Clinical Case Report

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Cutaneous mucormycosis caused by *Rhizopus microsporus* in an immunocompetent patient

A case report and review of literature

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Abstract

Rationale: Cutaneous mucormycosis is an uncommon disease and occurs rarely in immunocompetent patients.

Patient concerns: We reported the case of a 37-year-old man presenting with a skin lesion on the left side of the chest wall with no history of trauma or primary diseases. He was firstly misdiagnosed as tuberculosis and the proper treatment was thus delayed.

Diagnoses: Histopathological examination and fungal culture of the lesion confirmed cutaneous mucormycosis. The isolate was identified as Rhizopus microspores by ITS sequencing.

Interventions: The patient was treated with oral posaconazole 400 mg bid for 150 days.

Outcomes: The patient recovered satisfactorily. No recurrence was found during the follow-up and no side effect of liver function was found.

Lessons: This case helps doctors to consider the possibility of serious fungal infection in immunocompetent patients. It also suggested that posaconazole could be an alternative choice for the treatment of mucormycosis considering the severe side effect of Amphotericin B.

Abbreviations: CT = computer tomography, HIV = human immunodeficiency virus, ITS = internal transcribed spacer, PAS = periodic acid-Schiff staining, RPR = rapid plasma reagin test.

Keywords: cutaneous mucormycosis, ITS region, posaconazole, *Rhizopus microsporus*

1. Introduction

Mucormycosis is a rare opportunistic and invasive infection caused by fungi in the order Mucorales of subphylum Mucoromycotina.[1] Mucoraceae are the most important family, comprising *Rhizopus*, *Mucor*, and *Lichtheimia* as the most common species and *Rhizomucor*, *Mortierella*, *Saksenaea*, *Syncephalastrum*, *Cunninghamella*, and *Apophysomyces* as less common agents of mucormycosis.[2] There are 6 main clinical forms of mucormycosis: rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous.[3] Cutaneous mucormycosis forms <10% of cases of mucormycosis,[4] and it remains a rare infection in the immunocompetent population.[5] We reported a case of cutaneous mucormycosis at the site of chest wall in a male patient with no obvious predisposing factors.

2. Case report

The study was approved by the Independent Ethics Committee of Huashan Hospital and written informed consent was obtained. All the experiments were carried out in accordance with the relevant guidelines and regulations of Huashan Hospital. A 37-year-old driver presented with a skin lesion on the left side of the chest wall, which had been present for 17 years. There had been recent deterioration. The lesion had, at first, been a thumb size tender purple area. It gradually enlarged to include the whole left chest wall. Over the subsequent 5 years, it had become swollen. In the most recent 2 years, the lesion had ruptured recurrently emitting a clear yellowish fluid. Half a year ago, the patient had been sent to the emergency room of local hospital because of hemorrhagic shock after he removed the crust on the lesion. Chest computer tomography (CT) suggested cystic masses in the left chest and abdominal wall, deformity of the chest wall, enlarged lymph nodes in both axillae, left-sided pneumonia, lower left hilar lymphadenopathy, and thickened pleura on the left side.

Histopathological examination of the lesion revealed an abscess with multinuclear giant cells underlying a dense eosinophils accumulation in the dermis. The serological examination showed that the T-SPOT was positive, whereas the rapid plasma reagin test (RPR) and human immunodeficiency

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virus (HIV) were negative. The patient was then diagnosed as "cutaneous tuberculosis" in the local hospital and was treated with amikacin, isonicotinic acid hydrazide, para-aminosailcylic acid, rifampicin, ethambutol, pyrazinamide, and levofloxacin for 2 months without significant improvement.

After that, the patient was admitted into our hospital. He denied any history of diabetes, immunodeficiency, or malignancy. He had lost >5 kg in weight in 6 months. Physical examination showed a large area of red plaques, nodules, and necrotic ulcers with a yellow purulent effusion combined with a

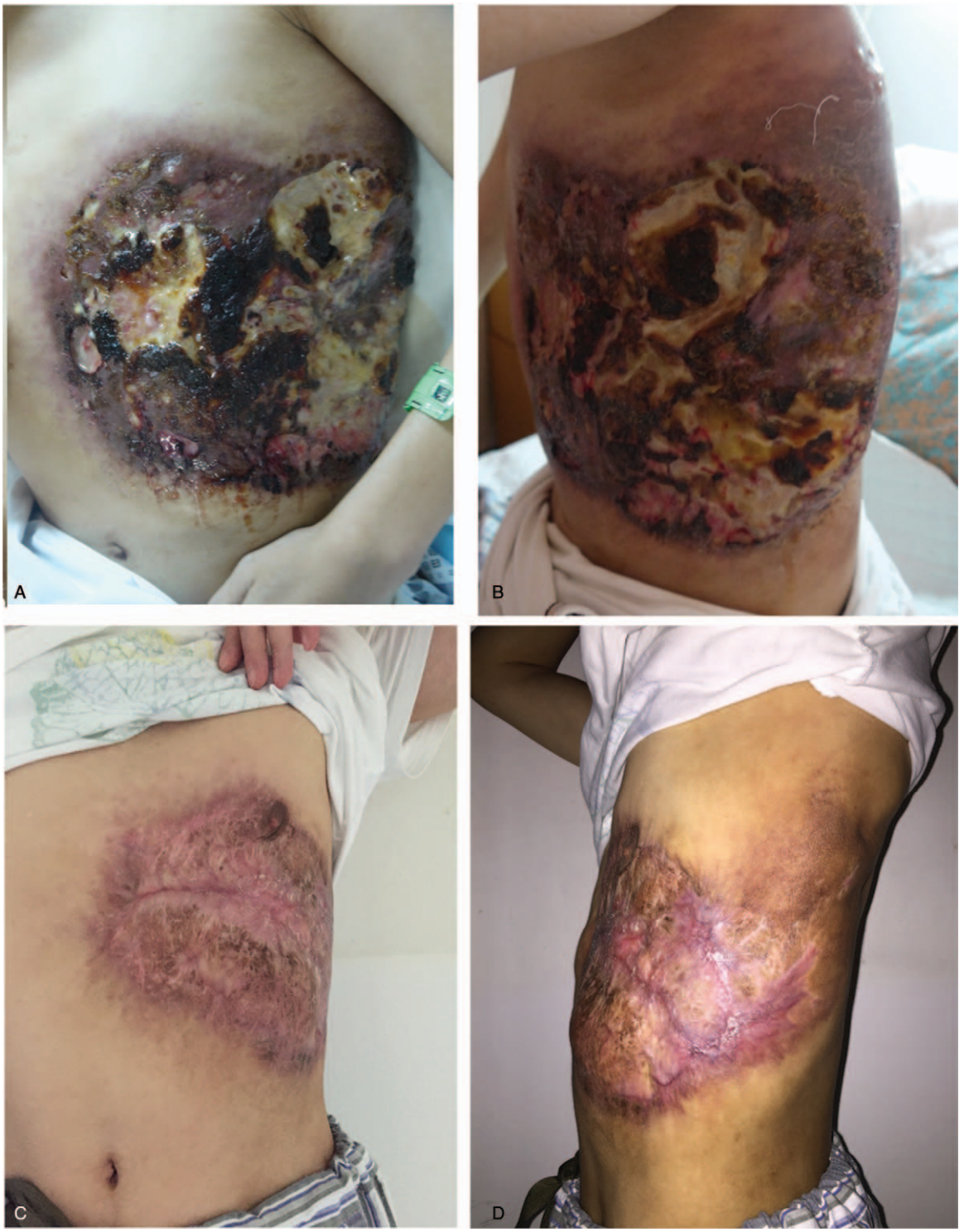

Figure 1. Clinical presentation of the case before the treatment showing a large area of red plaques, nodules, and necrotic ulcers with yellow purulent effusion combined with black crust on the surface and swelling on the edge (A and B). Obvious regression with fresh granuloma and scarring over the skin lesion after 5-month treatment with oral posaconazole (C and D).

black crust formation on the surface and swelling at the edge (Fig. 1A and B). A routine full blood count showed a white blood cell count of 10.20×10^9/L, of which 70.30% were neutrophils. The hemoglobin was decreased to 76 g/L. The eosinophils count was 374×10^6/L and the erythrocyte sedimentation rate was 54 mm/h. Blood biochemical tests revealed hypopotassaemia and hypoalbuminemia. The lymphocyte subpopulation analysis and liver and renal function tests were all normal. The result of the *G* test was negative, but the T-SPOT test was positive. The autoantibodies were all negative, except for the antinuclear antibodies which were 1:100. Chest and enhanced upper abdominal CT scan showed a left-sided pneumonia, atelectasis in the lower lobe of the left lung, thickened left pleura, enlarged lymph nodes in both axillae with necrosis of those on the right side, swelling of the soft tissue of the left chest and abdominal wall, a posteriorly situated abscess on the left, an expended esophagus with retention, and a thickened cardia (Fig. 2A and B). Electronic gastroscopy showed achalasia. No abnormalities were found on brain MRI or paranasal sinus CT scan. Histopathological examination of tissue biopsy showed hypertrophy of the stratum spinosum as well as multicellular granulomas in the dermis. Periodic acid-Schiff staining (PAS) was positive with hyphae-like structures in the lesion (Fig. 3A). The pustule of the lesion was processed by KOH mounting, which showed broad, aseptate, and transparent hyphae with uneven caliber and right-angle branching (Fig. 3B). *Mucor* spp. was isolated from the secretion fungal culture. The isolated strain was 100% (1142 bp/1142 bp) identical with *Rhizopus microsporus* (CBS 344.29) by internal transcribed spacer (ITS) sequencing, and the accession number is KX165341 in GenBank. Bacterial culture of the lesion was negative. Sputum smear and culture as well as blood culture were all negative.

Based on the history, physical examination, and laboratory results, a diagnosis of cutaneous mucormycosis was made. Considering the risk of surgical debridement, the patient was given antifungal agents without debridement. Antifungal treatment options consist of amphotericin B as the first-line therapy and posaconazole as salvage therapy. As the patient did not have severe internal organ involvement, the potential risk of adverse effect of amphotericin B might exceed the benefit it could provide. The patient was then treated with oral posaconazole empirically (400 mg bid/d). External application was given to his wound with silver sulfadiazine after cleansing with hydrogen peroxide and normal saline. After 5 months of treatment, the chest CT scan showed an obvious diminution of the abscess with a little residual chronic infection in the left lung (Fig. 2C and D). The patient recovered satisfactorily with fresh granuloma and scarring of the skin lesion (Fig. 1C and D). No recurrence was found during the follow-up and no side effect of liver function was found. The patient is currently still undergoing regular follow-up.

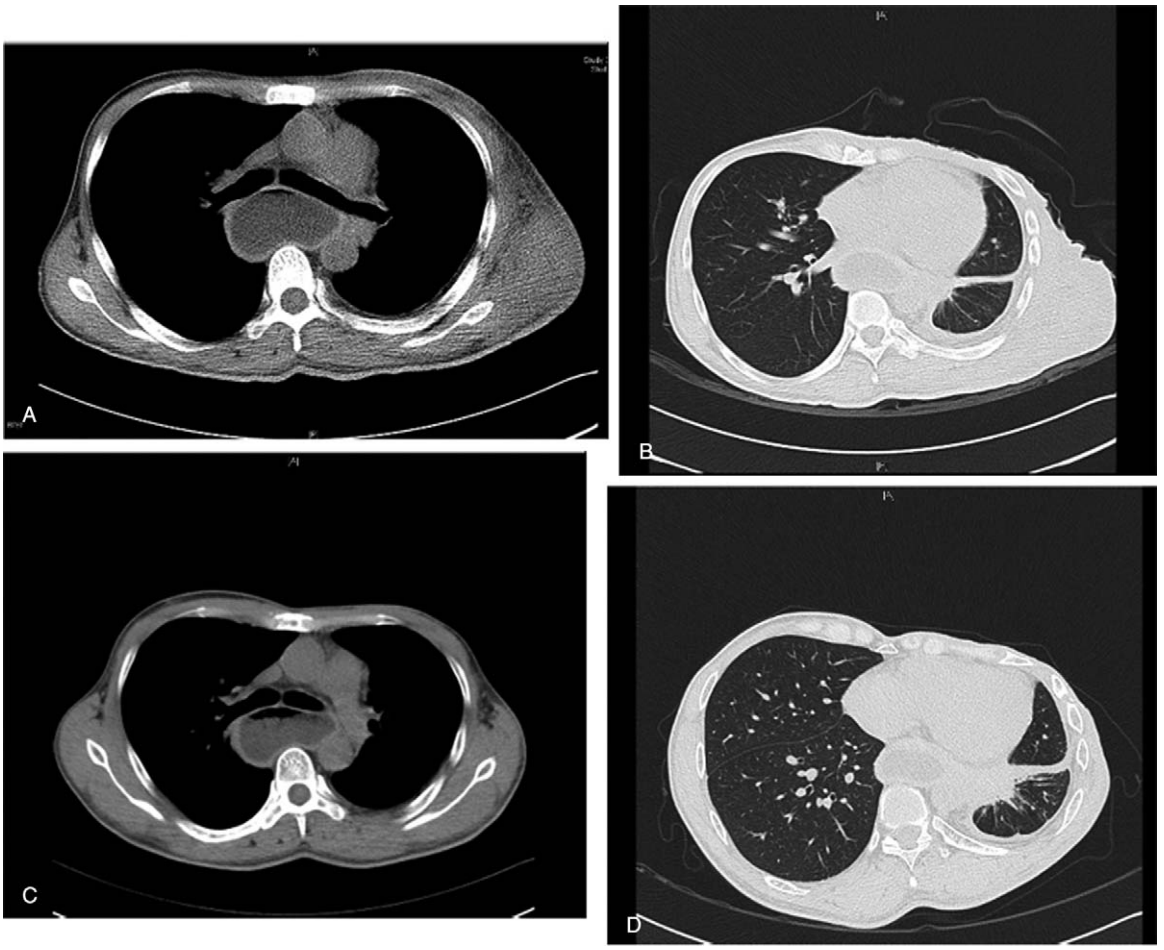

Figure 2. Chest CT scan before the treatment indicated swelling of the soft tissue of the left chest and abdominal wall (A for mediastinal window and B for pulmonary window). After 5-month treatment, the chest CT scan showed obvious diminution of the mass (C for mediastinal window and D for pulmonary window).

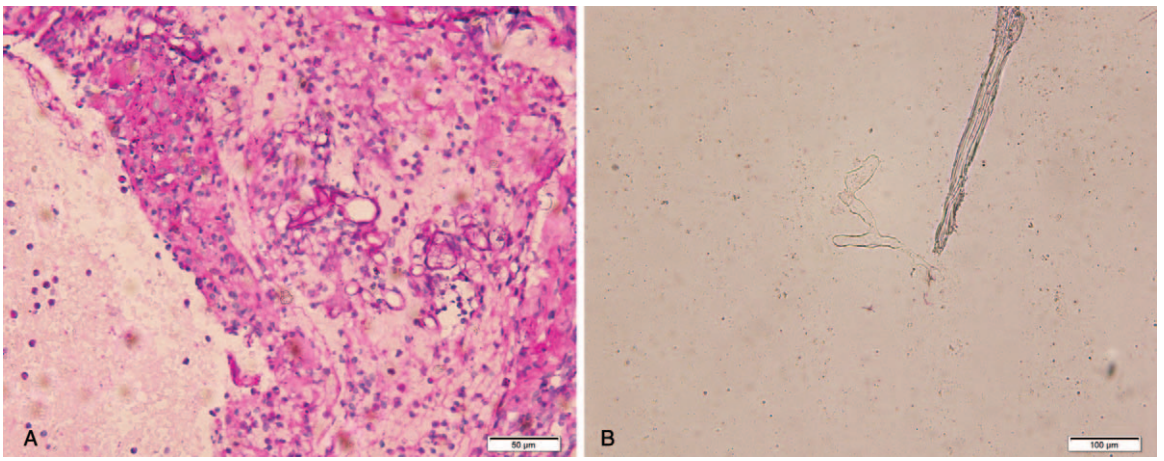

Figure 3. Tissue biopsy showing hyphae-like structures in the lesion (PAS staining, scale bar = 50 μm) (A). The pustule of the lesion showing broad, aseptate, transparent hyphae with uneven caliber, and right-angle branching (KOH, scale bar = 100 μm) (B).

3. Discussion

Most cutaneous mucormycosis may occur from primary inoculation, including surgery, burns, trauma, injections, insect bites, abrasions, lacerations, and direct contact. Scattered case reports of invasive mucormycosis in normal hosts remain a rarity and are often related to trauma. The cutaneous mucormycosis infection can extend deeply to tendon, muscle, or bone, and develop hematogenous dissemination from the original cutaneous site to another organ.[6] The mortality of mucormycosis remains high.[7] Although Roden et al have described the epidemiology and outcome of 929 cases of mucormycosis including 11 cases were caused by *Rhizopus microspores*,[6] they did not give specific information about the infection site, the treatment or the underlying disease of the patients. In the present case, the patient was an immunocompetent young man with no history of trauma or primary diseases. He had massive skin necrosis and a collapsed deformity of the left chest wall. The course of his disease was protracted. The lesion progressed rapidly into inflammatory and necrotic morphology, including cellulitis, ulceration, swelling, and crust formation. As the lesion of our patient presented large area irregular ulcers with a large number of purulent secretions, we performed multiple fungal and bacterial cultures to exclude mixed or contaminated infection. However, the patient refused multiple biopsies because it was invasive. The pathological result did not suggest any evidence of other infectious granuloma, cutaneous tumors, cutaneous vasculitis, or pyoderma gangrenosum, which could manifest as crusted ulcer lesions with pustules and therefore could be easily colonized by *Rhizopus* spp. Diagnosis of cutaneous mucormycosis caused by *R. microspores* was based on histological examination highlighting the characteristic mycelium within infected tissue, together with ex vivo mycological identification using morphological and molecular methods.

Although chest CT scan indicated the patient had a left sided pneumonia, the imaging findings of this chest CT scan were not similar to those of pulmonary mucormycosis, which may present with focal consolidation, lung masses, pleural effusions, or multiple nodules.[8] In addition, the patient's result of sputum smear and culture as well as his blood culture were all negative. Bronchoalveolar lavage or pulmonary biopsy was not performed because the patient declined. Based on that, we could not draw a conclusion that the pneumonia was caused by mucormycosis. The pneumonia could possibly be a reactive inflammation. The case was first misdiagnosed as tuberculosis and the proper treatment was thus delayed. Therefore, this report helps doctors to consider the possibility of serious fungal infection in immunocompetent patients. It also emphasizes the importance of performing a fungal examination and using special staining for pathology to achieve a correct clinical diagnosis.

Antifungal chemotherapy, control of the underlying predisposing condition, and surgery are the cornerstones of management to treat mucormycosis.[9] Amphotericin B remains the first-line therapy for most cases of cutaneous mucormycosis,[10–12] but its use is limited by its potentially severe side effects[7] such as impairment of kidney function, impairment of liver function, chills, arrhythmia, and it is not an effective treatment in many cases, particularly if the patient presents late in the disease course or has disseminated disease.[13,14] Posaconazole is the options for second-line treatment.[9] Posaconazole is highly lipophilic, orally absorbed, and extensively distributed in tissues. Like other azoles, posaconazole inhibits sterol 14α-demethylation, resulting in faulty cell membrane synthesis. However, its sterol inhibitory activity in mucormycosis is better than that of itraconazole.[15] In vitro susceptibilities of antifungal medication against clinical isolates of mucorales including *Rhizopus* spp. showed that the MICs (means) of posaconazole were about 1.6-fold lower than those of itraconazole, 33-fold lower than those of voriconazole, and 47-fold lower than those of fluconazole.[16] The complete response and partial response in 96 cases of mucormycosis treated with posaconazole published between 2003 and 2011 was 64.6% and 7.3%, respectively.[17] Another study to evaluate the in vivo efficacy of posaconazole against *R. microsporus* on mice with disseminated infection showed posaconazole had a clear dose–response effect.[18]

Treatment needs to be adjusted according to patient characteristics, progression of the disease, and toxicity of therapy agents. For the patient in our case who did not have severe internal organ involvement, we thought the potential risk of adverse effect of amphotericin B might exceed the benefit it could provide. Besides, thrombophlebitis is a common adverse effect of intravenous amphotericin B, whereas posaconazole had its oral preparation and the adverse reactions are fewer. As a result, we selected posaconazole to treat our patient. The patient received oral posaconazole 400 mg bid for 150 days with a satisfactory effect.

Our result suggested that posaconazole could be an alternative choice for the treatment of mucormycosis among patients who could not tolerate the severe side effect of amphotericin B. This clinical case report also highlights the severity of mucormycosis. Rapid diagnosis and correct antifungal therapy might be life-saving.

Author contributions

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Resources: Min Zhu.
Supervision: Jun Liang.
Writing – original draft: Yilun Wang.
Writing – review and editing: Yilun Wang.

References

[1] Hibbett DS, Binder M, Bischoff JF, et al. A higher-level phylogenetic classification of the Fungi. Mycol Res 2007;111(Pt. 5):509–47.
[2] Bonifaz A, Tirado-Sanchez A, Calderon L, et al. Cutaneous mucormycosis: mycological, clinical, and therapeutic aspects. Curr Fungal Infect Rep 2015;9:229–37.
[3] Prabhu RM, Patel R. Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect 2004;10(Suppl. 1):31–47.
[4] Verma R, Nair V, Vasudevan B, et al. Rare case of primary cutaneous mucormycosis of the hand caused by *Rhizopus microsporus* in an immunocompetent patient. Int J Dermatol 2014;53:66–9.
[5] Lineberry KD, Boettcher AK, Blount AL, et al. Cutaneous mucormycosis of the upper extremity in an immunocompetent host: case report. J Hand Surg Am 2012;37:787–91.
[6] Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005;41:634–53.
[7] Cheng W, Wang G, Yang M, et al. Cutaneous mucormycosis in a patient with lupus nephritis: a case report and review of literature. Medicine 2017;96:e8211.
[8] Muqeetadnan M, Rahman A, Amer S, et al. Pulmonary mucormycosis: an emerging infection. Case Rep Pulmonol 2012;2012:120809.
[9] Skiada A, Lanternier F, Groll AH, et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). Haematologica 2013;98:492–504.
[10] Ledgard JP, van Hal S, Greenwood JE. Primary cutaneous zygomycosis in a burns patient: a review. J Burn Care Res 2008;29:286–90.
[11] Vaezi A, Moazeni M, Rahimi MT, et al. Mucormycosis in Iran: a systematic review. Mycoses 2016;59:402–15.
[12] Li H, Hwang SK, Zhou C, et al. Gangrenous cutaneous mucormycosis caused by *Rhizopus oryzae*: a case report and review of primary cutaneous mucormycosis in China over Past 20 years. Mycopathologia 2013;176:123–8.
[13] Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev 2000;13:236–301.
[14] Desoubeaux G, Leperlier M, Chaussade H, et al. [Cutaneous mucormycosis caused by *Rhizopus microsporus*]. Ann Dermatol Venereol 2014;141:201–5.
[15] Greenberg RN, Mullane K, van Burik J-AH , et al. Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother 2006;50:126–33.
[16] Sun QN, Fothergill AW, McCarthy DI, et al. In vitro activities of posaconazole, itraconazole, voriconazole, amphotericin B, and fluconazole against 37 clinical isolates of zygomycetes. Antimicrob Agents Chemother 2002;46:1581–2.
[17] Vehreschild JJ, Birtel A, Vehreschild MJ, et al. Mucormycosis treated with posaconazole: review of 96 case reports. Crit Rev Microbiol 2013;39:310–24.
[18] Dannaoui E, Meis JF, Loebenberg D, et al. Activity of posaconazole in treatment of experimental disseminated zygomycosis. Antimicrob Agents Chemother 2003;47:3647–50.