



# Bilateral microsporidial keratoconjunctivitis in a clinically healthy female receiving intravitreal steroid injections: Associations and potential risk factors

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## ARTICLE INFO

### Keywords:

Microsporidia  
Keratitis  
Keratoconjunctivitis  
Uveitis  
Cystoid macular edema  
Intravitreal steroid injection

## ABSTRACT

**Purpose:** To present a unique case of bilateral microsporidial keratoconjunctivitis in a clinically healthy female receiving intravitreal steroid injections, and explore several associations and potential risk factors.

**Observations:** A 75-year-old woman with chronic idiopathic anterior uveitis was receiving regular intravitreal steroid in both eyes for secondary cystoid macular edema. Flare-ups of iritis were usually treated with topical non-steroidal anti-inflammatory drops, but in the left eye the patient also received a few limited courses of topical corticosteroid. The patient regularly instilled topical cyclosporine 0.05% for dry eyes. She was otherwise clinically healthy but had low serum immunoglobulin (Ig) M levels. There was no history of trauma or exposure to contamination. In her course of treatment, she developed a bilateral punctate keratitis. Corneal scrapings were diagnostic of Microsporidia. Topical voriconazole and moxifloxacin, as well as corneal debridement, were effective in resolving the infection.

**Conclusions and importance:** We propose that the factors and associations described in this case—intravitreal steroid, topical steroid, topical cyclosporine, and IgM deficiency—contributed variably to create relative, local, immunologic suppression in our patient. Among these potential risk factors, we believe that intravitreal steroid exposure may be prominent. In aggregate, they facilitated development of her opportunistic microsporidial corneal infection. Eye care specialists should have a high index of suspicion for microsporidial keratitis, if they observe an atypical chronic punctate keratitis in patients with similar clinical associations.

## 1. Introduction

Microsporidial infections of the ocular surface are extremely uncommon; they represented only 0.4% of microbial keratitis cases reported in one study from southern India.<sup>1</sup> Corneal eye infections from microsporidia have been predominantly found in patients with acquired immunodeficiency syndrome due to human immunodeficiency virus (HIV).<sup>1–8</sup> Microsporidial keratitis (MSK), however, is now also considered an “emerging” infection in immunocompetent individuals, being frequently associated with ocular trauma, exposure to soil or contaminated water, contact lens wear, and use of topical corticosteroids.<sup>1,2,5,6,8–14</sup> In this report we present a unique case of bilateral microsporidial keratoconjunctivitis (MSKC), in a uveitic patient receiving intravitreal steroid injections, with discussion of potential

associations and risk factors.

## 2. Case report

A 75 year old Caucasian female was referred to our University Cornea Service with keratoconjunctivitis of unclear etiology. Notably, for the past two years, she had been under treatment for chronic bilateral anterior uveitis with secondary cystoid macular edema (CME). She instilled ketorolac eyedrops intermittently for flare-ups of iritis. She also regularly used cyclosporine (CSA) 0.05% drops twice per day in both eyes, for dryness. On two occasions when the anterior chamber inflammation was relatively greater, she was additionally prescribed short courses of topical steroid in the left eye. For the CME, the patient had been injected with intravitreal triamcinolone twice in the right eye

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<https://doi.org/10.1016/j.ajoc.2022.101659>

Received 14 June 2021; Received in revised form 31 May 2022; Accepted 8 July 2022

Available online 9 July 2022

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and three times in the left. More recently, she had also received dexamethasone 0.7mg intravitreal implants in each eye. Past uveitis workup had revealed no underlying connective tissue or infectious processes. However, Immunoglobulin (Ig) M levels had been found to be low, at 25 mg/dl (normal range 40–230). There was no history of ocular trauma, exposure to soil or contaminated water, or travel abroad.

About one-and-half years into her uveitis and CME treatment, the patient—with only minimal irritation—was noted to have developed a band of slightly elevated white punctate deposits in the interpalpebral region her left cornea. The corneal lesions were thought at first to represent calcific band keratopathy related to chronic uveitis, and later Thygeson's superficial punctate keratitis, as their appearance seemed to wax and wane. Several months later, the patient had a flare-up of injection and irritation of the right eye. There were now numerous elevated white punctate deposits throughout the right cornea (Fig. 1), similar to the spots previously seen on the left. The patient was evaluated by our Cornea Service, where diagnostic corneal scrapings were performed. On pathologic examination, numerous plump oval bodies with rounded ends were observed within epithelial cells (Fig. 2). The bodies were Gram-positive, and also positive with Fite's acid-fast stain. Periodic acid-Schiff staining demonstrated dot-like positivity. The composite of histopathological features along with the characteristic clinical appearance<sup>3,6,12</sup> were consistent with microsporidia, and the patient was therefore diagnosed with MSKC.

Therapy with topical voriconazole and moxifloxacin was initiated; epithelial lesions were also gently debrided with a cotton tip applicator on several of the visits. After 7 more weeks, the keratoconjunctivitis completely resolved in both eyes.

### 3. Discussion

Because MSKC does not commonly occur in non-HIV patients, the condition can possibly elude diagnosis due to low index of suspicion in patients who may be similar to ours.<sup>6,7</sup> The appearance of the keratitis, for one, may mimic other more common conditions such as dry eye syndrome, calcific band keratopathy, adenoviral keratitis, and Thygeson's superficial punctate keratitis, and is frequently misdiagnosed as Herpes simplex keratitis.<sup>1,2,6,7,12–15</sup> Our patient also did not neatly fit the



Fig. 1. Slit lamp photo of right cornea, demonstrating microsporidial keratoconjunctivitis.

typical description of immunocompetent patients with MSK. In healthy individuals, microsporidial corneal infections classically present in the form of deep stromal keratitis (MSSK).<sup>1,3,6</sup> Our patient developed MSKC, the more superficial form of MSK, which is usually seen in more severely immunocompromised individuals.<sup>1–3</sup> The great preponderance of immunocompetent MSK patients are male, outnumbering females 8:1 in one study.<sup>10</sup> Cases commonly present in the fourth decade,<sup>1,9,10</sup> and tend to be unilateral,<sup>2,9,14</sup> while our patient was in her 8th decade, and had bilateral infection. Because the patient demographic was slightly atypical, symptoms were mild, and findings resembled other more common conditions, MSK in our patient was not initially suspected. Once suspected, the diagnosis can be made in a straightforward fashion from corneal scrapings and employing a variety of stains, based on characteristic pathological appearance under light and fluorescent microscopy.<sup>1,6,7,14</sup> In vivo confocal microscopy has also been employed.<sup>6,16</sup> Once identified, our patient's infectious keratitis responded readily to appropriate antimicrobial therapy.

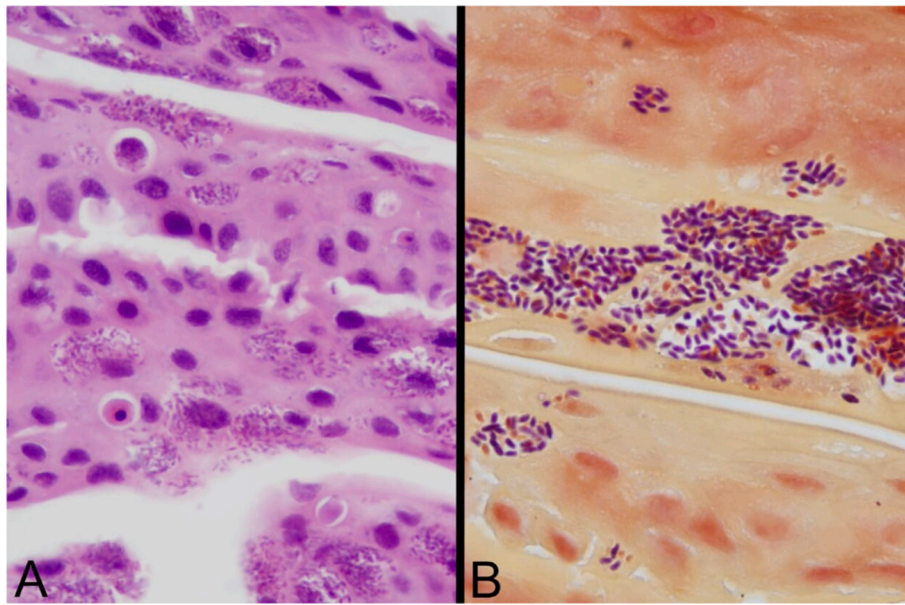
Topical steroids have been cited as a risk factor for MSK, as noted previously. Our patient, however, only used topical steroid intermittently in her left eye. She had more extensive local corticosteroid exposure in the form of repeated intravitreal steroid injections and a steroid implant in both eyes. We therefore postulate that the intravitreal steroid likely had a greater influence on the patient's development of MSKC, than did the steroid drops.

Both cell-mediated and humoral immune responses appear to be involved in mammalian adaptive immunology against microsporidial infection.<sup>17</sup> Cyclosporine was found to have affected the immune response to microsporidia in experimentally infected mice, increasing spore secretion while decreasing serum IgG levels.<sup>18</sup> Although topical CSA has not previously connected with MSK, the drug does have immunomodulatory properties, particularly T-cell inhibition. In uveitis, Ig levels can be increased<sup>19</sup>; paradoxically, our patient was found to have decreased IgM levels. Up to the time of this report however, she had never been unusually susceptible to infection, opportunistic or otherwise. For this reason, we refer to her as being "clinically healthy". We do not consider this attribution of general healthfulness to be unreasonable; Joseph et al. considered all of their study patients "healthy", merely because they tested HIV-negative.<sup>1</sup> Nevertheless, our patient's limited immunodeficiency may very possibly have additionally factored into her development of MSK. In an illustrative case report, a child with both IgA and IgM deficiency developed intestinal microsporidia.<sup>20</sup>

A word about the patient's medical treatment: There have been a number of therapeutic regimens described for treatment of MSK. For the deeper form of stromal keratitis, oral albendazole (an anti-helminthic) has been utilized, in conjunction with topical fumagillin or antiseptic (anti-protozoan) agents like polyhexamethylene biguanide (PHMB) and chlorhexidine, but penetrating keratoplasty is often required for cure.<sup>2,6,7,15</sup> MSKC is often self-limited,<sup>2,14</sup> and may also respond to repeated swabbing with a cotton swab, mechanical debridement, or even simple topical lubrication.<sup>1,7,8,12,14</sup> As with MSSK, the more superficial MSK has been treated with topical fumagillin and oral albendazole.<sup>7,8</sup> Administration of topical fluoroquinolones<sup>10</sup> and topical antifungals such as voriconazole,<sup>2,21</sup> both as monotherapy or in combination,<sup>16</sup> has been reported to be also effective. Oral antifungals, metronidazole (an antiprotozoan/antibiotic), and topical antiseptics again such as PHMB, chlorhexidine, and propamidine isethionate have been employed successfully for MSKC as well.<sup>1,2,7,8,12,13</sup> There is no real consensus as to which regimen should be considered preferred, or first line. We chose the dual regimen of moxifloxacin and compounded topical voriconazole, both of which happened to be available at our patient's pharmacy at the time. Conceivably, other therapeutic regimens could also have been effective.

### 4. Conclusions

We have reported a case of bilateral MSKC in a clinically healthy



**Fig. 2.** A) Hematoxylin and eosin section demonstrates several fragments of corneal epithelium in which many epithelial cells harbor cytoplasmic ovoid-shaped bodies that appear as coarse granular material within the cytoplasm of affected cells. There is no inflammation. B) Tissue Gram stain reveals Gram-positive microsporidia spores. They are also acid-fast (not shown). Original magnification: A) 600x, B) 1000 x.

older female with a unique collection of clinical associations—intravitreal steroid, topical steroid, topical cyclosporine, and IgM deficiency. These likely contributed variably to create relative, local, immunologic suppression in our patient. In aggregate, they facilitated development of an opportunistic microsporidial corneal infection. We believe that prominent among these potential risk factors may be local steroid exposure, not only topically, but also in the form of repeated intravitreal steroid injections. Eye care specialists should have a high index of suspicion for MSK, if they observe an atypical chronic superficial punctate keratitis in patients—even ostensibly healthy ones—having similar clinical risks and associations.

#### Patient consent

The Stony Brook University Institutional Review Board (IRB) has declared that IRB review and approval are not required for single-case case reports. The patient has given written consent for publication of this case report on her ocular condition. A copy of the consent has been scanned into her electronic medical records.

#### Disclosures

The following authors have no financial disclosures: TC, JB, RS, AR, DM. All authors attest that they meet the current ICMJE criteria for Authorship. Bobbi S. Pritt, M.D., (Director of Clinical Parasitology Laboratory, Mayo Clinic) provided assistance and advice.

#### Declaration of competing interest

None.

#### Acknowledgements

No funding or grant support

#### References

- Joseph J, Sridhar MS, Murthy S, Sharma S. Clinical and microbiological profile of microsporidial keratoconjunctivitis in southern India. *Ophthalmology*. 2006;113(4): 531–537. <https://doi.org/10.1016/j.ophtha.2005.10.062>.
- Garg P. Microsporidia infection of the cornea—a unique and challenging disease. *Cornea*. 2013;32(11):S33–S38.
- Weber R, Bryan RT, Schwartz DA, Owen RL. Human microsporidial infections. *Clin Microbiol Rev*. 1994;7(4):426–461.
- Sharma S, Das S, Joseph J, Vemuganti GK, Murthy S. Microsporidial keratitis: need for increased awareness. *Surv Ophthalmol*. 2011;56(1):1–22.
- Taju S, Tilahun Y, Ayalew M, Fikrie N, Schneider J, Kempen JH. Diagnosis and treatment of microsporidial keratoconjunctivitis: literature review and case series. *J Ophthalmic Inflamm Infect*. 2011;1(3):105–110.
- Moshirfar M, Somani SN, Shmunes KM, et al. A narrative review of microsporidial infections of the cornea. *Ophthalmol Ther*. 2020;9(2):265–278. <https://doi.org/10.1007/s40123-020-00243-z>. Epub 2020 Mar 10. PMID: 32157613; PMCID: PMC7196102.
- Grillo LM, Epstein IJ, Donnenfeld ED, Perry HD. Late-onset microsporidial keratitis in femtosecond astigmatic keratotomy after laser-assisted phacoemulsification. *Cornea*. 2018;37(11):1471–1473. <https://doi.org/10.1097/ICO.0000000000001743>. PMID: 30161056.
- Fan NW, Lin PY, Chen TL, Chen CP, Lee SM. Treatment of microsporidial keratoconjunctivitis with repeated corneal swabbing. *Am J Ophthalmol*. 2012;154(6):927–933. <https://doi.org/10.1016/j.ajo.2012.06.002>. e1, Epub 2012 Sep 5. PMID: 22959880.
- Tung-Lien Quek D, Pan JC, Krishnan PU, Zhao PS, Teoh SC. Microsporidial keratoconjunctivitis in the tropics: a case series. *Open Ophthalmol J*. 2011;5:42–47. <https://doi.org/10.2174/1874364101105010042>.
- Loh RS, Chan CM, Ti SE, Lim L, Chan KS, Tan DT. Emerging prevalence of microsporidial keratitis in Singapore: epidemiology, clinical features, and management. *Ophthalmology*. 2009;116(12):2348–2353. <https://doi.org/10.1016/j.ophtha.2009.05.004>.
- Chan CM, Theng JT, Li L, Tan DT. Microsporidial keratoconjunctivitis in healthy individuals: a case series. *Ophthalmology*. 2003;110(7):1420–1425.
- Das S, Sharma S, Sahu SK, Nayak SS, Kar S. Diagnosis, clinical features and treatment outcome of microsporidial keratoconjunctivitis. *Br J Ophthalmol*. 2012;96(6):793–795. <https://doi.org/10.1136/bjophthalmol-2011-301227>.
- Joseph J, Vemuganti GK, Sharma S. Microsporidia: emerging ocular pathogens. *Indian J Med Microbiol*. 2005;23(2):80–91. <https://doi.org/10.4103/0255-0857.16045>. PMID:15928435.
- Mohanty A, Mitra S, Das S, Priyadarshini S, Sahu SK. Clinical profile of bilateral microsporidial keratoconjunctivitis in healthy individuals—a case series with long-term follow-up. *Cornea*. 2020;39(7):902–908.
- Das S, Sharma S, Sahu SK, Vemuganti GK. Intraocular invasion by microsporidial spores in a case of stromal keratitis. *Arch Ophthalmol*. 2011;129(4):513–515. <https://doi.org/10.1001/archophthalmol.2011.61>. PMID:21482880.
- Malhotra C, Jain AK, Kaur S, Dhingra D, Hemanth V, Sharma SP. In vivo confocal microscopic characteristics of microsporidial keratoconjunctivitis in immunocompetent adults. *Br J Ophthalmol*. 2017;101(9):1217–1222. <https://doi.org/10.1136/bjophthalmol-2016-309794>. Epub 2017 Jan 27. PMID: 28130350.
- Han Y, Gao H, Xu J, et al. Innate and adaptive immune responses against microsporidia infection in mammals. *Front Microbiol*. 2020;11:1468. <https://doi.org/10.3389/fmicb.2020.01468>. eCollection.2020.
- Galván AL, Agudelo Sdel P, Restrepo JG, Toro F, Galviz LA, Botero J. Efecto de la ciclosporina A en ratones C57BL/6 infectados con *Encephalitozoon intestinalis*

- [Cyclosporine A effect in mice C57BL/6 infected with *Encephalitozoon intestinalis*]. *Biomedica*. 2006;26(1):126–137. Spanish. PMID: 16929910.
19. Kahn LS, Schlaegel Jr TF, Weber JC, Biegel A. Serum immunoglobulins and uveitis. *Arch Ophthalmol*. 1983;101(3):458–459. <https://doi.org/10.1001/archophth.1983.01040010458025>. PMID:6830503.
20. Usluca S, Aksoy U. İmmün sistemi baskılanmış bir çocukta *Microsporidium* spp. Enfeksiyonunun polimeraz zincir reaksiyonu ile tanımlanması [*Microsporidium* spp. infection in an immunocompromised child diagnosed by polymerase chain reaction]. *Mikrobiyoloji Bulteni*. 2010;44(4):679–683. Turkish.
21. Khandelwal SS, Woodward MA, Hall T, Grossniklaus HE, Stulting RD. Treatment of microsporidia keratitis with topical voriconazole monotherapy. *Arch Ophthalmol*. 2011;129(4):509–510. <https://doi.org/10.1001/archophthalmol.2011.54>. PMID: 21482878; PMCID: PMC3412052.