Complicated multiple organ infection of *Purpureocillium lilacinum* and varicella-zoster virus infection in a patient with Evans' syndrome

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Abstract

Purpureocillium lilacinum (*P lilacinum*) is a rare pathogenic fungus, which mainly involves immunocompromised individuals. Here, we report a case of complicated multiple-organ infections involving skin, lungs, and spleen in a 63-year-old female with Evans' syndrome after 9 months of glucocorticoid treatment. Microbial examinations of skin biopsy and blood samples revealed *P lilacinum* infections. Posaconazole was effective in this patient. During anti-fungi treatment, she developed varicella-zoster virus infection and was diagnosed through next-generation sequencing examination. In conclusion, *P lilacinum* may affect different organ systems and is susceptible to posaconazole treatment. The molecular-based methods like microbial cell-free DNA sequencing could provide accurate and timely identification of a wide range of infections.

Keywords: Evans' syndrome, Fungal infection, Posaconazole, *Purpureocillium lilacinum*, Varicella-zoster virus

1. INTRODUCTION

Fungal infections have become emerging causes of human mortality worldwide. *Purpureocillium lilacinum (P lilacinum)*, formerly known as *Paecilomyces lilacinus*, is a saprophytic, asexual, and filamentous fungus.[1,2] It is increasingly reported to cause opportunistic infections in immunocompetent and immunocompromised individuals, ranging from superficial mycoses to life-threatening systemic infections.[3-6] But current knowledge on infections with *P lilacinum* is mainly based on case reports and small case series.

Cutaneous infections can be caused by a variety of pathogens, especially in patients with compromised immune function.

Histological examination and microbial examination are useful for the diagnosis. If the condition worsens again during treatment, infection of new pathogens should be considered. Due to the application of antibiotics, the infection of rare and drug-resistant pathogens has increased, and the false-negative rate increased after empiric treatment.[7] When microbial evidence cannot be obtained by traditional detection methods, new technology like next-generation sequencing (NGS) would be helpful.

Here, we reported a case of complicated infections in an elder female with Evans' syndrome after 9 months of glucocorticoid treatment. She was first diagnosed with fungal infections and effectively treated with posaconazole. But her condition worsened again during anti-fungal treatment, and then genetic examination revealed varicella-zoster virus infection.

2. CASE REPORT

A 63-year-old female was hospitalized on June 30, 2020, due to cytopenia and skin infection. She had been diagnosed with Evans' syndrome in September 2019 and received intravenous dexamethasone, followed by oral methylprednisolone tablets. Her hemoglobin (HGB) and platelet (PLT) returned to normal after treatment. Due to the epidemic of COVID-19, the patient did not regularly visit a clinic and maintained with 28 mg methylprednisolone per day for half a year. When she was administrated to our hospital, she had been suffered from skin infection for 4 months and was in poor condition. Skin lesions first appeared as asymptomatic small red papules on her right calf, then slowly progressed to painful ulcerations and spread to the contralateral limb and upper limbs. Cephalosporin and vancomycin were given but her condition did not improve. The lady did not experience any trauma or insect bites before skin alteration. Her fasting blood glucose was 4.89 mmol/L, and diabetes was not diagnosed prior to the glucocorticoid therapy.

She came with HGB concentration of 57 g/L, PLT count of 23×10^9/L, absolute reticulocyte (RET) count of 0.49×10^{12}/L, white blood cell (WBC) count of 1.78×10^9/L, and absolute neutrophil (ANC) count of 1.63×10^9/L. The patient had elevated lactate dehydrogenase level as 425.3U/L, significantly elevated indirect bilirubin level, and normal ALT and AST. Direct antiglobulin test was positive for IgG and C-3d. The patient's fasting blood glucose was up to 18 mmol/L. She complained of anorexia and discomfort in the left upper abdomen, as well as symptoms like dizziness, fatigue, and jaundice with deepened urine color. The patient had an enlarged spleen, 2 cm below the ribcage. Necrotic ulcers with sinus tract and pus formation presented on her right lower limb (Fig. 1A), and empyema under her right patella with fluctuating sensation.

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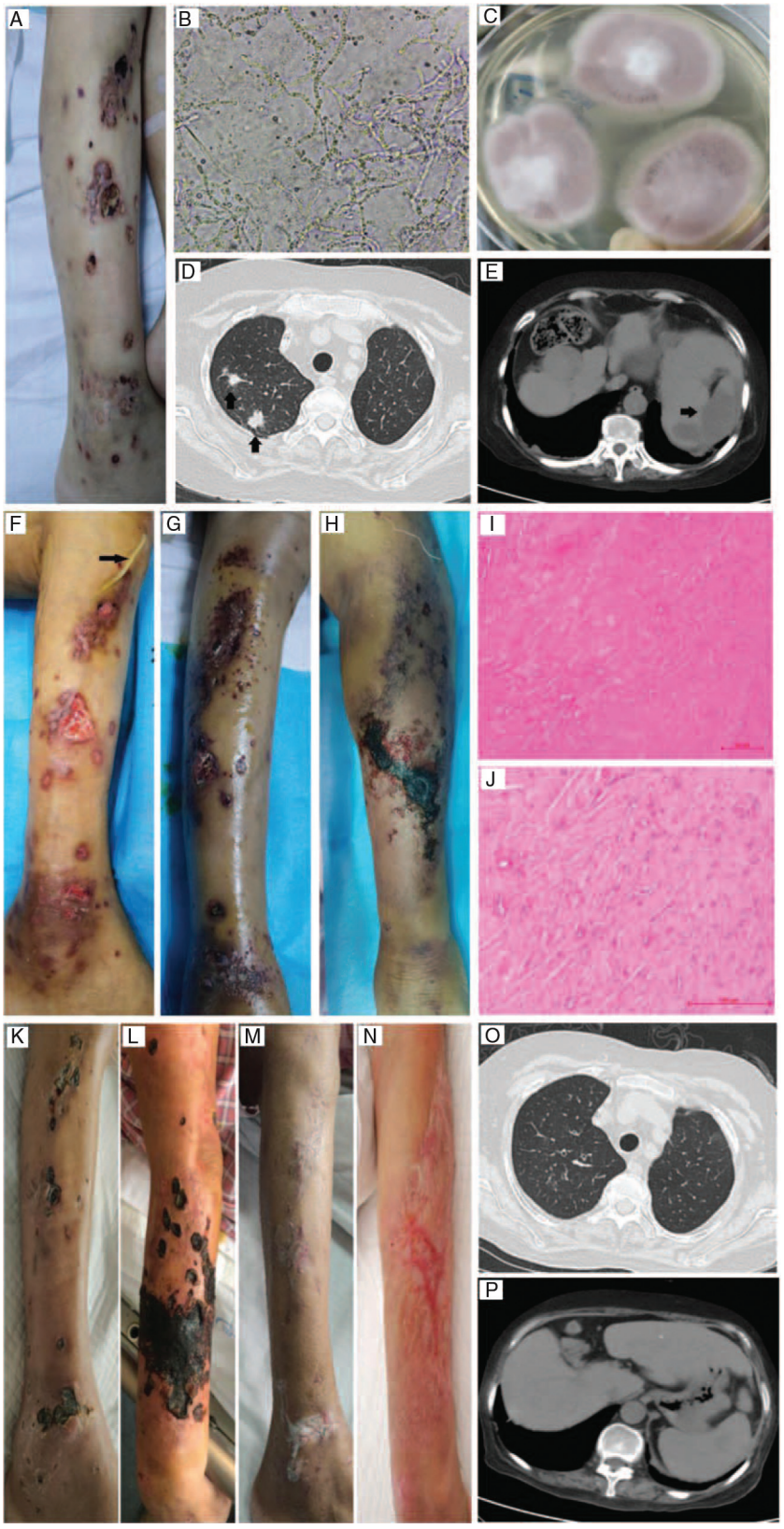

FIGURE 1. Dynamic changes of the patient's infections. (A) First image of cutaneous infections at hospitalization. There were ulcers on the right lower limb accompanied by sinus and pus formation. (B) Septate branching hyaline hyphae were found on skin biopsy slide (direct microscopy with 10% KOH wet mount, × 400). (C) Morphology of purple fungal colony. (D and E) Computed tomography images suggested multiple patchy shadows of bilateral lungs and low-density shadows of spleen (black arrows). (F) Skin ulcers were replaced by granulation tissue after posaconazole treatment. Pus under the right patella was drained with a catheter (black arrow). (G and H) Skin infections worsened with scattered miliary papules and blisters. (G) The miliary papules on the right lower limb. (H) The left upper limb swelled with atypical blisters. (I and J) Skin necrosis with lots of fungal hyphae (skin pathology, HE staining. I: × 100, J: × 200). (K–N) Skin infections improved over time. K and L: Blisters gradually scabbed and fell off (2 months since posaconazole treatment, 10 days after antiviral treatment); M and N: Skin infections got healed 4 months since posaconazole treatment. (O and P) The patchy shadows of lungs disappeared, and the low-density shadows of spleen shrank after treatment.

A skin biopsy was done to obtain evidence of infection and 30 ml of pus was drawn by puncture under the right patella for microbial culture. The skin biopsy sample showed septate branching hyaline hyphae under KOH wet mount microscopy (Fig. 1B) which revealed fungal infection. The pus culture showed a wooly colony with faint lilac color in the center surrounded by white color (Fig. 1C). Cutaneous hyalohyphomycosis caused by *P lilacinum* was diagnosed based on the results of the mycological examinations and fungal culture. Further, blood microbial test showed elevated GM value (1.48). CT findings indicated lung infections (Fig. 1D) and multiple low-density shadows in the spleen (Fig. 1E). Pulmonary fungal infections were clinically diagnosed. Diagnosis of splenic embolism was made, but we could not determine whether it was related to hemolysis or infection.

Posaconazole tablets (300 mg/d) were given orally and posaconazole suspension was applied externally to the skin ulcers. The patient's transaminase was significantly elevated (ALT 121.2U/L, AST 226.3U/L), which was considered to be related to the oral posaconazole treatment. We further detected the plasma concentration of posaconazole of the patient which was 3.04 μg/ml. Since the minimum inhibitory concentration (MIC) of posaconazole in vitro is 1 μg/ml, we reduced the dosage of posaconazole tablets to 200 mg/d, and then her transaminase returned to normal. After treatment, skin ulcers were replaced by newly grown granulation tissue (Fig. 1F).

However, 23 days after the initiation of posaconazole treatment, the patient's cutaneous infection worsened again with the formation of painful scattered miliary papules and blisters (Fig. 1G and H), different from previous lesions. The new lesions were pleomorphic, and involved both lower limbs, upper limbs, neck, chest, sacrococcygeal, and vulva. The limbs of the patient were swollen and painful. The pathology of skin biopsy showed necrosis of the skin with a large number of fungal hyphae (Fig. 1I and J). No new pathogen was found in the bacteriological examination. Daptomycin and meropenem treatments were ineffective, and her skin lesions were getting worse. Finally, we adopted NGS examination for both blood and skin biopsy (Table 1). Microbial cell-free DNA (mcfDNA) sequencing identified three microorganisms, including varicella-zoster virus (VZV, human alphaherpesvirus 3), *P lilacinum*, and torque teno virus 24. We believed that the new infection was caused by VZV, and the blisters gradually scabbed and fell off after penciclovir treatment (Fig. 1K and L).

As for Evans' syndrome, the patient received two courses of high-dose immunoglobulin therapy (0.4 g/kg/d × 5d) and the corticosteroid was withdrawn quickly. By the last follow-up, her blood cells counts were stable (WBC 2.15×10^9/L, ANC 1.17×10^9/L, HGB 100 g/L, PLT 112×10^9/L, and RET 0.1017×10^{12}/L). Posaconazole was maintained for 4months until her skin ulcer completely healed (Fig. 1 M and N). The patchy shadows of the lungs disappeared (Fig. 1O), and the low-density shadows of the spleen shrank (Fig. 1P). During follow-up, the patient's symptoms have been stable, and she had experienced no recurrence.

3. DISCUSSION

The majority of reported *P lilacinum* infected cases are ocular infections due to the increased use of contact lenses. Cutaneous and subcutaneous infections are relatively common in individuals with primary immunodeficiency, acquired immune deficiency syndrome, diabetes mellitus, malignancy, solid organ or bone marrow transplants, and those patients receiving corticosteroid therapy.[8-10] *P lilacinum* infection results in a variety of skin changes, from small erythematous papules to plaques with central umbilication, to hemorrhagic vesicle or ulceration. It is also increasingly recognized as an etiological agent of invasive fungal infections, such as pneumonia, peritonitis, invasive sinusitis, and bloodstream infections.[11,12] The diagnosis of *P lilacinum* infection is based on the culture of the fungus and pathology of the lesions. Its lilac obverse color and its characteristic to sporulate in infected tissues together help the identification of *P lilacinum* infections.[13,14]

Species identification of the causative agent is crucial for treatment because different species of the genus *Paecilomyces* show variable susceptibilities to antifungal medicines. *P lilacinum* has a poor response to traditional antifungal agents.[15,16] But it shows susceptibility to novel triazoles like voriconazole and posaconazole because new triazoles have lower MIC in vitro.[17] Among the triazoles, posaconazole has the lowest MIC (0.12–0.5 mg/L).[18,19] The lady in this report has risk factors for opportunistic infections: hematological disease and long-term immunosuppressive therapy. *P lilacinum* was identified both in skin biopsy and blood samples. *P lilacinum* infections in multiple systems (skin, lungs, and spleen) were diagnosed and cured after posaconazole treatment.

Immunocompromised patients are prone to repeated infections. When the microbial evidence cannot be obtained using regular methods, newly specific detections should be considered. As a high-throughput technology, mcfDNA sequencing shows higher sensitivity (68.1 vs 40.4%) for bloodstream infection than blood culture.[20] The sensitivities and specificities of NGS were 83.6% and 84.5% for bacteria, 84.2% and 92.3% for virus, and 100% and 97.5% for fungi.[21] It can detect a high breadth of microorganisms and achieve high diagnostic specificity.[22,23] It also is a timely diagnostic method. The genetic testing of the case in this report revealed varicella-zoster virus infection, and antiviral treatment showed good outcome.

Table 1

The microbial results detected by next-generation sequencing.

	Name of pathogen	Reads	Coverage
Blood	*P lilacinum*	3	228/38,534,601
	Varicella-zoster virus (VZV, human alphaherpesvirus 3)	5123	114,115/124,884
	Torque teno virus 24	190	1191/3246
Skin biopsy	Varicella-zoster virus (VZV, human alphaherpesvirus 3)	3,165,733	124,884/124,884
	Torque teno virus 24	33	889/3246

In conclusion, we reported a case of multiple organ *P lilacinum* infections which was effectively treated by posaconazole. Further, the molecular-based methods like mcfDNA sequencing could provide accurate and timely identification of a wide range of infections.

4. ACKNOWLEDGMENTS

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