10 Yeast Infections in Immunocompromised Hosts

EMMANUEL ROLLIDES¹, THOMAS J. WALSH¹

CONTENTS

I. Introduction ........................................... 225
II. Candidiasis ........................................... 225
   A. Mucosal Candidiasis ............................... 225
   B. Deeply Invasive Candidiasis ....................... 226
III. Cryptococcosis ....................................... 227
IV. Infections due to Trichosporon ..................... 228
V. Infections due to Blastoschizomyces capitatus .... 229
VI. Infections due to Malassezia spp. ............... 230
VII. Infections due to Dematiaceous yeasts ......... 230
VIII. Conclusions ......................................... 230

References ............................................... 231

I. Introduction

A number of yeast fungi are pathogenic, but the two genera that contain the most important animal and human pathogens are Candida and Cryptococcus. In addition, there are a number of other yeasts that have been, more rarely, implicated in disease.

II. Candidiasis

Members of the genus Candida cause superficial infections of the skin, nails and mucosal membranes of the gastrointestinal tract and vagina. They can also invade the tissues and cause fungemia and deep-seated infection of the body.

A. Mucosal Candidiasis

Candida albicans is a normal component of the mucocutaneous flora of humans. Other Candida species, such as C. tropicalis, C. parapsilosis, C. krusei, C. glabrata and C. lusitaniae, are occasionally isolated but are more frequently recovered in immunocompromised patients and in those receiving antifungal therapy. Among the host defenses against mucosal candidiasis, endogenous bacterial flora are an important factor in suppressing proliferation of Candida spp. on mucocutaneous surfaces. Cell-mediated immunity (CMI) and mucosal immunity are closely related to inhibit proliferation and germination on mucosal surfaces (Fidel 2005). Epithelial cells of oral cavity have direct anti-Candida activity. In addition, during mucosal infection with Candida, a large number of pro-inflammatory and immunoregulatory cytokines are generated by epithelial cells. These cytokines may stimulate chemotaxis, phagocytosis and intracellular killing of infiltrating neutrophils as well as functions of CD4+ and CD8+ T-cells (Chauhan et al. 2006). Phagocytes can recognize Candida blastoconidia and hyphae by Toll-like receptors (van der Graaf et al. 2005). A potential link between lower levels of certain pro-inflammatory cytokines and susceptibility to oral C. albicans infection has been found suggesting involvement of such cytokines in protection (Dongari-Bagtzoglou and Fidel 2005). Antibody of the IgA class also may assume a role in mucosal immunity to Candida infections. Mucus and an intact epithelial cell surface appear to provide an additional line of defense to local Candida invasion of mucosal surfaces. Abrogation of these mucosal host defenses against Candida may lead to proliferation, local invasion and blood-borne dissemination.

The clinical spectrum of mucosal candidiasis includes oropharyngeal, esophageal, epiglottic and vaginal candidiasis (Pankhurst 2005; Spence 2005). Broad-spectrum antibacterial antibiotics, especially third generation cephalosporins and carbapenems (Maraki et al. 1999; Samonis et al. 2006), may lead to mucosal candidiasis by reducing the normal competing bacterial flora. Mucosal
candidiasis following the administration of antibiotics is often manifested as oral candidiasis or vaginal candidiasis. However, esophageal candidiasis and severe gastrointestinal candidiasis can develop in immunocompromised patients following the administration of broad-spectrum antibiotics.

The natural history of HIV infection has underscored the critical role of intact CMI in contributing to mucosal host defense against Candida (Ohmit et al. 2003). Mucosal candidiasis evolves as an early and frequent manifestation of HIV infection (Klein et al. 1984). As a reflection of impaired CMI, oropharyngeal candidiasis developing in an HIV-positive patient carries an ominous prognosis of developing advanced complications of acquired immune deficiency syndrome (AIDS), such as Pneumocystis jirovecii pneumonia. Vaginal candidiasis also may be a recurrent debilitating infection in HIV-positive women. As a logical extension of these mucocutaneous manifestations, development of esophageal candidiasis without other predisposing events in a previously asymptomatic HIV-positive patient has been deemed as an AIDS-defining illness (Laine 1994).

Chronic mucocutaneous candidiasis (CMC) is yet another example of the importance of systemic CMI to mucosal host defense against Candida (Kirkpatrick 2001). Chronic mucocutaneous candidiasis is a disease identified most frequently in children. Patients with this disease may have severe recurrent episodes of mucocutaneous candidiasis related to impaired CMI recognition, processing, or response to Candida antigens. Recently, altered patterns of cytokine production in response to Candida spp. with decreased production of some Th1 cytokines and increased levels of interleukin-10 were found (Lilic 2002). The underlying genetic defect remains unknown but studies are in progress addressing the putative role of dendritic cells and pattern recognition receptors in directing cytokine responses.

Systemic and inhalational corticosteroid therapy also may lead to mucosal candidiasis in patients (Buhl 2006). Studies of experimental mucosal candidiasis reveal that parenterally administered corticosteroid therapy leads to a marked increase in esophageal and gastrointestinal candidiasis in comparison to saline-treated controls. Rabbits treated with parenteral corticosteroid have profound depletion of gut-associated lymphoid tissue (GALT; Roy and Walsh 1992). Lymphoid domes and follicles in such animals are considerably reduced in size. The dome epithelial layer is markedly depleted of M cells and lymphocytes, while the follicular B cell and T cell regions are severely involuted, thus indicating the potentially profound effect of systemic corticosteroids on mucosal immunity (Walsh and Pizzo 1992).

Disruption of an intact epithelium is an important component of locally invasive candidiasis, particularly in those patients who are receiving cytotoxic chemotherapy for cancer. This disruption of mucosal integrity permits invasion of Candida into the submucosal regions of the alimentary tract, invasion of blood vessels and systemic dissemination.

Mucosal candidiasis often can be treated by topical therapy, such as with nystatin, clotrimazole, or miconazole (Odds 1992). More severe forms of mucosal candidiasis can be treated with fluconazole (Pons et al. 1993), itraconazole (Saag et al. 1999), voriconazole, amphotericin B formulations or echinocandins, caspofungin, micafungin and anidulafungin. The latter drugs are usually more potent in vitro and have a broader spectrum of activity, including activity against fluconazole-resistant Candida species and may be used in the management of refractory mucosal candidiasis (Vazquez 2003).

B. Deeply Invasive Candidiasis

Neutrophils, peripheral blood monocytes and macrophages maintain a critical role in host defense against deeply invasive Candida infections. Neutrophils and peripheral blood monocytes phagocytose Candida blastoconidia and damage the cell walls and cell membranes of blastoconidia, pseudohyphae and hyphae. Macrophages in liver and spleen clear circulating blastoconidia (Kappe et al. 1992). A number of Th1 and Th2 cytokines as well as hemopoietic growth factors modulate the effector functions of these innate immune cells in response to Candida spp. (Roilides and Walsh 2004).

Patients who are neutropenic due to cytotoxic chemotherapy or aplastic anemia have a high risk of invasive candidiasis, particularly in the setting of severe mucosal disruption (Maksymiuk et al. 1984). Additional corticosteroid-mediated suppression of phagocytosis of Candida by macrophages further increases the risk of deeply invasive candidiasis in neutropenic patients. Preterm