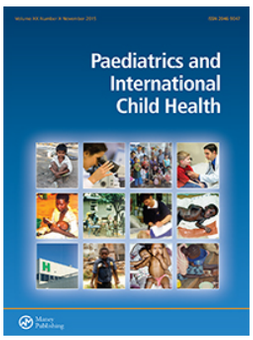

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Basidiobolomycosis: an unusual, mysterious, and emerging endemic fungal infection

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Entomophthoramycosis refers to subcutaneous chronic granulomatous infection caused by fungi of the order entomophthorales in tropical and subtropical countries. The two forms of entomophthoramycosis includes conidiobolomycosis (caused by *Conidiobolus coronatus* and *C. incongruus*), and Basidiobolomycosis (caused by *B. ranarum*). Although *B. ranarum* is found worldwide, basidiobolomycosis is endemic to the tropical and subtropical areas of South America, Africa, Asia, and the southwestern United States. It is a saprophytic fungus typically found in decaying plants, soil, and gastrointestinal tract of amphibians, fish, bats, reptiles, and insects [1–3]. Fifty percent of trapped reptiles and amphibians in Florida were found to be colonized with *Basidiobolus* [4]. It is hypothesised that insects and arthropods consume *B. ranarum* found on vegetation and organic matter, which in turn fall prey to lizards, frogs, and other animals. They might be responsible for further disseminating the fungus in the environment [5].The precise mechanism of human exposure and acquisition of *B. ranarum* is incompletely understood. Despite widespread presence of *B. ranarum* in the environment, human infection is extremely uncommon and is thought to result from insect bites, local inoculation, or minor trauma. For example, walking through contaminated soil or using decaying leaves for cleansing after a bowel movement have been implicated as activities leading to direct inoculation and infection [3]. One of the earliest reports of human infection with *B. ranarum* describes two young children who contracted subcutaneous basidiobolomycosis of the chest wall in Indonesia [6]. Humans may also be exposed to *B. ranarum* through unintentional ingestion of contaminated soil, fruits and vegetables as evidenced by a report of an eight-month-old child who contracted gastrointestinal basidiobolomycosis after consumption of a lizard, and several case reports and case series of gastrointestinal basidiobolomycosis, wherein extensive involvement of abdominal organs occurred in the absence of subcutaneous infection [2, 7]. Although clear-cut predisposing conditions have not been established for systemic infection beyond subcutaneous tissues, certain host factors such as gastric acid suppression, gastrectomy, diabetes, and duration of residence in endemic areas may enhance risk of infection [8, 9].

In contrast to infections caused by Mucorales which are mainly confined to immunosuppressed hosts, entomophthorales infections are predominantly described in otherwise healthy, immunocompetent children and adults. Majority of infections with *B. ranarum* involve exposed areas such as upper and lower extremities, trunk, buttocks, and perineum; occasionally, the arms, head and neck (sinuses, palate, turbinates, nose), lungs, gastrointestinal tract, or other intraabdominal organs are involved [2, 10–14]. It disproportionately affects men and children. At the site of inoculation, a single, painless, firm subcutaneous nodule develops with gradual peripheral extension and enlargement. The overlying skin can develop a purplish color at the advancing edge. Pruritus, burning, or purulent drainage is often due to bacterial superinfection [5]. The affected limb can enlarge significantly or develop chronic lymphoedema.

Gastrointestinal basidiobolomycosis (GIB) is an uncommon, yet serious manifestation of infection due to *B. ranarum*. Sporadic cases have been reported worldwide. A recent publication described the emergence of this infection in the southwestern United States and reviewed all cases of GIB published in the literature [2]. Of a total 44 patients with GIB, 19 patients (43%) were from the United States (17 from Arizona) and 11 (25%) were reported from Saudi Arabia. Although 64% of patients had previously been healthy, 34% had either diabetes mellitus or gastric disorders. Clinical manifestations included abdominal pain (84%), abdominal mass

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(43%), constipation (39%), abdominal distension (32%), fever (32%), and weight loss (27%). Sites of involvement included the large bowel (82%), small bowel (36%) and liver or gall bladder (30%). Prior to GIB diagnosis being established, most patients were felt to either have an abdominal malignancy, inflammatory bowel disease, diverticulitis, appendicitis, lymphoma, or tuberculosis. Essentially all patients had characteristic histopathologic findings; Basidiobolus was isolated in culture in 71%, while 76% had peripheral eosinophilia. A detailed review of abdominal imaging findings in 73 patients with GIB identified masses in the colon, liver or multiple sites and bowel wall thickening as the most common findings [15]. Masses involving the kidney often resulted in urinary obstruction. All masses revealed an inflammatory component and adjacent soft tissue stranding, with or without underlying abscess formation. Over 85% of patients had a combination of surgical excision and prolonged antifungal therapy. Eighty percent survival was noted for the duration of follow up. Another case series of 14 patients with GIB was reported from Fars province in Iran [16]. All patients had characteristic histopathologic findings. Only one patient had a positive culture for *B. ranarum*. Two young patients (<2 years old) died from disseminated disease involving both upper and lower gastrointestinal tract. Itraconazole with or without amphotericin B was utilized along with surgery in all patients. All 14 cases were thoroughly investigated to exclude underlying congenital or acquired immune deficits.

Diagnostic confirmation is based on characteristic histopathology and pathogen isolation in culture. Histopathologic findings of basidiobolomycosis have been described in detail [1, 12]. Granulomatous inflammation with abundant multinuclear giant cells, palisading histiocytes and other cells (neutrophils, lymphocytes, and plasma cells) around central necrosis or abscess is noted. Thin-walled, pauciseptate, broad fungal hyphae of *B. ranarum* surrounded by a radiating, dense eosinophil-rich cellular infiltrate (Splendore-Hoeppli phenomenon) is the pathologic hallmark of basidiobolomycosis. Abundant tissue eosinophilia and Charcot-Leyden crystals are also noted in some patients. *B. ranarum* can be isolated in culture on Sabouraud dextrose agar at 30 °C and appear as flat, waxy, greyish-yellow colonies with radial folds. Microscopic examination reveals zygospores with characteristic 'beak-like' protrusions, which if visible are diagnostic of *Basidiobolus*. The utility of serodiagnosis by immunodiffusion for *B. ranarum* is uncertain. Among 16 patients with GIB who underwent serologic testing, specific serum antibodies were detected in only 50% [2]. Lack of widespread availability of serum immunodiffusion testing (even in reference laboratories) and prolonged turnaround time hinders timely diagnosis. Molecular identification of *B. ranarum* in a single patient from formalin-fixed, paraffin-embedded tissue was based on the application of species-specific oligonucleotide primers [17]. Although promising, molecular diagnostics for invasive fungal infection requires rigorous standardisation and validation before widespread clinical use [18].

Management of basidiobolomycosis often includes surgical resection of infected areas followed by prolonged courses of antifungal therapy. The optimal antifungal choice and duration of therapy for various forms of basidiobolomycosis has not been established. Several azoles (itraconazole, fluconazole, ketoconazole, voriconazole), amphotericin-B, and Potassium Iodide (KI) have been used with varying success. In vitro susceptibility testing has revealed low minimum inhibitory concentrations to azoles, especially itraconazole and ketoconazole; amphotericin MIC is variable [19, 20]. In general, MICs tend to be isolate-dependent. Of note, none of the strains were inhibited or killed *in vitro* at maximum concentrations of KI [19, 20]. In a recent study of GIB [2], antifungal susceptibilities were performed on four unique strains of *B. ranarum*. There was uniform resistance to amphotericin B and flucytosine. Two strains were resistant to fluconazole, all four were itraconazole susceptible, and one was susceptible to ketoconazole and miconazole. One strain was susceptible to both voriconazole and posaconazole but resistant to caspofungin. Two patients with GIB responded favourably to voriconazole. Additional case reports have also described the efficacy of voriconazole in patients with GIB [21, 22].

In this issue of the journal, two case reports of unusual manifestations of basidiobolomycosis have been published. The first report describes a seven-year-old boy from rural south India with progressive weight loss and painful swelling of his left thigh [23]. He presented with a hypertensive emergency, posterior reversible encephalopathy syndrome, and was found to have bilateral hydronephrosis and a perinephric abscess. Infiltration of the pelvic muscles and multiple fistulous tracts to the lower rectum was also detected. Biopsy of the thigh lesion revealed characteristic histopathologic findings, while both the thigh and perinephric abscess grew *B. ranarum*. The boy appears to have made a full recovery after receiving 3 weeks of intravenous amphotericin-B followed by six months of oral itraconazole and KI. Exposure to manure and defecation in open areas followed by cleansing with leaves is postulated to have been the mode of exposure to *B. ranarum*. The second case alludes to a two-year-old boy from southern Iran with GIB who had a 'dramatic' response to KI [24]. At laparotomy, he had a large mass in the transverse colon, lower border of the stomach, and in the subhepatic area. Characteristic histopathology and Splendore-Hoeppli phenomenon was visualized. Despite amphotericin-B, recurrence of infection involving the liver and abdominal abscess was noted. This was followed by rib, pulmonary, and pleural involvement requiring a total of four

laparotomies, rib resection, and pleural fluid drainage. He received amphotericin-B and itraconazole throughout the course of his illness. KI was added to this combination after his 4th surgery. Following three months of triple-drug therapy, there was complete resolution of all lesions with no relapse 24 months later. A case series of eight patients with subcutaneous basidiobolomycosis from India is also reported in the same journal [25]. Lesions mainly involved the gluteal region and thigh, while one patient had scrotal infection; lesions had been present for 1–18 months prior to diagnosis. It is worth noting that basidiobolomycosis was frequently confused for chronic abscess, tumor (testicular, sarcoma), histiocytosis, or tuberculosis. Several patients had incision and drainage in addition to antifungal therapy. The authors indicate that four weeks of itraconazole in seven children and fluconazole in one led to complete cure without relapse.

Several points are worth noting from the above publications in the journal. Krishnamurthy et al. used a combination of three antifungals (amphotericin-B, itraconazole, and KI), vancomycin for secondary staphylococcal infection and surgical aspiration of the perinephric abscess [23]. Hence, the contribution of each of these antifungals towards disease resolution cannot be ascertained. Dashti et al. report a dramatic response to KI in an unfortunate two-year-old boy with extensive *Basidiobolus* infection [24]. However, their patient had four surgeries for resection of large abdominal and rib lesions, and was treated with amphotericin-B and itraconazole for months before KI was added as the third drug following his fourth surgery; all three antifungals were continued for 3 months. Hence, their claim of a 'dramatic' response to KI is overstated. Physical removal of large (possibly necrotic) masses likely facilitated antifungal delivery to residual areas of infection resulting in a cure. Kumaravel et al's publication illustrates several manifestations of subcutaneous basidiobolomycosis and emphasizes the varied differential diagnosis that was initially entertained in their patients [25].

Potassium iodide (KI) as a saturated solution has been utilized for the treatment of cutaneous dermatoses, sporotrichosis, and entomophthoramycoses, in addition to several non-infectious entities [26]. There is little knowledge of its exact mechanism of action. Toxicity caused by high doses, advent of newer antifungals, lack of a conventional standard prescription recommendation, and unawareness to the exact amount of KI salt being delivered, has led to subdued enthusiasm for using this drug. In vitro studies have documented complete absence of inhibition or killing of *B. ranarum* at maximum concentrations of KI [20]. However, several published reports attest to dramatic and complete response, mainly in patients with subcutaneous basidiobolus infection. Its immunomodulatory properties may have a role to play in its observed *in vivo* efficacy in some patients. It is unclear if combination of KI with azoles and/or amphotericin-B translates into synergistic activity by potentiating the performance of the parent antifungal. If available and accessible, azole antifungals appear to have a more favorable efficacy and toxicity profile compared to KI.

Basidiobolomycosis remains an infrequent, multi-system fungal infection with a wide range of clinical manifestations masquerading as infectious, malignant or inflammatory lesions based on the site of involvement. Tissue biopsy with or without specimen culture is mandatory for a conclusive, unequivocal diagnosis of basidiobolomycosis and to exclude other aetiologies. Improvement in personal hygiene and sanitation in rural areas as well as access to protective clothing and footwear for farmers and outdoor labourers in endemic regions might reduce the incidence of basidiobolomycosis. Likewise, better food hygiene and thorough washing of uncooked fruits and vegetables might lower the incidence of GIB, although the exact mechanism of acquisition is unknown. The most effective antifungals, mono- versus combination therapy, and the optimum duration of treatment for various forms of basidiobolomycosis remain to be established. A recent review draws attention to entomophthoramycosis and several other neglected endemic mycoses around the world; mycetoma was included as the only fungal infection in the WHO list of neglected tropical diseases in 2016, and chromoblastomycosis was added in 2017 [27].

It is time for investigators in endemic areas to join forces, work together and share knowledge to illuminate the mysteries of this fascinating but serious infection. The creation of a comprehensive prospective database of patients with basidiobolomycosis encompassing the majority of endemic regions with a central registry is crucial to achievement of this goal. The overwhelming success of a similar approach for the study of endocarditis (International Collaboration on Endocarditis) underscores the value of such a concept [28, 29].

Disclosure statement

No potential conflict of interest was reported by the authors.

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