Gastrointestinal Basidiobolomycosis

Morphologic Findings in a Cluster of Six Cases

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Abstract

We describe the histopathologic features of 6 cases of gastrointestinal basidiobolomycosis examined at 4 Phoenix, AZ, area hospitals during the last 4 years. Resected stomach and intestinal specimens were characterized by marked mural thickening with fibrosis, prominent tissue eosinophil infiltration and palisading granulomatous inflammation around pale fungal hyphae. In 2 cases, there was colonic perforation. Basidiobolus ranarum *hyphae (associated with spore-like spherules in 4 cases) were identified within tissue sections; the irregularly branched, thin-walled, occasionally septated hyphae were typically surrounded by a thick eosinophilic cuff (Splendore-Hoeppli phenomenon). Although the histologic features of* B ranarum *are well described in the skin and subcutaneous tissue, gastrointestinal involvement has presented considerable diagnostic difficulty. Before the occurrence of this cluster of cases, intra-abdominal* B ranarum *infection has been reported only rarely.*

Basidiobolus ranarum is a fungal organism belonging to the family Entomophthoraceae of the order Entomophthorales. It is known as a causative agent of some cases of subcutaneous zygomycosis, a disease characterized by subcutaneous masses in the trunk and proximal extremities and classically found in tropical climates of Africa and southeast Asia.[1] To date, only 9 cases (including 3 reported herein) of well-documented *B ranarum* infection primarily involving the human gastrointestinal tract have been reported.[2–9] We now report the pathologic findings and illustrate the distinctive morphologic features in a cluster of 6 cases of gastrointestinal *B ranarum* infection seen during a period of 4 years. Case 1 has been previously reported in detail,[5] cases 1 and 2 mentioned in a brief report,[7] and the early course of case 3 in another report.[8]

Material and Methods

Case Histories

The clinical aspects of the 6 cases of *B ranarum* infection are summarized in **Table 1**. In cases 1, 5, and 6, surgical resection was thought to be complete; in case 3, extensive perinephric and retroperitoneal infection could not be surgically resected; and in case 2, resection of only the descending colon was possible (periappendiceal retroperitoneal involvement, a large hepatic abscess, and omental disease could not be excised). Each patient received oral itraconazole after surgery. Case 1 is free of any evidence of infection after almost 4 years of follow-up, and case 2 has been free of *B ranarum* infection for almost 1 year after completing a 1-year course of antifungal therapy. Case 3 continues to receive oral antifungal therapy and shows evidence of slow resolution of

Table 1

Clinical Aspects of 6 Cases of Gastrointestinal Basidiobolomycosis

Case No./ Sex/Age (y)	Race	Initial Examination	Symptoms	Sites Involved	Prior History	Initial Clinical Impression	Confirmation of Diagnosis	Follow-Up
1/F/49	White	April 1995	Abdominal and rectal pain, bloody mucous discharge, constipation	Rectosigmoid colon (resected)	Recurrent peptic ulcer disease	Possible Crohn disease with stricture of the sigmoid colon	Positive serology for *Basidiobolus ranarum* (no cultures obtained)	No evidence of residual disease after surgical resection and 6 months of treatment with itraconazole
2/M/47	White	September 1996	Abdominal pain, palpable mass	Partial resection and biopsies: descending colon, rectum, appendix, retroperitoneum, omentum, liver	Alcohol abuse	Cancer of descending colon and right lower quadrant abdominal mass	Culture positive for *B ranarum;* positive serology for *B ranarum*	Complete resolution of intra-abdominal disease after partial resection of descending colon and 1 year of treatment with itraconazole
3/M/56	White	November 1997	Abdominal pain, fever, anorexia, weight loss	November 1997, resection of transverse colon (perforation) and portion of stomach; January 1998, radiologic evaluation: inflammatory mass involving tail of pancreas and left kidney; February 1998, right hemicolectomy with involvement of colon; May 1998, resection of involved rectosigmoid	Diabetes mellitus	Inflammatory bowel disease and enlarging abdominal mass	Culture positive for *B ranarum*; positive serology for *B ranarum*	Resolving retroperitoneal mass after colectomy and prolonged antifungal therapy
4/M/52	White	December 1998	Abdominal pain, fever	Sigmoid colon (resected)	Sinusitis, cholecystitis, appendicitis	Diverticulitis	Positive serology for *B ranarum* (no cultures obtained)	No evidence of residual disease after surgical resection and 2 months of treatment with itraconazole
5/F/37	Black	February 1999	Abdominal pain, weight loss, anemia	Stomach with extension to peripancreatic soft tissue and transverse colon mesentery (partial resection)	Iron deficiency	Carcinoma of stomach or lymphoma	Culture positive for *B ranarum*	No evidence of disease after gastric resection, partial pancreatectomy, splenectomy, and segmental colectomy (limited follow-up)
6/M/59	White	February 1999	Abdominal pain	Resection: perforated rectosigmoid colon	—	Perforated diverticulitis	Culture positive for *B ranarum*	Left lower quadrant abscess 1 week after resection; successfully drained percutaneously (limited follow-up)

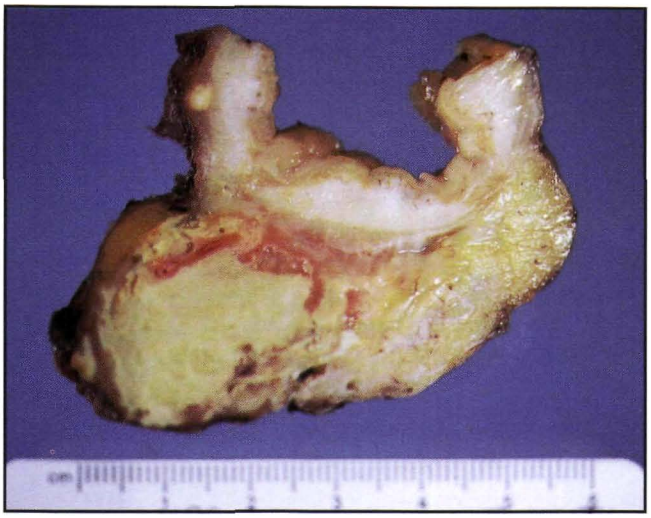

Image 1 (Case 2) Rectosigmoid colon showing diffuse mural thickening with yellowish granulomatous nodules in the bowel wall and in the serosa. Serosal fat involvement is present.

extensive retroperitoneal and perinephric disease. Cases 4 and 5 are currently undergoing therapy with itraconazole. Case 6 is very recent.

The source and pathogenesis of these gastrointestinal infections are as yet unknown, but as *B ranarum* is a soil fungus found in decaying plant matter, accidental ingestion of soil or soil contamination of foodstuffs is one possibility. In this regard, preliminary studies have found pica (soil ingestion) by 1 patient and occupation as a landscaper for another. Two other affected persons live in the same trailer park. An epidemiologic investigation under the auspices of the Arizona Department of Health and the Centers for Disease Control and Prevention is underway. All patients were born in the United States and reside in Arizona. No one was immunosuppressed.

Pathologic Findings

Grossly, all cases were characterized by diffuse mural thickening of the intestine (cases 1–4 and 6) or stomach (case 5). Yellow nodules ranging from pinpoint size up to 3 cm in diameter were present throughout the thickness of the wall and adjacent fat; larger nodules had central necrosis **Image 1**. Luminal stenosis was present in 3 cases. The mucosal surface showed only focal prominence of mucosal folds reminiscent of a cobblestone appearance in 2 cases and focal hemorrhage and ulceration in the third. Fibrinous exudates at the serosal surface were seen in 1 case. The gross appearance of the colon specimens suggested Crohn disease, but the mucosal involvement usually seen in that disease was lacking except at sites of perforation (cases 3 and 6). Gastric involvement in case 5 was associated with ulceration, necrosis and marked mural thickening (up to 2.5 cm).

Microscopically, the cases demonstrated granulomas that were striking in their appearance **Image 2**, **Image 3**, and **Image 4**. In the colonic specimens, the granulomatous inflammation was centered in the muscularis propria with extension to the subserosa, attached fat, and submucosa in all cases. The granulomas were well-formed and tight with abundant multinucleated giant cells. Many showed discrete palisading of histiocytes around central necrosis or abscess formation. The abscesses were eosinophilic, neutrophilic, or mixed. Within the granulomas, fungal organisms often were present: hyphae 8 to 40 µm in width, thin-walled, and branched. Septations were infrequent. A dense eosinophilic cuff, representing the Splendore-Hoeppli phenomenon, often surrounded hyphal fragments. The hyphae, though focal, were readily seen on H&E stains; staining with periodic acid–Schiff with diastase and Gomori methenamine silver tended to be faint and did not further highlight their presence (Image 3).

The granulomatous inflammation was associated with a marked fibrotic response and pronounced atrophy of the muscularis propria. There were massive numbers of eosinophils in the submucosa and throughout the wall and adjacent fat. Charcot-Leyden crystals were found in case 5 (Image 4). Eosinophils extended into the lamina propria (at least focally) in all cases. In addition to eosinophils, lymphocytes (including scattered lymphoid aggregates) and plasma cells were seen throughout the affected portion of the wall. In the rectosigmoid specimen from case 3, plasma cells and lymphocytes were the dominant inflammatory component, although tissue eosinophils were still prominent. Case 5, with gastric involvement, showed dramatic necrosis and loss of the muscularis propria (Image 4). Lymph nodes present in the specimens from 4 cases showed reactive lymphoid hyperplasia without granulomas.

Four cases showed round structures, 20 to 40 µm in diameter, in the foci of necrosis **Image 5**. These occurred singly or in clusters. Some were hollow (reminiscent of empty coccidioidomycosis spherules), whereas most had a nucleus-like structure with surrounding flocculent material. These structures were numerous in cases 2 and 6 and found focally in cases 3 and 4. In some foci in cases 2 and 6, the spherules were continuous with hyphae and had a Splendore-Hoeppli reaction around them. These structures were thought to be spores (see "Discussion" and "Acknowledgments").

Discussion

The marked tissue eosinophil infiltrate and the identification of the typical fungal hyphae, which stain relatively faintly with special stains in tissue sections, is the basis for

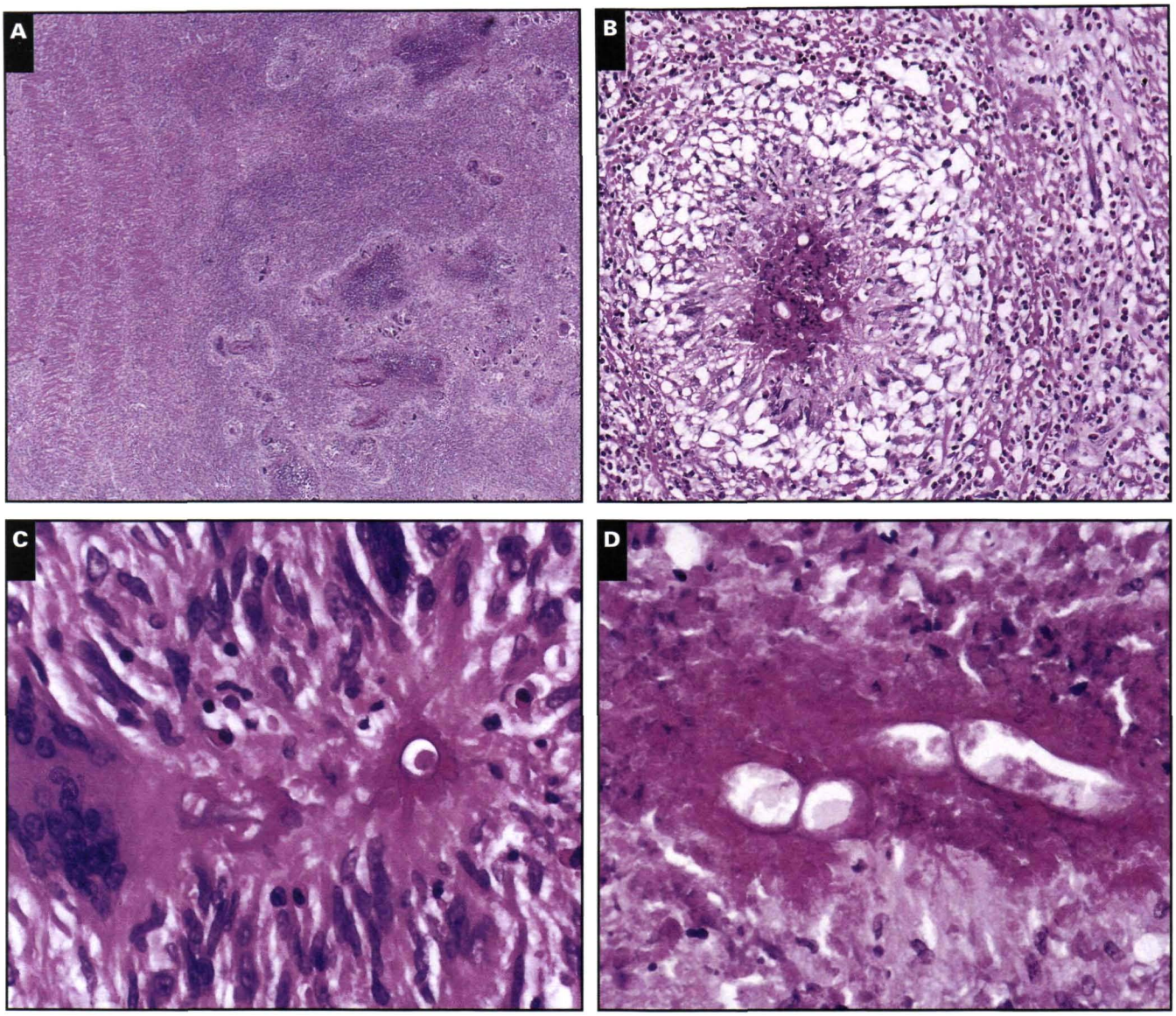

Image 2 (Case 1) Histopathology of representative lesions from the rectosigmoid colon. A, Muscularis propria replaced by necrotizing granulomatous reaction with marked palisading (H&E). B, Extensive eosinophil infiltration around a palisaded granuloma containing fungal hyphae (H&E). C, Granuloma with palisaded histiocytes and multinucleated giant cells and eosinophilic cuff representing the Splendore-Hoeppli phenomenon surrounding central hyphae (H&E). D, Septated hyphae with pale-staining central cores and associated Splendore-Hoeppli phenomenon (H&E).

suspecting the correct diagnosis of basidiobolomycosis and its ultimate distinction from other granulomatous disorders. Fungal organisms that bear some resemblance to *Basidiobolus* in tissue sections are *Aspergillus* and the many *Aspergillus* look-alikes (*Fusarium*, *Paecilomyces*, *Acremonium*, *Bipolaris*, *Pseudallescheria* and its sexual anamorph, *Scedosporium*) and the various causative organisms of mucormycosis. *Aspergillus* is differentiated by acute 45-degree angle branching and numerous septa, as opposed to the irregular branching and few septa seen in *Basidiobolus*. The various fungi in the order Mucorales (eg, *Rhizopus*, *Mucor*, and *Absidia* genera) have similar, nonseptated hyphae and are associated with vascular invasion and thrombi, features distinctly unusual with *Basidiobolus* infection. They also are found customarily in a background of suppurative or infarctive necrosis with occasional poorly formed granulomas as opposed to the marked granulomatous reaction and striking Splendore-Hoeppli phenomenon that is characteristic of basidiobolomycosis. *Conidiobolus coronatus*, a cause of nasofacial zygomycosis, is histologically indistinguishable from *Basidiobolus*.[1]

The morphologic clues to separate the various fungi are often subtle, and it becomes important to confirm morphologic impressions with ancillary methods whenever possible.

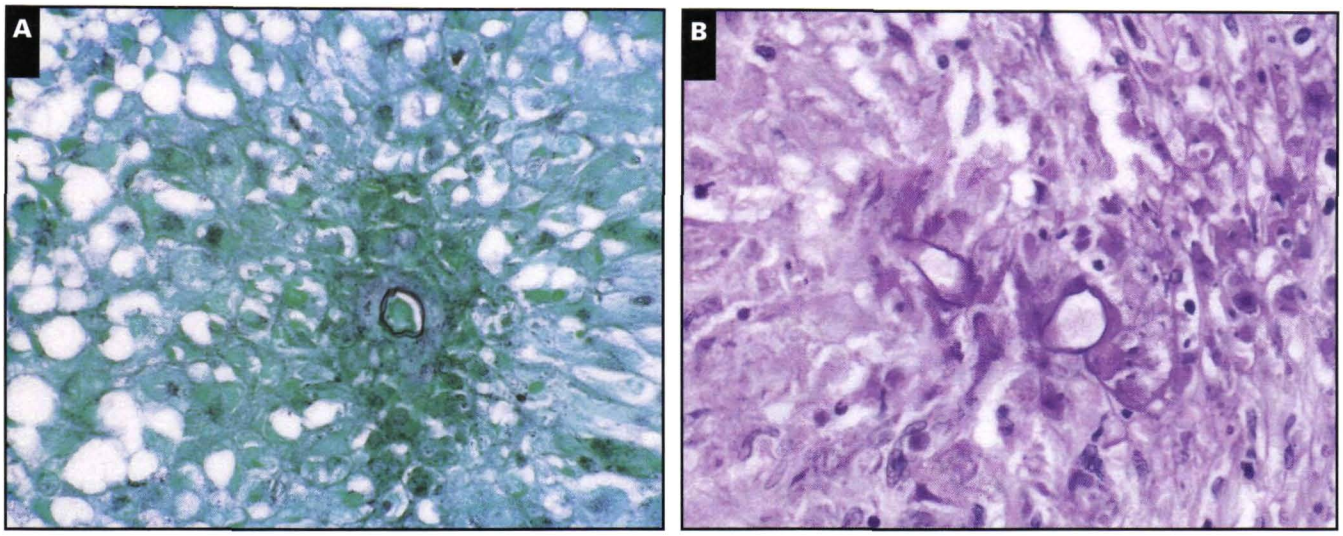

Image 3 Granulomas with hyphae that stain faintly. (A, Gomori methenamine silver; B, periodic acid–Schiff with diastase).

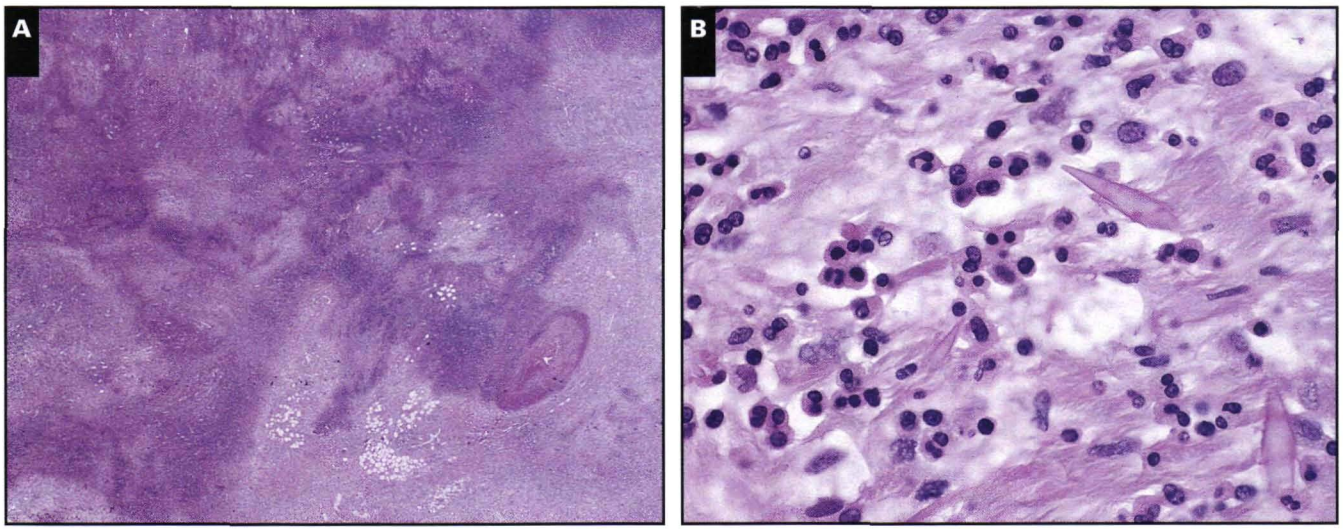

Image 4 (Case 5) Gastric basidiobolomycosis. A, Geographic necrosis replaced the muscularis propria, a small remnant of which runs horizontally slightly above center (H&E). B, The surrounding infiltrate is rich in eosinophils, including Charcot-Leyden crystals (H&E).

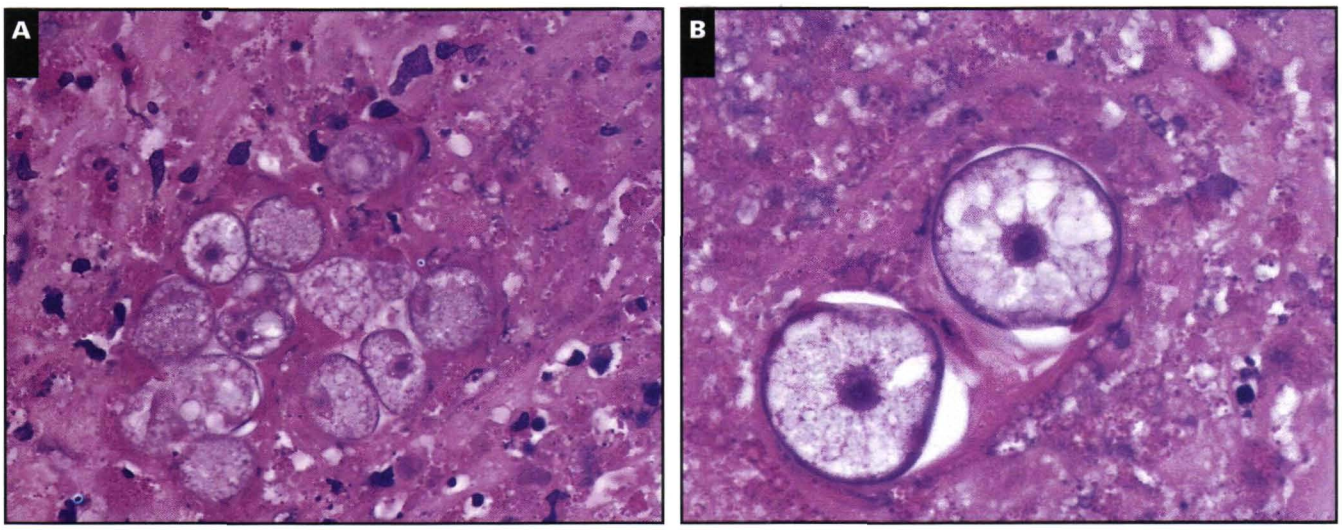

Image 5 (Case 2) Spherical structures. The rounded structures with grayish flocculent cytoplasmic material have a central nucleus-like structure (A,B, H&E).

Table 2
Summary of Presumed or Culture-Proven Cases of Gastrointestinal Basidiobolomycosis From the Literature*

Reference	Sex/Age (y)	Country of Origin	Sites Involved	Presentation	Outcome and Course
de Aguiar et al[2]	M/4	Brazil	Stomach, transverse colon	Epigastric mass	DOD after resection, 2.5 months after presentation
Edington[9]	M/6	Nigeria	Skin, ileum, transverse colon, rectum, bladder	Subcutaneous mucormycosis and rectal obstruction	DOD after antibiotic and iodide therapy and colostomy, 1 year after onset of subcutaneous mucormycosis
Bittencourt et al[3]	M/13	Brazil	Stomach, duodenum, transverse colon, pancreas, liver, biliary system	Intestinal obstruction	DOD without therapy, 4 months after presentation
Khan et al[4]	M/30	Bangladesh	Rectum	Rectal mass	Lost to follow-up 4 weeks after initial response to amphotericin B and ketoconazole therapy
Bittencourt et al[3]	M/60	Brazil	Stomach, transverse colon	Gastric mass	Alive without disease after resection and amphotericin B therapy, at time of discharge
Schmidt et al[6]	M/69	United States	Duodenum, ileum, cecum, ascending colon	Right lower quadrant mass	DOD after resection and amphotericin B therapy, 1.5 months after presentation

DOD = died of disease.
* Excluding the previous reports of our cases.[5,7,8]

In this context, while culture remains the "gold standard" for definitive diagnosis, immunologic methods can support a morphologic diagnosis. An immunodiffusion test for the serodiagnosis of *B ranarum* infection developed at the Centers for Disease Control and Prevention[10] successfully confirmed 4 of our cases.

The spherical structures identified in 4 of our cases have not been well described in *B ranarum*. Their presence had been noted rarely in cases of subcutaneous mucormycosis (R.L. Neafie, MS, personal verbal communication, May 1999). The size and shape of these structures raise the possibility of coccidioidomycosis spherules, amebae, and exogenous matter such as vegetable particles, although their presence in 4 cases of proven *B ranarum* and the fact that they could be shown to be continuous with hyphal structures suggest they are part of this infection. Their exact nature remains to be clarified. Possibilities mentioned by the reviewers of this manuscript and persons named in the Acknowledgments include meristospores, chlamydospores, zygospores, chlamydioconidia, and gemma. *B ranarum* is known to produce zygospores that may have a beaklike protuberance,[11] although such protuberances were not appreciated in our cases. The precise mycologic characterization of these structures is beyond the scope of our report, which emphasizes clinicopathologic aspects.

Cases of primary gastrointestinal *B ranarum* infection previously reported by others[2–4,6] and an additional case of gastrointestinal infection in a patient who also had subcutaneous mycosis involving the genitalia and lower abdomen[9] are summarized in **Table 2**. *Basidiobolus* infection was established microbiologically in half of these cases and presumed on the basis of histologic findings in the remainder. The histologic features of these cases were similar to ours.

Because of the distinctive appearance, a presumptive diagnosis of basidiobolomycosis can be made on the basis of the histologic features if one is aware of *B ranarum* with this unusual presentation.

Addendum

Since the manuscript was accepted for publication, a seventh case of gastrointestinal basidiobolomycosis from the Pheonix area was encountered (April 1999). The patient is a 59-year-old male with a history of diabetes, hepatitis C, and renal dialysis. Initial clinical suspicion was carcinoma of the cecum. Ileocolectomy specimen showed basidiobolomycosis involving cecum, attached small bowel, and mesenteric fat.

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References

1. Binford CH, Connor DH. *Pathology of Tropical and Extraordinary Diseases*. Washington, DC: Armed Forces Institute of Pathology; 1976:591–593.
2. de Aguiar E, Moraes WC, Londero AT. Gastrointestinal entomophthoromycosis caused by *Basidiobolus haptosporus*. *Mycopathologia*. 1980;72:101–105.
3. Bittencourt AL, Ayala MAR, Ramos EAG. A new form of abdominal zygomycosis different from mucormycosis: report of two cases and review of the literature. *Am J Trop Med Hyg*. 1979;28:564–569.
4. Khan ZU, Prakash B, Kapoor MM, et al. Basidiobolomycosis of the rectum masquerading as Crohn's disease: case report and review. *Clin Infect Dis*. 1988;26:521–523.
5. Pasha TM, Leighton JA, Smilack JD, et al. Basidiobolomycosis: an unusual fungal infection mimicking inflammatory bowel disease. *Gastroenterology*. 1997;112:250–254.
6. Schmidt JH, Howard RJ, Chen JL, et al. First culture-proven gastrointestinal entermophthoromycosis in the United States: a case report and review of the literature. *Mycopathologia*. 1986;95:101–104.
7. Smilack JD. Gastrointestinal basidiobolomycosis. *Clin Infect Dis*. 1998;27:663–664.
8. Zavasky D-M, Samowitz W, Loftus T, et al. Gastrointestinal zygomycotic infection caused by *Basidiobolus ranarum*: a case report and literature review. *Clin Infect Dis*. 1999;28:1244–1248.
9. Edington GM. Phycomycosis in Ibadun, western Nigeria: two postmortem reports. *Trans R Soc Trop Med Hyg*. 1964;58:242–245.
10. Kaufman L, Mendoza L, Standard PG. Immunodiffusion test to serodiagnose subcutaneous zygomycosis. *J Clin Microbiol*. 1990;28:1887–1890.
11. Rippon JW. *Medical Mycology*. 2nd ed. Philadelphia, PA: Saunders; 1982:312–313.