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Invasive retroperitoneal infection due to *Basidiobolus ranarum* with response to potassium iodide—case report and review of the literature

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Summary We report a case of invasive retroperitoneal zygomycotic infection caused by *Basidiobolus ranarum* in a healthy 8-year-old boy. The youngster responded dramatically to potassium iodide. The clinical and pathological features are reviewed to highlight the problems encountered in the management of this rare infection.

Introduction

Zygomycotic infections are caused by fungi belonging to the orders Mucorales and Entomophthorales. Basidiobolus and Conidiobolus species (Entomophthorales) cause a chronic, inflammatory granulomatous disease collectively called entomophthoromycosis, reported in otherwise healthy inhabitants of tropical and subtropical regions.[1] The disease is generally restricted to the subcutaneous tissues of the trunk and extremities or the mucosa of nasal and paranasal regions.[1,2] Deeply invasive zygomycosis due to *B. ranarum* involving the lungs, liver, muscles and gastro-intestinal tract, either primary or secondary to subcutaneous disease, is rare and affects mainly immunocompromized hosts.[2–4] If left untreated, it results in severe disfigurement and can be life-threatening. We report a case of primary invasive retroperitoneal zygomycosis due to *B. ranarum* in a healthy 8-year-old boy. The objective is to highlight the difficulties encountered in diagnosing and treating this rare infection.

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Case report

In October 1994, a previously healthy 8-year-old boy from a rural province in Pakistan presented with right flank pain, low grade fever and weight loss of 2 months duration. There were no gastro-intestinal or pulmonary symptoms. His past medical history was unremarkable apart from a negative appendicectomy at a local hospital 5 months prior to admission. There was no evidence suggestive of immunodeficiency and his immunizations were up to date. At presentation, results of the physical examination were normal, except for evidence of weight loss (< 10th percentile) and mild tenderness in the right flank. A well healed scar was visible in the right lower quadrant. Laboratory data revealed haemoglobin 11.4 g/dl, haematocrit 36%, WCC 17,300/mm^3, neutrophils 57%, lymphocytes 26%, eosinophils 16%, and monocytes 1%. The ESR was 30 mm at the end of 1 hour. The biochemical profile and the results of a

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chest X-ray were normal. An ultrasound and CT scan of the abdomen revealed a 5 × 6 cm irregular, solid mass in the right suprarenal area. A 24-hour urine sample for vanillyl mandelic acid (VMA) was normal. At exploratory laparotomy a firm, inflammatory mass adherent to the upper pole of the right kidney and the undersurface of the liver was resected. Histopathology revealed a chronic granulomatous inflammation together with many fungal hyphae. The hyphae were broad and refractile, surrounded by acidophilic acellular material (Splendore-Hoppeli phenomenon). The infiltrate also contained numerous polymorphs and eosinophils. While awaiting microbiology reports and with a provisional diagnosis of mucormycosis, the boy was started on amphotericin B (1.5 mg/kg/day). Over the next 4 weeks he showed no response to the treatment. He continued to remain febrile, sustained a further weight loss of 3 kg and developed a firm, mildly tender, visible swelling in the right thoracolumbar region. Tissues submitted at surgery for routine, acid-fast bacillus (AFB) and fungal cultures failed to reveal any growth of organisms. Laboratory data 4 weeks after surgery revealed a haemoglobin of 8.9 g/dl, haematocrit 25.9%, WCC 24 200/mm^3, neutrophils 65%, lymphocytes 26%, eosinophils 7%, monocytes 2%, platelets 797 000/mm^3 and ESR 80 mm in the 1st hour. The total bilirubin was 4.3 mg/dl, gamma GT 156 IU/l, ALT 286 IU/l, and alkaline phosphatase 358 IU/l. Serum creatinine and electrolytes were normal. Total proteins were 6.4 g/dl, albumin 2.0 g/dl and globulin 4.4 g/dl. Immunoelectrophoresis revealed no evidence of monoclonal gammopathy. A tuberculin purified protein derivative (PPD) skin test was positive and HIV-1 antibody was not detected by EIA. A bone marrow aspiration showed reactive changes. Repeat cultures of blood, bone marrow, urine, sputum and tissue obtained from the thoracolumbar mass were again reported to be negative. A repeat chest X-ray and CT scan of the abdomen and thorax at this stage revealed recurrence of the suprarenal mass with extension into the muscles of the thoracic wall (Fig. 1). The boy was re-examined in December 1994 with a view to debulk the lesion. Due to widespread infiltration of the chest wall and overlying muscles, the surgical procedure were abandoned after taking adequate tissue samples for histology, microbiology and mycological studies. The results of repeat histology were similar to that reported previously and the boy continued to deteriorate, in spite of amphotericin B. Five days after surgery, tissue cultures on Sabouraud-dextrose agar at 37°C and 30°C revealed colonies which appeared flat, waxy and greyish-white and showed radial folding suggestive of *B. ranarum*. As the colonies grew older, short aerial hyphae filled with spores became evident. A small piece of a colony from Sabouraud-dextrose agar mounted in lactophenol cotton blue showed numerous globose smooth-walled zygospores with a beak attached to one side (Fig 2). Several conidia containing meristospores were also observed. There was no growth on mycosal agar. After morphological confirmation of *B. ranarum*, amphotericin B was discontinued and a saturated solution of potassium iodide (KI) (30 mg/kg/day) was started orally. The boy became afebrile within a week and there was a noticeable decrease in the thoracolumbar swelling. Within 6 weeks of this treatment, the thoracolumbar mass and the suprarenal lesion resolved completely, as documented on a CT scan of the abdomen and

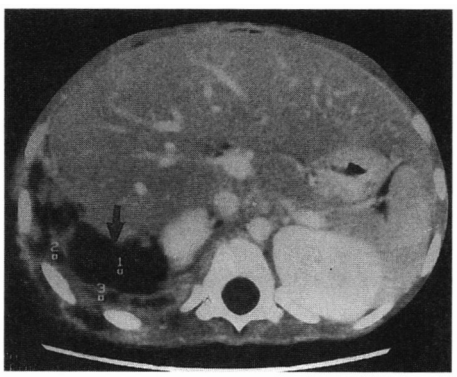

FIG. 1. CT scan of the upper abdomen/chest showing an infiltrating *Basidiobolus ranarum* lesion extending into the abdominal and thoracic wall.

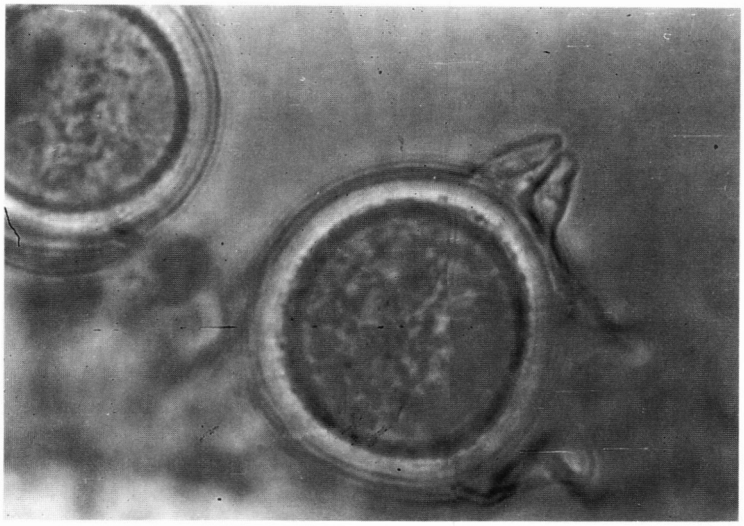

FIG. 2. Zygospore with 'beak' in culture mount of *Basidiobolus ranarum* (× 240).

thorax. The boy when last seen in February 1996 was asymptomatic and had gained 4.5 kg in weight.

Discussion

B. ranarum is a normal inhabitant of soil and has been isolated from decaying vegetation, mammalian dung, insects and the gastro-intestinal tracts of many amphibians and reptiles.[1,2] The mode of transmission of infection to human beings remains unknown. It is generally assumed that infection is acquired by direct contact with the contaminated material. Minor trauma, e.g. intramuscular injections and insect bites, have been implicated.[1,2,5–7] In the boy presented here, inoculation into the retroperitoneum during appendicectomy may have been the mode of transmission.

In spite of its ubiquitous distribution, zygomycosis caused by *B. ranarum* is rare in humans, suggesting low virulence of the organism. Since the first description of the infection in a patient from Indonesia by Joe *et al.* in 1956,[8] approximately 300 cases have been reported in the world literature, mostly from tropical Asia, Africa and South America.[1–8] To our knowledge this is the first culture-proven case of this rare infection from Pakistan and probably the first report of one affecting primarily the retroperitoneum.

Entomophthoromycosis due to *B. ranarum* is primarily a disease of children. A majority of the reported cases have been in children under 10 years of age, predominantly boys (the male to female ratio varies from 3:1 to 6:1).[1,2,6] The disease is generally restricted to the subcutaneous tissues of the trunk and extremities of previously healthy individuals.[1,2,6] The involvement of deeper structures such as the lung, liver, muscle and gastro-intestinal tract, either primarily or secondary to subcutaneous tissue infection, has rarely been described in the absence of predisposing factors such as diabetes mellitus, malnutrition and immunosuppressive disorders.[2–4,7] Liberation of lysolecithin and proteinase by the fungus and transient immunosuppression which may occur during common viral infections and surgery have been postulated as factors responsible for invasive and progressive disease in previously healthy individuals.[1] With the increase in human immunodeficiency virus (HIV) infections, this infection may be seen more frequently in the future.

Diagnosis requires a high index of suspicion among physicians working in tropical areas. Due to the nature of their presentation, these

infections can be confused with malignant lesions such as Burkitt's lymphoma or chronic infections such as tuberculosis.[1,9] Biopsy of the lesion with histological and microbiological evaluations are most effective in making the correct diagnosis. Serological tests are not yet available as diagnostic aids.

Histologically, lesions produced by *B. ranarum* are characterized by an acute and/or chronic inflammatory reaction in association with broad, irregular (8–32 mm in diameter), erratically septate hyphae, each surrounded by a distinctive eosinophilic sheath (Splendore-Hoppeli phenomenon) on eosin-haematoxylin staining. In contrast with mucormycosis, the tendency to vascular invasion, tissue infarction and necrosis is uncommon.[1,2] The colonies of *B. ranarum* are flat, folded, furrowed, greyish and waxy in consistency, whereas the zygospores are 20–50 mm in diameter and have a prominent 'beak' on one side, which is characteristic of the order Entomophthorales (Fig. 2).

No standardized treatment is available for this infection as no single agent has proved to be totally effective against *B. ranarum*. Evaluation of treatment of this rare infection is difficult because of the rarity of its occurrence in humans and occasional reports of spontaneous resolution.[1] Therapeutic trials using amphotericin B, oral azole antifungals (ketoconazole, itraconazole and fluconazole), rifampicin, KI and trimethoprim/sulfamethoxazole have revealed variable responses.[1,2] *In vitro* susceptibility studies by Yangco *et al.*[10] have shown minimal inhibitory effects of amphotericin B, miconazole and 5-fluorocytosine. KI, although demonstrating no *in vitro* activity against *B. ranarum*, proved to be dramatically effective in the patient in this report. The proposed mechanism of action is reported to be resolution of granulomas by enhancement of proteolysis and phagocytosis.[10] A direct anti-fungal effect of iodine cannot be discounted. Ketoconazole, an orally administered antifungal drug, has been shown to be effective in both *in vitro* and *in vivo* studies and may be considered as an adjuvant or alternative to KI.[7,10] The role of surgery in entomophthoromycosis should be limited to biopsies aimed at establishing a diagnosis as extensive procedures can lead to spread of the infection.

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