

A Case of Fungal Keratitis Due to *Cladosporium anthropophilum* and *Cladosporium cf. subuliforme* After Corneal Transplantation

Kornea Nakli Sonrası *Cladosporium anthropophilum* ve *Cladosporium cf. subuliforme*'ye Bağlı Fungal Keratit Olgusu

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ABSTRACT A 70-year-old male patient had previously undergone trabeculectomy with mitomycin-C in the left eye because of high left intraocular pressure. The eye was needled with 5 fluorouracil 2 weeks after the operation. Seven days after the needling procedure, the patient complained of pain, redness, stinging, and decreased vision in the left eye. Abiomicoscopic examination was performed. The corneoscleral infiltration area, including the bleb area, was detected at the 12 clock positions. During follow-up, the patient underwent therapeutic penetrating keratoplasty because of the progression of corneal infection at the infiltration site. Conjunctival swabs and corneal samples taken from the patients were examined in mycology. *Cladosporium cf. subuliforme* and *Cladosporium anthropophilum* were named using molecular methods. The patient was followed up by starting treatment with moxifloxacin, fortified voriconazole every hour, and cyclopentolate. The patient, whose complaints regressed, was discharged with oral voriconazole. At day 30 after penetrating keratoplasty, showed graft rejection.

Keywords: Fungal keratitis; penetrating keratoplasty; *Cladosporium pseudensiforme*; *Cladosporium cf. subuliforme*

ÖZET Yetmiş yaşında erkek hasta daha önce sol göz içi basıncının yüksek olması nedeniyle sol gözünden mitomisin-C ile trabekülektomi geçirmişti. Ameliyattan 2 hafta sonra göze 5-fluorourasil ile iğneleme yapıldı. Bir hafta sonra sol gözde ağrı, kızarıklık, yabancı cisim hissi ve görmeye azalma şikâyeti ile kliniğimize başvurdu. Biyomikroskopik inceleme yapıldı. Bleb alanı da dâhil olmak üzere korneoskleral infiltrasyon alanı 12 saat konumunda tespit edildi. Takip sırasında, infiltrasyon bölgesinde kornea enfeksiyonunun ilerlemesi nedeniyle hastaya terapötik penetran keratoplasti uygulandı. Hastalardan alınan konjonktival sürüntüler ve kornea örnekleri mikolojide incelendi. *Cladosporium cf. subuliforme* ve *Cladosporium anthropophilum* moleküler yöntemler kullanılarak adlandırıldı. Hasta moksisfloksasin, saat başı güçlendirilmiş vorikonazol ve siklopentolat tedavisi başlanarak takibe alındı. Şikâyetleri gerileyen hasta oral vorikonazol ile taburcu edildi. Penetran keratoplastiden sonraki 30. günde greft reddi görüldü.

Anahtar Kelimeler: Fungal keratit; penetran keratoplasti; *Cladosporium pseudensiforme*; *Cladosporium cf. subuliforme*

Corneal transplantation is an important treatment method for various corneal disorders.¹ It is the most widely used clinical transplantation method.² Fungal infections of the *Candida*, *Fusarium*, and *Aspergillus* spp. are the frequently isolated organisms in fungal keratitis.³

Candida species, especially *Candida albicans*, are responsible for the majority of reported cases of post-keratoplasty fungal keratitis.⁴ *Cladosporium* spp. usually cause allergic rhinitis or superficial lesions.⁵ It is also an opportunistic pathogen in humans.⁶

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Cladosporium spp. are considered the most heterogeneous genus of dematiaceous hyphomycetes.⁷ Three species (*Cladosporium cladosporioides*, *Cladosporium pseudocladosporioides*, and *Cladosporium subuliforme*) belonging to the *C. cladosporioides* complex with leaf spot symptoms on walnut (*Carya illinoensis*) and cultivated plants of *C. subuliforme* (pepper-*Capsicum annuum*) have been associated with the appearance of many yellow-spotted leaves.^{8,9} *Cladosporium anthropophilum*, another species in the *C. cladosporioides* complex, causes fruit rot symptoms in raspberry.¹⁰ It has been seen in the literature that *Cladosporium* related species have been identified in corneal samples taken using cadaver as a donor. Cadaveric *Cladosporium* spp. has also been reported.¹¹ In this article, we present a case of fungal keratitis after postkeroplasty caused by *C. cf. subuliforme* and *C. anthropophilum*, which are generally accepted as plant pathogens.

CASE REPORT

A 70-year-old male patient underwent trabeculectomy on 27.02.2019 due to high left intraocular pressure (Figure 1). The left eye was needled with 5 fluorouracil (250 mg/5 mL) 2 weeks after the operation. Seven days after the needling procedure, the patient complained of pain, redness, stinging, and decreased vision in the left eye. The patient's left visual acuity was at the level of counting fingers at 1 m. The patient was followed up with fortified cefazole (50 mg/mL)+gentamicin (14 mg/mL) alternately every hour, and fortified voriconazole (10 mg/mL) and fortified fluconazole (2 mg/mL) every hour alternately. The patient underwent therapeutic penetrating keratoplasty on 29.05.2019 due to the progression of the corneal infection at the infiltration site during the follow-up of the patient (Figure 2). The patient was discharged by starting moxifloxacin (5 mg/mL) 4×1 drops, fortified voriconazole (10 mg/mL) 8×1, dexamethasone (5 mg/mL) 4×1 drops, cyclosporine (0.5 mg/mL) 2×1, cyclopentolate (0.05 g/mL, 1%) 3×1 drops. On ophthalmic examination of the patient, who complained of pain, blurred vision, and redness in the left eye four months later, it was determined that his left vision was at the level of hand movement, a large stromal infiltration area was ob-

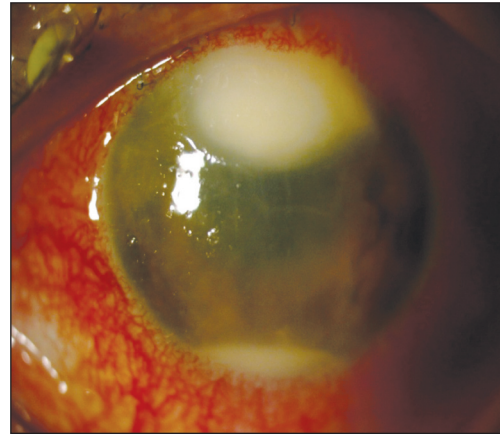


FIGURE 1: Corneal abscess and hypopyon due to *Cladosporium* spp.

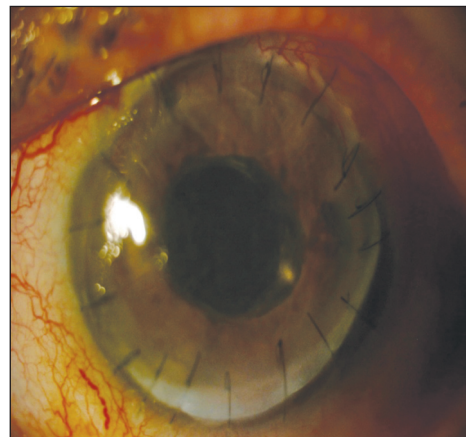


FIGURE 2: Postoperative image after penetrating keratoplasty.

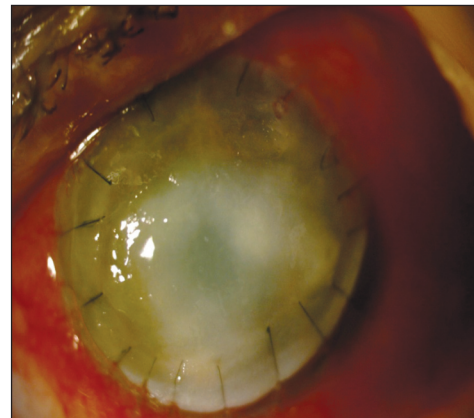


FIGURE 3: Corneal infiltration and recurrence of the corneal infection after penetrating keratoplasty.

served in the center, and a corneal scraping sample was taken. The patient was diagnosed with fungal keratitis due to mold growth in the scraped sample (Figure 3). The conjunctival swab sample taken from

the patient was inoculated on Sabouraud dextrose agar and brain heart infusion agar at 25 °C and 35 °C, respectively, and incubated on brain heart infusion agar at 37 °C. On the fifth day, two different types of growth occurred at medium intensity in each petri dish. On the fifth day, colonies developed. The morphological characteristics of the two different types of colonies (mycelial growth, sporulation, width, and length of conidia and ramoconidia) were evaluated and used for identification (Figure 4, Figure 5).¹² *C. cf. subuliforme* and *C. anthropophilum* were identified using molecular methods along with their macroscopic and microscopic properties. Previously, gene regions targeted for species identification were amplified using ITS1-ITS4 primers as universal primers in a polymerase chain reaction study. Sanger sequencing was used for sequence analysis. Species



FIGURE 4: *Cladosporium cf. subuliforme*.



FIGURE 5: *Cladosporium anthropophilum*.

identification was confirmed by performing phylogenetic data analysis of the DNA base using the obtained sequence sequences. The nucleotide sequences obtained in this study were submitted to the National Center for Biotechnology Information registration service under the accession numbers SUB10353490 seq1 OK070775: *C. anthropophilum*, SUB10353490 seq2 OK070776: *C. cf. subuliforme*.

The patient was followed up by starting treatment with moxifloxacin (5 mg/mL) 4×1 drops, fortified voriconazole (1%) every hour, and cyclopentolate (0.05 g/mL, 1%) 3×1. Intrastromal and intracameral voriconazole (50 mg/0.1 mL) was administered 2 times at 48 hour intervals. In addition, oral voriconazole (50 mg) 2×1 tablet was started. The patient, whose complaints regressed, was discharged with oral voriconazole (50 mg) 2×1, fortified voriconazole (10 mg/mL) 8×1 drops, cyclopentolate (0.05 g/mL) 4×1 drops and moxifloxacin (5 mg/mL) 4×1 drops. At day 30 after penetrating keratoplasty, showed graft rejection.

Written informed consent was obtained from the patient for publication of his case particulars and for images.

DISCUSSION

Candida species are the main cause of fungal infections following corneal transplantation.⁴ In a study by Keyhani et al. in 2005, three patients developed endophthalmitis and one patient developed fungal keratitis after corneal transplantation from 2,466 donors. All cultivated fungi were *Candida* species. The incidence of fungal infections after penetrating keratoplasty has been reported to be as low as 0.16% (4/2,466).¹³ In a 10-year study by Rosa et al., fungal keratitis was reported in 125 patients. In this study, fungal keratitis was detected in five patients who used contact lenses and in one patient who used contact lenses for treatment. *Fusarium oxysporum* was the most commonly detected *Fusarium* spp. (62%), whereas *Candida parapsilosis*, *Aspergillus terreus*, *Candida tropicalis*, and *Trichosporon beigelii* were isolated as other agents. Penetrating keratoplasty was performed in 34 patients (27%). Recurrence of fungal keratitis was reported after penetrating keratoplasty

in six patients. Trauma was the most common associated risk factor (44%) for fungal keratitis.¹⁴ A fungal investigation of the corneal tissue was conducted in 47 cadavers by Dixon et al. In this study, 11 *Cladosporium* spp., nine *Penicillium* spp., six *Rhodotorula* spp., four *C. parapsilosis*, two *Exophiala jeanselmei*, and *Wangiella dermatitidis* were isolated from corneal tissue samples.¹¹ The corneal tissue of the cadaver presented here was taken and transplanted to the patient for penetrating keratoplasty in the patient who applied to the Ophthalmology Department, Trakya University of Medicine. After the operation, corneal infiltration was detected in the left eye, and *C. subuliforme* and *C. cf. anthropophilum* were isolated from the sample culture. Until recently, the capacity of plant pathogenic bacteria and fungi to cause diseases in humans and animals has been considered unimportant. Many species belonging to the genus *Cladosporium* have been isolated from infected human samples and have been demonstrated molecularly.¹⁵ Walker et al. showed for the first time that the *C. cladosporioides* complex (*C. cladosporioides*, *C. pseudocladosporioides*, and *C. subuliforme*) is a pathogen that causes leaf spot on pecan (*C. illinoensis*) in Brazil in 2018.⁸ The Taylor & Francis online, Google Scholar, Web of Science, Scopus, and PubMed databases could not find records of this species as an eye infection agent. The keratitis case presented here is thought to be the first report in which *C. cf. subuliforme* and *C. anthropophilum*, which have not been reported in humans until now, were isolated as fungal keratitis agents after penetrating keratoplasty.

The American Eye Bank Association has initiated studies to avoid the negative effects of fungal in-

fections after keratoplasty. These studies identified several risk factors related to transplanted donor tissues that could lead to higher rates of postkeratoplasty fungal infections.⁴ The fact that being taken from a cadaver was one of the possible sources of infection in our case can be considered a risk factor. As a result, it may be possible that the isolated *Cladosporium* pathogens and donor tissue used for keratoplasty carry a risk of contamination in the hospital environment. Saprophytic fungal agents may also cause infections in patients, especially in cases of treatment-resistant keratitis.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Melek Tikveşli, Şaban Gürcan, Hande Güçlü; **Design:** Melek Tikveşli; **Control/Supervision:** Melek Tikveşli, Şaban Gürcan, Hande Güçlü; **Data Collection and/or Processing:** Melek Tikveşli, Şaban Gürcan, Berrak Çakmakçı; **Analysis and/or Interpretation:** Melek Tikveşli, Şaban Gürcan, Hande Güçlü; **Literature Review:** Melek Tikveşli, Berrak Çakmakçı; **Writing the Article:** Melek Tikveşli, Şaban Gürcan, Hande Güçlü, Berrak Çakmakçı; **Critical Review:** Şaban Gürcan; **References and Fundings:** Melek Tikveşli, Şaban Gürcan; **Materials:** Berrak Çakmakçı.

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