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ORAL MANIFESTATIONS OF MYCOTIC INFECTIONS-A REVIEW

Oral Pathology

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ABSTRACT

Fungal infections in humans occur as a result of defects in the immune system. The majority of opportunistic oral mucosal fungal infections are due to Candida albicans and Aspergillus fumigatus species. Mucor and Cryptococcus also have a major role in causing oral infections, whereas Geotrichum, Fusarium, Rhodotorula, Saccharomyces and Penicillium marneffei are uncommon pathogens in the oral cavity. . Oral candidiasis is generally a localized infection and rarely appears as a systemic fungal disease whereas oral non-Candidal fungal infections are usually signs of disseminated disease. Some of the non-Candidal fungi that were once considered exotic and geographically restricted are now seen worldwide. This review discusses various opportunistic fungal infections affecting the oral cavity including their morphology, clinical features and diagnostic methods.

KEYWORDS

oppurtunistic infection,mucormycosis,aspergilliosis,histoplasmosis

INTRODUCTION :

Normal oral flora is composed of different organisms which includes eubacteria, archaea, fungi, mycoplasmas and protozoa. Of the all above fungi comes under eukaryotes, [1]

Humans beings may be exposed to hundreds of fungal spores everyday but they do not produce any harmful effect on the health. This is due to the protection by many pulmonary defense mechanisms that eliminate those fungal spores.[2]

The oral fungal infections or oral mycosis are result of the opportunistic conditions. The Host resistance impairment will allow for the initiation and progression of pathogenic conditions through the local colonization in the oral mucosa. The frequency of oral mycosis has remarkably increased worldwide with increase in use of the immunosuppressive drugs and immunodeficiency viral infections [3, 4].

Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis, Paracoccidioides brasiliensis and dermatophyte fungi which can infect healthy and immunologically competent individuals.[2] By contrast, species such as Candida, Aspergillus, Rhizopus and Fusarium are normally avirulent in healthy individuals , but can cause disseminated fatal infections in patients with suppressed immunity. So,These are called as opportunistic pathogenic fungi. The fungus Cryptococcus neoformans can be considered both as a true and opportunistic pathogen as it can cause infections in immunologically competent as well as immunocompromised individuals.[2]

The occurrence of superficial infection as well as invasive opportunistic fungal infections has been increased significantly in the past two decades. This increase can be attributed to the growing number of immunocompromised patients- including those with AIDS, neoplastic disease, older age, long-standing diabetes mellitus, underwent blood and marrow transplantation, solid-organ transplantation, major surgery, receiving immunosuppressive therapy and premature infants.[6] Genetic predisposition to the invasive fungal infection are reported recently due to deficient NADPH oxidase activity, abnormal production of tumor necrosis factor- α, interleukin 10 and other cytokines.[7,8]

The majority of invasive fungal infections are still due to Aspergillus and Candida species; but infections due to mycelial fungi other than Aspergillus and non-albicans species of Candida are becoming increased now are becoming common.[10] Any fungus present in the environment can be potentially pathogenic in immunocompromised patients.[11]

Besides Candida spp. other fungi that can cause fugal disease in human beings are Aspergillus fumigatus, Cryptococcus neoformans, Histoplasma capsulatum, Blastomyces dermatitidis, Zygomycetes class, Coccidioides immitis, Paracoccidioides brasiliensis, Penicillium marneffei, Sporotrix schenckii and Geotrichum candidum .[12,13]. This review considers the main general and oral aspects of these emerging uncommon opportunistic fungal infections

Table 1: Candidal and non-Candidal **oral fungal infections and etiologies [9]**

Candidiasis	*C. albicans, C. tropicalis, C. glabrata, C. parapsilosis, C. krusei, C. kyfer, C. dubliniensis
Aspergillosis	Aspergillus fumigatus
Cryptococcosis	Cryptococcus neoformans
Histoplasmosis	Histoplasma capsulatum
Blastomycosis	Blastomyces dermatitidis
Zygomycosis Orders Mucorales and Entomophthorales	
Coccidioidomycosis	Coccidioides immitis
Paracoccidiomycosis	Paracoccidioides brasiliensis
Penicilliosis	Penicillium marneffei
Sporotrichosis	Sporothrix schenckii
Geotrichosis	Geotrichum candidum

*Candida

Candidiasis Due To Candida Species Other Than C. Albicans

Oral candidiasis is the most common human fungal infection.[17] Even though C. albicans is the most common pathogen responsible for candidiasis, other Candida species causing oral infections have been identified which includes C. glabrata, C. krusei, C. parapsilosis, C. dublieniesis, C. tropicalis, C. kefyr and C. guilliermondii.[18-21] Less commonly isolated species are C. inconspicua, C. lusitaniae, C. norvegensis and C. rugosa.[22] These species are resistant to the commonly used antifungal drugs such as azole.[23] These non-Candida albicans species lack most of the virulence factors present in

the virulent C. albicans i.e. their ability to form hyphae and phenotypic switching. They have less adherence capacity to buccal epithelial and vascular endothelial surfaces. They secrete low proteinases. Thus they a cause candidiasis of very less severity of Candidiasis.[24]

C. dublieniesis is associated with oral lesions in HIV-infected patients.. It is morphologically and genotypically closely similar to C. albicans.[25,26] C. dublieniesis is the only Candida species other than Candida albicans that creates true hyphae.They show very less susceptibility to fluconazole.[27]

C. glabrata is now emerging as an important pathogen in mucosal and blood stream infections and is most commonly isolated from the oral cavity of HIV-infected individuals.[21,24] C. glabrata-associated oropharyngeal candidiasis in HIV infection individuals and cancer patients is more severe form and very difficult to treat because of their quick development of resistance to fluconazole.[28]

C. guilliermondii infects patients undergoing surgical procedures , patient suffering from endocarditis, intravenous drug users and fungemia in immunocompromised patients.[29] They show resistance to amphotericin B.[30]

C. krusei infection occur in critically ill patients mainly in patients with severe neutropenia. It is also an uncommon pathogen causing candidemia. The increase in C. krusei infection in HIV-infected patients is due to the widespread use of fluconazole prophylaxis.[31]

C. tropicalis is the most virulent of the non-albicans Candida species. This might be due to its ability to stick to epithelial cells in vitro and secrete moderate levels of proteinases.[24] It is mostly isolated from oral cavity and skin and may cause infections in esophagus in patients with systemic diseases.[32]

Diagnosis

The diagnosis of candidiasis is always made on the basis of clinical suspicion of the typical changes in the oral mucosa and angular cheilitis. They are atmost associated with some extent of discomfort .[33] Microscopic examination of the smears which are stained with either periodic acid Schiff's method (PAS), or KOH preparation will show candidal hyphae and blastospores.[34]

Biopsy will be mainly done to rule out hyperplastic candidiasis. In hyperplastic candidiasis, histopathological examination will reveal epithelial parakeratosis with polymorphonuclear leukocytes in the superficial layers whereas in PAS-staining it will show the presence of Candidal hyphae in those areas.[9]

Aspergillosis

Aspergillosis is the second most prevalent opportunistic fungal infection worldwide[35]

Aspergillus species are generally found in humid areas, damp soil, grain, cereal, mouldy flour and organic decaying and decomposing matter.[36] Most species of Aspergillus do not grow at normal human body temperature, only the pathogenic species have the ability to do so.[12] Aspergillus fumigatus is the most common speices that affects human beings.[37]They usually do not affect immunocompetent individuals[38]

Clinical Features

Paranasal sinuses, larynx, eyes, ears and the oral cavity may be involved in primary aspergillosis[39,40]. Oral aspergillosis is typically characterized by black or yellow necrotic tissue on an ulcer base over the palate or in the posterior tongue. Aspergillosis organisms exhibit centrifugal linear growth and eventually develop into ball-shaped masses[42]. On radiographic examination, the center of these mass contains calcium and phosphate and is identified as foreign bodies.[43]

A. fumigatus is the usual agent of sinus aspergillosis, whereas A. flavus is more common in invasive lesions in immunosuppressed individuals[41]

Diagnosis

Histopathologically, invasive lesions show chronic granulomatous reactions. In hematoxylin and eosin-stained sections hyphal forms can be seen faintly in the center of an area of necrosis. Microscopic examination of aspergillosis cases shows fungal hyphae that branch at 45° angle. It is also worth to note that hyphae of mucormycosis show non-septate hyphae that branch at 90° angle [44,45].

Mucormycosis

Mucormycosis is the third most common opportunistic fungal infection after candidiasis and aspergillosis, caused by mucorales.[46]. Mucormycosis primarily affects immunocompromised, bone marrow–transplanted, hematological malignancies, or poorly controlled diabetic individuals.[47]Impaired phagocytic functions increase the hyphae levels in the blood vessels, which results in ischemia, thrombosis, and finally infarction and tissue necrosis. .Up to 40-50% of patients suffering from mucormycosis have diabetes mellitus (DM).[50,51]. In diabetic patients there is a high occurrence of mucormycosis caused by Rhizopus oryzae, because they produce the enzyme ketoreductase, which enables them to make use of the patient's ketone bodies[52]

Clinical Features

Eisenberg et al. described six clinical variants- rhinocerebral (rhinomaxillary), pulmonary, cutaneous, gastrointestinal, central nervous system and disseminated type[52] Rhinocerebral form is the most common clinical variant which has been further divided into two subtypes;(1) A highly fatal rhino-orbito-cerebral form (2) A less fatal rhino-maxillary form.Oral mucormycosis occurs usually in paranasal sinuses or nasal areas. Serious involvement of paranasal sinuses leads to palatal necrosis and/or ulceration [53,54].

Diagnosis

Clinical presentation of mucormycosis usually provides an invasive picture of perforation into bony areas. The histopathological examination of tissue shows broad, non-septate type of hyphae with the pathognomonic nature of hyphae branching at right angles. Cases with bony perforations may show the presence of fungal organisms in marrow areas during histopathological examination. Confirmation of clinical diagnosis requires microscopic examination of the biopsied tissue. The organisms are mainly seen within the walls of necrotic blood vessels.[55]

Cryptococcosis

Cryptococcosis is an invasive fungal infection that affects the lungs.The pathogen responsible for cryptococcosis is Cryptococcus neoformans ,is the most frequent type of species isolated in immunocompromised individuals, whereas Cryptococcus gattii is identified in immunocompetent individuals and healthy hosts.

Clinical presentation

C. neoformans infections usually occurs after inhalation of fungal spores from the soil and excreta of birds like pigeons, parrots and canaries. In immunocompetent individuals the infection remains subclinical within the lungs. In the immunocompromised host, the fungus produces rapid disseminated infection involving central nervous system, skin, mucous membranes and many other tissues.[57]

The face, scalp and neck are the common sites of cutaneous lesions, presenting as papules, acne form pustules, abscesses, ulcers, superficial granulomas or sinus tracts. The most common clinical presentation is meningo encephalitis[56]. Intraoral sites commonly affected are gingiva, palate and tooth socket after extraction. Violaceous nodules of granulation tissue, swellings and ulcers are the various forms of oral lesions reported[13]Oral ulcerations may have an induration which resembles carcinomatous tissue.[59]

Diagnosis

The diagnosis of cryptococcosis requires histopathological documentation of the infection.Themicroscopic examination of cryptococcosis varies in patients The definitive diagnosis of cryptococcosis is established with periodic acid Schiff (PAS), methanamine silver and mucicarmine-stained preparations. The fungal cytoplasm appears bright magenta by PAS stain and mucicarmine stains the fungal capsule.[60,61]Culture and assay of serum or cerebrospinal fluid for capsular antigen is useful.[13]

Histoplasmosis

Histoplasmosis is caused by Histoplasma capsulatum , a fungus mainly found in the Ohio and Mississippi river valleys of the United States.[63]. Histoplasmosis capsulatum is a dimorphic fungus with a yeast and mold form. The disease can affect the lungs and cause acute or chronic respiratory problems in the immunocompromised

population[62].Histoplasma capsulatum entry into the host tissue leads to subcellular localization, intracellular survival, and proliferation. Entry of the organism attracts neutrophils, macrophage, lymphocytes, and natural killer cells to the infected site.

Clinical features

The mucocutaneous form of histoplasmosis may produce ulcerative, erosive lesions on the tongue, palate, and/or buccal mucosa .The oral lesions may also appear granulomatous and may be painful, localized on the oral mucosa, tongue, palate or lips. The ulcers may often resemble carcinoma or tuberculosis because of the raised and rolled borders, usually covered by a yellow or greyish membrane.[62]

Diagnosis

Diagnosis is usually confirmed by microscopy, culture and serology. The microscopic examination of histoplasmosis is characterized by a chronic granulomatous condition, and the stroma shows multinucleated giant cells and macrophages. The serum immunodiffusion assay that detects antibodies against the H and M antigens of H. capsulatum is reported to be a reliable diagnostic method.

Pencilliocis

Penicilliosis is caused by Penicillium marneffei , and was considered a rare disease before the advent of HIV/AIDS[13]. The prevalence of infection has increased considerably in the past decade, especially in persons who are infected with HIV[64].currently it is reported to be the third most common opportunistic infection in AIDS. In HIV seropositive patients the disease usually manifests in the disseminated form[13].

Clinical features

Clinical feature of disseminated P.marneffei infection in AIDS patient are fever, anemia, weight loss , lymphadenopathy, hepatosplenomegaly, respiratory signs and skin lesions. Oral lesions usually appear as shiny papules, erosions, or as shallow ulcers covered with whitish yellow, necrotic slough .They are found on the palate, gingiva, labial mucosa, tongue and oropharynx.

Diagnosis

Diagnosis is usually confirmed by histology and culture. In the presence of lymphadenopathy fine needle aspiration has proven to be a useful diagnostic tool.

Geotrichosis

Geotrichosis is an uncommon opportunistic fungal infection caused by Glostrichum candidum , which is isolated from the skin, sputum and feces of humans[9]. It is carried in the alimentary tract of some individuals and can sometimes cause opportunistic infection.[13]

Clinical features

Geotrichosis can be present as pseudomembranes, mucosal ulcerations, edematous and erythematous gingivae. Easily scrapable creamy-white pseudomembranous plaques with an erythematous background is seen mainly on the tongue, which results in glossitis and on the cheeks. The most common symptoms are burning pain and impaired swallowing .The oral lesions of geotrichosis are similar clinically to pseudomembranous candidiasis and differentiated only by histolopathological examination and culture of the organism.[13]

Diagnosis

Microscopic examination of a culture for the identification of the pathogenic organism is essential for the confirmation of a geotrichosis diagnosis. The microscopic examination of geotrichosis is characterized by small, rectangular-shaped spores with rounded edges. Culture media available for geotrichosis includes Sabouraud dextrose agar (SDA), chloramphenicol, and CHROM agar media [64] .Demonstration of multiple septate hyphae with rectangular arthroconidia is a useful criterion for diagnosis.[64]

Paracoccidioidomycosis

Paracoccidioidomycosis is caused by Paracoccidioides brasiliensis and they are endemic to South and Central America.[65] . In most of the cases, the first main clinical manifestations are the oral lesions.[37] The oral lesions are multiple in number which usually involve the lip, gingival, buccal mucosa, palate, tongue and floor of the mouth. They are described as mulberry-like ulcerations.

Diagnosis can be made by demonstration of multiple budding daughter yeasts on the parent cells which results in “Mickey mouse ears” appearance under microscope with Gomori-Grocott methenamine silver or PAS-stained histopathological sections and culture.[12]

CONCLUSION :

Opportunistic infections are most commonly caused by fungal agents . Most of them are not pathogenic,but when they infect an immunocompromised host, can cause a wide range of diseases ranging from superficial to disseminated infections involving the vital internal organs. Dental clinicians play an important role in the diagnosis and management of oral fungal diseases. Therefore, an adequate knowledge is pivotal in recognizing the various guises of oral Candidal and non Candidal infections, which could be markers of immune deterioration.

The range of patients at risk for invasive fungal infections continues to expand beyond the normal host to encompass patients with acquired immunodeficiency syndrome; diabetes mellitus, those undergoing therapy for cancer and organ transplantation and major surgical procedures.

Awareness of the signs and symptoms of oral fungal diseases could aid in early diagnosis, proper treatment and prevention of disease dissemination thereby decreasing morbidity.

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