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Interface infectious keratitis after anterior and posterior lamellar keratoplasty. Clinical features and treatment strategies. A review

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ABSTRACT

Interface infectious keratitis (IIK) is a novel corneal infection that may develop after any type of lamellar keratoplasty. Onset of infection occurs in the virtual space between the graft and the host where it may remain localised until spreading with possible risk of endophthalmitis. A literature review identified 42 cases of IIK. Thirty-one of them occurred after endothelial keratoplasty and 12 after deep anterior lamellar keratoplasty. Fungi in the form of *Candida* species were the most common microorganisms involved, with donor to host transmission of infection documented in the majority of cases. Donor rim cultures were useful to address the infectious microorganisms within few days after surgery. Due to the sequestered site of infection, medical treatment, using both topical and systemic antimicrobials drugs, was ineffective on halting the progression of the infection. Injection of antifungals, right at the graft–host interface, was reported successful in some cases. Spreading of the infection with development of endophthalmitis occurred in five cases after Descemet stripping automated endothelial keratoplasty with severe sight loss in three cases. Early excisional penetrating keratoplasty showed to be the treatment with the highest therapeutic efficacy, lowest rate of complications and greater visual outcomes.

INTRODUCTION

Microbial infection of a corneal transplant is a complication that is a bane to all corneal surgeons, the sequelae of which can be devastating. Although infrequent, in the early postoperative period, keratitis after keratoplasty may threaten corneal graft clarity and result in severe vision loss and, in worst cases, may cause endophthalmitis with potential need for enucleation.

During the last two decades, lamellar keratoplasty (LK), in the forms of anterior lamellar keratoplasty (ALK) and endothelial keratoplasty (EK), has largely supplanted penetrating keratoplasty (PK) for selective replacement of the diseased corneal stroma or damaged endothelium.[1] Advantages of these techniques are reduced risk of allograft rejection, shorter postoperative steroid treatment, early removal of sutures, no 'open-sky' surgery and preservation of globe integrity.[2] All these benefits contribute to the reduced risk of early and late complications occurring after LK when compared with PK. Common feature to all LK procedures is the formation of a surface of contact between the donor graft and the recipient bed, namely, graft–host interface.[3] Infection arising at this anatomical level represents a rare peculiar complication that may develop after all forms of LK. Diagnosis and treatment of this type of keratitis is a challenge for the surgeon due to the sequestered location of the infection in the deep stroma, with impaired access for microbiological testing and penetration of antimicrobial drugs. For these reasons, diagnosis of the infectious agent may be delayed or remain presumptive and treatment is often initiated empirically.

Cases of corneal interface infection after both anterior and posterior lamellar keratoplasty are reported in the literature. Due to its infrequent occurrence, knowledge of this new form of infection is limited and treatment strategies as well as clinical outcomes widely vary according to different authors.

The purpose of this review is to describe the clinical features of interface infectious keratitis (IIK) occurring after ALK and EK and to analyse the treatment outcomes in order to establish a rationale for therapy.

METHOD OF LITERATURE SEARCH

We searched PubMed database (1949–2018) and Ovid Medline (1946–2018) for peer-reviewed publications relevant to the topic of corneal interface infection following lamellar keratoplasty. Key words included: keratitis, corneal interface infection, deep anterior lamellar keratoplasty (DALK), endothelial keratoplasty (EK), Descemet stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK). We did not use any date or language restrictions in the electronic searches. Articles in all languages were considered, provided that the non-English articles included English abstracts. The last electronic search was made on June 2018. Data on patients anagraphic, keratoplasty procedure, time to onset of infection, microorganism isolates, therapy and visual acuity were compiled using Microsoft Excel software V.15.25 (Microsoft, Redmond, Washington, USA) and summarised using SPSS software V.20 for Microsoft Windows.

RESULTS

The literature search retrieved 122 titles and abstracts in English or with English translations. All papers available were reviewed by two authors (LF and EM) to check for adherence to the topic

interface infection following lamellar keratoplasty. We selected 18 single case reports and eight case series of patients who developed infection originating at the graft–host interface after anterior or posterior LK. Cases where onset of infection did not originate in the graft–host interface were omitted. Single cases, part of case series, not referable to IIK were excluded from the analysis (ie, Tsui *et al*[4] cases 1, 2, 3, 4, 5, 8, 9).

Patient characteristics and clinical outcomes of all cases included in this review are reported separately in tables 1 and 2 according to the type of surgery: DALK and EK. In the latter group, we included patients who underwent either DSAEK or DMEK.

Deep anterior lamellar keratoplasty

Twelve cases (11 case reports)[5–15] of IIK, developed after DALK, are reported in the literature since 1999 (table 1). The causative microorganism was *Candida* spp in seven cases (63%) and *Klebsiella pneumoniae*, *Rhodotolura* spp, *Actinomyces* spp and *Mycobacterium* spp in four cases. Infectious organisms were identified from cultures of the excised donor buttons in 10 cases and from the liquid employed to rinse the graft–host interface in one case. Donor rim cultures, obtained in five cases, resulted negative in two cases and positive in three cases, with correspondence to the organisms identified in the recipients. Culture results were available 5–7 days after surgery.

The median time to development of clinical infection, calculated for all patients, was 29 days (range 2–120 days). Infection was managed initially with topical and systemic antifungals in combination with antibiotics. The choice of a specific drug was made on the available information resulting from donor rim and/or excised donor button cultures. None except one patient[15] responded to medical treatment alone and 9 out of 12 patients required excisional PK with removal of the infected donor button and the host Descemet membrane (DM). One case was successfully treated by simply replacing the donor button, while preserving the intact host DM.[5] Irrigation of the donor–host interface with and without antifungals, attempted in six cases, resulted successful in only one case[11] and caused DM rupture in three cases. None of the patients developed endophthalmitis and no recurrence of infection was observed during follow-up. Median best spectacle corrected visual acuity (BSCVA) at 4–6 months follow-up was 20/30 (range 20/630–20/20).

Endothelial keratoplasty

Thirty-one cases (17 case reports)[16–33] of IIK, developed after EK, are reported in the literature since 2009 (table 2). Twenty-nine of them occurred after DSAEK and two after DMEK. Infectious microorganisms were identified in 28 patients from cultures of the explanted donor lenticules (15 cases) or from aqueous and vitreous taps (13 cases). The remaining three cases were diagnosed and treated empirically as fungal infection on the basis of their clinical appearance.[24 31] *Candida* spp was isolated in 21 specimens (75%) and *Aspergillus fumigatus* in one case, while bacteria in the form of *Staphylococcus aureus* (two cases), *Staphylococcus epidermidis* (one case), *Enterococcus faecalis* (one case) and *Nocardia* spp (one case) were identified in the remaining patients. Donor rim cultures, obtained in 28 cases, resulted negative in 13 cases and positive for *Candida* spp in the other 15 cases. Correspondence between the infectious microorganisms isolated from specimens and the ones cultured from positive donor rim was found in all patients.

The median time to development of clinical infection, in these patients, was 28 days (range 1–120 days). Rim cultures results became available after a median time of 5.5 days (range 3–14 days) after surgery.

Despite combined topical and systemic antifungals, medical treatment alone was unsuccessful in halting the progression of the infection in all except one case.[17] Surgical intervention by means of lenticule removal, intracameral and/or intravitreal antifungals injections and eventually PK was required to eradicate the infection in the majority of patients. In three cases, regression of infection was obtained with multiple intrastromal injections of amphotericin B (5 mg/mL) or voriconazole (50 mg/mL) inoculated closest possible to the graft–host interface, causing temporary focal graft detachment.[24 31]

Of all patients, five (16%) developed endophthalmitis and required pars plana vitrectomy and three (9%) developed surgical postoperative complications with severe sight loss. Median BSCVA measured 4–12 months after resolution of infection was 20/40 (range 20/500–20/20).

DISCUSSION

IIK represents a subset of infectious keratitis originating at the graft–host interface and occurring exclusively after LK procedures. A recent report of the Eye Bank Association of America[34] encompassing 4 years (2017–2010) of activity, reported a cumulated frequency of postkeratoplasty infection of 0.026% for fungal and bacterial agents together, with a higher rate of fungal isolates (63%). The frequency of fungal infections after LK was nearly the double than PK, being 0.023% and 0.012%, respectively. The rate of fungal infection after anterior lamellar keratoplasty was 0.052% and 0.022% after EK. According to this report, there might be an increasing trend of occurrence of postkeratoplasty fungal infection since the introduction of EK as the procedure of choice for the treatment of corneal endothelial failure. A single-centre review of 1088 consecutive DSAEK surgeries, over an 8 years time lapse, reported 10 (0.92%) cases of interface infection, seven of them with culture positive results.[25] We should consider that the overall perception of an increased risk of fungal infection after EK may be the consequence of over-reporting a novel complication occurring after a new surgical procedure. Due to the lack of a physiological hypothesis, whether IIK may represent a significant threat after LK remains is yet to be defined.

Tissue manipulation either in the eye bank or in the operating room does not seem to influence the postoperative risk of bacterial or fungal infection.[34 35] In our review, postoperative interface keratitis occurred using tissues for EK prepared either by surgeons in the operating room (13 cases) or by eye bank technicians (eight cases). Correlation between recipient and donor rim isolates was found for most of the tissues prepared in eye banks, indicating the donor and not the processing as the source of infection. In this respect, Brothers *et al*[36] demonstrated that tissue warming during EK processing is responsible for promoting *Candida* growth in donor rims, advocating antifungal drug supplementation of storage media. Ritterband *et al*[37] proved the efficacy of added voriconazole to Optisol GS on reducing the rate of positive rim cultures. Organ culture is the preferred method of cornea preservation in Europe. With this storage method, prolonged storage time allows to conduct routine microbiology tests and to identify and discard contaminated corneas before they are issued for transplantation.[38] To date, lack of strong evidence of effectiveness of antifungals in storage media kept at hypothermic temperature (2°C−8°C), along with doubts regarding safety for the corneal endothelial cells, are presently not advising the addition of antifungals to cold storage media.[34]

Table 1 Literature review of clinical cases and case series of interface keratitis following DALK

	Patients (n)	Age (years)	Microorganism isolated from specimens	Time to infection onset (day)	Donor rim culture	Time to positive donor rim culture report (day)	Medical treatment topical and /or systemic	Surgical treatment	Endophthalmitis	Visual outcome (BSCVA Snellen)	Postoperative complications
Panda *et al*[5]	1	55	*Rhodotorula* sp (donor button+interface biopsy)	5	nr	nr	Topical natamycin 5% Amphotericin B 0.15%	Donor button exchange	No	nr	No
Fontana *et al*[6]	1	30	*Candida albicans* (donor button)	28	*C. albicans*	5	Topical amphotericin B (3 mg/mL) Liposomal amphotericin B (3 mg/kg) IV	Donor button exchange+interface amphotericin B (5 µg/0.1 mL) PK	No	20/25	No
Kanavi *et al*[7]	2	21	*Candida glabrata* (donor button)	60	nr	nr	Topical amphotericin B, oral ketoconazole 400 mg once in a day	Interface irrigation with DM rupture PK	No	nr	No
		25	*C. albicans* (donor button)	75	nr	nr	Natamycin 5%, oral ketaconazole 400 mg once in a day	PK	No	nr	No
Zarei-Ghanavati *et al*[8]	1	35	*Klebsiella pneumoniae* (donor button)	2	*Klebsiella pneumoniae*	2	Topical vancomycin (50 mg/mL), ceftazidime (50 mg/mL)	PK	No	20/20	No
Caretti *et al*[9]	1	21	Actinomyces species (donor button)	6	nr	nr	Topical ofloxacin 0.3%, betamethasone 0.13%+chloramphenicol 0.25%, amphotericin B	PK PK graft exchange	No	20/25	No
Bahadir *et al*[10]	1	23	Candida species (donor button)	30	Not performed	na	Topical amphotericin B (5 µg/mL), cefuroxime (1 mg/mL) Liposomal amphotericin B (3 mg/mL) IV Oral itraconazole 200 mg OD	Interface irrigation DM rupture PK	No	nr	No
Sedaghat*et al*[11]	1	18	*C. albicans* (irrigation liquid)	120	Negative	nr	Topical ceftazidime (50 mg/mL), vancomycin (50 mg/mL), natamycin 5%	Interface irrigation (amphotericin B 0.15%) DM rupture	No	20/30	No
Wesse *et al*[12]	1	39	*Candida orthopsilosis* (donor button)	5	Yeasts	6	Topical voriconazole, oral voriconazole 400 mg two times a day	Interface irrigation voriconazole (0.25 mg/mL)+amphotericin B (0.5 mg/mL) PK	No	20/630	No
Murthy *et al*[13]	1	26	Atypical Mycobacterium (donor button)	90	nr	nr	Topical amikacin 2.5%	Donor button exchange PK	No	20/40	No
Le *et al*[14]	1	31	*C. glabrata* (donor button)	6	Medium culture negative Donor rim culture not performed	nr	Topical levofloxacin 0.5%, fluconazole 0.5%	Interface irrigation cefuroxime 5%+fluconazole (0.8 g/L) donor button exchange PK	No	20/40	No
Kodavoor[15]	1	32N	Negative	90	nr	nr	Topical voriconazole, natamycin, oral itraconazole 100 mg twice a day	None	No	20/80	Leucomatous scar

BSCVA, best-spectacle corrected visual acuity; DM, Descemet membrane; PK, penetrating keratoplasty; na, not applicable; nr, not reported.

Table 2 Literature review of clinical cases and case series of interface keratitisfollowing DSAEK and DMEK

	Patients (n)	Age (years)	Type of surgery	Donor preparation	Microorganism isolated from specimens	Time to infection onset (days)	Donor rim culture	Time to positive donor rim culture report (days)	Medical treatment topical and /or systemic	Surgical treatment	Endophthalmitis	Visual outcome (BSCVA Snellen)	Postoperative complications
Koenig *et al* [16]	1	80	DSAEK	Uncut	*Candida albicans* (donor lenticule)	7	*C. albicans*	5	None	Donor lenticule removal then PK	No	NPL	Phtisis bulbi Enucleation
Kitzmann *et al*[17]	2	80	DSAEK	nr	*C. albicans* (aqueous tap)	39	*C. albicans*, *Candida glabrata*, *Streptococcus*	3	Topical amphotericin B 0.15% Oral fluconazole 200 mg two times a day	Donor lenticule exchange+intracameral amphotericin B (5 µg/0.1mL)	No	20/50	No
		80	DSAEK	nr	*C. albicans* (anterior corneal infiltrate scraping)	41	*C. albicans*, *C. glabrata*, *Streptococcus*	3	Topical amphotericin B 0.15% Oral fluconazole 200 mg two times a day	Intracameral amphotericin B (5 µg/0.1 mL)×2 Intravitreal amphotericin B (10 µg/0.1 mL) Peripheral patch graft	No	20/40	No
Chew *et al*[18]	1	72	DSAEK	Uncut	*C. parapsilosis* (aqueous and vitreous tap)	2	Negative	na	Topical amphotericin B (1 mg/mL) Oral voriconazole 200 two times a day	Intravitreal amphotericin B (0.1 mg)×3 PK+vitrectomy	Yes	20/40	No
Lee *et al*[19]	2	81	DSAEK	Precut	*C. glabrata* (donor lenticule)	30	*C. glabrata*	3	Topical amphotericin B 0.15% Oral voriconazole 100 two times a day	PK+intravitreal amphotericin B (10 µg/0.1 mL)	No	20/25	No
		76	DSAEK	Uncut	*C. albicans* (corneal scraping)	21	Negative	7	Topical amphotericin B 0.15% Oral fluconazole 200 mg two times a day	PK	No	NPL	Supra choroidal haemorrhage Phtisis bulbi
Ortiz-Gomariz *et al*[20]	1	76	DSAEK	Uncut	*C. albicans* (donor lenticule, aqueous+vitreous taps)	90	Not tested	na	Voriconazole 200 mg two times a day intravenous Topical voriconazole	Donor lenticule removal+vitrectomy PK+trabeculectomy	Yes	20/200	No
Sharma *et al*[21]	1	62	DSAEK	nr	*Aspergillus fumigatus* (donor lenticule)	30	Negative	na	Natamycin 5% Voriconazole 200 mg two times a day	PK	No	20/40	No
Yamazoe *et al*[22]	1	74	DSAEK	nr	*C. albicans* (aqueous tap)	34	*C. albicans*	nr	Topical voriconazole 1%+micafungin 0.1% Intravenous voriconazole 200 mg two times a day	Donor lenticule removal+posterior stroma debridement; 4 months later PK+gonioplasty+intraocular lens exchange	No	20/22	No
Holz *et al* [23]	2	69	DSAEK	Precut	*C. albicans* (donor lenticule)	7	*C. albicans*	nr	Topical amphotericin B+voriconazole Oral fluconazole 200 mg two times a day	Donor lenticule removal Intracameral amphotericin B (5 mg)+vancomycin (1 mg)+ceftazidime (2.2 mg) PK+glaucoma tube	No	20/30	No
		54	DSAEK	Precut	*C. albicans* (donor lenticule)	49	*C. albicans*	nr	Topical amphotericin B (2 mg/mL)+voriconazole 1%. Oral fluconazole 200 mg two times a day	Intravitreal amphotericin B (5 µg/0.1 mL)×4 Lenticule removal PK	No	20/80 (previous RD surgery)	No
Tu *et al* [24]	2	66	DSAEK	nr	Not assessed	90	Negative	na	Oral fluconazole 200 mg two times a day	Several intrastromal amphotericin B (5 µg/mL)	No	20/500	Corneal oedema
		70	DSAEK	nr	Not assessed	49	Negative	na	Oral voriconazole 100 mg BD	Intrastiomal voriconazole (50 mg/mL) weekly for 3 weeks	No	20/60	No

Continued

Table 2 Continued

	Patients (n)	Age (years)	Type of surgery	Donor preparation	Microorganism isolated from specimens	Time to infection onset (days)	Donor rim culture	Time to positive donor rim culture report (days)	Medical treatment topical and /or systemic	Surgical treatment	Endophthalmitis	Visual outcome (BSCVA Snellen)	Postoperative complications
Nahum *et al* [25]	7	52	DSAEK for all cases	Uncut for all cases	*Candida parapsilosis*	112	Negative for all cases	na for all cases	Same treatment for all patients. Topical fortified antibiotics and antifungals.			20/20	No
		83			*Staphylococcus aureus*	56						20/100	No
		67				21						20/100	No
		70			*Candida parapsilosis* (donor lenticule)							20/200	No
		63			Nocardia species	28				Same procedure for all patients. PK+intracameral amphotericin B, amikacin, vancomycin, ceftazidime	Not for all cases	20/50	No
					Staphylococcus								
		63			*C. albicans* (donor lenticule)				No				
		71			*Staphylococcus*	28			No				
						112							
Weng *et al* [26]	1	80	DSAEK	nr	*C. glabrata* (donor lenticule and vitreous tap)	28	*Candida glabrata*	6	Topical amphotericin B 0.15%, vancomycin (50 mg/mL), tobramycin (14 mg/mL). Oral fluconazole 200 mg once a day	Lenticule removal+pars plana vitrectomy+intravitreal amphotericin B, vancomycin, ceftazidime	Yes	20/200	Corneal oedema
Hsu *et al* [27]	1	45	DSAEK	nr	*C. albicans* (aqueous tap, donor lenticule)	1	*C. albicans*	nr	Topical voriconazole 1% Oral fluconazole 200 mg two times a day	Donor lenticule removal+intravitreal voriconazole 100 µg PK+pars plana vitrectomy Repeat vitrectomy+glaucoma tube	Yes	20/100	No
Villarubia *et al* [28]	1	73	DSAEK	Uncut	*C. albicans* (donor lenticule)	10	*C. albicans*	10	Topical voriconazole 1% Oral voriconazole 200 mg once a day	Intracameral voriconazole 0.15 PK+intracameral and intravitreal voriconazole 0.1% Repeat PK+pars plana vitrectomy+glaucoma valve	No	HM	Optic atrophy
Tsui *et al* [4]	2	85	DSAEK	Precut	*C. albicans* (donor lenticule)	20	*C. albicans*	1	Topical amphotericin B 0.15%	Multiple intracameral amphotericin B 5 µg/0.1 mL	No	20/40	No
		75		Precut	*C. albicans* (donor lenticule)	20	*C. glabrata*	1	Oral fluconazole 200 mg once a day	Donor lenticule exchange PK	No	20/40	No
Wilde *et al* [29]	1	57	DSAEK	Uncut	*Scopulariopsis gracilis* species	2	*S. gracilis* species	2	Topical amphotericin B 0.15% Topical voriconazole 1% Oral voriconazole 200 mg two times a day	Donor lenticule removal+multiple amphotericin B 5 µg/0.1 mL PK	No	20/40	No
Thompson *et al* [30]	1	75	DMEK	Prestripped	*C. glabrata* (donor lenticule)	8	*C. albicans*	2	Topical voriconazole 1% Oral voriconazole 100 mg two times a day	Intracameral and intravitreal voriconazole 100 µg Donor lenticule removal DSAEK	No	20/60	No
Tu *et al* [31]	1	61	DMEK	nr	Not assessed	30	*C. glabrata*	14	Oral fluconazole 200 mg two times a day	Two intrastromal amphotericin B 5 µg/0.1 mL	No	20/25	No
Porter *et al* [32]	1	68	DSAEK	nr	*Enterococcus faecalis*	120	Not tested	na	Topical moxifloxacin 1%	PK Pars plana vitrectomy	Yes	20/50	No
Palioura *et al* [33]	2	81	DSAEK	Precut	*C. albicans* (aqueous tap donor lenticule)	28	*C. albicans*	7	Topical amphotericin B (5) mg/mL+	Intracameral and	No	20/30	No
		67	DSAEK	Precut	*C. albicans* (aqueous tap)	42	Negative	na	Voriconazole (10 mg/mL		No	20/20	No

BSCVA, best spectacle corrected visual acuity; DSAEK, Descemet stripping automated endothelial keratoplasty; DMEK, Descemet membrane endothelial keratoplasty; PK, penetrating keratoplasty; HM, hand movement; NPL, no perception of light; RD, retinal detachment; na, not applicable; nr, not reported.

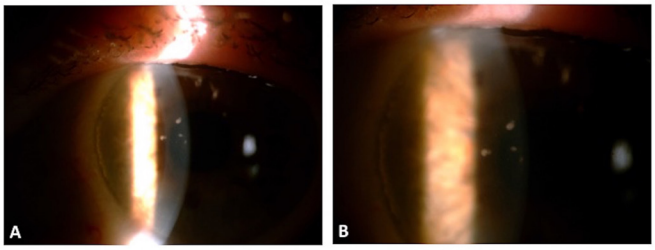

Figure 1 *Candida glabrata* interface infection developed after Descemet membrane endothelial keratoplasty. (A) Slit-lamp photography showing multiple white infiltrates within the graft–host interface 28 days after surgery. (B) A high magnification view at the slit lamp.

Microorganisms involved in the development of IIK are more commonly fungi, in the form of *Candida* spp and less frequently bacteria (tables 1 and 2). In both cases, the source of infection is primarily the donor cornea, with a high correspondence between the organisms isolated from the corneoscleral rims and the ones identified in the recipients postoperatively.[4] Regardless of the type of lamellar keratoplasty, early signs of infection may be noticed in the form of deep stromal infiltrates developing on average 1 month after surgery (tables 1 and 2). Onset of infection may occur as early as few days[27] and up to 3 months[11] after surgery, depending on the pathogenicity, microbial load and virulence of the infectious agent. A high index of suspicion is required to diagnose IIK, as it often presents with minimal inflammatory signs and symptoms. At onset, slight ocular pain and redness may be the only symptoms reported by patients, while visual acuity may be unaffected. At slit lamp examination, the cornea is usually clear, single or multiple whitish infiltrates, ranging from less than 0.5–2 mm in diameter,[13] located at the graft–host interface, are the only visible signs of infection (figure 1). The anterior chamber is usually quiet with no inflammation. Anterior segment optic coherence tomography is helpful to confirm the location of

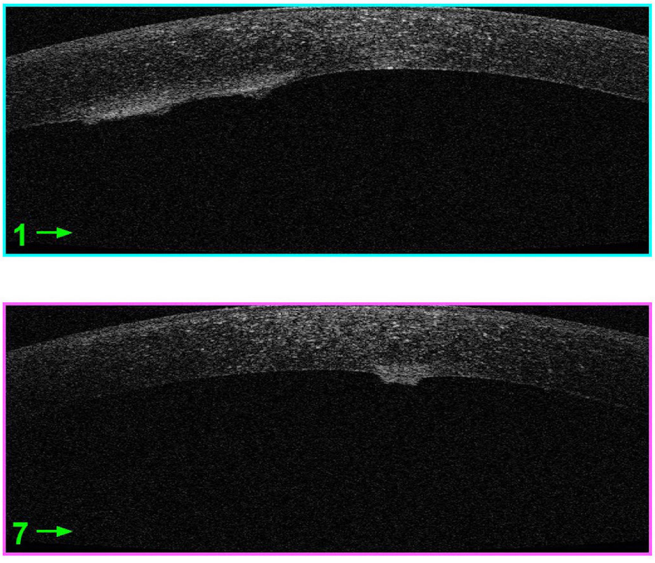

Figure 2 *Candida glabrata* interface infection. Optical coherence tomography showing infiltrates placed anterior to the Descemet membrane within the area of the Descemet membrane endothelial keratoplasty graft.

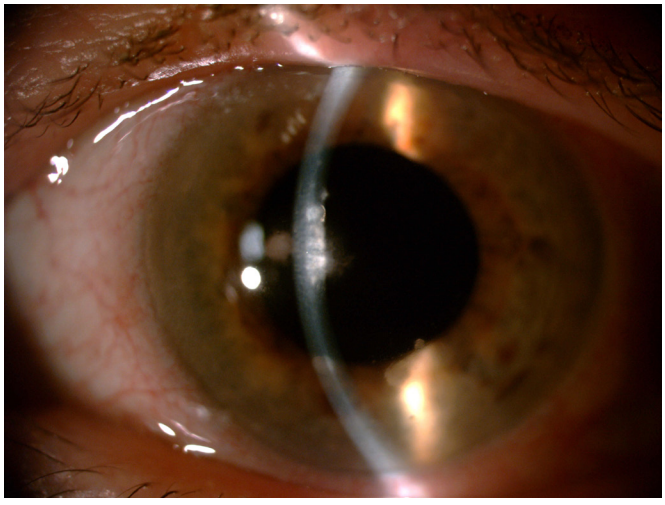

Figure 3 *Candida glabrata* interface infection developed after Descemet membrane endothelial keratoplasty. Slit-lamp photography showing worsening of the infection with infiltrates enlargement displaying a fluffy appearance.

the infiltrates at the graft–host interface (figure 2),[39 40] but does not offer diagnostic hints of the causative agent.[14 31] In vivo confocal microscopy can be useful in cases where *Candida* spp infection is suspected by detecting hyperreflective round budding-like structures with a granular appearance, measuring 2–4 µm, with the absence of hyphae-like structures.[7 14 19 24] Nonetheless, the sensitivity and specificity of this examination are highly dependent on operator experience,[39 40] and its diagnostic capability is yet to be confirmed in the setting of IIK.

Worsening of the infection is characterised by coalescence of the infiltrates that increase in size and assume less-defined margins, with oedema and infiltration of the overlaying stroma. The anterior chamber may show reaction with cells and seldomly hypopyon (figure 3). At this point, ocular pain and photophobia are markedly increased and visual acuity is reduced from previous visits. Hsu *et al*[27] reported a case of *Candida albicans* interface infection after DSAEK rapidly developing corneal perforation and endophthalmitis few days after surgery.

Due to the initial asymptomatic clinical picture and the similarity to epithelial ingrowth, IIK diagnosis and treatment are often postponed until symptoms and signs of spreading of the infection become evident. Early warning of a possible risk of infection may come from donor rim cultures that can address identification and drug sensitivities of the potential infectious microorganism within few days after surgery. This information is particularly useful in the event of an interface infection due to inherent difficulty to obtain microbiological samples, without surgical intervention and to the high correspondence between microorganisms isolated from recipient specimens and the ones cultured from donor rims (tables 1 and 2). This may hold true particularly when donor rims are infected by *Candida species*[4 34] where the risk of contamination of the donor mate cornea has also to be taken into account.[17 33 34] In our literature review, positive donor rim cultures were highly predictive of the infectious agents isolated from recipients, not only for the majority of fungal but also for the minority of bacterial isolates. *Candida* species was the isolate most commonly involved in the development of interface keratitis after both DALK and EK (DSAEK and DMEK), suggesting a possible predisposition of this microorganisms for growing in

a sequestered hypoxic environment, protected from the host immune system response.

Therapeutic algorithms for IIK are not yet defined. Conventional approach to the diagnosis and treatment of microbial keratitis is not applicable to IIK due to the deep stromal location of the infiltrates that precludes access for scrapings and cultures and impedes topical drug penetrations. Kitzman *et al*[17] described a case of IIK after DSAEK, caused by *C. albicans,* with an unusual extension to the corneal surface, allowing for scraping and cultures, that was successfully treated with topical antimicrobials. On the basis of the clinical appearance and of the available information (donor rim culture), treatment is usually started empirically with broad spectrum antimicrobial drops including antifungals (amphotericin B 0.15% or voriconazole 1%) and, in cases of highly suspected or proved fungal infection, with systemic antifungals (oral voriconazole 100–200 mg two times a day or oral fluconazole 200 mg two times a day). In our literature review, topical and systemic treatments were not successful alone on halting the progression of fungal and bacterial infection in the majority of DALK and EK cases, probably due to the difficulty to reach a therapeutic concentration at the site of infection. In order to provide maximum drug load exactly at the graft–host interface, irrigation of the DM after DALK and injection of antifungal drugs in the deep stroma after EK have been attempted with the aim of salvaging the graft and avoiding PK. Treatment was efficacious in some cases[24 31] but carries a risk of DM rupture (DALK)[7 10 11] or graft dislocation (EK) with a potential hazard for anterior chamber contamination. Furthermore, interface scarring may result after treatment limiting the visual outcome.[24]

Surgical intervention by donor graft removal was carried out in several cases with the dual purpose of reducing the microbial load and provide ample material for microbiology in order to address postoperative treatment. Disadvantage of this procedure is the risk of disseminating the infection into the anterior chamber and causing endophthalmitis. For this reason, donor lenticule removal was often followed by multiple intracameral and/or intravitreal injection of antifungals with a possible risk of toxicity for the intraocular structures. In our review, five patients (16%) with IIK after EK developed endophthalmitis requiring combined PK and pars plana vitrectomy. Among these, three were initially treated by donor lenticule removal.[20 26 27] To the contrary, none of the patients with IIK after DALK developed endophthalmitis, but donor graft exchange, attempted in three cases, was successful only in one.[5] Collected data suggests that in DALK, the host DM is temporary capable to withhold the infection and avoid dissemination, explaining the better visual outcomes and the fewer complication recorded after excisional PK in patients with DALK compared with patients with EK.

Early excisional PK with removal of the sequestered infection may be advocated as a safe and effective measure to treat a post-LK infection of fungal origin. In a large series of IIK cases after DSAEK, Nahum *et al*[25] described the results of early excisional PK with intracameral antimicrobials injection at the end of surgery. None of these patients developed endophthalmitis and most patients retained good visual acuity and a long-term graft clarity. Because the procedure was conducted in relatively quiet eyes, postoperative complications (ie, recurrence of infection, graft failure, macular oedema, glaucoma), frequently developing after longstanding inflammation, were few.

In conclusion, any small whitish interface opacity occurring days to weeks after any kind of LK should be followed closely and considered infectious, especially in the setting of a positive rim culture. Whenever we suspect a IIK, fungal infection by *Candida* species, originating from the donor graft, has to be considered the most likely diagnosis. Donor rim cultures of the grafted cornea as well as the mate cornea should be traced with the help of the eye bank to gather clues of the possible infectious agent. Medical treatment with direct injection of antimicrobials in the graft–host interface can be attempted to spare further surgical intervention. In view of the endophthalmitis risk, early intervention with excisional PK should be considered whenever signs of spreading of the infection become evident despite treatment.

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