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A case of recurrent keratitis caused by *Paecilomyces lilacinus* and treated by voriconazole

Uso do voriconazol na ceratite recorrente causada por fungo *Paecilomyces lilacinus*

Carolina Pelegrini Barbosa Gracitelli[1], Pedro Vanalle Ferrar[1], Carlos Alberto Pires Pereira[2], Flávio E. Hirai[1], Denise de Freitas[1]

1. Department of Ophthalmology and Visual Sciences, Universidade Federal de São Paulo, São Paulo, SP, Brazil.
2. Department of Infectious Diseases, Universidade Federal de São Paulo, São Paulo, SP, Brazil.

RESUMO | Descrevemos aqui um caso de uma mulher de 21 anos que apresentou baixa acuidade visual, dor e hiperemia no olho esquerdo por 45 dias. O olho apresentava infiltrado corneano extenso, com fusão e perfuração central colada com cianoacrilato, mas com Seidel (+). Ela foi submetida a transplante de córnea tectônica e lavagem de câmara anterior com infiltração subconjuntival com voriconazol, além de injeções intracamerais de anfoterecina B. Testes laboratoriais revelaram *Paecilomyces lilacinus* como agente infeccioso. A paciente foi então mantida com voriconazol oral e colírio por período de três meses, após o qual a infecção foi considerada curada. No entanto, no sexto mês de pós-operatório, ela apresentou rejeição endotelial e, duas semanas após, sinais de recidiva de infecção fúngica. Ela foi tratada com mais duas lavagens de câmara anterior e injeção subconjuntival de voriconazol, seguida por voriconazol intravenoso que foi substituído por gotas após 10 dias. A infecção piorou inicialmente, mas depois regrediu e, no último seguimento, o paciente ainda estava livre de infecção.

Descritores: Ceratite/tratamento farmacológico; Infecções oculares fúngicas/ tratamento farmacológico; *Paecilomyces lilacinus*; Câmara anterior; Irrigação terapêutica; Voriconazol/uso terapêutico

ABSTRACT | We describe here a case of a 21-year-old woman who presented with low visual acuity, pain, and hyperemia in the left eye for 45 days. Her eye had extensive corneal infiltrate, with melting and a central perforation that was glued with cyanoacrylate, but with Seidel (+). She underwent tectonic corneal transplantation, and anterior chamber lavage with subconjunctival infiltration with voriconazole, as well as intracameral injections of amphotericin B. Laboratory tests revealed *Paecilomyces lilacinus* as the infectious agent. The patient was then maintained with oral voriconazole and eye drops for three months, after which the infection was considered cured. However, in the sixth postoperative month she presented with endothelial rejection, and two weeks later signs of recurrence of the fungal infection. She was treated with two further washes of the anterior chamber and subconjunctival injection of voriconazole, followed by intravenous voriconazole that was replaced with drops after ten days. The infection initially worsened, but then regressed, and at last follow-up, the patient was still infection-free.

Keywords: Keratitis/drug therapy; Eye infections, fungal/drug therapy; *Paecilomyces lilacinus*; Anterior chamber; Therapeutic irrigation; Voriconazole/therapeutic use

INTRODUCTION

Paecilomyces lilacinus is a filamentous fungus that inhabits the soil, decaying plants, and food products; though usually considered a contaminant, and it also causes infections in humans and animals[1]. The use of extended wear soft contact lenses, ocular trauma and the prolonged use of topical corticosteroids have been associated with infection-induced keratitis[2].

Several drugs have been used to treat ophthalmic infections caused by Paecilomyces. Amphotericin B (AMB) is probably the most commonly used drug; however, its efficacy is poor[3], as would be expected given its poor in vitro efficacy against Paecilomyces[4]. Although studies on the clinical use of voriconazole (VRC) are limited, it appears to be an effective antifungal with regard to Paecilomyces[4]. Here we describe a case of AMB-resistant Paecilomyces eye infection with related keratitis that was treated with topical voriconazole.

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Corresponding authors: Carolina P. B. Gracitelli.

Rua Botucatu, 821 - São Paulo, SP - 04023-062 - Brazil - E-mail: carolepm@gmail.com

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However, it is often difficult for a clinician to decide which antifungal to use and the route of administration in fungal infections. Corneal epithelium serves as a barrier to the penetration of most topical antifungal agents. In some cases, intracameral injections could be used to improve drug penetration.

This report shows a case of Paecilomyces keratitis treated with topical voriconazole.

CASE REPORT

A 21-year-old woman with a history of Turner syndrome (confirmed by karyotype) was referred to our service due to a 45-day long, continuing corneal infection. Her past medical, ocular, and family histories were mostly unremarkable, although she did report a history of severe bilateral blepharitis and corneal opacities due to phlyctenulosis. She was using 0.1% moxifloxacin eye drops (q.i.d.) and 0.1% dexamethasone ointment (b.i.d.). The ophthalmologic exam showed visual acuity of 20/100 in her right eye and light perception in her left eye. The corneal exam revealed severe stromal infiltration and melting with an area of tissue adhesive applied for a corneal perforation in her left eye. The patient underwent tectonic corneal transplantation. During the operation, microbiological testing identified *P. lilacinus* as the infective agent. At the end of the surgery, intracameral (100 µg) and subconjunctival (10 mg) VRC were injected; additional intracameral injections of AMB were administered. The infected material was sent to a mycology laboratory for antifungal susceptibility testing; the minimum inhibitory concentrations of AMB, fluconazole, and VRC were 16 ag/ml, 64 ag/ml, and 16 ag/ml, respectively.

The patient was placed on hourly topical (10 mg/ml) and oral (100 mg b.i.d.) VRC (the dosage was adjusted for the short stature typical in Turner syndrome), and after three months of treatment all the medication was discontinued and the patient was considered free of infection.

Three months after discontinuing the medication, the patient presented signs of endothelium rejection. She was treated with topical 1% prednisolone, and signs of improvement were noted one week later. However, two weeks after initiating the prednisolone, a deep corneal infiltration and anterior chamber reaction were observed during an exam, suggesting the fungal infection had recurred (Figures 1 and 2). She underwent a second intracameral VRC injection and sampling of the aqueous humor, lab cultures of which were positive for *P. lilacinus*. At this time, she was admitted to the hospital and administered intravenous VRC for ten days. On the fifth day of hospitalization, the stromal infiltration worsened and a third intracameral VRC injection was given. Lab cultures of aqueous humor were still positive for *P. lilacinus*.

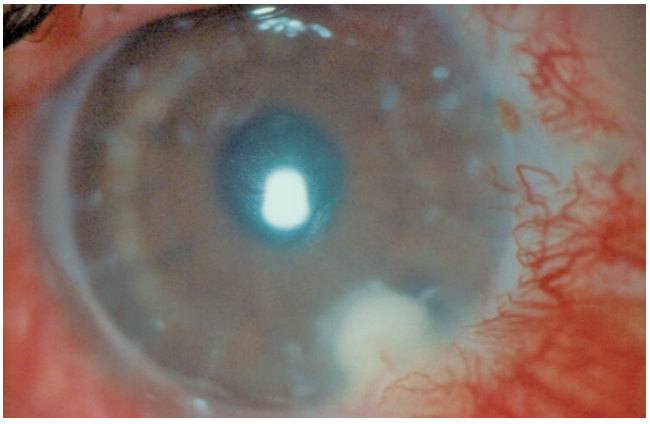

Figure 1. Deep corneal infiltration and anterior chamber reaction suggestive of fungal infection recurrence.

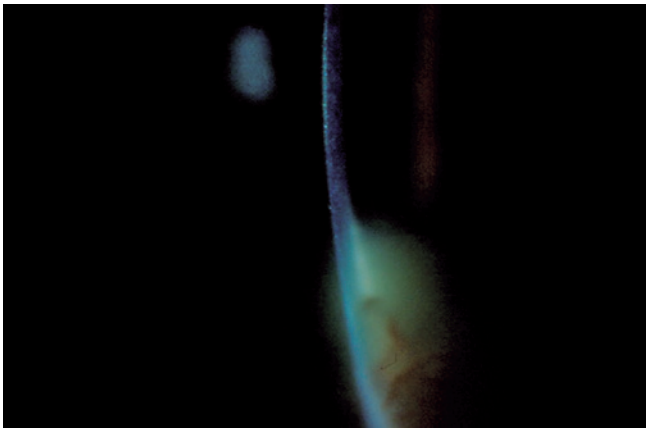

Figure 2. Slit lamp showing infiltration of the deep layers of the cornea.

After one month of intense topical (hourly) and oral (100 mg b.i.d.) VRC administration the stromal infiltrate regressed. The patient was then maintained on topical and oral VRC for an additional 6 months, after which she was maintained on topical VRC drops for six more months. Should the eye remain free of inflammation for one year after cessation of the medication a new corneal graft will be planned.

DISCUSSION

The prognosis following *P. lilacinus* infection is often poor due to its relatively high resistance to medical

treatment. Loss of the eye is not an uncommon outcome. *P. lilacinus* has been reported to be resistant to amphotericin B and natamycin, the most commonly used antifungal agents[5]. In the case herein, the infection was resistant not only to amphotericin B but also to fluconazole and voriconazole. Our findings are similar to Marangon et al. study which reported similar resistance to all antifungals, including voriconazole, fluconazole, ketoconazole, and itraconazole[6].

Yuan et al. believe that topical amphotericin B and natamycin are often not effective regardless of the severity of disease[7]. Although usually resistant to fluconazole, *P. lilacinus* has shown to be susceptible to other imidazoles such as miconazole and triazoles such as itraconazole[8]. Voriconazole has excellent oral bioavailability, and like other azoles can achieve therapeutic concentrations in the cornea and successfully control experimental *P. lilacinus* keratitis, so it could be an option in cases with poor response to other antifungal therapies[9]. Anderson et al. reported a case of fungal keratitis caused by *P. lilacinus* resistant to routine antifungal agents but successfully treated with systemic voriconazole and terbinafine[9].

One potential issue is the difficulty clinicians face in deciding which antifungal and route of administration to use. Corneal epithelium serves as a barrier to the penetration of most topical antifungal agents. Yoo et al. described a case in which they used iontophoresis to increase the penetration of antifungal drugs into the cornea and aqueous humor[10]. In some cases, intracameral injections could be used to improve drug penetration.

Our patient reported no history of ocular trauma, pesticide exposure, or previous ocular surgeries. She was taking antibiotics and steroids when referred to our service, a commonly used approach by ophthalmologists due to the difficult diagnosis. Despite the recurrence of the infection at 6 months, and the high resistance of the fungus, at her last follow-up, the patient's infection continued to appear resolved.

In summary, we report the successful medical treatment of a case of *P. lilacinus* keratitis with repeated intracameral injections of amphotericin B and voriconazole. Early detection of the organism and appropriate treatment are necessary to eradicate such an infection and prevent complications such as endophthalmitis and perforations. An approach using intracameral injections of amphotericin B and especially voriconazole can be successful in treating *P. lilacinus* keratitis.

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