Mycopathologia
DOI 10.1007/s11046-011-9409-7

Cutaneous Hyalohyphomycosis Caused by *Paecilomyces lilacinus* Successfully Treated by Oral Voriconazole and Nystatin Packing

Ching-Yu Huang · Pei-Lun Sun · Hsiang-Kuang Tseng

Received: 19 November 2010 / Accepted: 28 February 2011

Abstract *Paecilomyces lilacinus* causes multiple diseases in humans, especially in immunocompromised patients. Cutaneous infections are the second most commonly encountered circumstance. We describe a woman with liver cirrhosis with hemorrhagic, bullous, ulcerative leg lesions caused by *Paecilomyces lilacinus.* The lesions improved after treatment with oral voriconazole and topical nystatin powder. We also reviewed previously reported cases of cutaneous *P. lilacinus* infection that were treated by oral voriconazole.

Keywords Hyalohyphomycosis · *Paecilomyces lilacinus* · Voriconazole · Nystatin

C.-Y. Huang · P.-L. Sun
Department of Dermatology, Mackay Memorial Hospital, No. 92, Section 2, Zhongshan N. Rd, Zhongshan District, Taipei 10449, Taiwan

P.-L. Sun
Institute of Ecology and Evolutionary Biology, National Taiwan University, Taipei, Taiwan

H.-K. Tseng (✉)
Division of Infectious Diseases, Department of Internal Medicine, Mackay Memorial Hospital, No. 92, Section 2, Zhongshan N. Rd, Zhongshan District, Taipei 10449, Taiwan
e-mail: eric120008@gmail.com

H.-K. Tseng
Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan

Introduction

Paecilomyces species are rare but emerging causes of hyalohyphomycosis. These opportunistic organisms are tremendously threatening for humans, especially immunocompromised patients. *P. lilacinus* may cause oculomycosis, cutaneous and subcutaneous infections, sinusitis, lung abscess, osteomyelitis, or peritonitis [1, 2]. The clinical presentation varies from an insidious onset to overwhelming infection. According to Pastor et al. [1], one-third of *P. lilacinus*-related disorders are cutaneous and subcutaneous infections. Accurate and prompt identification is of great importance in providing optimal therapy. Besides selecting effective systemic antifungal agents, adequate wound management is also essential for successful treatment. However, physicians may have difficulties in deciding the method of wound dressing and choosing the kind of topical agents because topical antimicrobial agents are manufactured in different vehicle bases. We report a case of cutaneous *P. lilacinus* infection that responded well to oral voriconazole and topical nystatin powder. In addition to the antifungal nature of voriconazole, the clinical benefit could possibly be attributed to the synergistic effect of combining nystatin powder. Nystatin powder, which is made in powder form, may lower the humidity of wounds and possibly limit the growth of fungus. We consider this a practical method in treating cutaneous *P. lilacinus* infection.

Published online: 20 March 2011

Case Report

A 66-year-old woman presented with lesions on the left shin. It began as a red area that gradually became swollen and painful and then developed multiple hemorrhagic vesicles, pustules, and erosions. The patient had multiple comorbidities, including liver cirrhosis (HCV related), congestive heart failure (ischemic heart disease related), rheumatic arthritis, and osteoporosis with T-L spine compression fractures. She had the habit of bathing in hot water every day. There was no history of trauma to the left shin. However, shortly before the lesion appeared, her house had been flooded by heavy rain. She tried topical antiseptic medications, but the lesion continued to worsen. She was admitted to the hospital with the tentative diagnosis of cellulitis.

On examination, there were multiple ulcerated, hemorrhagic bullae on a swollen erythematous base (Fig. 1a). She was initially treated empirically with oxacillin and gentamicin, but there was little improvement. The differential diagnosis included infection or an immunobullous disorder. A biopsy was performed, with pathology findings of no bullous change; there was dermal edema with an infiltrate of mixed inflammatory cells. A direct immunofluorescence study was negative.

Antibiotics were changed to aqueous penicillin and levofloxacin, but again, there was no response. Culture of the wound revealed mold-form fungi. Potassium hydroxide examination of the ulcerative debris showed septate hyaline hyphae with features of adventitious sporulation (Fig. 2a). A second biopsy specimen at that time had diffuse infiltration of inflammatory cells in the dermis and subcutis. Periodic acid-Schiff stain of both biopsy specimens revealed septate fungal hyphae within the necrotic tissue (Fig. 2b). Masson-Fontana (melanin) stain was negative.

Fungal culture of the ulcerative tissue on potato dextrose agar showed violet floccose colonies on the obverse that were light brown on the reverse. On microscopy, there were erectile rough-walled conidiophores bearing densely clustered tenpin-shaped phialides with elliptical conidia. These features

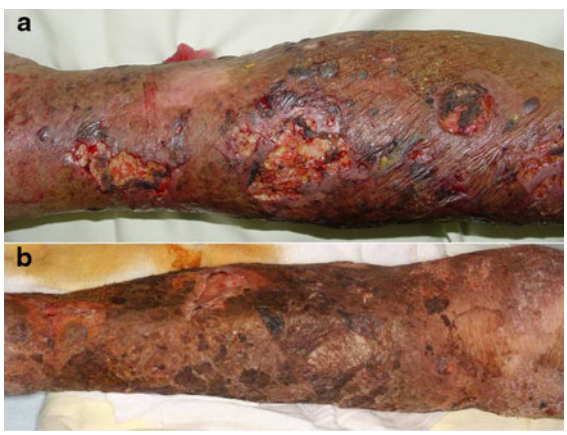

Fig. 1 **a** Multiple hemorrhagic vesicles and bullae with oozing ulceration over erythematous swollen base on left lower leg. **b** After treatment with voriconazole and topical nystatin, the ulcers and hemorrhagic bullae dried with crust formation

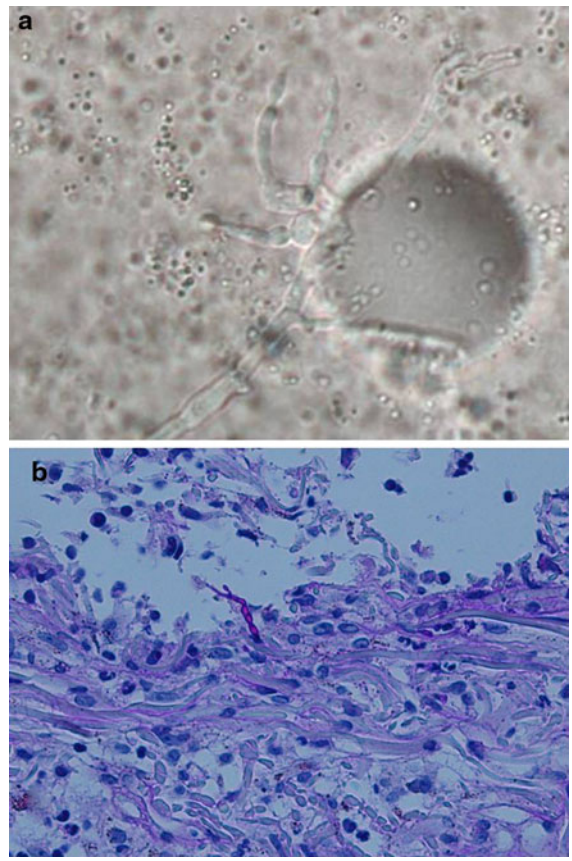

Fig. 2 **a** Microscopic examinations of ulcerative debris treated with potassium hydroxide showed septate hyaline hyphae. The phialides were swollen at their bases and tapered toward the apices. Conidia were identified at the tips of phialides. These features indicate adventitious sporulation. **b** Septate hyphae with adventitious sporulation were highlighted by periodic acid-Schiff stain. (Original magnification ×400)

identified the organism as *P. lilacinus*. Fungal cultures of blood had no growth.

Once the pathogen was identified, treatment was begun with oral voriconazole 400 mg twice a day and nystatin powder mixed with normal saline and applied to the wound once daily. After 3 weeks of treatment, the lesions had improved with less oozing, gradually healing with crusting and re-epithelialization (Fig. 1b). The pain also decreased. However, the patient's general condition worsened with fever, unstable angina, poor liver function, empyema, and change in the level of consciousness intervening. Blood and urine cultures at that point grew methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecalis*. The patient succumbed to sepsis and multiorgan failure on the fiftieth hospital day.

Discussion

The treatment of *P. lilacinus* is troublesome because of its broad resistance to many antifungal agents, including amphotericin B, miconazole, itraconazole, ketoconazole, fluconazole, and flucytosine [3]. The successful treatment in our case illustrates the promise of the new generation of azoles, such as posaconazole and voriconazle, for which there is in vitro evidence of a good antifungal effect [3, 4]. With *P. lilacinus,* Castelli et al. [5] found high minimal inhibitory concentrations (MIC) for amphotericin B and itraconazole, whereas those for voriconazole, posaconazole, and terbinafine were lower. We found three reported cases in the English literature of cutaneous *P. lilacinus* infection successfully treated with voriconazole (Table 1). All three patients were middle-aged men with compromised immune function. Treatment courses lasted from 3 weeks to 10 months.

In our case, we combined systemic oral voriconazole with topical nystatin for her leg wound and saw gradual improvement over 3 weeks. Like amphotericin B, nystatin is a polyene antimycotic that binds to ergosterol and alters the permeability of the organism's lipid bilayer. Conventionally, nystatin is given for candidiasis. No studies have proven that it works in *Paecilomyces* infection. However, despite the poor effect of amphotericin B alone on *P. lilacinus*, its MIC drops dramatically if combined with voriconazole [1, 6]. Since nystatin and amphotericin B are similar structures and have the same antifungal mechanism, we reasoned that there might also be synergy between nystatin and voriconazle. The combination of voriconazole and terbinafine reportedly also has therapeutic benefit [6]. We have published our experience using this combination to treat *P. lilacinus* peritonitis [2].

In addition to a possible synergistic effect, topical nystatin in the present case may have been effective as it was administered in direct contact with the injured epidermis. This would be expected to increase the local drug concentration, which might then better work together with the systemic voriconazole to yield a fungicidal effect. The use of a powder base may also create an arid environment that inhibits fungal growth. We speculate that all of these factors might have had a role in clearing the patient's infection.

The clinical presentation of *P. lilacinus* infection is quite variable, making identification of the pathogen difficult. Initially insidious, the infection may worsen with the development of erythematous maculopapules, nodules, patches, and necrosis appears [7]. Our patient presented with ulceration and multiple hemorrhagic bullae. The preliminary differential diagnosis included cellulitis and autoimmune bullous disease. Direct immunofluorescence did not support the later impression, and the lesions did not respond to potent

Table 1 Reported cutaneous *P. lilacinus* infection cases treated with voriconazole

Author	Year	Age	Gender	Location	Predisposing factors	Dose	Outcome
Hilmarsdottir et al. [14]	2000	59	Male	Right dorsal foot	Renal transplant	300 mg BID for 3 weeks	Recovery
Martin et al. [15]	2002	40	Male	Right calf	AIDS	300 mg BID for 10 months	Recovery
Van Schooneveld et al. [16]	2008	56	Male	Left knee	Liver transplant	300 mg BID for 12 weeks	Recovery
Current case	2009	66	Female	Left lower leg	Liver cirrhosis	400 mg BID for 3 weeks	Recovery[a]

[a] Our patient expired because of uncontrollable bacterial sepsis and multiorgan failure

antibiotics. A potassium hydroxide examination of ulcerative debris finally pointed toward the correct diagnosis with the finding of fungal elements. The second skin biopsy revealed fungal invasion of the dermis. These features indicate that this pathogen was able to sporulate in tissue, an unusual phenomenon termed adventitious sporulation, which has been observed with *Fusarium*, *Paecilomyces*, *Acremonium*, and *Scedosporium* species [8]. Microscopic findings from the fungal culture revealed tenpin-like phialides that are characteristic of *Paecilomyces* species. The three major pathogens in this genus are *P. lilacinus*, *P. variotii,* and *P. marqundi*, which can be differentiated morphologically. Both *P. variotii* and *P. marqundii* have smooth-walled conidiophores, as opposed to a rough appearance in *P. lilacinus*. In addition, phialides of *P. variotii* are more widely spaced than those of *P. lilacinus* [9, 10].

Correct identification of the species is important for treatment. In contrast to *P. lilacinus*, *P. variotii* is more susceptible to amphotericin B and itraconazole than to voriconazole [5]. Naggie et al. [11] recommended that posaconazole or voriconazole be used as first-line therapy for *P. lilacinus*, rather than amphotericin B, which is preferred over the azoles for treating *P. variotii* infection. Because *P. lilacinus* is often resistant to broad spectrum antifungal agents [3], the susceptibility test of *P. lilacinus* may still be needed in order to choose the most optimal and appropriate therapeutic policy.

Cutaneous infection by *P. lilacinus* may occur after direct skin inoculation or by hematogenous spread [12]. An outbreak among patients undergoing bone marrow transplant was attributed to contaminated skin lotion [7]. It has been reported to occur after a dog bite in an immunocompetent patient [13]. In our case, there was no evidence of hematogenous spread, and fungal blood cultures were negative. We speculate that the patient's skin barrier may have been attenuated by her frequent hot baths. The source of the organism may have been the flooding in her house. Additionally, she had chronic hepatitis C-related liver cirrhosis, a risk factor that reportedly predisposes to cutaneous and subcutaneous *P. lilacinus* infection [1].

In summary, we present a patient with several comorbidities who presented with a cutaneous infection caused by *P. lilacinus*. Treatment with systemic voriconazole and topical nystatin resulted in resolution. We did not measure the MICs of the antifungal agents, so we can only tentatively suggest a synergistic effect. However, we think this may provide another therapeutic option in managing cutaneous *P. lilacinus* infection.

Conflict of interest None.

References

1. Pastor FJ, Guarro J. Clinical manifestations, treatment and outcome of *Paecilomyces lilacinus* infections. Clin Microbiol Infect. 2006;12:948–60.
2. Chang BP, Sun PL, Huang FY, Tsai TC, Lin CC, Lee MD, Chen YC, Sheu JC, Tsai JD. *Paecilomyces lilacinus* peritonitis complicating peritoneal dialysis cured by oral voriconazole and terbinafine combination therapy. J Med Microbiol. 2008;57:1581–4.
3. Aguilar C, Pujol I, Sala J, Guarro J. Antifungal susceptibilities of *Paecilomyces* species. Antimicrob Agents Chemother. 1998;42:1601–4.
4. Espinel-Ingroff A, Chaturvedi V, Fothergill A, Rinaldi MG. Optimal testing conditions for determining MICs and minimum fungicidal concentrations of new and established antifungal agents for uncommon molds: NCCLS collaborative study. J Clin Microbiol. 2002;40:3776–81.
5. Castelli MV, Alastruey-Izquierdo A, Cuesta I, Monzon A, Mellado E, Rodriguez-Tudela JL, Cuenca-Estrella M. Susceptibility testing and molecular classification of *Paecilomyces* spp. Antimicrob Agents Chemother. 2008;52:2926–8.
6. Ortoneda M, Capilla J, Pastor FJ, Pujol I, Yustes C, Serena C, Guarro J. In vitro interactions of approved and novel drugs against *Paecilomyces* spp. Antimicrob Agents Chemother. 2004;48:2727–9.
7. Orth B, Frei R, Itin PH, Rinaldi MG, Speck B, Gratwohl A, Widmer AF. Outbreak of invasive mycoses caused by *Paecilomyces lilacinus* from a contaminated skin lotion. Ann Intern Med. 1996;125:799–806.
8. Schell WA. New aspects of emerging fungal pathogens. A multifaceted challenge. Clin Lab Med. 1995;15:365–87.
9. Hsu CH, Chuan MT, Chiu WT, Hu SL. Cutaneous hyalohyphomycosis caused by *Paecilomyces marquandii*—A case report. Dermatol Sin. 2006;52–7.
10. Larone DH. Medically important fungi. 4th ed. Washington, D.C.: ASM Press; 2002.
11. Naggie S, Perfect JR. Molds: hyalohyphomycosis, phaeohyphomycosis, and zygomycosis. Clin Chest Med. 2009;30:337–53, vii–viii.
12. Itin PH, Frei R, Lautenschlager S, Buechner SA, Surber C, Gratwohl A, Widmer AF. Cutaneous manifestations of *Paecilomyces lilacinus* infection induced by a contaminated skin lotion in patients who are severely immunosuppressed. J Am Acad Dermatol. 1998;39:401–9.
13. Zendri E, Martignoni G, Benecchi M, Fanti F, De Panfilis G. *Paecilomyces lilacinus* cutaneous infection associated with a dog bite. J Am Acad Dermatol. 2006;55:S63–4.

14. Hilmarsdottir I, Thorsteinsson SB, Asmundsson P, Bodvarsson M, Arnadottir M. Cutaneous infection caused by *Paecilomyces lilacinus* in a renal transplant patient: treatment with voriconazole. Scand J Infect Dis. 2000;32:331–2.
15. Martin CA, Roberts S, Greenberg RN. Voriconazole treatment of disseminated paecilomyces infection in a patient with acquired immunodeficiency syndrome. Clin Infect Dis. 2002;35:e78–81.
16. Van Schooneveld T, Freifeld A, Lesiak B, Kalil A, Sutton DA, Iwen PC. *Paecilomyces lilacinus* infection in a liver transplant patient: case report and review of the literature. Transpl Infect Dis. 2008;10:117–22.