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Successful treatment of *Candida albicans* anterior chamber infection after penetrating keratoplasty

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ABSTRACT

Purpose: To report the successful management of an anterior chamber (AC) infection after penetrating keratoplasty (PK) caused by *Candida albicans*.

Observation: A 53-year-old female had a PK in her right eye. The donor rim tested positive for *Candida albicans* one week later. Despite initiation of prophylactic topical 1% voriconazole drops, the patient presented with a white mass in the anterior chamber one month later. Biopsy confirmed *Candida*. Antifungal therapy was intensified with the addition of intravenous fluconazole, and with repeated irrigations of the AC and intracameral administration of amphotericin B (off-label use). After two weeks of apparent lack of treatment response, the infection suddenly quiesced. The final outcome was visual acuity of 0.2 and a clear graft with an endothelial cell density of 2260 cells/mm. [2]

Conclusions and Importance: Fungal intraocular infections after PK are usually devastating. Due to low intraocular penetration of topical antifungals, serial intracameral injections were used to maintain a therapeutic concentration of amphotericin B within the anterior chamber, and intravenous fluconazole was administered to protect against the spread of infection into the vitreous. A clinical response developed after two weeks. The reported case represents a favorable outcome using a multimodal approach.

1. Introduction

The incidence of fungal infection due to donor-to-recipient transfer following penetrating keratoplasty is very low (0.16%).[1] Recent retrospective tissue bank studies have shown a negligible rate of post-keratoplasty infection even among cases of fungal-positive rim cultures.[2,3] The very low incidence of recipient fungal keratitis has raised questions whether rim cultures and prophylactic antifungal therapy in fungal-positive rim cultures are necessary,[4,5] and whether adding an antifungal to cold storage medium changes the final outcome.[6–8]

However, the low incidence and lack of clear treatment guidelines are exactly why every report from the literature is of value to the surgeon facing a case of potentially fulminant and devastating intraocular fungal infection.[9–11] Most of the post-keratoplasty fungal infections are in fact so fulminant and intense, that all interventions aim to rescuing the graft and to preventing immediate therapeutic repeated keratoplasty.[9,12]

The reported case illustrates a successful treatment approach for donor-to-recipient transferred post-penetrating keratoplasty fungal infection in the anterior chamber.

2. Case report

A 53-year-old systemically healthy female patient with a right eye chronic full thickness corneal scar due to childhood infection and suspected concomitant amblyopia, underwent uneventful penetrating keratoplasty (PK) in her right eye (RE). The preoperative RE best corrected visual acuity (BCVA) was 20/400, Snellen. She was phakic with a clear lens. The left eye (LE) exam was unremarkable, with BCVA of 20/20, Snellen. Postoperatively, standard topical therapy for the RE was initiated with methylprednisolone 0.5% hourly, moxifloxacin 0.5% (Vigamox®, Alcon, Fort Worth, Texas) hourly and artificial tears drops hourly. She was discharged on the sixth day after transplantation with uncorrected visual acuity (UCVA) in the RE of 20/100, Snellen, intraocular pressure of 12 mmHg, no conjunctival injection, a smooth and

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clear graft, and no signs of intraocular inflammation. The topical therapy was tapered to six times a day for all three drops.

The corneal tissue had been retrieved, evaluated and stored in the Eye tissue bank of the University Eye Hospital Ljubljana. At this tissue bank the hypothermic method of storage is practiced. The storage medium was Eusol-C (Alchimia, PD, Italy), a hypothermic medium with added gentamicin. Following our institutional routine, microbiological cultures of the donor rim were performed. On postoperative day seven, the rim proved positive for *Candida albicans*. Prophylactic topical voriconazole 1% drops 6 times daily were prescribed to the patient immediately. The moxifloxacin was continued at 6 times daily, and corticosteroid drops were decreased to twice daily. Twice weekly follow up visits were scheduled.

One month postoperatively, the patient reported occasional irritation of the RE. UCVA was stable at 20/100 and the intraocular pressure was 14 mmHg. A white anterior chamber mass attached to the donor corneal endothelium and mild anterior chamber exudation were noted (Fig. 1a). There were no cells in the vitreous, and the fundus exam was normal. A fungal infection in the anterior chamber was suspected, and the patient was admitted to the hospital. A biopsy of the anterior chamber mass was performed through a 23 gauge limbal incision under sterile conditions, followed by copious irrigation of the anterior chamber with balanced salt solution to remove the remnants of the mass. Intracameral amphotericin deoxycholate 5 μg in 0.1 ml (Fungizone®, Bristol-Myers Squibb, Pharmaceuticals Ltd, Ireland off-label use) was injected. Topical voriconazole 1% drops were prescribed hourly, and intravenous fluconazole 400 mg (Diflazon®, Krka, Novo mesto, Slovenia) daily was administered. Topical steroid drops were continued at just once daily to decrease the likelihood of graft rejection.

Microbiological analysis of the biopsy confirmed *Candida albicans,* which was susceptible to fluconazole, voriconazaole, amphotericin B and caspofungin, and which matched the antifungal susceptibility pattern of the *Candida albicans* isolated from the donor rim.

Irrigation of the anterior chamber, removal of fluffy white material and intracameral injection of amphotericin 5 μg as described above was repeated every 2–3 days. Despite this, the clinical status deteriorated during the first two weeks of therapy. The UCVA dropped to finger counting, epithelial defects developed, and the transplant showed Descemet's membrane folds, endothelial keratic precipitates and a recurring endothelial white mass at the donor host border (Fig. 1b and c). Regular ultrasound exams were performed to rule out spread of infection into the vitreous cavity.

No improvement in anterior chamber inflammation was observed until the end of the second week, when the inflammation suddenly subsided, and the white mass in the anterior chamber no longer recurred (Fig. 2a). The patient was discharged on oral fluconazole 200 mg (Diflazon®, Krka, Novo mesto, Slovenia) daily, and on topical voriconazole treatment six times per day, which was slowly tapered over two months. The BCVA was 20/100 Snellen, and the transplant was clear with an endothelial cell count of 2260/mm^2 and without changes at the donor host interface 6 months after surgery (Fig. 2b and c).

The patient underwent cataract surgery 4 years later with postoperative BCVA 20/32, limited by amblyopia, and endothelial cell count 1132/mm.[2]

3. Discussion

Transferred post-keratoplasty *Candida* infection usually has a devastating outcome, with most cases requiring further surgery, including repeat grafting. The invasive hyphae phase of *Candida albicans* infection in a favorable environment destroys host cell membranes, invades tissues and is difficult to eliminate, requiring prolonged and combined treatment.

Routine rim cultures enable initiation of preventive treatment with antifungals and close follow up of recipients for early signs of transfer before deeper intraocular penetration of fungus and tissue damage occur.[4,10,11] Recently, in cases of lamellar keratoplasties, the numbers of fungal transfer increased, which brought back the debate of the importance of routine rim cultures,[13] especially for corneas undergoing hypothermic storage, where there is no chance of fungal detection before transplantation.[14] In our case, the rim proved positive for *Candida albicans* on the 7th postoperative day, at which time there were no signs of infection in the recipient, and antifungal treatment was started prophylactically. To further reduce the likelihood of fungal infection, which are the case in a significant percentage (7%) of corneas with positive donor rim fungal culture, some eye banks are adding antifungals to cold storage and transport media.[9,14,15] A faster method of detecting donor fungal infection via PCR at the time of tissue harvesting is also being developed.[16,17]

There are no established treatment guidelines for fungal infection

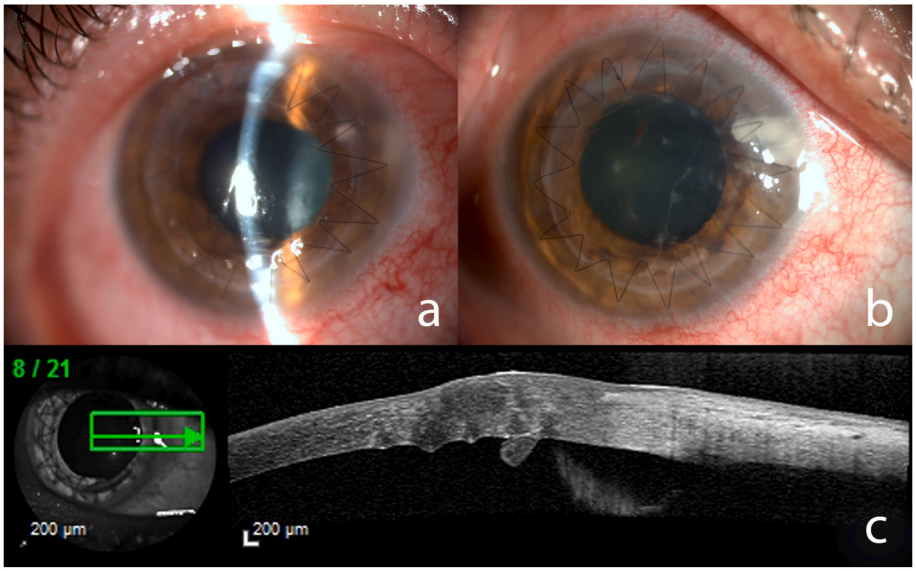

Fig. 1. a One month after penetrating keratoplasty, anterior chamber inflammation and a white mass (biopsy proven *Candida albicans*) are seen, b No clinical improvement during the first two weeks of intensive antifungal therapy. c Anterior chamber optical coherence tomography showing the mass attached to the corneal endothelium.

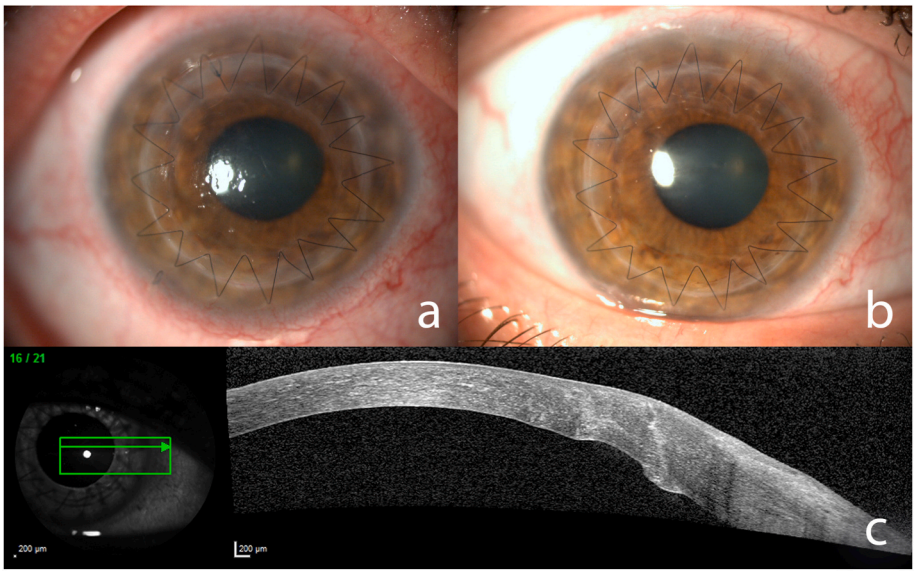

Fig. 2. a After two weeks of intensive antifungal therapy, sudden improvement in the clinical picture occurred, b Six months after the original penetrating keratoplasty, the outcome was excellent, with a clear corneal graft. c optical coherence tomography showing resolution of the mass that had previously been attached to the corneal endothelium.

after PK. Generally, a combination of antifungals topically, in the form of intraocular injections, and in severe cases also early concomitant systemic antifungal is used as a start, and adjusted according to the clinical picture or microbiological results afterwards.[14,18,19] Topical corticosteroids are minimized or substituted for cyclosporin.[14] Lately, studies are underway in order to apply therapeutic corneal cross linking for such cases.[14]

The clinical efficacy of an antifungal agent depends on its capability to reach and kill all the possible fungal phases and aggregated forms. The effective concentration and duration of treatment achieved in the target ocular tissue depend on the molecular mass of the drug, the concentration of the administered drug, and the route of administration.[20,21] Therapeutic intraocular concentrations of antifungals cannot be achieved by topical use,[21] and intraocular administration is required. Intravitreal injection(s) of amphotericin B (1–5 μg in 0.1ml) with vitrectomy are recommended for fungal endophthalmitis.[10,19] In our case, vitrectomy was not indicated, nor was intravitreal antifungal injection, as there was no vitreous involvement. Serial intravitreal amphotericin B injections are not routinely performed because of concerns for retinal toxicity. For fungal keratitis and anterior chamber infections, intracameral amphotericin B injections (5–10 μg in 0.1 ml) are recommended, which do not cause significant retinal toxicity.[22–25] Toxicity of amphotericin B to the endothelium was proved in cell cultures.[26] There are no clinical studies on humans available, so it has to be used with caution. Compared to intravitreal injections, the frequency of serial intracameral injections has to be higher because of rapid aqueous humor turnover (1.5–2 hours). As reported in animal studies, effective drug levels of fungistatic and concentration-dependent fungicidal amphotericin B are achieved in the aqueous humor 30 minutes after a single injection, but drug levels decrease abruptly within 1 day.[27,28] We delivered intracameral amphotericin B every one to two days for two weeks despite the lack of clinical improvement, but with reassurance that infection did not extend to the posterior chamber during this time. After two weeks, a sudden reversal of the clinical picture occurred. The clinical picture is a product of fungal invasion and the immune response to live and dead fungal particles, which makes it difficult to judge when treatment becomes successful.

4. Conclusions

In conclusion, we report the successful management of an anterior chamber infection after penetrating keratoplasty caused by *Candida albicans*. We attribute the favorable outcome to the following factors:

1. treatment tailored to the fungal culture and antifungal susceptibility pattern obtained from rim tissue and from the intraocular biopsy,
2. intensive combined topical, intracameral, and systemic antifungal treatment with
3. serial intracameral injections of amphotericin B for two weeks.

Patient consent

Informed consent was obtained from the patient for all aspects of her treatment, and for the publication of this case report.

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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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