Basidiobolomycosis: An Unusual Fungal Infection Mimicking Inflammatory Bowel Disease

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Basidiobolus ranarum **is a fungus belonging to the Entomophthoraceae family and is mainly associated with subcutaneous soft tissue infection. The disease is usually characterized by an insidious onset of massive induration of the subcutaneous tissue involving the limbs, trunk, or buttocks. Most cases of basidiobolomycosis have been reported from Africa, South America, and tropical Asia. Visceral involvement is extremely rare. Only 4 cases with involvement of the gastrointestinal tract, including 1 fatal case originating in the United States, have been well documented in the English-language literature. This case report describes the first successfully treated patient residing in the United States who had *B. ranarum* infection involving the gastrointestinal tract.**

Zygomycotic infections are caused by fungi belonging to the orders Mucorales and Entomophthorales.[1] The family Mucoraceae of the order Mucorales consists of *Rhizopus, Mucor, Absidia, Rhizomucor,* and *Apophysomyces,* which usually infect debilitated patients and can involve most organs in the body. The family Entomophthoraceae of the order Entomophthorales consists of *Basidiobolus ranarum* and *Conidiobolus coronatus,* which usually cause infection limited to the subcutaneous tissue in otherwise healthy individuals.[2] *B. ranarum* is a soil fungus and is commonly found in decaying plants. It may be present as a commensal in the intestinal tract of amphibians such as frogs and toads, fish, and reptiles.[3] Basidiobolomycosis infection is characterized by a slowly developing, massive induration of the subcutaneous tissue involving the limbs, trunk, or buttocks. Most cases have occurred in Africa, South America, and tropical Asia.[2,4–6] Visceral involvement is extremely rare. There has been only one case of gastrointestinal infection with *B. ranarum* reported in the United States.[7] We report the first successfully treated case of *B. ranarum* infection involving the gastrointestinal tract acquired in the United States as well as other cases described in the literature.

Case Report

A 49-year-old woman presented with complaints of abdominal and rectal pain, mucus discharge, and constipation. She had been otherwise healthy except for a history of recurrent peptic ulcer disease.

In September 1994, bloody diarrhea and lower abdominal cramping developed in the patient. Colonoscopy to a length of 45 cm showed diverticulosis in the descending colon as well as an area of "inflammation" at 30 cm unassociated with diverticulosis. Biopsy specimens showed acute inflammation consistent with an acute self-limited colitis; pseudomembranous colitis was also considered. Laboratory tests of fecal specimens were negative for pathogenic bacteria, parasites, and *Clostridium difficile* toxin. A water-soluble radiopaque radiographic examination showed no abnormalities. The patient was treated with mesalamine rectal suspension enemas.

By November 1994, the patient was having one to three bowel movements daily; however, she continued to pass blood and mucus per rectum. In addition, her lower abdominal cramping persisted.

When the patient first presented to Mayo Clinic Scottsdale in January 1995, these symptoms persisted but she had a recurrence of dyspepsia and postprandial bloating as well. Fecal leukocytes were found, but bacterial cultures and examination for parasites were nonrevealing. A pyloric channel stricture was shown by esophagogastroduodenoscopy. Esophageal biopsy specimens showed *Helicobacter pylori*–negative inflammation. Colonoscopy showed patchy erythema and edema but no ulceration from 10 to 40 cm; diverticulosis was noted proximal to this area. The rectum, transverse and ascending colon, and terminal ileum were normal. Biopsy specimens showed focal acute cryptitis, slight architectural alterations, and focally prominent eosinophils suggestive of inflammatory bowel disease with chronic active colitis. After balloon dilation of her pyloric channel stricture, the dyspeptic symptoms resolved. Because of a presumptive diagnosis of inflammatory bowel disease, the patient was treated with 2.4 g/day mesalamine, later increased to 4.8 g/day because of continuing symptoms. In spite of the addition of 40 mg/day prednisone to the treatment regimen for 3 weeks, her symptoms progressed.

By April 1995, abdominal cramping, rectal and vaginal pain, and a bloody mucus rectal discharge were still present.

Abbreviations used in this paper: GMS, Gomori methenamine silver; PAS, periodic acid–Schiff.

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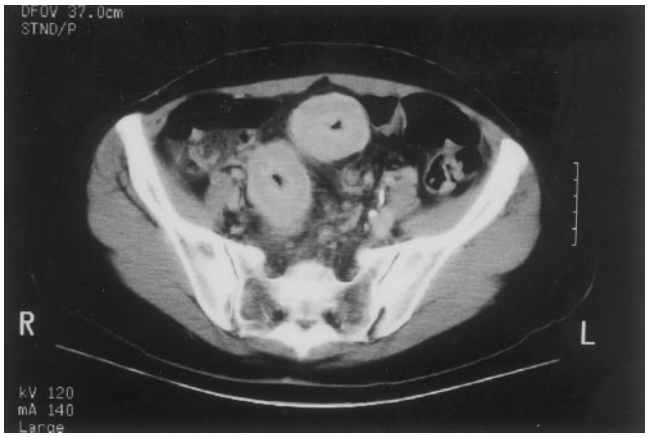

Figure 1. A contrast-enhanced computerized tomographic image of the lower abdomen shows marked thickening of the wall and critical terminal narrowing of the rectosigmoid colon.

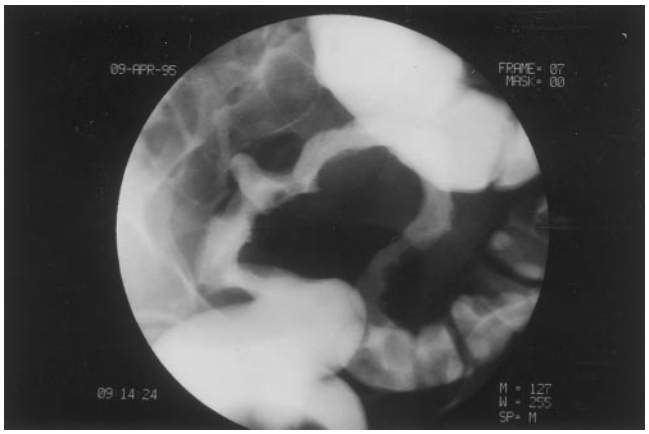

Figure 2. A spot film from a radiopaque contrast enema shows a long well-demarcated segment of rectosigmoid colon constriction.

Bowel movements were infrequent, and the patient complained of constipation. On physical examination, the patient was tearful and distressed. Pulse, blood pressure, and temperature were normal. Her abdomen was flat and soft, but the patient was very tender in the left lower quadrant where there was a vague palpable fullness. Examination of the rectum showed tenderness without a detectable mass. Laboratory studies included a white blood cell count of 23,400 cells/μL with 83% polymorphonuclear cells and 11% lymphocytes. Hemoglobin level was 12.2 g/dL. Stool studies were again negative for ova and parasites, *Salmonella, Shigella, Campylobacter,* and *C. difficile* toxin. A flexible sigmoidoscopy showed a thickened, firm, edematous sigmoid colon to 20 cm. The mucosa was friable, but there were no active ulcerations. Biopsy specimens showed mild architectural distortion and prominent eosinophils in both the mucosa and submucosa. No ulceration or granulomas were seen. Computed tomographic images showed a very thickened rectum and sigmoid colon measuring up to 5 cm in diameter to the level of the midsigmoid colon (Figure 1). A radiopaque contrast enema showed a 30-cm-long segmental stricture with fairly abrupt margins (Figure 2). The differential diagnosis included Crohn's disease, infiltrating neoplasm, or lymphoma. Because of uncertainty over the diagnosis and impending colonic obstruction, a laparotomy was performed. The thickened and inflamed sigmoid colon and upper rectum were resected, and a sigmoid colostomy and a Hartmann's pouch were created. A primary anastomosis was not performed because of poor bowel preparation, inflammation, and unknown diagnosis.

Gross pathological examination of the specimen showed diffuse mural thickening of the sigmoid colon over a distance of 40 cm without any obvious mass or mucosal ulceration. Externally, the appearance was reminiscent of Crohn's disease, but the absence of mucosal ulceration was considered distinctly unusual. Microscopic sections showed replacement of the muscularis propria by necrotizing granulomatous inflammation and a marked infiltration of eosinophils (Figure 3). The changes were primarily limited to the muscularis propria, although there was some extension into the submucosa and serosa. The necrotizing granulomas were composed of central necrotic debris, much of it derived from necrotic eosinophils, with surrounding palisading histiocytic and giant cell reaction. Within the granulomas, there were irregular rounded, oval, and cylindrical structures, the walls of which stained positively with periodic acid–Schiff (PAS) and Gomori's methenamine silver (GMS) stains. Some of these structures, measuring up to 40 μm in diameter, were surrounded by eosinophilic proteinaceous material (so-called Splendore–Hoeppli phenomenon). The histopathologic sections were reviewed by the Infectious Disease Branch of the Armed Forces Institute of Pathology (Drs. Aileen M. Marti and Ronald C. Neafie) as well as mycologists at the Centers for Disease Control and Prevention; they were considered to show changes most consistent with invasive *B. ranarum* infection. In May 1995, three specific *B. ranarum* antibodies were detected in the patient's serum by immunodiffusion.[8] Microbiological cultures of the resected surgical specimen were not performed.

Postoperatively, the patient remained afebrile. Except for nonspecific mild abdominal discomfort and lethargy, she had no complaints. Her surgical wounds healed well. Oral itraconazole, 200 mg twice daily, was prescribed. An endoscopic examination of the colon 2 months after surgery showed no abnormalities; biopsy specimens showed normal colonic mucosa without granulomas or increased numbers of eosinophils. During this period, serial serological studies showed that the number of *B. ranarum* precipitin antibodies progressively declined to two and then one. In September 1995, the colostomy was taken down and a colorectal anastomosis performed. There was no evidence of intra-abdominal disease at laparotomy. Pathologically, the tissue showed typical features of a colostomy site without eosinophilic infiltrate or granulomas. Itraconazole therapy was continued for an additional month after anastomotic surgery. There were no complications during the postoperative period. A colonoscopy with biopsy 2 months after surgery showed no abnormalities. When seen approximately 3 months after colon reanastomosis, the patient was symptom-free and appeared to have recovered fully. In May 1996, the patient was admitted to the

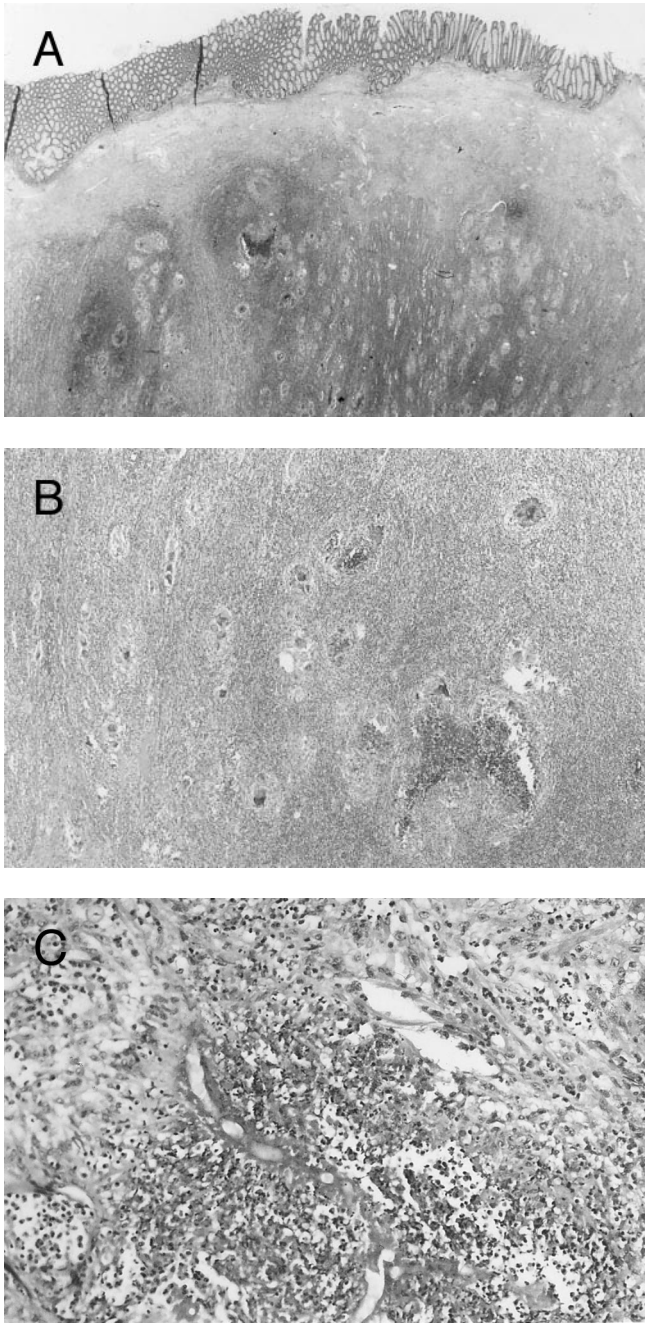

Figure 3. Photomicrographs of sections from the resected portion of the colon. (*A*) Dense inflammatory infiltrate in the submucosa and muscularis propria. (*B*) Acute and chronic inflammatory reaction with focal collections of eosinophilic hyalinization within granulomas. (*C*) Detailed view of large fungal hypha surrounded by eosinophilic Splendore–Hoeppli material and numerous eosinophils and polymorphonuclear leukocytes (H&E).

hospital with crampy abdominal pain and evidence of bowel obstruction. Surgery was performed for lysis of adhesions. No gross evidence of infection was found, and pathological specimens were negative for *B. ranarum*. No *B. ranarum* antibody was detectable in serum specimens obtained 6 and 13 months after the initial surgery.

Discussion

Zygomycotic infection of humans is most often recognized in the immunocompromised individual. Mucormycosis refers to infection caused by fungi of the order Mucorales, among which species of the genera *Rhizopus, Absidia,* and *Apophysomyces* are the most common. Infection of the oral and nasal mucosa, ascending locally into the sinuses and central nervous system, represents the prototypical form of mucormycosis, but localized pulmonary, cutaneous, and gastrointestinal disease as well as disseminated infection have been well described.[9] Conidiobolomycosis and basidiobolomycosis caused by species in Entomophthorales, the other order of Zygomycetes, are less familiar. In contrast to infection with members of the Mucorales, entomophthoromycosis has been reported mostly in immunocompetent individuals.[2]

Most entomophthoromycotic infections involve the skin and soft tissue. Conidiobolomycosis, infection caused by *Conidiobolus coronatus* and other *Conidiobolus* species, typically involves the nasal and facial skin and soft tissue, although deeply invasive disease has been described.[10] Infection with *B. ranarum,* the only recognized human pathogen in the genus *Basidiobolus,* is generally manifest as soft tissue abscesses of the buttock, trunk, or the lower extremities.[2] Most infections have been reported in children and adolescents from Africa, southern and southeast Asia, and Latin America,[2] although a report from Australia[11] indicates the occasional presence of infection elsewhere.

First isolated in 1955 from decayed leaves in the United States,[12] *B. ranarum* has since been isolated from soil and decaying vegetation from throughout the world. Animal sources from which the organism has been recovered, or in which infections have been described, include the chameleon and turtle,[2] frogs, toads, and lizards,[2,13] horses,[14] and dogs.[15]

Gastrointestinal basidiobolomycosis is extremely unusual. Only four previous cases of well-documented infection have been reported (Table 1).[7,16,17] Infection has occurred in both sexes over a wide age range (4–69 years) but has been limited to tropical countries and the southern United States. Most patients were in apparent good health before acquiring infection. Symptoms included fever, abdominal pain, diarrhea, constipation, weight loss, and, rarely, such constitutional symptoms as chills and rigors. Blood in the stools was an unusual feature. Peripheral blood eosinophilia was a feature in two of the cases described. The stomach, duodenum, and the colon were the primary sites of gastrointestinal tract involvement. The granulomatous inflammation and fibrosis that accompanied all cases were limited to the

Table. Case Reports of Gastrointestinal Entomophthoromycosis

Country of origin	Patient's age (*yr*)/sex	Underlying disease	Site of involvement	Method of diagnosis	Treatment	Outcome
Brazil[16]	13/M	None	Stomach, duodenum, transverse colon pancreas, liver, biliary system	Histology	None	Died
Brazil[16]	60/M	None	Stomach, transverse colon	Histology	Surgical resection, amphotericin (dose not stated)	Survived
Brazil[17]	4/M	None	Stomach, transverse colon	Histology, *B. ranarum* culture	Surgical resection	Died
USA[7]	69/M	Diabetes mellitus, anergy	Duodenum, terminal ileum, cecum, ascending colon	Histology, *B. ranarum* culture	Surgical resection, amphotericin (dose not stated)	Died
USA (present case)	49/F	None	Rectosigmoid colon	Histology, serology	Surgical resection, itraconazole (see text for details)	Cured

muscularis propria; the mucosa was not involved in any of the cases described. In only 1 patient did *B. ranarum* invade tissues other than the gastrointestinal tract (the pancreas, liver, and biliary tract were affected). The time from development of symptoms to a definitive diagnosis ranged from 1 to 7 months. The diagnosis required surgical exploration to obtain tissue showing the fungal hyphae and characteristic Splendore–Hoeppli phenomenon. In 2 of the patients, the fungus was isolated in cultures. Vascular invasion was not seen in any of these cases. Mortality was high; only 1 patient before the present report survived. The cause of death was not consistently reported but usually involved progressive infection, fistulae, or obstruction.

Our case was quite similar to those previously described. The source of infection in the patient was not identified. Although *B. ranarum* is a ubiquitous soil fungus, the patient had no unusual exposure to soil and denied contact with any animal species in which the organism is known to be a saprophytic colonizer. The patient was previously healthy and was not immunocompromised. As reported in previously described cases, her symptoms predominantly included abdominal pain, minimal rectal bleeding, and mucus production. Because the intestinal mucosa is generally spared by this infection, as it was with the present case, we hypothesize mucosal congestion to be the cause of blood loss.

The unequivocal diagnosis of basidiobolomycosis requires microbiological cultivation of the fungus from tissue specimens. Although the tissue reaction produced in entomophthoromycosis is distinctive, species identification or differentiation of basidiobolomycosis from conidiobolomycosis is not possible histologically. *B. ranarum* can be seen in standard H&E-stained tissue sections, but PAS and GMS staining results in optimal demonstration of the septate or nonseptate, thin-walled hyphae. A particularly characteristic granulomatous inflammatory reaction with eosinophil debris surrounding hyphal structures, the Splendore–Hoeppli phenomenon, although not pathognomonic for basidiobolus infection, is highly suggestive in the appropriate setting. In contrast to infection by members of the Mucorales, vascular invasion and neutrophilic infiltration are rarely encountered. Growth of the fungus in appropriate laboratory media can be accomplished, but failure to consider fungal infection in the differential diagnosis often prevents definitive microbiological confirmation of the infecting microorganism. Kaufman et al.[8] have described immunodiffusion tests to detect and distinguish *B. ranarum* antibodies from those of *C. coronatus* and other fungal pathogens, thereby offering the opportunity to provide specific evidence of basidiobolomycosis. In the case we report, the production of three immunodiffusion bands of identity after reaction of the patient's serum with *B. ranarum* antigen and the absence of *C. coronatus* antibody provide strong support for the notion that the patient's infection was caused by *B. ranarum.* That the specific *B. ranarum* precipitins gradually disappeared over a period of 8 weeks after successful surgical and medical treatment and were nondetectable 6 months after surgical resection provides additional proof that the organism was truly pathogenic. Serial serological studies showed that the immunodiffusion test results not only contributed to the diagnosis of *B. ranarum* infection but also correlated with its resolution.

Antifungal chemotherapy for basidiobolomycosis is not well defined. Anecdotal reports cite treatment success with potassium iodide, clotrimazole, miconazole, and ketoconazole in a small number of cases, but amphotericin B seems to have an uncertain role.[18] In vitro data,

although limited, have shown inhibitory and fungicidal activity of miconazole and ketoconazole at clinically achievable concentrations.[19] Van Cutsem et al.[20] included two isolates of *B. ranarum* in their analysis of in vitro activity of itraconazole against a large variety of superficial and deep mycoses and found a concentration of 0.1–1.0 μg/mL to be inhibitory. Whether itraconazole was crucial for eradication of the infection in our patient or whether surgical resection of the involved colon alone was curative cannot be answered with assurance.

In conclusion, we report a case of intestinal basidiobolomycosis, a manifestation of a very rare disease that is seldom diagnosed at an early stage. It seems to occur at any age in either sex and generally in previously healthy individuals. From the few cases described, it seems that the esophagus and small bowel are spared. Symptoms include abdominal pain, vomiting, diarrhea or constipation, fever, anorexia, weight loss, and, rarely, bleeding. Because the infection seems to involve the nonmucosal layers of the gastrointestinal tract, imaging and endoscopic studies typically show thickening of the bowel wall with minimal or no mucosal abnormality, and endoscopic biopsy specimens tend to show nonspecific inflammation. Surgical intervention is necessary not only to establish a diagnosis but also to resect obstructing masses resulting from extensive fibrosis and granulomatous inflammation in late stages of the disease. Any resected tissue should be submitted for microbiological cultures as well as histopathologic study. We found the basidiobolomycosis immunodiffusion test[8] helpful in confirming the identity of the fungal infection and in monitoring its resolution. Because experience with antifungal medication is extremely limited, firm recommendations for treatment cannot be offered. However, the oral antifungal agent itraconazole may be a useful adjunct to surgical resection.

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