• Letter to the Editor •

Atypical progression of microsporidial keratoconjunctivitis to immune ring keratitis: a case report

Mariya B Doctor[1], *Brenda P Walaba*[2], *Merle Fernandes*[1]

[1]Shantilal Sanghvi Cornea and Anterior Segment Services, L V Prasad Eye Institute, Hyderabad 500034, India
[2]Academy of Eye Care Education, L V Prasad Eye Institute, Visakhapatnam 500034, India
Correspondence to: Mariya B Doctor. Shantilal Sanghvi Cornea and Anterior Segment Services, L V Prasad Eye Institute, Hyderabad 500034, India. drmariyabashir@lvpei.org
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Dear Editor,

A microsporidial infection of the cornea predominantly manifests in two forms, the more common epithelial keratoconjunctivitis (MKC), and the less common stromal keratitis (MSK)[1]. MKC typically presents as multifocal, coarse, punctate, raised, corneal epithelial lesions, with a characteristic "stuck-on" appearance. This form is usually self-resolving, either with or without leaving any residual scar[2-3]. In contrast, MSK is generally infective, runs a chronic indolent course, and presents as suppurative, mid-stromal, multifocal corneal infiltrates[4]. MSK is usually diagnosed by corneal biopsy and is less responsive to medical therapy, often requiring penetrating keratoplasty[5].

MKC and MSK are two distinct entities, each with its own presentation and treatment protocols. However, the occurrence of microsporidial immune stromal keratitis (MISK) following MKC has not been reported in literature. We present a case of epithelial MKC that progressed to MISK. This case provides valuable insight into the occurrence, clinical features, and treatment of MISK. Differentiating this from infective stromal microsporidial keratitis is essential to avoid unnecessary antibacterial therapy or surgical interventions such as therapeutic keratoplasty. Hence, awareness about this rare sequela is crucial for an ophthalmologist treating these conditions.

CASE REPORT

All procedures adhered to the tenets of Declaration of Helsinki. Written informed consent was obtained from the patient. A forty-two-year-old woman presented to our hospital with a history of pain, redness and watering of the right eye (RE) over three weeks. She gave a history of trauma to the eye with a blade of grass prior to the onset of symptoms. She had sought treatment elsewhere, where she was prescribed eye drops moxifloxacin 0.3% four times a day, with no resolution in her symptoms.

On presentation, her visual acuity was 20/60 and 20/20 in the RE and left eye (LE) respectively. RE showed diffuse conjunctival injection, multiple coarse, elevated, superficial punctate corneal epithelial lesions (Figure 1A, 1B), having a "stuck-on" appearance and staining positive with fluorescein (Figure 1C). Rest of the findings were normal. The anterior and posterior segment examination findings of her LE were within normal limits. A corneal scraping was performed using a No.15 bard parker blade under topical anesthesia. The smears were sent for Gram's and potassium hydroxide (KOH) staining. The Gram's stain showed gram-positive, stippled, ovoid structure, while KOH with calcofluor white (CFW) stain showed significant oval fluorescing bodies against a dark background suggestive of microspodial spores (Figure 1D). Hence a diagnosis of microsporidia keratoconjunctivitis was made. The patient was noted to be immunocompetent. She was started on two-hourly carboxy methyl cellulose 0.5% and a combination of chloramphenicol 1 mg with polymixin B 5000 IU eye drops four times a day in the RE, since an epithelial defect was created while performing the corneal scraping.

At one week review, the RE visual acuity was unchanged (20/60); the corneal epithelial defect had healed; and the raised, stuck-on corneal epithelial lesions had resolved. However, she developed a seven-millimeter, anterior stromal, faint greyish, ring-shaped peripheral corneal infiltrate, with underlying keratic precipitates (Figure 2A, 2B). There was no corneal edema or epithelial defect. The surrounding cornea was clear, and the anterior chamber was quiet. At this point, we suspected immune-stromal keratitis, however infective stromal keratitis could not be ruled out. Hence, we continued her on topical lubricant therapy. On subsequent reviews (Figure 2C, 2D), she was symptomatically better, her RE visual acuity had improved to 20/40, and the immune ring remained stable. Since there

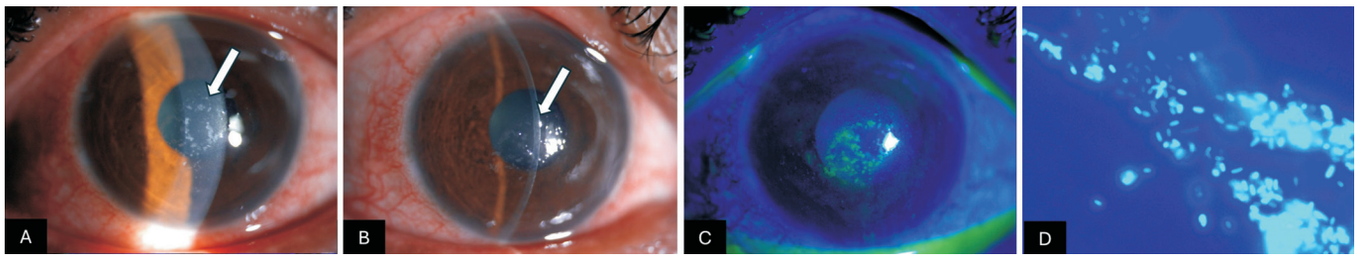

Figure 1 Images at presentation A: Slit lamp image showing multiple coarse punctate lesions over the corneal epithelium; B: Slit beam showing raised lesions over the corneal epithelium; C: Fluorescein stain in cobalt blue filter light showing stain positive stuck on lesions over the corneal epithelium; D: Potassium hydroxide with calcofluor white (KOH-CFW) stained image taken under fluorescence microscope (10×) showing plenty of ovoid fluorescent microsporidial spores.

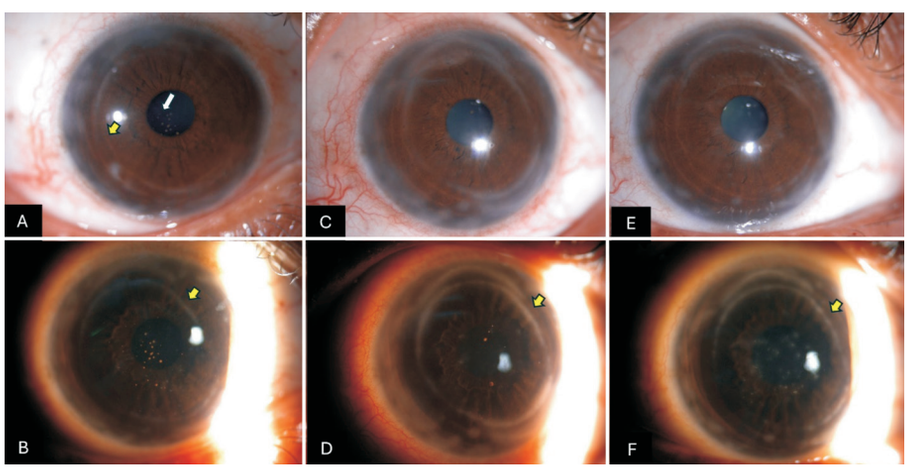

Figure 2 Diffuse and sclerotic scatter image on slit lamp of the patient at various follow ups A: At 1wk visit showing resolution of the raised epithelial lesions. Diffuse slit lamp image shows greyish opacity in the peripheral corneal and keratic precipitates (KP) in the central cornea (white arrow); B: Sclerotic scatter image shows greyish white ring in the mid peripheral cornea (yellow arrow) and KPs in the central cornea; C: Image taken at 2wk, showing conjunctival congestion, and increase in the ring-shaped opacification of the cornea as compared to the first visit; D: Sclerotic scatter image showing increase in the size and density of the whitish ring-shaped corneal opacification (yellow arrow) as compared to previous visit (B); E: At 1mo after starting steroids, diffuse slit lamp image showing reduced density of the corneal ring like infiltrate; F: Sclerotic scatter image taken at the same visit showing reduced density of the ring like opacification of the cornea as compared to D image (yellow arrow).

was no worsening of symptoms or increase in the size and density of lesion, we started her on topical prednisolone acetate 1% four times per day, in a weekly tapering dose. She showed significant improvement within a month. Her visual acuity improved to 20/20, though there was a persistent mid stromal nebular corneal scar (Figure 2E, 2F).

DISCUSSION

Microsporidia are obligate, intracellular spore forming parasitic fungi that primarily cause gastrointestinal, ocular, musculoskeletal and cerebral infections[6]. They account for 0.4% cases of microbial keratitis[2]. While initially considered a disease of the immunocompromised, it is now recognized that microsporidial infection of the cornea can occur regardless of an individual's immune status[4]. Known risk factors include trauma, exposure to contaminated water or rainwater, contact lens use, dust, insect or other foreign body, and exposure to wild and domestic animals[4,7].

Microsporidia can be diagnosed using light microscopy. Gram positive, stippled, round to oval spores are observed on Gram's stain, while KOH-CFW stain shows oval, fluorescent spores against a dark background. The spores vary in size ranging from 2×5 μm to 2×10 μm and occasionally have elongated tubular structures at their poles. KOH-CFW staining has the highest detection rate (96.7%) followed by modified Ziehl-Neelsen stain (93.3%), Gram stain (90%), and Giemsa stain (73.3%)[8]. Anterior segment optical coherence tomography and confocal microscopy are other diagnostic modalities which can be used as an adjunctive for diagnosis of Microsporidial keratitis[9].

Ocular infection with microsporidia can manifest as epithelial keratitis (keratoconjunctivitis), stromal keratitis (infective stromal keratitis), uveitis (iritis, anterior uveitis) and endophthalmitis. MKC is the most common ocular presentation, characterized by unilateral, multifocal,

superficial, coarse, punctate corneal epithelial lesions with a classic stuck-on appearance[4,10-11]. The subepithelial infiltrates are typically 1-1.5 mm in size, coin-shaped stromal lesions, which resolve with anti-inflammatory therapy, usually in the form of topical steroids[8-9]. MSK on the other hand, presents with non-purulent conjunctivitis and diffuse multifocal stromal infiltrates, typically requiring surgical intervention[1]. MKC is self-limiting and responds well with topical lubricants alone which is given only for symptomatic relief[3]. Known sequalae following MKC include sub-epithelial infiltrates, endothelitis, and uveitis[12]. The sub-epithelial infiltrates can be 1-1.5 mm in size, coin-shaped stromal lesions and resolve with anti-inflammatory therapy in the form of topical steroids[12-13].

Following resolution of the epithelial lesion, our patient developed a large, seven-millimeter stromal infiltrate without other signs of infection, raising suspicion for immune stromal keratitis. Mohanty *et al*[14] described immune stromal keratitis due to microsporidia in their study. They performed corneal scrapings for all patients presenting with nummular or interstitial keratitis. Those with microscopically proven microspodial infection were included in the study. Their results showed clinical features such as a relatively short history (ranging from one week to three months), rapid response to topical steroids, large nummular lesions, and disciform or ring-like lesions in the stroma of 2 mm, with the absence of vascularization, anterior chamber reaction or raised intraocular pressure (IOP). We believe that our patient, while not exhibiting the characteristic size as described above, displayed all the other features necessary to classify it as a case of MISK.

The corneal immune ring was first described by the German ophthalmologist Wessely[15] in 1911 as an allergic or hypersensitive reaction in the cornea. Studies later showed that the ring was composed of antigen-antibody complexes along with the deposition of inflammatory cells in the corneal stroma[16]. In bacterial keratitis, ring formation occurs due to the release of endotoxin or exotoxins, which activate the complement pathway, and trigger the release of pro-inflammatory cytokines. The formation of a ring is hypothesized as a result of differences in the distribution of the antigen-presenting cells, Langerhans cells, and the dendritic cells between the peripheral and central cornea. Additionally, the proximity of the peripheral cornea to the vascular supply of conjunctiva makes it more prone to the deposition of immune complexes in the peripheral cornea. Therefore, a Wessely[15] ring or an immune ring, irrespective of the cause, is typically seen in the peripheral or mid-peripheral cornea with a sparing of the central zone[17]. We hypothesize that in our patient, the ring formed due to an exaggerated immune reaction to microsporidial antigens in the corneal stroma. Consequently, it required anti-inflammatory therapy in the form of topical steroids or tacrolimus for resolution[14]. Various other causes of corneal immune stromal ring include infections (*Acanthamoeba* keratitis, fungal keratitis, viral keratitis-herpes simplex, varicella zoster, cytomegalovirus; or bacterial keratitis) or non-infectious causes (such as a foreign body, refractive procedures, medications, and contact lens use) which must always be ruled out.

A close differential diagnosis for this condition is herpes simplex virus (HSV) associated immune stromal keratitis (ISK)[18]. Clinically, both conditions can present with an immune stromal ring along with keratic precipitates. HSV ISK is typically associated with corneal edema, footprint scars, corneal vascularization, ghost vessels, and reduced corneal sensations. A history of recurrent episodes and a longstanding course of disease favors HSV keratitis. Although both microsporidial and HSV ISK share a few overlapping features, a diagnosis of HSV keratitis should be made with extreme caution due to its lifelong implications on visual morbidity and the need for prolonged therapy. Microbiological analysis can help confirm the diagnosis, with polymerase chain reaction (PCR) being highly sensitive to the diagnosis of HSV[19].

In this report, we describe a rare, natural sequela of microsporidial keratoconjunctivitis. This case contributes to our existing knowledge of microsporidia-induced ocular infection, the natural progression of the corneal epithelial disease into a stromal component, and its complete resolution with topical steroids. Unlike MKC, which resolves without leaving any scar, MISK is likely to heal with a residual ring-shaped corneal stromal scar.

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