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FUNGAL INFECTIONS OF THE ORAL CAVITY

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ABSTRACT

Fungi, both yeasts and filamentous types, can cause infection of different sites in the oral cavity like buccal mucosa, gingiva and tongue. They are also components of the normal oral microbiota. In specific settings like denture usage, immunodeficiency due to HIV infection and inhalational steroid therapy, fungi, especially yeasts can affect different sites of the oral cavity producing different types of lesions. Studying these infections is important since they might lead to complications if left untreated and usually respond quite favourably to correct and timely antifungal treatment.

Keywords: Fungi, oral cavity, lesions.

INTRODUCTION

Fungi are eukaryotic unicellular or multicellular organisms producing various infections in man⁽¹⁾. Infections of the different structures in oral cavity can be caused by bacteria, viruses and fungi^(2,3). Different practices like wearing dentures, cigarette smoking and immunosuppressive conditions like HIV infection and inhalational steroid use predispose individuals to oral infection by fungi⁽⁴⁾. These infections are produced predominantly by yeasts belonging to *Candida* spp., although yeasts belonging to other genera as well as filamentous fungi can also cause these infections⁽⁵⁾. Hence studying these infections is very important for proper understanding of pathogenesis and treatment. Studies aimed at reviewing the clinical features, pathogenesis and complications of oral infections by fungi are not many in number, notwithstanding the fact that this entity is often encountered in the clinical setting. So we attempted to summarise fungal infections of the oral cavity in a lucid and scientific manner. Scientific literature search was carried out from various indexed journals, national and

international in order to collect material for the article and summarise existing knowledge of the oral mycoses.

Normal microbial flora of the oral cavity

The oral cavity abounds in a plethora of different microorganism like bacteria and fungi that colonise or coat the different structures in the oral cavity. Bacteria like oral streptococci and *Hemophilus* spp. commonly colonise the mouth cavity of healthy subjects⁽⁶⁾. *Candida* spp. also constitute the microflora of approximately 25-40% of normal subjects⁽⁷⁾. Colonisation by *Candida* spp. increases significantly in settings like poor oral hygiene, old age, wearing dentures and inhalational steroid use^(8,9,10,11). These factors increase the risk of developing subsequent oral candidiasis.

Risk factors and how they predispose to oral fungal infections

Cigarette smoking

Smoking is a known predisposing factor for development of oral candidiasis. It has been documented in-vitro by researchers that candidal adhesion and expression of virulence factors like

aspartyl protease expression are enhanced in presence of cigarette smoking concentrate⁽¹²⁾.

Dry mouth

Dry mouth or xerostomia can be found in Sjogren's syndrome, HIV infection and intake of certain drugs. These factors lead to impaired saliva production and consequent loss of protective lactoferrin, antibodies and Histidine-rich protein, leading to increased colonisation and infection with *Candida* spp⁽¹³⁾.

Inhalational steroid and broad-spectrum antimicrobial use

It has been shown in several studies that use of inhalational steroids and broad-spectrum antibiotics alter the normal bacterial flora of the mouth cavity and results in overgrowth of *Candida* spp. by removing competition for growth⁽¹⁴⁾.

Extremes of age

In extremes of age, mounting a robust protective local immune response against yeast pathogens becomes very difficult. This results in yeast overgrowth and infection⁽¹⁴⁾.

Wearing of dentures

The acrylic in denture material along with its surface irregularities promotes adhesion and colonisation by *Candida* spp. on oral cavity⁽¹⁵⁾. Besides, dentures lead to irritation of the oral mucosal lining and loss of epithelium, due to which there is prompt colonisation with *Candida* spp.⁽¹⁶⁾.

HIV infection

Oral candidiasis is very commonly encountered in HIV infection. In fact, in this context it has been found that oral candidiasis is the commonest oral lesion in HIV infected patients. These lesions are significantly associated with a CD4 T cell count of less than 200/ μ l⁽¹⁷⁾.

Diabetes mellitus

Uncontrolled diabetes mellitus can predispose to oral candidiasis. Candidiasis is found more in diabetics due to several factors like poor glycemic control, usage of broad-spectrum antibiotics and reduced flow of saliva⁽¹⁸⁾.

Zygomycosis is also frequently encountered in this group of patients, contributing factors being hyperglycemia and ketoacidosis, the latter culminating in impaired neutrophil function⁽¹⁹⁾.

Agents causing fungal infections of the oral mucosa

- a. Other than *Candida* spp., which is the principal aetiological agent of oral candidiasis, other fungi like *Blastomyces* spp., *Histoplasma capsulatum* and *Cryptococcus neoformans* can also cause oral disease, as a part of disseminated fungal infection⁽²⁰⁾.
- b. Histoplasmosis, caused by *Histoplasma capsulatum*, a dimorphic fungus, can produce verrucous or granulomatous lesions (indurated and painful ulcer) in any area of the mouth, especially tongue, gingiva or palate, usually as a component of systemic infection, although primary affection has also been documented⁽²¹⁾.
- c. *Aspergillus* spp. have been implicated in sinusitis and further extension into the oral cavity can cause involvement of the hard palate, resulting in manifestations like loosening of teeth. Oral aspergillosis has been graded from Grade I to Grade V according to severity⁽²²⁾.
- d. Similarly mucormycosis can extend into the oral cavity from Maxilla and nasal sinuses, manifesting mainly as spreading sinusitis or facial cellulitis with palatal ulcer⁽²³⁾. *Rhizopus* spp. is the principal agent associated with this disease entity, and the jaw is almost always involved⁽²⁴⁾.
- e. Rarely fungi, previously considered as saprophytes, e.g. *Rhodotorula* spp. can cause infection of the oral mucosa, usually in the immunocompromised host (HIV infected patient)⁽²⁵⁾.

Agents causing infection of the periodontal tissue

Gingiva can be affected in oral candidiasis, risk factors being the same as enumerated before.

Histoplasma capsulatum, a dimorphic fungal pathogen, can also involve the gingiva, initially producing plaque-like lesions that usually ulcerate later. It is usually associated with disseminated infection in about 66% cases⁽²⁶⁾. There is one report of Job's syndrome (primary immunodeficiency along with eczema, recurrent skin and lung infections, elevated serum IgE, and connective tissue and skeletal abnormalities), presenting with gingival infection with *Candida albicans*⁽²⁷⁾.

Fungi and progression of dental caries

According to recent research, *Candida* spp. have got a possible role in precipitating dental caries. They can break down dietary carbohydrates to from organic acids which help in the tooth decay. Besides, *Candida* spp. have the potential of breaking down collagen of teeth by expressing the protein collagenase⁽²⁸⁾.

Clinical features

Oral candidiasis usually manifests as pseudomembranous, white patchy lesions (oral thrush) distributed over buccal mucosa in HIV infected patients. The lesions often show erythematous raw areas when the plaques are removed manually. Other types of lesions described are atrophic in old patients and those using dentures, chronic hyperplastic in HIV infected patients and angular cheilitis at angles of mouth⁽¹³⁾. There is also a strong association between oral candidiasis and Median rhomboid glossitis, a lesion characterised by central papillary atrophy, found in the midline of dorsum of tongue⁽²⁹⁾.

Oral aspergillosis often presents with granulomatous affection with late central necrosis of the hard palate, while the typical picture in oral zygomycosis is facial cellulitis with late palatal perforation. In oral zygomycosis, there may be bone destruction, oro-antral fistula and characteristic redness and hyperplasia of the gingiva, called "strawberry tongue"^(30,31).

Complications of oral mycoses

The chronic hyperplastic variant of oral candidiasis (CHC), typified by parakeratinisation of epithelium and found exclusively in HIV-infected patients, carries a risk of malignant transformation. In studies it has been observed that the risk of developing oral squamous cell carcinoma is about 60-66% when left untreated and minimal when treated early with antifungal agents⁽³²⁾. High-risk groups like patients suffering from End-stage renal disease are at risk of developing invasive fungal infections from Oral fungal infections (OFI)⁽³³⁾.

PATHOGENESIS

Candida spp. have several virulence factors like adhesins of HWP (Hyphal wall protein) family which are essentially glycoprotein in nature, besides possessing secreted aspartyl proteases (SAPs) that can damage host tissues. This pathogen can show phenotypic switching or conversion to hyphal stage from yeast stage in tissues, and can also form structured multilayered yeast communities called biofilms which make them immune from host defenses and antifungal drugs administered. This type of biofilm formation has most consistently been demonstrated over dentures made up of Polymethylacrylate⁽³⁴⁾.

On the other hand, zygomycetes like *Rhizopus* spp., causing mucromycosis, can bind to collagen of blood vessels and induce self-phagocytosis by endothelial cells. Hence the angioinvasive nature of these pathogens. They can also metabolise heme of Red Blood corpuscles (RBCs)⁽³⁵⁾.

Laboratory diagnosis of oral mycoses

- a) **Direct Microscopy:** Direct smear prepared with 10% KOH showing budding yeasts and hyphae along with leucocytes indicates oral infection by fungi. Staining with PAS (Periodic Acid Schiff) and GMS (Gomori's Methenamine Silver) can show yeasts and hyphae in smear and tissue sections. Fluorescent microscopy after staining with

optical brighteners like Calcofluor white is a faster method since the dye binds with chitin of fungal cell wall⁽³⁶⁾.

- b) **Biopsy:** Biopsy is an adjunct to microscopy in diagnosis of oral mycoses and is also useful in investigating correlation of infection with diseases like median rhomboid glossitis and oral dysplasia⁽³⁷⁾.
- c) **Culture:** *Candida* spp. can be commonly recovered by culture from oral mucosal lesions on Sabouraud's Dextrose agar⁽³⁸⁾.

TREATMENT

Treatment can be instituted with polyenes like topical Amphotericin B or Nystatin oral suspension. Among triazoles, Clotrimazole troche can also be administered⁽³⁹⁾. Only Chlorhexidine mouth wash has also been demonstrated to be very effective. However Nystatin should not be combined with Chlorhexidine gluconate since they mutually inhibit each others' actions because of the formation of a low- solubility chlorhexidine-nystatin salt⁽⁴⁰⁾.

Oral mucormycosis and aspergillosis are best treated with timely surgical debridement along with antifungal medication with Amphotericin B, either conventional (deoxycholate) or liposomal, the latter having a better safety profile^(41,42,43).

DISCUSSION

Oral affection by various fungi tend to produce diverse clinical manifestations and their resultant complications. Therefore more studies are required in this subject to elucidate the etiology and pathogenesis of different oral mycoses as well as newer options for prompt diagnosis and treatment.

CONCLUSION

Oral mycosis is a less reported and discussed entity which is often encountered in clinical and laboratory practice. Further studies are required in this regard to understand its full aetiology, pathogenesis and clinical importance so that patients suffering from oral mycoses are

benefited and clinicians are fully abreast with the intricacies of the disease.

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