Disseminated angioinvasive basidiobolomycosis with a favourable outcome

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ABSTRACT

Basidiobolomycosis, a rare fungal infection, is of worldwide distribution but areas commonly involved include the tropical areas of Africa, USA and South East Asia. 88% of the cases are reported among patients younger than 20 years. Many of the case reports in Saudi Arabia are from Tohama area where our patient lives. The diagnosis tends to be overlooked as the presentation may mimic colonic carcinoma in adults or inflammatory bowel diseases and tuberculosis in both children and adults. Angioinvasion seen in our patient is extremely rare suggesting the diagnosis of mucormycosis and resulting in a delay in choosing the most appropriate treatment. We report this case to remind physicians and surgeons to consider this diagnosis in patients from endemic area presenting with such conditions.

1. Introduction

Basidiobolomycosis is a rare fungal disease caused by *Basidiobolus ranarum*. It is increasingly recognised as one of the chronic non-angioinvasive subcutaneous fungal infections in immunocompetent patients. Gastrointestinal involvement is rare. The majority of reported cases of gastrointestinal basidiobolomycosis (GIB) were from the southwestern USA as well as subtopics regions of Asia [1]. There are currently less than 80 reported cases of GIB; of these, 23 occurred in the USA (Arizona), 23 in Saudi Arabia, and 17 in Iran. It is believed that a warm and humid climate enhances the growth of *B. ranarum* in these environments. Many case reports in Saudi Arabia are from the Tohama area, Asir province, in the southern region of the Kingdom [2]. Most cases (88%) occur among male patients younger than 20 years old [2]. Of 71 cases, only 6 were in women [3].

The diagnosis of GIB tends to be overlooked in most patients since the presentation of the disease can mimic colon carcinoma in adults or inflammatory bowel diseases and tuberculosis in both children and adults [4].

A conclusive diagnosis of GIB demands isolation of *B. ranarum* in culture. As most patients are identified postoperatively, many patients never underwent a microbiological examination. Consequently, the diagnosis is frequently established based on distinctive findings in a histopathological examination. The Splendore–Hoeppli phenomenon, consisting of fungal hyphae surrounded by star-like, deeply eosinophilic amorphous substance, is a characteristic feature of GIB [5]. Though not pathognomonic, these features aid in establishing the diagnosis of GIB, particularly in the presence of the classical symptoms and epidemiologic setting [6]. In addition to tissue eosinophilia, leukocytosis with peripheral eosinophilia that regresses dramatically following surgery supports a diagnosis of GIB. A recent review by Vikram et al. observed peripheral eosinophilia in 76% of cases.[1] The persistence of peripheral eosinophilia may indicate an on-going source of infection [1].

Different antifungal drugs are used to treat basidiobolomycosis. Itraconazole is the most commonly used azole and has shown promising results [7]; both voriconazole and posaconazole have also been used successfully [8]. Conversely, results with amphotericin B and related compounds were unsatisfactory, with 50% of *B. ranarum* isolates being resistant to amphotericin [9]. Whereas some patients with GIB have been managed medically only, most have undergone surgery combined with prolonged medical treatment.

2. Case

A 58-year-old man was admitted to the hospital in May 2014 with a 1-month history of left iliac fossa (LIF) pain, worsening constipation, bleeding of the rectum, and weight loss. The abdominal pain had recently worsened, and he had developed a fever. The patient had

bronchial asthma and chronic hepatitis B. He denied the use of herbals or antacids but admitted to using a homemade enema with a hose and tap water.

Examination showed a pulse rate of 93/min, blood pressure of 122/61 mmHg, respiratory rate of 30/min, temperature of 38.3 °C, and oxygen saturation of 98%. The abdomen was diffusely tender, with a tender mass in the LIF and external haemorrhoids. The results of the examination were otherwise normal apart from quadriplegia and a scar from spinal surgery following a traffic accident 20 years previously.

The white blood cell, eosinophil, and platelet counts were 5.7×10^9/L, 0.8×10^9/L, and 703×10^9/L, respectively; the haemoglobin concentration was 7.3 g/dL. The C-reactive protein, creatinine, and albumin concentrations were 141 mg/L, 43 μmol/L, and 25 g/L, respectively. HbA1c was 5.8%, liver enzymes were normal, and he tested negative for HIV.

An initial computed tomography (CT) scan of the abdomen at another hospital had displayed a mass and perforated descending colon with pericolic fluid collection, suggesting colon carcinoma. Emergency exploration on **day 0** identified a mass in the sigmoid and descending colon extending to the splenic flexure. The mass was dissected, followed by the Hartmann procedure to create a diversion colostomy. On gross pathology, a hard mesenteric mass measuring 11.0×5.0 cm with a yellowish necrotic cut surface encasing the bowel segment was identified. Histopathology showed severe chronic granulomatous inflammation with necrosis (Fig. 1A) and extensive fungal elements with marked necrosis, consistent with mucormycosis (Fig. 1B). In addition, multiple foci of angioinvasion (Fig. 1C) were noted.

The patient was started on liposomal amphotericin 5 mg/kg/day. A CT scan for abdominal pain on **day 16** showed segmental perfusion defects of the liver and segmental wall thickening of the colon (Fig. 2A). A subsequent colonoscopy revealed a circumferential mass at the hepatic flexure with a tiny polyp in the caecum (Fig. 2B). A biopsy of the mass showed necrosis and ulcerations but was negative for malignancy and mucormycosis.

After one month of amphotericin treatment, the patient was discharged home on posaconazole suspension 400 mg twice daily.

A follow up abdominal CT scan on **day 90** showed 2 hypodense hepatic lesions, measuring 2.1×1.9 cm and 4.0×4.0 mm, and a suspected filling defect in the portal vein. The patient was not compliant to treatment. He was advised to continue on posaconazole and attend the outpatient clinic.

On **day 180**, the liver lesion worsened, measuring $5.7 \times 4.4 \times 8$ cm with central hypodensity, suggesting a fungal abscess (Fig. 3). Gross segmental biliary tract dilatation was noted. Furthermore, increases in the eosinophil count (3.3×10^9/L) and alkaline phosphatase levels (1360 IU/L) were seen.

Despite drainage of the abscess to decompress the biliary tract, the liver lesions continued to worsen. Thus, left lobe hepatectomy was performed on day 270. Histopathology reviewed at our centre and the Mayo Clinic confirmed necrotizing granulomatous inflammation with eosinophilia and sparsely septate, thin-walled, irregularly branching fungal hyphae surrounded by eosinophilic deposition (Splendore–Hoeppli phenomenon) (Fig. 4A, B).

A review of the initial colon biopsy showed similar changes. The
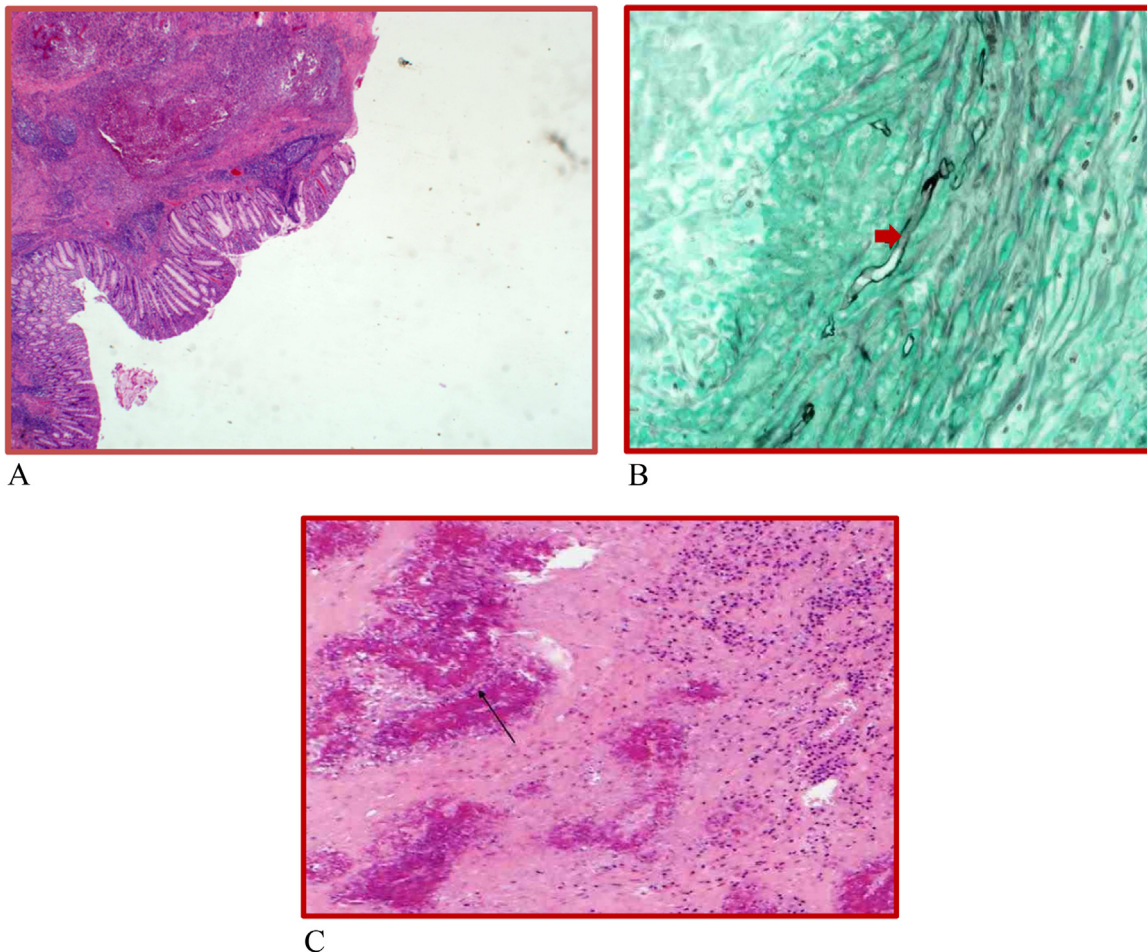
Fig. 1. A. Colonic resection showed severe chronic granulomatous inflammation with necrosis. H&E x 200. **B.** Colon tissue; Fungal hyphae (red arrow) with morphological features most consistent with basidiobolomycosis (thin-walled, branching, sparsely septated and surrounded by eosinophilic deposition/splendore-Hoeppli phenomenon); GMS x 600. **C.** Colon tissue. Angioinvasion (arrow); H&E stain; Magnification 100x.
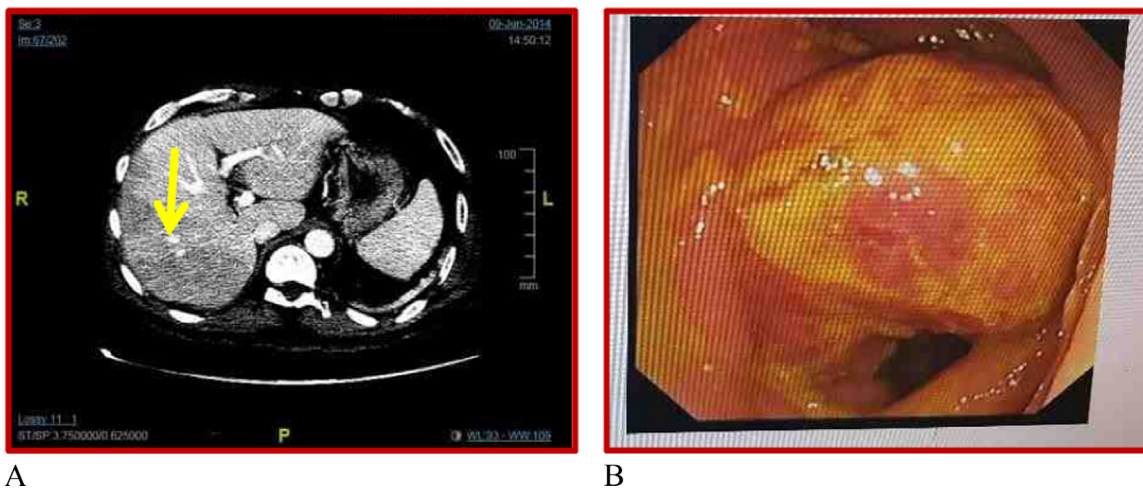
Fig. 2. A. CT abdomen showing a hypoperfused area in the (R) lobe of the live (yellow arrow). **B**. Colonoscopy showing a large circumferential mass in the hepatic flexure. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)


Fig. 3. CT abdomen showing a large (L) lobe of the liver abscess (Orange arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

histopathology-based differential diagnosis included mucormycosis and basidiobolomycosis. However, based on the presence of angioinvasion, mucormycosis was deemed more likely.

Following surgery, the patient showed progressive improvement with a decline in peripheral eosinophilia to 0.9×10^9/L and alkaline phosphatase levels to 240 U/L. Based on the lack of response to initial therapy,the epidemiological background, indolent course, favourable outcome, eosinophilia that regressed after surgery, and the Splendore-Hoeppli phenomenon we favoured a diagnosis of basidiobolomycosis. Molecular testing was not available to us at the time. The treatment was shifted to itraconazole suspension 100 mg twice daily, which the patient continued for 8 months.

One year following his treatment, molecular testing confirmed basidiobolomycosis. DNA was extracted from formalin-fixed, paraffin-embedded tissue. Tissue sections were deparaffinized in xylenes and washed three times with ethanol. DNA was extracted using QIAamp DNA Kit (Qiagen), after mechanical homogenization using TissueLyser (Qiagen). This was followed by amplification of the internal transcribed spacer (ITS) region of the fungal rDNA using primers and PCR conditions previously reported.[10,11] The PCR products were sequenced using 3730xl Genetic Analyzer (Applied Biosystems).

Sequences were compared with existing databanks using the Basic Local Alignment Search Tool (BLAST) algorithm, the National Centre
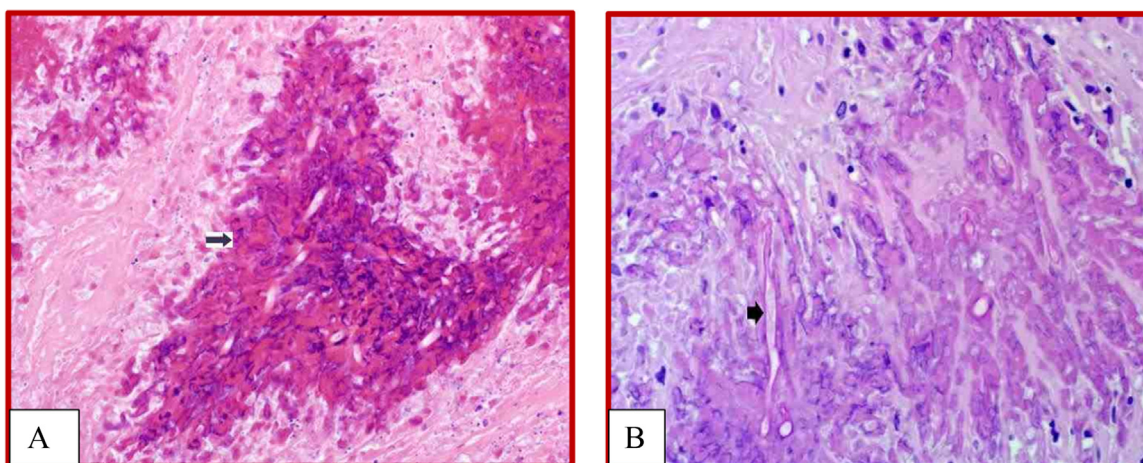
Fig. 4. A. Liver tissue; Fungal hyphae with morphological features most consistent with basidiobolomycosis (Thin-walled, branching, sparsely septated and surrounded by eosinophilic deposition/splendore-Hoeppli phenomenon (black arrow)); H&E x 600. **B.** Liver tissue; Fungal hyphae with morphological features most consistent with basidiobolomycosis (Thin-walled, branching, sparsely septated (black arrow) and surrounded by eosinophilic deposition/splendore-Hoeppli phenomenon); PAS x 600.

for Biotechnology Information (NCBI) website.

The BLAST result of the sequence obtained showed 92–97% similarity with *Basidiobolus ranarum* and other *Basidiobolus* species which considered synonymous with *Basidiobolus ranarum*.

The best match in the BLAST search was *Basidiobolus meristosporus* accession number FJ786040 with 97% similarity. The BLAST result obtained also showed 95% and 92% similarity with the ITS region of *Basidiobolus meristosporus* ATCC14450 (accession number EF392533) and *Basidiobolus ranarum* strain ATCC 14449 (accession number EF392532) respectively.

Forty months after the patient's initial presentation, no clinical or radiological evidence of recurrence was noted.

3. Discussion

The exact mode of transmission of *B. ranarum* is not clear. The organism lives in insects, decaying vegetation, and was isolated from the intestines of reptiles and amphibians, horses, dogs, and bats [11]. Accidental ingestion of contaminated soil or vegetables and environmental exposure are suspected sources of transmission. Early reports suggested that "toilet leaves" used for skin cleaning following bowel movements, resulting in minor trauma, may lead to direct inoculation of the fungi into the perineum, particularly in children [7]. Our patient is quadriplegic with minimal environmental exposure. The likelihood that the fungus was introduced during the use of the homemade enema cannot be excluded.

Individuals younger than 15 years accounted for over 70% of patients with GIB, with few reports in middle-aged patients like ours [12]. Infected patients usually present with abdominal pain, an abdominal mass, and constipation. In a study of 44 patients with GIB, the colon and rectum were most frequently involved (82%), followed by the small bowel (36%), liver/gallbladder (30%), and stomach (14%). Intraabdominal malignancy was the initial provisional diagnosis in the majority of cases (43%), followed by inflammatory bowel disease (16%), and diverticulitis [3]. In endemic areas, patients might be treated for abdominal tuberculosis, leading to a delay in definitive diagnosis and treatment, with increases in morbidity and mortality [13].

Our patient had colon and hepatic masses with bowel thickening and perforation. Flicek et al., in a review of GIB, observed that a colorectal mass was the most common finding on CT (48%), followed by a hepatic mass (20%), and a small bowel mass (11%). Bowel perforation, such as detected in our case, is very unusual and occurred in only 2 patients. On the other hand, thickening of the bowel wall was seen in 25% of cases [14].

The findings of our patient are exceptional in that they showed angioinvasion and dissemination. Compared to basidiobolomycosis, mucormycosis is a very aggressive disease that is characterized by vascular invasion with subsequent thrombosis, endarteritis, and infarction. Therefore, the disease is associated with an extremely high mortality rate, ranging from 62.5% in rhino-cerebral to almost 100% in disseminated disease [15]. Conversely, basidiobolomycosis tends to be chronic, indolent, nonangioinvasive, and rarely disseminates. Angioinvasion does not usually occur in GIB [16–20]. The presence of portal vein occlusion and vascular invasion, as seen in our patient, is rare; the concomitant liver and colonic masses indicating dissemination are also unusual for GIB [13]. Disseminated serious disease has been described in fatal cases of concomitant liver and pulmonary dissemination. Van den Berk et al. reported a similar case of colonic tumour accompanied by a liver mass, while Bigliazzi et al. presented a case of disseminated basidiobolomycosis associated with pulmonary involvement as the initial clinical presentation. A thrombus in the pulmonary vein, partially obstructing the right atrium was documented in a post-mortem examination [21,22]. The mortality rate of GIB is typically around 20%; however, in the above described disseminated cases, the outcome was fatal. Similarly, two children with disseminated GIB disease died shortly after admission to the hospital [21–23].

Although simultaneous colon and liver masses are scarce, isolated liver and biliary involvement is not uncommon in GIB. A liver mass or lesion was more common in a paediatric case series; almost 80% of the patients had liver involvement [24]. Of note, a recent case report showed fulminant basidiobolomycosis 2 weeks following a liver graft in a 44-year-old patient on fluconazole prophylaxis [25].

Our case illustrates the difficulty of identifying GIB in non-endemic areas. The pathological changes were more suggestive of mucormycosis on presentation, which resulted in the selection of an inadequate initial treatment strategy. Ambisome, the drug of choice in mucormycosis, is associated with an increased resistance in 50% of basidiobolomycosis cases. Disease progression and, in retrospect, molecular testing confirmed that this was a rare case of angioinvasive GIB.

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