals |
| Lundstorm et al. 1984   | 41 OLP patients   | 18 (44%)                  | 15 (83%)               |                           | 3 C. tropicalis (02), C. glabrata and C. parapsilosis (01) |
| Krogh et al. 1987       |                   |                           |                        |                           |              |
| Hatchuel et al. 1990    | 185 OLP patients  | 33 (17.8%)                |                        |                           |              |
| Jainikittivong et al. 2007 | 30 OLP patients  | 23 (76.7%)               | 21 (91.3%)             | 12 (40%)                  | 2 (4.3%), C. tropicalis (01), C. glabrata (01) |
| Zeng et al. 2009        | 300 OLP patients  | 86 (28.67%)              | 86                     | 26 (33.3%)               | 1 C. lusitaniae |
| Mehdiipour et al. 2010  | 21 OLP cases      | 20 (33.3%)               | 20 (33.3%)             | 21 (28.5%)               | 1 C. krusei |
| Masaki et al. 2011      | 15 OLP patients   | 12 (80%)                 | 9                      | 2                        | 3 C. glabrata (01), C. fukuyamaensis (01), C. parapsilosis (01) |
| Shivanandappa et al. 2012 | 34 OLP patients  | 15 (44.11%)              |                        |                          |              |
| Artico et al. 2014      |                   |                           |                        |                          |              |
| Ebrahimi et al. 2014    | 37 OLP patients   | 18 (49%)                 | 7 (37%)                | 12 (63%)                 | 0            |
| Arora et al. 2015       | 80 OLP patients   | 26 (33%)                 | 19 (73%)               | 0                        | 7 (27%), C. parapsilosis (02), C. glabrata (03), C. krusei (01), C. dubliniensis (01) |

Percentage of Candida species—47%

Percentage of Candida species—29%
Table 2: Virulence factors associated with Candida species

| Virulence factor | Effect | Mechanism of action |
|------------------|--------|---------------------|
| Adherence to buccal epithelium. | - First step in the pathogenesis of infection.  
- Promotes retention in the mouth. | Binding of the Candida to host cells, host cell proteins, or microbial competitors prevents or at least reduces the extent of clearance by the host's defense mechanisms. |
| Biofilm formation | - Increases the ability to withstand host defenses and also confers significant resistance to antifungal therapy. | After adhesion, proliferation of these yeast cells occur followed by formation of hyphal cells, extracellular matrix accumulation and finally, dispersion of yeast cells from the biofilm complex. |
| Hemolytic activity | Survival and persistence. | Candida uses hemolysins to degrade hemoglobin and obtain elemental iron which helps pathogens to survive and persist. |
| Production of extracellular hydrolytic enzymes; | Play an important role in adherence, tissue penetration, invasion, and the destruction of host tissue. | |
| Enzyme coagulase | Enzyme coagulase binds plasma fibrinogen and activates a cascade of reactions that induce clotting of plasma. Phospholipases and proteinases are the most important hydrolytic enzymes which are produced by Candida spp. | Enzymes hydrolyze phospholipids into fatty acids and also expose receptors on host cell membrane to facilitate adherence and damage the host cell membrane. |
| (i) Phospholipases | Host cell membrane and hence facilitate invasion of tissue. | Disruption of host membrane and by degrading important structural and immunological defense proteins. |
| (ii) Proteinase | Facilitates Candida invasion and colonization of host tissue. | |

Table 3: Risk factors associated with Candida species

| Risk factors | Candida species | Mechanisms |
|--------------|----------------|------------|
| Advanced age | Extremes of age may predispose to Candida infection. | Due to immature or weakened immunity. |
| Prolong use of denture | *Candida albicans* is commonly associated with denture use followed by *Candida glabrata*, are frequently recoverable from dentures and underlying mucosal tissues. | Produces a microenvironment conducive to the growth of Candida with low oxygen, low pH and anaerobic environment. This may be due to enhanced adherence of Candida species to acrylic, reduce salivary flow under denture. |
| Drugs | Topical corticosteroid application is associated with a growing number of different species of Candida in OLP patients, whose predominant pathogen is *C. albicans*. Undoubtedly, non-*Candida albicans* strains, such as *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. glabrata*, are frequently detected during the OLP therapy. | Less virulence factors of NCA causes increase in ability to withstand host defenses response and significant resistance to antifungal therapy. |
| Habits | The rate of oral Candida carriage is higher among smokers and smokeless tobacco users as compared to non-smokers | Tobacco usage leads to an increase in thickness of epithelial keratinized layer, decrease in levels of salivary immunoglobulin A, and suppression in functions of polymorphonuclear leukocytes, thus facilitating the proliferation of Candida species. It is also hypothesized that cigarette smoke enhances adhesion, growth and biofilm formation of *C. albicans*. |
| Diabetes | Non-*C. albicans* species are frequently isolated from subjects with diabetes. | Poorly controlled DM causes increased glycogen levels and other metabolic alterations, which lower oral PH resulting in Candida colonization at a rate higher than that of commensal bacteria and infection. |
| Iron deficiency | *C. albicans* species are more frequently isolated from subjects with iron deficiency. | Due to impaired cellular immunity. |
| Other factors | Persons with increased blood group H antigen, old age, pregnancy and nutritional status of the patients. | |

Table 4: Direct microscopic examination

| Type | Methodology | Interpretation | Significance |
|------|-------------|----------------|--------------|
| Potassium hydroxide (KOH) wet mount | Smear of the representative area is taken. A drop of potassium hydroxide solution is placed on a slide and examined under microscope. | *Candida* seen as yeast cell with or without budding or pseudohyphae | Used to differentiate between yeast and bacterial growth |
| Gram stain | Smear taken from the lesional site is heat fixed on to microscope slides and then stained by the gram stain for microscopic examination. | Gram positive organisms appear dark violet whereas gram negative organisms appear pink in color. | To differentiating between yeast and hyphal forms smear is consider important tool but is less sensitive than cultural methods |
Table 5: Conventional/indirect microscopic examination

| Type                          | Methodology                                                                 | Interpretation                                                                 | Significance                                                                 |
|-------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| (A) Microbiological test      |                                                                             |                                                                                |                                                                            |
| Culture: Sabouraud’s dextrose agar (SDA) with Chloramphenicol | Swab from the representative area is inoculated on SDA plate and incubated aerobically at 37°C for 24–48 hours | Candida develops as cream, smooth, pasty convex colonies on SDA | SDA culture is the most frequently used primary isolation medium for Candida. Although permitting growth of Candida, it suppresses the growth of many species of oral bacteria due to its low pH |
| Germ tube test                |                                                                             |                                                                                |                                                                            |
| Thermo-tolerant test          |                                                                             |                                                                                |                                                                            |
| Sugar assimilation and fermentation test |                                                                             |                                                                                |                                                                            |
| (B) Serological tests         |                                                                             |                                                                                |                                                                            |
| Candidial antigen from either cell-wall mannan or cytoplasmic constituents helps for identification of species. | The detection of IgA and IgM antibodies is important to identify Candida species. | Variability in antibody production was seen in immunosuppressed individuals and hence in such case the use of an antigen detection test is recommended. |
| (C) Molecular diagnostic techniques |                                                                             |                                                                                |                                                                            |
| Genetic based identification of Candida species were done by analyzes of restriction fragment length polymorphisms (RFLPs) and electrophoretic karyotype differences using DNA–DNA hybridization or gel electrophoresis. | Results can be obtained based on final PCR product sizes, PCR product sequence variation or gel electrophoresis resolution, following cutting of PCR sequences with restriction endonucleases. | Sensitivity and specificity of this technique is 98.7–100% and 100% respectively, allowing for the discrimination of C. albicans from the phenotypically similar C. dubliniensis. |
| (D) Histopathological features (special stains) |                                                                             |                                                                                |                                                                            |
| Gomori’s methenamine silver (GMS) |                                                                             |                                                                                |                                                                            |
| Periodic acid–Schiff (PAS)     |                                                                             |                                                                                |                                                                            |
Flowchart 2: Methods for identification of Candida species

Identification of Candida species

- Direct microscopic examination
- Conventional/Indirect microscopic examination

- To provide tentative diagnosis prior to growth in culture media.
- Also it is a cost effective, rapid method and requires less expertise.

- Current gold standard for Candida species isolation and identification, which take up to several days to get results.

Table 6: Candida species resistance to antifungal agents

| Candida species          | Resistance to antifungal agents |
|-------------------------|---------------------------------|
| Candida albicans         | Ampicillin B                     |
| Candida glabrata         | Isavuconazole                    |
| Candida tropicalis       | Fluconazole                      |
| Candida krusei           | Itraconazole                     |
| Candida parapsilosis     | Fluconazole                      |

Antifungal Susceptibility Profile of Candida Species in OLP

OLP patients treated by corticosteroid therapy can have superimposed and/or secondarily infected candidiasis. Studies show that topical corticosteroid application in OLP has been associated with increase in different Candida species. Also, NCA species have been shown to be immune to commonly used antifungal agents. NCA species are more commonly found in erosive OLP cases. Studies show that in erosive OLP lesion, the yeast strongly adheres to the epithelial cells when compared to healthy subjects or transplanted patients even in absence of corticosteroid therapy. Lundstrom et al. reported both transformation of erosive lesions to the reticular form and clinical improvements in 90% of cases after antifungal treatment. Li et al. suggested that the genotypes and antifungal susceptibility test of Candida isolates in OLP was considered for the use of an antifungal agent. Studies show that among NCA species, C. tropicalis and C. glabrata were more commonly isolated from OLP patients. The incidence of C. glabrata was highest in azole resistance among Candida isolates. This may be due to decrease in intrinsic resistance to theazole class of antifungals, including the isavuconazole (newest addition to the class). Another study showed that the C. tropicalis has greater ability for biofilm formation when compared to CA due to which they show variable resistance to antifungal therapy, mainly fluconazole, as they increase its capacity to withstand host defenses. As antifungal agents especially fluconazole is resistance to variable Candida species, it has made susceptibility testing of Candida important. The testing shows significant progress. For species-specific breakpoints for each agent, broth dilution, E test, microtiter method, and disk diffusion are now available. Evaluations of susceptibility to antifungal agents are carried out for azoles, such as fluconazole, itraconazole and/or voriconazole. Hence, for initiation of adequate and appropriate therapeutic modalities in treating OLP cases, it is important to differentiate and identify Candida species (Table 6).

Treatment

To treat symptomatic OLP, various treatments modalities have been employed, but complete resolution is difficult to achieve. The first line of treatment for OLP is usually topical corticosteroids, but its prolonged use causes decrease in the immune mechanism of mucosa along with reduction in salivary flow, leading to altered microflora, thus enhancing candidal growth. Various other drugs have found to be effective in certain Candida species. For all these Candida species, nystatin is the most effective antifungal drugs. Singh and Chakraborty also found that more effective drugs against NCA species (80%) was clotrimazole, which is analogous to the study done by Ajitha et al., where they found that around 67% of NCA species were sensitive to clotrimazole. Susceptibility to antymycotic drugs was significantly different in various Candida species. Singh and Chakraborty conducted the antifungal susceptibility test which revealed that amphotericin B exhibited a higher sensitivity against CA, C. dubliniensis, respectively, and hence concluded that this drug can be a good adjuvant for CA and C. dubliniensis infections. This finding is analogous to the opposite studies done by Kaur et al. and Mondal et al. However, high degree of resistance against amphotericin B was shown by NCA and non-dubliniensis.

The current drug regimen seems to be only palliative and has also shown to have various adverse effects, including colonization of Candida species. To avoid such effects, valuable natural therapies, such as curcumin and aloe vera, have been considered for effective treatment, as they show antifungal effects that would prevent the development of Candida infection over the OLP lesions.

Conclusion

Candida species are not just present in OLP but also play a role in its progression. Prevalence of CA is high when compared to other species. However, ongoing increase within the incidence of NCA species isolate in OLP may be a rising concern. This rising trend is not going to wane, given the unwarranted use of antifungal drugs and patient susceptibility. The exact mechanisms behind the role of CA and NCA in OLP are unknown. Hence, a thorough research and understanding is needed for better therapeutic management and results.

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