Case Report

Subcutaneous Zygomycosis in Children: 2 Case Reports

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Basidiobolus ranarum is an uncommon subcutaneous zygomycosis mostly found in immunocompetent children in tropical countries. Presence of slow growing non-tender, non-inflammatory, subcutaneous swelling that does not spread beyond the subcutaneous tissue are classic clinical features. The authors report two cases of subcutaneous zygomycosis which tissue cultures were positive for Basidiobolus ranarum. The first case was a 10-months-old boy presented with prolonged high fever and a rapidly expanding ulcerated plaque unresponsive to systemic antibiotic. The second case was a 2-years-old girl presented with slow expanding mass at the buttock. Histopathology of both cases showed lobular panniculitis with eosinophilic infiltration and fungal culture revealed Basidiobolus ranarum. Oral itraconazole was given with good clinical response in both cases.

Keyword: *Subcutaneous zygomycosis, Basidiobolus ranarum, Children*

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Deep fungal infections are uncommon and comprise of two distinct groups of conditions, the subcutaneous and systemic mycoses. The subcutaneous mycoses are infections caused by fungi that have been introduced directly into the dermis or subcutaneous tissue through a penetrating injury. The organism can be found in soil, plant debris and in the intestinal tracts of reptiles[1].

Zygomycosis represents a group of infections caused by fungi of the order Entomophthorales and Mucorales of the class Zygomycota. The order Entomophthorales has three important pathogenic species: Basidiobolus ranarum, Conidiobolus coronatus and Conidiobolus incongruus[1]. Traditionally, there are two types of subcutaneous zygomycosis, ones localized to the trunk or upper part of lower limbs in children caused by *Basidiobolus ranarum* or one that is present on the face of adults caused by *Conidiobolus coronatus* .

Subcutaneous zygomycosis (entomophthoromycosis basidiobolae, subcutaneous zygomycosis, subcutaneous phycomycosis, basidiobolomycosis) is a rare subcutaneous mycoses mostly found in tropical country[2-4]. Children infected with Basidiobolus ranarum are usually immunocompetent host. Classic presentation of subcutaneous zygomycosis is presence of slow growing non-tender, non-inflammatory, subcutaneous that does not spread beyond the subcutaneous tissue[5]. Being limited to the sub-cutis,a helpful sign is that the mass can be lifted by passing a finger below the edges, especially in non-facial lesion[6]. The overlying skin is normal but can be dull red or slightly hyperpigmented. Ulceration and regional lymphadenopathy are rare[7].

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Case 1

A 10- month-old, previously healthy boy, presented with painless swelling of upper lip that had been enlarging for 3 weeks. There was a previous history of trauma at the upper lip. The patient was diagnosed as bacterial skin infection. Oral antibiotics were given without improvement. Three weeks later, the lesion grew rapidly to involved perioral area and left cheek. He also developed intermittent high grade fever and difficulty eating. The patient was admitted with a diagnosis of perioral abscess. Examination revealed a febrile, uncomfortable child with an ill-defined, extensive, wooden hard, erythematous indurated ulcerated plaque involving the upper lip and extending to the left cheek. Left cervical lymphadenopathy was also present. The rest of the physical exam was otherwise unremarkable (Fig. 1).

Important laboratory findings showed, hemoglobin of 10.3 g/dl, white blood cell count of 18,400/mm^2 (50% neutrophil, 36% lymphocyte, 2% eosinophil, 12% monocyte), a platelet count of 764,000/mm^2, high erythrocyte sedimentary rate (39 mm/h) and high C Reactive Protein (14.5). Despite empirical broad spectrum systemic antibiotics, there was no clinical improvement. Panniculitis-like T-cell lymphoma was suspected. Tissue biopsy was requested but the parent refused consent. Computed Tomography of head and neck was performed to define the extent of the lesion, which showed vascularized soft tissue mass at the upper lip extended superiorly to the base of the left dorsum of nose and inferiorly to the lower lip more on the left side. There was no extension to the bone and central nervous system. The patient was diagnosed as expanding vascular tumor so we started systemic corticosteroid. After few days of intravenous hydrocortisone, the mass started to expand rapidly (Fig. 2).

Tissue biopsy from left cheek was performed for definite diagnosis. Histopathology revealed lobular eosinophilic panniculitis (Fig. 3). GMS staining demonstrated a few fungal hyphae (Fig. 4). Fungal culture from the tissue biopsy revealed colonies of *Basidiobolus ranarum.*

Intravenous amphotericin B in gradually increasing doses up to 1 mg/kg/day was given along with itraconazole 5 mg/kg/day. After two weeks of treatment, fever was subsided. Perioral swelling decreased and the patient's appetite gradually improved. Amphotericin B was withdrawn and oral itraconazole was continued for 5 months duration. No side effects were reported.

Case 2

A 2-years-old Thai girl, previously healthy, presented with non-tender firm slowly enlarging mass at left buttock for 7 months PTA. The mass had been

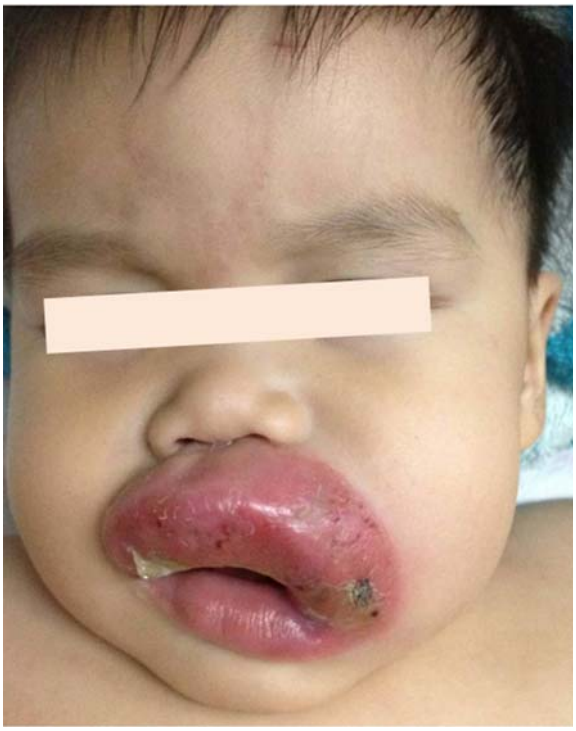

Fig. 1 A 10-months-old boy with a painless swelling and erythema of upper lip extending to the surrounding soft tissue.

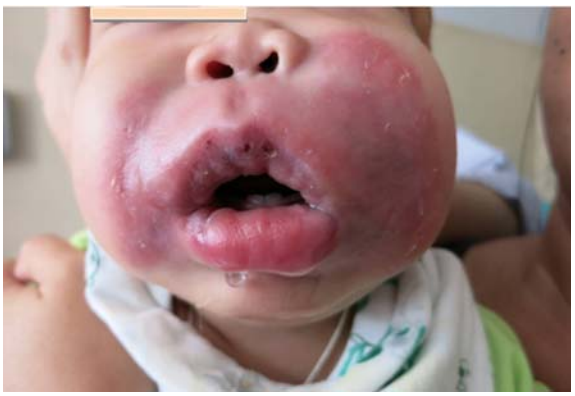

Fig. 2 One week after intravenous hydrocortisone had started, the mass rapidly expanded extending to the left cheek and soft tissue underneath.

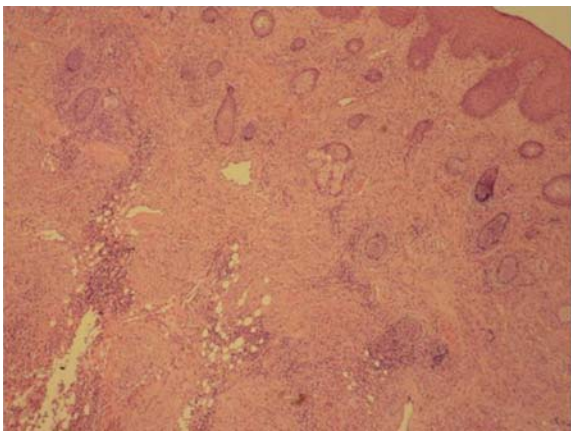

Fig. 3 Tissue biopsy from left cheek with H&E staining (Haematoxylin and eosin) 10x showing lobular panniculitis.

progressively growing from tiny firm nodule to large plague with mild itching. She was afebrile and had no history of weight loss or other systemic illnesses.

On physical examination, she was afebrile and well nourished. There was a firm, nodular surfaced, non-erythematous, non-tender mass, 8x12 cm in size. occupied at left lower back extended to left buttock (Fig. 5). The patient was suspected to have deep fungal infection.

Skin biopsy from left buttock was performed for histopathology and mycological culture. The section revealed granulomatous inflammation with giant cells and large number of eosinophil infiltration of subcutaneous tissue. Broad, non-septate hyphae and Splendore-Hoppli phenomenon were identified (Fig. 6). Fungal culture reported Basidiobolus ranarum, which confirmed the diagnosis of subcutaneous zygomycosis.

Itraconazole 5 mg per kilogram daily was given for 3 months with rapid clinical improvement 2 weeks after treatment.

Discussion

Entomopthoromycosis consists of two different infections, caused by the Entomopthoraceae's family, genus Basidiobolus and Conidiobolus. Entomopthoromycosis was known as a saprophytic fungus, which is usually found in soil, decaying vegetable and intestine of reptiles. Basidiobolomycosis is a common cause of subcutaneous zygomycosis in immunocompetent children younger than 20, the youngest patient recorded being 9 months old[1,6]. It occurs more commonly in males than female[6, 8].

In 1956, Joe et al reported the first cases of subcutaneous mycoses due to basidiobolus ranarum in Indonesia. Thereafter, many cases of basidiobolomycosis have been reported worldwide especially in tropical countries[9]. Many cases of subcutaneous zygomycosis due to Basidiobolus ranarum have been reported in Thailand since the first case reported in 1965[10,11]. Slow growing, non-inflammatory, non-

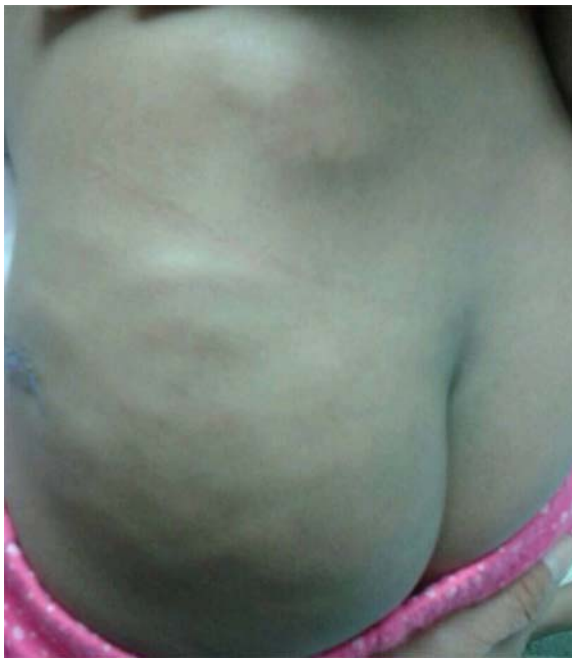

Fig. 5 Firm, nodular surface, skin-color, non-tender mass occuping at the left lower back and extending to the left buttock.

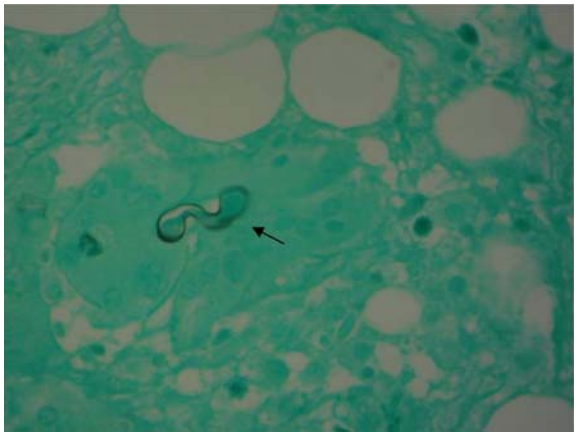

Fig. 4 Gomori methenamic silver (GMS) showing fungal element which appear as a short broad, non-septate short hyphae.

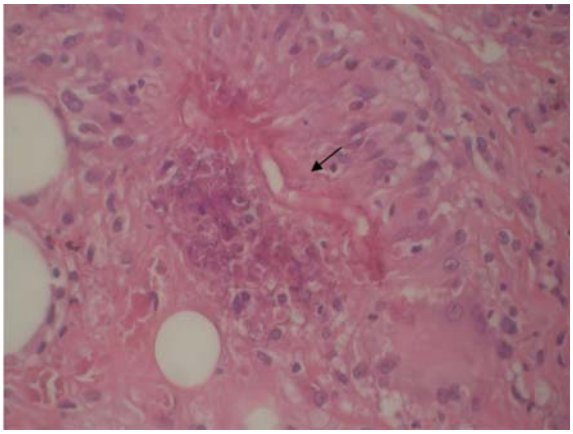

Fig. 6 Haematoxylin and eosin stain of tissue biopsy showing broad non-septate fungal hyphae (400x) in sub cutis with Splendore-Hoeppli phenomenon.

ulcerated subcutaneous swelling are classic features which usually affects buttock and thigh. However, Mendiratta V et al reported inflammatory, ulcerated plaque resembling subcutaneous panniculitis-like lymphome in very young children[7]. Chiewchanvit et al have reviewed cases of entomopthoromycosis in Maharaj Nakorn Chiang Mai Hospital from 1985 to 2001. Three cases were diagnosed as subcutaneous zygomycosis, two cases of rhinofacial zygomycosis and one case of gastrointestinal entomopthoromycosis[12]. Pornpanich et al also reported a rare case of entomopthoromycosis of the orbital tissue with dacryocystitis in a 9-months-old girl[13].

Histologically, Basidiobolus ranarum is shown as dense eosinophilic infiltration with a presence of broad non-septated hyphae surrounded by intensely eosinophilic "Splendore-Hoeppli" material, which was also seen in both of our cases. Invasion of blood vessels is not seen in Basidiobolomycosis in contrast to mucomycosis[14]. The fungal morphology and Splendore-Hoeppli phenomenon (asteroid bodies) are characteristic histological features of fungal infection[15].

The fungal elements appear as broad, pleomorphic, non-septated hyphae, which stain faintly with Gomori Methenamic Silver (GMS) and Periodic Acid Schiff (PAS)[16].

The Gold standard for diagnosis of subcutaneous zygomycosis is fungal culture. However, there is also an immunodiffusion test, which is not only practical, sensitive and specific but can also be used to monitor patients infected with Basidiobolus ranarum. The titer of the antibodies specific to Basidiobolus ranarum antigens decreases as the lesions subside[21].

The authors report two rare cases of subcutaneous zygomycosis caused by basidiobolus ranarum (basidiobolomycosis) in two otherwise healthy children. The first case was a 10-months-old boy who had prolonged fever for 3 weeks and painless wooden hard, inflammatory ulcerated mass at the upper lip extended to left cheek. Our patient was previously mistaken for a recalcitrant abscess, vascular tumor or panniculitis-like T-cell lymphoma. The diagnosis and treatment were delayed, as the clinical presentation was not straight forward. Therefore, the authors emphasize that early tissue biopsy is very important to diagnose subcutaneous zygomycosis. Mendiratta V has also reported a 9-months-old who had a rapid expanding malignant presentation of basidiobolomycosis with non-healing ulcers, which spread to underlying muscles. He concluded that subcutaneous zygomycosis due to Basidiobolus ranarum might have an explosive, malignant presentation in very young children[7]. Facial region involvement is an uncommon location of subcutaneous zygomycosis in children. However Ramesh V et al, have also reported facial lesion caused by Basidiobolus ranarum[8]. It is important to note that the regional preference is not absolute[19,20].

The authors' second case report was a 2-years-old girl with slow growing painless mass at left buttock for 7 months, which is the classic presentation of subcutaneous zygomycosis. Tissue culture was positive for *Basidiobolus ranarum* in both cases. They were treated with itraconazole dose of 5 mg per kilogram daily. Improvement was observed within 3 months after treatment with no side effects.

Regarding the antifungal therapy, either oral potassium iodide or azole group, particularly itraconazole is effective in most cases[8]. Trimethoprim sulfamethoxazole has been reported effective in a patient with visceral infection[17]. Mathew and Kraimak S et al also reported success in treatment of Basidiobolomycosis with potassium iodide without combination of any azoles[14,18]. However, Mendiratta V has shown slow clinical response with oral itraconazole alone but a dramatic improvement after adding oral potassium iodide. Other treatment options are amphotericin B, ketoconazole, fluconazole, terbinafine. The duration of treatment is uncertain and depends on the severity of the disease and clinical response, however most patients required the medication from months to years. Surgical intervention, either for definite diagnosis or mass debulking may be necessary in extensive lesions, involving visceral organ[17].

In the present first case, combination of amphotericin B and oral itraconazole were chosen because of severe systemic symptoms and rapid expanding of lesion. On the other hand, oral itraconazole alone was effective in the second case, which may be due to early diagnosis and the fact that the symptom was limited to the skin and sub-cutis. Both cases were well tolerated and no side effects were reported.

In conclusion, for children who present with subcutaneous non-tender firm, slowly enlarging mass, tissue biopsy and fungal culture is very crucial for diagnosis and early treatment. The authors emphasize that subcutaneous Basidiobolus ranarum in very young children can have an atypical and aggressive clinical feature. Early recognition of the disease may prevent further tissue damage and unnecessary surgical

intervention. Itraconazole alone can be effective. The duration of treatment varies depend upon the patient's clinical response.

Potential conflicts of interest

None.

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รายงาน subcutaneous zygomucosis ในผู้ป่วยเด็ก 2 ราย

นุชนาฏ มหเมธากิจ, ศรีศุภลักษณ์ สิงคาลวณิช, วนิดา ลิ้มพงษานุรักษ์

Basidiobolus ranarum เป็นเชื้อก่อโรคที่พบไม่บ่อยทำให้เกิดการติดเชื้อที่บริเวณชั้นใต้ผิวหนัง และพบในเด็กที่ภูมิคุ้มกันปกติพบได้บ่อยในประเทศเขตร้อน ลักษณะทางผิวหนังที่ค่อนข้างจำเพาะได้แก่ ลักษณะก้อนนูน แข็งในชั้นใต้ผิวหนัง มักไม่เจ็บและไม่มีลักษณะของการอักเสบ ก้อนขยายขนาดอย่างช้า ๆ และมักไม่ลามเกินกว่าชั้นใต้ผิวหนัง ผู้ป่วยทั้งสองรายได้รับการวินิจฉัยเป็น subcutaneous zygomycosis และทั้งสองรายตรวจพบเชื้อรา Basidiobolus ranarum โดยผู้ป่วยรายแรกเป็นเด็กชายอายุ 10 เดือน มาพบแพทย์ด้วยไข้สูงเรื้อรังร่วมกับลักษณะรอยโรคที่อักเสบลุกลามรวดเร็วและรายที่สองเป็นผู้ป่วยเด็กหญิงอายุ 2 ปี มีลักษณะรอยโรคที่จำเพาะของ subcutaneous zygomycosis ได้ การตรวจทางพยาธิวิทยาจากผิวหนังพบลักษณะการอักเสบในชั้นไขมันประกอบด้วยเซลล์ eosinophil จำนวนมากในผู้ป่วยทั้งสองรายและพบว่าการใช้ยา itraconazole ได้ประสิทธิภาพดีไม่พบผลข้างเคียงในผู้ป่วยทั้งสองราย