

Sequelae of microsporidial keratoconjunctivitis and its management

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Purpose: To characterize the sequelae of microsporidia keratoconjunctivitis (MKC) and outline its management. **Methods:** Retrospective analysis of microbiologically proven MKC returned with persistent disease between January 2015 and December 2019 was done. Demographics, clinical features, management, and outcome were analyzed. **Results:** Sixteen patients (21 eyes) of 332 treated for MKC returned with the persisting disease. The mean age of 11 males (68.7%), and 5 females was 35.1 ± 12.2 years. Three-quarter of them did not have a known predisposing risk factor and one-quarter of them were referred for chronic conjunctivitis. Past medications included topical antivirals ($n = 8$) and topical corticosteroid ($n = 6$). Three predominant presentations were persistent (>3 weeks) superficial punctate keratitis (SPKs, $n = 7$), sub-epithelial infiltrates (SEIs, $n = 13$), and uveitis ($n = 2$). The lesions recurred in eight eyes (SPK and SEI 4 each) after a disease-free interval of 60.4 ± 40.6 days; there were 13 episodes of recurrence. Topical low potent corticosteroids (loteprednol/fluorometholone), and tacrolimus ointment 0.03% were used in 17 (80.9%) and 8 (38%) eyes, respectively, for a mean duration of 44.8 ± 31.6 and 226.8 ± 180.5 days, respectively. At follow-up, 172.3 ± 183.6 days, visual recovery was statistically significant in persistent eyes (BCVA 0.07 ± 0.07 logMAR; $P < 0.00001$) but, not in recurrent eyes (BCVA 0.16 ± 0.08 logMAR; $P = 0.07$). Five of 21 eyes were left with residual significant scar. **Conclusion:** The sequelae of microsporidial keratoconjunctivitis are not uncommon. Topical 0.03% tacrolimus ointment appeared to be an effective corticosteroid-sparing agent for the treatment of SEIs and prevention of recurrence.

Key words: Keratoconjunctivitis, microsporidia, non-resolving, persistence, recurrent, subepithelial infiltrates, superficial punctate keratitis, tacrolimus

Microsporidial infection of cornea manifests predominantly in two forms, more common epithelial keratoconjunctivitis (MKC), and less common stromal keratitis (MSK).^[1,2] MKC presents as multifocal superficial raised, coarse, punctate corneal lesion that resolves with nummular scarring resembling adenoviral keratoconjunctivitis.^[3] It occurs in both immunocompetent and immunocompromised individuals. It is commonly unilateral, seen mostly in middle-aged males, with or without predisposing factors or seasonal variation.^[1] It is confirmed by detection of round to oval spores by routinely used stains such as 10% potassium hydroxide, 0.1% calcofluor white (KOH+CFW), Gram's stain, Kinyoun's, and Giemsa stain under light microscopy.^[4] Various antibacterials, antifungals, and anti-parasitic drugs have been used previously with inconsistent results.^[1,2] It is believed to be self-limiting among healthy individuals, usually resolves in less than 3 weeks and rarely leads to visually significant scarring or recurrence.^[5-7] MSK, on the other hand, is long standing, presents with ill defined, often microbiologically negative lesion, and is less amenable to medical therapy.^[8]

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But all cases of MKC do not necessarily follow this natural history and can present as persistent conjunctivitis, punctate or nummular keratitis, uveitis, or recurrence.^[3,9-11] This communication describes 16 such patients where the disease course was either prolonged or the disease recurred.

Methods

Electronic medical records of all clinically diagnosed and microbiologically proven cases of MKC over 5 years (January 2015–December 2019) were retrieved after obtaining approval of the Institutional Review Board. The search terms were 'microsporidia', 'keratitis', 'conjunctivitis', and 'Microsporidial keratoconjunctivitis'. Detection of microsporidial spores in KOH+CFW and/or Gram stain was considered to be confirmatory of diagnosis in all cases. MKCs usually resolves in 3 weeks of time^[7]; hence, we decided twice of this period, that is, 6 weeks, for the patient search. Demographic profile, clinical features pertinent to persistence of disease, treatment, and visual acuity of all patients were collected and analyzed.

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Individuals with any other ocular morbidities attributed to vision impairment were excluded. Our data also included the past treatment data of the people referred to us.

Comprehensive ophthalmic examination included record of presenting and corrected Snellen visual acuity, chart placed at 4 meters; slit-lamp biomicroscopy, Goldmann applanation tonometry when possible (biprism sterilized with 70% isopropyl alcohol swab), and ophthalmoscopy. Conjunctival congestion (CC) was graded as mild to severe (Grade 0-3) as per the Ocular Allergology Society (Japan).^[12] On slit-lamp examination of cornea, the superficial punctate keratitis (SPKs) was characterized by white, coarse, multifocal, raised epithelial lesion with or without fluorescein staining. Resolution of SPKs was usually accompanied by the appearance of sub-epithelial infiltrate (SEIs) that appeared as areas of focal cellular infiltrates in superficial stroma with or without localized stromal edema.

We defined 'persistence' of disease as non-resolving corneal lesions (SPKs/SEIs) or uveitis beyond 3 weeks from the day of appearance and 'recurrence' as reappearance of corneal lesions (SPKs/SEIs) after initial complete resolution. There was 'disease-free days' for at least 4 weeks in between two episodes of active phase.

Corneal scraping smears in all cases were examined under light microscope after staining with 0.1% CFW + 10% KOH and Gram stain; aerobic culture was performed on blood agar plates and incubated at 37°C for 2 weeks and examined daily to rule out any significant microbial growth.^[4] Rescraping was done in cases of persistent SPKs at 2 weeks. In view of atypical clinical presentations and course, additional investigations were done to rule out the common differentials. Conventional Polymerase Chain Reaction (PCR) test was done for adenovirus in eight patients, HSV and microsporidia in one patient each, as per standard protocols.

The treating physicians had treated all eyes initially alone with topical lubricants (Carboxymethyl cellulose 0.5%) for 6–8 times/day till the resolution of corneal lesions. Topical immunosuppressants were added in events of persisting or recurring SPKs, centrally located SEI, and the lesions affecting the vision or causing annoying visual symptoms. The treatment consisted of low potent topical corticosteroids (loteprednol etabonate 0.5% or fluorometholone 0.1%) in tapering doses for 3–6 weeks and topical prednisolone acetate 1% was added as rescue medication in non-responding cases. From 2017, tacrolimus 0.03% in ointment formulation as bedtime application was used to prevent corticosteroid dependence in cases of persistence or recurrence. The eyes with features of uveitis (anterior chamber cells grade 2+) were also treated with topical corticosteroids [Table 1].

The data were entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0, paired sample *t* test was used for normally distributed variables. A value $P < 0.05$ was considered statistically significant.

Results

In 5-year period, 2015–2019, we examined 332 patients with microbiologically proven MKC. Forty-nine of 332 individuals returned for review at or beyond 6 weeks. Sixteen patients (4.8%) returned for symptoms of MKC, and

other 33 patients had non- MKC eye problems (refractive error, dacryocystitis). This communication is on these 16 patients (21 eyes). Five of them had bilateral infection. Following further treatment all patients healed, but six patients ($n = 8$ eyes) returned with recurrence after a variable period. Broadly, there were three manifestations of persistence—SPKs, SEIs, and uveitis [Fig. 1].

The age range was 14 to 54 years (35.1 ± 12.2). There were 11 males and 5 females. By occupation, there were three farmers. Only four patients (25%) had a known MKC- predisposing risk factors such as fall of mud and trauma with insect, two patients each. Past medications included use of topical antivirals in eight (50%) patients, antibiotics, and corticosteroids in six (37.5%) patients each and lubricants in three (18.7%) patients. Common symptoms were redness, watering, lid swelling, foreign body sensation, discomfort, and progressive decrease in vision. Four (25%) patients were referred as cases of chronic conjunctivitis treated with infrequent use of topical corticosteroids. Conjunctival congestion was mild, moderate and severe in 2, 14 (66.6%) and 5 eyes, respectively.

SPKs

All eyes had SPKs on presentation, either diffuse (61.9%; $n = 13$) or central (38.1%; $n = 8$), with variable fluorescein staining. Following treatment, SPKs resolved in a mean time of 18.7 ± 9.8 days (range 7–45 days). Persistent SPKs (>3 weeks) were seen in 7 (33.3%) eyes, of which three patients had bilateral infection. Six eyes required topical corticosteroids; topical tacrolimus was added in two eyes and the remaining eyes resolved with lubricants alone. Rescraping was done in all four eyes with persistent SPKs at 2 weeks; it was microbiologically negative in three eyes and scraping of one eye could not be processed due to inadequate specimen.

SEIs

Persistent SEIs (>3 weeks) were seen in 13 (61.9%) eyes; it was bilateral in two patients, and one eye also had uveitis (AC cells $\geq 2+$). The mean time of appearance was 10.5 ± 3.5 days, and in half of them it appeared in the first week. The mean duration of resolution was 26.1 ± 7.4 days. All lesions of persistent SEIs were larger than 1 mm and were associated with significant stromal edema impacting vision. Three eyes resolved with topical lubricants alone, six eyes needed additional topical corticosteroids, and four eyes needed both topical tacrolimus and corticosteroids.

Uveitis

Greyish-white round keratic precipitates were present in 10 (47.6%) eyes; mean time of appearance was 8.5 ± 4 days. It resolved in eight eyes with lubricants alone within 2 weeks and two eyes with significant anterior chamber reaction (2+ cells) required topical corticosteroids.

Treatment

Topical low potent corticosteroids (loteprednol etabonate 0.5% or fluorometholone 0.1%) in tapering doses was required in 17 (80.9%) eyes with persistent disease. The remaining four (SPK $n = 1$, SEI $n = 3$) eyes had persistent lesions at periphery not significantly affecting vision and resolved with lubricants. The mean duration of use of low potent corticosteroids (loteprednol etabonate 0.5% or fluorometholone

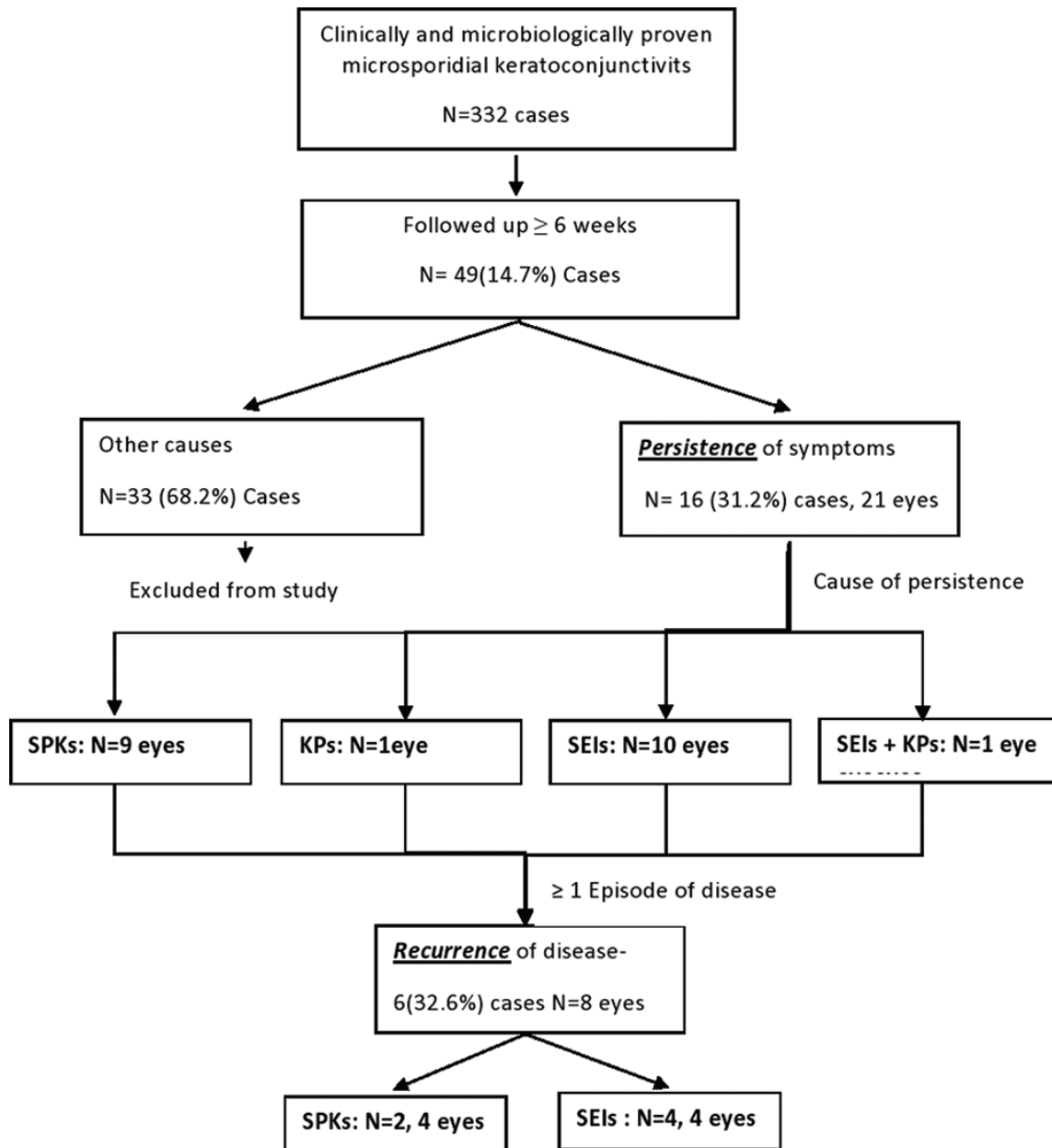


Figure 1: Schematic description of clinical course of all cases

0.1%) was 28 ± 4.2 days. Tacrolimus eye ointment 0.03% at bed time was added along with topical corticosteroids in six eyes and its mean duration of use was 57.8 ± 5.2 days.

Resolution

Superficial corneal lesions resolved with faint nummular scar in 18 eyes (85.7%) and the remaining 3 eyes had a clear cornea. Mean duration of resolution was 47 ± 5.4 days (range 42 to 60 days). Visual acuity with pin hole at presentation was $\geq 20/30$ in 7 (33.3%) eyes; with resolution of lesions vision (BCVA) $\geq 20/30$ increased to 16 (76.2%) eyes. The recovery of vision was statistically significant with final BCVA 0.07 ± 0.07 (logMAR) ($P < 0.00001$) (paired *t* test). Corneal scar in pupillary area was the main reason of suboptimal ($< 20/30$) vision in five eyes.

Recurrent disease

Six of 16 patients (37.5%; eight eyes) of persistent MKC, returned to us with recurrence of corneal lesions after initial complete recovery, including three patients initially referred with a diagnosis of chronic conjunctivitis. In three patients, the lesions recurred after discontinuing topical tacrolimus (the other three patients had not used tacrolimus). The mean duration of disease-free interval was 64.4 ± 40.6 (range, 31 to 150) days. It presented as either recurrent SPK (two patients; four eyes) or SEI (four patients; four eyes). More than one recurrence were seen in three patients (2 SEI, 1 SPK) on discontinuing topical tacrolimus; hence it was reinstated combined with topical corticosteroids. The corticosteroid was tapered over a month. Topical tacrolimus was used for 8–34 weeks in these patients. There were 13 episodes of recurrences in these 6 patients [Table 2].

Table 1: Treatment plan of MKC in the institute

Medication	Disease status		Topical Lubricants	Topical Tacrolimus	Topical Corticosteroid
	Time	Description			
MKC	At presentation <2 weeks	CC grade 0-1, SPKs; Peripheral asymptomatic SEIs, AC cells 0-1; Scar	+	-	-
SPK	>2 weeks/Recurrence	BCVA \leq 20/30, CC Grade \geq 2, central location, glare or halos	\pm	+	\pm
SEI	At any point of time	BCVA \leq 20/30, CC Grade \geq 2, central location, glare or halos	\pm	\pm	+
Uveitis	At any point of time	AC cells \geq 2	\pm	-	+

AC - Anterior Chamber; BCVA - Best corrected visual acuity; CC - Conjunctival congestion; SEI - Sub-epithelial infiltrates; SPK - superficial punctate keratitis

Table 2: Clinical courses and management of persistent and subsequent recurrent cases of MKC*

Case	Age/sex	Eye (s)	Pathology	Persistent Cases <i>n</i> =16 (Treatment)		Recurrent cases <i>n</i> =6 (Treatment)				Follow-up (Days)
				Steroid (weeks)	Tacrolimus (weeks)	Number	DFI Days	Steroid (weeks)	Tacrolimus (weeks)	
1.	54/F	Both	SEIs	4	-	-	-	-	-	60
2.	14/M	Left	SEIs	4	-	-	-	-	-	60
3.	44/M	Right	SPKs	-	-	-	-	-	-	42
4.	41/M	Right	SEIs	4	-	-	-	-	-	150
5.	37/M	Right	SEIs	4	-	1	31	4	8	180
6.	49/M	Left	SEIs	4	8	1	60	4	8	180
7.	36/M	Right	SEIs	-	-	-	-	-	-	42
8.	51/M	Left	SEIs	4	6	-	-	-	-	68
9.	10/M	Both	SPKs	3	-	1	30	6	-	96
10.	34/F	Both	SPKs	4	8	-	-	-	-	96
11.	20/F	Both	SPKs	6	8	1	33	-	8	300
						2	60		12	
						3	150		12	
12.	40/F	Left	KPs	4	-	-	-	-	-	45
13.	32/F	Left	SEIs	4	-	-	-	-	-	45
14.	41/M	Right	SEIs	4	8	1	45	4	12	730
						2	73	6	12	
						3	30	3	12	
						4	90	6	16	
						5	30	-	20	
15.	36/M	Both	SEIs	4	8	-	-	-	-	180
16.	24/M	Right	SEIs + KPs	4	-	1	56	6	34	485
						2	150	4	12	

*All eyes were treated with topical lubricants. DFI - Disease free interval, F - Female; M - male; MKC - microsporidial keratoconjunctivitis; SEI - sub-epithelial infiltrates; SPK - superficial punctate keratitis

Treatment of recurrence and outcome

Low potent steroids were used in eight episodes of recurrence tapered over 3 to 7 weeks. One eye with SEIs and significant stromal edema also required prednisolone acetate 1% for 6 weeks [Fig. 2e]. Presenting Visual acuity with pin hole of recurrent cases was 0.20 ± 0.08 (logMAR) which improved to 0.16 ± 0.08 on resolution ($P = 0.07$) (paired t test). The improvement in vision was not significant; significant worsening (two-line change) of BCVA was noted in two eyes.

In the final analysis, 17 (80.9%) eyes were treated with topical low potent corticosteroid for a mean duration of 44.8 ± 31.6 days and 8 (38.1%) eyes were treated with topical

tacrolimus for a mean duration of 226.8 ± 180.5 days. All eyes were treated with topical lubricants. The mean duration of follow-up was 172.3 ± 183.6 days. There was no secondary infection. Polymerase chain reaction (PCR) for adenovirus and HSV done in 8 and 1 patients, respectively, was negative. PCR for panmicrosporidia (using 16S rRNA gene-based^[13]) was positive in patient # 14 [Fig. 2f].

Presenting vision (spectacles/pinhole) at presentation was 0.25 ± 0.14 (logMAR) and statistically significant improvement (BCVA) was seen after treatment on the last follow-up, 0.10 ± 0.10 (logMAR) ($P = 0.0003$) (paired t test). This change was equivocal (± 1 line change) in 12 (57.1%) eyes, improvement (≥ 2 lines) in seven (33.3%) eyes and

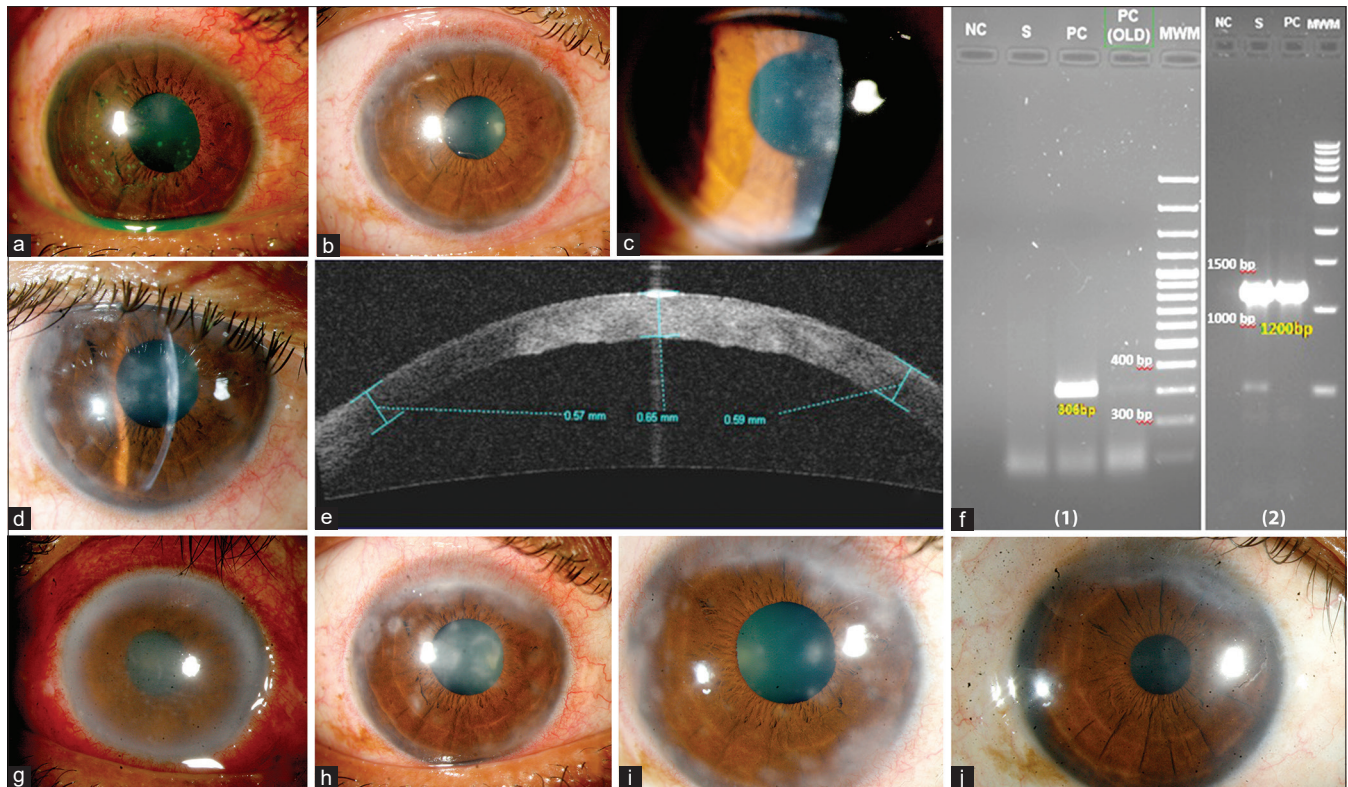


Figure 2: Case 14 (a) central SPKs-Day 1 (b) Resolving peripheral SEIs-Day 14(c, d, g, h and i). recurrent SEIs-6th, 36th, 68th, 80th and 104th weeks, respectively, (e) AS-OCT on 36th week; Sub-epithelial hyperreflective lesions up to deep stroma with a smooth surface. Pachymetry: 650µ. (f)Agarose gel electrophoresis (1.5%) using species-specific PCR primer sets. NC:Negative control, S:Sample, PC: Positive control, MWM:(A) 100bp (B) 1000bp DNA size marker for adenovirus (1) and pan-microsporidia (2): showing no band for adenovirus but positive band (1200 bp) for panmicrosporidial DNA in S as compared to PC(j) resolution

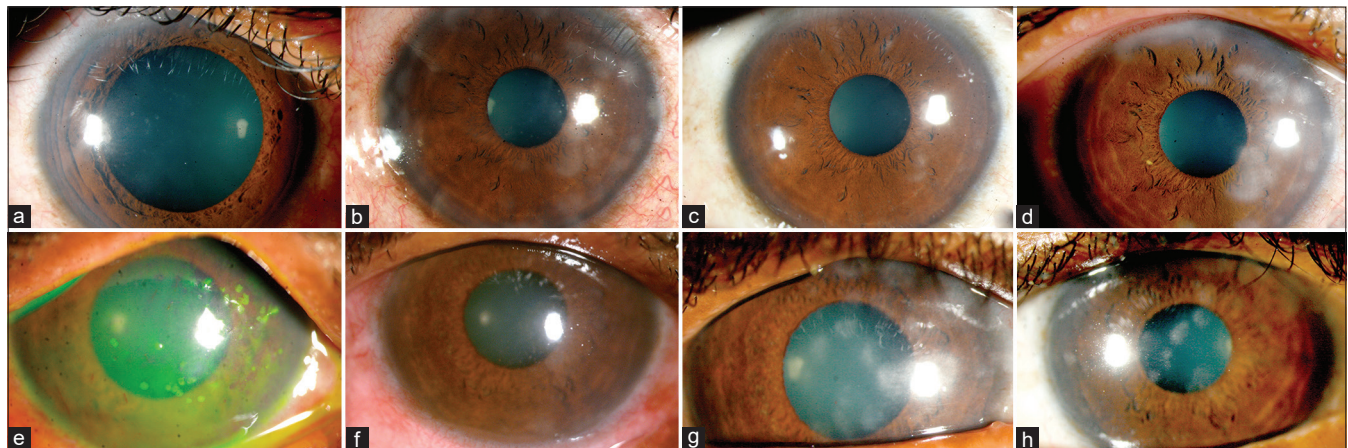


Figure 3: Case 5: (a) Central SPKs- Day 1 (b) Peripheral SEIs- Day 14 (c) Clear cornea- Day 45 (d)Recurrence of SEIs with localized stromal edema- Day 76. Case 8: (e) Diffuse SPKs- Day 1 (f) Resolution of SPKs with appearance of KPs- Day 7 (g) Persisting SEIs and KPs- Day 30 (h) persisting SEIs- Day 60

worsening (<1 line) in two eyes; worsening of vision was due to non-resolving SEIs.

The mean of maximum recorded IOP during the follow-up in all patients was 14.7 ± 2.1 (range 10–20) mm of Hg. No other adverse side effects to topical corticosteroid were reported and bedtime application of tacrolimus was tolerated well in all patients.

Detailed clinical course of patients # 14, 5, and 8 are described in Figs.2 and 3 a-h, respectively.

Discussion

MKC have evolved since its first report in a 30-year-old, HIV-seropositive man in 1990.^[14] In early twentieth century it was reported as a cause of bilateral chronic conjunctivitis in

immunocompromised patients, non-responsive to antibacterial antibiotic.^[15,16] Currently it has emerged as a self-limiting epidemic keratoconjunctivitis in healthy individuals, that invariably resolves without affecting vision.^[5-7,9-11] But we guess, its sequelae are under-reported or underestimated. There is no established protocol for long-term management and follow-up care. In a series of 277 patients, we had reported visually insignificant sub-epithelial scarring in 39.2% of resolved eyes.^[7] In a series of 124 patients, Loh *et al.* had reported healing in 96.8% eyes without reduction in vision and recurrence in 4 eyes only.^[9] In a series of 550 patients, Agashe *et al.* had reported resolution in 63.1%.^[10] In the non-resolved eyes ($n = 126$) they reported persistent SPK in 22.9% ($n = 68$) eyes, sub-epithelial nummular keratitis in 10.1% ($n = 30$) eyes, persistent conjunctivitis in 7.4% ($n = 22$) eyes and in 1% ($n = 3$) patient each had uveitis and/or fellow eye involvement.^[10]

In our study, 4.8% (16 of 332) patients (21 eyes) had non-resolving microbiologically proven MKC. A third of these patients had received prior topical corticosteroids for a prolonged period (said to predispose persistence and scarring).^[3,17,18] Bilateral involvement was seen in 31.2% ($n = 5$) eyes with non-resolving MKC, more common than expected. Four referred patients of chronic keratoconjunctivitis resolved on treatment but recurred in 3 patients. Diffuse or central SPKs were seen in all eyes and the bilateral cases mimicked Thygeson's superficial punctate keratitis with minimal SEIs: these eyes had a prolonged course.^[19] Although role of topical corticosteroids is controversial in MKC few authors had advocated early use to prevent subsequent sequelae.^[11,20]

We feel that these eyes require topical immunosuppressants and a step ladder treatment approach.

We suggest the treatment could begin with topical immunosuppressants (tacrolimus) and topical corticosteroid is added only in recalcitrant cases. In our experience, SPKs respond well to topical tacrolimus and do not need topical corticosteroid. A close watch is needed for eyes with KPs; most of them could resolve without topical corticosteroids (it resolved in eight eyes of six patients in this series), and few could need topical corticosteroid treatment (two eyes in this series).

Multifocal SEIs are the pathognomonic sequelae of epidemic keratoconjunctivitis (EKC), commonly caused by adenovirus serotype 8. It could be seen in more than 50% of times after resolution of acute phase and could persist for weeks to years causing visual morbidity.^[21,22] Histopathologically, it represents accumulation of lymphocytes, macrophages/monocytes, and activated fibroblasts at anterior stroma in response to viral antigen. Topical corticosteroids, typically, may hasten recovery without affecting long term outcome but prolongs the viral shedding and recurrence after discontinuing treatment.^[22,23] Corticosteroid sparing agents like 0.05%/1% cyclosporine and 0.03% tacrolimus have been studied with significant benefits.^[24-27] Topical tacrolimus is a safe corticosteroid-sparing agent and with possible benefit in preventing recurrences.^[27,28] In our series, the SEIs following MKC were identical to the ones seen in adenoviral corneal infection. In absence of a detailed analysis, our current observed clinical differentiation includes large size (1–1.5 mm), coin or ring shape, significant localized stromal edema, and peripheral location. (Supplemental Digital content; Fig. 1. Comparison with PCR positive adenovirus

keratoconjunctivitis). Anterior segment- Optical coherence tomography (AS-OCT), recently used as a diagnostic modality for MKC may be of limited value in early cases of SPKs, and with development of SEIs, it could be difficult to distinguish from adenoviral keratoconjunctivitis.^[29,30]

The fact that 80% of the eyes with persistence and/or recurrent MKC required topical immunosuppressants for symptomatic relief and vision restoration, is a pointer to possible immunologic reaction to microsporidial antigen. Tacrolimus is a macrolide lactone and acts by inhibiting calcineurin involved in the production of interleukin-2, vital to body's adaptive immune response. Tacrolimus is approximately 100 times more potent than cyclosporine.^[31] It has been successfully used in various inflammatory and allergic ocular disorders, such as atopic and vernal keratoconjunctivitis,^[32,33] giant papillary conjunctivitis,^[34] autoimmune uveitis,^[35] high-risk corneal grafts,^[36] scleritis^[37] and dry eye disease.^[38] In MKC too, tacrolimus can be used for a prolonged period as an alternative to corticosteroids in treating and preventing recurrences of MKC sequelae with good tolerability and less side effects.

In this study the visual recovery was better in MKC persistence than MKC recurrence, but in absence of contrast sensitivity and/or aberrometry, we are unable to comment on quality of vision. This is a study limitation. PCR for microsporidial DNA in all cases could have identified the causative species.

Conclusion

The sequelae of microsporidial keratoconjunctivitis are not uncommon. The SPKs and subsequent sub-epithelial lesions could be easily mistaken for atypical or unusual adenoviral keratoconjunctivitis. Patients with similar episode in past, diffuse or central corneal epithelial lesions, bilateral involvement, prior use of topical corticosteroids and presence of SEIs should arouse suspicion. It calls for a careful examination and longer follow-up. Our observations are that persistence of SEIs and bilateral SPKs are more prone for recurrence. Topical 0.03% tacrolimus ointment appeared to be an effective corticosteroid-sparing agent for the treatment of SEIs and prevention of recurrence.

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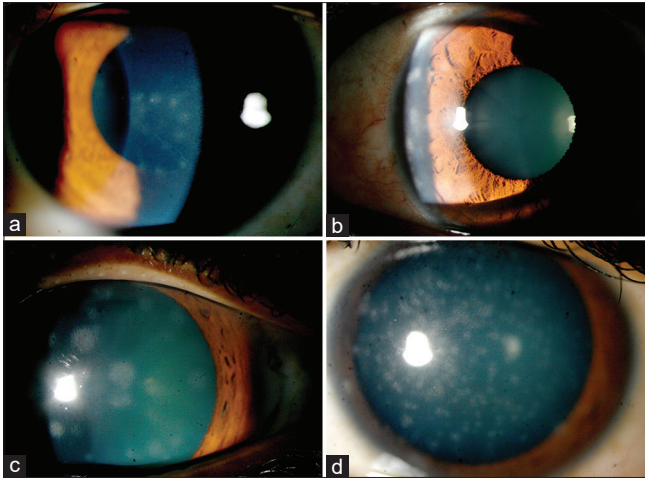
Conflicts of interest

There are no conflicts of interest.

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Supplemental Digital content; Figure 1. Slit-lamp pictures representing sequelae of microsporidial (a) Nummular scar, (b and c) Peripheral and Central SEIs and adenoviral (d) keratoconjunctivitis