Emerging Fungal Pathogens

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Fungi such as \textit{Fusarium} spp., \textit{Curvularia} spp., \textit{Alternaria} spp. or \textit{Trichosporon beigelii}, had been thought to represent contamination or harmless colonization when isolated from humans. More recently, the role of these and other newly recognized fungi as serious pathogens has been clearly established. Three diverse groups of fungi are responsible for these infections: the agents of phaeohyphomycosis and hyalohyphomycosis and certain yeasts. These infections, which have been encountered in both presumably healthy and immunocompromised individuals, tend to be localized in the former, and disseminated and frequently fatal in the latter group of patients. A major concern is that these organisms are not uniformly susceptible to amphotericin B. Standardization of antifungal susceptibility testing may, therefore, be helpful in determining the antifungal drug of choice for each infection. It is also hoped that the advent of newer antifungals and biologic response modifiers will have a significant impact on the morbidity and mortality of these emerging infections.

Invasive fungal infections are occurring with increasing frequency in immunocompromised patients, particularly among those with malignancies and the acquired immunodeficiency syndrome (AIDS) (1-4). Broad spectrum antibacterial agents, adrenal corticosteroids, cytotoxic chemotherapy, organ transplantation and prolonged use of indwelling catheters have all contributed to this phenomenon. While most invasive fungal infections were previously thought to be due to \textit{Candida} spp., \textit{Aspergillus} spp., \textit{Cryptococcus neoformans}, the \textit{Zygomycetes}, \textit{Coccidioides immitis}, \textit{Histoplasma capsulatum} variety \textit{capsulatum}, and \textit{Blastomyces dermatitidis}, reports from multiple institutions are now emphasizing the importance of several newly recognized fungal pathogens (3, 5-10). This paper will review the role of some specific agents responsible for these opportunistic infections.

\textbf{Phaeohyphomycosis}

Phaeohyphomycoses are fungal infections incited by a group of darkly pigmented (dematiaceous) fungi whose etiologic agents form in tissue, either yeast-like cells that are solitary or in short chains, or hyphae that are septate, often irregularly swollen to toruloid, branched or unbranched, or any combination of the above mentioned forms (11). These fungi are dematiaceous due to the presence of melanin in their cell walls. It is not unusual that these fungi are confused in tissue with the more common \textit{Aspergillus} spp. At many institutions, the preliminary histopathologic diagnosis of infections caused by some of these dematiaceous fungi is aspergillosis. However, on staining with the Fontana-Masson technique (a melanin specific stain), the dematiaceous elements are seen and the correct diagnosis is made. The often-used Gomori methenamine silver stain stains all fungi black irrespective of their natural pigmentation and in some instances the hematoxylin and eosin and/or periodic acid Schiff stains will not allow visualization of the dematiaceous nature of fungi in tissue. Hence, the Fontana-Masson technique becomes useful. This staining method can also be particularly helpful when the fungal cultures are negative.

There are considerable differences in the clinical spectrum of infection and response to therapy among various agents of phaeohyphomycosis (3). Because of these differences and the similarity in histopathology, correct identification of the infecting organism is essential for appropriate therapy. While antifungal chemotherapy may play a role in some cases of phaeohyphomycosis, surgery is important for both diagnosis and treatment, especially when the paranasal sinuses or the central nervous system are involved (12). Phaeohyphomycosis represent a significant and increasingly prevalent group of opportunistic fungal diseases. Approximately 71 species classified in 39 genera have been documented to cause human and animal infection thus far (13). Table 1 lists all the...
currently known agents of phaeohyphomycosis in humans and animals. Four genera have been most frequently encountered in humans and are: *Curvularia*, *Bipolaris*, *Exserohilum*, and *Alternaria*.

*Curvularia* spp. are common soil inhabitants. Despite their ubiquity in the environment, human infections caused by *Curvularia* spp. have been uncommon and have recently been reviewed (14). Three species have been associated with human infection. These are: *Curvularia lunata* (20 cases), *Curvularia geniculata* (2 cases), and *Curvularia pallescens* (1 case). Only four patients had disseminated infection. Sites of involvement included paranasal sinuses (6 cases), cornea (6 cases), lower respiratory tract (5 cases), skin and subcutaneous tissues (2 cases), bone, endocardium and nasal septum (1 case each). One case of peritoneal catheter obstruction has also been reported (15). The pathogenesis of the infection is unknown, although skin inoculation has been incriminated in four instances. A case of endocarditis occurred four months after implantation of an aortic valve (16). Only two patients were systemically immunosuppressed. The patient with endocarditis was being treated with adrenal corticosteroids while a second patient was receiving chemotherapy for acute leukemia (16, 17). The latter patient had a dual infection of the nasal septum with *Curvularia* and *Alternaria*. Infection occurred during neutropenia and responded to surgical excision of the involved tissue and resolution of myelosuppression.

At the M. D. Anderson Cancer Center (MDCC) we recently cared for a patient with *Curvularia* sinusitis. The patient was a 25-year-old male with Hodgkin’s disease who was receiving high dose chemotherapy and allogeneic bone marrow transplantation. While profoundly neutropenic, he developed fever and clinical and radiologic evidence of sinusitis. Biopsy of the nasal septum revealed acute branching septate hyphae and the presumptive histopathologic diagnosis was aspergillosis. Nasal septum cultures yielded *Curvularia* and the Fontana-Masson stain showed dematiaceous fungal elements. The patient recovered uneventfully following extensive surgical debridement, amphotericin B and resolution of his myelosuppression. The majority of reported patients with localized disease had improvement or resolution of their infection. Patients with disseminated disease however tended to do poorly (14). Because of the paucity of cases, there is no established therapy for *Curvularia* infections. At present, antifungal therapy, together with surgical debridement, would represent a rational approach to therapy. The antifungal agent of choice remains to be determined. In vitro susceptibility studies suggest that amphotericin B, miconazole and ketoconazole could be used. All strains tested have shown resistance to 5-fluorocytosine (14).

The genera *Bipolaris* and *Exserohilum* are fungi that were erroneously classified as *Helminthosporium* spp. or *Drechslera* spp. They are fungi with wide geographic distribution. According to McGinnis et al. (18), it appears that only *Bipolaris australiensis*, *Bipolaris hawaiiensis*, *Bipolaris spicifera*, *Exserohilum longirostratum*, *Exserohilum mcginnisii* and *Exserohilum rostratum* are confirmed agents of phaeohyphomycosis. Infections caused by these agents share many clinical and pathological similarities with those due to *Aspergillus* spp., such as dissemination in the immunocompromised host, vascular invasion, tissue necrosis, involvement of the central nervous system and sinuses, and association with allergic bronchopulmonary disease (5). The most common form of disease caused by species of *Bipolaris* and *Exserohilum* is sinusitis occurring in otherwise healthy patients with nasal polyposis and allergic rhinitis (19, 20). The treatment of choice for this condition appears to be amphotericin B and surgical excision of infected tissues (5). The role of ketoconazole and the newly synthesized azole derivatives needs to be studied in this setting.

*Alternaria* spp. are ubiquitous fungi known to be soil saprobes and plant pathogens. Inhalation of conidia has been associated with bronchial asthma and hypersensitivity pneumonitis (21–23). Human infections caused by *Alternaria* spp. have occurred in presumably healthy and immunocompromised patients, and included cutaneous infections, keratitis, paranasal sinusitis with osteomyelitis, peritonitis in a patient undergoing peritoneal dialysis and a granulomatous pulmonary nodule (12, 24). The most common species involved in human infections is *Alternaria alternata* although infection by other species has also been reported. Therapy consists of surgical debridement and amphotericin B. In vitro and clinical resistance of *Alternaria* spp. to ketoconazole have been demonstrated (24).