Encouraging Result of Voriconazole Treatment for Cladosporium Corneal Keratitis

Luís Antonio Gorla Marcomini1, Gleilton Carlos Mendonça da Silva2, Sidney Júlio de Faria-e-Sousa2
1 Department of Medicine of the Center of Biologic Sciences and Health of the Federal University of São Carlos – UFSCar – São Carlos (SP) Brazil
2 Department of Ophthalmology of the Faculty of Medicine of Ribeirão Preto, University of São Paulo – USP – Ribeirão Preto (SP) – Brazil.

Correspondence address:
Luís Antonio Gorla Marcomini
Department of Medicine – Federal University of São Carlos
Rodovia Washington Luis – Km 235 – São Carlos (SP) – Brazil - CEP 13565-905
Phone: (16) 3351-8340
E-mail: lamarcomini@gmail.com

ABSTRACT

A 45-year-old man submitted to radial keratotomy 19 years ago acquired Cladosporium sp. infection in one of the incisions of the left eye. The infection was resistant to topical amphotericin B, topical natamycin and systemic fluconazole. The keratitis was cured with voriconazole 200 mg PO, BID for 10 days.

Keywords: corneal infection, fungal keratitis, infectious keratitis, radial keratotomy, refractive surgery, voriconazole.

INTRODUCTION

Radial keratotomy (RK) is an obsolete form of surgical correction of myopia. The surgery consists in deep symmetric radial corneal incisions around a small central circular area that is left intact.1 Fyodorov was the first to present good results with this procedure in human eyes. His data were first published in English literature in 1979.2 In the late 80s, RK became popular around the world. Later, it was revealed that the radial incisions did not heal completely, generating two main complications: progressive hyperopia and propensity to corneal infection.3-5

Since the surgery was popular among young adults, ophthalmologists still need to be prepared to treat late complications of the procedure. The purpose of this paper is to report a case of very late onset infection in a RK incision caused by a recalcitrant fungus, quickly cured by oral voriconazole. Voriconazole is a synthetic derivative of fluconazole with an expanded activity. It has good penetration into the corneal stroma and reaches high concentrations in the vitreous and aqueous, even when administered orally.6

CASE REPORT

A 45-year-old male, owner of a pet food shop, came to our corneal service complaining of foreign body sensation in the left eye that started six days before. In the first three days, he used a combination of 0.35% neomycin and 0.1% dexamethasone eye drops QID, showing no improvement of the symptoms. In this interval, he noticed a corneal white spot in the affected eye. He consulted an ophthalmologist, who diagnosed corneal ulcer and started treatment with 0.5% moxifloxacin (Vigamox®, Alcon, São Paulo, Brasil) hourly around the clock. About 48 hours later, he was referred to our service because his eye was not improving.

Visual acuity was 0.7 in the right eye and light perception in the left eye. Slit lamp biomicroscopy of the right cornea showed eight regular scars of RK negative to fluorescein staining. The left cornea also showed eight RK scars. The ones of the upper quadrant were epithelialized. The incisions of the inferior quadrant were partially opened and stained with fluorescein. The most vertical incision of this quadrant presented a deep 3 millimeter-diameter paracentral grayish-white infiltrate (Figure 1A). The lesion stained with fluorescein. There was no visible anterior chamber reaction. In terms of antecedents, the patient referred that he had RK in both eyes 19 years ago and Diabetes mellitus type II diagnosed two years ago.

Due to the presence of onychomycosis on every fingernail of the patient’s hands and feet, we suspected fungal etiology. After scraping the lesion, we started with topical 0.25% amphotericin B and 5% natamycin hourly and 1% atropine eye drop BID. The result of
the culture came on the 5th day revealing Cladosporium sp. Oral Fluconazole 150 mg BID was started as an adjunctive therapy; topical medication was maintained.

Two days later, the patient presented shallow chamber and an aqueous humor leakage through the ulcer bed and one of the adjacent RK incisions. Both perforations were treated with cyanoacrylate glue and soft contact lens (Figure 1B).

The next day slit lamp examination revealed restoration of the anterior chamber and decreased redness of the eye. Twenty days later, the glue fell off, and the eye was much better (Figure 1C). One week later the condition worsened again. The ulcerated area became thinner and accompanied by a massive vascularization of the lower RK incisions and hypopyon (Figure 2A).

A corneal transplantation at this time would have had a bad prognosis due to intense inflammatory reaction. Recurrence of the fungal infection on the graft was another important concern. As a last resort, to avoid surgery, all previous medications were stopped and a systemic treatment with oral voriconazole (VFEND, Pfizer) 200 mg BID was started. On the third day, one could see a marked reduction of the stromal infiltration and vascularization accompanied by total clearance of the hypopyon. On the tenth day, the ulcer was completely healed and oral voriconazole was interrupted.

Due to the high inflammatory activity triggered by fungal infection, the patient developed nearly 360° posterior synechia, resulting in glaucoma of difficult control leading to trabeculectomy in the left eye. At that time, we noticed that the patient was completely free from the onychomycosis.

Nine months after the first examination, the best-corrected visual acuity was 0.7 in the right eye and 0.25 in the left eye. Slit lamp biomicroscopy showed no changes in the right eye. The left eye showed a central corneal scarring with fine vessels, anterior synechiae, partial cataract and a conspicuous trabeculectomy bleb on the superior limbus (Figure 2B). Intraocular pressure was 12 mm Hg in both eyes. The patient was using only artificial tears QID in both eyes. He was last seen on December 14, 2010 (3½ years later). Visual acuity with the best spectacle correction was 0.7 in the right eye and 0.4 in the left eye. Slit lamp biomicroscopy of the left eye showed the same changes of the last examination, but the scarring was less dense (Figure 3B).

**DISCUSSION**

Cladosporium is a pigmented mold widely distributed in the air and rotten organic material and frequently isolated as a contaminant on foods. It commonly grows on insulation in AC systems, on bathroom ceilings when there isn’t enough ventilation, on walls in rooms where insulation is lacking, on foundation walls and on attic sheathing. Indoors species can cause respiratory infections, especially in people with existing respiratory problems such as asthma. Many of them also produce toxins which stimulate allergic responses. The prevalence of Cladosporium keratitis among the fungal corneal infections seems to be small. In our service, it is 2%; in northern India it is about 3% and in south India about 5%. Very limited
data are available on the susceptibility profiles of Cladosporium species. RK surgery, pet-food-shop laboring and the use of antibiotic-steroid eye drops probably were the main factors responsible for the fungal infection in the corneal incisions. The generalized onychomycosis raises the suspicion that the patient had already some sort of deficient immune response to fungal infection. Maybe Diabetes mellitus type II was playing a role in this scenario. No test was done to find out the etiology of onychomycosis. It is probable that its etiology was the same of the corneal infection since the nail colonization was eradicated only with the specific treatment that cured the cornea. Fungal treatment begun before the result of the culture tests due to the evident failure of the previous therapy. Amphotericin B was chosen owing to its action against yeasts and filamentous fungi. It acts by binding to ergosterol, a major component of the cytoplasmic membrane of fungi. However, it also binds to molecules of mammalian cells, such as cholesterol, which explains the toxicity of this drug to the human body when used systemically. Natamycin was also used because of its proved efficacy against filamentous fungus infections of the eye surface. We were not concerned with the poor penetration of these drugs in deep-seated corneal infections because the lesion was placed in the gap of an open incision. Since both drugs belonged to the same antifungal group, i.e., polyenes, we accepted the risk that if the etiological agent was resistant to one of them, it would be more prone to be resistant to the other.

After the lab's confirmation of fungus infection, we decided to continue with both amphotericin B and natamycin since very little data were available about the susceptibility profile of Cladosporium. Antifungigram was not available in our service at that time. The decision to include oral fluconazole in the therapy was based on favorable reports in literature regarding the use of this antifungal in the treatment of Cladosporium infections. Oral and IV fluconazole are very safe and penetrate very well into corneal tissue. It belongs to the first generation triazoles (fluconazole and itraconazole). The azoles act by inhibiting ergosterol synthesis by selective inhibition of an enzyme present in fungal cell: the 14-α-demethylase. These drugs do not interfere with the synthesis of components of mammalian cells membranes, and for this reason are less toxic than the polyenes. The major limitation of fluconazole is its narrow spectrum of antifungal activity. Literature also presents a case of Cladosporium keratitis that was cured with oral itraconazole. Since this drug is commonly associated with gastrointestinal side-effects and has poor penetration into the cornea after systemic administration, we were not confident about using it.

When the situation became critical, we started thinking about surgery. Theoretically, we were left with two options: covering the cornea with a conjunctival flap or performing a corneal transplantation. Conjunctival flap was the main treatment before the development of antifungal agents. The rationale for this procedure is that bringing vessels to the site of infection should facilitate the action of the blood over the infectious agents; bringing conjunctive tissue should improve its healing. The problem with this procedure is that we end up losing visual control over the evolution of the infection. If the treatment fails the trouble is even worse. We definitely are not
enthusiasts of this kind of therapy particularly for fungi that can progress inside the cornea even after epithelialization.\textsuperscript{17} Corneal transplantation would be a reasonable solution to reestablish the tectum of the globe albeit not a good solution for vision in the long run. The chances of rejection were high due to the acute inflammation. Yet, acute inflammation should not be the only factor to put the blame on. In our corneal service, corneas from healed fungal infections, without any visible vascularization that were submitted to transplantation six or more months later had a rate of rejection of 90\% in five years. Would this be a particular finding of our service\textsuperscript{18} or an intrinsic consequence of a severe infection like a persistent dysfunction of the hemato-aqueous barrier? When no other option besides corneal transplantation was left, we decided as a last resort to use voriconazole that was hitting Brazilian market at the time. Voriconazole belongs to the second generation of triazoles. It is a synthetic derivative of fluconazole with an expanded activity.\textsuperscript{19} Being quite soluble, voriconazole has good penetration into the corneal stroma, and reaches high concentrations in the vitreous and aqueous even when administered orally.\textsuperscript{6} Voriconazole concentrations achieved in the cornea are sufficient to cover a wide spectrum of fungi agents.\textsuperscript{19}

Elated with this result, we tried the same therapy in one patient with severe Fusarium corneal ulcer without vascularization, unresponsive to 5\% natamycin eye drops and oral ketoconazole. The ulcer improved very slowly with voriconazole 200 mg, PO, BID for 20 days. The treatment was suspended before cure for economic reasons. Each 200 mg tablet costs about 300 U.S. $ in our country. Eventually the lesion healed, with the subsequent use of eye drops of amphotericin B 0.25\% six times per day during another 20 days. We do not know if the latter eye drops had any effect at all. The point is: if the protracted course of this case cannot be explained by the lack of corneal vascularization since literature says the drug has enough penetration to reach high concentrations in the cornea,\textsuperscript{5,19} one has to suspect that voriconazole might have a modest effect on this type of fungus, which contradicts the expectation conveyed by the same literature that the drug is the one that has the best activity against Fusarium species.\textsuperscript{20,21} This raises a last question: at what extent should one trust data from the literature?

\section*{CONCLUSION}
Voriconazole administered orally seems to be a good alternative for treatment of \textit{Cladosporium} spp. corneal infection, particularly when the current clinical options of treatment have failed.\textsuperscript{\ldots}