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Case Report

A Rare Microsporidial Infection in Lamellar Corneal Tissue, following Transepithelial Photorefractive Keratectomy

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Keywords
Microsporidia · Stromal keratitis · Keratoconjunctivitis · Deep anterior lamellar keratoplasty

Abstract
The aim of this study was to report a unique case of microsporidial keratitis over deep anterior lamellar keratoplasty after transepithelial photorefractive keratectomy surgery that was successfully treated with therapeutic lamellar keratoplasty without recurrence at King Khaled Eye Specialist Hospital in Riyadh, Saudi Arabia. The patient presented with recurrent attacks of eye pain, redness, photophobia, and decreased vision. The patient was initially treated as a case of presumed herpetic keratouveitis using antiviral medication and topical steroids with partial improvement. During the last episode, the condition deteriorated and patient underwent therapeutic lamellar keratoplasty. Histopathology indicated an infected graft with evidence of microsporidial infection. The patient was discharged with complete corneal epithelial healing and no signs of recurrence during follow-up. Microsporidial infection is a rare cause of stromal keratitis that affects both immunocompetent and immunosuppressed patients. Microsporidia should be suspected after surface ablation refractive surgery if the patient presents with recurrent symptoms of keratoconjunctivitis or stromal keratitis that are partially responsive to topical steroid therapy.

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Introduction

Microsporidia are a group of obligate intracellular protists belonging to the phylum Microspora that can cause ocular, gastrointestinal, muscular, and renal infections [1]. Microsporidial keratitis is a rare ocular infection that can present as either stromal keratitis in immunocompetent patients or as superficial punctate keratoconjunctivitis which mainly affects immunocompromised patients but has also been reported in immunocompetent patients [1, 2]. Risk factors include eye trauma, contact lens wear, prior refractive surgery, and exposure to contaminated water [3–6]. In this report, we present a case of microsporidial keratitis over deep anterior lamellar keratoplasty (DALK) in an immunocompetent patient following transepithelial photorefractive keratectomy (Trans-PRK) that was diagnosed at King Khaled Eye Specialist Hospital (KKESH). The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000528894).

Case Report

A 41-year-old Saudi female with hypothyroidism presented in June 2019, complaining of redness, photophobia, and blurry vision in her right eye for 1 week. Past ophthalmic surgical history of the right eye included DALK for keratoconus in February 2017, followed by suture removal in July 2018, then Trans-PRK with mitomycin C for post-keratoplasty compound hyperopic astigmatism in April 2019.

On examination, the visual acuity was 20/50 and slit-lamp examination indicated follicular conjunctivitis, mild diffuse subepithelial haze, anterior chamber reaction with keratic precipitates (shown in Fig. 1). She was diagnosed with presumed herpetic keratouveitis and treated with valganciclovir (Virgan®; Thea Pharmaceuticals Ltd., Staffordshire, UK) five times a day for 10 days, valacyclovir (Valtrex®, GlaxoSmithKline PLC., Brentford, UK) 1 g twice a day tapered over 1 month and then maintained on 500 mg once daily, and 1% prednisolone acetate (Pred-Forte®; Allergan, Irvine, CA, USA) every 3 h tapered slowly over weeks to once daily. The patient clinically improved; however, whenever the medications were tapered down or stopped, the symptoms recurred.

In January 2021, she presented to the ophthalmic emergency department with pain, redness, photophobia, and decreased vision in the right eye. Ophthalmic examination of the right eye revealed a visual acuity of 20/300 and an intraocular pressure of 16 mm Hg. Slit-lamp examination indicated moderate conjunctival injection, diffuse subepithelial haze on the graft with multiple white infiltrates, mild superior graft edema, corneal epithelial defect, and occasional cells (Fig. 2a).

Corneal scraping was obtained for smears (Gram, Giemsa, KOH, Gomori methenamine silver, and calcofluor white staining), cultures (blood, chocolate, Sabouraud dextrose, and non-nutrient agars), and polymerase chain reaction for herpes simplex virus DNA. The patient was started on valacyclovir 1 g three times a day, valganciclovir five times a day, prednisolone acetate 1% every 3 h, and moxifloxacin (Vigamox®, Alcon Laboratories, Inc., Fort Worth, TX, USA) every 3 h. One week later, there was no improvement. The patient was admitted and started on fortified cefazolin (50 mg/mL) and fortified ceftazidime (50 mg/mL) every hour. Corneal smears, cultures, and polymerase chain reaction results came back negative. Enzyme-linked immunosorbent assay indicated the patient was seronegative for HIV.

After 2 weeks, the visual acuity decreased to hand motion with an increase in the size and density of the superior superficial infiltrate and epithelial defect (shown in Fig. 2b). Therapeutic DALK surgery was performed. The infected graft tissue was sent for histopathological

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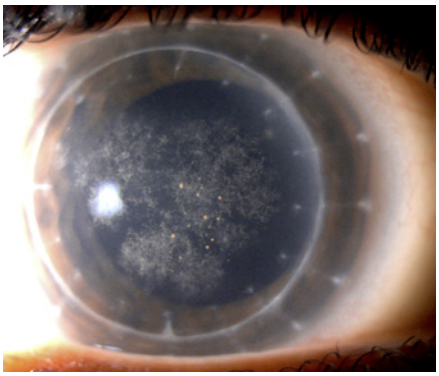

Fig. 1. Diffuse superficial corneal haze over DALK.

diagnosis. The histological sections consisted of corneal tissue partially lined by epithelium. The superficial stroma showed minimal infiltration with chronic inflammatory cells. Modified Ziehl-Neelsen stain (shown in Fig. 3a) and Masson's trichrome stain (shown in Fig. 3b) showed bright red spores, visible against a blue background, consistent with microsporidial infection.

Postoperatively, the patient was prescribed topical moxifloxacin every 3 h tapered over 3 weeks and topical voriconazole 1% every 2 h tapered over 6 weeks then discontinued. One week postoperatively, the patient was discharged with complete corneal epithelial healing and no signs of recurrence. One year after therapeutic DALK, the patient reported no similar episodes and the graft is clear with no signs of recurrence (shown in Fig. 2c). The best corrected visual acuity was 20/30.

Discussion

Microsporidial keratitis is a rare ocular infection with a wide range of presentations either as keratoconjunctivitis or stromal keratitis. Microsporidial keratitis is commonly misdiagnosed as herpetic keratitis due to similar presenting symptoms of recurrent redness, pain, photophobia, and decreased vision. This misdiagnosis may lead to treatment with antivirals and topical steroids [7]. Chan et al. [2] reported two patients with microsporidial keratoconjunctivitis who developed an anterior chamber reaction and keratic precipitate that improved with topical steroids.

Microsporidial stromal keratitis is a slowly progressing infection. Garg et al. [8] reported the mean duration of symptoms at presentation of 332 days, with 37.9% of patients presenting 1 year after the onset of symptoms. The clinical signs vary depending on the disease stage. Signs and symptoms include diffuse multifocal stromal infiltrates, non-purulent conjunctivitis, stromal edema, endothelial exudates, and epithelial defects [4]. However, unlike other forms of infectious keratitis, there seems to be no characteristic hallmark sign of the disease [8]. Some consider microsporidial stromal keratitis a different entity from microsporidial keratoconjunctivitis [4].

Our patient presented with follicular conjunctivitis, subepithelial haze, and recurrent attacks of anterior chamber inflammation early after Trans-PRK surgery. She was treated for presumed herpetic keratouveitis; however, the stromal keratitis manifested 6 months later. This may suggest that the patient initially had microsporidial keratoconjunctivitis that partially improved with topical steroids and with the prolonged use of steroids; it contributed to the persistent infection that manifested later as stromal keratitis.

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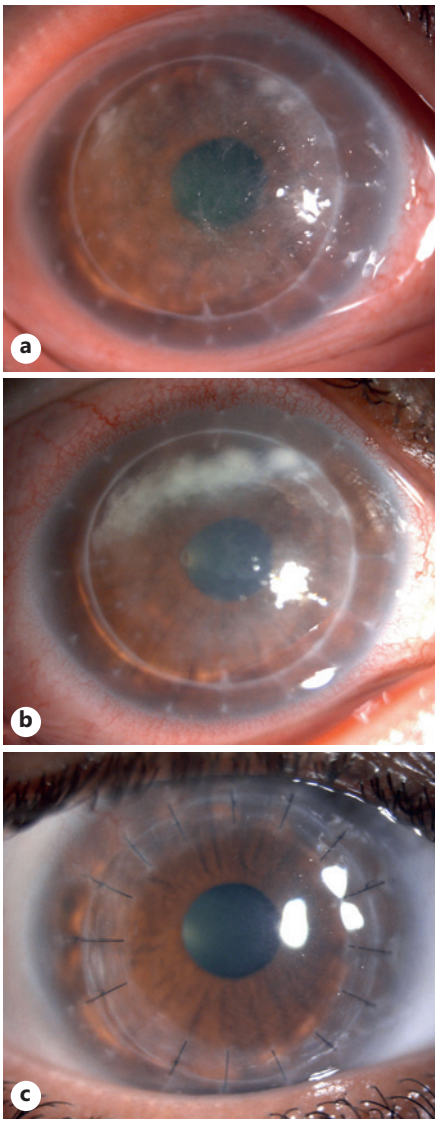

Fig. 2. Clinical presentation of microsporidial keratitis in the right eye. **a** The presentation at the emergency with multiple superior white corneal infiltrates. **b** After 2 weeks with increased size and density of the superior stromal infiltrate. **c** Clear graft with no recurrence 6 months after therapeutic lamellar keratoplasty.

Definitive diagnosis of microsporidiosis is clinically challenging and depends on detection of the spores in tissue samples. The spores appear oval to piriform in shape, measuring 2–7 μm in length and 1.5–5 μm in width. Gram's chromotrope and Modified Ziehl-Neelsen stains are ideal for detecting microsporidia. Other stains that could be used for identifying microsporidia are PAS, calcofluor white, Gemsa, and Gram [1, 7, 9, 10]. In our case, microsporidia were detected only after histopathological examination of the graft tissue using Modified Ziehl-Neelsen and Masson's trichrome stains.

The two commonly reported genera that are associated with ocular infections are *Encephalitozoon* and *Nosema* species. Identifying *Microsporidium* species usually requires electron microscopy or immunofluorescent staining techniques which were not performed in our case [1, 7].

Microsporidial keratitis following keratoplasty has been reported, and it can present as keratoconjunctivitis or graft rejection [9]. The occurrence of infection following keratoplasty can be attributed to local immunosuppression induced by prolonged use of topical steroids. However, in the current case, the patient did not show symptoms of infection following DALK despite the longer duration of topical steroid therapy and prolonged follow-up.

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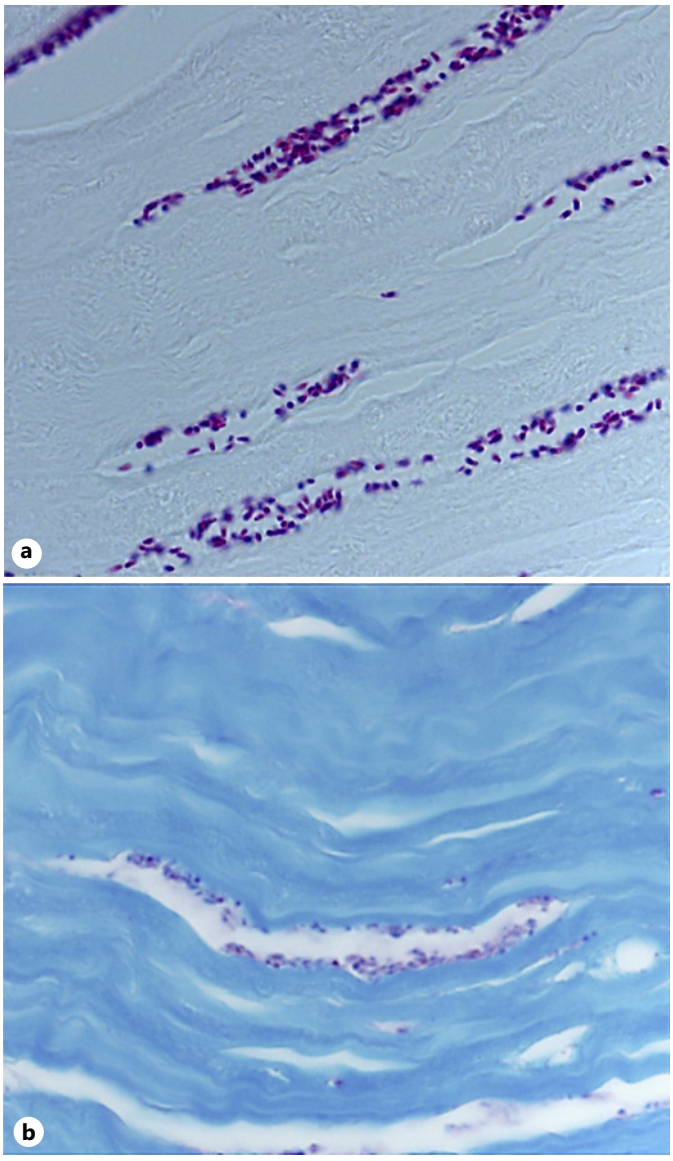

Fig. 3. Histopathology of microsporidial keratitis over DALK graft. **a** Modified Ziehl-Neelsen stain showed bright red spores that are visible against a blue background (magnification, ×1,000). **b** Masson's trichrome spores appeared red against a blue background with ill-defined internal morphology (magnification, ×1,000).

Microsporidial stromal keratitis has also been reported after uncomplicated femtosecond-assisted astigmatic keratotomy that presented with corneal infiltrate shortly after the procedure with the use of topical steroids [11]. Additionally, late-onset microsporidial stromal keratitis has been reported several years after laser-assisted in situ keratomileusis in immunocompetent patients with no history of trauma or contact lens use [6]. There were no reported cases of microsporidial keratitis after Trans-PRK.

Currently, there are no definitive guidelines for the treatment of microsporidial epithelial keratitis. Corneal scraping plays a crucial role in both diagnosis and treatment of superficial keratitis. Medical management with systemic albendazole and topical fumigilin is effective in mild cases of microsporidial keratoconjunctivitis. Furthermore, monotherapy with topical

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fluoroquinolone or topical voriconazole 1% has been reported to be an effective treatment of early superficial epithelial keratitis [3, 6, 12].

Recent evidence indicates that oral treatment may not be warranted for microsporidial epithelial keratitis. In more severe cases of stromal keratitis, surgical management is needed if medical management fails to control disease progression. Penetrating grafts seem to be preferred over lamellar grafts to reduce the possibility of recurrence [13]. However, successful management of superficial microsporidial stromal keratitis was achieved with DALK using the big-bubble technique [14] and femtosecond laser-assisted surgery [15]. Although the big-bubble technique could be an alternative to improve surgical outcomes, this procedure is technically challenging and carries the risk of Descemet membrane perforation, leading to subsequent intraocular spread of infection. In the current case, the patient underwent repeated DALK surgery, in which the infected graft was replaced and the infection was successfully eradicated without recurrence.

Conclusion

Microsporidial infection is a rare cause of stromal keratitis that affects both immunocompetent and immunosuppressed individuals. Microsporidia must be considered in the differential diagnosis of any patient presenting with a prolonged history of recurrent attacks of keratoconjunctivitis or stromal keratitis that is partially responsive or non-responsive to topical steroids. Therapeutic DALK can be considered a safe and effective surgery for superficial stromal keratitis when the diagnosis is not confirmed or the patient shows poor response to medical therapy.

Statement of Ethics

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by the Human Ethics Committee/Institutional Review Board (HEC/IRB) at King Khaled Eye Specialist Hospital (KKESH) in Riyadh, Saudi Arabia, approval number [21057-CR]. A written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mohammad Alabduljabbar and Rawan AlShabeeb contributed to the manuscript concept and writing, editing, and final revision of the manuscript. Fatima Sirajuddin and Azza Maktabi contributed to the writing, editing, and final revision of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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