Recurrent Fungal Keratitis Following Penetrating Keratoplasty: An Unusual Source of Infection

The management of fungal keratitis following penetrating keratoplasty, which has a reported incidence of 0.16%,1 can be challenging. This case highlights the complexity of simultaneously managing recurrent Candida parapsilosis keratitis isolated from the lacrimal sac in the setting of a rejection-prone graft.

Report of a Case. A 75-year-old woman visited us in 2007 with left ocular discomfort for 1 month. She had previous bilateral penetrating keratoplasties (for the right eye in 1998 and for the left eye in 2004) for decompensated Fuch’s endothelial dystrophy. She had undergone trabeculectomy with mitomycin C (in 2006) and was using topical dexamethasone sodium phosphate, 0.1%, daily in the left eye. Her medical history included uterine carcinoma, treated Hodgkin lymphoma, pulmonary embolism, emphysema, hypertension, ischemic heart disease, hyperthyroidism, and renal failure.

Visual acuity was 6/12 (20/40) OD with clear corneal graft and 6/36 (20/100) OS. Examination of the left eye revealed a deep stromal infiltrate measuring 2 × 1.3 mm and with hypopyon (Figure, A). Steroid eyedrops were temporarily stopped, and treatment with cefuroxime sodium, 5%, and gentamicin sulfate, 0.3%, was commenced. Anterior chamber tap and corneal biopsy yielded a heavy growth of C parapsilosis. The treatment regimen was changed to intensive topical fluconazole, 0.2%, ofloxacin, and oral voriconazole (400 mg loading followed by 200 mg twice daily). Topical dexamethasone was reintroduced owing to evidence of rejection at day 7 and was gradually tapered as the abscess and graft edema resolved over the following 2 months. Keratitis recurred 2 months after discontinuing antifungal agents (Figure, B). Empirical treatment with fluconazole, 0.2%, and oral itraconazole, 100 mg twice daily, was commenced. Gentamicin, 1.5%, and cefuroxime, 5%, were added, and itraconazole was changed to voriconazole as the keratitis progressed.

Figure. Clinical appearance of the first stromal abscess in the recipient cornea (A), recurrence involving the graft and graft-host junction (B), and 2 suture abscesses with feathery edges in the regraft (C). Histological examination of corneal tissue removed at penetrating keratoplasty was performed. D, Abscess of the cornea with purulent exudate, within which the Descemet membrane (arrows) can be identified (hematoxylin-eosin, original magnification ×200). E, Fungal spores (black arrows) and occasional hyphae (arrowhead) within purulent exudate on the posterior corneal surface (periodic acid–Schiff, original magnification ×400).
to involve almost the entire graft. Histopathological examination of tissue removed at regraft isolated the same organism (Figure, D and E). Postoperative prophylactic topical fluconazole, 0.2%, and amphotericin B, 0.15%, were combined with dexamethasone, 0.1%, 4 times daily. However, 2 new abscesses were identified along the suture tracks 1 month following regraft (Figure, C).

The recurrence of fungal keratitis led to speculation that the lacrimal sac was harboring the organism, which had become resistant to treatment by forming a biofilm. Culture and sensitivity of a lacrimal sac aspirate yielded *C parapsilosis*. To manage the lacrimal sac infection, treatment with topical caspofungin acetate, 1%, 4 times daily (off-label use) was commenced. The lacrimal sac was actively irrigated once with 0.5 mL of caspofungin acetate, 1%, solution using a 2-mL syringe and a lacrimal cannula introduced through the lower punctum. Topical caspofungin caused ocular irritation and was replaced by topical amphotericin B, 0.15%, combined with prednisolone, 0.03%, 4 times daily after 1 week. As the abscesses resolved, prednisolone was switched to dexamethasone, 0.1%, 4 times daily. Treatment with amphotericin B was stopped 4 months later, while treatment with dexamethasone was tapered over the subsequent 8 months. The patient remains free from fungal keratitis to date, 1 year after stopping antifungal treatment.

**Comment.** Although our patient did not manifest any symptoms or signs of dacryocystitis, we believe that the lacrimal sac was creating a niche for the pathogen. Fungal dacryocystitis is reported in 3.3% of chronic dacyrocystitis cases in adults; however, to our knowledge, *C parapsilosis* dacryocystitis has been described in only 1 case.3

The pathogenicity of *C parapsilosis*, an organism commensal with human skin, is limited by intact integument. However, adherence to mucosal surfaces and hydrolytic enzyme secretion enable its invasion and colonization of tissues in susceptible hosts.4 In the mature biofilm, its chief virulence factor, fungal cells are ensheathed in a thick extracellular matrix that is highly resistant to antimicrobial agents such as azoles5 and host immune responses.4 Echinocandins such as caspofungin inhibit β-1,3-glucan synthesis in fungal cell walls, making them selective against the pathogen. At therapeutic levels, caspofungin inhibits yeast cells within the biofilm irrespective of its maturation stage.4 Solutions of caspofungin, 0.5% and 1%, have been used successfully to treat fungal keratitis,6 as in our case.

This report highlights the importance of thorough assessment and the use of diagnostic tools such as corneal biopsy, anterior chamber tap, and lacrimal sac aspirate to identify the offending organism and its source. In this case, asymptomatic *C parapsilosis* dacryocystitis was identified as a source of recurrent fungal keratitis in a corneal graft and was successfully eradicated following irrigation of the lacrimal drainage system with caspofungin, 1%, solution.

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**Author Contributions:** Dr Gregory had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Financial Disclosure:** None reported.

**Additional Contributions:** Fiona Roberts, FRCPATH, University Department of Pathology, Western Infirmary, Glasgow, Scotland, provided and assisted in the interpretation of histology micrographs.


**Genotype at Polymorphism rs11200638 and HTRA1 Expression Level**

*G* enetic factors strongly contribute to age-related macular degeneration (AMD). The loci at chromosomes 1q32 and 10q26 have been repeatedly and consistently linked to the disease. Compared with the successful discovery of the first AMD susceptibility gene *CFH* at the chromosome 1q32 locus, it has been difficult to identify with certainty the susceptibility variation(s) responsible for linkage and association at the chromosome 10q26 locus. One major reason for the inconclusive findings is that the polymorphisms in genes *ARMS2* and *HTRA1* are in such strong linkage disequilibrium that their effects are indistinguishable using statistical analysis. *HTRA1* was proposed as the susceptibility gene, partly based on the result that the risk allele (A) of the polymorphism rs11200638, which is strongly associated with AMD, was reportedly correlated with a higher level of *HTRA1* in lymphocytes and retinal pigment epithelium.12 However, this result remains controversial.13 We therefore conducted this study to test whether the genotype at rs11200638 is correlated with *HTRA1* expression in peripheral blood and retina.

**Methods.** Retinal tissues (including retina, retinal pigment epithelium, and choroid) were punched from the macula of fresh frozen eyes retrieved within 24 hours of death from 24 unrelated white subjects (mean [SD] age, 76.4 [14.5] years) without any known eye diseases, and RNA was extracted with the RNeasy lipid tissue kit (Qiagen Inc, Valencia, California). The RNA was also extracted from whole blood samples of 52 white subjects including 46 cases (mean [SD] age, 79.0...