**Scedosporium apiospermum** keratitis treated with voriconazole

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**Abstract**

Fungi are among the most common agents of microbial keratitis, especially in developing countries and tropical regions. Early diagnosis and appropriate antifungal treatment are critical for clinical success in fungal keratitis (FK). A 35-year-old female patient was referred to our hospital because of the diagnosis of keratitis with resistant to topical antibacterial treatment. Her visual acuity was counting fingers at one meter for the right eye. Biomicroscopic examination revealed a large, white keratitis center with peripherally extension on cornea. Fungal hyphae were observed in microscopic examination and a filamentous fungus was isolated in culture of the corneal scrapings. It was identified as *Scedosporium apiospermum* by both phenotypic and molecular methods. She was treated with topical and oral voriconazole according to susceptibility testing result. It is important to early diagnosis, determine the causative agent and perform a susceptibility testing in FK.

**Keywords:** Keratitis; *Scedosporium apiospermum*; voriconazole.
Case Report
A 35-year-old female patient admitted to an eye clinic with burning, pain, and blurred vision in her right eye 2 days later the soil-related trauma. Although topical gentamicin and acyclovir treatments were started with diagnosis of keratitis, clinical improvement was not observed and then she was referred to our hospital. In the ophthalmologic examination, her visual acuity was counting fingers at 1 m for the right eye and complete for the left eye. Biomicroscopic examination revealed fulminant edema and hyperemia in conjunctiva in addition to diffuse blurring and a large, white keratitis center with peripherally extension on cornea of the right eye (Fig. 1). The patient had not any predisposing factor such as immunosuppression or underlying disease. All medications used by the patient were stopped, and corneal scraping sampling was made for direct microscopic examination and culture to determine the etiological agent. Topical cefazolin, amikacin, and cyclopentolate were started empirically. Besides, topical amphotericin B and oral fluconazole were also added to the therapy due to the possibility of fungal infection because of the story of the trauma, appearance of the corneal lesion, lack of response to the previous antibacterial treatment, and negative microbiological test results.
Although the 5-day of antibacterial and antifungal treatment, there was no regression in the keratitis area in the follow-up and there was an increase in patient’s complaints. Therefore, repeated corneal scraping sample was taken from the deep tissue and inoculated on blood agar, chocolate agar, and Sabouraud dextrose agar, and prepared a direct microscopy slide. Polymorphonuclear leukocytes and septate fungal hyphae were observed on Gram-stained microscopic examination of the corneal scraping smear (Fig. 2). Although there was no bacterial growth on the culture plates, white cottony mold colonies began to appear on the inoculation lines on the 3rd day of incubation. Older colonies began to darken from the center to the periphery, and mature colonies were a smoky gray-brown appearance (Fig. 3). Microscopic examination of these colonies was compatible with *S. apiospermum*. The microscopic identi-
fication was confirmed by PCR amplification of the D1-D2 region of 28S rRNA gene and sequencing of the amplicons; PCR amplification of fungal genomic DNA was performed using primers and conditions as previously described; \cite{4} the resulting 414 bp sequence showed 99% identity with the \textit{S. apiospermum} ATCC 28206 ribosomal RNA gene in the NCBI GenBank database.

The antifungal susceptibility of the isolate was evaluated using E-test (AB Biodisk, Solna Sweden) method; minimal inhibitory concentration (MIC) values were 0.032 µg/mL for voriconazole, >32 µg/mL for amphotericin B, >256 µg/mL for fluconazole, and 2 µg/mL for itraconazole. According to microbiological testing results, antifungal and antibiotic treatments were stopped and voriconazole treatment was started. Following the effective surgical debridement, 1% topical voriconazole per hour and oral voriconazole 2x200 mg on the 1\textsuperscript{st} day, 2x100 mg on the next days were started. After the 21-day treatment, the patient’s signs and symptoms improved, the keratitis focus regressed and a small opacity remained on the corneal center (Fig. 4). Visual acuity improved to 5/10. Ocular side effects did not develop against the drugs.

**Discussion**

\textit{Scedosporium} species are saprophytic filamentous fungi that are common in nature, especially on soil, manure, and decaying organic materials. However, they cause a broad range of clinical manifestations, from colonization of the re-

\textbf{Fig. 3.} \textit{S. apiospermum} colonies (6\textsuperscript{th} day of incubation); Sabouraud dextrose agar and chocolate agar.

\textbf{Fig. 4.} Clinical improvement in ocular findings with voriconazole treatment.
spiratory tract, superficial infections, and allergic reactions, to severe localized or disseminated invasive infections in both immunocompetent and immunocompromised hosts. Although Scedosporium species are essentially known as the agents of trauma-related infections in healthy individuals, they can cause serious opportunistic infections in immunocompromised patients. Keratomycosis caused by Scedosporium spp generally occurs following corneal trauma in immunocompetent individuals. Treatment of invasive Scedosporium infections is challenging due to the limited susceptibility of the agent to available antifungal drugs. Scedosporium spp are frequently resistant to 5-flucytosine, amphotericin B and first generation triazoles (fluconazole and itraconazole) and have decreased sensitivity to echinocandins such as caspofungin and anidulafungin.

The efficacy of natamycin, which is widely used in the topical treatment of ocular infections, is limited due to its poor penetration into the corneal stroma. Toxicity is an important problem in the use of amphotericin B. Voriconazole is a new generation triazole antifungal drug with a broad spectrum of action, including many filamentous fungi. It has an increasing importance in the treatment of FK because of its excellent ocular penetration. In a study evaluating numerous case reports treated with voriconazole, it has been reported that voriconazole may be used safely and effectively against broad range of fungal pathogens. Besides, it was determined that voriconazole following oral administration reached therapeutic levels in the vitreous and aqueous humor, and its activity spectrum included common fungal species of ocular infections. In another study evaluating the in vitro susceptibility of keratitis isolates of S. apiospermum (n=5), voriconazole exhibited significant activity at the low MIC values (mean 0.5 µg/mL), whereas amphotericin B and natamycin generally did not show any activity.

It has been reported that oral medication of voriconazole provides more steady-state drug levels at the site of infection compared to topical treatment, and successful results were obtained in cases treated with topical voriconazole in conjunction with the systemic medication.

Ramakrishnan et al. reported that in a S. apiospermum case series consisting of 13 patients, a topical combination treatment containing an azole and a polyene antifungal was administered to all of the patients, nine patients recovered with this treatment, and seven of them were treated with a combination of natamycin and fluconazole. Although there are many reports of successful results with topical antifungal drug combinations (usually a polyene and an azole) in the treatment of keratomycosis caused by S. apiospermum, there are limited reports on the success of the antifungal treatment with the combination of a topical drug and a systemic drug or a combination of topical and systemic formulations of the same antifungal drug.

We presented a case of S. apiospermum keratitis treated successfully by a combination of topical and systemic formulations of voriconazole, while clinical improvement could not be achieved with topical amphotericin B and systemic fluconazole treatment in this paper.

Conclusion
Although S. apiospermum is a relatively rare agent of keratomycosis, it is an important fungal pathogen due to its high antifungal resistance and clinically serious illness that often require surgical treatment. Therefore, it should be considered as a potential pathogen in differential diagnosis, especially in the presence of predisposing factors, appropriate microbiological examination and antifungal susceptibility testing should be performed for accurate management of the infection. In our case, S. apiospermum was isolated from a deep tissue sample and identified by both phenotypic and molecular methods. She was treated by a combination of topical and oral formulations of voriconazole according to susceptibility testing result. Voriconazole is the preferred drug against S. apiospermum, and in the present case, a successful result was obtained with topical and oral voriconazole combination which was applied considering the antifungal susceptibility testing result. It is important to determine the causative agent and perform a susceptibility testing in cases of FK. It should not be forgotten that the combination of various antifungal agents may be required in medical treatment and surgical debridement is an important therapeutic procedure in terms of drug penetration.

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References