

Voriconazole Treatment for Two Consecutive Cases of Aspergillus Fumigatus Keratitis Without Ocular Injury

Oküler Travma Olmaksızın Görülen Ardışık İki Aspergillus Fumigatus Keratiti Olgusunda Vorikonazol Tedavisi

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ABSTRACT

A 47-year-old man and 14-year-old boy presented with a persistent redness and pain in their eyes. The diagnosis was keratitis. Aspergillus fumigatus was isolated from their corneas. Fungal keratitis occurs very rarely without trauma and shows persistency if not treated properly. The resistance to antibiotic treatment should be noticed and the diagnosis of fungal keratitis considers. Here we present two consecutive cases of Aspergillus fumigatus keratitis that developed without any trauma and their treatment. 1% voriconazole should be considered as the first-line medication in spontaneous Aspergillus fumigatus keratitis.

Key Words: Aspergillus fumigatus, keratitis, voriconazole.

ÖZ

Kırk yedi yaşında ve ondört yaşında iki erkek hasta gözlerinde inatçı kızarıklık ve ağrı şikayetleri ile başvurdu. Keratit tanısı ile tedavi başlandı. Hastaların kornealarından Aspergillus fumigatus izole edildi. Fungal keratitler çok nadiren herhangi bir korneal travma olmaksızın ortaya çıkabilir ve uygun olarak tedavi edilmezlerse devamlılık gösterirler. Antibiyotik tedavisine direnç olması dikkate alınmalı ve fungal keratit düşünülmelidir. Biz burada herhangi bir travma olmaksızın gelişmiş olan ardışık iki Aspergillus fumigatus olgusunu ve tedavilerini sunmaktayız. Vorikonazol %1 spontan olarak gelişmiş olan Aspergillus fumigatus keratitlerinde ilk tedavi seçeneği olarak düşünülmelidir.

Anahtar Kelimeler: Aspergillus fumigatus, keratit, vorikonazol.

INTRODUCTION

Aspergillus is a filamentous and ubiquitous fungi found in nature. It is known to cause opportunistic infections, especially in immunosuppressed individuals. Any organ system in the body may be involved. Ocular trauma is a predisposing factor for ocular involvement. As in other filamentous fungi, most cases of Aspergillus keratitis have a history of ocular injury, particularly with plant matter.¹⁻² Here we present successful treatment of two consecutive spontaneous (no ocular injury, no predisposing factor) Aspergillus fumigatus keratitis cases with 1% of voriconazole combined with systemic formulations as a first-line antifungal therapy.

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CASE REPORT

Case 1

A 47-year-old male was referred to our clinic with the chief complaint of pain in the right eye. One week ago, he felt foreign-body sensation in his right eye and he washed his eyes with a plenty of tap water. Then he was admitted to a local clinic with this complaint and he was referred to our clinic. From his medical history, he was known to have a diagnosis of diabetes for two years. He had experienced itching and redness in his eyes two or three times over the last year, and had been given some anti-allergic eye drops. On ocular examination, the visual acuities were 20/200 and 20/20 in right and left eyes respectively. Intraocular pressure was 7 mmHg in the right eye and 10 mmHg in left eye. Slit-lamp biomicroscopy examination of the right eye showed a 2x2 mm central white-colored corneal ulcer involving almost the full thickness of the cornea and 0.4 mm hypopyon (Figure 1). The fundus could not be evaluated in the right eye.



Figure 1: Hypopyon and conjunctival hyperemia were seen. Keratitis was located very close to the center of the cornea, involving visual axis.

The left eye was normal. On B-mode ultrasound; retinal detachment, vitreous hemorrhage or condensation were not present in either eye. He was hospitalized and the ulcers were scraped, using a Kimura spatula. Smears were obtained for 10% KOH and Gram staining was performed. Cultures were taken.

Fortified ceftazolin and fortified gentamicin hourly/alternately, fucidic acid 2x1 and ciprofloxacin 500 mg orally 2 times a day were started. The patient's examination on the third day showed that visual acuities were 20/200 and 20/20 in the right and left eye respectively. Intraocular pressure was 6 mmHg in the right and 10 mmHg in the left eye. Slit-lamp biomicroscopy revealed a 2x2 mm keratitis focus near the central corneal region and hypopyon was seen in the right eye. Conjunctival hyperemia had increased. Conjunctival hyperemia was thought to be related with gentamicin toxicity and fortified gentamicin was stopped. He was thought to have fungal keratitis, and topical fortified 0.1% voriconazole hourly was started.

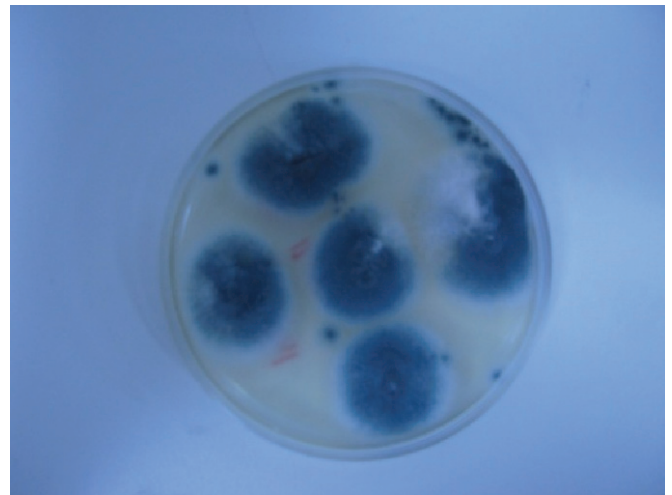


Figure 2: Sabouraud dextrose agar colony appearance of strains isolated from case 1.

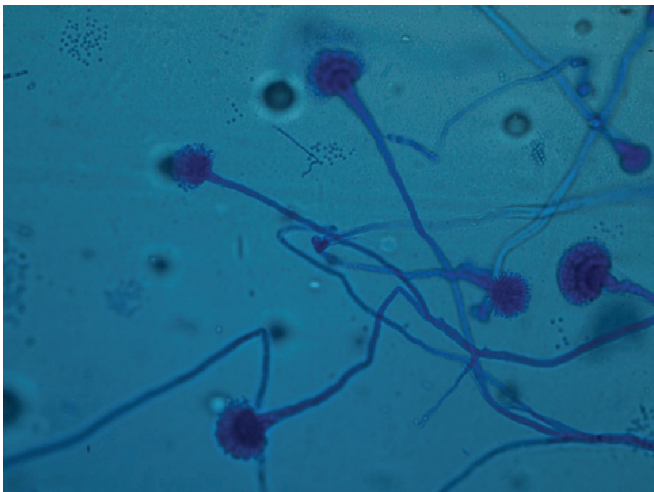


Figure 3: Lactophenol cotton blue preparation of the cel-
lophane band image of *Aspergillus fumigatus* is seen (with
 $\times 40$ magnification).

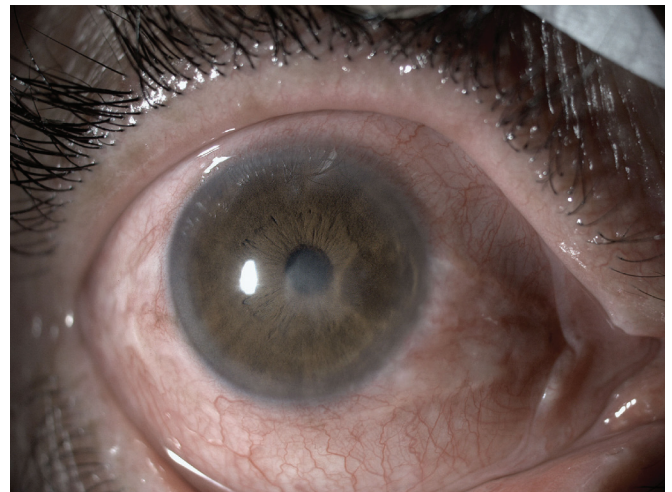


Figure 4: Hypopyon had disappeared. Conjunctival hyper-
emia was quite low. Mild corneal haze could be observed in
the cornea.

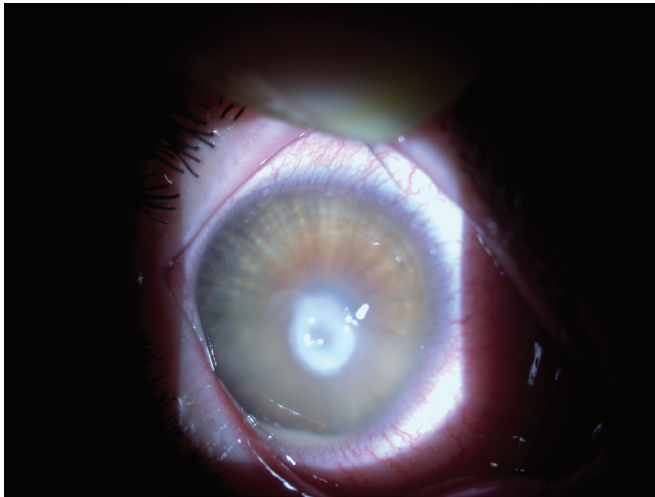


Figure 5: Keratitis was located at the center of the cornea, on the visual axis. Hypopyon and conjunctival injection were seen.

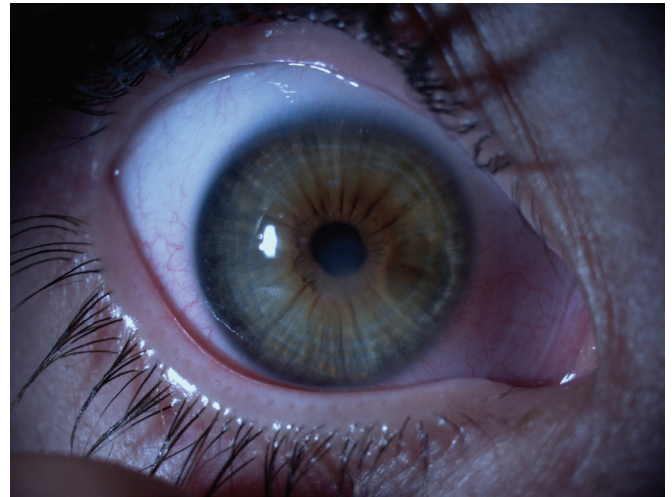


Figure 6: No hypopyon. No conjunctival hyperemia. Mild corneal haze was seen in the cornea.

On the 5th day ocular examination, there was 0.5 mm hypopyon in the anterior segment. 0.1% voriconazole treatment was replaced with the 1% dose. Seven days after the cultures were taken, *Aspergillus fumigatus* was identified and anti-fungal susceptibility tests were performed (Figure 2,3). The patient was consulted to the Infectious Diseases department. At their suggestion, the patient was started 6 mg/kg 2x1 IV voriconazole for the first day and then 4 mg/kg 2x1 as the maintenance dose. Antimycotic sensitivity tests showed sensitivity to voriconazole. The 7th day visual acuity was 20/200 in the right eye. There was still a 2x2 mm keratitis focus in the central cornea of the right eye, the conjunctiva was hyperemic and the hypopyon was 0.4 mm. The visual acuity of the right eye had increased to 20/120 and hypopyon was decreased to 0.1 millimeters on the 8th day. Examination on the 10th day showed vision had increased to 20/80 OD. The hypopyon regressed completely and the fortified cefazolin drops were decreased to 6 times a day and oral ciprofloxacin tablets were also decreased. Artificial tear drops 6 times a day were added to the treatment.

Examination on the 20th day revealed best-corrected visual acuity of 20/80. There was a mild haze on the cornea (Figure 4). Fluorometholone four times a day was added and planned to be tapered by one drop weekly. 1% voriconazole was continued hourly. Intravenous voriconazole was switched to oral voriconazole (2x 200 mg). He was discharged with these medications and given an appointment for follow-up.

Case 2

A 14-year-old boy was admitted to our clinic with a complaint of a white appearance of the left eye. He had experienced burning, stinging and pain in both eyes for 5 days. He had a history of going to a picnic with his family at the weekend.

Since that day, he had felt itching and discomfort in both eyes. His parents said there were a couple of fig trees around them and fig pollens might have gone into his eyes. He also had mental retardation. On ocular examination, the visual acuities were 20/20 and hand motions in the right and left eyes, respectively. Intraocular pressures were within normal limits OU. Slit-lamp biomicroscopy examination of the left eye showed a 2.5x2.5 mm central corneal ulcer, 0.3 mm hypopyon and conjunctival hyperemia (Figure 5). A dilated fundus examination was unremarkable on the left. The right eye was normal. He was hospitalized and cultures were taken from the cornea.

Fortified cefazolin 24x1, 1% voriconazole 24x1, and fucidic acid 2x1 were started topically; oral ciprofloxacin 500 mg 2x1 and iv sefozol 50 mg/kg/day were added. Intravenous voriconazole was also started (in the first days 2x6 mg/kg and 2x4mg/kg as maintenance therapy) on the recommendation of the Infectious Diseases department. On the 5th day, the visual acuity was 20/400 OS. The hypopyon disappeared and oral ciprofloxacin was stopped. On the 6th day, the visual acuity had increased to 20/200. Conjunctival hyperemia was improved. At the end of the 10th day, culture results were reported as *Aspergillus fumigatus*, and the medication regime was continued. Over the next 10 days, the initial corneal infiltrate became more transparent. On the 15th day, intravenous voriconazole therapy was stopped. He was then switched to 50 mg oral voriconazole twice a day and discharged. On the 18th day, his visual acuity was 20/80, and a central corneal haze was observed (Figure 6). He was started on Fluorometholone qid. On the 21st day, the visual acuity reached 20/60 OS. Fluorometholone was planned to be tapered by one drop weekly, while the fortified voriconazole 1% hourly and voriconazole tablets twice a day were continued. Follow-up was recommended for 1 month later.

DISCUSSION

Aspergillus fumigatus endophthalmitis has been reported after a retinal detachment operation and has been associated with air conditioning in the literature.⁵

Our first case was an uncontrolled diabetic male who had admitted to a local clinic due to itching and redness in his eyes that occurred twice or more in a year. His diabetes was diagnosed two years ago and he was not a compliant patient. According to his medical history, he was not using his diabetic medications. A week before he presented at our clinic, he felt foreign-body sensation and he thought his eye allergy was flaring up again. He is living in a rural village with lots of trees around.

Our second case was a mentally retarded boy. He or his family did not mention any trauma to the eyes. They had gone to a picnic nearly a week ago. He felt discomfort in his eyes after the picnic. We thought that he might be infected with airborne spores or had caused micro trauma to his eyes by itching. He had not come to our clinic earlier since his complaints were not so disturbing or possibly he could not realize a serious problem in his eyes and could not express himself well enough. After a week his eye was seriously affected from the infection and his family felt an obligation to bring him to the eye clinic.

Fungal keratitis is often difficult to treat and often needs long-term topical and systemic antifungal therapy. Amphotericin B 0.15% has been recommended as effective in fungal ulcers.⁶ Mehta et al. presented a case of *Aspergillus fumigatus* keratitis in a patient with underlying diabetes, treated with systemic voriconazole and topical 1% voriconazole when he did not respond to standard antifungal therapy.¹

Voriconazole has been shown to have a broad spectrum of activity and reported to be fungicidal against most *Aspergillus* species.⁷⁻⁸ It is only available in oral and intravenous formulations but topical and intravitreal solutions can be prepared.⁷ High intraocular penetration with both systemic and topical administrations of voriconazole have been demonstrated.⁹

Thiel et al.,¹⁰ evaluated voriconazole concentrations in the human aqueous humor and plasma after topical (1%) or combined topical and systemic (oral) administration. The voriconazole concentrations were above the MIC for most fungi. They suggest that both topical and combined therapy can be effective for fungal keratitis.

Wemuganti et al.,¹¹ reported that corneal inflammation may continue even after the elimination of the fungus. Arıkan et al.,¹² reported a very resistant endophthalmitis case caused by *Aspergillus terreus* and *Aspergillus fumigatus*.

Despite appropriate treatment, these cases may not recover.¹² There is a history of plant-injury in the majority of *Aspergillus* keratitis cases as in other filamentous fungi keratitis.¹

We presented two *Aspergillus fumigatus* keratitis cases that developed without any underlying cause. The patients were administered topical 1% voriconazole when they came to us. There was no side effect due to the voriconazole treatment. There was no history of trauma in the first case but the history of itching and redness of the eyes two or three times in recent years may suggest a slow developing fungal infection on this background.

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