SHORT COMMUNICATION

Topical 1% Voriconazole for Mixed *Scedosporium* and *Exophiala* Subcutaneous Infection in a Kidney Transplant Recipient

Olivier PACCOUD[1], Pierre SOHIER[2], Camille COTTERET[3], Sarah GUÉGAN[4#] and Fanny LANTERNIER[1,5#]
[1]Necker-Pasteur Center for Infectious Diseases and Tropical Medicine, Necker – Enfants Malades Hospital, Assistance Publique des Hôpitaux de Paris (AP-HP), Paris Cité University, FR-75015 Paris, [2]Department of Pathology, Cochin Hospital, AP-HP, Paris Cité University Paris Cité, [3]Pharmacy Department, Necker-Enfants Malades Hospital, AP-HP, Paris, [4]Department of Dermatology, Cochin Hospital, AP-HP, Paris Cité University and [5]Pasteur Institute, Centre National de Référence des Mycoses Invasives et des Antifongiques (CNRMA), Paris, France. E-mail: olivier.paccoud2@aphp.fr
[#]These senior authors contributed equally to the manuscript.
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Subcutaneous hyalohyphomycoses and phaeohyphomycoses can be challenging to manage in solid-organ transplant recipients because of drug toxicities and drug-drug interactions. We report here a case of mixed subcutaneous infection caused by *Scedosporium* and *Exophiala*, which was successfully managed using a combination of systemic antifungals and a topical 1% voriconazole preparation.

CASE REPORT

A 40-year-old woman was referred to the department of Infectious Diseases of Necker - Enfants Malades hospital, Paris, France, with a suspicion of lower limb subcutaneous fungal infection. Her medical history was significant for renal transplantation 8 years previously, due to membranoproliferative glomerulonephritis, and for chronic idiopathic liver disease. She received mycophenolic acid (360 mg bid), tacrolimus (2 mg qd), and prednisone (5 mg qd) for post-transplant prophylaxis. Post-transplant follow-up had been notable for acute humoral rejection and BK virus nephropathy, and baseline creatinine levels were 200 µmol/L (estimated renal clearance 25 mL/min). Five months prior to presentation, the patient had returned from a 10-day trip to India, during which she reported falling in a sewage ditch and wounding her right leg. Upon her return, the patient was given a 5-day course of amoxicillin-clavulanic acid. Over the ensuing 3 months, the wound had reportedly healed. One month later, the patient reported skin redness and a discharge of pus. A skin swab sample performed in an outpatient setting yielded growth of *Scedosporium* spp. On admission, the patient was afebrile and in good overall condition. Dermatological examination revealed a 5 cm-long heterogeneous erythematous and pigmented infiltrated plaque of the right tibial crest area, with a single ecchymotic nodule (**Fig. 1**A). Physical examination was otherwise unremarkable. A skin biopsy specimen revealed suppurative granulomas in the subcutaneous fat associating 2 morphologically distinct fungal pathogens, including small pigmented hyphae evocative of phaeohyphomycosis and larger yeast-like pathogens with budding and internal septation (Fig. 1D–F). No mycetoma grains were observed. Mycological cultures yielded growth of *Exophiala* spp., which was identified as *Exophiala jeanselmei* by sequencing of the internal transcribed spacer (ITS) locus. Antifungal susceptibility testing was performed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) broth microdilution method following the E.DEF 9.3.2 procedure (1), with some modifications (2), and showed minimal inhibitory concentrations (MIC) for voriconazole, posaconazole, itraconazole, and caspofungin of 0.5 mg/l, 0.06 mg/l, 0.25 mg/l, and 4 mg/l, respectively.

Computed tomography of the leg showed no evidence of osteitis, and full-body imaging showed no dissemination. The patient was

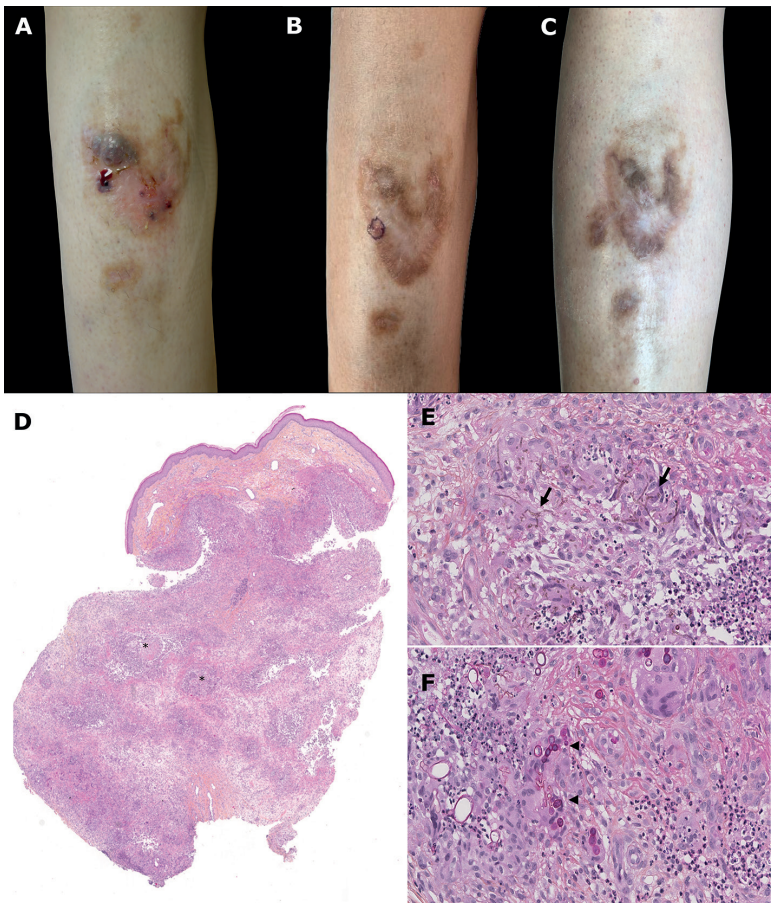

Fig. 1. (A) Heterogeneous pigmented and erythematous plaque with abscess. (B) Heterogeneously pigmented macules with 1 papular area that developed into suppuration. (C) Heterogeneously pigmented scar 1 year after treatment end. (D) Skin biopsy demonstrating heavy inflammation with suppurative granulomas in the subcutaneous fat (*asterisks*). Haematoxylin-eosin saffron (×13). (E) Suppurative granuloma with giant multinucleated cell containing small thin spontaneously pigmented branching hyphae evocative of phaeohyphomycosis (*arrow*) haematoxylin-eosin saffron (×200). (F) Suppurative granulomas with large yeast-like pathogens with budding and internal septation (*arrowheads*). Haematoxylin-eosin saffron (×200). Written consent for the publication of the figures was obtained from the patient.

started on oral voriconazole (200 mg bid). Within 48 h, the patient's liver function deteriorated (alanine transaminase (ALT) levels 11 times the upper normal limit), and voriconazole was suspended. After 10 days, treatment was switched to posaconazole (200 mg qd). Despite 2 months of antifungals and with trough levels of posaconazole within therapeutic range, pus was still discharging from the lesion, and skin biopsies showed persistent granulomatous inflammation. Mycological cultures yielded growth of *Scedosporium apiospermum* (MIC 0.5, 0.5, 0.125 and 1 mg/L for voriconazole, posaconazole, micafungin, and caspofungin, respectively). In addition, the patient's renal function had deteriorated, partly due to drug-drug interactions between tacrolimus and posaconazole, with increased creatinine levels at 270–290 µmol/L and new-onset proteinuria. Surgical debridement of the lesion was not deemed a viable option, due to the large surface of the affected area. Instead, antifungal treatment was intensified, with a 3-week course of intravenous caspofungin (50 mg qd) in addition to the posaconazole treatment, and daily topical 1% voriconazole cream was applied with an occlusive patch (details of this procedure were described previously (3)). Antifungal treatment was stopped at the end of a 6-month treatment course. Ten months later, local inflammatory symptoms relapsed. Mycological cultures from new skin biopsy specimen once again yielded colonies of *Exophiala jeanselmei*. In the absence of locoregional invasion and dissemination, it was opted to treat the patient exclusively with topical voriconazole. Over 6 months, local inflammatory signs progressively abated, leaving a heterogeneously hyperpigmented scar (Fig. 1C). The patient is currently without treatment, and has reported no signs of relapse after more than 1 year of follow-up.

DISCUSSION

Scedosporium apiospermum and *Exophiala jeanselmei* are ubiquitous fungi commonly isolated from environmental substrates, such as soil (*S. apiospermum and E. jeanselmei*), sewage, and polluted waters (*S. apiospermum*), and have been reported as causing chronic subcutaneous lesions after direct inoculation (4, 5). Management of these infections in immunocompromised individuals generally relies on surgical debridement when lesions are small and localized, in association with systemic triazoles to prevent dissemination (4–6). Although usually not life-threatening, these infections may be challenging to manage in immunocompromised patients (5), especially when long-term systemic antifungals cannot be administered due to toxicity or to concerns regarding drug-drug interactions (7). In this case, the use of triazole treatment was limited by renal and liver toxicity, and was only partially effective. Our group recently reported a case of cutaneous infection by *Fusarium* spp. in a patient with hyper-immunoglobulin E syndrome, linked to STAT3 deficiency, managed using this novel topical voriconazole formulation, combined with oral treatment (3). This voriconazole skin cream formulation was shown to be stable over time, and allowed for successful management of infection first in combination with oral voriconazole, and then alone as maintenance therapy (3). We believe that the topical formulation of voriconazole could allow for sustained release of high concentrations of antifungals at the site of infection, which could explain why it may have been more effective than the initial systemic treatment. It is, however, unclear at present whether clinical improvement was solely due to the topical formulation, or rather to the combination of topical and systemic antifungals. It is also important to note that the use of topical formulations of voriconazole should be reserved for the treatment of limited cutaneous mycoses, as its penetration into deep tissue planes is expected to be limited. We consider that, in the absence of locoregional dissemination, topical voriconazole may be of value in the tailored management of localized phaeohyphomycoses or hyalohyphomycoses in immunocompromised patients, in association with systemic antifungals during initial treatment or in place of long-term systemic antifungals when these are poorly tolerated.

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The authors have no conflicts of interest to declare.

REFERENCES

1. Arendrup MC, Meletiadis J, Mouton JW, Lagrou K, Hamal P, Guinea J. EUCAST Definitive document E.DEF 9.3.2. 2020; 23.
2. Guégan S, Garcia-Hermoso D, Sitbon K, Ahmed S, Moguelet P, Dromer F, et al. Ten-year experience of cutaneous and/or subcutaneous infections due to coelomycetes in France. Open Forum Infect Dis 2016; 3: ofw106.
3. Bouchand C, Nguyen D, Secretan PH, Vidal F, Guery R, Auvity S, et al. Voriconazole topical cream formulation: evidence for stability and antifungal activity. Int J Antimicrob Agents 2020; 56: 106083.
4. Chowdhary A, Meis JF, Guarro J, de Hoog GS, Kathuria S, Arendrup MC, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. Clin Microbiol Infect 2014; 20: 47–75.
5. Tortorano AM, Richardson M, Roilides E, van Diepeningen A, Caira M, Munoz P, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others. Clin Microbiol Infect 2014; 20: 27–46.
6. Gülmez D, Doğan Ö, Boral B, Döğen A, İlkit M, de Hoog GS, et al. In vitro activities of antifungal drugs against environmental Exophiala isolates and review of the literature. Mycoses 2018; 61: 561–569.
7. Xing Y, Chen L, Feng Y, Zhou Y, Zhai Y, Lu J. Meta-analysis of the safety of voriconazole in definitive, empirical, and prophylactic therapies for invasive fungal infections. BMC Infect Dis 2017; 17: 798.