Pediatric Basidiobolomycosis: An Uncommon and Misdiagnosed Entity

Abstract

Basidiobolomycosis is an unusual chronic subcutaneous zygomycosis reported from tropical regions which is usually misdiagnosed because of its rarity. In this retrospective review, we describe 6 children with basidiobolomycosis who were managed in the Department of Paediatric Surgery at a tertiary institute in central India over a period of four and half years (January 2018 to June 2022). All patients were less than 5 years of age and had no co-morbidities (immune-competent). All were males. All were misdiagnosed at outside hospital. All responded well to anti-fungal therapy. High index of suspicion and biopsy of the lesions lead to appropriate diagnosis and management. Management appears good with triazole antifungals with fewer side effects and safety in children.

Keywords: *Basidiobolomycosis, paediatric, subcutaneous, zygomycosis*

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Introduction

Basidiobolomycosis is an unusual chronic subcutaneous infection reported from tropical regions caused by subcutaneous implantation of fungus.[1,2] The most common causative fungal species implicated in children is *Basidiobolus ranarum*, a saprophytic fungus usually present in decaying fruit and vegetable matter and the intestines of amphibians and reptiles.[3] The hot and humid temperature of tropics provides a favorable environment for it. The mode of infection is trivial trauma or thorn prick which might go unnoticed or may be forgotten. Basidiobolomycosis has been reported to affect immune-competent children; adolescents and adults are less commonly affected. The males are usually affected more as per the reported literature. It is usually misdiagnosed because of its rarity and may be mistaken for chronic abscess, malignancy, or tuberculosis.[3] This leads to unnecessary investigations, unnecessary interventions, and prolonged treatment with unrelated drugs, adding to the morbidity of the patients as well as their caregivers.

Herewith, we describe six children with basidiobolomycosis, misdiagnosed at other hospital, who were treated at our hospital. The first case has been already published as a case report for diagnostic aspects.[4]

This is a retrospective review and analysis of six pediatric cases of subcutaneous basidiobolomycosis who were managed in the Department of Paediatric Surgery at a tertiary institute in central India over a period of four and half years (January 2018 to June 2022). After clinical suspicion of the diagnosis, detailed history of clinical symptoms and previous treatment was taken, and outside investigations were reviewed. Tissue biopsy was taken, and histopathology and fungal culture were sent to confirm the diagnosis. The confirmation of diagnosis was based on the presence of granulomatous inflammation with tissue eosinophilic infiltration (Splendore–Hoeppli – (SP) phenomenon) on histopathological examination as well as broad-based hyphae on Gomori methenamine silver (GMS). All cases were managed with oral antifungal agent itraconazole; intravenous fluconazole was added for one patient with extensive lesions. Intravenous fluconazole was added because he had extensive lesions on face and neck along with stridor. All patients were followed up regularly. The data was collected and analyzed on the basis of demographic details, clinical characteristics (symptoms and signs), laboratory investigations, radiology, histopathology and culture reports, management, and outcome.

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Case Series

The details of patients are summarized in Table 1. All patients were less than 5 years of age and had no co-morbidities. All were males. The history of the inciting event/trivial trauma leading to fungal inoculation was not elicited in any of the patients. Few of them were misdiagnosed at outside—private or peripheral—hospitals and were referred to us. For confirmation of diagnosis, an edge-wedge biopsy was sent in two samples—one in formalin for histopathology and the other in saline suspension for fungal culture. Histopathology suggested basidiobolomycosis in all six cases, but fungal culture was positive in only four cases.

All patients were managed by antifungal agent, itraconazole, given orally at the dose of 5mg/kg/dose once daily (either as syrup or capsule form depending on the weight and acceptability of the patient). They were kept on follow-up. The response could be seen initially in 15-20 days itself. The medication was continued till the lesions regressed completely in all patients. Only one patient with extensive lesions required multidrug therapy with intravenous fluconazole and oral cotrimoxazole therapy. All patients responded well and had no recurrences on follow-up.

Case 1: A 4-year-old boy presented with a painless swelling over the right distal arm since the last 4 months.[4] This swelling was gradually increasing in size.[4] No history of any trauma could be elicited.[4] He previously took a course of antibiotics from a private clinic without any improvement.[4] Fine needle aspiration cytology (FNAC) and ultrasonography suggested benign spindle cell tumor for which he was referred to us.

At presentation to us, a 6 × 5 cm subcutaneous, non-tender and indurated freely mobile swelling with smooth, round edges over the right distal arm and cubital fossa.[4] Overlying skin was normal, and movements of the limb were not restricted.[4] Subcutaneous fungal infection was suspected. Incisional biopsy was taken.[4] The diagnosis was confirmed on histopathology and mycology. He was started on itraconazole, and good response was seen on follow-up with complete regression of the lesion.[4]

Table 1: Clinical presentation, histopathology, and management of all six patients

Age (years), Gender	Site	Misdiagnosis	Previous treatment	Histopathology	Microbiology	Treatment and outcome
4, M	Rt. distal arm	Benign spindle cell tumor	Surgical excision advised	Granulomatous inflammation with broad thin-walled aseptate hyphae ensheathed by amorphous eosinophilic Splendore-Hoeppli material and PAS positivity	Furrowed creamy brown radially folded colonies	Oral Itraconazole - Complete remission at 3 months
2.5, M	Rt. thigh	Abscess	I and D, Oral antibiotics	Granulomatous inflammation showing aseptate hyphae with SP phenomenon and mixed inflammatory infiltrate	Fungal culture on 20% KOH mount showing the hyaline fungal sparsely septate hyphae with zygospores	Oral Itraconazole – Complete remission at 2 months
4, M	Lt. shoulder girdle area and left side of jaw	Extensive cellulitis	-	Granulomatous inflammation with broad thin-walled aseptate hyphae and PAS positivity	Furrowed creamy brown radially folded colonies	Oral Itraconazole – under follow-up, significant improvement at 2 months and complete resolution at one year of follow-up
1.5, M	Rt. Gluteal muscle (lateral aspect)	Benign spindle cell tumour	Surgical excision advised	Granulomatous inflammation with broad thin-walled aseptate hyphae, Splendore-Hoeppli phenomenon and PAS positivity.	Furrowed creamy brown radially folded colonies	Oral Itraconazole - Complete remission at 2 months
3, M	Diffuse hard indurated lesions at lower back and bilateral gluteal regions	Non-resolving cellulitis	Prolonged higher antibiotics	Granulomatous inflammation with broad thin-walled aseptate hyphae and PAS positivity	Furrowed creamy brown radially folded colonies	Oral Itraconazole - Complete remission at 3 months
3, M	Posterolateral aspect of left thigh	Sub-cutaneous mass	Surgical excision	Granulomatous inflammation with broad thin-walled aseptate hyphae and PAS positivity	Furrowed creamy brown radially folded colonies	Oral Itraconazole – Complete remission at 3 months

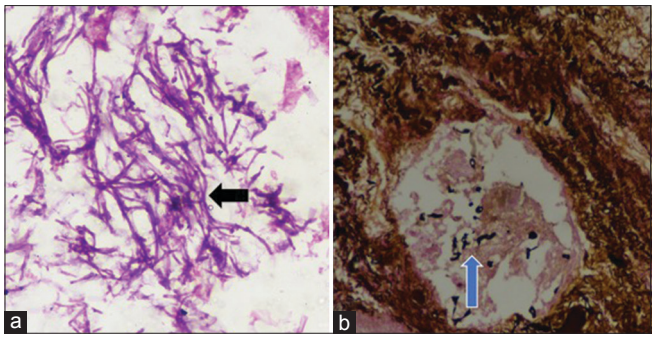

Figure 1: Histopathology image; (a) H and E stain (400X) showing aseptate thin and thick fungal hyphae (arrow) with surrounding eosinophilic infiltrates confirming basidiobolomycosis; (b) Gomori methanamine silver stain (10x) showing aseptate fungal hyphae amidst inflammatory cells

Case 2: A 2.5-year-old male child was referred for recurrent abscess at right thigh. A previous history of incision and drainage of a subcutaneous swelling at right thigh could be elicited; however, the swelling did not subside. At examination, a smooth, mobile, firm, 4 × 5 cm subcutaneous swelling at right thigh was present which was free from overlying skin and underlying muscles. Making a provisional diagnosis of basidiobolomycosis, an edge-wedge biopsy was taken, and diagnosis was confirmed by histopathology showing aseptate hyphae with SP phenomenon and inflammatory infiltrates and broad hyphae on GMS stain [Figure 1] and 20% KOH mount showing the hyaline fungal sparsely septate hyphae with zygospores [Figure 2]. Oral itraconazole was started and complete resolution of the lesion could be seen in 2 months.

Case 3: A 4-year-old male was referred to us from a private hospital for management of extensive cellulitis involving left upper limb, upper back, neck, and left side jaw. On examination, there was hard, diffuse, subcutaneous swelling involving the above-mentioned area. He was admitted based on clinical suspicion of basidiobolomycosis, and biopsy was sent for histopathology and fungal culture. After confirming the diagnosis, itraconazole was started orally. During the course, he developed mild stridor, because of neck involvement; hence, intravenous fluconazole was given for 15 days. The lesions began to regress, stridor resolved. He was advised physiotherapy for the drooping shoulder. He was discharged on two oral drugs—itraconazole and co-trimoxazole—to optimize the treatment and for quick response. It was continued for the next 3 months. Presently, he is on regular follow-up after complete resolution of the lesions in one year. Figure 3 depicts the pre-treatment and post-treatment clinical images of his face, neck, chest, and left upper limb; Figure 4 depicts the pre-treatment and post-treatment clinical images of the left upper limb lesions, and Figure 5 depicts the pre-treatment and post-treatment clinical images of upper back lesions of the same patient with extensive basidiobolomycosis.

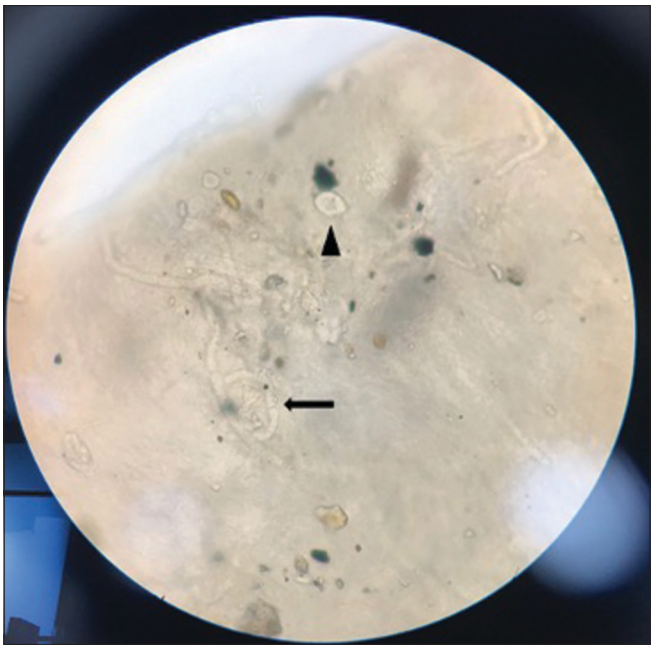

Figure 2: Direct microscopy on 20% KOH mount showing the hyaline fungal sparsely septate hyphae (arrow) and zygospores (arrow head)

Case 4: A 1.5-year-old male presented with subcutaneous lesion which was misdiagnosed as spindle cell neoplasm on FNAC at a private hospital and referred to us for management. There was a 3 × 3 cm indurated lesion at lateral aspect of right gluteal muscle. The patient was admitted, and diagnosis of basidiobolomycosis was confirmed at biopsy and fungal culture. The lesion showed complete resolution in 2 months on itraconazole therapy.

Case 5: A 3-year-old male was referred to us for non-resolving cellulitis at lower back and bilateral gluteal regions. He had received long course of higher antibiotics at a private hospital. At examination, there were diffuse hard indurated lesions involving both the gluteal regions and lower back. He was started on itraconazole after confirmation of diagnosis on biopsy and fungal culture. Complete resolution was seen in 3 months.

Case 6: A 3-year-old male presented with subcutaneous lesions at lateral aspect and posterior aspect of left thigh [Figure 6]. He was misdiagnosed as subcutaneous mass and underwent excision at biopsy at private hospital. He presented to us when he developed similar lesions in the vicinity. The biopsy confirmed the diagnosis to be basidiobolomycosis, and he responded well to oral Itraconazole.

Discussion

Basidiobolomycosis is reported from tropical regions as scattered case reports or series. It was first reported in Indonesia in 1956.[5] In India, most cases are reported from southern region.[3] The causative organism, as

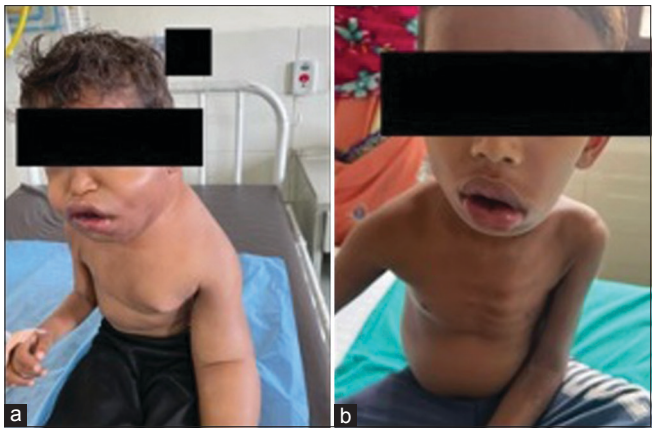

Figure 3: Clinical picture of child with extensive basidiobolomycosis depicting lesions over left side lower face, neck and left upper limb; (a) pre-treatment; (b) one year after treatment

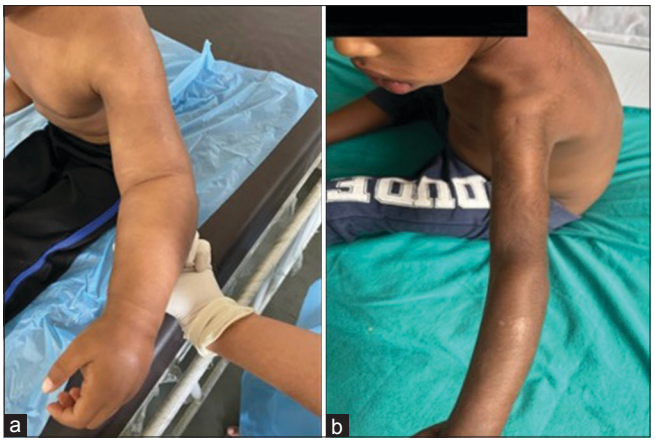

Figure 4: Clinical picture of the same child with extensive basidiobolomycosis depicting left upper limb lesions; (a) pre-treatment; (b) one year after treatment

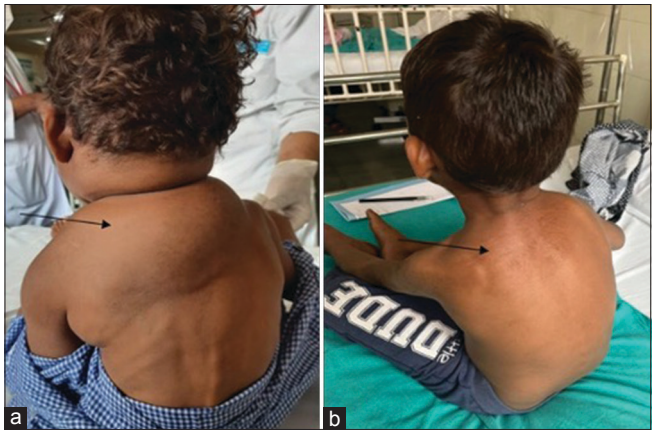

Figure 5: Clinical picture of the same child with extensive basidiobolomycosis depicting upper back lesions; (a) pre-treatment; (b) one year after treatment

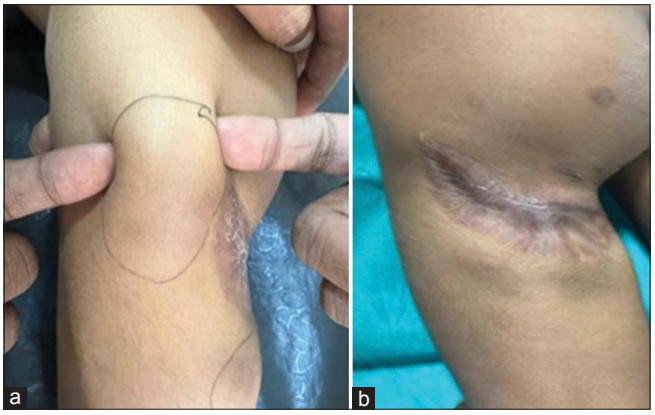

Figure 6: Clinical picture of child with left posterior thigh lesion; (a) pre-treatment; (b) after 3 months of starting itraconazole

already described in introduction section, is *B. ranarum.* It is a saprophytic fungus found in decaying fruit and vegetable matters and also in the intestines of amphibians and reptiles.[3] It is transmitted via implantation of spores through minor trauma like insect bites and thorn pricks, or even inhalation of spores.[1,3] Such trivial trauma may not be noticed or even forgotten. After inoculation, the fungus stays in subcutaneous tissue itself and grows slowly. All our patients were also males.

The commonly affected age group is children; adolescents and adults are less commonly affected.[3,4] Males have been reported to be more commonly affected. This infection presents as limited, chronic, slowly progressive local infection.[6] The usual sites reported to be affected more are face, lower limbs, and buttocks.[6] The clinical presentation of basidiobolomycosis shows two spectrums; first, it is characterized by a well-defined, non-tender, firm, freely mobile, slowly progressive subcutaneous swelling usually seen on upper or lower limbs, buttocks, shoulders, perineum, or trunk.[3] As the lesion is usually freely mobile and in subcutaneous plane, fingers can easily be insinuated deep to the swelling (classical doughnut lifting sign).[3] Patients who present with this localized swelling are usually mistaken for having soft tissue malignancy. The same was true for our patients—three of our patients were misdiagnosed as soft tissue tumor; one was misdiagnosed as abscess in peripheral hospital and even underwent an incision and drainage.

The other spectrum is clinical presentation of a firm to hard board-like induration present in limbs with extension to adjacent areas.[7] There may even be encasement of part of a limb.[7] The overlying skin is usually intact with normal, erythematous, bluish (light skin colored patients), edematous, or hyperpigmented changes, but ulceration is rare.[7] This clinically gives the impression of cellulitis as was seen in two of our patients. Both were misdiagnosed as extensive cellulitis. One of them even received high-grade antibiotics for 6–8 weeks before being referred to our institute.

Lymph nodes are usually not involved but if implicated, a non-pitting woody swelling results. The underlying bone and joints are rarely involved but limb swelling may restrict movement; even the extensive facial lesions

do not invade bones or central nervous system (CNS).[7] Lesions are usually asymptomatic but secondary infection may lead to pruritus, pain, or a burning sensation. If untreated complications include local spread, systemic dissemination is extremely uncommon and systemic signs are generally absent. Spontaneous resolution has also been reported.[1,3,7-9]

Clinical differential diagnosis includes other mycosis like mycetoma and sporotrichosis, skin infections like lupus vulgaris, filariasis, malignancies like soft tissue tumors, Burkitt's lymphoma, and synovial sarcoma.[1,3,7]

Although characteristic clinical appearance is very suggestive, other diagnostic workups include X-ray and MRI to know the extent and plane of involvement. Histopathology and culture are the gold standards for definitive diagnosis.[3] In histopathology, aseptate fungal hyphae could be seen ensheathed by amorphous eosinophilic Splendore–Hoeppli cells and surrounded by granulomatous inflammation with a mixed inflammatory infiltrate. Use of periodic acid–Schiff and GMS stains help in enhancing the fungal wall.[10] The furrowed creamy brown radially folded colonies of *B. ranarum* demonstrating wide hyphae and occasional septae can be cultured on Sabouraud dextrose agar at 25°C–30°C after three to five days of incubation.[11] The zygospores are smooth and thick-walled with prominent conjugation beaks.[11] As the sensitivity is low, it may come negative on most occasions. In our series, all cases showed fungal hyphae on histopathology and culture positivity as almost similar to the study by Kumaravel *et al*.[3] where fungal culture was positive in most of their cases. Potassium hydroxide shows a few branched, broad, sparsely septate hyphae.[6] Lactophenol cotton blue shows zygospores with characteristic lateral conjugation beaks.[6]

Basidiobolomycosis is mostly managed medically. Saturated solution of potassium iodide (KI) can be given as single daily dose or in three divided doses (30 mg/kg/day).[8,12] The other drug mostly preferred is itraconazole at 200-400 mg daily doses.[8,12] KI is not usually recommended in pediatric age group because of its implications on thyroid function. We managed all our patients with itraconazole therapy; only one patient with extensive involvement received intravenous fluconazole therapy. All patients responded well. Treatment responses with itraconazole have been reported to be faster and associated with fewer adverse effects.

Other drugs which can be used are trimethoprim-sulfamethoxazole, amphotericin B, ketoconazole and other azoles, terbinafine, and hyperbaric oxygen.[3,13] Data available on other treatment options are less and should only be tried if a patient is not responding to the above two modalities. We added cotrimoxazole (trimethoprim-sulfamethoxazole) in one patient with extensive lesions over neck and chest for optimum management and quick response in order to avert any respiratory compromise. The results from a recent study by Al-Qahtani *et al*.[14] confirmed the antifungal inhibitory property of cotrimoxazole, the mechanism being folic acid blockade.

Treatment should be continued till the complete resolution of lesions. The role of surgical resection of lesions is controversial.[9] Surgery has been reported to increase the spread of infection.[9]

Conclusion

Basidiobolomycosis is usually misdiagnosed because of its rarity and paucity of literature. Misdiagnosis causes morbidity, unnecessary multiple investigations, delay in diagnosis and appropriate management, and financial implications for care-givers. High index of suspicion by the clinician and timely biopsy of the suspected lesions helps in arriving at a diagnosis and initiation of appropriate management. Treatment with triazole antifungals is promising in children with good response and very few side effects.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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