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Case report

Late-onset fungal interface keratitis following endothelial keratoplasty with positive donor fungal culture

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ABSTRACT

Purpose: To describe late-onset fungal keratitis after Descemet's stripping endothelial keratoplasty (DSEK) with positive fungal culture of the donor corneal rim.

Observations: A case report of a patient undergoing DSEK is described whereby the donor corneal rim culture grew fungus. No infection was initially noted, but the patient developed fungal keratitis 1 year after the original DSEK procedure, despite prophylactic treatment at the time of the positive donor culture. The patient responded to antifungal therapy, but fungal keratitis recurred following completion of a 1-year course of antifungal treatment. The patient eventually underwent full thickness keratoplasty.

Conclusions and importance: A positive fungal culture of the donor rim tissue at the time of endothelial keratoplasty is a risk factor for fungal keratitis. Even with prophylactic antifungal treatment, fungal keratitis may eventually develop as late as 1 year after the initial endothelial keratoplasty procedure. Treatment may need to be aggressive, but keratitis may recur despite resolution with antifungal treatment.

1. Introduction

Lamellar keratoplasty has become a standard technique to replace diseased host corneal tissue,[1] although penetrating keratoplasty may still be preferred by some.[2] Descemet's stripping automated endothelial keratoplasty (DSAEK or DSEK) remains the primary endothelial keratoplasty (EK) procedure in the United States[3]; Descemet's membrane endothelial keratoplasty (DMEK) may offer additional advantages in visual recovery and lower rejection rate. EK procedures involve creating an interface between the host and donor cornea; that interface may develop complications that include infectious keratitis.

Fungal contamination may not be detected before transplantation, and if contamination occurs, it can be challenging to manage and control. Fungal interface keratitis has been reported after both deep anterior lamellar keratoplasty and DSAEK.[4,5] *Candida* interface keratitis and endophthalmitis have been reported after DMEK,[6] as has fungal interface keratitis.[7]

There is no standard for preparation of the donor material by an eye bank — some use antifungal agents in their donor storage medium, but the majority do not. It is common, however, for corneal surgeons to culture the discarded donor rim to ensure there are no fungal infections. Because of the low incidence of fungal interface keratitis after EK procedures, there are no set guidelines for treatment. We report a case of late-onset fungal keratitis 1 year after DSEK, after a positive donor rim fungal culture and subsequent prophylactic treatment.

1.1. Case report

A 73-year-old female underwent uncomplicated DSEK for Fuchs' dystrophy. The donor rim was sent for culture and grew *Candida*. The patient showed no signs of infection, but was treated empirically with oral fluconazole 200 mg twice daily for 3 months. Her graft remained clear, and her vision corrected to 20/40, but was limited by her macular degeneration. Her prednisolone acetate drops were gradually tapered down to once daily over the course of several months.

At her 1-year visit, she was still using prednisolone acetate once daily. Her visual acuity was still 20/40, and she was asymptomatic. Her eye was white and quiet, but she was found to have a white opacity in

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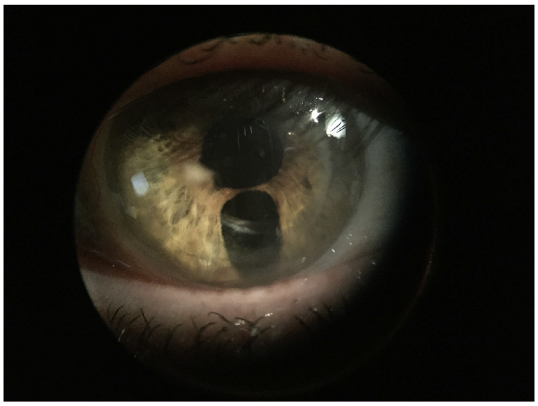

Fig. 1. Infiltrate in graft interface adjacent to pupil margin.

the interface of the graft and host, inferior temporal to the visual axis (Fig. 1). The epithelium was intact, and there were no cells in the anterior chamber. Following the occurrence of this infiltrate, we planned for a venting incision and injection with a planned continuous follow-up of 1 year.

Because of the potential fungal exposure resulting from the positive donor rim culture, the patient was started on oral fluconazole 200 mg twice daily and gatifloxacin drops four times daily. The next day, she was brought to the operating room. A venting incision was placed over the infiltrate. A needle was inserted into the incision to obtain material for culture. Amphotericin was then injected into the corneal stroma. The prednisolone acetate was discontinued. Amphotericin drops were started four times daily and gatifloxacin drops were continued four times daily. Over the next few days, the eye became more inflamed and the patient developed pain. A significant anterior chamber reaction began to develop, and the prednisolone acetate was restarted twice daily. The eye eventually quieted with the addition of the steroid drops.

The topical amphotericin drops were continued for 3 months. At the 3-month visit, her vision returned to 20/40 after having decreased to 20/80, and the eye remained quiet. While we could have re-injected, the patient seemed to resolve. The patient remained asymptomatic, and the intrastromal opacity remained. Oral fluconazole 200 mg four times daily was continued for 1 year. At the next follow-up visit, it appeared that the opacity was a scar and not an active infection. Following the discontinuation of the fluconazole, the patient returned with redness, corneal edema, and photophobia. A pocket of debris was visualized in the corneal optical coherence tomography image (Fig. 2), which was diagnosed as an active fungal keratitis. Due to the risk of seeding the fungal elements into the eye with a repeat DSEK, a full thickness penetrating keratoplasty was performed.

The patient was treated again with fluconazole 200 mg twice daily, amphotericin drops four times daily, gatifloxacin drops four times daily, and prednisolone acetate drops four times daily. The cornea was sent for culture and grew *Candida famata*, which was also detected on pathology. The patient's new corneal graft remains clear. After 20 months, her best-corrected visual acuity was 20/40 with spectacles and 20/25 with a gas permeable contact lens.

2. Discussion

Fungal infection following both penetrating and endothelial keratoplasty is a rare complication, reported in less than 1% of procedures.[8] However, the lamellar interface that results after endothelial keratoplasty creates a protected space that allows fungi to proliferate and produce early- or late-onset clinical infection. Fungal keratitis following lamellar keratoplasty is rarely reported.[8–15]

Risk factors for fungal keratitis following keratoplasty include contaminated donor tissue, topical steroid use, loose sutures, and persistent epithelial defects.[9] A recent literature review[2] of 24 fungal infections after DSEK identified grafts obtained from donors with a history of cardiac disease and alcohol abuse as higher risk for this complication.[16,17] When fungal interface keratitis occurs after DMEK, early and aggressive treatment is recommended, including graft exchange.[7]

The frequency of fungal culture-positive donor rims has been reported to be up to 12%.[8] Although positive corneoscleral rim cultures are generally thought to be a poor predictor of clinical infection, in the case of positive cultures for *Candida*, up to 14% of cases with positive rim cultures can develop clinical infection.[8] Accordingly, some practitioners have adopted the practice of prophylactic treatment topical and/or systemic antifungals in the case of *Candida*-positive donor rim cultures.[10] In the United States, only 29% of corneas transplanted undergo donor rim cultures.[18]

In North America, several methods can reduce the risk of contamination of donor tissue, including the use of sterile technique during tissue harvest, cold storage at 4 °C, and the addition of antibiotics (usually streptomycin and gentamicin) to the storage medium.[8] Outside the U.S., eye banks typically use organ culture at 34 °C.[19]

Although antifungals are not routinely incorporated in storage media in the United States, amphotericin B has been commonly added to storage media in Europe for more than a decade.[8] Ritterband et al.[11] compared rates of donor fungal culture positivity from tissue stored in standard Optisol-GS (Bausch + Lomb, Bridgewater, NJ, USA) with those stored in Optisol-GS fortified with voriconazole. In that study, none of the corneal rims stored in the voriconazole-fortified medium had positive fungal cultures, compared with 1.3% of those stored in conventional Optisol-GS. The voriconazole maintained its antifungal efficacy for 6–7 days.

In the first report of fungal keratitis following endothelial keratoplasty in 2009, clinical infection developed relatively rapidly, approximately 1 week following surgery.[9] Infection presenting as late as 3 months following surgery has also been reported.[12] To our knowledge, this is the first report of *Candida* keratitis presenting as late as 1 year following surgery.

In this case, the donor rim culture revealed *Candida*, and empiric prophylactic therapy with systemic antifungal medication was employed. Even though therapy was continued for 3 months, late-onset infection still occurred, with clinical infection first presenting 1 year postoperatively, 9 months after discontinuing prophylactic therapy.

Notably, at that time the presentation consisted of a quiet eye with a previously undetected interface opacity, presumed to be *Candida*. This case demonstrates both the indolent nature of *Candida* infection and how well the lamellar interface can isolate and sequester organisms. Topical and systemic therapy in these cases tends to be less effective due to poor penetration into the deep stroma and these treatments generally do not result in a clinical cure.[9–15]

Consequently, therapeutic approaches to lamellar infection of this type classically have included full thickness keratoplasty or removal of the donor lenticule. In our case, because the opacity appeared to be confined to the interface without significant infiltration of the donor lenticule or host, we were concerned that removal of the lenticule could seed the anterior chamber with infection. Tu and Hou described a technique of intrastromal injection of antifungal with secondary infusion of the lamellar interface that was successful in eradicating late-onset fungal keratitis in two cases, although repeated injections were required.[13]

Although intrastromal injection of antifungal agents can deliver higher concentrations of drug to the deep stroma, in endothelial keratoplasty, the bolus of medication from the injection itself could potentially dissect the donor from the host, seeding the anterior chamber with infection. In the cases reported by Tu and Hou, both patients presented 3 months or more following surgery, which allowed for peripheral graft-host scar formation to sequester the fluid accumulation to within the margins of the graft.[13] Tu and Majmudar also reported a

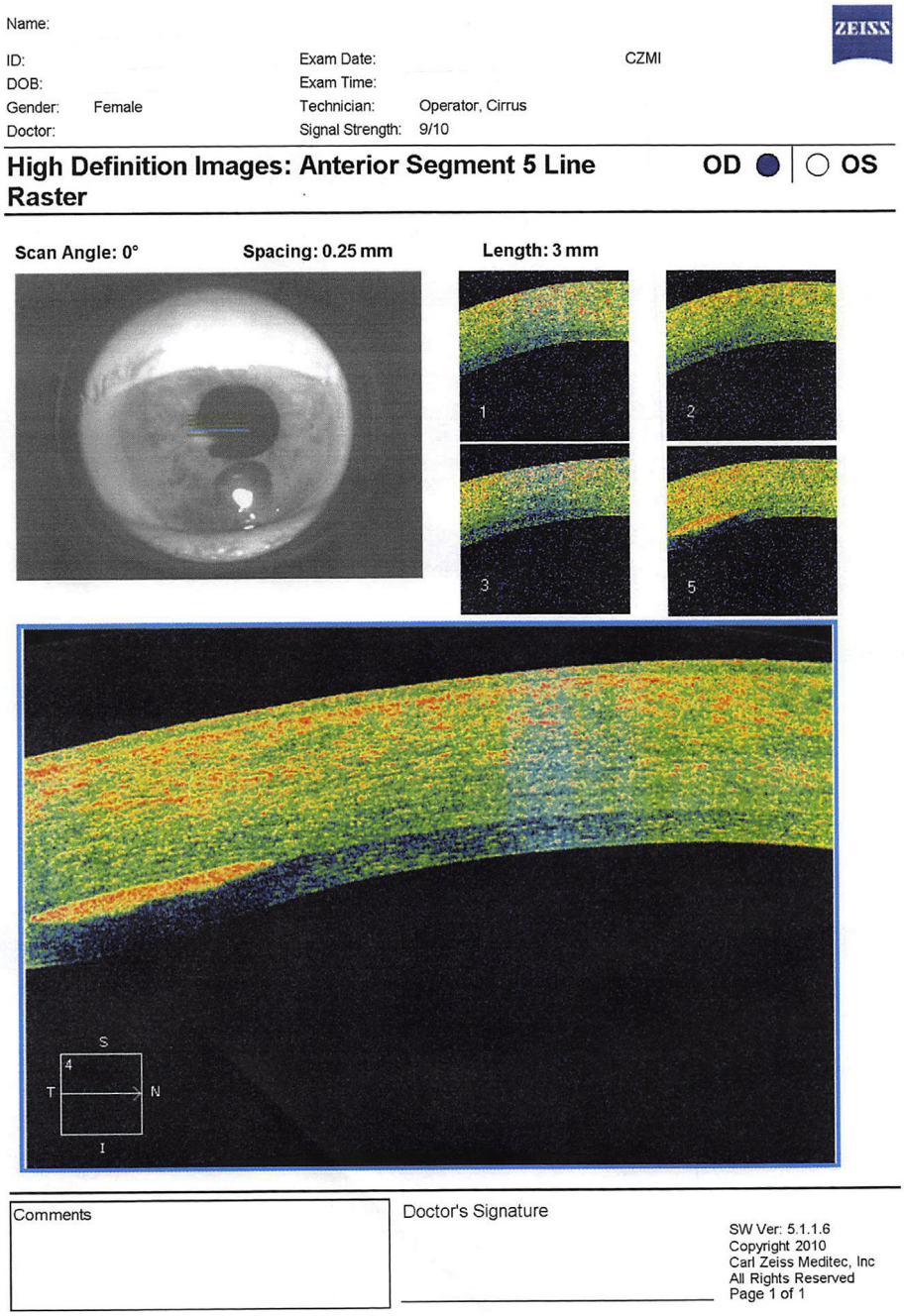

Fig. 2. OCT image of cornea demonstrating interface infiltrate.

case of *Candida glabrata* interface keratitis with onset 1 month following uncomplicated DMEK. Although donor rim cultures had been positive 2 weeks prior, no prophylactic treatment was initiated. Rapid and complete resolution of the infiltrate was achieved within 48 hours with oral fluconazole and a single intrastromal injection of voriconazole, thereby avoiding a regraft.[20]

Augustin et al. analyzed 3950 eyes that underwent DMEK and found six cases of fungal keratitis (0.15%) from *Candida*.[7] Four eyes developed fungal keratitis 3–5 days postoperatively and two eyes 16–42 days after surgery. All patients were treated with topical and systemic antifungal agents. Graft removal was performed in three of the four patients who presented early, and the later infections were resolved with graft exchange. They concluded that graft exchanges don't appear to be needed for late-onsite infections.

In our case report, a similar approach was attempted through a vent incision, without success. It is possible that the medication was able to leak out through the vent incision following injection (thus providing inadequate exposure) or that several injections over time would have been required. The fact that the eye quieted and the interface opacity remained unchanged for an entire year following the injection suggests at least partial efficacy, and underscores, once again, both the indolent nature of *Candida* infection and the protected nature of the interlamellar space. It is unknown if treating just the fungal infection earlier would have resulted in a different visual outcome. Similarly, we do not know if the patient would have avoided a penetrating keratoplasty if we had opted to re-inject rather than observe, but the length of time for the eye to remain quiet led us to believe the singular injection had been successful.

This case raises several issues. First, it is no longer uniformly routine to culture donor media or corneoscleral rims during keratoplasty.

Although the correlation between positive cultures and clinical infection are low for bacterial infection, the risk of clinical infection following a fungal-positive donor culture are 247 times greater.[12] Our case suggests continued surveillance with intraoperative rim cultures is recommended. Second, the addition antifungal medication to the storage medium appears beneficial in reducing the rates of donor culture positivity. It has also been shown to be efficacious in the Optisol-GS cold storage systems used in North America.[11]

In the case of a positive fungal culture from donor material, clearly close monitoring is warranted for at least 1 year as this late-onset case demonstrates. However, should we empirically start antifungal therapy before clinical infection becomes apparent? Topical medications may not provide adequate penetration.[8,21] Systemic antifungal medications have not been shown to produce high concentrations in ocular tissues, may produce untoward adverse events, and may interact with the patient's other systemic medication.[8] Although there is no clear evidence to suggest that prophylactic therapy is efficacious, further study is warranted. For example, a long term study from an eye bank on the rates of fungal infections in donor material may be able to inform the ophthalmic community about the incidence of positive rim cultures and advance the discussion on best methods to treat. That would also be helpful data for use in future studies on keratoplasty procedures.

In addition, assuming therapeutic concentrations of drug can be achieved in the deep stroma once initiated, it is not clear how long to continue prophylaxis. Kitzmann et al. suggested 4 weeks of topical and systemic therapy.[10] Our case suggests that 3 months of oral therapy alone may be insufficient.

Once clinical infection develops, it is possible that full thickness keratoplasty can be avoided in selected cases.[13] The technique described by Tu et al. using repeated intrastromal injections and lamellar irrigation of antifungals is probably best suited to focal interface infiltrates in grafts at least several months old in which there is a robust peripheral donor-host adhesion. Cases with significant inflammation, cases with infiltration that extends beyond the interface into the donor or host, and/or cases that present sub-acutely in the weeks following surgery will likely require early penetrating keratoplasty.

3. Conclusion

Positive donor cultures are becoming more prevalent, and these are one cause for developing fungal infections in post-EK procedures. Although the literature describes these rare cases, this is the first report of fungal interface keratitis that occurred 1-year post-EK and post-prophylactic treatment. Whereas other cases in the literature resolved after initial treatment, our patient had a recurrence despite a year-long course of treatment. It may be possible to prevent these types of infections in the future by including antifungals in the storage medium, but that has yet to be proven in a randomized clinical trial. This case should serve as a potential warning that patients with positive donor cultures should be monitored closely for much longer than the current literature might suggest.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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Appendix A. Supplementary data

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