Clinical and Etiological Profile of Mycotic Keratitis from a Tertiary Care Centre in South India

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ABSTRACT

BACKGROUND

Corneal ulcer is the leading cause of ocular morbidity and monocular blindness worldwide. To effectively prevent blindness in patients with corneal ulcer, a proper understanding of the risk factors predisposing to ulceration, its clinical and microbiological characteristics are essential. Timely identification of aetiological agents causing corneal ulcers and their prompt treatment helps to save the vision. We wanted to detect aetiological agents of corneal ulcer with special references to fungal causes and characterize the fungal aetiological agents to species level.

METHODS

This is a cross sectional study, conducted in Government Medical college, Kozhikode, between January 2016 and June 2017. All patients who were clinically diagnosed as cases of infectious corneal ulcer in the Ophthalmology department, Government Medical College, Kozhikode were included in the study. Corneal scrapings collected from the infected eye were subjected to microbiological examination and culture. A total of 120 cases were analysed. Each patient was examined with the slit lamp bio microscope after staining with fluorescein. Scrapings from cornea at the site of corneal ulcer were collected by ophthalmologist after a detailed clinical history and examination of the affected eye. The laboratory procedures used in the diagnosis of infectious keratitis were based on direct visualization of organisms by subjecting corneal scrapings to Gram stain and KOH wet mount and inoculation of material on to blood agar and Sabouraud dextrose agar.

RESULTS

Among the 120 cases, a total of 49 cases were culture positive. Twenty-one [17.5 %] were bacterial, twenty-two [18.34 %] were fungal and six [5.0 %] were poly microbial [bacteria and fungus]. Among the fungal aetiology, fusarium species was most common [32.14 %], followed by aspergillus species - 25.0 %. Trauma was the major risk factor. Diabetes mellitus, exposure keratitis were the other comorbidities / risk factors.

CONCLUSIONS

This study shows majority of infected corneal ulcers are associated with risk factors and the aetiology are mainly fungi. Microscopy, culture, and clinical correlation helped in adequate management. Thus, prognosis and outcome of corneal ulcers rely on timely identification of their aetiology and prompt treatment.

KEY WORDS

Corneal ulcer, Fungal Keratitis

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BACKGROUND

Corneal ulcer is a vision threatening disease and a leading cause of ocular morbidity and blindness worldwide.^{1,2} It is considered as an ophthalmic emergency which requires prompt treatment. The severity of corneal infection depends on the underlying condition of cornea and pathogenicity of the infecting organism.³ The incidence and spectrum of corneal ulcer depends on different factors, viz. geographical and location related factors, and the degree of development of a country. Corneal ulcer is the major cause of monocular blindness in developing countries.⁴ To effectively prevent blindness in patients with corneal ulcer, a proper understanding of risk factors predisposing to ulceration, and clinical and microbial characteristics of the disease is essential.

Infectious keratitis is a leading cause of corneal blindness in developing countries. It is a sight threatening disorder that affects both males and females across all age groups worldwide. Corneal ulceration results in 1.5 – 2 million new cases of corneal blindness annually, posing a major public health problem according to the World Health Organization (WHO) reports. Fungi are the most common etiological agents which account for 30 – 40 % whereas bacteria accounts for 13 – 48 % of all cases of suppurative keratitis; this varies by geographical area.^{5,6} It is widely accepted that bacterial and fungal keratitis have higher incidence in developing world and viral keratitis is prevalent in developed countries [US]. Predominance of bacterial and fungal keratitis in developed countries have been reported now.¹

Fungi are generally responsible for less than 10 % of corneal infections in most clinical cases reported in the United States whereas in India, fungal keratitis accounts for more than 60 % of the cases.⁷ When the integrity of ocular surface has been breached due to damage or trauma, it will be more vulnerable to be infected by fungi and other microbes resulting in fungal keratitis which is associated with traumatic corneal injury, especially from vegetative matter.

Fungal corneal ulcer is usually characterized by dry, raised slough, stromal infiltrates with feathery edges, satellite lesions and a thick [cheesy hypopyon] endothelial exudates.

The role of microbiologist in management of corneal ulcer is crucial as it has to be differentiated from other non-inflammatory conditions of cornea resulting from immune mediated reactions.

Fungal corneal ulcer must be differentiated from bacterial corneal ulcer as the treatment varies. Diagnosis and treatment of corneal ulcer is challenging as the culture reports are sometimes inconclusive.

Microbial keratitis should be detected early and treated timely to save the vision. Ocular morbidity such as corneal scarring and subsequent visual loss can be significantly reduced by prompt institution of appropriate therapy guided by the knowledge of the causative agents.⁵ Severe corneal ulcers might progress to corneal perforation, with poor visual outcome. Therefore, identification of the pathogens and appropriate treatment is critical for a good clinical outcome.⁸

Treatment of microbial keratitis is difficult due to delayed presentation and difficulties in obtaining appropriate

antifungal medications. Even with moderate corneal scarring, unilateral blindness is often the final result due to the lack of suitable donor material for a corneal graft.⁹

In this study we wanted to characterize the fungal etiological agents and the clinical outcomes.

METHODS

A cross sectional study was conducted at Ophthalmology and Microbiology departments of Government Medical College, Kozhikode between January 2016 and June 2017 after obtaining IRC approval. All patients clinically diagnosed with infectious corneal ulcers presenting to the Ophthalmology department of Government Medical College, Kozhikode were included in the study. Corneal ulcers of non-infectious aetiology were excluded from the study.

Each patient was examined with the slit lamp bio microscope by an ophthalmologist. After staining with fluorescein and with the variable slit on the bio microscope the details of the corneal ulcer including the location, size, shape, depth vascularization, and hypopyon were recorded. A sketch of each ulcer was also drawn on the casebook using standardized frontal and cross-sectional diagrams, and the presence or absence of a hypopyon was recorded and the size and height measured in millimetres. A standardized proforma was completed for each patient documenting sociodemographic information as well as clinical findings. Associated ocular conditions such as blepharitis, dacryocystitis, dry eyes, corneal anaesthesia or ocular leprosy were noted.^{10,11}

Scrapings from cornea at the site of corneal ulcer were collected by ophthalmologist, after taking detailed clinical history, and examination of the affected eye. Eye was anesthetized with sterile 0.5 % tetracaine or 4 % lignocaine 2 - 3 drops. The surrounding skin was wiped with sterile gauze soaked in sterile saline and excess of discharge and debris were removed. A sterile self-retaining lid retractor was applied to minimize contamination with conjunctival flora. Using No. 15 Bard Parker blade, ulcers were scraped thoroughly and gently from base and edges of ulcer.^{12,13}

The laboratory procedures used in the diagnosis of infectious keratitis were based on direct visualization of organisms in the material and inoculation of material on to blood agar and Sabouraud dextrose agar under appropriate conditions to allow multiplication of organisms.¹⁴

The scraped material was used to prepare a 10 % potassium hydroxide wet mount and Gram's smear. KOH wet mount was examined for fungal hyphae [pseudohyphae, true hyphae, conidia].^{12,13,15,16} Gram stain was examined for pus cells, yeasts, and fungal hyphae. If hyphae were observed in Gram stain microscopy or KOH mount preparation, but failed to grow in culture, the aetiology was reported as fungal.¹⁷

Portion of scraped material was directly inoculated onto blood agar and Sabouraud dextrose agar media with antibiotics which included chloramphenicol & gentamicin but without actidione [cycloheximide], 2 sets for isolation of fungi.^{14,15} All fungal cultures were incubated at 25° C and 37° C separately for 4 weeks.¹⁷

Samples were streaked on culture plates as 'C' or 'S' shapes. All cultures were checked every day for first week

and alternate days or twice weekly during next three weeks. The mycelial isolates were identified by their colony characteristics and microscopic appearance in Lactophenol Cotton Blue stained mount and finally by slide cultures (Fig. 1) The yeast isolates were identified by standard tests like germ tube, chlamydospores production on cornmeal agar, colonies on CHROMagar, urease test, sugar fermentation and assimilation.¹⁸ The criteria adopted for microbial evaluation was that the sample would be considered positive if any one of the following were met.

1. The growth of the same organism was demonstrated on two or more media on C - streak.
2. The same organism was grown from repeated scrapings.
3. It was consistent with clinical signs.
4. Smear results confirmed the finding from cultures.

Statistical Analysis

Data was entered in Epi info™ Version 7.2, CDC, Atlanta, Georgia.

RESULTS

A total of 120 cases of infective corneal ulcer have been studied clinically and corneal scrapings of all the 120 cases were processed in Microbiology laboratory, Government Medical College, Kozhikode. Out of total 120 cases, 71 [59.17 %] were males and 49 [40.84 %] were females. Age distribution of the cases is shown in Figure 1. 60 – 69 yrs. age group was most commonly affected. Manual labourers (38.3 %) accounted for majority of cases whereas 14.2 % of cases were agricultural workers. Majority (78.57 %) had history of trauma of some kind. Table: 1 shows the objects that caused trauma.

Objects of Trauma	No. of Positive Fungal Cases	Percentage
Unknown foreign body exposure	10	35.71
Vegetative matter, wooden twigs, sticks	9	32.14
Concrete particles and cement	2	7.14
Metal pieces	1	3.57
No trauma	6	21.43
Total	28	100

Table.1 Objects of Trauma

Diabetes mellitus and hypertension were the most common comorbidities associated with those cases where there was no history of trauma. No history of trauma in 6 / 28 [21.43 %] cases. The most common symptoms were pain [86.7 %] and redness [75 %] followed by watering [50 %].

Prior treatment with steroid lead to fungal corneal ulcer in one case. 26 out of 28 [92.9 %] fungal corneal ulcers had size less than 6 mm. All fungal ulcers involved stroma. All fungal ulcers had irregular margins. Ulcers were mostly central than peripheral. There were 35 suspected cases of fungal keratitis of which 22 cases fungi were isolated in pure. In 6 cases fungi grew along with bacteria. In 7 cases fungal elements were seen only by microscopy and failed to grow by culture. Of the 22 cases, fungi were the sole etiological agents for keratitis, fungi could be demonstrated both by microscopy and culture. In 17 cases fungi were demonstrated only by culture. In six cases fungal growth was obtained along with bacteria. In two of these cases, presence of fungi could be established both by microscopy and culture. In the rest, fungi could be demonstrated only by culture.

Microbiological Profile of Corneal Ulcer

Table 2 shows the microbiological profile of etiological agents of corneal ulcers in the current study.

Isolates	No. of Cases	Percentage
Bacteria	21	17.5 %
Fungus	22	18.34 %
Parasite	0	0 %
Mixed isolates [bacterial + fungal]	6	5 %
Organism not isolated	71	59.17 %
Overall total	120	100.0 %

Table 2. Microbiological Profile of Corneal Ulcer

Total Fungal Profile

Most common fungal isolate was fusarium spp [32.14 %]. Table 4 shows the profile of microbes obtained from corneal ulcers where fungi and bacteria were isolated together.

Fungal Isolates	Pure Isolates	%	Mixed Isolate	%	Total No. of Cases	%
<i>Fusarium solani</i>	3	5.84	2	1.7	5	7.5
<i>Fusarium oxysporum</i>	4		0		4	
Total	7		2		9	
<i>Aspergillus flavus</i>	3	5	0	0.8	3	5.9
<i>Aspergillus terreus</i>	2		0		2	
<i>Aspergillus fumigates</i>	1		1		2	
Total	6		1		7	
<i>Aureobasidium pullulans</i>	4	3.34	0	0	4	3.3
<i>scedosporium</i>	1	0.83	1	0.8	2	1.7
<i>apiospermum</i>	1	0.83	1	0.8	2	1.7
<i>acromonium spp</i>	1	0.83	0	0	1	0.8
<i>Candida albicans</i>	1	0.83	0	0	1	0.8
<i>cylindrocarpum spp</i>	0	0	1	0.8	1	0.8
<i>Fonsecaea pedrosoi</i>	1	0.83	0	0	1	0.8
<i>mucor spp</i>	1	0.83	0	0	1	0.8
Total	22	18.33	6	4.9	28	23.3

Table 3. Total Fungal Profile

Figure 1. Age Distribution of Cases

Mixed Isolates	No. of Cases	Percentage
CoNS+Fusarium solani	2	1.7 %
pneumococci + Aspergillus fumigatus	1	0.8 %
Pseudomonas aeruginosa + acremonium	1	0.8 %
CoNS + Scedosporium apiospermum	1	0.8 %
CoNS + cylindrocarpon	1	0.8 %
Total	6	4.9 %

Table 4. Mixed Isolates [Bacterial + Fungal]

Aetiology Vs Clinical Outcome

Aetiology	Improved	Recurrence / Complication	Total
Fungal	21	1	22
Mixed [Bacterial +fungal]	5	1	6
Not isolated / sterile	0	0	92
Total	26	2	120

Table 5. Aetiology and Clinical Outcome

Of the 28 cases where fungal aetiology was proved, 26 improved clinically and 2 had recurrence / complications. None of the cases healed completely. All seven suspected cases, where fungal elements were seen only by microscopy and not culture, healed well.

DISCUSSION

A total of 120 clinically diagnosed cases of corneal ulcers were studied. Demographic details, aetiology, risk factors, fungal profile and clinical outcomes were recorded. In this study, cases belonged to different age groups from 0 - 99 years. Median age was 55 and higher incidence was noted in 60 - 69 years. Males in age group 50 - 59 years, were most commonly affected, which might be due to more outdoor activity. The cases were most common amongst manual labourers accounting to increased ocular trauma in such cases.

A definite relationship between corneal injury and mycotic keratitis was observed. About 78.57 % of all fungal corneal ulcers [22 out of 28 positive fungal corneal ulcer cases] had history of corneal injury. Meena and Sharma in their study of fungal corneal ulcer observed that majority of patients had trauma to the eye as most common predisposing factor.¹⁹ Gopinathan et al. found that ocular trauma predisposed to infection in 736 (54.4 %) of 1,354 eyes²⁰ in this study. Unknown foreign body exposure [35.71 %], trauma due to vegetative matter and wooden twigs and sticks [32.14 %], followed by concrete particles and cement [7.14 %] and finally metal pieces [3.57 %] were the common objects of trauma. Diabetes mellitus was an important risk factor in injured and non-injured cornea. 6 out of 28 [21.43 %] cases had no history of trauma.

Peponis et al. analysed that the cases in their study suggested that in patients with fungal keratitis who previously received topical corticosteroids, the abrupt cessation of these agents was likely to lead to an acute rebound inflammatory reaction and even perforation.²¹ Among our study population two patients received steroid therapy prior to the onset of ulcer and one of them developed fungal ulcer.

Pain and redness were the common symptoms in this study followed by watering, photophobia, foreign body sensation, defective vision. Fungal ulcers [pure and mixed isolate] involved corneal stroma in all cases. All corneal ulcers

by fungi and mixed isolates had irregular margins. Clinical examination of corneal ulcer, especially margins give a clue to diagnosis by predicting its aetiology. Ravinder et al. observed that, fungal culture was positive in majority of cases with satellite lesions, thick, large hypopyon, irregular infiltrate margins, and endothelial infiltrate.²² In this study, central corneal ulcers were more common, than inferotemporal.

Of the 22 pure fungal cases, five were positive by microscopy and culture and 17 were microscopy negative but culture positive. In case of mixed isolates, out of six, two were microscopy and culture positive, four were microscopy negative but culture positive. In 7 cases, fungal elements could be demonstrated only by microscopy. This might be due to prior antifungal therapy and scanty scraping material. Gram stain positivity was 5.7 % of fungal elements in 35 suspected fungal cases. KOH positivity for fungus was 34.3 % [12 out of 35 cases]. Out of 120 cases, 28 cases [23.34 %] had definite fungal aetiology. The seven cases where fungal elements were seen only by microscopy were treated as mycotic keratitis. Mixed growth of fungi and bacteria were obtained from 6 cases. The mixed isolates were *Streptococcus pneumonia* + *Aspergillus fumigatus* - 1 out of 6 [16.67 %], *Pseudomonas aeruginosa* + *acremonium* - 1 [16.67 %], CoNS + *Fusarium solani* - 2 [33.34 %], CoNS + *Scedosporium apiospermum* - 1 [16.67 %], CoNS + *cylindrocarpon* - 1 [16.67 %]. Mixed ulcers had irregular margins and all involved stroma, one among them was perforated.

Fusarium spp accounted for 32.14 % of keratitis in the present study. Six out of nine cases, had history of trauma and one had diabetes mellitus. In 2 cases *fusarium* spp grew along with bacteria [CoNS], and one among them had prior steroid treatment history. All 9 cases had ulcer of size < 6 mm, except one. Margins of the ulcers were irregular and involved stroma. 55.56 % of cases had hypopyon. Further morphology was confirmed by slide culture and LPCB mount. 5 were *Fusarium solani* and 4 were *Fusarium oxysporum*. Ulcers were managed by repeated scrapings [debridement], topical natamycin and oral fluconazole. Antibiotics were given for mixed isolate with bacteria and to prevent secondary infection. Hassan et al. observed that, *fusarium* species were the most common cause of fungal infection in Southern US (45 % -76 % of fungal keratitis).²³ Leck et al. observed, that *fusarium* spp and *aspergillus* spp were isolated from 61 % of all fungal infections and comprised 83 % of identified fungal isolates, although *fusarium* species were the most prevalent fungal pathogens reported in Ghana. *Fusarium* spp have also been found to be the principal fungal pathogen in Florida, Paraguay, Nigeria, Tanzania, Hong Kong, and Singapore.²⁴ Wu et al. noted that, currently, natamycin is considered to be the most effective topical agent against *fusarium* and *aspergillus* and natamycin is more effective than voriconazole in treatment of fungal keratitis, especially *Fusarium* keratitis.²⁵

25 % of all keratitis was caused by *aspergillus* spp. Six out of seven *aspergillus* keratitis cases had history of trauma [mainly due to vegetative objects, soil], 2 had diabetes mellitus as additional risk factor. One of them was along with bacterial growth [pneumococci]. Ulcers were < 6 mm, with irregular margins, central, paracentral or peripheral ulcers, involving stroma. Of the seven *aspergillus* spp isolated, 3 were *Aspergillus flavus*, 2 *Aspergillus terreus*, 2 *Aspergillus fumigatus*. All ulcers were treated with debridement, natamycin and antibiotics. Ulcers improved except one, which had recurrence and complications, with a bad prognosis.

Khairallah et al. observed that the high prevalence of aspergillus spp. in their study, may be due to the fact that spores of aspergillus can survive the hot and dry weather of Saudi Arabia, and four of the 27 patients developed fungal endophthalmitis.²⁶

All 4 *Aureobasidium pullulans* keratitis cases had history of trauma. Ulcers were < 6 mm, irregular, stroma involved, central or peripheral with one perforated ulcer. All ulcers improved when they were treated by repeated scraping, natamycin and fluconazole. *Aureobasidium* is considered to be contaminant, but is potential to cause corneal ulcers. Panda et al. observed that, of 200 fungal organisms isolated from the cultures, 25 were identified as *A. Pullulans*. Of 25 eyes, 22 responded well to antifungal therapy and 2 required therapeutic penetrating keratoplasty and one patient progressed to phthisis bulbi.²⁷

Out of the 2 *Scedosporium apiospermum* keratitis cases, one had history of trauma [isolated along with CoNS]. Ulcers were < 6 mm with irregular margins, paracentral ulcers involving stroma. Ulcers improved on repeated scraping, natamycin, fluconazole and antibiotics. Malla reddy et al. observed that, 3 out of 36 fungal isolates were *Pseudallescheria boydii* (8.33 %) in their study.²⁸ Nulens et al. noticed that voriconazole, together with penetrating keratoplasty, was effective for the treatment of *S. apiospermum* keratitis.²⁹

Both the acremonium [cephalosporium] keratitis cases had history of trauma, one was isolated along with *Pseudomonas aeruginosa*. Ulcers were, < 6 mm with irregular margins, central or peripheral and stroma involved. Empirical antibiotics were started initially, and repeated scraping was done, natamycin was started after the microscopy reports. Ulcers improved. Kim et al. noted that management of fungal corneal ulcers can be difficult, particularly as there are no standard therapies for infections caused by acremonium. Nowadays, topical, and oral voriconazole have been reported to be effective for the treatment of fungal keratitis.³⁰

One *Candida albicans* had been isolated from 72-year-old, who had no history of trauma, but exposure keratitis and diabetes mellitus as risk factors. Ulcer was < 6 mm with irregular margins, central ulcer and involved stroma. Ulcer was initially treated with antibiotics, later based on culture reports, natamycin and fluconazole were added, and ulcer improved. Hassan et al. observed that, candida and aspergillus species were most common in Northern US and *Candida albicans* keratitis is a challenge for ophthalmologists due to its tendency to mimic other conditions.²³ *Candida* species are the most common fungal organisms causing keratitis in HIV - positive patients.²³

3.57 % of total fungal keratitis isolated are *Fonsecaea pedrosoi*, which had no history of trauma. Ulcer was < 6 mm, with irregular margins, central ulcer and stroma involved. Since dematiaceous fungi takes more time to grow on culture media, ulcer was managed by antibiotics initially. Based on culture reports, fluconazole and natamycin were added and debridement was done. Ulcer improved. Chaidaroon et al. noticed that, *F. pedrosoi* is a rare cause of corneal infection. Although the characteristic visible pigmented infiltrate can be an important diagnostic clue, this classical finding may not be apparent in all cases. Therefore, it is important to establish an accurate diagnosis through microscopic evaluation and culture. In this study, the treatment with topical antifungal

agents (ketoconazole and natamycin) and oral itraconazole resulted in the slow eradication of the infections.³¹

One cylindrocarron species was isolated along with CoNS, which had history of trauma with white cement. Ulcer was > 6 mm, with irregular margins, central ulcer and involved stroma and endothelium, to form corneal abscess. Moxifloxacin topical was started empirically, and natamycin and oral fluconazole on smear and culture results. Ulcer worsened and voriconazole was added as intracameral, intralesional and as a topical. Ulcer improved with no further deterioration. Irek et al. observed that, keratomycosis caused by *C. lichenicola* is rare in humans and challenging to manage. Although voriconazole has been used with success in some reports in managing *C. lichenicola*, its accessibility is limited.³²

Mucor was isolated from a single case in the present study and had history of trauma with no diabetes. Ulcer was < 6 mm, with irregular margins, central ulcer with stroma involved. Topical itraconazole was added based on culture reports along with antibiotics. Ulcer improved. Sanjeev et al. observed that, one (03.86 %) out of 26 isolates were *mucor* species, from a total of 127 cases suspected to have fungal keratitis.³³

CONCLUSIONS

To conclude, fungal ulcer shows gradual presentation and can be aggressive with delay in prompt management. Fungal corneal ulcer is difficult to treat and has become a challenge to microbiologists for identification and ophthalmologists to treat. Therefore, early identification and prompt timely treatment of corneal ulcer gives good clinical outcome, thereby saving the vision.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.

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