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Original Article

Microsporidial Keratoconjunctivitis in South India - Various Presentations, Role of Therapeutic Debridement and Topical Voriconazole

Sudhakar Potti, Aparna Nayak, Shashidhar Banigallapati, Madhuri Venigalla

Department of Cornea, Sankara Eye Hospital, Guntur, Andhra Pradesh, India.

Abstract

Purpose: *To report various presentations and the effect of therapeutic debridement with topical Voriconazole in Microsporidial epithelial keratitis*

Design: *Retrospective analysis*

Methods and Material: *33 eyes of 32 patients of clinically and microbiologically proven Microsporidial epithelial keratitis were included. Diagnosis was done with Gram staining and confirmed by modified Ziehl Neelsen (1% Acid fast). All lesions were therapeutically debrided and 1% topical voriconazole was given and followed up weekly until resolution.*

Results: *The mean age of our patients was 32 years (Range: 10-68 years). The disease was more common in young adults (21-30 years age group). All patients had undergone therapeutic debridement and prescribed 1% topical voriconazole and were symptomatically better. Visual acuity ranged from log MAR 0.6 to log MAR 0.00 which further improved after resolution. Significant visual loss did not occur in any patient.*

Conclusion: *Microsporidial epithelial keratitis is more common than expected in young, healthy individuals including doctors and are typically confused with viral keratitis. The disease showed complete resolution with no recurrence with therapeutic debridement and topical voriconazole therapy.*

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Keywords: *Microsporiadial Keratitis, Topical Voriconazole Therapy, Therapeutic Debridement, Microsporidiosis*

Introduction

The first case of Microsporidial keratitis in humans was reported in 1973.[1] It was also described in 1990 in three patients with AIDS who presented with bilateral superficial punctate epithelial keratitis (SPK).[2] Though thought to be rare at that time, many case series have since been reported in immunocompromised and immunocompetent individuals. Microsporidial keratitis account for 0.4% cases of microbial keratitis in some populations.[3] Two clinical disease entities have been reported: Microsporidial keratoconjunctivitis (MKC) and Microsporidial stromal keratitis (MSK). MKC is prevalent worldwide but most cases are often misdiagnosed as atypical viral keratoconjunctivitis.[4] Though it was reported to be a disease of immunocompromised individuals in the past, recent reports show that it occurs in immunocompetent hosts as well.[5] Microsporidia are ubiquitous organisms in the environment.6 Apart from immunocompromised state, other factors contribute to this disease, like exposure to soil/mud, contact lens wear and long term topical steroid abuse.7 Microsporidia were initially classified as primitive eukaryotes; however, recent studies by genomic evidence supports their reclassification as fungi.[6] Many studies have tried therapy with Fumagillin, Albendazole, Ciprofloxacin, Chlorhexidine, Moxifloxacin and Fluconazole.[7–11] We demonstrate various presentations of Microsporidial keratitis, treated with therapeutic debridement and topical 1% Voriconazole.

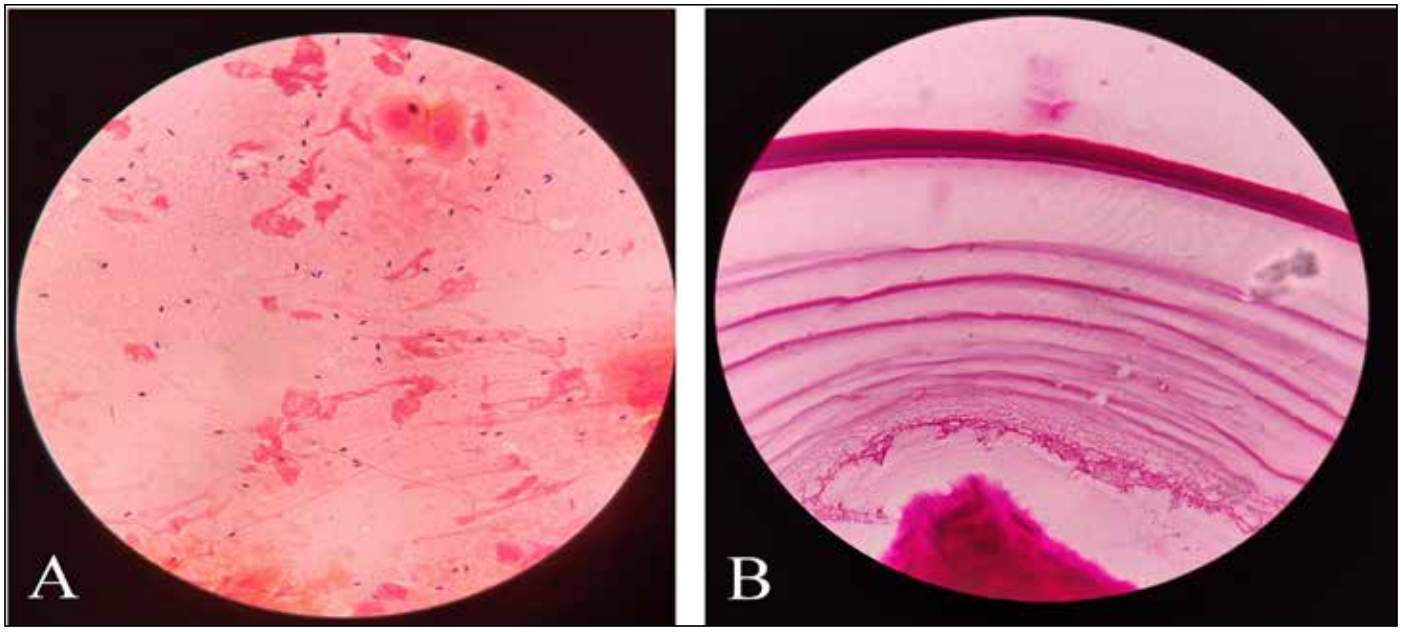
Methods

Ethics committee clearance was taken for the retrospective analysis. Patients of Microsporidial epithelial keratitis who visited Sankara Eye Hospital, Guntur, Andhra Pradesh, India between July 2018 and November 2019 were included in the study. History regarding topical steroid use and similar episodes in the past was noted to rule out viral etiology. Comprehensive slit lamp examination was done in all patients. All were considered as immunocompetent as they didn't have high- risk behavioural pattern. All patients underwent diagnostic scraping and microbiological analysis was performed with Gram staining (Figure 1 A) and modified Ziehl Neelsen (1% Acid fast) (Figure 1B) stain. All the lesions were therapeutically debrided. The smears were examined under 100X magnification using oil immersion microscope. Anterior Segment Optical Coherence Tomography (AS-OCT) was done to differentiate between SPK of Viral keratoconjunctivitis and Microsporidial keratitis. Topical Voriconazole 1% was prescribed hourly and the patients were kept on weekly follow up until resolution. Voriconazole was titrated according to patient's response and then stopped after complete resolution.

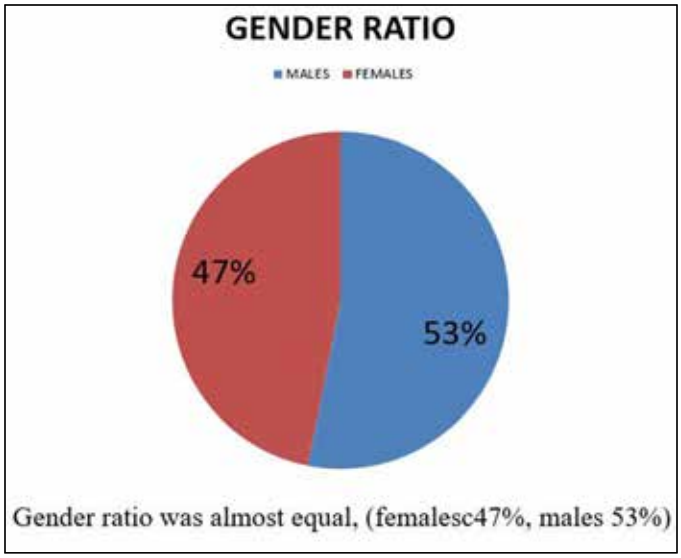
Results

The total number of cases during the study duration was 33 eyes of 32 patients out of which the gender distribution was 15 (47%) females and 17 (53%) males (Graph 1). Mean age was 32 years (Range: 10-68 years). The disease was more common in young adults (21-30 years age group; n=13) (Graph 2). There was no seasonal variation.

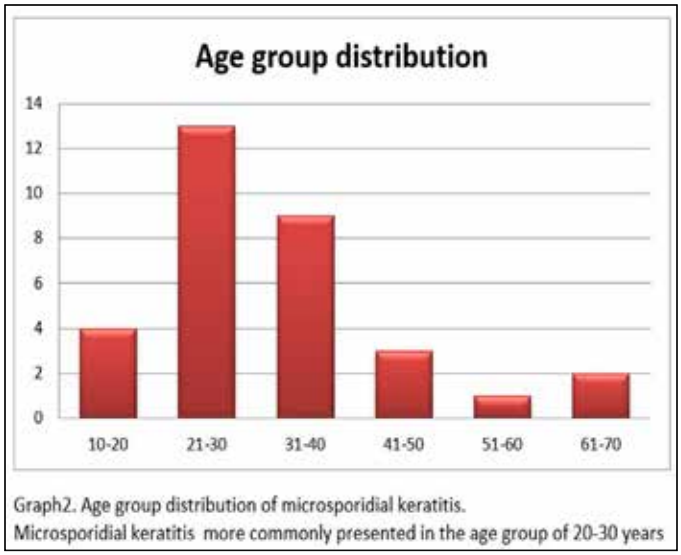
Presenting symptoms included redness, foreign body sensation, watering and blurring of vision. Clinical presentation of these patients included mild follicular conjunctivitis with coarse SPK's located at variable sites



Figures 1: *Gram stain (100x) showing oval gram positive microsporidial spores(A) And Modified Ziehl Neelsen (1% Acid fast) staining showing microsporidial spores (B)*



Graph 1: *Showing gender distribution of cases with MKC*



Graph 2: *Age group distribution of cases with MKC*

(central, paracentral, diffuse, peripheral). (Figure 2 A and B) 57.6% (n=19) cases presented to us primarily with history of redness, watering and foreign body sensation, 2 of which also gave an additional history of insect fall into their eyes. Remaining 42.4% (14/33) cases were referred to our hospital with no improvement/ worsening of symptoms. 33% were misdiagnosed as viral keratoconjunctivitis, treated with topical steroids and presented with worsening of symptoms. Similarly, another patient came for a second opinion misdiagnosed elsewhere as papillary conjunctivitis on topical steroids. One patient had a bilateral presentation. Another patient with bilateral stable keratoconus post corneal collagen cross linking developed Microsporidial epithelial keratitis in the left eye after 2 years with no triggering factor. Another patient with HSV stromal keratitis in the resolving stage developed superadded microsporidial keratitis while on topical steroids.

Three cases were associated with systemic immunosuppression. One patient gave recent history of Hepatitis for which he underwent treatment. Another patient was a doctor by profession, who was a known case of sero-negative spondyloarthritis and was on systemic immunosuppressants. Another patient was pregnant which is again an immunosuppressive state

All patients had undergone therapeutic debridement and were prescribed 1% topical voriconazole hourly. 32 out of 33 cases responded to single therapeutic debridement. One patient was uncooperative for complete debridement and required multiple debridement until all lesions healed. All patients had satisfactory vision and were symptomatically better with treatment.

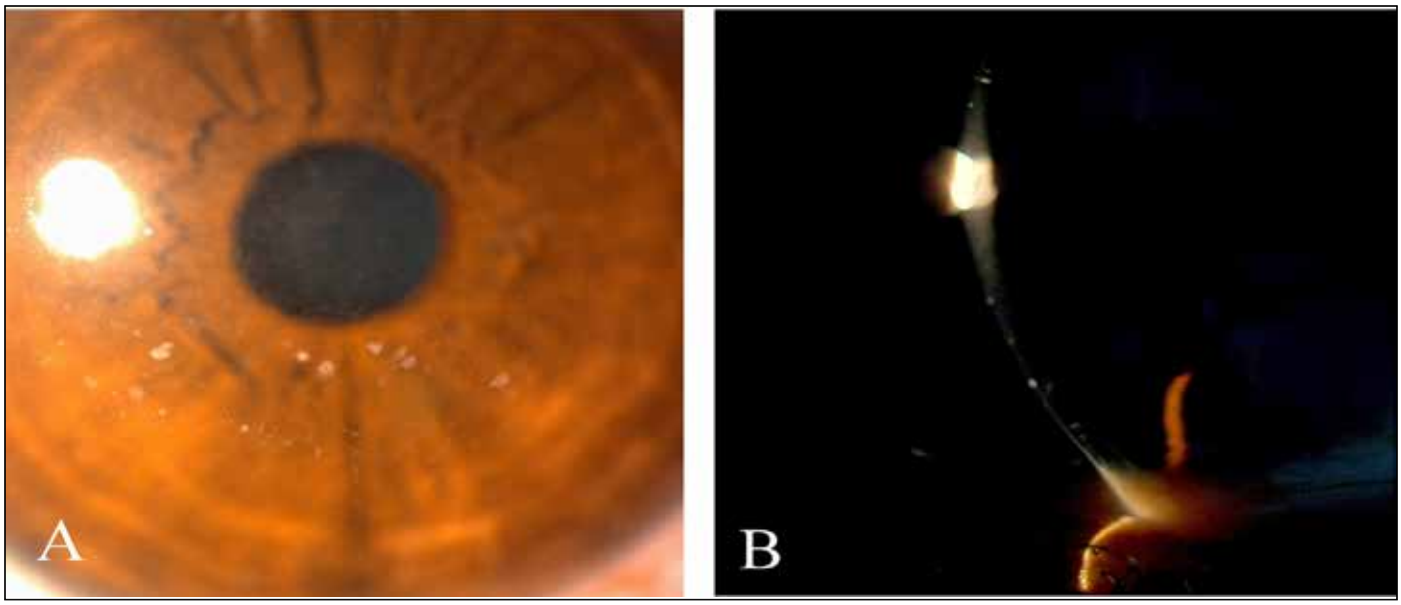


Figure 2: *Slit lamp photograph showing large coarse superficial punctate keratitis (SPK) on the inferior paracentral cornea sparing the visual axis (A) Diffuse and (B) Slit Image*

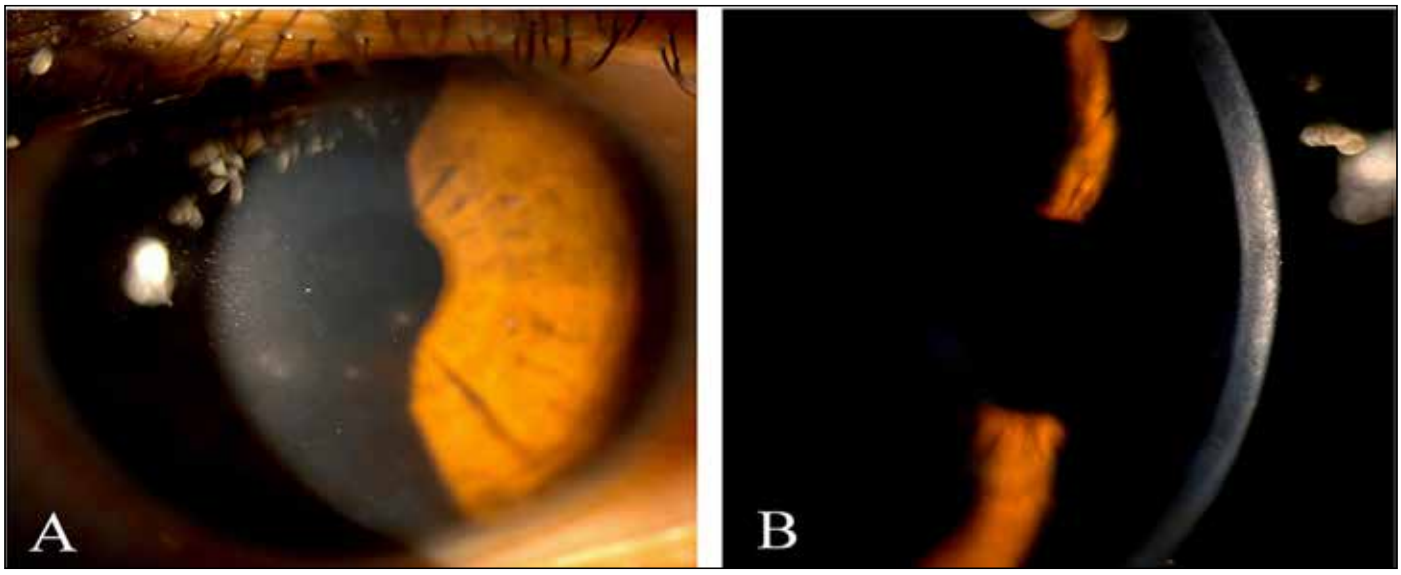


Figure 3: *Slit lamp photograph showing sub-epithelial infiltrates after therapeutic debridement on follow up (A) diffuse illumination and (B) Slit image*

18.1% patients had subepithelial infiltrates after debridement (Figure 3) during follow up which resolved within a month of using low dose topical steroids in tapering doses.

Visual acuity ranged from logMAR 0.6 to logMAR 0.00 which further improved after resolution. Significant visual loss did not occur in any patient. Two patients had reduction in visual acuity by 0.1 logMAR due to scarring. (Figure 4). One patient had a faint scar with senile immature cataract and visual acuity was corresponding to the grade of cataract.

Discussion

Microsporidia are small, spore forming, intracellular parasites, previously considered as protozoa, but recently classified of fungi.[12] More than 1300 species belonging to around 200 genera have been reported[13,14] out of which 14 infect humans.[15] Other than eye, they affect intestinal system, respiratory tract, urinary, muscular and central nervous systems.[16] Ocular infection is the second most common after infection of the digestive tract.[17] Microsporidial ocular infection can occur as an isolated entity or as a part of systemic disease.[18] Risk factors include exposure to soil/dust, contaminated water, ocular trauma with dust/insect bite, topical corticosteroid use, contact lens use and systemic immunosuppressant. The awareness of ocular microsporidiosis is increasing and more cases are being reported in the last decade from many countries. Microsporidia has been classified into two types, superficial epithelial keratitis with good prognosis and deep stromal keratitis with poor prognosis with high rate of medical therapy failure.[19] Superficial punctate keratitis is often mistaken as viral keratoconjunctivitis and is treated with topical steroids.[20] Similarly stromal component is also misdiagnosed commonly as viral/ bacterial/ fungal keratitis thereby delaying the targeted treatment for Microsporidiosis.[21]

Figure 4: *Slit lamp photograph showing visually insignificant scarring after therapeutic debridement on follow up visit.*

Microsporidiosis is more commonly seen in young adults although its seen in all age groups. Seasonal variation has been reported in many studies, more common in monsoon.[22] However, we did not find any seasonal variation in our study. Exposure to dust, insect, topical steroid use for misdiagnosed viral keratoconjunctivitis (most common) were some of the risk factors. Systemic risk factors leading to immunosuppression in our study was probably due to the use of immunosuppressants for seronegative spondyloarthritis, hepatitis and pregnancy. No one had history of contact lens use.

Persistence of microsporidial keratiti11s was reported by Chan et al and Lewis et al with the use of topical steroids.[23] The lesions of microsporidial keratitis were relatively larger and coarser with variable distribution (central / paracentral / peripheral / diffuse) than that of viral keratoconjunctivitis as seen in AS-OCT. A similar comparison was done by Sridhar et al [24]

It was reported that the epithelial lesions usually take 2-4 weeks to resolve, and show sub epithelial infiltrates on follow up, which is a natural course of the infection.[25]

The gold standard in diagnosis remains Transmission electron microscopy (TEM). Identification of microsporidial cysts using modified trichrome and KOH+ Calcofluor White is a sensitive tool but requires an expensive fluoroscein microscope. Modified Ziehl Neelsen and Gram stain are simple microbiological tools that are easily available. In one study, it was reported that Grams stain showed sensitivity of 90.3%, Giemsa stain 64.5%, modified Ziehl Neelsen (1% Acid-fast) 87% and KOH with Calcofluor white 93.5% for the detection of microsporidia.[26] Another study by Das et al. reported 90% sensitivity for Gram stain in detecting microsporidial spores.[27] Recently, use of PCR for reporting microsporidial cysts has been reported.[28] In our study we used gram stain as diagnostic tool and modified Ziehl Neelsen (1% Acid fast) for confirmation.

Table 1: Showing Initial and final best corrected visual acuity in eyes with microsporidial keratoconjunctivitis

SL NO	AGE	SEX	Initial BCVA	Final BCVA
			log MAR	
1	32	F	0.2	0
2	22	F	0.6	0.2
3	22	F	0.5	0
4	42	F	0.1	0.2
5	28	M	0	0
6	52	F	0.1	0
7	45	M	0.5	0.2
8	23	F	0.1	0
9	35	M	0.3	0.2
10	27	M	0	0
11	22	F	0.2	0
12	35	M	0.5	0
13	68	F	0.6	0
14	37	M	0.3	0
15	32	F	0.2	0
16	28	M	0.2	0
17	20	F	0.1	0
18	20	F	0.3	0
19	65	M	0.3	0.3
20	27	M	0	0
21	21	F	0	0
22	50	M	0.2	0
23	23	M	0.2	0
24	35	M	0.3	0
25	10	M	0.5	0
26	12	M	0	0.2
27	40	M	0.2	0
28	27	F	0.3	0.2
29	38	F	0	0
30	35	M	0	0.1
31	21	M	0	0
32	24	M	0.2	0.1
33	21	F	0.3	0

- 2 patients had reduction in visual acuity by 0.1 logMAR due to scarring
- I panent had scarring post debridement and senile cataract, visual acuity was corresponding to the grade of cataract
- 30/33 cases had no significant vision loss

Various drugs have been tried in the treatment of microsporidial keratitis like PHMB, Fumagillin, Moxifloxacin, Itraconazole, Albendazole and Fluconazole.[29] Das et al in 2014, reported no improvement in visual acuity or symptoms with scraping alone in clinically diagnosed microsporidial keratitis.[31] Another report shows meticulous corneal debridement alone eradicates microsporidial lesions.[32]

In our study we have tried therapeutic debridement with 1% topical voriconazole in line with the newer classification of microsporidia as fungi and titrated the drops based on response. It has a broad antifungal spectrum with excellent ocular penetration. Patients showed response within a week and showed complete resolution within one month with visually insignificant scarring. 18.5% (n=6) showed sub-epithelial infiltrates on follow up for which low dose topical steroids in tapering doses were given and showed complete resolution. Khandelwal et al. reported 2 cases of Microsporidial epithelial keratitis successfully treated with topical voriconazole 1% monotherapy in tapering doses.[30]

The visual prognosis of Microsporidial keratoconjunctivitis is good as the disease resolves with no or visually insignificant corneal scars.[31] 98% of our patients on follow up showed significant improvement in symptoms and visual acuity (Table 1).

One of the limitations is that species identification was not possible due to non-availability of PCR and Electron Microscope. Also, the patients were not tested for HIV and other causes of immunosuppression.

To the best of our knowledge, this is the first study from South India of Microsporidial epithelial keratitis treated successfully with therapeutic debridement and topical voriconazole. Our study is intended to create awareness among ophthalmologists that microsporidial keratitis is not uncommon as described previously in literature. It also emphasizes that meticulous debridement and a commonly available antifungal 1% voriconazole can be used for treatment with good outcomes.

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Address for correspondence

Aparna Nayak **MS, DNB, FICO (UK)**
Department of Cornea
Sankara Eye Hospital, Guntur,
Andhra Pradesh, India
Email : aparnayak@gmail.com

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