Dark Fungi Emerging as Cause Of Often Lethal Infections

BY NANCY WALSH
New York Bureau

LAS VEGAS — Dematiaceous, or darkly pigmented, fungi are emerging as an important cause of disease, and certain types of infections with these pathogens are associated with high rates of mortality, even among the immunocompetent, Dr. Sanjay G. Revankar said at a meeting on fungal infections sponsored by Imedex.

This is a heterogeneous group of fungi that includes more than 60 genera and 100 species found worldwide in soil and air. Melanin, present in the cell wall, provides the coloration of these pathogens and appears to be a virulence factor, providing protection from free radicals, hydrolytic enzymes, and ultraviolet damage.

Melanin in the cell wall provides coloration of these pathogens and seems to protect against free radicals, hydrolytic enzymes, and UV damage.

One of the clinical syndromes associated with various species of dematiaceous fungi increasingly being seen is phaeohyphomycosis. Most of the species implicated are opportunists, but some may be true pathogens, said Dr. Revankar of the University of Texas Southwestern Medical Center, Dallas.

The diagnosis of phaeohyphomycosis requires expert interpretation of colony and microscopic morphology. The typical histologic findings include irregularly swollen hyphae and yeastlike forms. In contrast to many other fungi, there are no adequate serologic or antigen tests for the species that cause phaeohyphomycosis, he said.

The range of clinical syndromes composing phaeohyphomycosis includes the following:

► **Superficial infections.** These typically manifest as subcutaneous nodules appearing after minor trauma to the skin and inoculation with species of *Exophiala, Alternaria*, or *Phialophora*. Successful treatment often requires only excision, although an azole is sometimes also given.

► **Allergic disease.** Most cases of sinusitis and bronchopulmonary mycosis are caused by species of *Curvularia* or *Bipolaris*. Sinusitis is characterized by the presence of allergic mucin and elevated IgE; treatment includes surgery plus corticosteroids. Bronchopulmonary mycosis is associated with elevated IgE or eosinophilia, and treatment relies on corticosteroids. Antifungal therapy is not routinely used for these infections, Dr. Revankar said.

► **Pneumonia.** This has been seen most in immunocompromised patients, and may be characterized by hemoptysis. Among the pathogens implicated are species of *Exophiala* and *Chaetomium*. Lipid amphotericin B is the preferred treatment for these seriously ill patients, followed by an azole if the patient stabilizes, but mortality is high, he said.

► **CNS phaeohyphomycosis.** This infection shows a 3:1 male predominance and occurs worldwide. "What is really unusual is that more than half of patients seem to have no risk factors—no chemotherapy, HIV, or other immunodeficiency," Dr. Revankar said. In a series of 101 patients with CNS infection, the classic triad seen with bacterial brain abscess—fever, headache, and neurologic deficits—was present in fewer than 5% of patients (Clin. Infect. Dis. 2004;38:206-16). Overall mortality was 72%. Many species have been isolated in CNS infections, but in nearly half of cases *Cladophialophora bantiana* was implicated.

There was little evidence of efficacy for any particular antifungal regimen in these patients with CNS disease. A combination of amphotericin B, 5-fluorocytosine, and itraconazole was associated with improved survival, but only six patients in the series received this combination. Voriconazole and posaconazole have shown in vitro activity, but there is very little clinical experience with these agents for this indication, he said.

► **Disseminated phaeohyphomycosis.** "This has been seen increasingly during the past 10-15 years, probably reflecting the type of patients we are seeing, such as those who are immunocompromised from treatment for other diseases," Dr. Revankar said. Prior cardiac surgery, particularly involving bioprosthetic valve replacements, also has been identified as a risk factor.

In a series of 72 patients, fever was present in only 76%. Skin lesions were seen in 33%, sepsis in 11%, and eosinophilia in 11% (Clin. Infect. Dis. 2002;34:467-76). Blood cultures were positive, most commonly revealing *Scedosporium prolificans* in more than half of patients. Most of the cases were in Spain and Australia.

Overall mortality was 79%. In the immunocompromised it was 84%, and in the immunocompetent it was 65%. *S. prolificans* is resistant to all available agents, and no single drug or combination of drugs was associated with improved outcome in this series. In two cases, however, the combination of an azole plus terbinafine was successful. "I wouldn't recommend this routinely, but if you have no other options it might be something to consider," he said. ■

New Azole Can Prevent Invasive Fungal Infections

BY NANCY WALSH
New York Bureau

LAS VEGAS — Results of two large studies have shown that prophylaxis with oral posaconazole can prevent invasive fungal infections in bone marrow transplant recipients and patients with hematologic malignancies, Dr. Catherine J. Hardalo reported.

Invasive fungal infections have emerged as a potentially lethal complication for immunosuppressed patients, and some of the pathogens involved are resistant to standard antifungal therapy. Posaconazole is a broad-spectrum agent with activity against *Aspergillus, Fusarium, Coccidioides, Candida,* pigmented and hyaline molds, and the Zygomycetes, she said at a meeting on fungal infections sponsored by Imedex.

Previously, the drug had been used primarily as salvage therapy for patients with invasive aspergillosis, with about 40% of patients responding. "In salvage therapy you will see at best a 40% response rate with any antifungal," said Dr. Hardalo, senior director of anti-infectives clinical research, Schering-Plough Research Institute, Kenilworth, N.J.

Studies performed in the 1990s suggested the potential benefit of prophylaxis against invasive fungal infections in high-risk patients. Current prophylaxis options include fluconazole and micafungin for patients undergoing hematopoietic stem cell transplantation, and itraconazole (in Europe only) for the prevention of fungal infections during prolonged neutropenia.

Posaconazole now has been evaluated in a multicenter, double-blind study that included 600 patients who had undergone allogeneic stem cell transplantation and had graft-versus-host disease. They were randomized to receive either posaconazole 200 mg three times daily, or fluconazole 400 mg/day, for 16 weeks. The incidence of invasive fungal infections and invasive aspergillosis were 2% and 1%, respectively, in the posaconazole group vs. 8% and 6% in the fluconazole group.

A total of 76 patients in the posaconazole group died, as did 84 in the fluconazole group. This difference was not significant. However, only 4 patients on posaconazole died from fungal causes, which was significantly fewer than the 12 patients with fungal-related deaths in the fluconazole group.

In a second study, 600 patients with acute myelogenous leukemia or myelodysplastic syndrome received the same dose of posaconazole or fluconazole, 400 mg once a day, or itraconazole, 200 mg twice a day. The number of cases of invasive fungal infection and invasive aspergillosis were "virtually the same" as in the other study: 2% and 1% for posaconazole, and 8% and 7% for the other azoles, Dr. Hardalo said.

There were 49 deaths among patients receiving posaconazole and 67 among patients receiving the other azoles. Five deaths in the posaconazole group were fungal related, as were 16 in the other-azole groups. These differences were statistically significant. Moreover, for the first time, a survival benefit was seen among neutropenic patients, she said.

Because posaconazole is an oral drug, concern has been expressed about its absorption by patients with gastrointestinal dysfunction related to graft-versus-host disease. In this experience, patients with neutropenia and mucositis didn't absorb the drug as well as healthy volunteers, but tissue levels were adequate for preventing infections, Dr. Hardalo said.

"We still have a lot of questions. We still don't know what is the best treatment for aspergillosis or for zygomycosis. We don't know what is the right moment to intervene in these high-risk patients. But we do know that randomized controlled trials are needed, and this will require an ongoing effort from a large group of clinicians in order to succeed," Dr. Hardalo said.

She disclosed that she owns stock in Schering-Plough. ■

Utah's Influenza Hospitalization Data Show Ethnic Disparities

ATLANTA — Blacks, Asian Americans, and Hispanics were significantly more likely to be hospitalized for influenza during the 2004-2005 flu season in Utah, compared with non-Hispanic whites, Lisa Wyman reported in a poster presented at the International Conference on Emerging Infectious Diseases.

Overall, the hospitalization rate per 100,000 person-years was 22.2 cases among blacks, 22.6 cases among Asians/Pacific Islanders, and 19.0 cases among Hispanics, compared with 7.2 cases among non-Hispanic whites. Children younger than 5 years had the highest hospitalization rates of any age group, and these rates were significantly higher among minority children, compared with non-Hispanic whites.

Ms. Wyman and her colleagues at the Utah Department of Health reviewed all laboratory-confirmed cases of influenza reported in Utah during the 2004-2005 season. A total of 253 hospitalizations were reported, and complete race and ethnicity data were available for 209 of those cases.

The type of influenza virus was determined for 224 hospitalized cases; 136 were associated with the influenza A virus, and 88 were associated with the influenza B virus. Hispanics and Asian/Pacific Islander Americans were significantly more likely to have the influenza B virus (46% and 69%, respectively), compared with non-Hispanic whites. Hispanics aged 25 years and older were more likely to have the influenza B virus, compared with non-Hispanic whites, with an odds ratio of 6.86.

Although the study was limited by relatively small numbers, a preliminary review of data from the 2005-2006 flu season showed similar trends with regard to ethnic disparities in hospitalization rates.

—Heidi Splete