Gastrointestinal Zygomycotic Infection Caused by *Basidiobolus ranarum*: Case Report and Review

Dani-Margot Zavasky, Wade Samowitz, Terrence Loftus, Helene Segal, and Karen Carroll

*From the Division of Infectious Diseases, Department of Medicine, and the Departments of Pathology and Surgery, University of Utah Health Sciences Center; and the Associated Regional and University Pathologists, Inc., Salt Lake City, Utah*

*Basidiobolus* species are filamentous fungi belonging to the order Entomophthorales. Unlike other zygomycetes, *Basidiobolus* species have been mainly associated with a tropical form of subcutaneous zygomycosis in otherwise healthy individuals. Visceral disease caused by this pathogen is rare, but cases of gastrointestinal infection with *Basidiobolus ranarum* have been reported worldwide. In many of these reports, the inflammatory disease of the colon has been confused with Crohn’s disease. We report the third case of *B. ranarum* gastrointestinal infection in the United States, which was initially treated as inflammatory bowel disease.

Zygomycetes constitute a class of filamentous fungi that embrace many species potentially pathogenic to humans. This group is placed in two orders: Mucorales and Entomophthorales. Members of the family Mucoraceae (in the order Mucorales) such as *Absidia*, *Apophysomyces*, *Mucor*, *Rhizomucor*, and *Rhizopus* species are more significant in clinical medicine and are known to cause acute and rapidly progressive opportunistic mycoses [1, 2]. Regardless of the dramatic severity of infections caused by the Mucoraceae, the invasive disease they cause is rare, affecting hosts immunocompromised by diabetes mellitus, lymphoid malignancies, severe burns, or other trauma. The order of Entomophthorales consists of two main genera: *Conidiobolus* and *Basidiobolus* [1]. These are less likely to cause human disease and have been mainly responsible for the tropical form of subcutaneous zygomycosis in otherwise healthy individuals. Isolated cases of visceral entomophthoromycosis have been reported in the world, including two cases of gastrointestinal infection with *Basidiobolus ranarum* in the United States. We report the third case of this extremely unusual *B. ranarum* gastrointestinal infection to occur in the United States.

Case Report

A 57-year-old insulin-dependent diabetic man developed lower abdominal pain, anorexia, fatigue, and constipation in September 1997. He presented to his local physician in Arizona. Esophagogastroduodenoscopy revealed a gastric ulcer. He was treated with an oral antibiotic and omeprazole. After a brief period of initial abatement, all of his symptoms persisted, now with low-grade fevers. His constipation seemed worse, with infrequent, small-caliber stools.

At the beginning of November, the patient returned to his primary care provider, who, at that time, palpated an abdominal mass. In the emergency department on 3 November the patient was found to be afebrile and pale, with a large mid-abdominal mass that was moderately tender to palpation and firm but without nodularity or associated peripheral adenopathy. Blood work revealed no acidosis and a WBC count of 16,400/µL with 79% neutrophils, 7% lymphocytes, 6% monocytes, and 8% eosinophils. An abdominal CT scan demonstrated a 7 cm × 18 cm × 10 cm mass in the space between the transverse colon and the stomach and involving the transverse colon. There was no adenopathy and there were no liver lesions.

The patient was admitted to the hospital for iv antibiotic therapy, iv fluid repletion, and further workup. Colonoscopy showed normal rectal mucosa up to 10 cm, followed by a 5-cm segment of circumferential ulceration with surrounding irregular, bumpy, firm mucosa; the rest of the descending colon appeared normal. Histopathology of an ileal biopsy showed no inflammation; examination of the transverse colon demonstrated active colitis, with ulceration and focal cryptitis but no granulomatous inflammation or malignancy. A left-colon biopsy showed active colitis with epithelioid granulomas and multinucleated giant cells without malignancy. Gross as well as microscopic evidence was mostly suggestive of Crohn’s colitis, and the patient began receiving mesalamine (Pentasa; Hoechst Marion Roussel, Kansas City, MO).

Enlargement of the mass, evident on repeated abdominal CT, prompted exploratory laparotomy with resection of the mass, partial colectomy with primary Anastomosis, and resection of part of the greater curvature of the gastric wall. The small bowel and the remainder of the colon were found free of inflammation. Histopathologic interpretation suggested diverticulitis disease with perforation and abscess and pseudotumor formation. Multifocal transmural inflammation was also noted, and the fungal and acid-fast bacilli stains were reportedly negative.

The patient was discharged on 20 November while still receiving mesalamine. His symptoms persisted, with more fre-
quent fever spikes and now diarrhea. He was readmitted in January 1998, and another abdominal CT scan revealed an extensive inflammatory process in the left abdomen involving the left kidney and ureter. On 21 January the patient was transferred to the University of Utah Hospital surgical service. Further radiological imaging revealed phlegmon in the area of the pancreatic tail and around the left kidney, with hydronephrosis. On 23 January he underwent cystoscopy, retrograde pyelography, and ureteral stent placement secondary to a fixed obstruction of the left ureter, of unclear etiology. A rectal mucosal ulcer was biopsied and showed a nonspecific ulceration. The patient continued his treatment with imipenem and mesalamine. Flagyl was added secondary to stool-culture positivity for Clostridium difficile. He was febrile (with temperatures reaching 40°C) and had abdominal pain and peripheral leukocytosis with stomach. Numerous necrotizing and nonnecrotizing granulomas in the submucosa and muscularis propria of the colon and eosinophilia. A parasitic workup was negative.

Hematoxylin and eosin– and Gomori methenamine silver–stained slides of histopathologic specimens obtained in Arizona (see below and figures 1A and 1B) were reviewed by members of the pathology and infectious diseases staffs, whose findings demonstrated necrotizing and nonnecrotizing granulomas, numerous eosinophils, and the presence of fungal elements. The patient’s urine was submitted for fungal culture and contained large hyphal elements on calcofluor-white staining and yielded a mold, subsequently identified as B. ranarum. On 31 January he started receiving Ambisome (Vestar, San Dimas, CA) at a dosage of 5 mg/(kg·d). Therapy with imipenem was discontinued.

The patient’s condition did not improve clinically following the first week of therapy with Ambisome. Itraconazole (200 mg b.i.d.) was added to the regimen until susceptibility testing (Fungus Testing Laboratory, University of Texas Health Science Center, San Antonio) revealed resistance of the organism to amphotericin B. The patient defervesced and the leukocytosis and eosinophilia resolved with itraconazole monotherapy. A follow-up urine culture was negative.

On 13 February the patient underwent right hemicolecotomy with ileostomy because of a persistent inflammatory mass in the abdomen and colonic obstruction. The resected specimen was extensively involved with necrotizing granulomas and fungi. Culture of intraoperative specimens yielded B. ranarum.

The patient was discharged on 11 March, following interim complications of an enterococcal urinary tract infection and Enterobacter bacteremia, both of which resolved with antibiotics. Long-term itraconazole therapy was planned.

Histopathology

Reviewed slides from the referring institution included those of specimens from a segment of the colon and portion of the stomach. Numerous necrotizing and nonnecrotizing granulomas in the submucosa and muscularis propria of the colon and in the mesentery of the colon and stomach were seen (figure 1A). Some of the granulomas were large and contained extensive areas of necrosis and suppuration. There were also areas of intense eosinophilic infiltration. Fungal hyphae were seen in the necrotic centers of the granulomas; these hyphae were often surrounded by eosinophilic material (Splendore-Hoeppli phenomenon; figure 1B).

The second operative specimen was a 27-cm portion of right colon (including cecum and ascending colon) with 2.5 cm of terminal ileum and a 5.0-cm appendix; 2.5 cm from the ileocecal valve was a large inflammatory mass, 6.5 cm × 4.0 cm × 2.7 cm. The mass consisted of suppurrative granulomatous inflammation containing broad septate hyphal elements on staining with both hematoxylin-eosin and Gomori methenamine silver, similar to findings in the previous operative sample.

Mycology

All clinical specimens were inoculated onto Sabouraud’s dextrose agar and mycobiotic and brain-heart infusion agar

Figure 1. A, histopathologic section of colon (stain, hematoxylin-eosin [H&E]; original magnification, ×10) showing a submucosal nonnecrotizing granuloma. Other granulomas exhibited central necrosis. B, hyphal form of Basidiobolus in the necrotic center of a granuloma. The amorphous material surrounding the empty-appearing hyphal structure was eosinophilic on H&E staining (Splendore-Hoeppli phenomenon) (original magnification, ×40).
with blood, chloramphenicol, and gentamicin. Colonies appeared within 3 days of inoculation, and initial colonies were whitish, becoming radially folded with short aerial hyphae. With age the colonies turned beige to yellow-brown. On microscopy, coenocytic hyphae (lacking septa) 5–15 µ wide were seen. Some of the hyphae fragmented into short hyphal bodies. Zygosporcs with two beak-shaped remnants of the copulation tube (figure 2A) established this organism as B. ranarum. Also observed were secondary obclavate conidia (figure 2B).

Discussion

Entomophthoromycosis is a rare form of zygomycosis. Two principal species responsible for the majority of these infections are Conidiobolus coronatus and B. ranarum [1, 2]. Historically, they have been known to cause skin and soft-tissue infections in otherwise healthy individuals in tropical areas of Africa, South America, and Asia. Visceral involvement is extremely unusual and so far has been reported only in association with Basidiobolus.

B. ranarum was first isolated in 1955 from decaying plants in the United States and subsequently has been found in soil and vegetation throughout the world [3]. B. ranarum may also be present as a commensal in the intestinal tracts of frogs, toads, turtles, chameleons, horses, and dogs [4, 5]. The first human case of infection caused by B. ranarum was one of subcutaneous mycosis, reported in 1956 in Indonesia [6], and other cases subsequently occurred in India [7], Africa [8], and South America [9]. In 1978 the first culture-proven case of invasive basidiobolomycosis of the maxillary sinus and the palate was reported in the United States [10], and reports of visceral involvement followed.

Before our report, there have been six cases of gastrointestinal basidiobolomycosis reported in the world (table 1). The first three cases were reported from Brazil [11, 12], followed by two from the United States [13, 14] and a recent case from Kuwait [15] involving a Bangladeshi patient. Except for one instance, all of these infections occurred in males of various ages, all in apparent good health. Patients presented with complaints of insidious onset of abdominal pain, fever, constipation, anorexia, weight loss, and, rarely, nausea and vomiting or lower gastrointestinal bleeding.

Intraabdominal inflammatory masses were found on imaging studies or during surgical exploration. Involvement of the colon has been the rule, with occasional gastric and duodenal involvement. In only one case was there extension of the infection into the liver, biliary system, and pancreas [12]. Diagnosis was usually delayed by several months. Patients had leukocytosis with eosinophilia and frequently anemia.

Histologic examination of affected tissue yielded very characteristic findings: giant-cell granulomas with eosinophilic infiltration and thin-walled, rarely septated fungal elements, surrounded by eosinophilic material (the so-called Splendore-Hoeplli phenomenon). No angioinvasion was present. B. ranarum was isolated in culture in only three prior cases [11, 14, 15]. Histology, in conjunction with serological immunodiffusion testing, was diagnostic in the remaining instances. Patients did not have any obvious risk for a fungal infection. Mortality
Table 1. Chronological summary of case reports of gastrointestinal basidiobolomycosis.

<table>
<thead>
<tr>
<th>Reference, country</th>
<th>Patient’s age (y)/sex</th>
<th>Risk factor</th>
<th>Symptom(s)</th>
<th>Site(s) involved</th>
<th>Diagnostic method</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[11] Brazil</td>
<td>4/M</td>
<td>None</td>
<td>Abdominal pain, fever, sweats, diarrhea</td>
<td>Stomach, transverse colon</td>
<td><em>Basidiobolus ranarum</em> culture, histology</td>
<td>Surgery</td>
<td>Died</td>
</tr>
<tr>
<td>[12] Brazil</td>
<td>13/M</td>
<td>None</td>
<td>Abdominal pain, weakness, fever, anorexia, memory loss</td>
<td>Stomach, duodenum, transverse colon, pancreas, liver, biliary system</td>
<td>Histology</td>
<td>None</td>
<td>Died</td>
</tr>
<tr>
<td>[12] Brazil</td>
<td>60/M</td>
<td>None</td>
<td>Abdominal pain</td>
<td>Stomach, transverse colon</td>
<td>Histology</td>
<td>Surgery/AmB</td>
<td>Survived</td>
</tr>
<tr>
<td>[13] USA</td>
<td>49/F</td>
<td>None</td>
<td>Abdominal and rectal pain, mucus discharge, constipation</td>
<td>Rectosigmoid colon</td>
<td>Histology, serology</td>
<td>Surgery, itraconazole</td>
<td>Survived, cured</td>
</tr>
<tr>
<td>[14] USA</td>
<td>69/M</td>
<td>DM</td>
<td>Fever, anergy, nausea, vomiting, abdominal pain</td>
<td>Duodenum, terminal ileum, cecum, ascending colon</td>
<td><em>Basidiobolus haptosporus (ranarum)</em> culture, histology</td>
<td>Surgery, AmB</td>
<td>Died</td>
</tr>
<tr>
<td>[15] Kuwait*</td>
<td>30/M</td>
<td>None</td>
<td>Rectal bleeding, constipation</td>
<td>Rectum</td>
<td><em>B. ranarum</em> culture, histology</td>
<td>AmB, ketoconazole</td>
<td>Unknown</td>
</tr>
<tr>
<td>[PR] USA</td>
<td>57/M</td>
<td>DM</td>
<td>Abdominal pain, anorexia, fatigue</td>
<td>Stomach, colon, rectum, ureter</td>
<td><em>B. ranarum</em> culture, histology</td>
<td>AmB, itraconazole</td>
<td>Still alive, therapy in progress</td>
</tr>
</tbody>
</table>

NOTE. AmB = amphotericin B; DM = diabetes mellitus; PR = present report.

* Patient was from Bangladesh.

was high. Only two patients survived, and the outcome in one of the previously described cases is unknown.

Our case shares many features with those previously reported. The onset of illness was insidious, with predominant symptoms of abdominal pain, anorexia, constipation, and, later, fevers. The patient was a diabetic, as in one of the previously described cases, but his blood sugar levels were well controlled and otherwise he was in good health. He made frequent trips to the desert (often picnicking there), where he may have been vulnerable to ingestion of the fungal spores. It is not clear how *B. ranarum* gains access to the gastrointestinal tract of patients, but previously reported cases of gastrointestinal basidiobolomycosis were attributed to ingestion, with the portal of entry being the stomach, or to direct inoculation via minor rectal trauma, followed by contiguous spread of infection [12, 15].

Our patient also had inflammatory involvement of the left kidney and ureter, and *B. ranarum* was recovered from the urine. Involvement of the colon was also proven on culture. Both our patient and one of those described in the literature [15] were initially misdiagnosed and treated for Crohn’s disease.

Appropriate treatment of visceral basidiobolomycosis has not been well outlined. Surgical resection of the inflammatory, frequently obstructing masses is necessary, in conjunction with administration of systemic antifungal agents. Subcutaneous entomophthoromycosis has been treated previously with amphotericin B, potassium iodide, clotrimazole, miconazole, and ketoconazole [16]. Besides amphotericin B, itraconazole was used with success in one of the previously reported cases [13]. In vitro testing of antifungal agents against *Basidiobolus* isolates [17] revealed good activity of miconazole and ketoconazole against the *Basidiobolus* isolates. In our case, resistance to amphotericin B was also demonstrated by in vitro susceptibility testing. Itraconazole showed inhibitory activity in our case as well as in previously reported ones in which in vitro testing was performed [18].

In summary, we report a case of gastrointestinal basidiobolomycosis, a very rare mycotic infection that is being reported with increased frequency, ours being the third in the course of 1 year. An increased awareness and consideration of this rare entity in the differential diagnosis for patients with inflammatory bowel disease or granulomatous inflammation on histopathology could potentially contribute to identification of other cases. Thus, obtaining specimens for fungal culture and histopathologic examination is crucial for patients with suspect inflammatory bowel and intraabdominal disease of unclear etiol-
ogy. For these patients, the importance of eliminating an invasive fungal infection is even more significant when steroid therapy is considered.

References