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ORIGINAL PAPER

Successful Treatment of Eczema-Like Mucormycosis in a Child by Combination of Intravenous Drip and Percutaneous Injection Amphotericin B

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Abstract We report a case of eczema-like cutaneous mucormycosis caused by *Rhizopus arrhizus*. A 4-year-old child was presented to our hospital with a history of gradually enlarging papule and plaque in the periumbilical area for nearly 4 years since 2 weeks after his birth, and it has been misdiagnosed as eczema for nearly 3 years. Based on histopathology examination, the fungus culture test and DNA sequencing, it was revealed that *R. arrhizus* should be the responsible fungus for skin infection. The patient was successfully cured by combination of intravenous drip and percutaneous injection amphotericin B for nearly 3 months, and no recrudescence was seen during a follow-up of 6-month observation.

Keywords Mucormycosis · *Rhizopus* · Child · Eczema-like

Introduction

As a life-threatening disease, mucormycosis almost invariably occurs in immunocompromised patients,

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especially those with uncontrolled diabetes mellitus, neutropenia, organ transplant and even congenital immunodeficiency [1]. Mucormycosis generally progresses rapidly, with a high mortality rate, approximately ranging from 23 to 100% [2], which may be attributed to the delayed diagnosis and subsequent antifungal treatment, partly due to highly intrinsic resistance to many commonly used antifungal drugs. Mucormycosis has different clinical presentations including rhinocerebral, sinusal, pulmonary, cutaneous and disseminated as the main clinical forms, with various underlying and triggering risk factors [3]. The clinical presentations and prognosis are also associated with the isolated microorganism, and *Rhizopus* sp. is one of the most frequently isolated fungus [3]. However, cutaneous mucormycosis caused by *Rhizopus arrhizus* has been rarely reported, especially in child which is usually characterized by progressive swelling, ulceration, tissue necrosis, disfigurement and even death in severe cases. In recent years, our team has reported several primary cutaneous mucormycosis in China [4, 5], indicating focus on skin infection by *Mucorales*. Here, we report a case mucormycosis caused by *R. arrhizus* in a 4-year-old boy presenting as an eczema-like lesion in his periumbilical area and successfully treated by intravenous drip and percutaneous injection amphotericin B.

Case Presentation

In July 2017, a 4-year-old boy was admitted to our hospital with a history of gradually enlarging papule and plaque in the periumbilical area for nearly 4 years. Upon recalling his birth history, we found that this boy was born through full-term normal delivery and has normal birth weight. Since 2 weeks after his birth, a red papule was found near his navel without any obvious trauma. At first, it was misdiagnosed as bacterial folliculitis and treated with antibiotic ointment. As time going on, the papule grew in number and merged into plaque with erythema and without any exudation or scales in the periumbilical area. Then, it was misdiagnosed as eczema and prescribed with glucocorticoid cream for topically using. Only until histopathology examination of the skin lesion biopsy was done about a year before his admission to our hospital, mucormycosis was considered. So, itraconazole syrup (8 ml per day) and terbinaphthyl cream were prescribed for nearly 6 months. As a result, the lesions shrinked mildly without an anticipated improvement.

On physical examination, the patient had normal temperature, pulse, respiration and blood pressure. His body weight was 16 kg. A dark red, irregular plaque was seen on the patient's periumbilical area in size of 7×10 cm, with some red papules distributed, but without exudation. The surface of the lesion was partially covered by very thin layers of scales with relatively clear boundary on the edge (Fig. 1a). The palpation revealed some deep nodules.

A histopathology examination with hematoxylin-eosin (HE)-stained (Fig. 1d), periodic-acid-Schiff (PAS)-stained (Fig. 1e) and periodic acid-silver metheramine (PASM) (Fig. 1f) sections revealed the presence of non-septate hyphae with pectinate hyphae with right-angled branching in the dermis, which are surrounded by mixed inflammatory cell composed of lymphocytes, neutrophils and multinucleated giant cells. For fungal identification, biopsy tissues were inoculated and cultured on Sabouraud dextrose agar (SDA) at 26, 37 and 40 °C (Fig. 1g). Microscopy result showed broad, aseptate hyphae, sporangia and rhizoids (Fig. 1h). DNA extraction was carried out for polymerase chain reaction by using fungus universal primers, and the sequence results were completely consistence with the records of *R. arrhizus* (GenBank Accession No. KF717369.1). It was diagnosed as mucormycosis caused by *R. arrhizus* consequently. Broth microdilution method (M38-A2) [6] was performed to determine susceptibility of antifungal agents. The MICs were amphotericin B (0.25 mg/ml), itraconazole (0.25 mg/ml), voriconazole (4 mg/ml), posaconazole (0.5 mg/ml), anidulafungin (> 8 mg/ml), micafungin (> 8 mg/ml) and fluconazole (> 256 mg/ml).

Based on the results of susceptibility of antifungal agents test, intravenous amphotericin B was used and it was started from 0.0625 to 0.625 mg/kg/day in the first 6 days and then sustained for 15 days. The lesion did not recede fast enough as expected (Fig. 1b); thus, amphotericin B was increased to 0.738 mg/kg/day and lasted for 20 days. During systematic using of amphotericin B, percutaneous injection amphotericin B was adopted at the same time. Many papules and plaque decreased significantly, only with pigmentation left (Fig. 1c). Further, the patient was recommended to

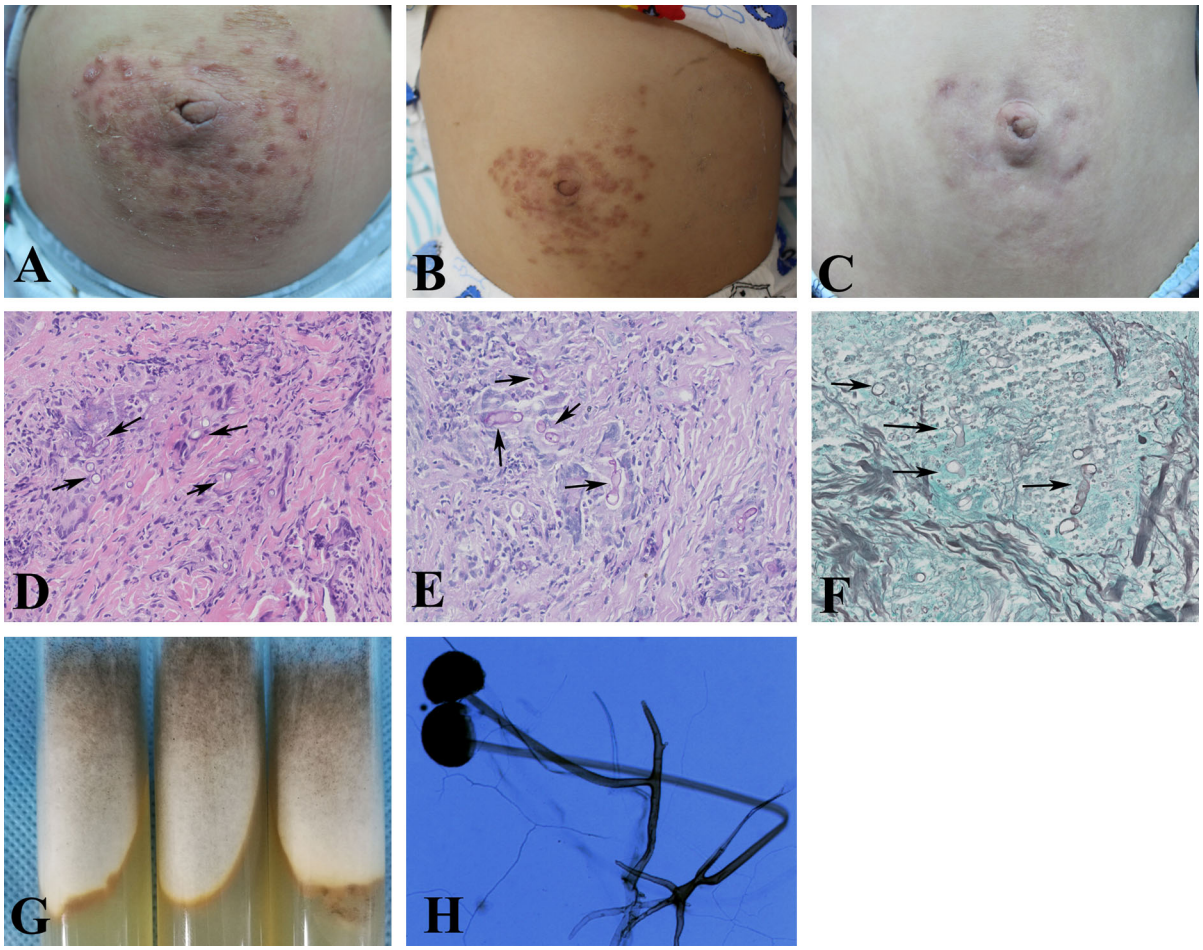

Fig. 1 **a** A dark red, irregular plaque area in size of approximately 7 × 10 cm was seen on the patient's periumbilical with some red papules distributed. **b** The lesion did not recede fast enough as expected upon prescribing amphotericin B (0.625 mg/kg/day) for 15 days. **c** Pigmentation left when he got out of hospital. **d** Hematoxylin-eosin (HE)-stained, **e** periodic-acid-Schiff (PAS)-stained and **f** periodic acid-silver metheramine (PASM) of histopathological specimen showed non-septate hyphae with pectinate hyphae with right-angled branching in the dermis (magnification, 200×). **g** Colonies of *Rhizopus arrhizus* grown on Sabouraud dextrose agar (SDA) at 26, 37 and 40 °C (from right to left). **h** Slide culture showed broad aseptate hyphae, sporangia and sporangiophores with opposite rhizoids (magnification, 200×). (Color figure online)

continue treatment with itraconazole capsule (100 mg per day) for orally and amphotericin B for percutaneous injection for about 2 months after he got out of the hospital. The boy almost completely recovered, and no recrudescence was seen during a follow-up of 6-month observation.

Discussion and Conclusion

Mucormycosis (zygomycosis) is the third most common type of invasive fungal infection (IFI), and the mortality rate can be as high as more than 50% [7]. *R. arrhizus* is among the widespread species worldwide that can cause opportunistic infections for those with immune disturbance [8]. There have been more than 20 cases reported in mainland China, most of them are with diabetes mellitus or chronic renal failure, and there is only one child infected but resulting in death pitifully for aplastic anemia complications [9]. Though rare incidence in children, *Rhizopus* spp. is the second most common pathogen in children with invasive mold infections [10], and it is inclined to affect preterm or immunocompromised newborns in most cases [11, 12]. No predisposing conditions can be found in this boy.

Cutaneous mucormycosis caused by *R. arrhizus* is rarely reported compared with rhinocerebral and pulmonary infections, and it occurs mostly due to wound or disruption of cutaneous barrier [3]. But in this case reported, the parents denied any trauma since his birth. Hemorrhagic or necrotic tissue is the most common representation of cutaneous zygomycosis for its tendency to invade vessels, and bull's eye appearance of skin has also been reported to be a distinct manifestation of mucormycosis [13], but eczema-like lesion can easily be misrecognized as eczema or dermatitis thus leading to improper treatment consequently. Julie L et al. once presented a 10-year-old acute myelogenous leukemia (AML) girl with a single erythematous plaque with annular bulla on her arm which was misdiagnosed as a reaction to insect bite initially, and diagnosis of zygomycosis was not made until histological examination [14]. In this case, similarly, the lesion did not possess any typical characteristics and the boy was treated inappropriately for more than 2 years, making conditions even worse. We can conclude that this is a rare case of primary cutaneous zygomycosis inflicts with an immunocompetent child imitating eczema atypically, and direct microscopy of the biopsy and culture confirmation are recommended when experiential treatment do not work well in clinical practice [15].

As for the treatment of mucormycosis, combination of amphotericin B and surgical debridement is highly recommended according to most reports [3, 8, 16–18]. And posaconazole as recorded has been an emerging agent to use in clinical, but data concerning with children are very limited [19–22]. Percutaneous injection of antifungal agents directly to the lesion can achieve the highest concentration at the site of infection [23], and this method can not only avoid long time using of antifungal agents but reduce the recurrence rate to some extent as well. Back in 2005, Zhang DL has used intralesional, intravenous and intrathecal amphotericin B to cure disseminated cryptococcosis successfully [24], and several cases have been reported about topical injection of amphotericin B in cutaneous leishmaniasis patients [23, 25, 26]. In this case presented, both intravenous drip and percutaneous injection of amphotericin B are adopted together and works better compared with oral itraconazole or intravenous amphotericin B alone. We can conclude that percutaneous injection of amphotericin B can serve as an effective supplementary method to treat cutaneous mucormycosis as well. However, decreased susceptibility of amphotericin B in *Rhizopus* spp. has been detected [27]. Thus, susceptibility test is strongly recommended upon diagnosis made in order to prescribe the most effective agents.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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