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Case Report

Isavuconazonium for the treatment of Purpureocillium lilacinum infection in a patient with pyoderma gangrenosum

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ABSTRACT

Purpureocillium lilacinum is a rare but emerging pathogen in immunocompromised patients that primarily infects the skin and subcutaneous tissue. We present a novel case of Purpureocillium lilacinum infection in a patient with pyoderma gangrenosum who was successfully treated with isavuconazonium, followed by a literature review of 13 total cases of infection with Purpureocillium lilacinum gathered from a review of the PubMed database. Previous reports have utilized voriconazole, an antifungal with significant toxic side effects. Our case highlights the importance of culture and biopsy in patients with pyoderma gangrenosum who are unresponsive to standard treatment irrespective of pathergy risk.

1. Introduction

Purpureocillium lilacinum, formally known as Paecilomyces lilacinus, is a ubiquitous fungus found in soil and vegetation [1]. Recently, there have been reports in the literature of *P. lilacinus* as an emerging pathogen in both immunocompetent and immunocompromised patients. In immunocompetent patients, the infection is typically isolated to skin or ocular infections. It has been reported in cases of onychomycosis, peritonitis in a peritoneal dialysis patient, sinusitis, vaginitis, endocarditis, and bursitis [2–7]. In immunocompromised patients, *P. lilacinus* presents as localized or invasive disease and often occurs in transplant recipients or those with hematologic malignancies.

When identified in culture, this mold is commonly believed to be a contaminant. It is important to quickly and appropriately identify the pathogen as treatment may differ from other fungal species. In addition, *P. lilacinum* may exhibit resistance to typical antifungals. Previously reported cases have been managed with monotherapy or combination treatment with griseofulvin, terbinafine itraconazole, ketoconazole, fluconazole, amphotericin and surgical debridement. To date, there are thirteen published cases of *P. lilacinum* infection treated with second-generation triazole antifungals including voriconazole and posaconazole.

Isavuconazonium (Cresemba) was FDA approved in 2015 for the treatment of invasive aspergillosis and mucormycosis [8]. Herein, we report the novel use of isavuconazonium in a patient with biopsy and culture proven *P. lilacinum* infection in the setting of pyoderma gangrenosum. We then review the previously published literature regarding the treatment of *P. lilacinum* infection with triazole antifungals. This case highlights the importance of performing a biopsy in patients with pyoderma gangrenosum who are unresponsive to standard treatment.

2. Case report

A 50-year-old male with chronic lymphocytic leukemia (CLL) on ibrutinib, history of Sweet's Syndrome and pyoderma gangrenosum was admitted for inpatient dermatologic evaluation. He reported a one-year history of purpuric nodules and a necrotic ulcer of the left lower extremity (Fig. 1). His community dermatologist diagnosed him with pyoderma gangrenosum and started the patient on oral prednisone. Despite improvement initially, the ulcer continued to progress and the patient reported taking up to 180 mg of prednisone daily over the past 6 months. In the weeks leading up to admission, he reported increased drainage and tenderness. Development of fever and chills prompted his presentation (day 0). On physical exam, the patient had an 8 cm ulcer with a necrotic and hemorrhagic base.

He was initially started on vancomycin and piperacillin-tazobactam with intravenous methylprednisolone and his ibrutinib was held. Punch biopsy from the necrotic plaque was concerning for a mucormycosis, however multiple fungal cultures returned positive for a *Penicillium* species (day 11) based on its morphology on lactophenol cotton blue

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Fig. 1. Necrotic ulcers and debrided wound site in *Purpureocillium lilacinum* infection.

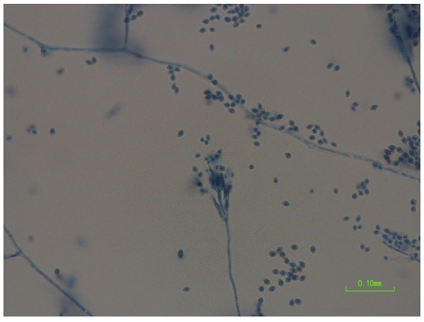

Fig. 2. *Purpureocillium lilacinum* mycelium with spore-forming conidiophores.

staining. Despite broad spectrum antibiotics and antifungals including liposomal amphotericin B 6 mg/kg daily, micafungin 150 mg daily and voriconazole 400 mg every 12 hours, the patient's lesions continued to worsen. Punch biopsy and tissue cultures were performed; broad based hyphae were seen on H&E and culture was again positive for *Penicillium* on day 17. Biopsies were repeated twice more (days 28 and 38) with both tissue cultures positive for *Penicillium*. While this species was originally overlooked given minimal virulence and assumed contaminant, the cultures were sent out to the fungal testing laboratory at UT Health San Antonio due to clinical suspicion for misidentification. Subsequent culture and staining revealed violet colonies with characteristic coniodophore morphology and the species isolated and identified as *P. lilacinum* (Fig. 2). Cultures remained positive while on voriconazole from days 29–40 (a trough drawn at 1 week returned 1.8 μg/mL), which was eventually discontinued after patient developed a drug rash after 12 days of treatment. He was then started on intravenous isavuconazonium 372 mg daily on day 41. He underwent multiple surgical debridements during his hospitalization. Tissue cultures sent from biopsy were negative one day after initiation of isavuconazonium on day 41 and remained negative on day 54. The patient was discharged on an oral maintenance dose of 372 mg of isavuconazonium daily.

3. Methods

We searched the English-language literature published until July 2018 in the PubMed database. Relevant studies were identified using key word combinations including “purpureocillium lilacinum” and its former name, “paecilomyces lilacinum.” 13 total cases were reviewed and the relevant demographics including age, gender, predisposing factors, clinical manifestations, treatment, adverse reactions and clinical outcomes are summarized in Table 1.

4. Discussion

P. lilacinum is a rare but emerging fungal infection in immunocompromised patients. Because of its minimal virulence, it is often considered a contaminant in culture. When pathogenic, infections most commonly involve the cutaneous and subcutaneous tissue [9]. Treatment may sometimes be difficult, as the fungus is intrinsically resistant to many antifungals including itraconazole, terbinafine, griseofulvin, and amphotericin B. Successful clearance of P. lilacinum has been demonstrated most frequently with second generation azoles including voriconazole and posaconazole (Table 1).

In the literature, there are twelve reported cases of voriconazole use and one reported case of posaconazole use for the treatment of *P. lilacinum* infection. Table 1 reviews the patient demographics of these cases including patient age, sex, relevant history, clinical features, treatment and outcome. Ten of thirteen cases were associated with underlying immunosuppression including organ transplantation, cirrhosis, and acquired immune deficiency syndrome. Clinical manifestations included papules, nodules, and vesicles; the location of lesions varied. In most cases, patients were started on conventional antifungals including terbinafine, itraconazole, and amphotericin B with unremarkable results. Following therapy with voriconazole or posaconazole, nine of thirteen had resolution of infection. Side effects noted during the use of voriconazole included acute renal failure, elevated hepatic enzymes, photosensitivity and temporary distortion of color perception. The current case resulted in adverse drug rash which prompted discontinuation of voriconazole.

Isavuconazole, a newer second generation triazole, is a broad-spectrum antifungal azole approved for treatment of invasive molds including Aspergillosis and mucormycosis, with additional activity against *Candida* spp., *Cryptococcus* spp. and endemic dimorphic fungi. This antifungal may be an emerging pharmacologic option due to tolerability and safety profile. The SECURE trial comparing isavuconazole with voriconazole noted similar efficacies but fewer study-drug-related adverse events. Isavuconazole-treated patients experienced lower frequencies of hepatobiliary, ophthalmic and dermatologic toxicities and overall fewer drug discontinuations [10]. Data provided to the FDA's Anti-Infective Drugs Advisory Committee suggest isavuconazole is better tolerated, citing only 42.4% of treatment emergent adverse events (TEAEs) occurring in subjects receiving isavuconazole compared to 59.8% of TEAE's occurring in subjects receiving voriconazole. The most common TEAEs of isavuconazole are nausea, vomiting, and liver enzyme elevations. Hepatotoxicity is less common compared to subjects treated with voriconazole [8].

Isavuconazole has successfully treated invasive fungal diseases in patients intolerant to voriconazole and posaconazole [11]. Our patient is the first reported case of *P. lilacinum* infection successfully treated with isavuconazole. Since treatment of *P. lilacinum* is often difficult due to antifungal resistance, therapy should be guided by in vitro susceptibility results. Voriconazole and posaconazole, have shown good in-vitro activity against *P. lilacinum* isolates with MIC's ranging from 0.12 to 8mg/L and 0.03–1mg/L, respectively. In comparison amphotericin B, echinocandins and first generation triazoles (itraconazole, ketoconazole) have MIC's greater than 16 mg/L [12]. While the MIC of isavuconazole has not been studied, our current case was susceptible with an MIC of 0.5 mg/L. The isolates were also susceptible to voriconazole (MIC 0.25 mg/L) and posaconazole (MIC 0.125 mg/L).

Lastly, it is important to consider a secondary infection when a patient with pyoderma gangrenosum is no longer improving on standard therapy. When infection is unresponsive to antibiotics or culture results are misleading then the benefit of a biopsy should outweigh the risk of pathergy.

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None.

Table 1
Cutaneous *P. lilacinum* infections treated with second-generation triazole antifungals.

Cases	Age(y)/ gender	Risk factors	Clinical Features	Initial treatment and duration	Salvage Treatment	Complications	Outcome
Trinh et al. [13]	33/M	Renal Transplant	Papules of left forearm, shin and right ankle	Voriconazole (12 weeks)	N/A	N/A	Resolved
Demitsu et al. [14]	72/F	Renal transplant	Nodular induration of right arm	Itraconazole 200 mg daily (6 weeks, no response)	Terbinafine 250 mg daily, Voriconazole 400 mg daily (8 weeks)	None	Resolved
Saghrouni et al. [1]	8/F	No	Erythematous nodules of face	Itraconazole 400 mg daily (12 weeks)	Voriconazole 400 mg daily(12 weeks)	N/A	Resolved
Rimawai et al. [15]	55/M	Steroid use	Swelling, erythema, and ulceration of left leg	Voriconazole 200 mg twice daily (90 days)	N/A	None	Resolved
Lavergne et al. [16]	63/M	Heart Transplant	Erythema, scaly and crusted nodules of right leg and right elbow	Voriconazole 200 mg oral twice a day (6 weeks), reduced 100 mg twice a day (6 weeks)	Voriconazole injectable 12 ng/mL (8 weeks) followed by terbinafine 250 mg daily (6 months)	Acute renal failure secondary to drug reaction with tacrolimus	Resolved
Keshtkar-Jahromi et al. [17]	60/F	None	Erythema, swelling of right hand	Voriconazole (4 weeks)	N/A	Photosensitivity and distortion of color perception; treatment stopped at 3 months	Resolved
Ezzedine et al. [18]	60/M	Rheumatoid arthritis	Pseudo-verrucous nodules with necrosis of face	Voriconazole 200 mg twice daily (10 days)	Posaconazole 400 mg twice daily (4 weeks)	Voriconazole: visual hallucinations; posaconazole: weight loss	Patient discontinued treatment, loss to follow up
Huang et al. [19]	66/F	Liver cirrhosis	Hemorrhagic vesicles and pustules of left leg	Voriconazole 400 mg twice daily (4 weeks)	N/A	N/A	Death due to sepsis
Ouinissi et al. [20]	48/F	Renal transplant	Hemorrhagic ulcers of left leg	Itraconazole 400 mg daily (6 weeks)	Voriconazole (unknown dose and duration)	N/A	Prolonged remission
Van Schooneveld et al. [21]	56/M	Liver transplant	Erythematous nodules of left knee	Terbinafine 200 mg BID (4 weeks)	Voriconazole 200 mg BID (lesions resolved 6 week, 12 week duration)	N/A	Resolved
Martin et al. [22]	40/M	AIDS	Indurated and nodular lesions of right leg	Amphotericin B deoxycholate, amphotericin B lipid complex (2 months); Itraconazole 300 mg BID (2 months)	Voriconazole with IV loading dose 4 mg/kg eevery 12 hours for 3 day shen 200 mg twice daily 40 weeks)	Elevated hepatic enzymes	No improvement
Hilmarsdottir et al. [23]	59/M	Renal transplant	Erythematous papulopustular lesions of 4th digit and right foot	Itraconazolew 400–600 mg per day (6 weeks)	Voriconazole 200 mg twice daily increased to 300 mg twice daily (6 weeks)	Renal failure secondary to possible candida infection	Improvement in lesions, but death due to enterococcal bronchopneumonia
Sotello et al. [24]	69/M	Liver transplant	Tender nodules on dorsum right hand	Voriconazole 200 mg twice daily (12 weeks)	N/A	N/A	Resolved
Current Case	50/M	Chronic lymphocytic leukemia	Ulcerative lesions and necrotic plaque of left shin	Voriconazole 400 mg daily; Amphotericin 650 mg daily	Isavuconazonium 372 mg daily	Drug rash	Resolved

N/A: non-applicable, case did not comment on side effects.

Declaration of competing interest

None

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