CASE REPORT
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Therapeutic Use of Posaconazole for Cutaneous *Purpureocillium lilacinum* Infection Refractory to Itraconazole

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Purpureocillium lilacinum is a saprophytic fungus with a ubiquitous environmental distribution. Unfortunately, no standard treatment has yet been established for cutaneous *P. lilacinum* infections. Based on the *in vitro* antifungal susceptibility test, posaconazole has been considered an effective treatment option. We herein present a case involving a 72-year-old woman who visited our clinic due to a peripherally spreading, well-demarcated, asymptomatic, scaly, and erythematous patch on her forehead that had persisted for 4 months. She had been diagnosed with cutaneous *P. lilacinum* infection and had been treated with itraconazole (200 mg/day). However, the lesion recurred in the same area. Histopathological findings revealed suppurative granulomatous dermatitis with fungal elements. Fungal culture confirmed *P. lilacinum* regrowth. Posaconazole was selected to treat the recurrence of *P. lilacinum* infection. After 10 weeks of treatment, the lesion decreased dramatically without any adverse drug events. We recommend posaconazole as a treatment option for *P. lilacinum* infection refractory to itraconazole.

Key Words: Cutaneous, Posaconazole, *Purpureocillium lilacinum*, Refractory to itraconazole

INTRODUCTION

Purpureocillium lilacinum, a ubiquitous mold found in soil and vegetation, has emerged as a pathogen in immunocompetent and immunocompromised patients[1]. Although no standard antifungal regimen has been established for *P. lilacinum*, it has been known for possessing resistance to typical antifungals, such as amphotericin B, fluconazole, and flucytosine. Therefore, *P. lilacinum* infections are hard to manage given their frequent recurrence with conventional antifungal agents. Nevertheless, several cases have shown that monotherapy or combination therapy with itraconazole, ketoconazole, terbinafine, and surgical debridement can be used to treat cutaneous *P. lilacinum* infections. Given the conflicting results of *in vitro* tests for susceptibility to itraconazole, recurrence or treatment failure has also often been reported with itraconazole treatment for *P. lilacinum*[2]. Therefore, new second-generation triazole antifungals, including voriconazole, posaconazole, and isavuconazole, have been used to treat cutaneous *P. lilacinum* infections.

Posaconazole (Noxafil®) had been approved by the Food and Drug Agency (FDA) in 2005 for the treatment of invasive aspergillosis and candida infections. However, emerging studies have shown that the effects of posaconazole can

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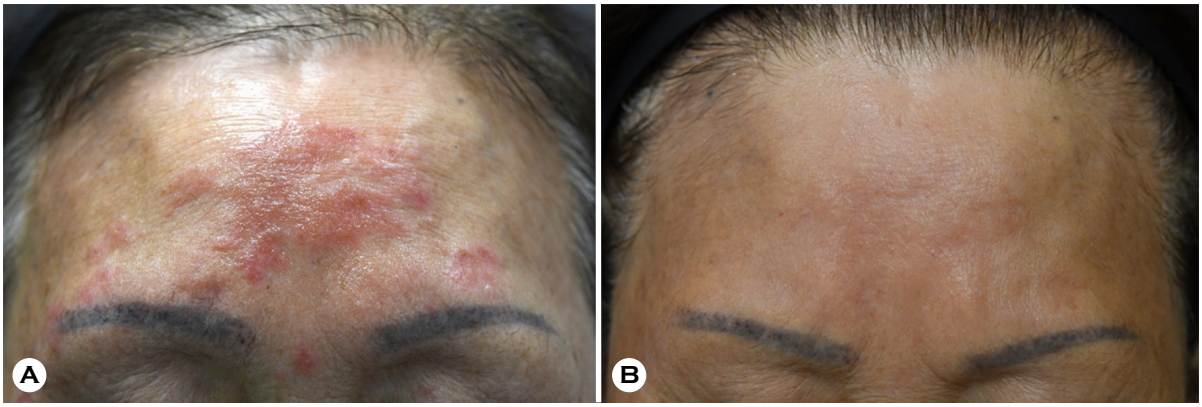

Fig. 1. (A) Peripherally spreading, well-demarcated, asymptomatic, scaly, and erythematous patch on the patient's forehead; (B) The lesion disappeared after 10 weeks of treatment with posaconazole.

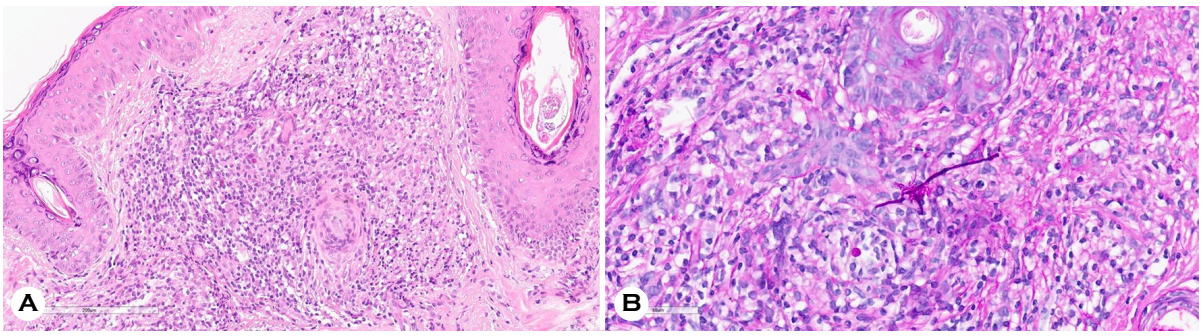

Fig. 2. (A) Histopathologic findings revealing superficial, interstitial, and perifollicular lymphohistiocytic infiltration and granulomatous inflammation with multinucleated giant cells (H&E, ×200); (B) Special periodic acid-Schiff staining with diastase showing fungal elements and mixed inflammatory and granulomatous infiltration in the dermis (×400)

extend to various fungal and mold infections[3]. Herein, we report the use of posaconazole in a patient with cutaneous *P. lilacinum* infection who failed to achieve complete remission with itraconazole in our last report[2].

CASE REPORT

A 72-year-old female presented with an asymptomatic, peripherally spreading, well-demarcated, scaly, and erythematous patch on her forehead that had persisted for 4 months (Fig. 1A). Approximately 2 years prior to presentation, she was been diagnosed with a subcutaneous *P. lilacinum* infection confirmed through skin biopsy, fungal culture, and sequence analysis of the internal transcribed spacer region of the rRNA gene. She had been treated with oral itraconazole (200 mg /day) for 4 months, with most of the skin lesions improving after 4 months of treatment. However, 2 months after ceasing itraconazole, the lesion recurred in her forehead. Despite repeated use of itraconazole for each recurrence, complete remission could not be achieved. Skin biopsy and fungal culture were then conducted. Hematoxylin and eosin staining revealed superficial, interstitial, and perifollicular lymphohistiocytic infiltration and granulomatous inflammation with multinucleated giant cells (Fig. 2A). Periodic acid-Schiff staining with diastase revealed fungal elements and mixed inflammatory and granulomatous infiltration in the dermis (Fig. 2B). Matrix-assisted laser desorption ionization time-of-flight mass spectrometry analysis identified *P. lilacinum*. The patient was then prescribed oral posaconazole (100 mg/day) for 10 weeks. Her skin lesions had dramatically decreased after 10 weeks of treatment, with no adverse events having been reported

Table 1. Clinical features of cutaneous *Purpureocillium lilacinum* infections treated with posaconazole

Authors	Age/ gender	Risk factors	Initial treatment	Secondary treatment	Complication	Outcome
Albert et al.[9]	52/F	Hepatoreanl transplantation	Posaconazole 300 mg/day	Surgical debridement	Digestive disorder	Remission
Chen et al.[10]	40/M	Evan's syndrome	Voriconazole 400 mg/day	Posaconazole 300 mg/day	None	Remission
Ezzedine et al.[11]	60/M	Rheumatoid arthritis	Voriconazole 400 mg/day	Posaconazole 800 mg/day	Anorexia, involuntary weight loss	Improvement
Hu et al.[12]	63/F	Evan's syndrome	Posaconazole 300 mg/day	None	AST/ALT elevation	Remission
Martinez et al.[13]	59/M	Heart transplantation	Posaconazole 200 mg/day	None	None	Remission
McGeachie et al.[14]	53/F	None	Voriconazole 400 mg/day	Posaconazole 300 mg/day	None	Remission
Paul et al.[15]	68/M	Kidney transplantation	Itraconazole 400 mg/day	Posaconazole	None	Remission
Xia et al.[16]	53/M	Autoimmune hemolytic anemia	Itraconazole 400 mg/day	Posaconazole 300 mg/day	None	Remission
Our case	72/F	None	Itraconazole 200 mg/day	Posaconazole 100 mg/day	None	Remission

during this period (Fig. 1B). Approximately 2 months after stopping posaconazole, her lesions were entirely resolved without any recurrence.

DISCUSSION

P. lilacinum causes a variety of clinical manifestations in immunocompetent and immunocompromised patients, ranging from superficial mycoses to life-threatening systemic infections[4]. Thus far, the Korean literature has reported nine cases of cutaneous *P. lilacinum* infections[2]. Five of the cases were successfully treated with itraconazole monotherapy. However, two cases showed resistance to itraconazole and required alternative therapy with voriconazole or terbinafine. Our patient also experienced treatment failure with itraconazole[2]. Therefore, alternative antifungal agents are necessary for the treatment of cutaneous *P. lilacinum* infections.

Although a standard treatment guideline has yet to be established, new azoles, such as voriconazole, posaconazole, and isavuconazole, have been used to treat cutaneous *P. lilacinum* infections. In fact, two recently reported guidelines[5,6] have moderately recommended voriconazole and marginally recommended posaconazole for the treatment of *P. lilacinum* infections.

However, we recommend using posaconazole as the first alternative therapeutic option in *P. lilacinum* infections refractory to itraconazole given its potentially better effectiveness and safety. First, we assert that posaconazole could be more effective than voriconazole in treating *P. lilacinum* infection. The effectiveness of posaconazole for *P. lilacinum* infections can be implied from the results of the antifungal susceptibility test. Although many cases have reported successful treatment of cutaneous *P. lilacinum* infections with itraconazole, itraconazole showed only intermediate antifungal activity against *P. lilacinum*. Overall, posaconazole showed the best *in vitro* activity against *P. lilacinum*, with MICs $\leq$0.5 mg/L. In addition, posaconazole was effective at a lower range (0.06~0.5 mg/L) than voriconazole (0.06~4 mg/L). Therefore, posaconazole could more effectively treat *P. lilacinum* infections than voriconazole.

Moreover, posaconazole could be safer than voriconazole due to fewer treatment-related adverse events. A controlled study comparing posaconazole with voriconazole for the treatment of invasive aspergillosis by Maertens et al.[8] revealed that the overall incidence of treatment-related adverse event

rates was 30% for posaconazole and 40% for voriconazole. Also, the American FDA suggests that isavuconazole and posaconazole are better tolerated than voriconazole with fewer neurological disorders (hallucinations, peripheral neuropathies), skin toxicities, and interactions with immunosuppressive treatment[9].

Nowadays, studies have reported the successful treatment of cutaneous *P. lilacinum* infections with voriconazole and posaconazole. In fact, over 30 cases of voriconazole use and 9 cases of posaconazole use have been reported for cutaneous /subcutaneous *P. lilacinum* infections[9-16]. We reviewed the demographic characteristics of these cases, including their age, sex, relevant history, treatment, complications related to posaconazole, and outcomes (Table 1). Seven of the nine cases were associated with underlying immunosuppression, including organ transplantation, Evans's syndrome, and long-term use of systemic corticosteroids. Six cases first used other antifungal agents, such as itraconazole and voriconazole. In particular, two cases who failed to respond to voriconazole treatment for *P. lilacinum* infection were subsequently cured after posaconazole treatment. One case could not continue using voriconazole because of adverse events.

Posaconazole is often connected with the following adverse drug reactions: neutropenia, electrolyte dysfunction, headache, vomiting, nausea, stomachache, diarrhea, dyspepsia, and hepatic disturbances including elevation of alanine transaminase (ALT) and aspartate aminotransferase (AST)[17]. Physicians need to carefully monitor the electrolyte levels of patients, including hypokalemia and hepatic function, throughout the course of therapy. Nevertheless, all of these adverse drug reactions, except for neutropenia, can be managed by reducing the dose or adding histamine-2 blockers or proton pump inhibitors. In the case reported by Hu et al.[12], the patient showed elevated AST and ALT levels during oral posaconazole treatment. The plasma concentration of posaconazole was 3.04 μg/mL, whereas its MIC *in vitro* was 1 μg /mL. After reducing the dosage of posaconazole to 200 mg /day, the patient's AST and ALT levels normalized, with a considerable decrease in her skin lesions also having been observed. In our case, we showed that posaconazole had a sufficient effect on cutaneous *P. lilacinum* infection without elevating AST and ALT levels despite using a posaconazole dose (100 mg/day) lower than that reported in other case studies. Given that posaconazole is often accompanied by gastric disturbances, famotidine (20 mg/day) can be added as a preventive measure. Our patient did not show any adverse reactions to posaconazole during treatment. Taken together, our experience suggests that the safety of posaconazole can be more reliable and easily managed.

In conclusion, we report a case involving a patient who developed recurrence of cutaneous *P. lilacinum* infection after itraconazole treatment. Posaconazole exhibited substantial efficacy and good tolerability in this case. We believe posaconazole can be a therapeutic option for cutaneous *P. lilacinum* infections refractory to itraconazole.

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CONFLICT OF INTEREST

In relation to this article, we declare that there is no conflict of interest.

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PATIENT CONSENT STATEMENT

The patient provided written informed consent for the publication and the use of her images.

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