

Gangrenous Cutaneous Mucormycosis Caused by *Rhizopus oryzae*: A Case Report and Review of Primary Cutaneous Mucormycosis in China Over Past 20 Years

HouMin Li · Sonia Kay Hwang · Cheng Zhou ·
Juan Du · JianZhong Zhang

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Abstract Cutaneous mucormycosis is a rare opportunistic infection caused by zygomycetes that can be rapidly fatal if unrecognized. We describe the clinical, histopathological, fungal and molecular features of a case of gangrenous cutaneous mucormycosis. The patient presented with great necrosis on his right forearm at the site of detained intravenous cannula needle. He had type II diabetes and chronic renal insufficiency. KOH mount of black eschar showed many broad, aseptate fungal hyphae with right-angle branching. PAS staining of the tissue sample revealed similar broad hyphae in the dermis and cutis. Fungal culture and ITS sequence analysis identified this fungus as *Rhizopus oryzae*. As no organ involvement was detected, the patient was diagnosed with primary cutaneous mucormycosis. Considering the poor state of the patient, complete excision of the infectious tissue was performed without skin graft instead of amputation. At the same time, intravenous liposomal amphotericin B was given, starting from a small dosage and increased to a total dosage amount of 5.45 g. The wound recovered well with granulation.

We emphasize that early recognition and prompt therapy including the control of the primary diseases were important. In this article, we also reviewed the features of primary cutaneous mucormycosis reported in China over the last 20 years.

Keywords Cutaneous · Mucormycosis · Gangrenous · *Rhizopus oryzae* · Intravenous cannula · Liposomal amphotericin B

Cutaneous mucormycosis is a rare opportunistic infection caused by the fungi of Zygomycetes that can be rapidly fatal if unrecognized. A majority of these infection happened in patients with predisposing factors such as prematurity, patients who use broad spectrum antibiotics or corticosteroids, immunosuppressed patients such as those with diabetes or trauma [1–3]. There have been several reports of sporadic cases of cutaneous mucormycosis related to contaminated material such as adhesive bandages or intravascular catheter [4, 5]. Here, we report a serious case of primary cutaneous mucormycosis (PCM) caused by *Rhizopus oryzae*. This patient was treated successfully (the first case reported in China) with a combined treatment of intravenous liposomal amphotericin B, surgical debridement, topical antifungal and fibroblast growth factor after debridement. In this article, we also reviewed the literature of primary cutaneous mucormycosis reported in China in the past 20 years.

H. Li · S. K. Hwang · C. Zhou · J. Du (✉) · J. Zhang
Department of Dermatology, Peking University, People's
Hospital, Beijing 100044, People's Republic of China
e-mail: dujuan223@medmail.com.cn

H. Li
e-mail: lhomin@yahoo.com.cn

Case Report

A 59-year-old hospitalized male patient in cardiac care unit complained of a painful erythema on his right forearm for 13 days on September 4. He had been embedded with a detained intravenous cannula needle on his right forearm 1 month before onset of the lesion. Seventeen days later, a local flare and pain appeared at the site of where the needle was planted. The lesion rapidly enlarged with emerging necrosis and severe pain. Intravenous transfusion of ceftriaxone and topical povidone iodine had been given for 5 days without any effect, and the area of necrosis enlarged continually. He had been suffering from many internal diseases including type II diabetes (insulin treatment mal-control), coronary atherosclerosis heart disease, atrial fibrillation, hypertension and chronic renal insufficiency with continued regular hemodialysis. Physical examination: T 36 °C, BP 155/95 mmHg, R 18/min, H 80/min, regular cardiac rhythm and coarse breath sounds of both lungs without dry or moist rales. Cardiac realm expanded to the left. No irregular noise was audible from each auscultatory valve areas, nor was pericardial rub. Abdomen was inflated without tenderness. Laboratory examinations showed: blood routine: WBC $15.59 \times 10^9/L$, NE 0.840, LY 0.059, Hb 67.5 g/L, PLT $140.5 \times 10^9/L$; urine routine: protein: 0.75 g/L, WBC 2–3/HP; blood biochemistry: TP 74.3 g/L, Alb 40.7 g/L, BUN 18.25 mmol/L, Cre 248 $\mu\text{mol/L}$, Glu 10.68 mmol/L, TG 2.56 mmol/L, LDL 1.05 mmol/L, HDL 1.00 mmol/L. Skin examinations showed an approximately 8.0×12.0 cm well-circumscribed lesion on the right forearm, great zonal necrosis with red border covered with thick black eschar and exudation (Fig. 1).

Fungal Examination

Both eschar and secretions from the necrosis were obtained for fungal microscopic and culture test. Under the microscope, many broad hyphae with branches at right angles without septum were seen (Fig. 2). Culture of the eschar in Sabouraud's agar medium in 25 °C showed cotton-form colony on the second day and a great quantity of flocc alba colony on the seventh day (Fig. 2). The spherical spores and broad swollen hyphae with branches were also seen



Fig. 1 Photograph of the patient **a** before the treatment, **b** after the treatment

under the microscope. Pseudorhiza was evidently visible from the colony with sporangiophore opposite to the pseudorhiza. Spherical or elliptical sporangium formed on the handle (Fig. 2). In the following days, cultures of different samples all demonstrated the isolation of *Mucor* species.

Histopathological Findings in the Skin

HE staining of the biopsy specimens showed that composition of the normal cutaneous was destroyed in the necrosis area. Denaturation and necrosis were seen in the dermis and cutis, with numerous infiltrations of inflammatory cells including neutrophils, lymphocytes, multinucleated giant cells and histiocytes. Thrombosis of blood vessel was also seen in the dermis (Fig. 3). HE and PAS staining both revealed the similar broad non-septate hyphae with right-angle branching in the dermis and cutis

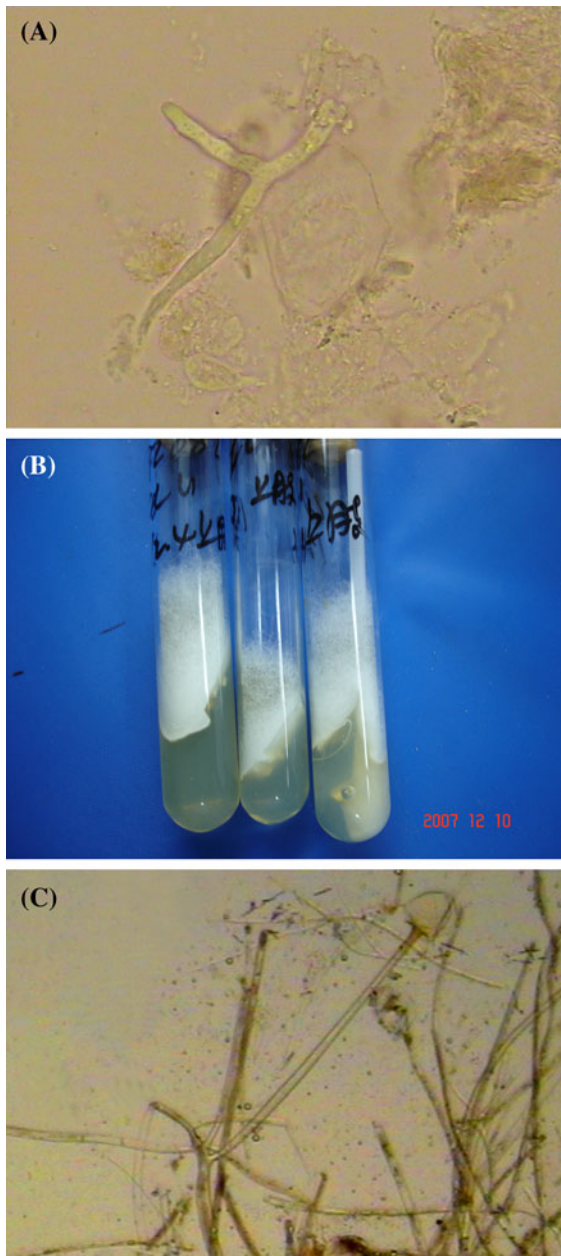


Fig. 2 **a** Under microscope, many broad hyphae with branch at right angles without septum were seen ($\times 400$). **b** Culture of the eschar showed a great quantity of flocc alba colony on the seventh day. **c** Pseudorhiza was obvious from the colony with sporangiophore opposite to the pseudorhiza. Spherical or elliptical sporangium formed on the handle ($\times 100$)

(Fig. 3). Fungal vascular invasion was also seen which supports a zygomycetic infection, which further confirms the diagnosis of cutaneous mucormycosis by the histopathology.

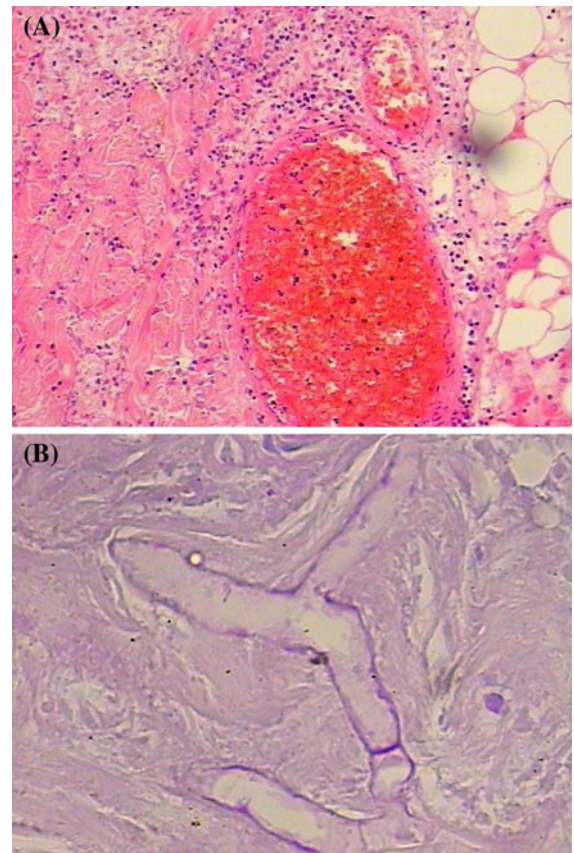


Fig. 3 **a** Thrombosis of blood vessel was seen in the dermis (\times , HE stain). **b** PAS stain revealed the broad non-septate hyphae with right-angle branching in the dermis and cutis ($\times 400$, PAS stain)

Molecular Cytogenetic Analysis

Genomic DNA was extracted from the culture product by pulverization in liquid nitrogen and repeated phenol–chloroform extractions. A segment of ribosomal RNA genes with internal transcribed spacers were amplified from genomic DNA by PCR using primers ITS1 (5'-TCCGTAGGTGAA CCT GCG G-3') and ITS4 (5'-TCC TCC GCT TAT TGA TAT GC-3'). The PCR products were purified and sequenced from both directions using one of the PCR primers as the sequencing primer. The nucleotide–nucleotide BLAST program (<http://www.ncbi.nlm.nih.gov/BLAST>) was used to query the National Center for Biotechnology Information GeneBank nucleotide database for homologous sequences. And finally, this isolation was identified as *R. oryzae* (GenBank accession: KC415762.1).

Diagnosis

Based on the history, clinical examination, fungus morphology and DNA sequencing results, the patient was diagnosed as gangrenous mucormycosis caused by *R. oryzae*. Since no organ involvement was detected by thorough examination, the patient was diagnosed as primary cutaneous mucormycosis.

Treatment and Follow-Up

Considering the poor condition of this patient, complete excision of total necrosis tissue was performed without skin grafting, instead of amputation. Intravenous liposomal amphotericin B was given starting from small dosages 50 mg/d; 3 days later increased to 100 mg/d; 5 days later increased to 150 mg/d and maintained this dosage in the following 28 days and then decreased to 100 mg for 6 days and stopped. The total dose was 5,450 mg. Meanwhile, topical solution of 2.5 mg/ml liposomal amphotericin B, basic fibroblast growth factor and Argentine zinc cream (the main ingredient: AgSD and ZnSD) was given after debridement. During the same time, all the primary diseases were treated by internists from relevant departments. The patient recovered satisfactorily with fresh granuloma and scarring over the skin lesion (Fig. 1). No recurrence was found during a 4-month follow-up. Fungal examinations and cultures were negative for three times after debridement.

Discussion

Zygomycetes, including *Rhizopus*, *Rhizomucor*, *Mucor*, *Absidia* and *Cunninghamella* [6], can cause invasive fungal infections called mucormycosis in humans. Clinical manifestations of mucormycosis are mainly divided into five categories: rhin-brain type, lung type, gastrointestinal type, skin type and disseminated type [3–5, 7, 8]. Primary cutaneous mucormycosis (PCM) is often reported in patients with local trauma or predisposing disease including diabetes, hypo-immune functions and chronic renal failure. PCM is segregated further into two subtypes according

to the cutaneous manifestation. The superficial variant presents with a gradual onset and slow progression of symptoms [3–5, 7, 8]. The gangrenous form of cutaneous mucormycosis advances rapidly like in our case, causing painful ulcers and eschars. Hematogenous spread is common, and the prognosis is grave [9].

In the present case, the patient had multiple predisposing factors including type II diabetes and chronic renal insufficiency with continued regular hemodialysis. Intravenous cannula embedded for up to 1 month was also associated with fungal infection. Clinical manifestation appeared as necrotic ulcers with black eschars. Histopathology examination showed PAS-positive hypha with thick, non-separated, vertical branch. Tissue culture found fungal growth, which was identified as *R. oryzae* via morphology and molecular biology examinations. Thus, the patient was diagnosed as gangrenous PCM.

Gangrenous PCM is a fast lethal infection. The most crucial treatment is treating the underlying predisposing diseases and use of antifungal drugs as soon as possible. In the present case, considering the poor condition of our patient, instead of amputation and dermoplasty, complete excision of total infected tissue was performed. For antifungal treatments, although there are some reports of effective treatment for cutaneous mucormycosis with itraconazole and fluconazole as shown in Table 1, most reports showed that systemic amphotericin B or its liposome was the most effective [2, 10]. Though high doses of amphotericin B or its liposome may be more effective in the treatment for PCM, we believe that individual treatment strategies should be suggested according to the state of the illness, therapeutic effect and extent of adverse effects. In the present case, on account of the poor condition of kidney, intravenous liposomal amphotericin B was initiated from a small dose and gradually increased to the treatment dose, which still had a good outcome. At the same time, correlated departments of our hospital cooperated with each other to treat the patient's other diseases, including the control of his blood sugar level, treatment of the diseases of the heart and renal inadequacy. Daily dressing changes, intensive nursing, topical solution of liposomal amphotericin B, basic fibroblast growth factor to promote the restoration of raw surface and

Table 1 20 cases of primary cutaneous mucormycosis from Chinese literature

No.	Year of Publish	Age years/sex	Underlying condition	Site of infection	Organism	Treatment	Outcome
1	1994	37/F	Immunocompetent	Right dorsum of hand	<i>Rhizomucor variabilis</i>	Naftifine solution	Effective
2	1994	54/F	Immunocompetent	Face	<i>Rhizomucor variabilis</i>	Oral fluconazole	Effective
3	1998	24/M	Immunocompetent	Face	<i>Mucor hiemalis F. Luteus</i>	Oral itraconazole	Cured
4	2002	60/M	Toxic epidermal	Left thigh	<i>Mucor</i>	Topical amphotericin B solution/Debridement	Recovered with scar
5	2002	31/M	Immunocompetent trauma	Right elbow	<i>M. racemosus Fr</i>	Oral terbinafine	Cured
6	2003	14/F	Immunocompetent rinse of lacrimal gland	Dorsum of nasi	<i>Mucor</i>	Systemic amphotericin B	Cured
7	2004	33/M	Immunocompetent trauma	Right upper extremity	<i>Rhizomucor variabilis</i>	Systemic amphotericin B	Cured
8	2004	18/F	Toxic epidermal necrosis	Face	<i>Mucor</i>	Oral itraconazole terbinafine solution	Cured
9	2006	40/F	Immunocompetent midges bite	Face	<i>Rhizomucor variabilis</i>	Systemic amphotericin B oral itraconazole	Cured
10	2006	20/F	Immunocompetent bone fracture	Left lower limb	<i>M. racemosus</i>	Intravenous fluconazole oral terbinafine/surgical resection/skin graft	Cured
11	2006	5/F	Immunocompetent	Face	<i>Rhizomucor variabilis</i>	Systemic amphotericin B	Cured
12	2007	22/F	Immunocompetent	Left hip	<i>Mucor racemosus Fres. Var. Chibinensis</i>	Liposomal amphotericin B itraconazole/skin graft	Cured
13	2009	44/M	Diabetes mellitus ketoacidosis	Chin	<i>Head mold</i>	Systemic amphotericin B debridement	Effective
14	2010	52/M	Immunocompetent history of lung TB	Face	<i>Rhizomucor variabilis</i>	Systemic amphotericin B	Cured
15	2010	45/F	Immunocompetent	Face	<i>Rhizomucor variabilis</i>	Systemic amphotericin B itraconazole	Effective
16	2010	37/M	Immunocompetent	Face	<i>Rhizomucor variabilis</i>	Systemic amphotericin B Release	Therapy
17	2011	65/M	Immunocompetent	Face	<i>Rhizomucor variabilis</i>	Systemic amphotericin B	Effective
18	2012	58/M	Immunocompetent electric burn	Left hand and forearm	<i>Rhizopus arrhizus</i>	Systemic amphotericin B	Effective
19	2012	6/F	Immunodeficiency	Right hand	<i>Rhizopus arrhizus</i>	Itraconazole fluconazole	Dead
20	2012	29/M	Immunocompetent after amputation	Right leg	<i>Rhizopus arrhizus</i>	Amphotericin B amputation again	Cured

Argentine zinc cream often used for burn were utilized after debridement. Through the above treatments, the wound recovered well with fresh granuloma tissue. No recurrence was found after a 4-month follow-up.

We reviewed 20 PCM cases reported in Chinese literature in the past 20 years as shown in Table 1. Sixteen of the 20 cases were immunocompetent. Out of the 16, 8 cases had local factors including trauma, insect bite, amputation and dacryocyst clysis. Four cases had underlying diseases, 2 with epidermal necrosis, 1 with tuberculosis and 1 with diabetes mellitus and ketoacidosis. Nine cases were caused by *Rhizomucor variabilis*, 3 by *Mucor racemosus*, 3 by *Rhizopus arrhizus*, 1 by *head mold*, 1 by *Mucor hiemalis* *Fusolativirus Luteus*, and the species were not identified in 3 other cases. Most of the patients recovered or were cured after combination therapy.

This report emphasizes the need for early and specific diagnosis with prompt antifungal management and complete excision of total necrosis tissue in PCM. A high awareness of this infection may improve the prognosis and obviate the need for disfiguring surgery, skin graft even causing death. Because of the propensity for PCM to affect areas of minor trauma [11], face and limbs have been favored areas of infection as showed in Table 1. The doctors need to have a high index of suspicion when evaluating non-healing lesions in the immunocompromised patient or even in the immunocompetent person.

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Conflict of interest None.

References

1. Chayakulkeeree M, Ghannoum MA, Perfect JR. Zygomycosis: the re-emerging fungal infection. *Eur J Clin Microbiol Infect Dis.* 2006;25:215–29.
2. Ameen M, Arenas R, Martinez-Luna E, Reyes M, Zacarias R. The emergence of mucormycosis as an important opportunistic fungal infection: five cases presenting to a tertiary referral center for mycology. *Int J Dermatol.* 2007;46:380–4.
3. Ledgard JP, van Hal S, Greenwood JE. Primary cutaneous zygomycosis in a burns patient: a review. *J Burn Care Res.* 2008;29:286–90.
4. Alsuwaida K. Primary cutaneous mucormycosis complicating the use of adhesive tape to secure the endotracheal tube. *Can J Anaesth.* 2002;49:880–2.
5. Baraia J, Muñoz P, Bernaldo de Quirós JC, Bouza E. Cutaneous mucormycosis in a heart transplant patient associated with a peripheral catheter. *Eur J Clin Microbiol Infect Dis.* 1995;84:813–5.
6. Fujimoto A, Nagao K, Tanaka K, Yamagami J, Udagawa SI, Sugiura M. The first case of cutaneous mucormycosis caused by *Rhizopus azygosporus*. *Br J Dermatol.* 2005;153:428–30.
7. Nouri-Majalan N, Moghimi M. Skin mucormycosis presenting as an erythema-nodosum-like rash in a renal transplant recipient: a case report. *J Med Case Rep.* 2008;19:112.
8. Uçkay I, Chalandon Y, Sartoretti P, Rohner P, Berney T, Hadaya K, van Delden C. Invasive zygomycosis in transplant recipients. *Clin Transpl.* 2007;21:577–82.
9. Prabhu RM, Patel R. Mucormycosis and entomophthoromycosis: a review of the clinical manifestations, diagnosis and treatment. *Clin Microbiol Infect.* 2004;10(Suppl 1):31–47.
10. Tehmeena W, Hussain W, Zargar HR, Sheikh AR, Iqbal S. Primary cutaneous mucormycosis in an immunocompetent host. *Mycopathologia.* 2007;164:197–9.
11. Moran SL, Strickland J, Shin AY. Upper-extremity mucormycosis infections in immunocompetent patients. *J Hand Surg Am.* 2006;31:1201–5.