Original Article

Toxic non-inflammatory fungal keratitis

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Purpose: To report a new entity called "toxic non-inflammatory fungal keratitis." **Methods:** Eyes manifesting infective keratitis with a history of prior administration of topical steroids were included in the study. The details pertaining to the type of injury, duration of injury, and primary treatment for corneal trauma were meticulously documented. The corneal tissues were scraped from the patients and were analyzed for fungal filaments by using a 10% KOH mount under a compound microscope. Moreover, these scraped materials were plated on blood agar and Sabouraud dextrose agar plates. **Results:** The corneal ulcers displayed a disproportionately reduced intensity of pain and improved visual acuity. Further, 10% KOH revealed profuse fungal filaments with few inflammatory cells in all the patients. The anterior chamber cells and flare were either reduced or entirely absent. There was no evidence of lid edema and surrounding corneal edema in any of the patients. The mean healing period was 28.8 days (standard deviation (SD): 10.05). The KOH mount revealed the presence of confluent fungal hyphae with a few inflammatory cell infiltrates. The Aspergillus species and Fusarium species were found in 47% and 40% of the cases, respectively. **Conclusion:** Toxic non-inflammatory fungal keratitis following steroid therapy needs to be considered in fungal ulcers with disproportionately less pain and good visual acuity. The fungal ulcers with altered clinical signs of classical inflammation need to be assessed for topical steroid misuse.

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With a growing number of reports from the Indian subcontinent, it has been established beyond doubt that fungal keratitis is the most common form of infective keratitis in routine clinical practice.[1] Corneal ulcers usually occur following trivial trauma.[2] Agriculture is the most common occupation in rural India.[3] Trauma caused by vegetative matter is commonly encountered among these populations.[3] The preliminary treatment of the corneal epithelial defect following a trauma plays an important role in the healing pattern.[4] The immunity of the ocular surface is critical for the growth of the epithelium and for the destruction of microorganisms. Immunoglobins present in the tear film accentuate the killing of bacteria and fungi.[5] However, fungal spores, which are resistant to innate immunity, are present over the ocular surface following a trauma or due to poor ocular hygiene.[6] During the healing process, if gross immunosuppression is present, it leads to the abnormal growth of spores.[7] Topical steroids are easily available and are accessible over the counter in the Indian subcontinent, which has resulted in their misuse.[8] In this report, we document a case series of steroid-treated epithelial defects that resulted in a toxic non-inflammatory fungal corneal ulcer.

Methods

This retrospective observational study was performed from January 2020 to December 2020. It was approved by the ethics committee of Ruby Eye Hospital, bearing research approval number REH 04/20. All patients had given informed written consent in congruence with tenets of the Declaration of Helsinki.

Fifteen non-consecutive cases of 10% KOH proven fungal keratitis were retrospectively collated and analyzed. Detailed patient history was obtained and meticulously documented. All patients with a prior history of usage of topical steroid eye drops were included in the study. These patients developed fungal corneal ulcers following an over usage of steroids for simple epithelial defects.

Description of the condition [Figs. 1a, 1c, 2a, and 2c]: Toxic non-inflammatory fungal keratitis (TNFK) is the term used for describing fungal infections of the cornea that develop following the use of topical corticosteroids. The visual acuity in these patients is disproportionately higher than the severity of corneal ulcers. The disproportion between the extent of ulcer and symptomatic complaints is commonly observed in this entity. Absence or relatively reduced pain is an important clinical sign of TNFK. In addition, there is a reduced intensity of anterior chamber cells and flare, which does not agree with the depth and intensity of the infiltrate. The anterior chamber can be clearly visualized through the non-infective transparent cornea. A corneal ulcer with relatively less lid

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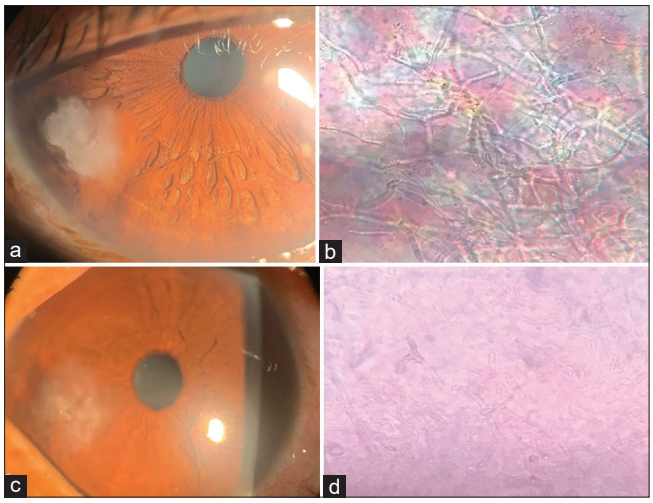

Figure 1: (a and c) Showing paracentral ulcers with clear central cornea. (b and d) Showing confluent fungal hyphae in KOH mount

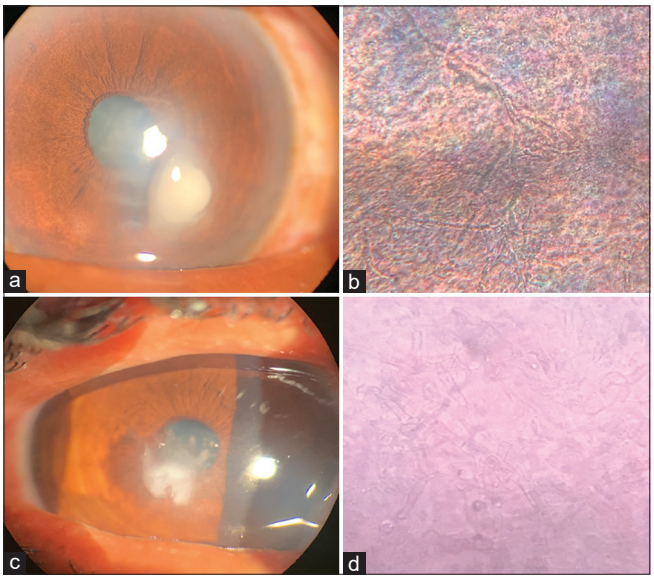

Figure 2: (a and c) Showing fungal ulcers involving central 3 mm of the cornea. (b and d) Showing fungal filaments in KOH mount under 40× magnification

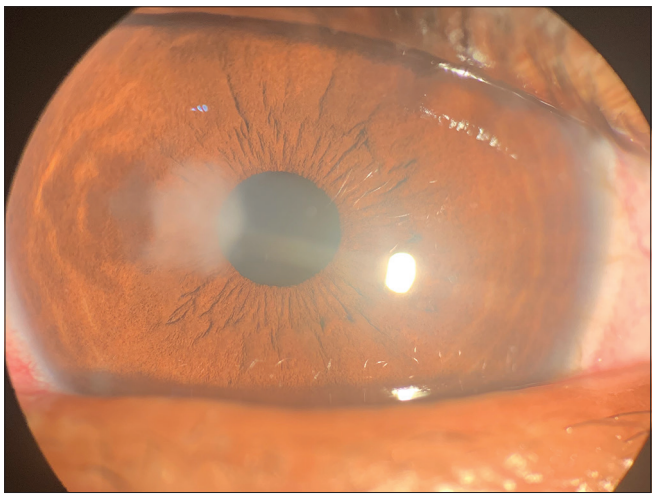

Figure 3: Showing healed corneal ulcer with a visual acuity of 6/12

edema, conjunctival congestion, chemosis, corneal edema, and pain is strongly presumed to be having TNFK. The corneal scraping examination under 10% KOH mount displays profuse fungal filaments with extremely few inflammatory cells. Upon carefully gathering the past medical history, patients revealed the use of topical dexamethasone, prednisolone, or difluprednate eye drops.

KOH mount [Figs. 1b, 1d, 2b, and 2d]: All corneal tissues were scraped using a 26-G needle under topical anesthesia, and the material was placed on a slide. A drop of 10% KOH was added with the help of a pipette, and a coverslip was placed over it. The fungal hyphae were visualized under 10 × magnification, which were further confirmed under the 40 × magnification. All patients had confluent fungal hyphae, with less number of inflammatory cell infiltrates.

Treatment protocol

All the patients were started on an hourly administration of natamycin 5% eye drops for a period of 72 h. For patients showing a favorable response, this regimen was continued at a frequency of 6 times per day until a complete resolution of the infective infiltrate was achieved. In case of ulcers with status quo after 72 h, itraconazole eye drops four times a day were added. In patients on dexamethasone eye drops, the treatment was abruptly discontinued, and they were started on fluorometholone eye drops daily two times for 2 weeks to prevent a sudden increase in paradoxical inflammation. An administration of systemic doxycycline 100 mg twice daily for 14 days was added to the therapy, followed by once daily for a further period of 28 days. Following the healing of the ulcers, the administration of anti-fungal eye drops was continued along with lubricating eye drops for a period of 4 weeks to prevent any form of recurrence.

Results

The mean age of the patients was 51.46 years, with a standard deviation of 10.8 years (maximum: 72 years; minimum: 37 years) [Table 1]. Twelve patients (80%) were farmers by occupation, and three patients were dairy farmers. The mean time period from the onset of trauma to consultation was 8.5 days, with a standard deviation of 15 days. Five patients revealed the usage of some form of native medications prepared at home (details not known) prior to the topical steroid application. Twelve patients (80%) developed ulcers away from the 3-mm zone, and three patients (20%) developed ulcers within the 3-mm zone. A patient developed a central ulcer that exhibited no signs of healing even after 96 h. Thus, the patient underwent temporary central tarsorrhaphy to facilitate the healing of the epithelial defect. The tarsorrhaphy was released after 3 weeks. The mean period of healing was 28.8 days (SD: 10.8 days; maximum: 55 days; minimum: 16 days), and a scar eventually developed [Fig. 3]. One patient who developed a significant central scar with a best-corrected visual acuity of less than 6/60 underwent optical penetrating keratoplasty. Two patients were prescribed rigid gas permeable contact lens to improve the visual acuity. Eleven patients who developed paracentral scars were prescribed glasses for improvement in visual acuity and no further surgical intervention was included. The culture report of these patients revealed that 47% of cases developed *Aspergillus spp*., 40% of ulcers developed *Fusarium spp*., and 14% of cases developed *Curvularia spp*.

Table 1: Showing 15 non-consecutive cases of toxic non-inflammatory fungal keratitis

Age of the patient	Type of injury	Use of native medicines	Type of steroid drops	Duration of instillation of steroid drops	Presenting UCVA	Location of ulcer	Healing time	Fungal growth in culture media	Topical antifungals	Follow up	Final BCVA	Final intervention
63	Vegetable injury	No	Dexamethasone eye drops	7	6/36	Paracentral	25	Aspergillus flavus	Natamycin 5%	60	6/12	Lubricating eye drops
51	Vegetable injury	No	Dexamethasone eye drops	10	3/60	Paracentral	32	Aspergillus niger	Natamycin 5%	45	6/9	Lubricating eye drops
38	Vegetable injury	Yes	Dexamethasone eye drops	8	6/36	Paracentral	24	Aspergillus fumigatus	Natamycin 5% with Itraconazole	65	6/12	Lubricating eye drops
48	Vegetable injury	No	Dexamethasone eye drops	14	6/36	Paracentral	41	Fusarium Solani	Natamycin 5%	80	6/6	Lubricating eye drops
54	Cow tail injury	No	Dexamethasone eye drops	5	3/60	Central	55	Aspergillus flavus	Natamycin 5% with Itraconazole	160	6/36	RGP contact lens
67	Corneal Foreign body	Yes	Dexamethasone eye drops	4	6/24	Paracentral	34	Fusarium Solani	Natamycin 5%	72	6/24	Lubricating eye drops and RGP contact lens
72	Stick injury	No	Prednisolone eye drops	3	4/60	Central	21	Curvularia lunata	Natamycin 5% with Itraconazole	210	6/60	Penetrating keratoplasty
43	Nail injury	No	Dexamethasone eye drops	6	6/60	Paracentral	18	Fusarium Solani	Natamycin 5%	36	6/12	Lubricating eye drops
52	Vegetable injury	Yes	Dexamethasone eye drops	4	6/24	Paracentral	35	Aspergillus flavus	Natamycin 5%	40	6/18	Lubricating eye drops
37	Stick injury	No	Dexamethasone eye drops	7	6/36	Paracentral	28	Fusarium Solani	Natamycin 5% with Itraconazole	65	6/12	Lubricating eye drops
46	Foreign body over cornea	Yes	Dexamethasone eye drops	3	1/60	Central	16	Aspergillus fumigatus	Natamycin 5% with Itraconazole	53	6/12	Penetrating keratoplasty
61	Vegetable injury	No	Dexamethasone eye drops	4	6/36	Paracentral	24	Aspergillus fumigatus	Natamycin 5% with Itraconazole	47	6/24	Lubricating eye drops
57	Cow tail injury	No	Dexamethasone eye drops	5	6/12	Paracentral	19	Fusarium Solani	Natamycin 5%	35	6/9	Lubricating eye drops
44	Vegetable injury	No	Prednisolone eye drops	6	6/12	Paracentral	29	Aspergillus fumigatus	Natamycin 5% with Itraconazole	50	6/6p	Lubricating eye drops
39	Vegetable injury	Yes	Dexamethasone eye drops	2	6/24	Paracentral	31	Fusarium Solani	Natamycin 5% with Itraconazole	57	6/9	Lubricating eye drops

Discussion

Epithelial defects following a vegetative injury and cow-tail injury are commonly observed among farmers.[9] The primary treatment of these epithelial defects plays a crucial role in non-eventful healing.[10] However, the use of native medicines and over-the-counter steroids worsens the clinical condition and has alarming consequences.[11] A de-epithelialized corneal surface favors the penetration of microorganisms owing to the hydrophilic nature of the stroma.[12] However, the conjunctival commensals and tear film antibodies assist in eliminating the pathogenic organisms.[13] Thus, any form of topical immunosuppression results in the proliferation of pathogenic organisms and the inefficiency of the beneficial commensals present on the conjunctival surface in suppressing them. Apart from this, any form of topical steroids delays the healing of the corneal epithelium.[14] A delay in corneal epithelial growth leads to the growth of fungal spores over the wet corneal surface.[6] These spores are the resultant pinched products of fungal hyphae that are present in the soil, which gain access to the ocular surface following trauma. The hydrophilic stroma enables the spores to absorb water and aids in activating the cytoplasm, eventually causing nuclear fission and the synthesis of new cytoplasm.[15] Lastly, the formation of fungal hyphae happens, which proliferate over the stroma and inhibit the healing of the corneal epithelium.

Fungal keratitis is the most common type of corneal ulcer in the Indian subcontinent.[16,17] Filamentous fungi, particularly Aspergillus and Fusarium, are commonly isolated from these specimens.[18] In the present case series, *Aspergillus spp.* were found in 46% of the cases, Fusarium in 40% of the cases, and Curvularia in 14% of the cases. The treatment of fungal keratitis with an administration of steroids needs to be done cautiously as sudden discontinuation of the drug may worsen the condition.[19] Thus, steroids should be continued at a lower frequency and subsequently tapered in addition to topical anti-fungal therapy.[20] Concurrent steroid therapy reduces the sudden resurgence of inflammation. Dead fungal filaments present following the anti-fungal therapy may trigger a strong inflammatory cell response, thereby causing stromal lysis, aggravating the risk of deep corneal penetration, and eventually resulting in corneal perforation.[21] Thus, the containment of the inflammatory cell response is critical in preventing fulminant stromal damage by inflammatory cells.

Conclusion

We propose the term "toxic non-inflammatory infective keratitis" for corneal ulcers sans inflammation. Therefore, any corneal ulcer with relatively good vision and an absence of corneal edema needs to be evaluated for over-the-counter topical steroid usage. Furthermore, steroids should be slowly tapered in these patients instead of abruptly discontinuing their usage.

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Conflicts of interest

There are no conflicts of interest.

References

1. Manikandan P, Abdel-Hadi A, Randhir Babu Singh Y, Revathi R, Anita R, Banawas S, *et al*. Fungal keratitis: Epidemiology, rapid detection, and antifungal susceptibilities of *Fusarium* and *Aspergillus* isolates from corneal scrapings. Biomed Res Int 2019;2019:6395840.
2. Farahani M, Patel R, Dwarakanathan S. Infectious corneal ulcers. Dis Mon 2017;63:33-7.
3. Jadhav R, Achutan C, Haynatzki G, Rajaram S, Rautiainen R. Review and meta-analysis of emerging risk factors for agricultural injury. J Agromedicine 2016;21:284-97.
4. Ahmed F, House RJ, Feldman BH. Corneal abrasions and corneal foreign bodies. Prim Care 2015;42:363-75.
5. Ueta M, Kinoshita S. Innate immunity of the ocular surface. Brain Res Bull 2010;81:219-28.
6. Dijksterhuis J. Fungal spores: Highly variable and stress-resistant vehicles for distribution and spoilage. Food Microbiol 2019;81:2-11.
7. Maser E, Lanišnik Rižner T. Steroids and microorganisms. J Steroid Biochem Mol Biol 2012;129:1-3.
8. Nagesh TS, Akhilesh A. Topical steroid awareness and abuse: A prospective study among dermatology outpatients. Indian J Dermatol 2016;61:618-21.
9. Pai HV, Jamal E, Yegneswaran PP. Corneal ulcer due to a rare pleosporalean member of the genus Bipolaris following cow tail injury to the eye: A case report and review of literature. Indian J Ophthalmol 2017;65:403-5.
10. Wirostko B, Rafii M, Sullivan DA, Morelli J, Ding J. Novel therapy to treat corneal epithelial defects: A hypothesis with growth hormone. Ocul Surf 2015;13:204-12.e1.
11. DelMonte DW, Kim T. Anatomy and physiology of the cornea. J Cataract Refract Surg 2011;37:588-98.
12. Edward A, Prausnitz MR. Predicted permeability of the cornea to topical drugs. Pharm Res 2001;18:1497-508.
13. Kugadas A, Christiansen SH, Sankaranarayanan S, Surana NK, Gauguet S, Kunz R, *et al*. Impact of microbiota on resistance to ocular pseudomonas aeruginosa-induced keratitis. PLoS Pathog 2016;12:e1005855.
14. Baratz KH, Hattenhauer MG. Indiscriminate use of corticosteroid-containing eyedrops. Mayo Clin Proc 1999;74:362-6.
15. Ou JI, Acharya NR. Epidemiology and treatment of fungal corneal ulcers. Int Ophthalmol Clin 2007;47:7-16.
16. Srinivasan M, Gonzales CA, George C, Cevallos V, Mascarenhas JM, Asokan B, *et al*. Epidemiology and aetiological diagnosis of corneal ulceration in Madurai, south India. Br J Ophthalmol 1997;81:965-71.
17. Gopinathan U, Garg P, Fernandes M, Sharma S, Athmanathan S, Rao GN. The epidemiological features and laboratory results of fungal keratitis: A 10-year review at a referral eye care center in South India. Cornea 2002;21:555-9.
18. Srinivasan M. Fungal keratitis. Curr Opin Ophthalmol 2004;15:321-7.
19. Acharya M, Farooqui JH, Jain S, Mathur U. Pearls and paradigms in infective keratitis. Rom J Ophthalmol 2019;63:119-27.
20. Pineda R 2nd, Dohlman CH. The role of steroids in the management of Acanthamoeba keratitis, fungal keratitis, and epidemic keratoconjunctivitis. Int Ophthalmol Clin 1994;34:19-31.
21. Yi K, Chung TY, Hyon JY, Koh JW, Wee WR, Shin YJ. Combined treatment with antioxidants and immunosuppressants on cytokine release by human peripheral blood mononuclear cells-Chemically injured keratocyte reaction. Mol Vis 2011;17:2665-71.