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FUNGAL INFECTIONS OF THE ORAL CAVITY-A SIMPLE REVIEW

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ABSTRACT

Fungal infections are commonly encountered in practice of dentistry. In the past decades there is increase in emergence of fungal infections due to rise in the immunodeficient and immunocompromised population .However some of them are serious and even fatal. It manifests with variety of clinical presentations and it should be considered in the differential diagnosis of oral lesions, particularly in immunocompromised patients. Most commonly encountered oral fungal infection is candidiasis. Candida species are major human fungal pathogens that cause both mucosal and deep tissue infections Out of this candida albicans is highly infective because of its greater level of pathogenicity and adherence properties. Histoplasmosis, Blastomycosis, Paracoccidiodomycosis, Zygomycosis are uncommon fungal infections in the oral cavity. This review delivers clinical features, diagnosis and management of fungal infections occurring in the oral cavity.

KEYWORDS: Mycotic Infections, Candidiasis, Uncommon fungal infections, Diagnosis, Management.

INTRODUCTION

The microorganisms found in the human oral cavity have been referred to as the oral microflora, oral micro biota, or more recently as the oral micro biome. The term micro biome was coined by Joshua Lederberg "to signify the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space and have been all but ignored as determinants of health and disease".[1]

Oral cavity is an ideal niche for the growth of microorganisms. The pathogenic microbiota or microflora of the oral cavity is complex and it can fluctuate with age, diseases, conditions.[2] These are the organisms with their collective genome residing in the oral cavity which is the critical components of health and disease. Disruption of this oral microbiome has been proposed to indicate, trigger, or influence the course of oral diseases, especially among immunocompromised patients.[3]

Fungi generally constitute a relatively small proportion of the oral microflora. The 'perfect fungi' (Fungi that divide by sexual reproduction) are rarely isolated from the oral cavity but are occasionally found infecting patients with advanced acquired immunodeficiency syndrome (AIDS). The main 'perfect fungi' causing oral infection are *Aspergillus, Geotrichium and Mucor species*. The perfect yeast species seen in healthy individuals may be transient rather than resident members of the oral microflora. In contrast, the 'imperfect yeasts', e.g. *Candida species.* (Which divide by asexual reproduction) are commonly found in the mouth.

The largest proportion of the fungal microflora in the human mouth is made up of Candida species *Candida albicans* is by far the most common species, but a large number of other yeasts have been isolated, including *Candida glabrata, Candida tropicalis, Candida krusei, Candida. parapsilosis,* and *Candida Guilliermondii.*[4]

Candidiasis

Oral candidiasis, the most common fungal infection in humans. It is a significant source of morbidity, as it can cause chronic pain or discomfort upon mastication, limiting nutrition intake in the elderly or immunodeficient patients.[5] A change from the harmless commensal existence of Candida to a pathogenic state can occur following alteration of the oral cavity environment to one that favor's the growth of Candida. The causes of such changes are the so-called

predisposing factors for Candida infection and most often these relate to a weakening of host immune defences.[6]

In the past, candidiasis was considered to be only an opportunistic infection, affecting individuals who were debilitated by another disease. Certainly, such patients make up a large percentage of those with candida infections today. However, now clinicians recognize that oral candidiasis may develop in people who are otherwise healthy. As a result of this complex host and organism interaction, candida infection may range from mild, superficial mucosal involvement seen in most patients to fatal, disseminated disease in severely immunocompromised patients.[7]

The classification proposed by Samaranayake in 1991 and modified by Axell et al, in 1997 divides candidiasis into two major categories namely(Table 1): (1) primary oral candidiasis (infection exclusively confined to oral and perioral tissues), and (2) secondary oral candidiasis (oral lesions as a manifestation of systemic mucocutaneous candidiasis).[8]

Predisposing factors

Candida species are present as commensals in normal healthy people. They begin to colonize in the mucosa of gastrointestinal tract, upper respiratory tract, pharynx, larynx and mouth soon after birth. The growth of candida species affect the general condition of the patient, therefore prompt recognition is necessary and every step should be taken to prevent the disease by recognizing the risk factors.[9] There are certain factors that predisposes (Table 2) to the condition.[10]

Clinical Manifestations

Primary oral candidiasis (acute and chronic forms)

Pseudomembranous

This form of the disease is the most common in immune compromised individuals such as infants, the elderly, those on corticosteroid or long term broad spectrum antibiotic therapy, those with severe underlying conditions such as poorly controlled diabetes mellitus, leukemia, and HIV infection/AIDS. It is characterized by whitish creamy plaques resembling milk curds on the tongue, palate and buccal mucosa (Figure 1). The lesions can be wiped away leaving behind an erythematous mucosal surface which may bleed slightly. The plaques consist of necrotic material, desquamated epithelial cells, fibrin, yeast cells and hyphae, food debris, and bacteria.[10]

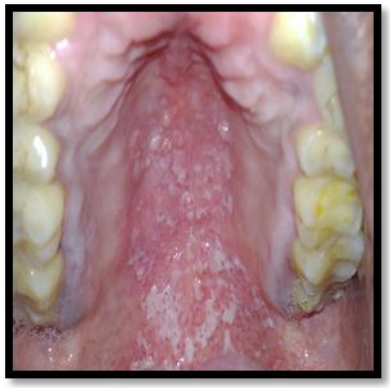

Figure 1: Pseudomembranous candidiasis.

Erythematous candidiasis

It is associated with a burning oral sensation, sore tongue or lip. Erythematous candidiasis involving the palate is quite common, particularly in HIV-positive patients. Erythematous patches may also be found on the buccal mucosa, and less commonly the mid-posterior dorsal tongue (Figure 2) which can appear bright red because of loss of the filiform papillae. Erythematous candidiasis can arise after the white pseudomembranes of thrush are shed, or may alternatively arise de novo.[11]

Clinically, central papillary atrophy appears as a well-demarcated erythematous zone that affects the midline, posterior dorsal tongue and often is asymptomatic. In addition to the dorsal of the tongue, the sites that show involvement include the junction of the hard and soft palate and the angles of mouth. The palatal lesion appears as an erythematous area when the tongue is at rest, contacts the dorsal tongue lesion, resulting in what is called a “kissing lesion” because of the intimate proximity of the involved areas of the mouth.[7]

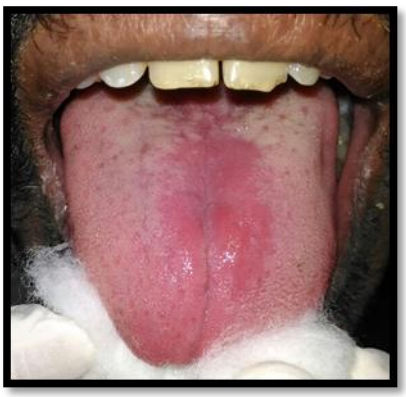

Figure 2: Erythematous candidiasis.

Hyperplastic

Chronic hyperplastic candidiasis has been referred to as candidal leukoplakia, owing to the possibility of progression to dysplasia or malignancy in some cases, if left untreated. Chronic hyperplastic candidiasis is one of the least common forms of oral candidiasis. Lesions generally occur on the buccal mucosa, and less commonly on the lateral sides of the tongue, as small or

large well circumscribed translucent-to-white homogeneous or speckled firm plaques or nodules. Unlike thrush, these plaques are resistant to removal by gentle scraping. Chronic hyperplastic candidiasis may resolve with smoking cessation.[11]

Candida-associated Lesions

Chronic atrophic candidiasis (denture stomatitis)

This occurs in areas occluded by dentures, such as the hard palate, and presents as erythema and edema between the dentures and oral mucosa.Restricted salivary flow may predispose to this distribution. Symptoms include burning or a sore mouth. Three clinical presentations have been described in chronic atrophic candidiasis. In type I, local inflammation manifests as pinpoint hyperemic macules. Type II (Figure 3) appears as diffuse erythema of part or the entirety of the denture-occluded area. Type III, or the granular type, most often involves the central hard palate or alveolar ridge forming papillary hyperplasia.[11]

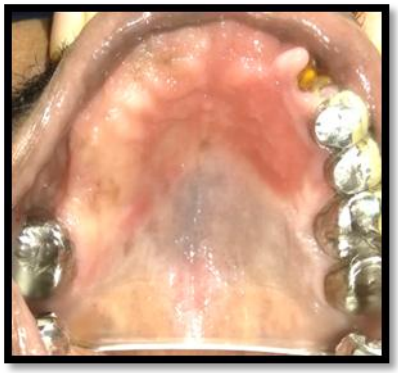

Figure 3: Type 2 denture stomatitis.

Angular chelitis

This form of candidiasis usually manifests as erythematous or ulcerated fissures, typically affecting unilaterally or bilaterally the commissures of the lip (Figure 4). Angular cheilitis often represents an opportunistic infection of fungi and/or bacteria, with multiple local and systemic predisposing factors involved in it. The factors associated include old age and denture-wearers (due to reduced vertical dimension), vitamin B12 deficiency and iron deficiency anemia.[12]

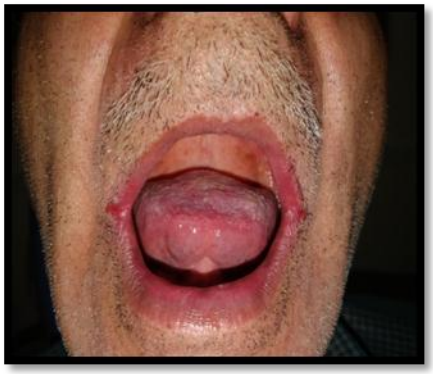

Figure 4: Angular chelitis.

Median rhomboid glossitis

Median rhomboid glossitis, also known as central papillary atrophy, was originally thought to be a developmental anomaly of the tongue. Now it is considered to be a variant of erythematous candidiasis. Clinically it presents as an erythematous, well‐demarcated, rhomboid or elliptical area of atrophy of the papillae of the dorsal tongue (Figure 5). It is usually localized to the posterior aspect of the tongue in front of the circumvallate papillae. Palatal "kissing lesion" usually results from direct inoculation that occurs when the dorsal tongue makes contact with the hard palate during deglutition. This presentation of erythematous candidiasis has been referred to as chronic multifocal candidiasis.[13]

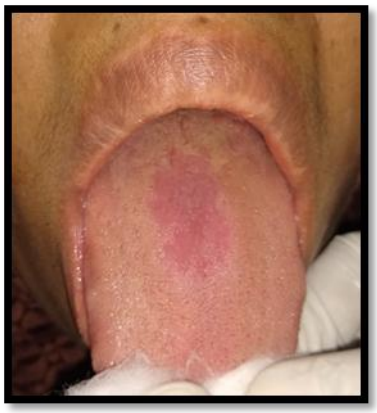

Figure 5: Median rhomboid glossitis.

Keratinized primary lesions superinfected with candida

In oral lichen planus there will be defects in epithelia cells which helps in the adherence of candidia to oral epithelium.Candida may act as secondary pathogen and this superinfection may possibly exacerbate the signs and symptoms of oral lichen planus which may be felt as burning sensation.[14] Candida is usually present in non-homogeneous leukoplakias, and it is believed that the organisms are secondary invaders.[15]

Chronic mucocutaneous candidiasis

Chronic mucocutaneous candidiasis is a heterogeneous disorder characterized by persistent or recurrent candidal infection of the skin, nails and mucosa. More than 90% of all of these patients exhibit oral candidiasis. It is often associated with a variety of endocrinopathies and immunodeficiencies.[16]

Candidiasis Associated with Systemic Diseases

Many systemic diseases have been associated with oral candidiasis. The primary cause is attributed to the decreased salivary secretion, leading to the reduced concentration of immunoglobulin in the saliva and less efficient humoral mediated host defense against *Candida albicans*.[17]

Diabetes mellitus

Candida species have been frequently isolated from the oral cavities of patients with diabetes mellitus.[18] Besides the reduced salivary flow; the high level of blood glucose also plays a significant role.[17] The presence of a high concentration of salivary glucose combined with low salivary secretion may enhance growth of yeasts and their adherence in epithelial oral cells.[18]

Iron deficiency anemia

Iron is critical for the growth and differentiation of all cells. Iron plays an important role in oxygen transport, electron transfer, and serves as a cofactor in many enzyme systems, such as peroxide-generating enzymes and nitrous oxide-generating enzymes that are critical for immune cells to function normally. Many studies have reported a highly significant reduction in the total epithelial thickness, particularly the thickness of the maturation compartment, and low enzyme levels in the buccal epithelium of iron-deficient patients. Continued iron deficiency leads to reduced Hb levels that carry insufficient oxygen to oral mucosa and finally result in mucosal atrophy. Iron deficiency, either acting locally or via systemic mechanisms, could significantly affect the pathogenesis of oral candidosis.[19]

Other Systemic diseases such as hypothyroidism, hypoparathyroidism, Addison's disease, Sjogren's syndrome have been associated with Oral candidiasis. A wide spectrum of opportunistic infections is seen in immunodeficiency disorders. Hereditary myeloperoxidase deficiency, Chediak‑Higashi syndrome, DiGeorge syndrome, human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) are some of the immunological disorders that can present with Oral candidiasis.[13]

Diagnosis

The diagnosis is often made based on clinical examination and thorough history. Additional adjunctive diagnostic methods such as direct examination of smears, swabs, biopsy, Imprint culture technique and Impression culture technique are valuable in confirming the diagnosis.[20]

Smears are taken from the infected oral mucosa, rhagades and the fitting side of the denture, preferably with wooden spatulas. Smears were fixed immediately in ether/alcohol 1:1 or with spray fix. Dry preparations may be examined by Gram stain method and periodic acid Schiff (PAS) method.[21]

Swabs are seeded on Sabouraud's agar (25ºC or room temperature), on blood agar (35ºC), on Pagano-Levin medium (35ºC) or on Littmann's substrate (25ºC). Incubation at 25ºC is done to ensure recovery of species growing badly at 35ºC. Sabouraud's dextrose agar is frequently used as a primary culture medium.[22]

The diagnosis of oral candidiasis can also be made based on a mucosal biopsy specimen. After the specimen is obtained, it is placed in 10% formalin to allow for proper fixation. The tissue is then processed, embedded in paraffin, cut into 4 to 6 mm sections, and placed on a glass microscope slide. Staining with the PAS method highlights the candidal hyphae.[20]

Imprint Culture Technique: Sterile, square (2.2 x 2.5 cm), plastic foam pads are dipped in peptone water and placed on the restricted area under study for 30 – 60 seconds. Thereafter the pad is placed directly on Pagano-Levin or Sabouraud's agar, left in situ for the first 8 hours of 48 hours incubation at 37ºC. Then, the candidal density at each site is determined by a Gallenkamp colony counter and expressed as colony forming units per mm^2 (Colony forming units mm^2). Thus it yields yeasts per unit mucosal surface. It is useful for quantitative assessment of yeast growth in different areas of the oral mucosa and is thus useful in localizing the site of infection and estimating the candidal load on a specific area.[23]

Impression culture technique is done by taking maxillary and mandibular alginate impressions, transporting them to the laboratory and casting in 6% fortified agar with incorporated Sabouraud's dextrose broth. The agar models are then incubated in a wide necked, sterile, screw-topped jar for 48-72 hours at 37ºC and the Colony forming units of yeasts estimated.[26]

Management

Management of oral candidiasis will vary, but some general rules can be applied. First local and systemic predisposing factors must be determined, and if possible treated. Improvement of oral hygiene, avoid or reduce smoking are helpful. Topical antifungals (Table 3) as nystatin oral suspension can be used, and depending on the severity systemic antifungals (Table 4) are indicated.[24,20] The mechanism of action involves an alteration of RNA and DNA metabolism or an intracellular accumulation of peroxide, which is toxic to the fungal cell.[20]

Table 1: Classification of Oral Candidiasis By Samaranayake In 1991 And Modified By Axell Et Al, In 1997.

Primary Candidiasis	Secondary Candidiasis
Acute forms Pseudomembranous Erythematous Candidiasis	**Oral manifestations of systemic mucocutaneous candidosis** Thymic aplasia Endocrinopathy syndrome
Chronic forms Hyperplastic Nodular Plaque-like Erythematous Pseudomembranous	
Candida-associated lesions Denture stomatitis Angular cheilitis Median rhomboid glossitis	
Keratinized primary lesions superinfected with Candida Leukoplakia Lichen planus Lupus erythematosus	

Table 2: Predisposing Factors To Oral Candidiasis.

Systemic factors	**Local factors**
Physiological factors	**Xerostomia**
Infancy, Old age	Sjogren's syndrome, Radiotherapy
Endocrine disorders	**Medications**
Diabetes mellitus, Hypothyroidism	Broad spectrum antibiotics, Corticosteroids
Nutritional factors	**High-carbohydrate diet**
Iron, Folate, or Vitamin B12 deficiency	**Dentures**
Blood dyscrasias and malignancies	Changes in environmental conditions, Trauma, Overnight denture wearing, Poor Denture hygiene
Acute leukemia, Agranulocytosis	**Smoking**
Immune defects, immunosuppression AIDS, Thymic aplasia	

Table 3: Topical Antifungal Agents for Oral Candidiasis.

Agents	**Form**	**Dosage**	**Comments**
Clotrimazole	Lozenge	10 mg 5 times a day for 2 week	Alters cell membrane and Antistaphylococcal activity
Miconazole	Buccal tablet	50 mg dissolved each morning for 2 week	For the treatment of oropharyngeal candidiasis
Nystatin Oral Suspension	Suspension	400,000–600,000 U swish and swallow 4-5 times a day	Fungicidal and fungistatic antibiotic obtained from Streptomyces noursei
Amphotericin B	Suspension	100–200 mg swish and swallow qid	Fungistatic and/or fungicidal
Ketoconazole	Cream	2% cream bid	May cause nausea, vomiting, rashes, and pruritus

Table 4: Systemic Antifungal Agents for Oral Candidiasis.

Agents	**Form**	**Dosage**	**Comments**
Fluconazole	Capsules	50 or 100 mg qd	Interferes with cell membrane and is eliminated via renal pathway; fungistatic activity with excellent bioavailability
Ketoconazole	Tablets	200 or 400 mg qd	Contraindicated in liver disease and pregnancy
Miconazole	Tablets	50 mg qd	Damages fungal cell wall membrane by inhibiting biosynthesis of ergosterol
Itraconazole	Capsules	100 mg qd	Contraindicated in liver disease and pregnancy

Uncommon Fungal Infections

Histoplasmosis

Oral Manifestations

Oral lesions manifests rarely. They occur in association with the disseminated form or sometimes as a localized lesion. The commonly involved sites in the oral cavity are tongue, hard and soft palate, buccal mucosa, gingiva, and lips. Oral lesions can manifest as papular, ulcerative, nodular, vegetative, furunculoid, granulomatous, or plaque-like lesions. Most common presentation being a shallow or deep infiltrated ulceration with a pseudomembrane. Gingival manifestations include ulcerative and painful granulomatous lesions. Sore throat, hoarseness of voice, and dysphagia can also manifest.[25]

Diagnosis

Isolation of *H.capsulatum* from clinical specimens remains the gold standard for the diagnosis of histoplasmosis. *H.capsulatum* can be identified in culture after specimen is inoculated on to appropriate medium and incubated sufficiently to allow for fungal growth or by staining and direct microscopy on body fluid and tissue specimens. When incubated on appropriate medium at 25 to 30°C, growth of the mycelial phase occurs most commonly within 2 to 3 weeks but may take up to 8 weeks.[26]

Management

Amphotericin B, at a dose of 2 gms Intravenous for 10 weeks, is used in the management of histoplasmosis, in HIV patients. Studies have shown that in immunocompetent patients without AIDS, Amphotercin B is effective by 68-92%, Itraconozole by 100%, and Ketaconozole by 56-70%, whereas, in patients with AIDS, Amphotercin B is effective by 74-88% and Itraconozole by 85%.[25]

Blastomycosis

Oral Manifestations

Caused by the dimorphic fungus known as *blastomyces dermatitidis*. Oral lesions of blastomycosis may result from either extrapulmonary dissemination or local inoculation with the organism.These lesions may have an irregular, erythematous or white intact surface, or they may appear as ulcerations with irregular rolled borders on the tongue and varying degrees of pain.[8]

Diagnosis

The presence of characteristic yeast cells allows a rapid diagnosis. Direct examination is less sensitive than culture; a negative result does not exclude the possibility of blastomycosis. A wet preparation is the simplest method for direct examination. The test most commonly used to confirm an identification of *blastomyces dermatitidis* is the commercially available chemiluminescent DNA probe.[27]

Management

Ketoconazole, Itraconazole, Fluconazole, Voriconazole, and Posaconazole are the azole antifungal drugs that are available for the treatment of blastomycosis. Ketoconazole was the first azole that was proven to be effective for the treatment of mild to moderate blastomycosis in immunocompetent patients. Fluconazole at a dose of 800 mg per day is an alternative for immunocompetent patients with mild to moderate blastomycosis who cannot absorb or tolerate Itraconazole or to avoid drug-drug interactions.[27]

Paracoccidioidomycosis

Oral manifestations

Caused by *paracoccidioides brasiliensis*.[8] Chronic painful oral ulceration often involves the gingiva or palate that have a mulberry-like (framboesiform) appearance with pinpoint hemorrhages and cervical lymph node enlargement.[28]

Diagnosis

Direct microscopic examination of the paracoccidiodomycosis specimens is typically made with 10 % potassium hydroxide (NaOH) or 4 % sodium hydroxide (KOH). Histopathological examination is of great value for the diagnosis of Paracoccidioidomycosis.[29]

Management

Itraconazole is considered the gold standard in mild and moderate conditions, with a dosage of 200 mg/day for 6 to 18 months. Combination of sulfamethoxazole 2400 mg + trimethoprim 480 mg (Bactrim), daily, from 12 to 24 months is a viable option with excellent results. In severe cases, amphotericin B is the drug of choice, at doses of 0.75 mg/kg/day; it presents high toxicity, side effects, possible hospitalization, and renal function monitoring.[30]

Zygomycosis

Oral Manifestations

Caused by *absidia, mucor, rhizomucor, and rhizopus*.Maxillary sinus is involved, as intraoral swelling of the maxillary alveolar process the palate, or both. If untreated, palatal ulceration may evolve, with the surface of the ulcer typically appearing black and necrotic.[7]

Diagnosis

Culture of a site confirms mucormycosis infection. Direct microscopy can demonstrate hyphae which is rapid and highly suggestive of disease. Specimens can be observed after treatment with potassium hydroxide, staining with an optical brightener (calcofluor white), or with Gomori methamine-silver.[31]

Management

Treatment involves surgical debridement and systemic intravenous amphotericin B followed by posaconazol. [32]

CONCLUSION

Fungal infections of oral cavity could be not so common, but when a fungal infection is seen, identifying the underlying suspected systemic illness and investigation for the same becomes prudent. Surveillance and education of the public and health care providers are needed to determine the disease burden of fungal infections. Development of better diagnostic tests and treatment lead to early diagnosis which will help in decreased morbidity and mortality.

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