Gastrointestinal Basidiobolomycosis: An Emerging, and A Confusing, Disease in Children (A Multicenter Experience)

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Abstract

Introduction Gastrointestinal basidiobolomycosis (GIB) is an emerging fungal infection in children that leads to diagnostic confusion.

Aim Our study aim was twofold: a systematic review of published literature and an update of some Saudi Arabia hospital series to analyze their as well as our own experience in diagnosis and management of GIB.

Material and Methods This clinical study included 18 children whose final diagnosis was GIB. The patients, who ranged in age from 5 to 10 years, were admitted between November 2009 and November 2015 with vague abdominal pains with or without abdominal masses for further investigation.

Results Abdominal pain was the most common presenting symptom (94.4%) followed by constipation and abdominal mass (83.3 and 77.8%, respectively); fever was present in only 22.2% of the cases. Elevated inflammatory markers and eosinophilia (94.4%) appeared as prominent laboratory findings.

Conclusion We conclude that diagnosing GIB in children requires a high index of suspicion, awareness, and consideration of its possibility in the differential diagnosis in patients with abdominal masses and eosinophilia, particularly in areas where it is endemic. Increased awareness of this clinical entity, early surgical resection of the infected tissue, and prolonged treatment with itraconazole offer the best chance for curing the disease.

Keywords
- basidiobolomycosis
- fungal diseases
- GIB
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Introduction

Basidiobolus ranarum (*B. ranarum*) is a fungus of the order entomophthorales that causes chronic subcutaneous zygomycosis. The fungus is found in environments around the world. The resulting human disease is concentrated in tropical and subtropical regions. It is endemic in Uganda and certain areas of Africa, India, and other parts of Asia. However, it can occur anywhere, even in areas where the disease has not been reported previously, and local physicians are often unfamiliar with it.[1,2]

Basidiobolomycosis is a rare chronic inflammatory disease caused by the fungus *Basidiobolus ranarum*. It is mainly restricted to subcutaneous tissue and usually involves the limbs, trunk, or buttocks. Patients with *B. ranarum* infection may present with gastrointestinal or systemic lesions. Visceral involvement is rare; recently, however, its etiological role in gastrointestinal infections has been increasingly recognized.[1–4]

Basidiobolus ranarum has been isolated from leaves and decaying plants in southern and northeastern states of the United States and from the gastrointestinal tract of reptiles, fish, amphibians, horses, dogs, and insectivorous bats. Occasionally, the fungus has been isolated from insects. Thus, stagnant water in ponds inhabited by fish or amphibians could be an important source of this fungus. Use of ponds as a water source for bathing or toilet purposes or ingestion of food contaminated with soil or animal feces are the most likely routes of gastrointestinal basidiobolomycosis (GIB) infection.[1,5] No specific risk factors for GIB have been identified; however, prior ranitidine use and prolonged residence in endemic areas may contribute to the risk.[6,7]

The presenting symptoms of GIB infection include fever, vomiting, abdominal pain, abdominal masses, and weight loss.[1,7] GIB infection simulates other conditions such as intestinal lymphoma and inflammatory bowel disease, for example, Crohn's disease or ulcerative colitis, intestinal tuberculosis, sarcoidosis, schistosomal granuloma, and amoebiasis, and thus may be misdiagnosed. Because of the nonspecific signs and symptoms of this disease, the diagnosis has sometimes been delayed, with increased morbidity.[8]

Dromer and McGinnis point out that leukocytosis, marked eosinophilia, elevated erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are often found in cases of GIB.[9] Diagnosis is based on histopathology; however, definitive diagnosis requires microbiological culture and serological testing through immunodiffusion method. The mold's structural elements include both hyphae and zygospores. Typical morphological features include hyphae that are irregularly branched, thin-walled, occasionally septated, and surrounded by a thick eosinophilic cuff (*Splendore–Hoeppli phenomenon*).[3]

Patients and Methods

This study was performed by the pediatric surgery departments of Assir Central Hospital; Abha Maternity and Children Hospital, Southern Region; and King Saud Medical City, Riyadh, Saudi Arabia, during the period from November 2009 to November 2015. After a systematic review of published literature, we studied some Saudi Arabia hospital series to analyze their as well as our own experience in diagnosis and management of GIB. This study included all children admitted through the emergency department with vague abdominal pain and those referred from primary hospitals with abdominal masses for investigation who were finally diagnosed with GIB. The study included 18 patients whose ages ranged from 5 to 10 years. There were 15 males and 3 females. Sixteen of the cases were from the Jazan provinces and two cases were from the Tohama area of Asser. All the locations are in southwestern Saudi Arabia, where GIB is endemic.

After admission, all patients were subjected to a thorough history taking and clinical examination. All patients were offered routine investigations including urine and stool analysis and culture, complete blood count, liver function tests, kidney function tests, ESR, and CRP. Blood culture was done only for febrile patients. Because all patients were living in areas where GIB is endemic, abdominal ultrasound and subsequent abdominal computed tomography (CT), with both oral and intravenous (IV) contrast, were mandatory for all cases.

The final diagnosis was elusive (because neither the clinical picture nor the results of investigations were pathognomonic for GIB), and biopsy and histopathology were required to reach a definitive diagnosis. Of the 18 patients, 15 (83.3%) had surgical exploration. Three (16.7%) cases were treated medically but biopsies were taken (►Table 1).

All tissue samples were sent for histopathological examination, which was the mainstay for diagnosis of suspected GIB (►Table1).

Antifungal treatment was given to all patients with presumed or proven GIB. For patients subjected to colonic resection (13 cases), the presumption of GIB infection was made, and antifungal treatment was started immediately on the first postoperative day. For the rest of the patients, the antifungal therapy started after review of the histopathological results. IV itraconazole was given in a dose of 4 mg/kg/day twice a day for 5 days for patients who underwent resection and anastomosis and for 2 days for patients who did not require a 5-day postoperative fasting period. Following the appropriate course of IV medication, oral itraconazole was started in a dose of 5 mg/kg twice a day. All patients were discharged on oral itraconazole for another 6 months.

Regular follow-up every 2 weeks at an outpatient clinic was advised. The mean follow-up period was 17.3 months.

Results

History and initial clinical examination revealed that 17 (94.4%) patients had abdominal pain (2 acute, 8 subacute, and 7 chronic), which was associated with variable symptoms and signs. Twelve (77.8%) patients had right side abdominal mass. In 83.3% (15 patients), the main complaint was constipation that was alternated with diarrhea in 7 patients (38.9%). Other gastrointestinal tract (GIT) symptoms included abdominal distension (38.9%) and vomiting (44.4%) Hepatomegaly was recorded in three (16.7%) patients, and four (22.2%) patients had weight loss. Four patients (22.2%) had fever, and in one of them, the only positive finding was prolonged

Table 1 Diagnosis and eventual treatment

Preliminary diagnosis (all D/D)	No. of patients (total 18)	Percentage (100%)	Definitive diagnosis (histopathology)	Treatment modality	
				Surgical resection + itraconazole (12 patients)	Biopsy + itraconazole (6 patients)
Acute intestinal obstruction	1	5.6	GIB	Urgent exploratory laparotomy revealed cecal mass; right hemicolectomy was done	
Appendicular mass	9	50	GIB	Elective exploration revealed cecal mass extending up to the ascending colon; right hemicolectomy was done	
Lymphoma	5	27.7	GIB		Laparoscopic colonic biopsy in two patients; open colonic biopsy and multiple mesenteric LN biopsies in three patients
Crohn's disease	2	11.1	GIB	Elective exploratory laparotomy revealed cecal mass extending up to hepatic flexure; right hemicolectomy was done	
Isolated liver abscess	1	5.6	GIB		Ultrasound-guided liver biopsy

Abbreviations: D/D, differential diagnosis; GIB, gastrointestinal basidiobolomycosis; LN, lymph node.
Note: The diagnosis was elusive because neither the clinical picture nor the results of laboratory investigations were pathognomonic for GIB, and biopsy and histopathology were required to reach a definitive diagnosis

fever. After the routine investigations, the final diagnosis was uncertain. Urine and stool analysis were normal in all patients, and blood cultures were negative. Two patients had impaired kidney function due to dehydration. All patients were anemic. Seventeen (94.4%) patients had leukocytosis with eosinophilia. Elevated ESR and high CRP were detected in 16 (88.9%) patients. Only one patient had elevated liver enzymes. The mandatory abdominal ultrasound and subsequent abdominal CT, with both oral and IV contrast, revealed that 17 patients had intestinal masses, mostly involving the cecum and ascending colon (►**Fig. 1**). One patient had a hepatic lesion that suggested liver abscess (►**Table 1**).

Various masses were revealed in the 15 patients who underwent surgical exploration. One patient had an acute intestinal obstruction; urgent exploratory laparotomy was done after correction of dehydration. A right cecal mass involving the terminal ileum was found with enlarged mesenteric lymph nodes, necessitating right hemicolectomy with ileotransverse anastomosis (►**Fig. 2**). Twelve patients had right abdominal masses and were subjected to elective exploration. All had cecal masses with varying involvement of the ascending colon, normal appendix, firm attachment to surrounding structures, normal terminal ileum and mesentery, and multiple enlarged mesenteric lymph nodes. Right hemicolectomy was possible and safe in nine cases. In the remaining 3 cases, excision was difficult and considered to be hazardous, and therefore colonic biopsy and multiple mesenteric lymph node biopsies were taken. Two cases had history and CT findings that were suggestive of Crohn's disease. Colonoscopy in each case revealed marked diffuse circumferential mucosal thickening, ulceration and pseudopolyps in the cecum, and ascending colon with thick exudate. Multiple biopsies were taken, but unfortunately, the histopathology showed nonspecific inflammation that was inconclusive. Both cases were surgically explored. Intraoperative findings included cecal mass extending up to the hepatic flexure with adhesion to duodenum and perinephric fascia, free terminal ileum, and normal mesentery. Right hemicolectomy was done with ileotransverse anastomosis (►**Fig. 3**).

Of the three cases treated medically, diagnostic laparoscopy was performed for *two* cases, and colonic masses were discovered attached to the anterior abdominal wall and

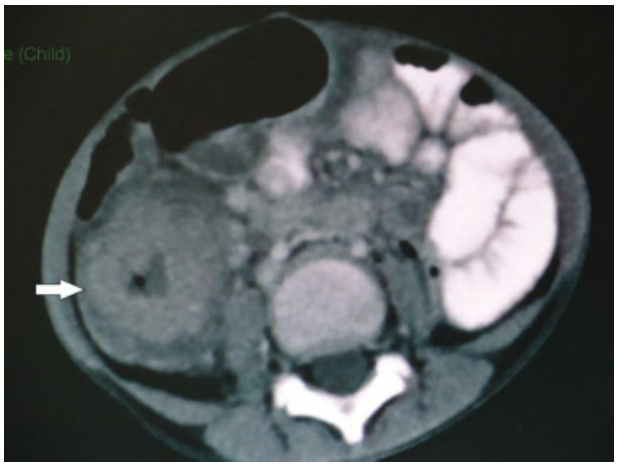

Fig. 1 Computed tomography abdomen shows mass in the cecum (arrow).

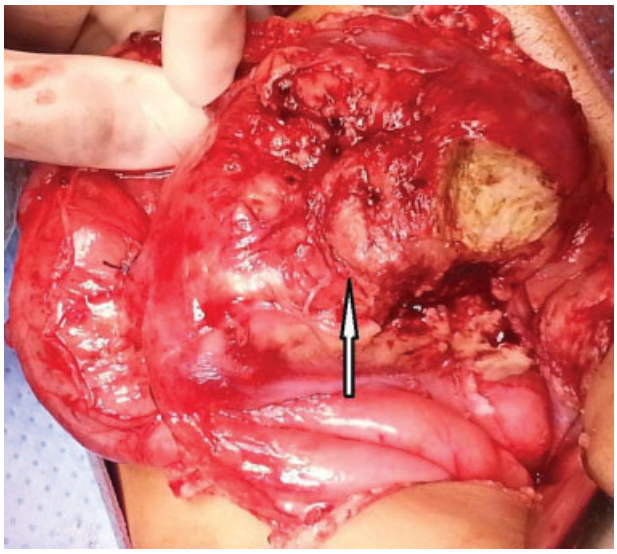

Fig. 2 Cecal mass (arrow).

surrounding structures. Biopsies were taken with difficulty. One patient was diagnosed with isolated liver abscess. Percutaneous liver abscess drainage was tried under ultrasound guidance, but there was no pus; therefore, an ultrasound guided liver biopsy was performed.

Histology (in all cases) was diagnostic for GIB. It showed transmural granulomatous inflammation with prominent eosinophilic component. There were broad, septate, hyphae-like structures surrounded by an eosinophilic sheath (Splendore–Hoeppli phenomenon (►**Fig. 4**). Periodic acid–Schiff staining and Grimelius methenamine silver-stained sections showed broad fungal hyphae and zygospores (►**Fig. 5**).

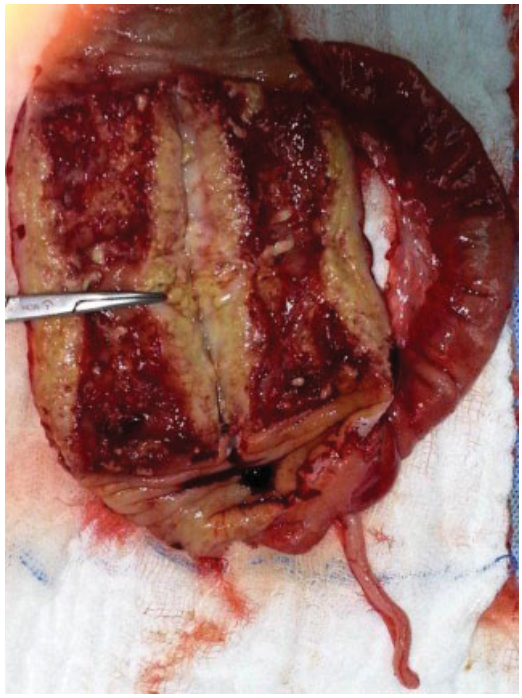

Fig. 3 Mass in the ascending colon. The mass has been opened longitudinally to show diffuse circumferential mucosal thickening.

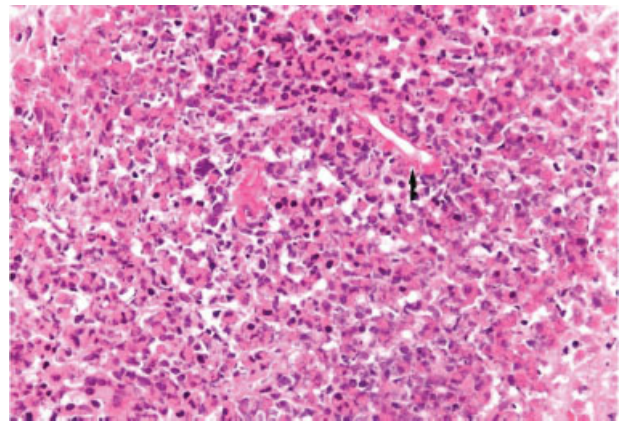

Fig. 4 Periodic acid–Schiff staining shows broad fungal hyphae and zygospores (black arrow).

Itraconazole therapy was followed by dramatic reduction of fever and abdominal manifestations, along with a decrease of eosinophils within 10 days of treatment.

The follow-up period ranged from 12 to 30 months (mean: 17.3 months). Complete clinical and radiological improvement was achieved after 6 to 8 months (mean: 6.7 months) for patients with surgical resection and after 9 to 12 months (mean 10.6 months) for patients without resection. No mortalities, morbidities, or recurrence were detected.

Discussion

Basidiobolomycosis is an emerging fungal infection that manifests in the skin and rarely involves other systems. Visceral involvement by basidiobolomycosis is rare, with relatively few cases (73) reported worldwide thus far. Most of the cases of pediatric GIB were reported from the southern region of Saudi Arabia.[10] It is caused by *B. ranarum*, which does not usually invade blood vessels and rarely disseminates.[7,11]

All age groups are susceptible to infection. In a recent review, the mean age was 37 years.[11] In our series, drawn from a pediatric age group, the mean age was 7.5 years. The male-to-female ratio in our series was 5:1, reflecting a greater

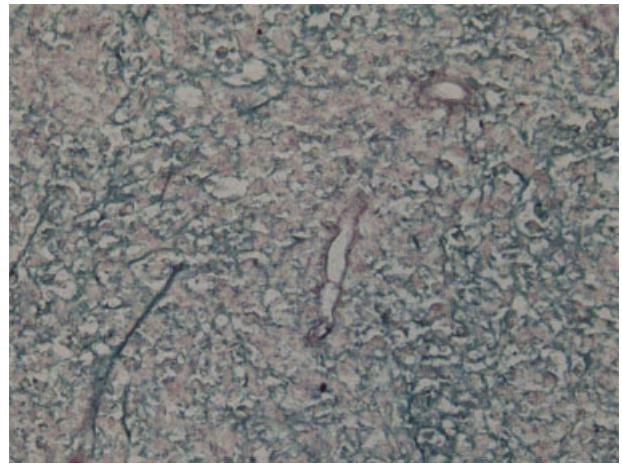

Fig. 5 Grimelius methenamine silver-stained specimen.

frequency of occurrence in males, which is in agreement with the findings by other authors.[1,3,12]

The diagnosis of GIB is often elusive for many reasons. First, its clinical presentation in immunocompetent patients is nonspecific. In our study, abdominal pain was the most common presenting symptom (94.4%) followed by constipation (83.3%) and abdominal mass (77.8%); fever was present in only 22.2% of cases. These results are very similar to those in other reports.[13] Elevated inflammatory markers and eosinophilia, present in our cases, appear to be prominent laboratory findings. Second, based on the radiographic appearance of an abdominal (usually colonic) mass with spread to surrounding organs, especially when associated with alteration in bowel habits, the disease often mimics malignancy or Crohn's disease, which may delay diagnosis.[1,7,14] Third, the infection usually involves the nonmucosal layers of the gastrointestinal tract so that endoscopic imaging and biopsy specimens may show only nonspecific inflammation, and neutrophilic infiltrate is rare.[15] For all these reasons, GIB is an infection that leads to diagnostic confusion.

We agree with other clinicians who emphasize that diagnosis of GIB requires a high index of suspicion, awareness, and consideration. The diagnosis might be suspected in previously healthy children, especially those living in or near tropical areas who develop symptoms that may suggest the diagnosis and are associated with abdominal masses and eosinophilia.[12,16,17]

Because the diagnosis is usually equivocal, tissue biopsy is mandatory. Although culture or serology tests are required for definitive diagnosis, histological analysis can provide a probable diagnosis of GIB. Surgical specimens should be inoculated soon after resection because the fungus does not survive at 4°C. Sabouraud agar is an adequate medium, and visible growth is usually present 2 to 3 days after incubation at 25°C to 30°C.[3]

Based on the data available from review of the literature, the current experience of treating patients with GIB is limited. Surgical resection of the infected tissue followed by prolonged antifungal therapy (more than 3 months) were the most commonly used options.[7,8,10,11,18] A few authors questioned the role of surgery in the management of GIB. They used antifungal therapy alone in the management of their cases. The long-term prognosis in such cases remains unclear however,[3,7,11,19] and obtaining tissue biopsy by interventional radiology, endoscopy, or laparoscopy is usually associated with high risk of GIT perforation. From our experience, and that of others,[19] we suggest that surgery is mandatory in most cases. If a patient is fit for surgery and the surgical resection is safe, then the aim is to resect only the affected bowel segments without mutilation. Surgery would provide a good specimen for histopathology and remove the nidus of infection, thus reducing the duration of antifungal therapy with fewer drug side effects.[19]

The best choice of antifungal agent is not clear, but many published articles as well as our study have suggested that itraconazole is a reasonable option; it showed complete resolution of the infection in most of the reported cases.[7,8,14] Voriconazole could be an alternative antifungal therapy for cases that have resistance to itraconazole.[11] The efficacy of amphotericin B in visceral infections has been unsatisfactory, with resistance observed in greater than 50% of cases. Potassium iodide has been used successfully for treatment of subcutaneous basidiobolomycosis but not GIB.[3]

Conclusion

GIB is an emerging infection in children that can lead to diagnostic confusion. Diagnosis of this disease requires a high index of suspicion, awareness, and consideration of its possibility in the differential diagnosis in patients with abdominal masses and eosinophilia, particularly in areas where GIB is endemic. Increased awareness of this clinical entity, early surgical resection of the infected tissue, and prolonged treatment with itraconazole offer the best chance for curing the disease.

Conflict of Interest

None.

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