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Successful Treatment of Postkeratoplasty Fungal Keratitis with Topical and Intrastromal Voriconazole

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Abstract

Objective: Corneal grafts have a major risk of fungal keratitis due to long-term local and sometimes systemic steroid/antibiotic use. The aim of this study was to evaluate the efficacy of intrastromal voriconazole as a therapeutic adjunctive for the management of fungal keratitis in corneal graft.

Design: Presentation of two cases of fungal keratitis occurring after corneal transplantation and treated at the University Eye Hospital "Svjetlost". Participants and Methods: Two cases of postkeratoplasty fungal keratitis are presented in the study. Both patients had decreased visual acuity, eye redness and severe pain occurring at 10 and 12 months after uneventful corneal transplantation. They were still receiving steroid/antibiotic topical treatment to protect their corneal graft. Patients presented with a stromal infiltrate in a donor tissue, accompanied with corneal ulcer at recipient/donor junction. Candida infection was proven by corneal scraping. Topical and systemic anti-mycotic treatment was started, fortified by intrastromal injection of voriconazole (50 µg/0.1 ml) given all around the junction of clear cornea and infiltrate (or ulcer).

Results: One week after injection, corneal ulcers had healed and corneal infiltrates decreased; resulting in visual acuity improvement from 20/100 to 20/20 in first, and from 20/80 to 20/40 in a second case. One year after infection visual acuity in the first case remained 20/20, and improved to 20/20 in a second case.

Conclusion: Intrastromal voriconazole seems to be a safe method for providing a higher concentration of the drug in the cornea affected by fungal keratitis; it can serve as an adjunctive treatment to topical and systemic antifungal therapy.

Keywords: Fungal keratitis; Intrastromal voriconazole; Corneal graft; Candida species

Introduction

Infectious keratitis is a leading cause of monocular vision loss in tropical and developing countries [1]. Worldwide, the reported incidence of fungal keratitis is 17% to 36%, most commonly caused by *Fusarium* and *Aspergillus* and other less common species like *Candida*, *Curvularia*, and *Monosporidium*, among others. The primary risk factors for infection are trauma particularly with vegetable matter, chronic ocular surface disease and epithelial defects, long-term use of broad-spectrum antibiotics and topical steroid, refractive surgery and specific contact lens disinfectant solutions [2]. Fungal infection can elicit a severe inflammatory response that can cause stromal necrosis and melting. It is a diagnostic and therapeutic challenge for every ophthalmologist. Difficulties are related to the establishment of a clinical diagnosis, isolation of the aetiological fungal organism in the laboratory, and treating the keratitis effectively with topical antifungal agents. Unfortunately, delayed diagnosis is common, primarily because of the lack of suspicion on fungal keratitis. Even if the diagnosis is made accurately, management remains a challenge, because of the poor corneal penetration and the limited commercial availability of antifungal agents.

Patients and Methods

We report two cases of keratomycosis with *Candida spp.* in patients who have had penetrating keratoplasty (PK). The first patient was a 43 year-old female who presented to her local ophthalmologist with a 2 day history of foreign body sensation, eye redness and pain. A year before, she underwent uneventful corneal transplantation due to keratoconus, with a postoperative visual recovery to best corrected visual acuity (BCVA) of 20/20. Before the onset of symptoms, she was using steroid/antibiotic drops once a day, artificial tears and lubricating gel. At that first exam severe inflammation, profuse secretion and 3 mm infiltrate at the edge of corneal graft was recorded; with BCVA of 20/25. Conjunctival swab was taken and both systemic (amoxicillin) and topical antibiotic (ciprofloxacin) on hourly basis was given. Three days after the onset of treatment she was admitted to our Clinic with BCVA of only 20/100. She had abundant yellowish secretion, red eye, ring-like infiltrate almost centrally and a 3 mm ulcer surrounded by 2 mm of feathery stromal infiltration close to the recipient/donor junction with endothelial precipitates. The anterior chamber was clear. Corneal scrapings were collected from the margin and bed of the corneal ulcer in a sterile environment and sent for microbiological examination. Topical treatment with voriconazole drops every hour and systemic fluconazole therapy was started immediately based on the clinical presentation. During

microbiological examination after overnight incubation on Sabouraud's Dextrose agar, colonies were small with irregular margins. Gram stain was performed from the culture growth, revealed gram positive budding yeast cells. Cultured cells were incubated in human serum at 37°C and examined under low power where it showed the germ tube (Reynolds- Braude Phenomenon). Isolated organism also grew at 45°C and fermented glucose, sucrose and maltose, but not lactose by changing color to red. On cornmeal agar, isolated yeast produced thick, terminal chlamydospores. On CHROMagar, after overnight incubation at 37°C there was light green colour. Ability to form Germ Tube, growth at 45°C, chlamydospore production and light green color on CHROMagar confirmed that isolated organism was *Candida albicans*. As cultures were positive for Candida spp. and the patient clinical presentation was not ameliorating intrastromal injection of voriconazole (50 µg/0.1 ml) was given at the junction of the clear cornea and infiltrate in all four quadrants, to form a barrage around the ulcer. Injection was made with 27 gauge needle (Terumo Neolus, Terumo Europe N.V.–3001 Leuven, Belgium) aiming into the upper third of corneal stroma. The thickness of the cornea was evaluated by anterior optical coherent tomography scan (OCT Visante, Carl Zeiss, Germany, 2006) prior to the corneal injection. Topical and systemic antifungal treatment was also continued for 4 weeks.

The second case was a 45 year-old female who had suffered from a transplant reaction one month after the corneal transplantation due to keratoconus, which was successfully treated with high dose topical steroid treatment, and a persistent epithelial defect which was treated with amniotic membrane transplantation. Ten months after the surgery she developed fungal keratitis on her transplanted eye. She presented with decreased visual acuity from 20/30 to 20/80, red eye, 4 mm of central stromal infiltrate and small ulcer at the margin of a corneal graft. Corneal scraping was sent for microbiological analysis as in a previous case, showing positive culture for *Candida spp*. The patient received topical and intrastromal (50 µg/0.1 ml) voriconazole treatment together with systemic fluconazole, in an identical manner as previously described.

Results

In the first case clinical presentation of fungal infection affecting the corneal graft was captured at the slit lamp and OCT scan was performed (Figure 1). OCT scan of her graft showed the ulcer and irregularity of the cornea. Significant healing of the corneal ulcer and clearing of the infiltrate was achieved 9 days after intrastromal voriconazole application. After 3 weeks of anti-fungal treatment, visual acuity recovered to 20/20, with a corneal haze in the area where the ulcer was present. Patient was followed up regularly on a weekly basis for a further month and on monthly basis thereafter, showing constant clearing of the corneal haze resulting in clear central cornea one year after the infection with stable visual acuity of 20/20, and OCT scan showed improved regularity of the cornea (Figure 2).

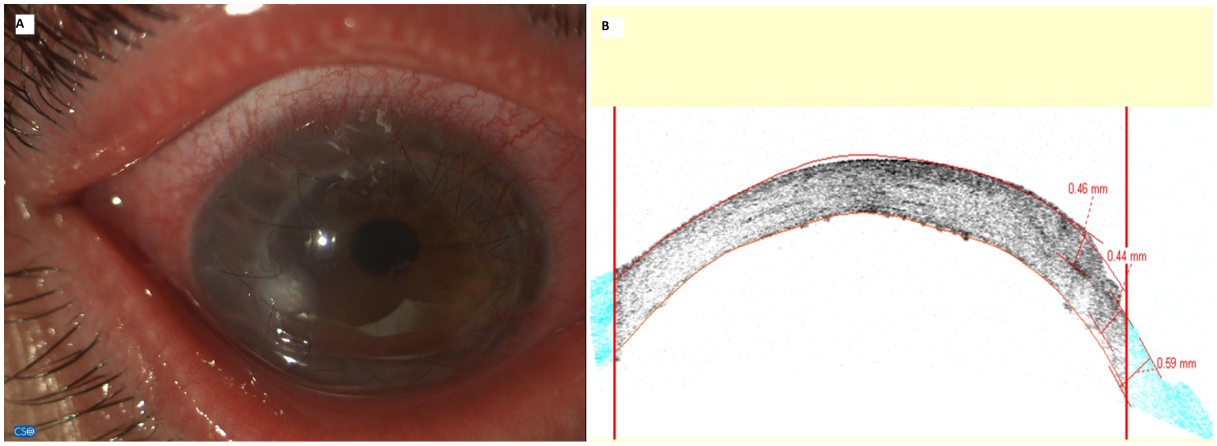

Figure 1: Case one. Fungal keratitis in a corneal graft: a) red eye, a paracentral ring-shaped infiltrate and 3 mm ulcer surrounded by 2 mm of feathery stromal infiltrate at recipient/donor junction with endothelial precipitates; b) optical coherent topography scan showing irregularity of the cornea and peripheral ulcer.

In the second patient, both high dose steroids and the disrupted epithelial barrier could have been the risk factors for the development of fungal keratitis that was present and captured at the slit lamp and OCT scan showing shallow small ulcer paracentrally on the graft (Figure 3). One week after intrastromal voriconazole application, a significant decrease in the size and density of the infiltrate and ulcer was noticed. Final BCVA after 1 month of anti-fungal treatment was 20/40 because of a remaining corneal haze in the central area of the corneal graft. However, over the following months clinical presentation improved, central corneal haze diminished and OCT scan showed improved regularity (Figure 4). All of this resulted in a final visual acuity of 20/20 at one year of follow-up.

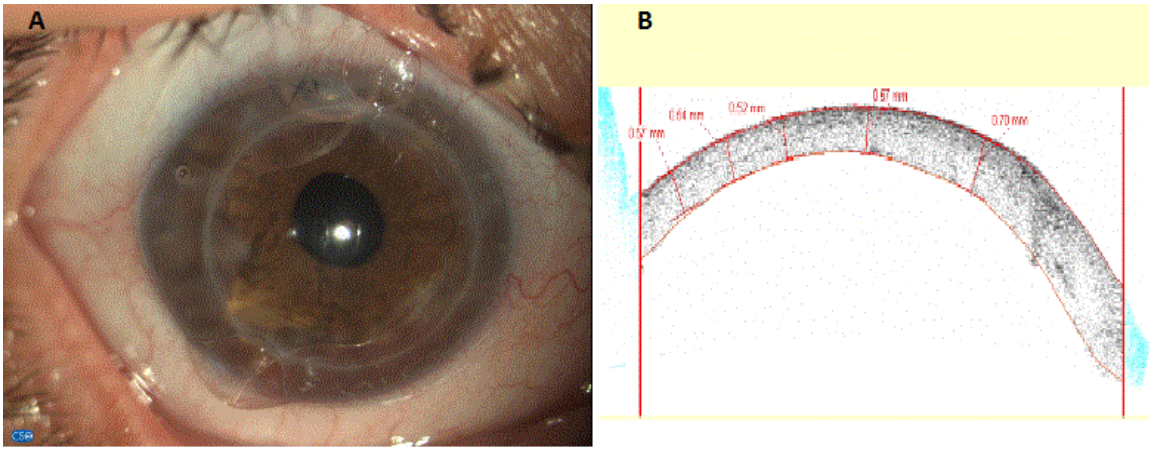

Figure 2: Case one. Corneal graft one year after fungal keratitis treated with intrastromal voriconazol application, combined with topical and systemic treatment: a) clear graft at visual axis and residual stromal opacification at the site of previous ulcer with visual acuity of 20/20; b) optical coherent topography scan showing regular cornea with healed peripheral ulcer.

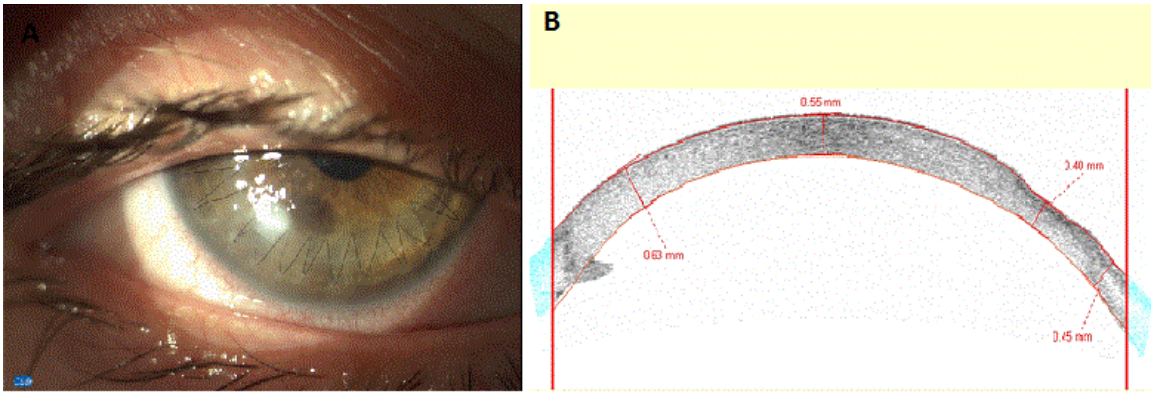

Figure 3: Case two. Fungal keratitis in a corneal graft: a) red eye, 4 mm of central stromal infiltrate and small ulcer at the margin of a corneal graft; b) optical coherent topography scan showing irregular cornea and shallow ulcer.

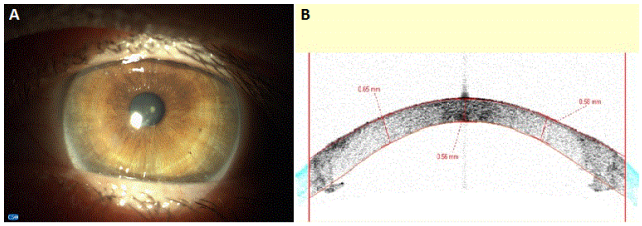

Figure 4: Case two. Corneal graft one year after fungal keratitis treated with intrastromal voriconazol application, combined with topical voriconazol and systemic fluconazol treatment: a) clear corneal graft with slight residual stromal opacification at the site of previous ulcer and visual acuity of 20/20. b) optical coherent topography: cornea is completely regular.

Discussion and Conclusion

Early fungal keratitis after corneal transplantation develops because of the contaminated donor cornea or intraoperative infection with fungal elements [3]. In the postoperative period, infection may develop due to predisposing factors such as the persistent epithelial defects, suture-related problems, application of high dose of topical or systemic corticosteroids and the use of broad-spectrum antibiotics that may alter normal ocular flora allowing fungal species to grow [4].

Candida species is the most often cause of fungal keratitis after corneal transplantation [5,6]. Other causes are *Cladosporium, Cryptococcus, and Aspergillus* species [7-9]. Early diagnosis and immediate initiation of treatment are crucial in achieving good results and preventing complications like scleral or anterior chamber involvement. In our two cases, fungal corneal infection was treated with the topical and stromal application of voriconazole in a combination with systemic fluconazole. Voriconazole is a second-generation triazole derived from fluconazole that offers broad-spectrum activity against various fungi affecting the eye. It primarily

inhibits the cytochrome P450 14-alpha demethylase and 24-methylene dihydrolanasterol demethylation in certain yeasts and filamentous fungi. It has been shown that its molecular mass allows good corneal penetration and therefore better ocular bioavailability [10]. Oral voriconazole also has good intraocular penetration with therapeutic levels of the drug achieved both in aqueous (1.7 μg/mL) and in vitreous (1.5 μg/mL) [11]. Intracameral voriconazole injection is conceivably the most direct and effective method for achieving higher aqueous concentrations [12], and reports have shown its efficacy [13-15]. However, intracameral use of voriconazole is still an "off-label" use, and a safe therapeutic dosage has not been established. Han et al., in their study, showed that intracameral voriconazole concentrations of ≥100 μg/ml may increase the risk of corneal endothelial damage, which is why it should be used with caution [16].

Recently, few studies have shown that the intrastromal administration of voriconazole is safe and cost-effective method of providing higher concentrations of the drug in the cornea [17]. Intrastromal injection of 0.05–0.1 ml of voriconazole (50 μg/0.1 ml) aided in the resolution of different fungal infections and repeated intrastromal injections of voriconazole (50 μg/0.1 ml) were tolerated with no long-term ocular toxicity noted [18]. Intrastromal injections of 0.1 ml of voriconazole (25 μg/ml) have also been used to treat Acanthamoeba keratitis with no complications [19]. Most recent data have shown that intrastromal voriconazole injection is successful in treating yeast keratitis; however this was not the case for filamentous fungal keratitis [20].

In our two cases, the intrastromal application of voriconazole did not show any side effects. On the contrary, corneal ulcer healed and infiltrates gradually reduced in size and density a few days after the initiation of treatment. Corneal infiltrates partially or totally affecting the visual axis have cleared completely over time, and both patients could see 20/20 one year after the infection. As in our two cases, the clinical efficacy and safety of intrastromal and intracameral voriconazole for fungal keratitis have been already supported by other studies, but not in an infected corneal graft [13-19].

Bearing in mind that patients have a significant risk of developing fungal keratitis after corneal transplantation due to the long-term local (and sometimes even systemic) steroid and antibiotic usage, early diagnosis and prompt treatment is crucial for curing those patients. The combination of intrastromal and topical voriconazole with systemic antifungal therapy seems to be safe and effective treatment for *Candida spp.* fungal keratitis after penetrating keratoplasty.

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