Review Article

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Oral Candidiasis - Widely Prevalent, Frequently Missed

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Abstract

A Candidiasis describes a group of yeast-like fungal infections involving the skin and mucous membranes. Infection is caused by *Candida* species, typically, *Candida albicans*. The candidiasis is seen orally in people with altered oral ecology (from dental appliances, hyposalivation, or the use of immunosuppressants or antimicrobials) and/or impaired immunity (e.g., transplant recipients, persons on immunosuppressive treatments, persons with HIV/AIDS, or other cellular immune defects). With the high prevalence and opportunistic nature, it is one of the most common infections found in the oral cavity, especially in the geriatric population. Due to asymptomatic nature of the infection and clinicians negligence during the examination, it is one of the frequently missed pathology. The purpose of this study is to enumerate in detail the various types, epidemiology, and management of oral candidiasis.

Key words: Candidiasis, Cheilitis, Erythema, Immunology, Leukemia, Pemphigoid, Stomatitis, Squamous cell carcinoma

INTRODUCTION

The candidiasis is an opportunistic infection commonly affecting the oral cavity. It is often undiagnosed among elderly, particularly in denture wearers and in many cases is avoidable with proper oral hygiene care. It can also be a mark of systemic diseases, such as diabetes mellitus and is a common problem among the immunocompromised.[1] The candidiasis of the oral cavity is caused due to overgrowth or infection by a yeast-like fungi, *Candida*.[2,3] The predominant ones are *Candida albicans* (the commonest), *Candida tropicalis*, *Candida glabrata*, *Candida guilliermondii*, *Candida pseudotropicalis*, *Candida krusei*, *Candida lusitaniae*, *Candida parapsilosis,* and *Candida stellatoidea*.

C. albicans, *C. glabrata,* and *C. tropicalis* represent more than 80% of isolates from clinical infection.[4] The oral candidiasis is the most common human fungal infection especially in early and later life.[5,6] In the general population, carriage rates have been found to range from 20% to 75% without any symptoms.[5] The incidence of candidiasis in the oral cavity with predominant *C. albicans* isolation has been reported to be 45% in neonates.[7] 45-65% in childrens,[8] 30-45% of healthy adults,[9] 50-65% in cases of long-term denture wearers,[10] 65-88% in those residing in acute and long-term facilities,[11-13] 90% in patients with acute leukemia undergoing chemotherapy,[14] and 95% of patients with HIV infection.[15] *C. albicans* is a normal commensal of the oral cavity and is usually asymptomatic in healthy individuals. However, extensive overgrowth of the fungi can sometimes lead to symptoms such as altered taste sensation, local discomfort, and occasionally dysphagia.

Systemic candidiasis carries a mortality rate of 71-79%.[16] It is important for all the clinicians treating the older patients to be aware of the risk factors, diagnosis, and treatment of oral candidiasis. In a recent study, it was found that 30% of clinicians agreed that, even without examining the oral cavity, they would prescribe nystatin for oral candidiasis on the request of assistant staff.[17] Such negligence can lead to an inaccurate diagnosis, missed pathologies, and failure to address the risk factors which may lead to recurrence of candidiasis.

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CLASSIFICATION AND TYPES

There are different types of oropharyngeal candidiasis including acute pseudomembranous, acute atrophic, chronic hyperplastic, denture stomatitis, median rhomboid glossitis, and angular cheilitis.[18]

Acute Pseudomembranous Candidiasis (Thrush)

They commonly occur as adherent white plaques resembling curdled milk or cottage cheese on the surface of the labial and buccal mucosae, hard and soft palates, tongue, periodontal tissues, and oropharynx. The membrane can be scrapped off with a swab to expose the underlying erythematous mucosa (Figure 1). It is often easily diagnosed and is one of the commonest forms of oropharyngeal candidiasis accounting for almost a third.[19] The diagnosis can be confirmed microbiologically either by culturing a swab from an oral rinse or by staining a smear from the affected area. Histologically, it is characterized by extensive white pseudomembranes consisting of desquamated epithelial cells, fibrin, and fungal hyphae. Predisposing factors include debilitating diseases such as diabetes mellitus, extremes of age, HIV infections, leukemias, those under steroid therapy, antibiotics or psychotropic drugs, and terminally ill patients.

Acute Atrophic Candidiasis

Acute atrophic candidiasis also known as erythematous candidiasis is commonly associated with burning sensations in the oral cavity or the tongue. Clinical appearance of white flecks may not be the prominent feature. The tongue may appear to be bright red or even give a bald appearance. The diagnosis may be sometimes difficult and should be considered in the differential diagnosis of a sore tongue, especially in a long-term denture wearing old patient who has received antibiotic therapy or who is on inhaled steroids. A swab from the affected area usually helps in confirming the diagnosis.

Chronic Hyperplastic Candidiasis

It characteristically occurs on the buccal mucosa or lateral border of the tongue as a speckled or homogenous white lesion (Figure 2). It is usually associated with smoking, and complete resolution of the infection seems to be dependent on cessation of the habit.[20] This condition can progress to severe dysplasia or malignancy and is also referred to as Candidal leukoplakia (Figure 3). *Candida* species may not always be isolated from the lesions of oral leukoplakia, and their presence in these premalignant lesions may be suggestive of a complicating factor rather than a causative one.[21] This condition may be confused with lichen planus, pemphigus or pemphigoid, or squamous cell carcinoma.

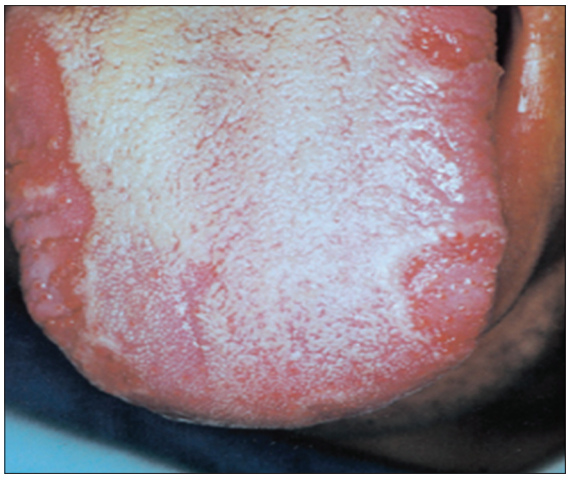

Figure 1: Pseudomembranous candidiasis involving the dorsal surface of tongue

Figure 2: Hyperplastic candidiasis involving the right lateral border of tongue

Figure 3: Candidal leukoplakia involving the left commissural region

Denture Stomatitis

This condition is characterized by a localized chronic erythema of tissues in a denture wearing area. Lesions usually occur on the palate and upper jaw but may also

affect the mandibular tissues (Figure 4). It is quite a common lesion with a high incidence rate of up to 65%.

Median Rhomboid Glossitis

It occurs as a chronic symmetrical lesion on the tongue anterior to circumvallate papillae. It is made up of atrophic filiform papillae. The presence of *Candida* is detected in more than 85% of the cases in a biopsy of this area.[22] It is often associated with smoking and the use of inhaled steroids.

Angular Cheilitis

It is an erythematous fissuring at one or both corners of the mouth, usually associated with an intraoral candidal infection. Other organisms implicated are staphylococci and streptococci. In case of staphylococci, the reservoir is commonly in the anterior region of the nostrils and spreads to the angle of mouth which has been confirmed by phage typing.[23,24] Facial wrinkling at the corners of the mouth and along the nasolabial fold, especially in older persons, leads to a chronically moist environment that predisposes to this lesion.[25] This wrinkling is even worse in long-term denture wearers, as resorption of the alveolar ridges leads to a reduction in height of the lower face when the mouth is closed.[26] Other factors implicated in the etiology of this condition are iron deficiency anemia and vitamin B12 deficiency.

Chronic Mucocutaneous Candidiasis

It describes a group of rare syndromes, which sometimes include a definable immune defect, in which persistent mucocutaneous candidiasis response is extremely poor to topical anti-fungal treatment. Recent studies have shown defect in cytokine (interleukine 2 and interferon-g) production with reduced lymphocyte function (TH1 and TH2) activity in response to candidal and few bacterial antigens.

PATHOPHYSIOLOGY

C. albicans is the predominant causal organism of most types of candidiasis. It is a relatively harmless organism inhabitating the oral cavity of almost 50% of the population. Other species including *C. krusei*, have been found in immunocompromised persons. *C. glabrata* is an emerging cause of oropharyngeal candidiasis in patients receiving radiation for head and neck cancer.[27] In patients with HIV infection, new species, such as *Candida dubliniensis* and *Candida inconspicua*, have been recognized.

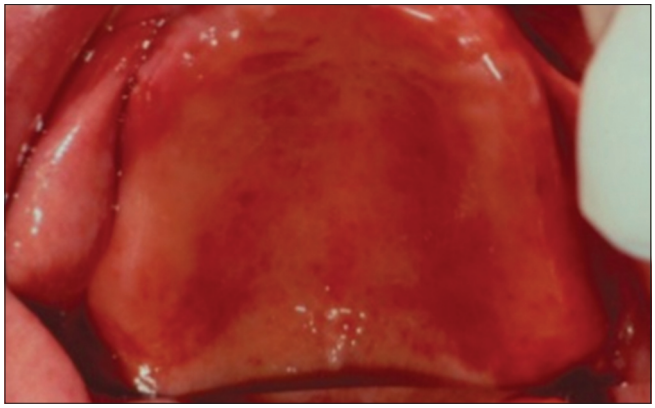

Figure 4: Denture stomatitis

EPIDEMIOLOGY

Frequency

The candidiasis is common in groups at risk, such as patients who are immunocompromised. Incidence of infection is rising, primarily because of HIV infection and both increase in candidal species and resistance to antifungals.[28]

Sex

The candidiasis is reported to occur with equal frequency in both the sexes worldwide, except in areas where males with HIV infection outnumber females.

Age

The candidiasis predominantly occurs in the older-aged persons; however, it is primarily seen in the third and fourth decades of life in those with HIV infections.

Mortality

The candidiasis may occasionally predispose to esophageal spread that may prove to be life-threatening.[29]

HISTOPATHOLOGY

Histologically, an increase thickness of the parakeratin layer with elongated rete ridges are seen. The candidal hyphae infiltrate the parakeratin layer and rarely penetrate into the cell layers of infected epithelium. Chronic inflammatory cell infiltrate in the connective tissue with neutrophilic microabscesses in the parakeratin layer is a prominent feature (Figure 5).[30]

MANAGEMENT

Taking a history followed by a thorough examination of the oral cavity, including the hard and soft palates, the buccal mucosae are usually good starting points. In case of denture wearers, the examination should be done after they have been removed. Predisposing factors should be identified and resolved followed by an assessment of the type, severity, and chronicity of the infection.

The correct diagnosis can be reached based on the finding of characterized lesion, ruling out the other possibilities,

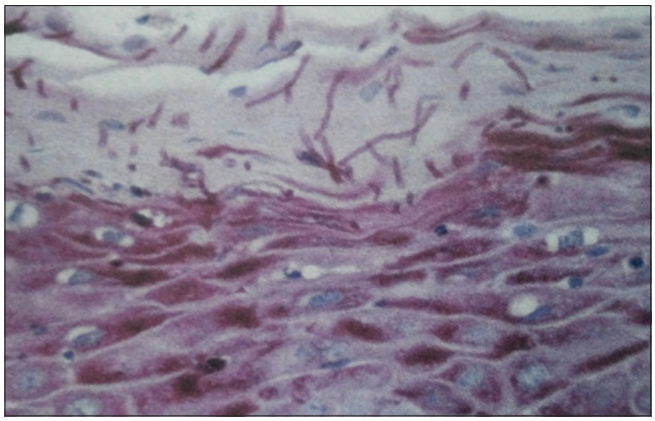

Figure 5: Histopathology showing tubular hyphae of *Candida albicans* embedded in the parakeratin layer (Periodic acid-Schiff stain)

and assessing the response to antifungal treatment. Acute pseudomembranous and chronic atrophic candidiasis can be treated based on the clinical features, however when the initial therapy is not successful, culture and sensitivity testing can be undertaken. Imprint cultures,[6] have also been used for identification of *Candida* species, where sterile foams dipped in Sabouraud's broth are placed for 30 s on the lesion, and then for an hour in Sabouraud's agar containing chloramphenicol, after which they are incubated. Acute atrophic and chronic hyperplastic types may mimic other lesions and to rule out any kind of malignancy, a biopsy is recommended in addition to the empirical therapy. The oral hygiene maintenance and topical antifungals are usually adequate for uncomplicated forms of oral candidiasis.[31]

The oral hygiene involves scaling of teeth and regular cleaning dentures. Dentures should be cleaned and disinfected daily and left out overnight or at least 6 h daily. The dentures soaked in a denture cleaning solution such as chlorhexidine has been found to be very effective in eliminating *Candida* than brushing.[32] This is because the porous and irregular surfaces of the dentures on which the *Candida* can easily adhere, cannot be removed by brushing alone. When rinsing the mouth with topical antifungal, the patient should ensure that the dentures are removed and that the entire oral mucosa is coated with antifungal and held in the mouth for a few minutes. The incorporation of an antifungal with a denture liner is recommended for patients with denture wearers. Furthermore, the mucosal surfaces should regularly be brushed using a soft brush. After disinfection, dentures should be allowed to air dry as this also kills adherent *Candida* on dentures.[33] Chlorhexidine can discolor both dentures and natural dentition if not removed adequately after disinfection. Other denture cleaning methods, like ultrasonic cleaning tanks using a suitable solution, are not routinely used but found to be effective.[34]

Topical Antifungal Therapy

Use of topical antifungal therapy is the first line treatment for uncomplicated oral candidiasis. In cases where systemic treatment is essential, topical therapy should continue, as this reduces the dose and duration of systemic treatment required.[35-37] The adverse effects and drug interactions are more likely to occur with systemic agents than with topical agents. In the early part of 20th century, gentian violet, an aniline dye was used for the treatment of candidiasis. However, because of its limitations such as staining of the oral mucosa and the developing resistance, polyene antibiotics such as nystatin (1951) and amphotericin B (1956) were introduced. They act by binding to the cell membrane sterols of the fungi, thereby altering the cell membrane permeability.[38,39] Nystatin and amphotericin are not absorbed from the gastrointestinal tract. Whereas other drugs such as miconazole, clotrimazole, or ketoconazole, used for the topical application have side effects such as vomiting and diarrhea.

Nystatin is the most widely used topical agent for the treatment of oral candidiasis.[2,3] It is available as an oral rinse, pastille, and suspension. The oral rinse contains sucrose and is found to be very useful in patients with HIV infections and also in completely edentulous patients. The clotrimazole troche can be an alternative to nystatin suspensions for those patients who find it unpalatable.

Systemic Antifungal Therapy

This therapy is appropriate in patients intolerant of or refractory to topical treatment and those at the high risk of developing systemic infections.[40]

Both nystatin oral rinses and clotrimazole troches have high levels of sucrose content and in diabetic or immunocompromised patients or in the presence of decayed teeth, triazoles such as fluconazole or itraconazole have been found to be effective.[41] The ketoconazole has also been found to be equally effective, but its use is not recommended in elderly patients, due to drug interactions and side effects which include hepatotoxicity.

The fluconazole is a potent and selective inhibitor of fungal enzymes which are involved in the synthesis of ergosterol. It disrupts cell wall formation followed by leakage of cellular contents and ultimately resulting in cell death. It is well absorbed by the gastrointestinal tract and does not produce side-effects such as hepatotoxicity. It is now listed in the dental practitioners' formulary as well as the British National Formulary and is widely used both the practices.

Itraconazole has a wider spectrum of activity than fluconazole, and is, therefore, valuable, in the treatment of candidiasis in immunocompromised patients who are resistant to fluconazole. Resistance to antifungals has

become increasingly common since the introduction of fluconazole especially in patients with advanced HIV disease and recurrent and long-term treatment.[42,43]

Topical antifungal steroid creams and ointments are recommended for the treatment of angular cheilitis. Any concurrent intraoral lesions should also be treated at the same time, dietary deficiencies should be excluded and treated if found. Failure to respond to therapy especially in chronic atrophic candidiasis is usually due to non-compliance with the treatment.

In patients undergoing treatment for cancers, oral prophylaxis with antifungal agents reduces the incidence of oral candidiasis, and in such cases, fluconazole have been found to be more effective than topical polyenes. Similar therapy has also been found to be effective in patients with HIV infections.

PROGNOSIS

The prognosis for oral candidiasis is good with appropriate and effective treatment. Relapse, when it occurs is more often due to, inability to resolve the underlying or predisposing cause of infection, poor compliance with the therapy and failure to remove and clean dentures appropriately, in case of denture wearers.

DISCUSSION

Infection with the yeast-like fungal organism *C. albicans* is termed as candidiasis or candidosis. *C. albicans* is the primary organism causing the infection, although another member of the *Candida* genus, such as *C. tropicalis*, *C. krusei*, *C. parapsilosis,* and *C. guilliermondii*, may be also found intraorally, but very rarely cause the disease. *Candida* species are a routine component of the normal oral microflora. Factors such as systemic diseases, habits such as smoking, tobacco chewing, and long-term denture use, predispose to candidal infections. Clinically, candidiasis may present as white irregular flecks to severe erythematous patches. They commonly occur in older patients, but of late, their incidence is increasing in the third and fourth decades of life. The diagnosis is usually confirmed by taking a swab culture or biopsy of the affected area if required. Management of candidiasis includes identifying and removing the predisposing factors, use of antifungal therapy, good oral hygiene maintenance, and long-term follow-up.

CONCLUSION

The candidiasis is of various types affecting different regions in and around the oral cavity. They are usually asymptomatic and rarely produce any problem to the patients, and hence, often missed during routine clinical examination. Obtaining a thorough history and identifying the underlying cause are the first step toward successful management. The treating practitioner should have a complete knowledge about the dosage, actions and side-effects of antifungal agents used for the treatment. Hence, it is important for all the clinicians, not to miss the candidal infection during routine examinations, and treat them appropriately.

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