A Review on Clinical Manifestations, Diagnosis and Treatment of Candidiasis among Immunosuppressed Pulmonary Tuberculosis Individuals

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Abstract: Immunocompromized individuals are subject to various forms of infections including that due to opportunistic pathogens like *Candida* species (candidiasis), which exhibits variety of manifestations seen in different parts of the body of the affected individual. The review aimed to highlight on the occurrence of candidiasis among immunocompromized individuals like TB patients that show various manifestations consistent with *Candida* infections that can be diagnosed and treated using different antifungal agents. Data were retrieved from various search engines, including Google, being and Yandex among others, using relevant search terns related to the subject matter. Information regarding candidiasis as opportunistic disease among immunocopromized individuals were obtained. Additionally, more data revealing the variety of manifestations related to this disease, diagnosis and various treatment options were also obtained. The obtained data suggests that some of the clinical manifestations observed among immunosuppressed individuals are associated with secondary infections due to *Candida* species and can be diagnosed through microscopy, culture and serology among other methods and are treatable using appropriate antifungal agents.
Key words: Candidiasis, Immlsunocompromized individuals, Clinical manifestations, Diagnosis and treatment.

INTRODUCTION

Candida species are the most common cause of human opportunistic infections due to fungi seconded by *Aspergillus* species especially in immunocompromised individuals like tuberculosis (TB) patients. Among them *Candida albicans* is the most frequently isolated with 70% or more in most candidiasis cases, but now the non albican species like *Candida tropicalis* are coming up with higher percentages than they used to have, thereby reducing the *C. albicans* dominance (Netea *et al.,* 2008). The *Candida* species constitute part of the normal microbiota of the human mucosal, oral cavity, vagina, gastrointestinal tract and even the skin.

Several species, including *Candida albicans, C. dublinensis, C. glabrata, C. guilliermondii, C. Lusitaniae, C. parapsilosis* and *C. tropicalis,* can be found as part of the normal human commensal flora, especially in all sections of the gastrointestinal tract (Netea *et al.,* 2008; Moran *et al*., 2012). In normal, healthy persons, there is usually a balance between *Candida* species as normal flora and the normal defence mechanism of the body, which if altered, give way for opportunistic infections like candidiasis in the presence of any of the predisposing factors like; diabetes mellitus, malnutrition and above all immunosuppression as in the case of tuberculosis (TB) patients (Conlon and Snydman, 2000). *Candida* spp., can convert from safe commensals into pathogenic roles as a results of disturbance in the host defence systems, in the gastrointestinal tract and other parts of the body (Walker *et al*., 2009). Pulmonary tuberculosis (PTB) is a chronic lung disease caused by *Mycobacterium tuberculosis* and characterized by lung damage, fibrosis and necrosis among other conditions. Fungal infections and pulmonary TB generally occur in immunosuppressed patients (Kali *et al*., 2013).

Co-infection is the simultaneous infection of a host with more than one disease causing agent. Worldwide, the prevalence or incidences of co-infection in the life of human were unknown but it is now known to be common (Cox, 2001), in some cases even more common than single infections in human. A global common co-infection is that of tuberculosis and HIV and of recent, tuberculosis and *Candida* species (Kali *et al*., 2013). Acquired immune deficiency syndrome (AIDS) involves co-infection of end-stage HIV with opportunistic pathogens leading to polymicrobial infections in a single individual, as also the case in TB patients that are colonised and infected by *Candida* species (Chen *et al*., 2015).

Despite all efforts made globally, tuberculosis as an infectious disease remains a global threat. Because about 9.6 million people were diagnosed with new cases of tuberculosis infection and about 1.5 million deaths were recorded as a result of this disease in 2014 alone. Approximately 1.2 million (12%) of these cases were related to HIV infection. Also, a total of 1.5 million people died from TB in 2018 including 251,000 people living with HIV (Ofori *et al*., 2020). An estimate in 2018 showed that 10 million people were sick with tuberculosis (TB) worldwide, out of these 5.7 million men, 3.2 million women and 1.1 million children (Ofori *et al*., 2020). The largest number of new TB cases occurred in the South-East Asian region, with 44% of new cases, followed by the African region, with 24% of new cases and the Western Pacific with 18% (Ofori *et al*., 2016). The 30 high TB burden countries accounted for 87% of new TB cases which are mostly associated with opportunistic pathogens including *Candida* species, with eight countries accounting for about two thirds of the total cases in decreasing order: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and the South Africa (WHO, 2010).

The rate of recurrence of infections and the number of immunosuppressive disease cases are on the increase. It is of great value research be carried out into potential secondary fungal diseases which can influence the progression of tuberculosis cases that might be life threatening, as *C. albicans* have been isolated from different areas such as hospital environment, the air, on surfaces (floors and roofs) as well as in food (Kali *et al*., 2013).

The burden of active tuberculosis still continue at an alarming rate especially amongst the low and middle income countries with estimated 580,000 new cases arising as a result of multiple drug resistance TB (MDR-TB) worldwide and in 2018, 7.0 million new cases were notified (Kali *et al*., 2013)

Clinical Manifestations

Clinical manifestations of invasive candidiasis which can spread to other body parts especially in tuberculosis patients are generally non-specific (Ahmad *et al*., 2012; Monday *et al*., 2021). The few exceptions are specific lesions associated with chronic disseminated candidiasis (CDC) as well as ocular candidiasis, also chronic disseminated candidiasis is a form of invasive fungal infection affecting the spleen and liver but in some cases it affects other organs (Monday *et al*., 2021). The typical feature observed is a small, target-like abscesses in the liver or spleen called "bull's-eyes", which is detectable on computed tomography, ultrasound or magnetic resonance imaging accompanied by elevated levels of serum alkaline phosphatase (Roberto *et al.,* 2020). Ocular lesions are normally visible as progressive retinal exudates or vitreal opacities seen during ophthalmologic examination (Sakai *et al*., 2021). A condition called *Candida* chorioretinitis or endophthalmitis occur in up to 45% of cases of invasive candidiasis associated with candidemia (Sakai *et al*., 2021). Other possibly observed symptoms and signs of invasive candidiasis usually do not differ from infections of another origins (Roberto *et al.,* 2020).

Presentations in the Oral Cavity

The candidiasis is the most common fungal infection in the oral cavity and is usually caused by *Candida* species. It was previously thought that 35%–80% of population are carriers of oral *Candida* (Williams *et al*., 2020). Recent research using molecular detection methods suggests that *Candida* species are found in all humans as part of the normal oral flora (Peters *et al*., 2017). The most common species associated with healthy mouths is *Candida albicans* and it is estimated to be found in over 80% of oral fungal isolates (Sakai *et al*., 2021). Other *Candida* species the (non-*albicans Candida* species) present in the mouth are *C. dubliniensis*, *C. tropicalis, C. krusei*, *C. glabrata*, and C. *parapsilosis* among others (Aslani *et al*., 2018; Sav *et al*., 2020). Oral candidiasis may present in a variety of clinical forms. The most commonly used classification of oral candidiasis is the one proposed by Lehner in 1967 (Williams *et al*., 2020).

The Pseudomembranous Candidiasis

This form of the disease is the most common in immunocompromised individuals, those on corticosteroid or long term broad spectrum antibiotic therapy, those with severe underlying conditions such as a poorly controlled diabetes mellitus, leukemia, HIV infection/AIDS and those with tuberculosis (TB) patients. The condition is characterized by whitish and creamy plaques resembling milk curds on the tongue, the palate and buccal mucosal membranes (Figure 1) (de Almeida *et al*., 2002). This lesions can be wiped away leaving behind an erythematous mucosal surface which sometimes slightly bleeds (Aslani *et al*., 2018). This plaques consist of many things including desquamated epithelial cells, necrotic material, yeast (cells and hyphae), food debris, bacteria and fibrin (Neville *et al*., 2002).

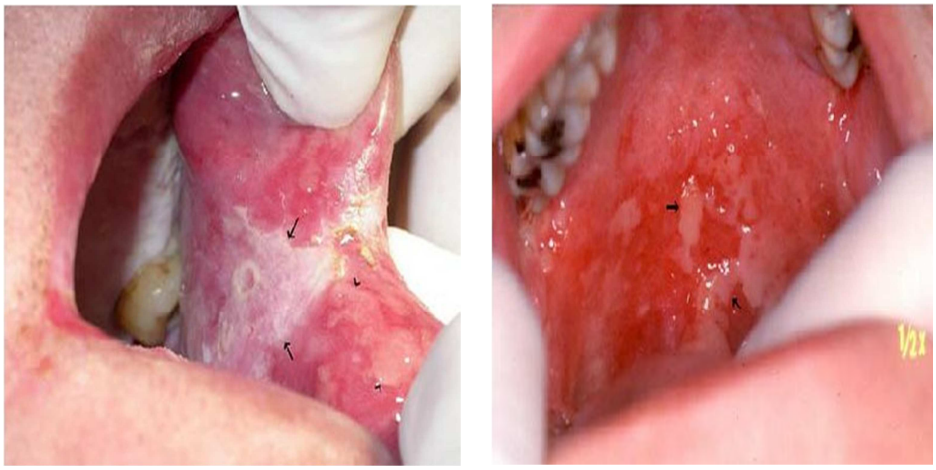

Figure 1: Pseudomembranous candidiasis
Source: Durania *et al.* (2006)

Chronic Mucocutaneous Candidiasis

Chronic mucocutaneus candidiasis (CMC) is essentially characterized by persistent or the recurrence of superficial candidiasis of the skin, nails, and mucosal membranes (Williams *et al*., 2020). Chronic mucocutaneus candidiasis (CMC) is associated with a defect in cell mediated immunity that is either limited to *Candida* antigens or be part of a more general immune abnormality (Williams *et al*., 2020). The disease is linked to a variety of primary immune-deficiencies, such as severe combined immunodeficiency syndrome and endocrinopathies especially Addison's disease and hypoparathyroidism among others (Sakai *et al*., 2021).

Superficial Candidiasis

The adhesion of *Candida* to epithelial cells, its multiplication and filamentation capacity are at the origin of inflammatory lesions called superficial candidiasis. Superficial candidiasis is believed to be the most common clinical form of *Candida* infections (Aslani *et al.*, 2018). They can occur in both healthy people and immunodeficient individuals. Depending on the affected site of the body, a distinction is made between the cutaneous candidiasis, mucosal candidiasis and the nail candidiasis (Coronado *et al.*, 2013).

Mucosal Candidiasis

Mucosal candidiasis is extremely common than the invasive forms and systemic candidiasis cases, although the invasive one receives more attention due to the accompanying mortality, more so, mucosal surfaces affected by candidiasis can be the oral mucosal membrane, the pharynx, esophagus and vaginal mucosa (René *et al.*, 2015). According to Erdogan and colleaques, *Candida* infections involving mucous membranes include esophageal, oropharyngeal, and urogenital candidiasis (Erdogan *et al.*, 2015). The Oropharyngeal candidiasis is also referred to as the oral candidiasis, oral thrush, moniliasis, muguet or sometimes *Candida*l stomatitis. Oropharyngeal candidiasis manifests as creamy or white lesions, usually on the tongue or inner cheeks (Figure 1) (René *et al.*, 2015), and sometimes it may spread to the roof of the mouth, the gums the tonsils or back of the throat (René *et al.*, 2015). *Candida albicans* is still the most commonly incriminated *Candida* specie in these diseases (Sakai *et al.*, 2021). The prevalence of oropharyngeal candidiasis remain very high in immunosuppressed patients (Samaranayake *et al.*, 2022).

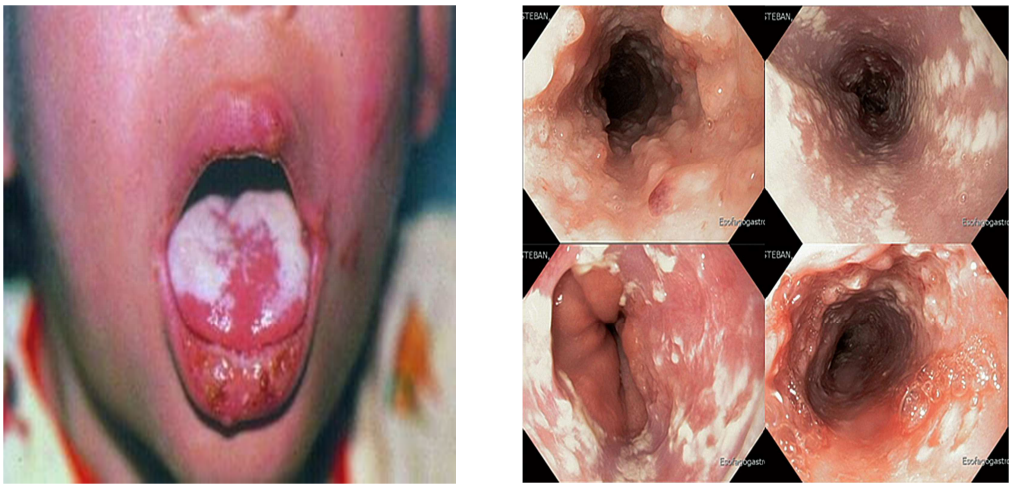

Figure 2: Oropharyngeal candidiasis
Source: René *et al.* (2015)

Diagnosis

The diagnosis of candidiasis depends on the sites affected, the recognizable symptoms, the clinical samples used and the diagnostic procedures that follows; which include direct examination, culture as well serodiagnostics procedures (Bouopda, 2020). According to the last update of the regularly revised consensus on the diagnosis of invasive fungal infections, the definition of probable invasive candidiasis is based on the assessment of host factors, clinical manifestations and mycological non-cultural evidence, however, the term possible infection in connection with invasive candidiasis is no longer defined (Donnelly *et al.*, 2020). Proven invasive candidiasis usually requires confirmation with "gold standard" methods.

Some Gold Standard Methods for the Diagnosis of Invasive Candidiasis

The "gold standard" for the diagnosis of invasive candidiasis has long been positive culture methods or alternatively, histolopathologic technique yielding positive results from normally sterile sites (Nieto *et al*., 2019). The last consensus guidelines on the diagnosis of invasive fungal infections introduced four possibilities to prove the diagnosis of invasive candidiasis. These are: 1). Histopathologic, cytopathologic or the direct microscopic detection of *Candida* pseudohyphae or the true hyphae in specimens from normally sterile sites obtained by needle aspiration or by biopsy. 2). Positive culture from a samples obtained by sterile procedure from a normally sterile site with clinical or radiological abnormality consistent with fungal infection. This includes samples from freshly placed drains (within 24 h). 3). The detection of *Candida* species by polymerase chain reaction (PCR) with subsequent DNA sequencing if yeasts are found microscopically in paraffin-embedded tissue or by culture. 4). Blood culture positive for *Candida* species (De Pauw *et al*., 2008).

Cultures of *Candida* species become positive with the concentration of 1 CFU/mL, demonstrating high efficacy in discovering viable cells of *Candida* species (Clancy *et al*., 2018). The easiest test to diagnose invasive candidiasis is the blood culture, though the efficiency or sensitivity of the procedure is low: *Candida* species are isolated from blood in only 21-71% of patients with autopsy-proven invasive candidiasis (Clancy *et al*., 2013). This method's sensitivity can be improved by increasing the volume of the blood sampled and also increasing the frequency of the blood culture technique for the isolation of the organism. These culture methods retain their significance and will continue to do so in many years ahead, due to easy possibility of isolation, identification and susceptibility determination of the infectious agents (Arendrup *et al*., 2012). The main drawback of culture methods is that, they have long turn-around time 72-96 h leading to delays in proper treatment that results in increased mortality (Taira *et al*., 2014). Another disadvantage is poor performance in neonates with candidemia and concurrent *Candida* meningitis when blood, as well as cerebrospinal fluid cultures are generally sterile (Pappas *et al*., 2016). These facts have led to the rating of positive urine cultures, similar to blood culture and the use of surrogate tests including thrombocytopenia and elevated C-reactive protein as predictors of candidemia in infants (Katragkou *et al*., 2017).

Treatment of Candidiasis

Taking care of candidiasis is based on preventive measures aimed at limiting the spread of infection and the use of appropriate antifungal agents. Historically, amphotericin B has long been used as the sole drug against fungal infections and candidiasis in particular. Over time, better knowledge of the structure and metabolism of pathogenic fungi has made it possible to develop other antifungal agents with different targets sites and the therapeutic offer has gradually diversified (Robert-Gangneux *et al*., 2010).

The Azoles Group of Antifungals

This group (azole derivatives) are the most used antifungal agents in the treatment of candidiasis. They are basically grouped into two subfamilies, imidazoles (like ketoconazole and miconazole) and triazoles (fluconazole and itraconazole) among others. They have a fungistatic action and their main target is normally the pathway of ergosterol biosynthesis. By blocking the expression of the Erg11 gene, which codes for 14α-lanosterol demethylase which is responsible for the transformation of lanosterol into ergosterol. The azoles cause accumulation of toxic methyl sterols and alteration of cell membrane of the involved Pathogens (Sanglard *et al*., 2003).

The Echinocandins

Echinocandins (like caspofungin, micafungin and anidulafungin) are synthetic derivatives of lipopeptides. They act by inhibit β-(1,3)-D-glucan synthetase, the enzyme responsible for the synthesis of β-(1,3)-Dglucan, one of the structural components that help in maintaining the integrity and the rigidity of the cell wall (Ostrosky-Zeichner). The weakening of this cell wall results in the leakage of intracellular materials thereby causesing lysis of the entire fungal cell (Stone *et al*., 2002).

The Polyenes

This group include (agents like nystatin, amphotericin B, natamycin), they are amphoteric macrocyclic lactones characterized by a lipophilic apolar part, having several conjugated double bonds and a polar part comprising of many hydroxyl groups. Their primary target is usually the ergosterol, which is the essential component of the yeast plasma membrane (Robert-Gangneux *et al*., 2010). Their ability to bind to ergosterol creates sufficient pores in the fungal cell membranes which increase its permeability leading to the escape of essential components for the life of yeast such as (K+ ions) which diffuse out of the cytosol leading to the death of the pathogen (Bellet, 2017).

CONCLUSION

It can be concluded based on the review that candidiasis is one of the opportunistic fungal infections associated with immunocompromized TB patients and are diagnosed using serology, histologic t echniques and culture methods among other methods and their treatment lies in the various groups of antifungal agents like azoles, Echinocandins and polyenes among others.

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