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Gastrointestinal basidiobolomycosis: An emerging mycosis difficult to diagnose but curable. Case report and review of the literature

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ABSTRACT

Background: Gastrointestinal basidiobolomycosis (GIB) is a rare mycosis affecting almost exclusively immunocompetent subjects.
Methods: We describe a case of GIB caused by *Basidiobolus ranarum* in a 25-year-old Italian immunocompetent man resident in Ireland who presented a 2-month history of epigastric pain. Suspecting colon cancer he underwent a right hemicolectomy subsequently leading to a diagnosis of GIB by means of molecular biology. After surgery a 9-month therapy with itraconazole was employed with a good outcome. A review of medical literature regarding GIB cases published in the period 1964–2017 is presented.
Results: One-hundred and two cases of GIB were included in this analysis. The disease was observed predominantly in male gender (74.5%) and children (41.2%). Abdominal pain was the single most common complaint (86.3%) followed by fever (40.2%) and evidence of an abdominal mass (30.4%). Peripheral blood eosinophilia was detected in 85.7% of cases. Most of the patients were diagnosed in Saudi Arabia (37.2%) followed by USA (21.6%) and Iran (20.6%). Surgery plus antifungal therapy was employed in the majority of patients (77.5%). An unfavourable outcome was documented globally in 18.6% of patients.
Conclusions: GIB seems to be an emerging intestinal mycosis among immunocompetent patients living in the Middle East and Arizona.

1. Introduction

Basidiobolus ranarum was initially described in 1886 as a fungus cultured from frogs and two years later cultured from their intestinal contents and excreta [1]. It was first isolated in 1955 from decayed leaves in the United States and subsequently from soil and decaying vegetation from throughout the world [2–5]. It is actually classified in the phylum Entomophthoromycota that includes one of the largest groups of early-diverging terrestrial fungi previously classified in the phylum Zygomycota (Table 1) [6,7]. *B. ranarum* belongs to the class Basidiobolomycetes which includes a single order and family and it is a commensal in the gut of amphibians (frogs, toads), fish, reptiles and insectivorous bats [7]. *B. haptosporus*, *B. heterosporos* and *B. meristosporos* have been considered in the past as synonyms of the species *B. ranarum* [8]. Human disease caused by *Basidiobolus* was first described as a skin and subcutaneous indolent and slowly progressing infection, affecting the limbs, trunk and buttocks of young males residing in tropical and subtropical regions [9–11]. The exact mode of transmission of the fungus has not yet been characterised but in the case of subcutaneous disease, it has been attributed to the more frequent habit (by males) of using decaying plant leaves as toilet paper after defecating in the open or otherwise via minor skin trauma and insect bites. However, it remains puzzling how the fungus is introduced into the host's gastrointestinal tract, thus resulting in gastrointestinal basidiobolomycosis (GIB). It has been suggested that ingestion of soil, animal faeces or food contami-

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Table 1
Taxonomic classification of *Basidiobolus ranarum* within Entomophthoromycota phylum.

Taxonomy	Previous	Actual
Phylum	Zygomycota	Entomophthoromycota
Class	Zygomycetes	Basidiobolomycetes
Order	Entomophthorales	Basidiobolales
Family	Basidiobolaceae	Basidiobolaceae
Species	*Basidiobolus*	*B. ranarum*; *B. haptosporus*; *B. heterosporus*; *B. magnus*; *B. meristoporus*; *B. microsporus* (plus undescribed new genera)

nated by either might be responsible, explaining the highest number of cases observed among children.

The first case of GIB was probably reported in 1964 as an autopsy diagnosis in a 6-year old children from Nigeria who had also subcutaneous lesions [4]. However, Brazilian authors were the first who recognised GIB as a distinct clinical entity affecting immunocompetent individuals [12].

Although considered an extremely rare disease, GIB seems to be an emerging fungal infection in Saudi Arabia, Iran, Iraq and Arizona in the United States of America. We report here a case of GIB observed in a young immunocompetent Italian patient together with a review of the literature.

2. Materials and methods

2.1. Definitions

We defined a confirmed case of GIB on the basis of either the characteristic histopathologic appearance of the fungus in tissue biopsy or from surgical specimens obtained from gastrointestinal organs (*i.e.*, stomach, small intestine, colon, rectum, liver, gallbladder, pancreas) or the isolation of *Basidiobolus ranarum* from such specimens or identification by molecular methods.

The PubMed and Scopus databases were searched for articles (in English, French, Spanish languages) published between 1964 and 2017 using the following combination of MESH terms: basidiobolomycosis AND gastrointestinal; basidiobolomycosis AND abdominal infection; *Basidiobolus ranarum* AND gastrointestinal infection; entomophtoromycosis AND gastrointestinal. Articles were reviewed in detail by 2 of us (M.D.P. and V.D.C.) to determine whether cases met the inclusion criteria. Additional cases were identified by reviewing references. Several cases were reported more than once and duplicates were excluded.

3. Results

3.1. Case report

In March 2013, a 25-year-old Italian male was admitted to a specialized oncological institute in Milan, for a suspect bowel neoplasm. He had a history of epigastric and lower right abdominal pain over the last two months so he had done on February an US abdomen which showed a mass in the right lumbar-hypogastric region of 65 mm in transverse diameter with associated retroperitoneal lymph nodes. The patient was an otherwise healthy man with an unremarkable past medical history; he was living in Cork, Ireland, working as a cook in a hotel.

Physical examination showed no abnormalities except a palpable tender mass on the right lower quadrant; on laboratory investigations white blood cell count was 10.1×10^9/L (normal value 4.4–11.3) with 0.99×10^9/L eosinophils (normal value 0.04–0.4), hemoglobin level of 15.6 g/dL, normal liver function tests, electrolyte levels and creatinine levels. CT scan of the pelvis and lower abdomen showed diffuse circumferential wall thickening affecting distal ileal loop and cecum, narrowing of lumen and regional lymph node involvement (Fig. 1a). Colonoscopy was performed, revealing a complete stricture of the ascending colon due to an ulcerated mass (Fig. 1b). Biopsies were taken and histopathology showed granulomatous and necrotizing inflammation. Because of a clinical profile suggestive of malignancy with colonic obstruction a right hemicolectomy was done. At the histology examination there were areas of necrotizing inflammation with marked eosinophilic infiltrate and foreign body-type giant cell reaction; fungal hyphae were seen within some of the multinucleated giant cells and a presumptive diagnosis of intestinal zygomycosis was done by the pathologist.

The patient was referred to our Infectious diseases ward for further evaluation and management. Upon reviewing the pathology material, the hyphae had few septa, were highlighted by the PAS and Grocott stains and surrounded by eosinophilic and hyaline material (Splendore-Höeppli phenomenon) (Fig. 2). The identification of the fungus was established by DNA extraction from formalin-fixed paraffin embedded tissue and panfungal polymerase chain reaction (PCR) amplification of 18S rRNA. Amplified fragment had 99% identity with *Basidiobolus ranarum* [13] (Fig. 3). Because preoperative diagnosis was presumed to be malignant, no tissue was sent for culture. Pending molecular typing of fungus, the patient was started on liposomal amphotericin B at the dose of 5 mg/kg, 4 days later substituted with itraconazole *po* 200 mg BID because resistance and clinical failure with amphotericin B has been described.

Immunological deficiencies were excluded by additional investigations (lymphocyte subpopulations, HIV, HBV, HCV, immunoglobulins, C3 and C4, oxidative BURST, T-lymphocyte maturation study and CD11b expression on neutrophils and monocytes). Complete blood

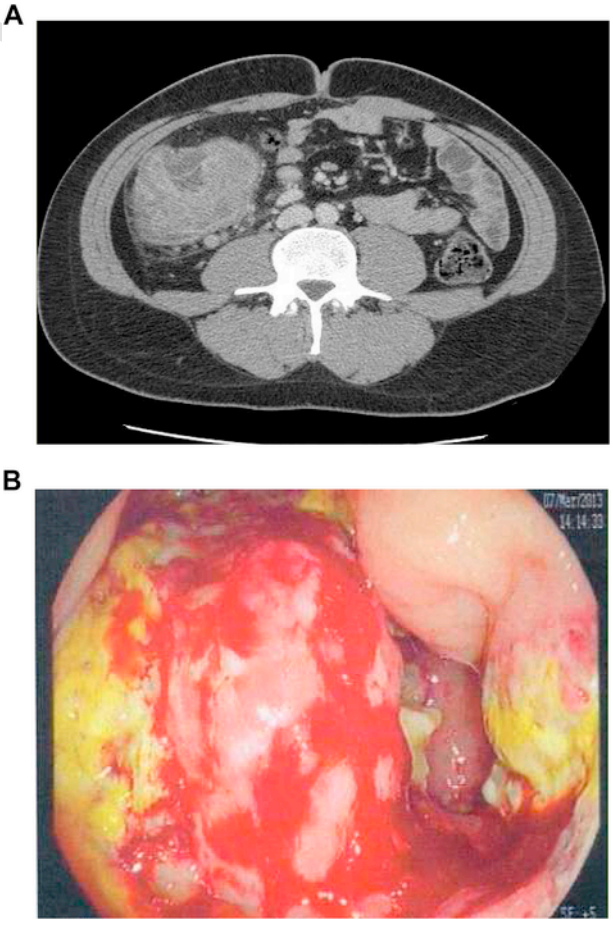

Fig. 1. Computed tomography scan showing a mass in the ascending colon.

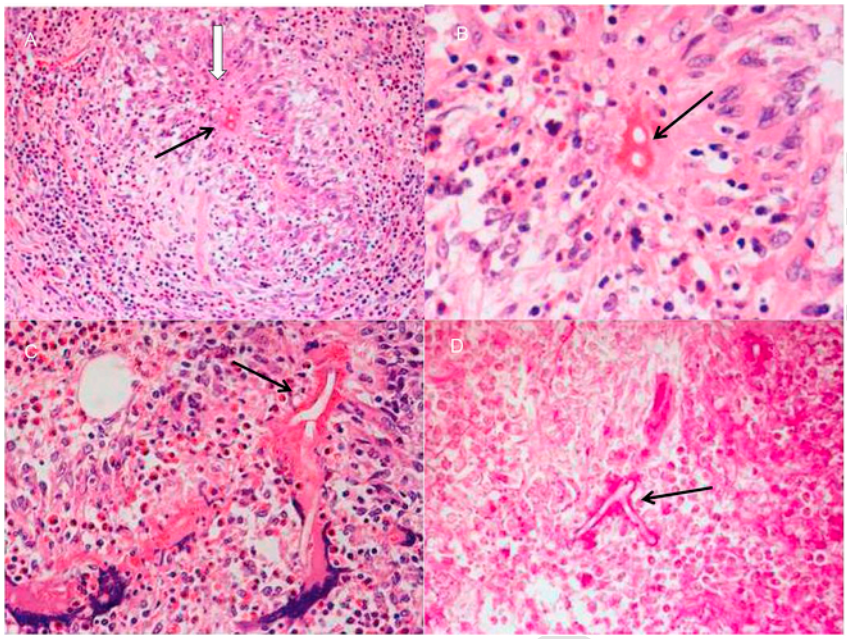

Fig. 2. (A,B) Histopathologic section of colon showing granumomatous inflammation of the colonic wall with prominent eosinophilic infiltrate with a transversely cut hypha (black arrow) surrounded by an intensely eosinophilic cuff (Splendore-Hoeppli phenomenon, white arrow) (Hematoxylin-eosin x100 and x400). (C,D) Detailed view of large fungal hypha surrounded by eosinophilic Splendore-Hoeppli material and numerous eosinophils and polymorphonuclear leucocytes (E&E x 400).

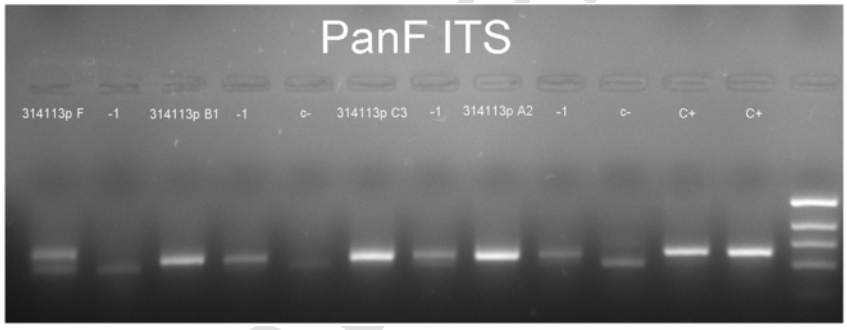

Fig. 3. Panfungal PCR that amplifies the internal transcriber space (ITS) region of the rDNA gene performed on multiple samples (F,B1,C3,A2) of paraffin-embedded tissue specimens from different areas of the mass. Sequenced amplicons gave a 99% matching with *Basidiobolus ranarum* (One μg and 100 ng, respectively were tested).

count, apart from eosinophilia (12% maximum), was normal as other laboratory results. US abdomen before discharge showed hepatosplenomegaly, normal ileal and colic loops without any mass. The patient was discharged in April with oral itraconazole 200 mg BID and regular follow-up was started.

After 3 months abdominal CT was negative. In January 2014 the patient repeated US abdomen, showing only splenomegaly, and laboratory tests (white blood cell count 7.4×10^9/L with 0.23×10^9/L eosinophils). He received itraconazole 200 mg x 2/daily for a total of 9 months; at one year follow up he is in good health without relapse of the disease.

3.2. Review of the literature

Gastrointestinal basidiobolomycosis (GIB) has been considered an extremely rare disease with only six cases reported in the literature up to 1994 [4,12,14–16]. However, starting from 1995 a cluster of cases of GIB was described from Arizona with 19 patients (89% resident in Arizona) identified between 1995 and 2009 at Mayo Clinic, Scottsdale (Arizona) [17–20]. Eight of these 19 patients had been described separately before being finally reviewed by Vikram et al., in 2012 together with other 25 cases observed outside the United States [21]. All the detailed published cases (with the exception of 12 cases reported in the review by Vikram and not singularly described) plus the one observed by us are summarised in Table 2 [4,12,14–20,22–62]. We noted that a further 18 pediatric cases of basidiobolomycosis were reported in 2017 but they are not included in the present review because of the lack of any detailed information regarding single cases [63]. Eleven cases were reported in a 36-year period (1964–2000; a mean of 0.3 cases/year) and 78 in the last seventeen years (2001–2017; a mean of 4.6 cases/year) with a 15.3-fold increase. Overall, we considered for the purpose of our review the forty-four cases previously reviewed by Vikram et al., in 2012 plus fifty-eight new cases (including our present observation) described in detail after 2008 [21] (Table 3). A male prevalence was observed (76/102, 74.5%) with a 3:1 ratio. All but one patient were immunocompetent [59]. The median age was 19 years (range 1–81 years) and 42 patients (41.2%) were children (age 1–13 years). The countries of residence in 79.4% of patients were only three: Saudi Arabia (37.2%), USA (21.6%) and Iran (20.6%) (Fig. 4). Abdominal pain (86.3%) was the most common presenting symptom followed by weight loss (33.3%), abdominal distension (16.7%), vomiting (15.7%) and diarrhea (13.7%) (Table 3). Fever was reported only in 40.2% of patients and an abdominal mass was palpable in 30.4% of cases. Peripheral blood eosinophilia was detected in 85% of patients for whom this data was available. An initial misdiagnosis was made in 68% of cases (68/102) with neoplasms and inflammatory bowel disease being

Table 2
Chronological summary of 89 case reports of gastrointestinal basidiobolomycosis.

Patient/Reference	Year observation/ Publication	Country	Age/sex	Clinical presentation	Leukocyte/Eosinophils/Splendore-Hoeppli phenomenon	Organ involvement	Diagnosis	Therapy	Outc
1/4	NR/1964	Nigeria	6/M	Subcutaneous lesions (penis, scrotum, perineum); bloody diarrhea	NR/NR/NR	I; C; R; bladder	Post-mortem (histopathology)	Colostomy; antibiotics	Deatl
2/12	1977/1979	Brazil	13/M	Abdominal pain, fever, weakness, anorexia	NR/16%/Yes	S; D; L; P; C; BT	Post-mortem (histopathology)	Laparatomy	Deatl days surge
3/12	NR/1979	Brazil	60/M	Abdominal pain	NR/NR/Yes	S; C	Histopathology; culture negative	Gastrectomy & hemicolectomy; AmB	Cure
4/14	1979/1980	Brazil	4/M	Fever, abdominal pain, sweats, diarrhea	13,500 μL/26%/Yes	S; C	Histopathology; culture (*Basidiobolus haptosporus*)	Surgery	Deatl days surge (peri
5/15	NR/1986	USA	69/M	Fever, abdominal pain, nausea, constipation, vomiting, right lower quadrant mass	19,500 μL/6%/Yes	I; Ce; C	Histopathology/culture (*B.haptosporus/ranarum*)	Surgery/AmB	Deatl week lapar
6/16	1989/1997	Brazil	19/M	Fever, abdominal mass, weight loss, sweats	12,600 μL/11%/Yes	I; Ce; C:	Histopathology	Surgery/	NR
7/17	1994/1997	USA	49/F	Abdominal and rectal pain, constipation followed by mucus and bloody diarrhea	23,400 μL/NR)/Yes	C; R	Histopathology/serology	Surgery/Itraconazole (5 months)	Alive 13 m
8/22	1996/1998	Kuwait (Bangladesh)	30/M	Rectal bleeding, constipation, rectal mass	18-22,000 μL/NR/NR	R	Histopathology/Culture (*B.ranarum*)/serology	Surgery/AmB (3weeks) + ketoconazole (1 week)	Lost follo
9/18	1998/1999	USA	37/F	Abdominal pain	26,400 μL/10%/NR	S; P	Histopathology	Surgery/Itraconazole (9.5 months)	Cure
10/18	1998/1999	USA	59/M	Abdominal pain, mucus, colonic obstruction	12,100 μL/6%/NR	C	Histopathology/Culture (*B.ranarum*)	Surgery/Itraconazole	Cure
11/19	1997/1999	USA	57/M	Abdominal pain, anorexia, fatigue, constipation	16,400 μL/8%/Yes	S; C; R; ureter	Histopathology/Culture (*B.ranarum*)	Surgery/AmB (1week) + itraconazole (11 months); terbinafine 2 months	Cure
12/20	1996/2001	USA	46/M	Abdominal pain, abdominal mass	NR/NR/Yes	I; Ce; appendix; retroperitoneum	Histopathology/Culture (*B.ranarum*)	Surgery/Itraconazole (19 months)	Alive mont mont itrac with
13/20	1998/2001	USA	52/M	Abdominal pain	12,800 μL/14,3%/Yes	C	Histopathology/culture negative/ serology	Surgery/Itraconazole (10 months)	Alive mont itrac with
14/20	1999/2001	USA	59/M	Abdominal pain, constipation	NR/NR/NR	Ce; C	Histopathology/Culture not done	Surgery/Itraconazole (10 months)	Alive
15/23	1999/2001	Kuwait (Indian patient)	41/M	Fever, abdominal pain, abdominal mass	NR/NR/Yes	Ce; C	Histopathology/Culture from urine (*B.ranarum*)/serology	Surgery/LAmB (4 weeks)	Lost follo
16/24	2000/2003	Saudi Arabia	12/M	Fever, abdominal pain, abdominal mass, scrotal swelling	16,000 μL/15%/Yes	I; Ce; C; L; BT	Histopathology/Culture (*B.ranarum*)	Surgery/Itraconazole (>24 months)	Alive

17/24	2001/2003	Saudi Arabia	12/M	Fever, abdominal pain	11,000 μL/20%/Yes	I; Ce; C	Histopathology	Surgery/AmB than itraconazole (12 months)	Alive

Table 2 (*Continued*)

Patient/Reference	Year observation/ Publication	Country	Age/sex	Clinical presentation	Leukocyte/Eosinophils/Splendore-Hoeppli phenomenon	Organ involvement	Diagnosis	Therapy	Outc
18/24	2001/2003	Saudi Arabia	9/M	Fever, abdominal pain	17,800 μL/19.8%/NR	Ce; C; R	Histopathology/Culture (*B.ranarum*)	Surgery/Itraconazole (10 months)	Alive
19/24	2002/2003	Saudi Arabia	4/M	Fever, abdominal pain, hepatomegaly	30,000 μL/30%/NR	L; intestine	Histopathology/Culture (*B.ranarum*) from liver biopsy	AmB than itraconazole (>12 months)	Alive
20/24	2001/2003	Saudi Arabia	3/M	Fever, abdominal pain, heaptomegaly, ascites	24,500μL/18%/Yes	L	Histopathology/Culture (*B.ranarum*) from liver biopsy	AmB + 5Flu	Deatl MOF after admi
21/24	2000/2003	Saudi Arabia	7/M	Fever, abdominal pain, abdominal distension, hepatosplenomegaly	16,900 μL/17%/Yes	R; D; BT	Histopathology (liver biopsy)	AmB + itraconazole (12 months)	Deatl (mas bleed
22/25	NR/2003	Saudi Arabia	12/M	Fever, abdominal pain, anorexia, weight loss, vomiting, constipation	17,900 μL/20%/Yes	I; Ce; C	Histopathology/Culture (*B.ranarum*)	Surgery/Itraconazole (10 months)	Alive
23/26	NR/2004	Iran	45/M	Abdominal pain	NR/NR/Yes	Ce; L	Histopathology	Surgery/Ketoconazole + cotrimoxazole (4 weeks)	Alive
24/27	NR/2004	Italy	40/F	Fever, subcutaneous lesions	28,320 μL/30%/Yes	L; P; S; M; lung; spleen; kidneys; uterus	Post-mortem (histopathology)	–	Deatl shocl pulm failu
25/28	1990/2005	Brazil	43/M	Fever, abdominal pain, vomiting, weight loss	10,800 μL/NR/Yes	P	Histopathology	Surgery/ketoconazole (35 days)	Follo not s
26/29	NR/2006	Iran	1.5/M	Fever, abdominal pain, diarrhea, hematochezia	NR/Yes/Yes	R	Histopathology	Surgery/AmB (1 week) than itraconazole (9 months)	Alive
27/30	NR/2006	The Netherlands	61/M	Abdominal pain, constipation	NR/27.7%/Yes	C; L; gallbladder	Histopathology; culture post-mortem *B.ranarum*	Cholangiodrain/AmB	Deatl MOF days start antifi thera
28/31	NR/2007	Saudi Arabia	13/M	Abdominal pain, tenderness	NR/NR/Yes	C	Histopathology/Culture negative	Surgery/Itraconazole	Alive
29/32	2002-2007/2007	Iran	18/M	Abdominal pain, constipation	12,000 μL/8%/Yes	I	Histopathology	Surgery/Itraconazole	Alive years
30/32	2002-2007/2007	Iran	2.5/M	Abdominal pain, constipation, rectal bleeding	26,800 μL/10%/Yes	C	Histopathology	Surgery/Itraconazole	Alive years
31/32	2002/2007	Iran	2/M	Abdominal pain, distension, ascites	29,400 μL/16%/Yes	C	Histopathology	Surgery/Itraconazole	Alive years
32/33	2000/2009	Saudi Arabia	77/M	Abdominal pain, abdominal mass, weight loss, rectal bleeding	Normal/NR/Yes	Ce; C	Histopathology	Surgery/Itraconazole (2 weeks)	Lost follo
33/33	2001/2009	Saudi Arabia	19/F	Fever, abdominal pain, weight loss	NR/NR/Yes	Ce; C	Histopathology/Culture (*B. ranarum*)	LAmB + itraconazole; ketoconazole (4 years)	Alive years
34/33	NR/2009	Saudi Arabia	20/M	Abdominal mass, weight loss, ematochezia	NR/NR/Yes	C	Histopathology/Culture (*B. ranarum*)	Voriconazole	Alive
35/34	NR/2011	Saudi Arabia	10/M	Fever, abdominal pain, vomiting	12,200 μL/17%/Yes	Ce;	Histopathology/PCR (*B.ranarum*)	Itraconazole (12 months)	Alive year)

Table 2 (*Continued*)

Patient/Reference	Year observation/ Publication	Country	Age/sex	Clinical presentation	Leukocyte/Eosinophils/Splendore-Hoeppli phenomenon	Organ involvement	Diagnosis	Therapy	Outc
36/35	2003/2011	Saudi Arabia	6/M	Fever, abdominal pain, abdominal mass	32,700 μL/11%/NR	Ce; C; L	Histopathology/Culture (*B.ranarum*)	AmB than itraconazole	Alive years
37/35	2003/2011	Saudi Arabia	13/F	Fever, abdominal pain	14,500 μL/18%/Yes	I; Ce; C	Histopathology	Surgery/AmB + itraconazole (12 months)	Alive years
38/35	2003/2011	Saudi Arabia	8/F	Fever, anorexia, abdominal distension, weight loss	13,800 μL/4%/Yes	P; L; BT	Histopathology	Surgery/AmB than itraconazole (18 months)	Alive years
39/36	NR/2011	Saudi Arabia	25/F	Abdominal pain, weight loss, nausea, rectal bleeding	12,800 μL/NR/Yes	C	Histopathology	Surgery/Itraconazole	Alive
40/37	2010/2012	Saudi Arabia	2/M	Fever, abdominal pain, abdominal mass, vomiting, diarrhea	14,000 μL/19%/Yes	I; Ce; C	Histopathology	AmB than voriconazole (12 months)	Alive year)
41/38	NR/2012	Iran	12/M	Fever, abdominal pain, vomiting, bloody diarrhea	28,100 μL/16%/Yes	C	Histopathology	Surgery/AmB (1 week) than posaconazole	Follo not s
42/39	2008-2012/2012	Iran	1.3/F	Abdominal pain, distension	23,000 μL/17%/Yes	S; C; M	Histopathology/Culture negative	Surgery/AmB than itraconazole	Deatl disse disea
43/39	2008-2012/2012	Iran	5/M	Abdominal pain, weight loss	21,300 μL/20%/Yes	C	Histopathology/Culture negative	Surgery/AmB than itraconazole	Alive mont
44/39	2008-2012/2012	Iran	5/M	Abdominal pain	16,100 μL/10%/Yes	C	Histopathology/Culture negative	Surgery/AmB than itraconazole	Alive years
45/39	2008-2012/2012	Iran	2/M	Abdominal pain, diarrhea	17,400 μL/20%/Yes	I; C	Histopathology/Culture negative	Surgery/AmB than itraconazole	Alive mont
46/39	2008-2012/2012	Iran	16/M	Abdominal pain	11,500 μL/14%/Yes	C	Histopathology/Culture negative	Surgery/AmB than itraconazole	Alive years
47/39	2008-2012/2012	Iran	1.3/M	Abdominal pain, diarrhea	18,200 μL/8%/Yes	S; I; C; M	Histopathology/Culture negative	Surgery/AmB than itraconazole	Deatl disse disea mont
48/39	2008-2012/2012	Iran	1.1/M	Abdominal pain, bloody stool	23,000 μL/16%/Yes	C	Histopathology/Culture negative	Surgery/AmB than itraconazole	Alive year)
49/39	2008-2012/2012	Iran	37/M	Abdominal pain	20,000 μL/10%/Yes	C	Histopathology/Culture negative	Surgery/Itraconazole	Alive mont
50/39	2008-2012/2012	Iran	28/M	Abdominal pain	14,000 μL/10%/Yes	C	Histopathology/Culture negative	Surgery/Itraconazole	Alive years
51/39	2008-2012/2012	Iran	52/M	Abdominal pain, vomiting, diarrhea	17,000 μL/15%/Yes	C	Histopathology/Culture negative	Surgery/Itraconazole	Alive mont
52/39	2008-2012/2012	Iran	42/F	Abdominal pain	17,000 μL/15.9%/Yes	I; C	Histopathology/Culture (*B.ranarum*)	Surgery/Itraconazole	Alive
53/40	NR/2013	USA	67/M	Abdominal pain	NR/NR/Yes	I	Histopathology/PCR (*B.ranarum*)	Surgery/Ureteral stent/Fluconazole (several months); posaconazole 600 (1 year)	Alive years
54/41	NR/2013	Saudi Arabia	4/M	Fever, abdominal pain, vomiting, weight loss	17,000 μL/13.6%/Yes	I; Ce; C	Histopathology/Culture (*B.ranarum*)	Surgery/Voriconazole (12 months)	Alive year)
55/42	NR/2013	Saudi Arabia	5/M	Fever, abdominal pain, bloody diarrhea, anorexia, weight loss	15,600 μL/15%/Yes	C	Histopathology/Culture negative	Voriconazole (6 months)	Alive mont

56/43	NR/2013	Iran	12/M	Fever, abdominal pain, hematuria	14,500 μL/No/Yes	I; C	Histopathology	Surgery/Itraconazole + AmB (2 weeks) then itraconazole	Deatl septi

Table 2 (*Continued*)

Patient/Reference	Year observation/ Publication	Country	Age/sex	Clinical presentation	Leukocyte/Eosinophils/Splendore-Hoeppli phenomenon	Organ involvement	Diagnosis	Therapy	Outc
57/44	2010/2013	Iraq	48/M	Fever, abdominal pain, weight loss	NR/12%/Yes	Ce; C; L	Histopathology	Surgery/Itraconazole (6 months)	Alive year)
58/44	2010/2013	Iraq	1.5/M	Fever, abdominal pain, weight loss, abdominal mass	NR/29%/Yes	NR	Histopathology	AmB	Deatl intes perfo
59/44	2010/2013	Iraq	59/M	Fever, abdominal pain, weight loss, abdominal mass	NR/No/Yes	Ce	Histopathology	Surgery/Itraconazole (6 months)	Alive year)
60/44	2012/2013	Iraq	53/M	Fever, abdominal pain, weight loss,	NR/NT/Yes	Ce; C	Histopathology	Surgery/Itraconazole (6 months)	Alive mont
61/44	2012/2013	Iraq	39/M	Fever, weight loss, cough, sore throat	NR/9%/Yes	O; C	Histopathology	Surgery/Itraconazole (7 months)	Alive mont
62/44	2012/2013	Iraq	1.5/M	Fever, abdominal pain, abdominal mass, weight loss	NR/21%/Yes	Ce; C	Histopathology	Surgery/Itraconazole (4 months)	Alive mont
63/45	NR/2013	Saudi Arabia	24/M	Fever, abdominal pain, weight loss, diarrhea	14,400 μL/22%/NR	I; Ce; C	Histopathology/Culture (*B.ranarum*)	Surgery/Itraconazole (12 months)	Alive year)
64/45	NR/2013	Saudi Arabia	21/F	Fever, abdominal pain, diarrhea alternate with constipation, weight loss	7100 μL/No/NR	Ce; C; R	Histopahology/Culture (*B.ranarum*)	Steroid/Itraconazole	Deatl HC-assoc infec
65/45	NR/2013	Saudi Arabia	72/M	Fever, abdominal mass	15,280 μL/No/NR	Ce; C	Histopahology/Culture (*B.ranarum*)	Surgery/Itraconazole	Deatl bowe perfo and A septi (32 d post-
66/45	NR/2013	Saudi Arabia	19/M	Fever, abdominal pain, abdominal mass	22,100 μL/6.65%/NR	Ce; C	Histopahology/Culture (*B.ranarum*)	Surgery/Itraconazole	Deatl HC-assoc infec
67/46	2009-2012/2013	Saudi Arabia	12/F	Fever, abdominal pain, constipation	17,600μL/35%/Yes	I; Ce	Histopathology	Surgery/Itraconazole	Alive
68/46	2009-2012/2013	Saudi Arabia	1.5/M	Fever, hepatomegaly	24,520 μL/10.2%/Yes	L	Histopathology	Surgery/Itraconazole	Deatl ARDS few d
69/46	2009-2012/2013	Saudi Arabia	9/F	Abdominal pain, constipation, vomiting	17,800 μL/14%/Yes	C	Histopathology	Surgery/Itraconazole (8 months)	Alive mont
70/47	NR/2013	USA	34/F	Abdominal pain, constipation, vomiting, weight loss	13,000 μL/16.9%/NR	I; Ce	Histopahology/Culture (*B.ranarum*)	Surgery/Itraconazole + LAmB (6 weeks)	Alive
71/48	NR/2013	Iran	3/M	Abdominal pain, abdominal mass	12,500 μL/6%/Yes	C	Histopahology/Culture (*B.ranarum*)	Surgery/Posaconazole (3 months) then itraconazole (12 months)	Alive mont
72/49	2001/2014	Saudi Arabia	43/M	Abdominal pain, weight loss	15,000 μL/27%/Yes	Ce; C; L	Histopahology/Culture/(*B.ranarum*) from liver	Surgery/Itraconazole (7 months)	Alive mont
73/49	2005/2014	Saudi Arabia	20/F	Abdominal pain, abdominal mass	NR/NR/NR	C	Histopahology/Culture (*B.ranarum*)	Surgery	Deatl
74/49	2008/2014	Saudi Arabia	63/M	Abdominal pain, weight loss	12,400 μL/14%/Yes	I; C	Histopathology/Culture negative	Surgery/Voriconazole (12 months)	Alive mont

75/49	2011/2014	Saudi Arabia	20/F	Rectal bleeding	14,000 μL/20%/Yes	R	Histopathology	Drainage/Terbinafine + voriconazole (12 months)	Alive mont

Table 2 (*Continued*)

Patient/Reference	Year observation/ Publication	Country	Age/sex	Clinical presentation	Leukocyte/Eosinophils/Splendore-Hoeppli phenomenon	Organ involvement	Diagnosis	Therapy	Outc
76/50	2012/2014	Oman	5/F	Abdominal pain, nausea, vomiting, low grade fever	14,200 μL/50%/Yes	Ce, C	Histopathology/Culture positive (*Basidiobolus* spp.)	Surgery/LAmB + posaconazole then voriconazole (4 months)	Alive mont
77/51	2014	Mali/France	55/M	Abdominal pain	NR/NR/Yes	I; C	Histopathology/PCR (*B. ranarum*)	Antituberculous treatment	Deatl mont
78/52	2012/2014	Iran	41/F	Abdominal pain, weight loss, nausea, fever	14,300 μL/12%/Yes	I; Ce; L	Histopathology	Surgery/Itraconazole (4 months)	Alive mont
79/53	2014	Saudi Arabia	11/M	Abdominal pain	NR/Yes/Yes	C	Histopathology	Voriconazole (12 months)	Alive mont disco thera
80/54	2014	Saudi Arabia	24/F	Abdominal pain, nausea, vomiting, abdominal distension, constipation	7070 μL/14,6%/Yes	L; C; P	Histopathology/Culture & PCR positive (*B. ranarum*)	Voriconazole	Alive mont
81/55	2014/2015	Saudi Arabia	36/M	Suspected appendicitis	16,000 μL/18%/Yes	Ce	Histopathology	Surgery/Itraconazole (4 months); voriconazole	Alive
82/56	/2015	USA (Arizona)	56/M	Abdominal pain, rectal pain	NR/NR/NR	Ce; R	Histopathology	Itraconazole (12 months)	Alive mont
83/57	2015	Iran	2/F	Abdominal pain	11-12,000 μL/25–35%/Yes	L	Histopathology	Surgery/AmB (1 month)	Alive mont
84/58	2015	Qatar	4/F	Abdominal pain, rectal bleeding, weight loss,	NR/NR/Yes	C	Histopathology	Surgery/Voriconazole (12 months)	Alive mont
85/59	NR/2016	India	44/M	Liver transplant patient; rise in transaminases	NR/NR/NR	L	Culture (*B. ranarum*) of liver aspirate	LAmB; itraconazole, caspofungin, posaconazole	Deatl and l sepsi
86/60	NR/2017	Saudi Arabia	7/M	Abdominal pain, rectal bleeding, weight loss, fever	10,030 μL/15.9%/Yes	R	Histopathology	Surgery/Voriconazole (12 months)	Alive mont
87/61	NR/2017	Saudi Arabia	7/F	Abdominal pain, constipation, fever, palpable mass	19,000 μL(3000)/Yes	C; R	Histopathology	Voriconazole (9 months)	Alive mont
88/62	NR/2017	Iran	5/M	Abdominal pain, fever, anorexia, weight loss, vomiting	23,900 μL/11%/Yes	Ce; C; I	Histopathology/Culture (*Basidiobolus* spp.)	Amphotericin B (2 months); posaconazole (6 months)	Alive mont
89/PR	2013/2018	Italy/Ireland	25/M	Abdominal pain	10,100 μL/10%/Yes	I; Ce; C	Histopathology/PCR (*B.ranarum*)	Surgery/Itraconazole (8 months)	Alive mont

Twelve patients reported with no details in the review by Vikram et al. are not described in table. D, duodenum; E, esophagus; S, stomach; I, ileum; Ce, cecum; C, colon; R, rectum; O, oropharynx; BT, biliary tract; L, liver; P, peritoneum; M, mesentery; AmB, amphotericin B; LAmB, liposomal amphotericin B.

Table 3
Clinical manifestations, laboratory studies, sites of involvement and preliminary diagnosis in 102 patients with gastrointestinal basidiobolomycosis.

Characteristic	Patients, proportion (%) –Review by Vikram (1964–2008)[21]	Patients, proportion (%)- Present review (2009–2017)	Total
Number of pts	44 (43.1%)	58 (56.9%)	102
Age, years, median	37.3 (2–81)	17.5 (1.1–77)	19 (1.1–81)
Male sex	36 (81.8%)	40 (68.9%)	76 (74.5%)
Country of residence			
Brazil	4 (9%)	–	4 (3.9%)
Iran	4 (9%)	17 (29.3%)	21(20.6%)
Iraq	–	6 (10.3%)	6 (5.9%)
Saudi Arabia	11 (25%)	27 (46.5%)	38 (37.2%)
USA	19 (43%)	3 (5.2%)	22 (21.6%)
Other	6 (13.6%)[b]	5 (8.6%)[c]	11 (10.8%)
Signs and symptoms			
Abdominal pain	37 (84%)	51 (87.9%)	88 (86.3%)
Abdominal mass	19 (43%)	12 (20.7%)	31 (30.4%)
Constipation	17 (39%)	6 (10.3%)	23 (22.5%)
Abdominal distension	14 (32%)	3 (5.2%)	17 (16.7%)
Fever	14 (32%)	27 (46.5%)	41 (40.2%)
Weight loss	12 (27%)	22 (37.9%)	34 (33.3%)
Diarrhea	7 (16%)	7 (12.1%)	14 (13.7%)
Vomiting	6 (14%)	10 (17.2%)	16 (15.7%)
Lower gastrointestinal bleeding	6 (14%)	9 (15.5%)	15 (14.7%)
Hepatomegaly	5 (11%)	1 (1.7%)	6 (5.9%)
Laboratory test results[a]			
Peripheral blood eosinophilia	26/34 (76%)	43/47 (91.5%)	69/81 (85.2%)
Positive *Basidiobolus* serology	8/16 (50%)	–	8/16 (50%)
Growth of *Basidiobolus* in culture	17/24 (71%)	17/29 (58.6%)	34/53 (64.2%)
Characteristic histopathology	43/44 (98%)	57/57 (100%)	100/101 (99%)
Organ involvement			
Stomach	6 (14%)	2 (3.5%)	8 (7.9%)
Small bowel	16 (36%)	16 (28.1%)	32 (31.7%)
Colon/rectum	36 (82%)	50 (87.7%)	85 (84.2%)
Liver/gallbladder	13 (30%)	10 (17.5%)	22 (21.8%)
Pancreas	–	3 (5.3%)	3 (2.9%)
Preliminary diagnosis			
Malignancy	19 (43%)	6 (10.9%)	25 (24.7%)
Inflammatory bowel disease	7 (16%)	6 (10.9%)	13 (12.9%)
Diverticulitis	5 (11%)	–	5 (4.9%)
Appendicitis	3 (7%)	5 (9.1%)	8 (7.9%)
Lymphoma	2 (5%)	4 (7.3%)	6 (5.9%)
Gastrointestinal tuberculosis	2 (5%)	3 (5.5%)	5 (4.9%)
Ameboma	–	1 (1.8%)	1 (0.9%)
Schistosomiasis	–	1 (1.8%)	1 (0.9%)
Other	4 (9%)	–	4 (3.9%)
Antifungal treatment	37/43 (86%)	56/58 (96.5%)	93/101 (92.1%)
Itraconazole	26/37 (70.3%)	24/56 (42.9%)	50/93 (53.8%)
Amphotericin B	8/37 (21.6%)	2/56 (3.6%)	10/93 (10.7%)
Voriconazole	2/37 (5.4%)	10/56 (17.9%)[d]	12/93 (12.9%)
Posaconazole	0/37 (0%)	2/56 (3.6%)	2/93 (2.2%)
Amphotericin B plus (or followed by azole)	3/37 (8.1%)	18/56 (32.1%)	21/93 (22.6%)
Outcome	8 (18%) died	11 (18.9%) died	19 (18.6%) died

[a] Laboratory data are reported only when available.
[b] One patient each from:Nigeria, India, Bangladesh, Italy, The Netherlands; for 1 country was unknown.
[c] One patient each from: India, Ireland, Mali, Oman, Qatar.
[d] In one case associated with terbinafine.

the more frequently considered diagnosis (55.8%). In 32 cases (31.4%) the diagnosis was obtained by histopathology plus culture and/or polymerase chain reaction (PCR), in 66 patients (64.7%) only by histopathology. In four cases the correct diagnosis was achieved only *post-mortem*. Overall, culture for *B. ranarum* was positive in 34/53 cases (64.2%). Identification by PCR was obtained in 5 cases. Colon-rectum were involved in 84.2% of cases. On histopathology the presence of fungal hyphae, granulomatous inflammation, eosinophilic infiltration together with the Splendore-Höeppli phenomenon observed in the gastrointestinal tract should be considered highly suggestive for *B. ranarum*. Overall 93/102 (91.2%) patients received an antifungal therapy Surgery plus antifungal treatment was employed in 79/102 (77.5%) of patients. Eleven patients received only antifungal treatment of which four died (36.4%). Overall death was observed in 18.6% of patients.

4. Discussion

Basidiobolus ranarum is an environmental filamentous fungus that belongs to the phylum Entomophthoromycota, class Basidiobolomycetes formerly designated as zygomycetes. Recent phylogenetic studies showed that Entomophthromycota is a monophyletic lineage characterised by coenocytic vegetative cells, sporulation by production of infective conidia and production of zygospores capable of survival under unfavourable environmental conditions. *Basidiobolus* spp. form uninucleate cells with extremely large nuclei and had an haploid genome that has been estimated to be 10 times larger (350 Mb) than that of the average size of fungi [64]. The fungus grows at 30 °C in 2–3 days with yellow-gray flat colonies but after 7–10 days colony become overgrown with mycelia as masses of zygospores.

After its initial description by Eidam in 1886 [1], *Basidiobolus ranarum* was subsequently cultured from intestinal contents of frogs [65] and several other species of amphibians and reptiles, from decaying plant material, from an insectivorous bat (*Rhinopoma hardwickei hardwickei*) in India and from the faeces of kangaroos in Australia. The disease initially associated with *B. ranarum* was described in Indonesia in 1956 by Joe et al. [9] as subcutaneous phycomycosis and subsequently the same presentation was identified in other areas of tropical and subtropical climate, especially from Uganda, Nigeria and Indonesia. In 1964 the first case of gastrointestinal involvement was described in a 6-year old Nigerian boy at *postmortem* examination [4]. Gastrointestinal basidiobolomycosis (GIB) has been considered an extremely rare disease with only six cases reported up to 1999 [63]. Within the past 2

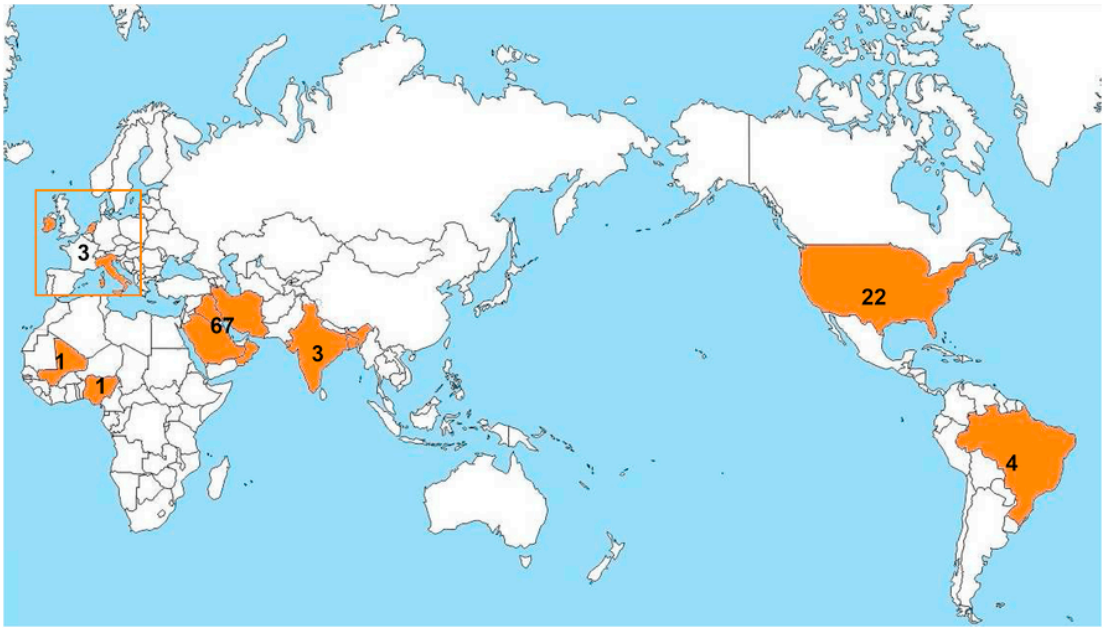

Fig. 4. Geographical distribution of cases of 101 gastrointestinal basidiobolomycosis reported worldwide (for one case the country was unknown).

decades a 15-fold increase in cases of gastrointestinal infection by *B. ranarum* has been reported worldwide. Although most of the cases have been described in the Middle East (Saudi Arabia, Iran, Iraq, Kuwait, Oman, Qatar) [23–26,29,31–39,41–46,48–50,52–55,57,60,62] and the southwestern of United States (Arizona and Utah) [15,17–20,40,47,56], sporadic reports came from South America, Africa, Europe and the Indian Subcontinent [4,12,14,16,27,28,30,51, 59,PR] and no clear environmental risk factors have been identified. In the case-control study performed by Lyon et al. in Arizona, ranitidine use (OR 6.0) and a longer period of smoking (OR 2.1/additional 20 years of smoking) were both associated with the development of the disease [20]. It has been hypothesized that the decreased gastric acidity together with the alteration of white blood cells activity induced by smoking might contribute to the survival of ingested *B. ranarum*. However, rural environment and activities such as gardening and landscaping as well as ingestion of contaminated soil or fruits and vegetables seem to be associated with a higher risk of exposure to the infection [21]. Since *B. ranarum* usually involves immunocompetent subjects, factors associated with health history of the hosts are not helpful for the diagnosis that is therefore frequently delayed. Of the three patients reported in Europe [27,30, PR], only the one described here was diagnosed during life. However, at least in endemic areas, a higher awareness of GIB by clinicians might partially account for the increase in the number of cases reported in the last decades. As in previous cases, in our patient the route of acquisition of the disease remains unknown; however since *B. ranarum* can be found in soil and decaying vegetables, we hypothesized that the consumption of homebrew unpasteurized and unfiltered beer might have been the source of fungal ingestion and subsequent involvement of the intestine.

A preliminary misdiagnosis among patients with GIB was commonly reported in the literature, the most frequent being gastrointestinal malignancy and inflammatory bowel diseases [17,22,30,33,34,36,37,41,42,56,61,62, PR], although a suspicion should be raised whenever fever and abdominal pain occur in young patients with gastrointestinal, abdominal mass or intestinal wall thickening in association with high eosinophilia.

Although a definite diagnosis can be obtained with culture [14,15,18,19,22–24,30,33,35,41,45,47,49–51,54,59,62], it was frequently missed in previous reports because of the lack of suspicion that made tissue specimens unavailable for culture purpose. Therefore, the diagnosis of gastrointestinal infection by *B. ranarum* was mainly obtained on histologic examination, which typical morphologic features include granulomatous inflammation and a diffuse eosinophilic infiltrate with thin walled branched hyphae surrounded by eosinophilic material (Splendore-Höeppli phenomenon) and sometimes zygospores (spherical bodies with foamy cytoplasm) [4,6,12,16,17,20,24,26–29,31–33,35–39,42–44,46,49,52,53,55,58,60,61]. The immunodiagnostic test such as immunodiffusion is not standardized yet, since it showed a high specificity but a controversial sensitivity [20]. Finally, since suitable specimens for culture purpose are often unavailable, molecular diagnosis from formalin fixed paraffin embedded tissue represents the optimal adjunctive diagnostic method to histology, as it showed a high specificity and high sensitivity [34,40,51,54,PR].

Treatment of GIB usually requires a combination of surgical and medical approach. Surgical resection of infected bowel tissues must be followed by itraconazole for at least 6 months to prevent recurrence. There are also a few cases described in the literature that showed a successful outcome with antifungal treatment alone [33–35,42,56,61]. The role of amphotericin B has been overcome since resistance has been observed in more than 50% of cases [25]. Potassium iodide (KI) has been traditionally used for the treatment of subcutaneous basidiobolomycosis and more recently it was employed successfully in a single case report of a child with GIB [21,66,67]. However, as suggested by Bering et al., the absence of demonstrable *in vitro* activity of KI against *B. ranarum* coupled with several possible limitations (toxicity associated with high doses, lack of any standard prescription recommendation, available new azoles) do not recommend its use in GIB [68]. More recently successful treatments with voriconazole [42,49,50,53–55,58,59] and posaconazole [40,48,50] have been reported. On the basis of the experience reported in the literature azoles should be considered the drugs of choice for GIB.

5. Conclusions

In conclusion, GIB should be suspected in patients complaining abdominal pain associated with gastrointestinal and/or colon mass who has concomitant peripheral eosinophilia especially if they come from the Middle-East or arid zone from USA. Moreover, the observation of

the Splendore-Höeppli phenomenon (although not pathognomonic being associated with several microorganisms) [69] in the presence of zygomicetes in tissue samples from immunocompetent patients should raise the suspicion of basidiobolomycosis and confirmation by using molecular diagnosis should be sought through pathologists able to do it. Although some reports indicate successful outcome by using only medical therapy, surgery with resection of affected bowel segments associated with prolonged antifungal treatment should be advised. Itraconazole seems to be the best available treatment although other new azoles have also been successfully employed. The exact length of duration of antifungal therapy remains to be established.

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