Unexplained GI Fungal Infections Seen in Arizona

The source of the fungus remains unknown; symptoms include anorexia, diarrhea, and pain.

BY NANCY WALSH
New York Bureau

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.

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 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[32]:710-3)."I personally don't think it is a risk factor. We just don't know," he said.

It is not clear whether surgery is always needed or if molecular techniques such as polymerase chain reaction would negate the need for a tissue diagnosis or if antifungal therapy alone would suffice.

In most cases, the diagnosis has been made only after surgery, but it is conceivable that medical treatment would be adequate if the diagnosis could be made without surgery, Dr. Smilack said. ■

Crohn's Caused by Weak, Not Exaggerated Immune Response?

BY MARY ANN MOON
Contributing Writer

Crohn's disease appears to be caused by a weak immune response, not the exaggerated response of a hyperreactive immune system that has long been suspected as the cause, according to Dr. Daniel J. B. Marks, of University College London, and his associates.

The researchers conducted a series of experiments on a small number of patients and control subjects to examine the immunologic underpinnings of Crohn's disease. They concluded that the disease stems from an impaired immune response that allows bacteria in the intestinal contents to accumulate in areas of the bowel. There, some bacteria breach the mucosal barrier of the bowel wall. Their persistence within the tissue results in granuloma formation and a secondary chronic inflammation.

If their theory proves to be correct, it means that current immunosuppressive therapies for the disorder are actually exacerbating the underlying immunodeficiency even as they dampen the secondary intestinal inflammation, Dr. Marks and his associates said (Lancet 2006;367:668-78).

The investigators began by obtaining serial biopsies of the posterior rectal wall in six patients with quiescent Crohn's disease, three with ulcerative colitis, and nine control subjects with noninflammatory bowel disorders. Biopsies also were taken from other locations in the bowel in three more Crohn's patients who had undergone colectomy and in two patients with familial adenomatous polyposis. The procedures confirmed that there was no endoscopic or microscopic evidence of Crohn's lesions.

The biopsies served a second purpose, which was to induce a tiny area of trauma to the bowel wall so that local immune responses could be monitored. The control subjects showed a vigorous inflammatory response at the biopsy sites, with large increases in neutrophils and cells positive for interleukin-8. In contrast, the Crohn's patients showed 79% fewer neutrophils and 63% fewer interleukin-8–positive cells.

To determine whether this abnormal response was localized to the bowel, the researchers then induced a small area of skin trauma by abrading a 3-cm patch on the volar surface of the forearm. Crohn's patients and control subjects showed similar degrees of trauma in these skin lesions and had equivalent levels of C3a, histamine, prostaglandin E_2, and leukotriene B in response to the wounds.

However, neutrophil efflux to the cutaneous wounds was impaired in the Crohn's patients after 5 hours, and was still reduced by half at 24 hours, compared with controls. This indicates that people with Crohn's disease have a generalized constitutional abnormality in their immune response, the investigators said.

Crohn's lesions typically develop at sites within the bowel where bacterial concentrations are highest. "Our present findings suggest that reduced or delayed recruitment of neutrophils to sites at which bacteria penetrate the mucosa might lead to persistence of bacteria and other organic debris in the tissues, possibly within macrophages. Secondary secretion of proinflammatory cytokines, after the failure of initial clearance, could drive the development of chronic inflammation," they noted.

To assess whether the response to bacteria within bodily tissues was abnormal in patients with Crohn's disease, the researchers then examined the response to subcutaneous injections of heat-killed *Escherichia. coli*.

The injections yielded vigorous inflammatory responses in all subjects, including pain, erythema, and swelling. Control subjects showed a fivefold increase in blood flow around the lesions at 8 hours and a ninefold increase at 24 hours, which returned to baseline levels within 48 hours. But Crohn's patients showed abnormally low increases in blood flow even though the superficial appearance of the lesions was identical. In particular, Crohn's patients with colonic disease showed a 77% reduction in blood flow, compared with controls; those with ileal disease showed a 50% reduction.

"In 2 patients with ulcerative colitis, blood flow response was greater than that in patients with Crohn's disease and did not show the normal resolution after 48 hours, clearly distinguishing it from the hyporesponsiveness characteristic of Crohn's disease. The inflammatory response was so florid in one patient with ulcerative colitis that we terminated these studies in patients with this condition," they said.

The investigators then studied whether treatment with the vasodilator sildenafil might correct the deficient blood flow in Crohn's patients. "Oral administration of 50-mg sildenafil to 5 healthy individuals and 10 patients with Crohn's disease at 24 or 48 hours after bacterial injection resulted in marked increases in blood flow," they noted.

"We propose that the underlying impairment of acute inflammation that predisposes to Crohn's disease can be boosted by a second tier of immune enhancers," the investigators said. "It might be feasible to introduce interleukin-8 or other proinflammatory stimuli directly into acute lesions, either by direct enteral administration or through synthesis by genetically modified gut organisms, since this cytokine would penetrate the bowel wall only through damaged mucosa."

In addition, agents such as sildenafil that increase blood flow and proinflammatory drugs also might be useful in healing or preventing lesions. ■

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