Review

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Gastrointestinal basidiobolomycosis in children: an overlooked emerging infection?

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Basidiobolus ranarum is a known cause of chronic subcutaneous zygomycosis. During the past decade, many cases have been reported with extracutaneous basidiobolomycosis. We aimed to review the medical literature on gastrointestinal basidiobolomycosis (GIB) as an emerging fungal infection causing a serious, and occasionally fatal, paediatric disease. We reviewed all reported cases of visceral basidiobolomycosis with special focus on the gastrointestinal involvement in children. Twenty-six cases of GIB have been reported worldwide, in 14 adults and 12 children. All cases presented with fever, abdominal pain with mass and high blood eosinophilia and were misdiagnosed as other chronic granulomatous diseases or malignancies. A few cases of retroperitoneal, pulmonary, nasal and disseminated basidiobolomycosis have also been reported. Basidiobolomycosis mostly affects young males as a subcutaneous infection. The visceral form of infection is rare. GIB has been scarcely reported in the medical literature, but recently it has been increasingly recognized. GIB poses diagnostic difficulties. Abdominal pain with mass and eosinophilia were present in all cases, highlighting the necessity of considering GIB in the differential diagnosis of this presentation. *B. ranarum* has been reported to cause disseminated fatal disease in both immune-competent and -compromised individuals. Culture is the gold standard for diagnosis, but the characteristic histopathological picture of chronic granulomas rich in eosinophils and the Splendore–Hoeppli phenomenon are the usual diagnostic tools. Surgery plus long courses of itraconazole treatment, up to 1 year, appear to be the best management options. GIB is an emerging infection that might lead to diagnostic confusion, morbidity and mortality. Diagnosis requires a high index of suspicion in the differential diagnosis of patients with fever, abdominal pain with mass and eosinophilia.

Introduction

Basidiobolus is a fungus of the order Entomophthorales causing chronic subcutaneous zygomycosis of worldwide environmental distribution. 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, but is found worldwide, even in areas where the disease has not surfaced (Sugar, 1995). *Basidiobolus* has been isolated from leaves and decaying plants in southern and north-eastern states of the USA (Gruhn & Sanson, 1963) as well as Australia (Zahari *et al.*, 1990).

Basidiobolus ranarum was first described as an isolate from frogs in 1886 (Gugnani, 1983). It was later cultured from the intestinal contents (Sutherland-Campbell, 1929) and ultimately the excreta (Thaxter, 1888) of frogs. The organism spends part of its life cycle in the intestine of the agamid lizard and is liberated as spores and mycelia in the lizard excreta. The spores germinate, and the organism grows saprophytically on lizard droppings, from which it may be picked up by individuals with traumatic lesions (Echetebe & Ononogbu, 1982). In addition to being isolated from insects and reptiles, *Basidiobolus* has been

isolated from several mammalian species. It has been found in bats (Zahari *et al.*, 1990), horses (Miller & Pott, 1980; Vismer *et al.*, 1980), dogs (Miller & Turnwald, 1984) and humans (Nazir *et al.*, 1997).

The mode of transmission for *Basidiobolus* has not been absolutely confirmed, but is assumed to be via minor trauma and insect bites (Clark, 1968; Cameroon, 1990). Fungal spores are found on bristles of mites and are probably also carried by other insects. Infected insects are eaten by reptiles and amphibians, which subsequently pass the spores in their excreta (Drechsler, 1956). Clark (1968) described a case involving the hand of a patient bitten by a caterpillar. The patient had caught the insect and squeezed the 'juice' onto the site of the bite. The organism may also be transmitted from soil and vegetation that is contaminated with animal faeces (Vismer *et al.*, 1980). Mugerwa (1976) noted that *Basidiobolus* may be picked up on contaminated 'toilet leaves' used for skin cleansing after a bowel movement resulting in direct inoculation in the perineum. Consistent with this theory is the fact that the buttocks, thighs and perineum are often the sites of infection in patients (Cameroon, 1990; Goodman &

Rinaldi, 1991). The occurrence of rhinocerebral disease in a hyperglycaemic host suggests that inhalation of spores, as seen in many cases of zygomycosis with the Mucorales, may also play a role in infection for some patients with *Basidiobolus* (Dworzack *et al.*, 1978). Iatrogenic infection has been reported. Nazir *et al.* (1997) reported a case of possible inoculation during appendectomy, and Kamalam & Thambiah (1984) reported inoculation from a needle injection. *B. ranarum* typically causes a chronic infection of the peripheral or subcutaneous tissue, usually on the arms, trunk and buttocks (Goodman & Rinaldi, 1991). Skin and subcutaneous tissue infection is characterized by a hardened nodule which expands and spreads locally. Although the nodules will eventually ulcerate the overlying skin, dissemination usually does not occur (Chandler & Watts, 1987).

Low virulence of *Basidiobolus* has been postulated based on the small number of cases worldwide, which approximates 300 (Sugar, 1995; Nazir *et al.*, 1997). This lack of virulence is also suggested by experiments in mice. Following experimental inoculation of *Basidiobolus* in mice, invasive disease was not seen (Arney *et al.*, 1960). It has been suggested that some unknown abnormality must account for the disease (Sugar, 1995) and that invasive and progressive infection in previously healthy individuals may result from transient immune suppression during viral infections or following surgery (Sugar, 1990). If immune suppression indeed accounts for this mycosis, infection with *Basidiobolus* may become more prevalent due to the human immunodeficiency virus pandemic (Nazir *et al.*, 1997). Yangco *et al.* (1986) demonstrated production of exo-antigens by *Basidiobolus*. *In vitro* production of proteases (Okafor *et al.*, 1987; Okafor, 1994) and lipases (Okafor *et al.*, 1987; Okafor & Gugnani, 1990) has also been seen, allowing it to survive and thrive under various growth conditions (Echetebe & Ononogbu, 1982). Echetebe & Ononogbu (1982) also suggested that growth of the organism and release of enzymes *in vivo* may be related to the level of fat deposits under the skin and that one of its lipases is phospholipase A. A product of hydrolysis of phosphatidylcholine by phospholipase A is lysolecithin, a protein which is able to digest human serum proteins, and the authors hypothesized that hydrolysis of lecithin to lysolecithin destroys cell membranes (blood, skin and muscle cells) and may be the pathogenic mechanism used by the organism. The authors reasoned that protein components of liberated extracellular contents are digested by proteinases produced by *Basidiobolus* and serve as nutrients for organism growth. *Basidiobolus* is relatively thermotolerant and is capable of growing, although poorly, at 37 °C (Kwon-Chung & Bennett, 1992; St Germain & Summerbel, 1996). It is hypothesized that thermotolerance is an important virulence factor for these organisms, allowing them to establish infections *in vivo* with those possessing growth capabilities above 37 °C having the advantage of survival in the febrile patient (Reinhardt *et al.*, 1970).

Basidiobolomycosis rarely involves extracutaneous systems. Gastrointestinal (GIB) (Hussein *et al.*, 2007), retroperitoneal (Finelli *et al.*, 1997; Nazir *et al.*, 1997) and pulmonary (Bigliazzi *et al.*, 2004) basidiobolomycosis have been reported in the medical literature. Surgery and prolonged antifungal therapy are usually required for treatment (van den Berk *et al.*, 2006). To the best of our knowledge, only 26 cases of GIB have been reported worldwide: 14 adult cases (eight from the USA, two from Brazil, two from Kuwait, one from Nigeria and one from the Netherlands; Kian Joe *et al.*, 1956; Greer & Friedman, 1966; Dworzack *et al.*, 1978; Zahari *et al.*, 1990; Khan *et al.*, 2001; Lyon *et al.*, 2001) and 12 paediatric cases (eight from Saudi Arabia, two from Brazil, one from Iran and one from Nigeria; Zahari *et al.*, 1990; Khan *et al.*, 2001; Al Jarie *et al.*, 2003; Wasim Yusuf *et al.*, 2003). A report on the 12th paediatric case, which is the 8th paediatric case in the kingdom of Saudi Arabia (KSA), is in press (El-Shabrawi *et al.*, 2011).

In this article, we will review the literature on GIB, which might be an emerging serious, and occasionally fatal, paediatric fungal infection.

Clinical, laboratory, imaging and histopathological findings in GIB

All patients reported with GIB had fever and abdominal pain as their main symptoms, with no response to conventional therapy. Peripheral blood leukocytosis with marked eosinophilia as well as elevated erythrocyte sedimentation rate and C-reactive protein were found in all cases (Wardlaw & Kay, 1995; Lyon *et al.*, 2001). On physical examination, intra-abdominal masses were always detected and confirmed by imaging studies including ultrasonographic and computed tomography (CT) scanning as well as during surgical exploration. In all cases, a provisional diagnosis of either a chronic inflammatory or malignant process was suggested. The main clue for diagnosis was a meticulous histopathological examination revealing: (i) inflammatory changes with many eosinophils (Wardlaw & Kay, 1995) and broad pleomorphic, sparsely septated hyphae (Kwon-Chung & Bennett, 1992; Yousef *et al.*, 1999) on silver staining; (ii) fungal elements often appearing as empty spaces surrounded by an intensely staining eosinophilic material (Splendore-Hoepli phenomenon) on haematoxylin and eosin staining, as seen in Fig. 1 (Kwon-Chung & Bennett, 1992; Yousef *et al.*, 1999).

All paediatric GIB patients were male with no significant medical history or apparent predisposing factor(s). Seven of them were from the KSA; six were reported by Al Jarie *et al.* (2003) (Table 1). The seventh, reported by Hussein *et al.* (2007), was a 13-year-old boy with GIB presenting with sudden-onset acute abdominal pain with diffuse abdominal rigidity and tenderness. At surgery, a mass was seen in the lower part of the ascending colon. Hemicolectomy was performed and antifungal treatment with itraconazole was started. The patient remained well on long-term follow-up. We consider our patient the eighth

Fig. 1. (a) Colonic *Basidiobolus ranarum* appearing as broad, septate hyphae surrounded by an eosinophilic sheath (Splendore–Hoeppli phenomenon) and numerous eosinophils. (b) Broad fungal hyphae of *B. ranarum* (periodic acid–Schiff diastase stain). (c) Multinucleated giant cells phagocytosing fungal zygospores. The latter appear as spherical bodies that measure up to 30 µm in diameter. They have a thin outer wall, foamy cytoplasm, and a nucleus containing a large nucleolus (haematoxylin and eosin stain). (d) Broad, septate fungal hyphae (black; Grimelius methenamine silver stain). Figure reprinted from Hussein *et al.* (2007) with permission from Elsevier/The British Mycological Society.

paediatric case with GIB in the KSA. Similarly, the patient presented with fever, recurrent abdominal pain with mass and vomiting and was diagnosed after intensive investigations (El-Shabrawi *et al.*, 2011). The remaining four paediatric cases were reported from Nigeria (one case) (Edington, 1964), Brazil (two cases) (Bittencourt *et al.*, 1979; de Aguiar *et al.*, 1980) and Iran (one case) (Fahimzad *et al.*, 2006) as shown in Table 2.

In 1986, the first culture-proven case of GIB in the USA was reported by Schmidt and his colleagues (Schmidt *et al.*, 1986). The patient was a 69-year-old diabetic man with lesions involving the duodenum, ileum, caecum and ascending colon. He was treated with amphotericin B, but died within 6 weeks. In 1997, Pasha *et al.* (1997) reported basidiobolomycosis of the rectosigmoid region in a 49-year-old woman from Arizona, USA. After surgical resection of the lesion and itraconazole treatment, no evidence of residual disease was seen on follow-up. In 1998, Khan and his group reported a case of GIB of the rectum masquerading as Crohn's disease in a Bangladeshi male living in Kuwait (Khan *et al.*, 1998). In 1999, Zavasky and coworkers reported the third case of GIB in the USA, which was initially treated as inflammatory bowel disease (Zavasky *et al.*, 1999). In the same year, Yousef *et al.* (1999) reported six cases of GIB (Table 3) from Phoenix, Arizona (Lyon *et al.*, 2001), and in all, the diagnosis was

established by histopathology with or without fungal culture.

Nguyen (2000) reported a 57-year-old insulin-dependent diabetic man with GIB who was misdiagnosed initially as having peptic ulcer disease with no improvement. He underwent subtotal gastrectomy and partial transverse colectomy for transmural granulomatous disease of the colon compatible with Crohn's disease with no improvement. He developed left hydronephrosis, left perinephric phlegmon, and thickening of the caecum, descending colon, sigmoid colon and rectum. A left ureteral stent was placed and right colectomy was done. Careful histopathology diagnosed *B. ranarum* infection and the patient improved and was discharged on itraconazole. Later, he developed intermittent nausea, anorexia, fever and continuing weight loss. Left renal obstruction, perinephric inflammation and rectosigmoid abscess were found.

Unfortunately, renal stenting and medical treatment with itraconazole and terbinafine failed and a fistula developed between the left collecting system and small bowel and finally ended with left nephrectomy.

In 2001, Khan and his colleagues in Kuwait reported a 41-year-old Indian man with GIB who presented with abdominal pain and fever for 20 days (Khan *et al.*, 2001). A mass in the right iliac fossa was identified with marked

Table 1. Clinical and laboratory features of six patients with GIB in KSA reported by Al Jarie *et al.* (2003)

Culture +, culture-positive; Histopath +, histopathology-positive; TB, tuberculosis; GI, gastrointestinal; WBC, white blood cell; ESR, erythrocyte sedimentation rate; IVC, inferior vena cava; FNA, fine needle aspiration; Ampho-B, amphotericin B; 5FC, flucytosine; p.o., orally. Table reproduced from Al Jarie *et al.* (2003) with permission from Wolters Kluwer/Lippincott Williams & Wilkins.

Patient	Age	Sex	Date	Method of diagnosis	Clinical presentation	$10^{-3} \times$ WBC count (cells ml^{-1})	% Eosinophils	ESR (mm h^{-1})	Immuno-logical workup	Radiological findings	Surgical procedures	Treatment	Follow-up
1	12	M	May 2000	Culture + Histopath +	Abdominal pain, fever $\times 2/12$ Abdominal distension and right-sided scrotal swelling $\times 1/12$ Started on anti-TB treatment	16	15	76	Normal	Huge abdominal mass occupying the right upper part of the abdomen Liver lesions Retroperitoneal with right kidney involvement	Right hemicolectomy Biliary duct stenting	Ampho-B Itraconazole	Asymptomatic Itraconazole p.o.
2	12	M	June 2001	Histopath +	Abdominal pain, fever C3/12 Operated as appendicitis	16	20.6	114	Normal	Right liver lobe mass Right kidney mass	Resection of terminal ileum, caecum and ascending colon	Ampho-B Itraconazole	Asymptomatic Itraconazole p.o. Resolved renal and liver lesions
3	12	M	Oct 2001	Culture + Histopath +	Abdominal pain, fever $\times 2/12$ Operated as appendicitis with appendicular mass	17	19.7	85	Normal	Right iliac fossa mass engulfing caecum with surrounding lymphadenopathy Liver mass Retroperitoneal extension	Right hemicolectomy	Ampho-B Itraconazole	Asymptomatic Itraconazole

Table 1. cont.

Patient	Age	Sex	Date	Method of diagnosis	Clinical presentation	$10^{-3} \times$ WBC count (cells ml^{-1})	% Eosinophils	ESR (mm h^{-1})	Immunological workup	Radiological findings	Surgical procedures	Treatment	Follow-up
4	4	M	March 2002	Culture + Histopath +	Fever, abdominal pain $\times 1/12$ Massive hepatomegaly	30	30	138	Normal	Hepatomegaly Hepatic lesion with an area of necrosis	FNA liver lesion	Ampho-B Itraconazole	Asymptomatic Itraconazole p.o.
5	3	M	August 2001	Culture + Histopath +	Abdominal pain, fever $\times 3/12$ Abdominal distension, weight loss $\times 2/12$ Anti-TB treatment	24	18	105	Normal	Liver mass Extensive lesions involving liver, spleen, gall bladder, mesentery, lesser sac, compressing IVC Right kidney not seen	FNA liver lesion	Ampho-B 5FC Ambisome	Died within 2 days of diagnosis
6	7	M	August 2000	Histopath +	Abdominal pain, distension, fever, vomiting, jaundice and weight loss Hepatosplenomegaly GI bleeding	16.9	17	96	Normal	Liver lesion Hepatosplenomegaly Retroperitoneal mass	Endoscopy, revealed oesophageal varices + duodenobiliary fistula Laparotomy revealed extensive highly vascular inoperable lesions	Ampho-B Itraconazole	Died at referred hospital with massive GI bleeding

Table 2. Summary of presumed or culture-proven cases of paediatric GIB outside KSA

Country and reference	Age (years)	Sex	Risk factor	Symptoms and signs	Site(s) involved	Diagnostic method	Therapy	Outcome
Brazil (de Aguiar <i>et al.</i> , 1980)	4	M	None	Abdominal pain, fever, sweats, diarrhoea, epigastric mass	Stomach, transverse colon	Histology and culture	Surgery	Died of disease 2.5 months after presentation
Brazil (Bittencourt <i>et al.</i> , 1979)	13	M	None	Abdominal pain, weakness, fever, anorexia, memory loss	Stomach, duodenum, transverse colon, pancreas, liver, biliary system, intestinal obstruction	Histology	None	Died of disease without therapy 4 months after presentation
Nigeria (Edington, 1964)	6	M	None	Skin infection, rectal obstruction	Skin, ileum, transverse colon, rectum, bladder	Histology	Antibiotics, iodide therapy	Died of disease 1 year after presentation
Iran (Fahimzad <i>et al.</i> , 2006)	1.5	M	None	Abdominal pain, fever, diarrhoea, haematochezia, bowel obstruction, urinary retention	Rectum with bowel obstruction, pressure effects on the bladder	Histology	Surgery and antifungal	On regular follow-up, his condition was perfect with no complications

thickening of the ascending colon and caecum and bilateral increased renal echogenicity. A presumptive diagnosis of intestinal tuberculosis was made. He underwent surgical resection and a biopsy was sent for confirmation. This was negative for tuberculosis, and GIB was diagnosed by the characteristic histopathological picture of the specimen as well as similarity in clinical picture to their patient reported in 1998. Meanwhile, the patient developed difficulty in passing urine and his urine culture revealed several colonies of *B. ranarum*. Liposomal amphotericin B at a dose of 1 mg (kg body weight)⁻¹ per day was started for 4 weeks, but his condition did not improve. The dose was doubled to 2 mg (kg body weight)⁻¹ per day for 4 weeks, but his condition deteriorated. The *B. ranarum* isolate was later found to be resistant to amphotericin B. The patient requested to go back to his native country (India) and was lost to follow-up. This patient was apparently otherwise healthy except for chronic anaemia, and the only recognizable risk factor was the history of surgical correction of a left inguinal hernia 2 years earlier. The possibility that the fungus was implanted during the surgical procedure could not be excluded. In this context, it should be mentioned that this patient was from the southern part of India where many cases of subcutaneous *B. ranarum* infection have been described (Kamalam *et al.*, 1992). This case is similar to that described by Zavasky *et al.* (1999), in that infection disseminated to involve the urinary tract and the diagnosis was made by isolation of *B. ranarum* from urine samples. Moreover, the isolate in both instances was resistant to amphotericin B.

van den Berk *et al.* (2006) reported a 61-year-old man who presented with progressive left abdominal pain and

constipation for a few months. Colonoscopy showed an obstructing mass in the descending colon, and a hemicolectomy was performed. Histology showed inflammation, possibly caused by a fungal or parasitic infection, without definite identification of an organism. A few weeks post-operatively, a CT scan performed for abdominal discomfort revealed a liver mass of 6 cm diameter. Treatment with metronidazole, directed against an amoebic liver abscess, was unsuccessful. He developed marked eosinophilia (27.7%). Liver biopsy was performed. Review of colonic and liver biopsy samples suggested a diagnosis of *B. ranarum* infection. Treatment with amphotericin B was started because itraconazole was contra-indicated due to renal insufficiency. A few days later, the patient died of a septic shock. After autopsy, *B. ranarum* was cultured from the liver, gall bladder and colon.

Conclusions

Although the histological features of *B. ranarum* are well described in the skin and subcutaneous tissue, gastrointestinal involvement has presented considerable diagnostic difficulties and confusion. It should be suspected in the differential diagnosis of any GI mass with eosinophilia. The small number of reported cases of GIB is probably related to the limited awareness of this disease and may not reflect its true incidence worldwide. Its diagnosis is usually delayed or overlooked if attention is not focused on the possibility of this fungal infection, and the diagnosis must be made on the histological picture of the fungal morphology and the Splendore–Hoeppli phenomenon, which, although not entirely specific, are characteristic

Table 3. Clinical characteristics of patients with GIB in Arizona, 1994–1999 (Lyon *et al.*, 2001)

Histo, histopathology; ND, not done; Abd, abdominal; RLQ, right lower quadrant; PUD, peptic ulcer disease; IRDM, insulin-requiring diabetes mellitus; ESRD, end-stage renal disease; WBC, white blood cell; eos, eosinophil; BE, barium enema; infl, inflammation; +, positive. Table reproduced from Lyon *et al.* (2001) by permission of Oxford University Press/Infectious Diseases Society of America.

Patient no./age (years)/sex	Date and method of GIB diagnosis	Onset of symptoms	Medical and social history	$10^{-3} \times \text{WBC}$ count (cells ml^{-1}), absolute eos count	Radiological findings	Surgical procedure(s)	Treatment	Follow-up findings
1/49/F	5/95: Histo +, culture ND	9/94: Abd pain, constipation, mucous discharge	PUD, avid gardener	3/95: 13.3, 2.5; 4/95: 23.4 WBC	CT: thickened rectal/sigmoid wall; BE: 30 cm segmental stricture	5/95: Rectosigmoidal resection, colostomy; 7/95: reanastomosis	Itraconazole (400 mg per day for 3 months)	Asymptomatic; no medication
2/46/M	9/96: Histo +, culture +	9/96: RLQ abd pain	Landscaper, alcoholism, pancreatitis	9/96: 11.9, 1.2	BE: concentric stricture of descending colon; CT: large intra-abd mass, left hepatic lobe lesion	9/96: Resection of mass, descending colon, biopsies of liver and retroperitoneum	Itraconazole (400 mg per day for 19 months)	Asymptomatic; no medication
3/56/M	2/98: Histo +, culture +	9/97: Abd pain; 11/97: constipation, abd mass	IRDM, owns trailer park in a rural, desert area	11/97: 16.4, 1.3	Left hydronephrosis, retroperitoneal infl	11/97: Subtotal gastrectomy, partial colectomy, excision of mass; 2/98: ascending colon and mass resection	Itraconazole (800 mg per day for 11 months), terbinafine (250 mg per day for 2 months)	Asymptomatic; no medication
4/52/M	12/98: Histo +, culture +	10/98: Abd pain	Diabetes mellitus, lived in same trailer park as case 3, high school superintendent, former smoker	12.8, 2.0 (14%)	BE: diverticula; CT: sigmoid colon diverticula, 6 × 10 cm sigmoid mass	12/98: Incomplete excision of sigmoid mass, adherent to bladder and small bowel; 6/99: resection of diseased sigmoid colon and partial excision of mass	Itraconazole (400 mg per day for 10 months)	Asymptomatic; no medication

Table 3. cont.

Patient no./age (years)/sex	Date and method of GIB diagnosis	Onset of symptoms	Medical and social history	$10^{-3} \times \text{WBC}$ count (cells ml^{-1}), absolute eos count	Radiological findings	Surgical procedure(s)	Treatment	Follow-up findings
5/37/F	2/99: Histo +, culture ND	11/98: Abd pain	Pica, respite worker, smoker	26.4, 2.6	CT: thickened gastric walls, intra-abd lymph nodes	1/99: Subtotal gastrectomy, partial colectomy	Itraconazole (400 mg per day for 9.5 months)	Asymptomatic; no medication
6/59/M	2/99: Histo +, culture +	12/98: Mucus in stool	Pyloroplasty for PUD, thyroidectomy (hypothyroid), plumbing contractor, smoker	12.1, 0.7	BE: sigmoid colon stricture	1/99: Sigmoid colon resection	Itraconazole (400 mg per day for 7 months)	Asymptomatic; no medication
7/59/M	4/99: Histo +, culture ND	3/99: Constipation abd pain	IRDM, ESRD on haemodialysis, coronary heart disease	Both elevated	CT: caecal mass, thickened sigmoid colon wall	3/99: Excision of mass, right colon resection	Itraconazole (for 10 months)	Recovering

histological features. There are no apparent risk factors for this disease. Surgery is usually required, followed by prolonged antifungal therapy, and the preferred drug is itraconazole. The prognosis is uncertain because of the insidious progression of the disease and its delayed diagnosis. Better familiarity with this condition may prevent a fatal outcome. Further studies are awaited for better defining of its risk factors and best modalities of diagnosis and treatment.

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