Rare Fungal Infection Emerges in Southwest

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Las Vegas — A mycologic mystery has been brewing in the desert Southwest of the United States.

During the past dozen years, there have been 16 cases of gastrointestinal infection with *Basidiobolus ranarum*, a filamentous fungus previously associated almost exclusively with skin and soft tissue infections in Africa and Southeast Asia, Dr. Jerry D. Smilack said. Fifteen of the 16 cases occurred in Arizona, and 1 occurred just across the state line in St. George, Utah.

B. ranarum is present throughout the world and was first isolated more than 100 years ago from frog and lizard intestines and other environmental sources such as decaying vegetable matter. The first human infections were reported in Indonesia during the 1950s.

The mystery is, why does this infection occur? Why in Arizona? Why in the United States? And is it only a gastrointestinal infection?

Basidiobolus infection, which usually occurs in children after inoculation secondary to trauma, is typically characterized by a gradually enlarging subcutaneous mass or nodule that ultimately may ulcerate.

There have been anecdotal reports of treatment with a saturated solution of potassium iodide, trimethoprim-sulfamethoxazole, and antifungal agents. Skin or soft tissue infection with this pathogen has not been reported in the United States, Dr. Smilack noted at a meeting on fungal infections sponsored by Imedex.

Prior to 1995, only six cases of gastrointestinal basidiobolomycosis had been reported in the literature: one in Florida, one in Nigeria, and four in Brazil. Only two of the affected patients survived.

Cases began appearing in Arizona during the late 1990s. Typical of them was a 79-year-old man seen by Dr. Smilack at the Mayo Clinic in Scottsdale, Ariz.

The patient had experienced 4-5 weeks of anorexia, left-sided abdominal pain, and diarrhea with a 35-lb weight loss, but he reported no fever, chills, nausea, or vomiting. He had been seen at another hospital, where the work-up showed narrowing of the descending colon and a possible inflammatory or neoplastic mass. Many years earlier, he had undergone sigmoid resection for diverticular disease; he was presumed to have recurrent diverticulitis and was given antibiotics but did not respond.

On physical examination, a palpable mass was discerned in the left upper quadrant, Dr. Smilack said. The patient's vital signs were normal, as were laboratory tests with the exception of a slight elevation in blood glucose; he had type II diabetes and was taking glyburide.

On plain film x-ray, gas bubbles were seen in the left upper quadrant, displacing the colon medially, and on CT, a considerable accumulation of inflammatory material was seen in the lumen of the colon as well as external to the colon.

The patient was taken for surgery, where a large inflammatory mass was found adherent to the small bowel, spleen, kidney, and lateral abdominal wall. A partial colon resection with end-to-end anastomosis was performed.

Histopathologic evaluation of the mass revealed marked inflammation and the Splendore-Hoeppli phenomenon, in which eosinophils are deposited around the fungus. "The histopathologic appearance is virtually diagnostic," Dr. Smilack said.

The main clinical features reported with gastrointestinal *Basidiobolus* infection are abdominal pain and weight loss; fever is unusual. The infection was formerly thought to be limited to the sigmoid colon, but multiple extraintestinal sites of involvement have now been reported, including the liver, stomach, and mesentery. There have been five cases of disseminated infection as well.

All the Arizona patients have been treated with surgery and itraconazole, and all have survived, Dr. Smilack said. In vitro susceptibility data suggest that ketoconazole is active against this fungus but that fluconazole and flucytosine are inactive.

The diagnosis should be suspected in a patient who has abdominal pain, possibly with a palpable mass, especially if there is radiographic evidence of bowel-wall thickening, he said. This pathogen is found in the bowel wall itself, rather than in the mucosa, so a full-thickness histopathologic examination of the bowel wall is needed. Cultures also should be done if possible. In at least two-thirds of the cases, peripheral eosinophilia also has been present, Dr. Smilack said.

Important questions about this cluster of infections remain unanswered. "The mystery is, why does this infection occur? Why in Arizona? Why in the United States? Is it only a gastrointestinal infection? What is the source—something in food or water? We assume it is something ingested, but other than that, I wish I knew," he said.

A case-control study performed by the Centers for Disease Control and Prevention sought to identify potential host and risk factors, and there was some suggestion that prior use of ranitidine was a possible risk factor (MMWR 1999;48:710-3). "I personally don't think it is a risk factor. We just don't know," he said. ■

High-Dose Aspergillosis Tx No Better Than Standard Dose

Las Vegas — High-dose liposomal amphotericin B was no more effective than standard doses for the treatment of invasive aspergillosis in a large randomized study, and was associated with significantly more adverse effects, according to Dr. Mark Bresnik.

Invasive fungal infections remain a significant cause of morbidity and mortality in seriously immunocompromised patients, such as those with hematologic malignancies. Conventional amphotericin B deoxycholate has long been used, but is limited in efficacy and has significant toxicity. Three lipid formulations of the drug now are available and they are more easily tolerated.

For one of these, liposomal amphotericin B, the standard dose in invasive fungal infections is 3 mg/kg per day. However, preclinical investigations have suggested that efficacy may increase with higher doses, and preliminary human studies found no significant increase in adverse effects with doses of 10 mg/kg per day, Dr. Bresnik said at a meeting on fungal infections sponsored by Imedex.

To test the hypothesis that higher doses of liposomal amphotericin B might improve outcomes, a prospective, double-blind study was done to compare dosages of 10 mg/kg and 3 mg/kg daily in 201 highly immunocompromised patients.

After the first 2 weeks of therapy, all patients could remain on the standard 3-mg/kg dosage for as long as the investigators deemed appropriate. The trial was conducted at 46 sites in Europe and Australia.

A total of 93% of patients in both groups had hematologic malignancies, and in two-thirds, the disease was uncontrolled. More than 70% were neutropenic at baseline. All the patients had proven or probable invasive aspergillosis, or infection with another filamentous fungus; 95% had invasive pulmonary aspergillosis.

A favorable overall response rate, which included complete plus partial responses, was seen in 50% and 46% of the standard- and high-dose groups, respectively. Survival at 12 weeks in the two groups was 72% and 59%, said Dr. Bresnik, director of medical affairs for Gilead Sciences, the manufacturer of liposomal amphotericin B (Ambisome).

These between-arm differences were not statistically significant, and were comparable with those previously reported for voriconazole, a broad-spectrum triazole agent, compared with conventional amphotericin B (N. Engl. J. Med. 2002;347:408-15).

Median duration of treatment was 15 days in the standard-dose arm and 14 days in the high-dose arm, but treatment duration for some patients in both arms extended upwards of 5 weeks, he said.

No unusual or new safety issues were noted in the study. Discontinuations due to toxicity were significantly more frequent in the high-dose group, at 32%, compared with 20% in the standard-dose group.

"So what the trial has told us is that the appropriate dose is 3 mg/kg per day, but 95% of patients in this trial had invasive pulmonary aspergillosis. What that means is that the data are not yet available to determine whether benefits could be obtained with higher doses in nonpulmonary sites of infection or with non-*Aspergillus* molds such as zygomycetes," Dr. Bresnik said. ■

Aerosolized Amphotericin B in The Works as a Fungal Prophylaxis

Las Vegas — An inhaled formulation of amphotericin B, currently in development, may fill the need for antifungal prophylaxis in immunocompromised patients, according to Michael J. Weickert, Ph.D.

Regimens that protect against bacterial, viral, and yeast infections are widely used for patients undergoing chemotherapy to prepare for bone marrow or stem cell transplantation, to prevent rejection of a solid organ transplant, to treat hematologic malignancy, or to control graft vs. host disease.

These patients—of whom about 150,000 reside in the United States and Europe—remain susceptible to infections with molds such as *Aspergillus fumigatus*, and mortality is high, reportedly between 44% and 87%.

To meet the need for antifungal prophylaxis, a dry powder aerosol formulation of amphotericin B has been developed, and a multidose clinical study is underway, said Dr. Weickert, an employee and shareholder in Nektar Therapeutics, the manufacturer.

The powder is packed into a capsule that is inserted into a small pulmonary delivery device. The drug is delivered to the lungs in a single inhalation, and because the particles have the same aerodynamic properties as fungal spores, they distribute to the same sites that the spores would if inhaled, Dr. Weickert explained at a meeting on fungal infections sponsored by Imedex.

In the regimens being tested, a loading dose is given on day 0 that would achieve a concentration of the drug in the lung that is many times higher than the minimum inhibitory concentration (MIC) required during the early, high-risk period for colonization and infection with *Aspergillus*.

The loading dose is followed by a lower maintenance dose, self-administered weekly to maintain adequate MIC long term.

Systemic levels of the drug are expected to be very low, and the hope is that the toxicities that have long prevented the use of intravenous amphotericin B prophylactically will be avoided, he said.

The drug has been tested in doses of 5 mg, 10 mg, and 25 mg. For the 25-mg dose, the peak systemic level of the drug was 20 ng/mL, which is about 2% of the level generally regarded as the threshold of toxicity for amphotericin B, Dr. Weickert said.

Adverse events, such as cough, headache, and taste distortions have been seen, but these were not serious. "In general [amphotericin B] has been very well tolerated."

The product received orphan drug designation on Dec. 15, 2005, and a phase III trial should begin next year. ■