

# Mixed Fungal Endophthalmitis After Cataract Surgery Due to *Aspergillus terreus* and *Aspergillus fumigatus* in an Immunocompetent Patient: Case Report

## İmmün Direnci Yerinde Bir Hastada Katarakt Cerrahisinden Sonra *Aspergillus terreus* ve *Aspergillus fumigatus* Nedeniyle Gelişen Karma Fungal Endoftalmit

Gül ARIKAN,<sup>a</sup>  
Nilüfer KOÇAK,<sup>a</sup>  
Vildan AVKAN OĞUZ,<sup>b</sup>  
Mine DOLUCA,<sup>c</sup>  
Süleyman KAYNAK<sup>a</sup>

Departments of  
<sup>a</sup>Ophthalmology,  
<sup>b</sup>Infectious Disease and Clinical Microbiology,  
<sup>c</sup>Microbiology,  
Dokuz Eylül University Faculty of Medicine,  
İzmir

Geliş Tarihi/Received: 04.03.2011  
Kabul Tarihi/Accepted: 18.09.2011

Yazışma Adresi/Correspondence:  
Gül ARIKAN  
Dokuz Eylül University Faculty of Medicine,  
Department of Ophthalmology, İzmir,  
TÜRKİYE/TURKEY  
gulozdenarikan@gmail.com

**ABSTRACT** A 55-year-old, otherwise healthy woman was referred to our clinic for pars plana vitrectomy with the diagnosis of fungal endophthalmitis due to *Aspergillus fumigatus* in her right eye. Five months earlier, she had undergone cataract surgery elsewhere. Ten days before presentation to our clinic she was hospitalized in another clinic with the diagnosis of fungal endophthalmitis and she received systemic and intravitreal voriconazole therapy. Pars plana vitrectomy could not be performed due to hazy cornea. *Aspergillus terreus* was isolated from the anterior chamber aspirate in our institution; thus mixed fungal infection due to *Aspergillus terreus* and *Aspergillus fumigatus* was considered in this case. Despite appropriate intravitreal and systemic antifungal therapy ocular condition continued to deteriorate and unfortunately, the eye was eviscerated. In resistant endophthalmitis, fungi (especially *Aspergillus* species) should be considered even in non-immunocompromised cases. In such cases, steroids must be avoided and early pars plana vitrectomy is recommended.

**Key Words:** Endophthalmitis; phacoemulsification

**ÖZET** Elli beş yaşında, daha önceden sağlıklı kadın hasta, sağ gözünde *Aspergillus fumigatus*'a bağlı fungal endoftalmit tanısı nedeniyle pars plana vitrektomi yapılmak üzere başvurdu. Beş ay önce, başka bir merkezde katarakt ameliyatı geçirmişti. Bize başvurudan on gün önce başka bir klinikte fungal endoftalmit tanısı ile yatırılmış ve sistemik ve intravitreal vorikonazol tedavisi almıştı. Bulanık kornea nedeniyle pars plana vitrektomi yapılamadı. Kurumumuzda ön kamara aspiratında *Aspergillus terreus* izole edildi; bundan dolayı vaka *Aspergillus terreus* ve *Aspergillus fumigatus*'un neden olduğu karma mantar enfeksiyonu kabul edildi. Uygun intravitreal ve sistemik antifungal tedaviye rağmen gözün durumu kötüleşmeye devam etti ve maalesef eviserasyon yapıldı. Dirençli endoftalmit nedeni olarak mantarlar (özellikle *Aspergillus* türleri) immün baskılanma olmayan olgularda dahi akılda tutulmalıdır. Bu gibi durumlarda steroid kullanımından kaçınılmalıdır ve erken pars plana vitrektomi önerilir.

**Anahtar Kelimeler:** Endoftalmit; fakoemülsifikasyon

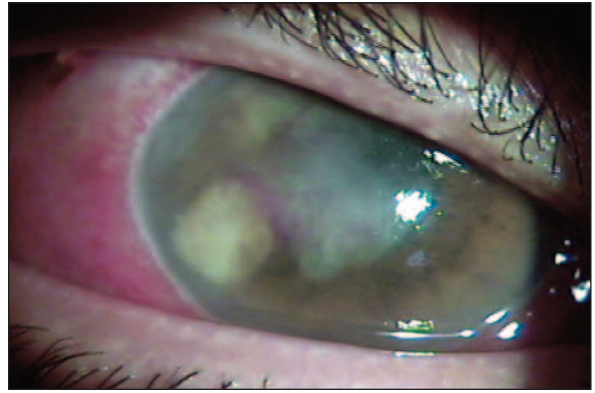
**Türkiye Klinikleri J Med Sci 2013;33(1):234-7**

**F**ungal endophthalmitis is an infrequent but potentially devastating ocular condition. It may occur endogenously both in immunocompromised patients and intravenous drug abusers by hematogenous dissemination of the fungi; exogenously after ocular surgery, trauma or due to progression of fungal keratitis.<sup>1,2</sup> *Aspergillus fumigatus*, *Aspergillus flavus* and *Candida albicans* are the most common organisms in fungal endophthalmitis.<sup>1,2</sup> More than one species of *Aspergillus* associated with endophthalmitis in the same patient is uncommon.

Herein, we presented an unusual case of delayed fungal endophthalmitis after cataract surgery due to mixed infection by *Aspergillus terreus* and *Aspergillus fumigatus*.

## CASE REPORT

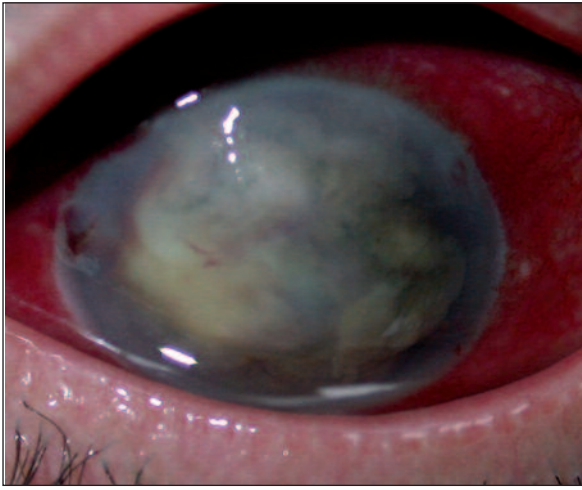
A 55-year-old, otherwise healthy woman was referred to our clinic for pars plana vitrectomy with the diagnosis of fungal endophthalmitis in her right eye. Her medical history was unremarkable except for phacoemulsification and intraocular lens implantation surgery in a private clinic five months earlier. Ten days ago she had complained of pain and decreased vision in her right eye and had been hospitalized with the diagnosis of endophthalmitis in another clinic. On her first day, she had received intravitreal vancomycin 1 mg/0.1 ml, ceftazidime 2 mg/0.1 ml and dexamethasone 0.4 mg/0.1 ml injection with a presumptive diagnosis of bacterial endophthalmitis. After 48 hours, intravitreal treatment had been continued with intravitreal vancomycin 1 mg/0.1 ml, amikacin 0.4 mg/0.1 ml and dexamethasone 0.4 mg/0.1 ml injection because there was no response to the prior treatment. On day four of hospitalization *Aspergillus fumigatus* had been isolated from the vitreous culture and she had received intravitreal voriconazole 0.1 mg/ 0.1 ml injection in addition to intravenous (IV) voriconazole. She was referred to our clinic on day 10 of follow-up due to the progression of the disease for vitreoretinal surgery. On the first examination, visual acuity was hand motion in the right eye and 10/10 in the left eye. Slit-lamp examination of the right eye revealed severe conjunctival injection and corneal edema. Anterior chamber was shallow. A marked fibrinous reaction and hypopyon were present. Infectious infiltrate was noted on the temporal iris surface and in the pupillary area (Figure 1). Posterior segment could not be visualized. The left eye was normal. She was hospitalized with a presumptive diagnosis of fungal endophthalmitis due to *Aspergillus fumigatus* and full dose of IV voriconazole treatment (6 mg/kg b.i.d. on first day, 4 mg/kg b.i.d. maintenance dose for one week) was continued. No clinical improvement was observed despite voriconazole treatment. Thus, voriconazole



**FIGURE 1:** Anterior segment of the right eye at presentation: Severe conjunctival injection, corneal edema, infectious infiltrate on the temporal iris surface and in the pupillary area are shown.

(See for colored form <http://tipbilimleri.turkiyeklinikleri.com/>)

treatment was replaced by IV liposomal amphotericin B (3 mg/kg/day) treatment in order to broaden the antifungal spectrum. Pars plana vitrectomy could not be planned due to hazy cornea. On the second day of the hospitalization, anterior chamber lavage and vitreous tap were performed and amphotericin B 5 µg/0.1 cc was injected intravitreally. Besides, intravitreal vancomycin 1 mg/0.1 ml and ceftazidime 2 mg/0.1 ml were added to the treatment regimen, due to the presumptive diagnosis of combined bacterial infection. Direct microscopy of the anterior chamber aspirate showed fungal hyphae. Culture of the anterior chamber aspirate was positive for *Aspergillus terreus*. No organism was identified by direct microscopy of vitreous tap specimen. Subsequent culture of vitreous tap was also negative. *Aspergillus terreus* is known to have innate resistance to amphotericin B.<sup>3</sup> With the suggestion of the infectious diseases specialist, systemic amphotericin B treatment was stopped and intravenous voriconazole (6 mg/kg b.i.d. loading dose for one day, 4 mg/kg b.i.d. maintenance dose) treatment was reinitiated. Despite antifungal treatment, the ocular condition continued to deteriorate, periorbital redness and swelling developed, light perception was lost (Figure 2). Four weeks after the admission, the eye was eviscerated. Vitreous material obtained at evisceration was sent to the mycology and bacteriology laboratories for culture. *Aspergillus terreus* was isolated from both specimens. After evisceration, preseptal cellulitis



**FIGURE 2:** Severe inflammatory reaction in the anterior chamber even after intravitreal injections just before the surgery.

(See for colored form <http://tipbilimleri.turkiyeklinikleri.com/>)

developed. Intravenous antifungal treatment with voriconazole in addition to IV clindamycin and ciprofloxacin were initiated. Periorbital inflammation subsided gradually. Eight days after evisceration, IV clindamycin and ciprofloxacin treatment and ten days after evisceration IV voriconazole treatment were stopped. Patient was discharged from the hospital on voriconazole 600 mg orally two times daily for six weeks. One year after surgery, the patient had no complaints.

## DISCUSSION

Combined endophthalmitis with more than one *Aspergillus* species is rare.<sup>4,5</sup> The first *Aspergillus terreus* endophthalmitis was reported as an endogenous fungal endophthalmitis by Kalina et al.<sup>6</sup> in 1991 in a patient with chronic lymphocytic leukemia. The first postsurgical *Aspergillus terreus* endophthalmitis was reported by Das et al. in 1993.<sup>5</sup> Herein, we described a case with postoperative mixed fungal endophthalmitis due to *Aspergillus terreus* and *Aspergillus fumigatus*. Our literature search revealed no cases of postoperative endophthalmitis caused by combined *Aspergillus* species. To our knowledge, this is the first case of postoperative endophthalmitis due to combined infection with *Aspergillus fumigatus* and *Aspergillus terreus*. An endogenous endophthalmitis case due to coinfection with *Aspergillus fumigatus* and *Paecilomy-*

*ces lilacinus* was published earlier.<sup>7</sup> *Aspergillus fumigatus* had been isolated in another clinic before the referral of the patient to our clinic. Before fungal identification, the patient had received intravitreal antibiotic with steroid twice, two days apart due to the likelihood of bacterial etiology. After the identification of fungus, she had received IV voriconazole and intravitreal voriconazole. In the treatment of endophthalmitis the second intravitreal injection is recommended to be given 48-72 hours after the first injection to avoid retinal toxicity.<sup>8</sup> It is also not preferred to give steroids intravitreally in the second injection. In this case, before antifungal treatment was started, steroid was given intravitreally. This may be a contributing factor for worsening of the clinical condition despite appropriate antifungal treatment. Although we considered mixed fungal infection and bacterial cultures yielded no pathogen, bacteria that could not be isolated might have contributed to the devastating result. When the patient presented to our clinic, vitreous culture was positive for *Aspergillus fumigatus* and the eye had worsened despite intravitreal and systemic voriconazole treatment. We initiated systemic liposomal amphotericin B due to the likelihood of infection with another fungal organism. However, after the isolation of *Aspergillus terreus* from the anterior chamber aspirate, mixed fungal endophthalmitis due to coinfection with *Aspergillus terreus* and *Aspergillus fumigatus* was considered. The isolation of a second *Aspergillus* species was unexpected under antifungal treatment. However, deterioration of the clinical condition and isolation of a second *Aspergillus* species suggest mixed fungal infection in this patient. On the other hand, it should be noted that the agents were not isolated from the same sample in the same laboratory and it was not possible to check the correctness of the previous species identification. Since *Aspergillus terreus* is known to have innate resistance to amphotericin B, amphotericin B treatment was stopped and intravenous voriconazole treatment was reinitiated. Although the treatment of choice in such cases is pars plana vitrectomy, it was not possible due to hazy cornea. Unfortunately, the eye was eviscerated. Although there is controversy over enucleation versus evisceration in endoph-

thlinitis, evisceration is mostly preferred.<sup>9,10</sup> In enucleation transaction of the optic nerve may lead to meningeal spread of the infection. Furthermore, orbital inflammation may ensue after enucleation. In evisceration, evacuation of the infective material easily without touching the orbital tissue is possible and retrograde spread of the infection is unlikely. Thus, in endophthalmitis even with orbital signs evisceration should be the treatment of choice.

Voriconazole is a second-generation triazole antifungal agent.<sup>11</sup> It has a broad-spectrum potency against both yeasts and molds and in some studies it is more active than amphotericin B against filamentous fungi such as *Aspergillus* species.<sup>12,13</sup> It is currently the first choice antifungal agent for invasive aspergillosis.<sup>14</sup> Reports show that high aqueous and vitreous levels are achieved after the oral administration of voriconazole.<sup>15</sup> In *Aspergillus terreus* infections voriconazole can also be chosen as first-line antifungal therapy for fungal endophthalmitis. However, response to voriconazole therapy may vary.<sup>16</sup>

The case presented here is noteworthy in three ways. First, she was not an immunocompromised patient and despite an efficient antifungal treat-

ment for both *Aspergillus fumigatus* and *Aspergillus terreus*, no clinical improvement was achieved. At presentation, the patient was presumed to have bacterial endophthalmitis and intravitreal steroid injections were made. Poor outcome of this case might be partially attributed to those initial steroid injections. Second, after evisceration orbital infection persisted for a long time. Thus, aggressive and accurate treatment at an early stage is essential in such patients. Otherwise orbital as well as systemic spread of the infection is likely. Finally, *Aspergillus terreus* is a rare cause of endophthalmitis and has innate resistance to commonly used antifungal agent amphotericin B and it may cause devastating consequences like in our case. In the probability of fungal infections, steroids must be avoided and early surgical interventions should be made to save those eyes.

In the light of this case report, systemic and intravitreal voriconazole treatment is recommended in the management of such patients. However, avoiding steroids, performing early pars plana vitrectomy in clear corneal period and intravitreal injection of appropriate antifungal agents should be considered for saving the globe and visual acuity.

## REFERENCES

1. Benz MS, Scott IU, Flynn HW Jr, Unonius N, Miller D. Endophthalmitis isolates and antibiotic sensitivities: a 6-year review of culture-proven cases. *Am J Ophthalmol* 2004;137(1):38-42.
2. Chakrabarti A, Shivaprakash MR, Singh R, Tarai B, George VK, Fomda BA, et al. Fungal endophthalmitis: fourteen years' experience from a center in India. *Retina* 2008;28(10):1400-7.
3. Sutton DA, Sanche SE, Revankar SG, Fothergill AW, Rinaldi MG. In vitro amphotericin B resistance in clinical isolates of *Aspergillus terreus*, with a head-to-head comparison to voriconazole. *J Clin Microbiol* 1999;37(7):2343-5.
4. Bradley JC, George JG, Sarria JC, Kimbrough RC, Mitchell KT. *Aspergillus terreus* endophthalmitis. *Scand J Infect Dis* 2005;37(6-7):529-31.
5. Das T, Vyas P, Sharma S. *Aspergillus terreus* postoperative endophthalmitis. *Br J Ophthalmol* 1993;77(6):386-7.
6. Kalina PH, Campbell RJ. *Aspergillus terreus* endophthalmitis in a patient with chronic lymphocytic leukemia. *Arch Ophthalmol* 1991;109(1):102-3.
7. Okhravi N, Dart JK, Towler HM, Lightman S. *Paecilomyces lilacinus* endophthalmitis with secondary keratitis: a case report and literature review. *Arch Ophthalmol* 1997;115(10):1320-4.
8. Bohigian GM, Valluri S. Endophthalmitis. *Handbook of Ocular Infections, Inflammation, and External Disease*. 1<sup>st</sup> ed. Thorofare, NJ: Slack Inc; 2000. p.73-99.
9. Migliori ME. Enucleation versus evisceration. *Curr Opin Ophthalmol* 2002;13(5):298-302.
10. Rishi P, Rishi E, Nandi K, Khan B. Endophthalmitis in eyes presenting with orbital signs: a case-control study. *Retina* 2010;30(3):491-4.
11. Sen P, Gopal L, Sen PR. Intravitreal voriconazole for drug-resistant fungal endophthalmitis: case series. *Retina* 2006;26(8):935-9.
12. Kramer M, Kramer MR, Blau H, Bishara J, Axer-Siegel R, Weinberger D. Intravitreal voriconazole for the treatment of endogenous *Aspergillus* endophthalmitis. *Ophthalmology* 2006;113(7):1184-6.
13. Marco F, Pfaller MA, Messer SA, Jones RN. Antifungal activity of a new triazole, voriconazole (UK-109,496), compared with three other antifungal agents tested against clinical isolates of filamentous fungi. *Med Mycol* 1998;36(6):433-6.
14. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008;46(3):327-60.
15. Hariprasad SM, Mieler WF, Holz ER, Gao H, Kim JE, Chi J, et al. Determination of vitreous, aqueous, and plasma concentration of orally administered voriconazole in humans. *Arch Ophthalmol* 2004;122(1):42-7.
16. Smith J, Safdar N, Knasinski V, Simmons W, Bhavnani SM, Ambrose PG, et al. Voriconazole therapeutic drug monitoring. *Antimicrob Agents Chemother* 2006;50(4):1570-2.