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Demography, clinical features, and outcome of fungal keratitis presenting in tertiary eye care in Nepal

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ABSTRACT

Background: Fungal keratitis is an important cause of ocular morbidity in developing countries. **Aims and Objectives:** To study fungal keratitis in detail along with its outcome. **Materials and Methods:** This is a retrospective study of fungal keratitis that had presented between October 2013 and March 2015. **Results:** 168 fungal ulcers were enrolled. 145 had fungus isolated in the culture; 23 had fungal elements seen only in potassium hydroxide mount examination. The average age of patients was 46.7 years. 55.3% were male. 75% were farmers. Patients presented at an average of 23.6 days since the onset of symptoms. In 85 cases (50.6%), trauma was the risk factor followed by steroid use (12.5%, n = 21) and diabetes mellitus (7.7%, n = 13). 72 out of 85 cases of trauma were due to vegetative matter. 94 (55.9%) ulcers had hypopyon. 56 (33.3%) ulcers had infiltrate size of ≥¼ of corneal surface. 12 (7.1%) ulcers were perforated at presentation. Out of 145 fungal isolates, *Aspergillus* species and *Fusarium* species were isolated in equal numbers (n = 41, 28.3% each), followed by unidentified hyaline fungus (14.4%, n = 21). The ulcers were treated with combination of topical natamycin 5% and fluconazole 0.3% with or without oral fluconazole. 111 (66.1%) fungal ulcers improved with medical treatment, 37 (n = 22.0%) underwent therapeutic penetrating keratoplasty, 6 (3.6%) were eviscerated and outcome unknown in 14 (8.3%). Smaller-sized ulcers, ulcers without hypopyon and those presenting within 7 days had better prognosis (>80% healing with medical treatment) with statistical significance. **Conclusion:** Farmers were constantly at risk of fungal keratitis due to work-related trauma. Fungal ulcers presented late with large sized ulcers and with complications, thus making treatment challenging and necessitating surgical intervention. Timely treatment had better prognosis.

Key words: Fungal keratitis; Fungal ulcer; Infective keratitis

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INTRODUCTION

Microbial keratitis is common corneal pathology which is prevalent mostly in developing countries.[1] Timely treatment will make healing faster, but delay in presentation, improper treatment, lack of facility for culture, antibiotic-resistant microbes, delay in referral to higher centers all contribute to complications like perforated or non-healing ulcers which would necessitate therapeutic keratoplasty. Fungal ulcers are particularly difficult to treat because they tend to present relatively late due to slow growing nature of fungus, having less symptoms compared to bacteria and limited number of antifungals with poor penetration in the ocular tissue.[2] The incidence of fungal ulcer is high in hot and humid tropical climate as well as in developing countries where agriculture is the main occupation.[3-6] Hospital-based studies in these regions, including our previous descriptive study, report a higher proportion of fungi compared to bacterial.[3-6] Hence detail study of fungal keratitis is important in endemic regions for planning proper control and management of fungal keratitis.

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Aims and objectives

The current study is done to find out the demography, clinical features, and outcome of fungal keratitis along with the prognostic factors related to the outcome. The study is done at the Tilganga Institute of Ophthalmology, a tertiary referral institute in Nepal.

MATERIALS AND METHODS

This is a retrospective study based on our previous descriptive, non-interventional study of infective ulcers presenting in our institute between October 2013 and March 2015 (18 months' duration). Readers are referred to our previously published article.[5] Descriptive data of fungal keratitis were segregated from 602 non-viral microbial keratitis presenting within that period.[5] Ulcers with positive corneal cultures for fungus or the presence of fungal elements in potassium hydroxide (KOH) mount were included for the study. Demographic parameters, risk factors and clinical features (size of ulcer, presence of hypopyon, perforated or impending to perforate) of the fungal ulcers were studied. Data were collected about the outcome of the fungal ulcers with the help of a standard pro forma designed for this study and were evaluated on the basis of how many responded to medical treatment and healed and how many underwent surgical interventions. Visual outcome was evaluated for those that healed or responded to treatment. The outcome of fungal ulcer was evaluated with respect to clinical factors such as size of ulcer, duration of symptoms, and presence of hypopyon.

Treatment undertaken for fungal ulcers

Combination of topical natamycin 5% and fluconazole 0.3%, each was given hourly as the mainstay of treatment in majority of cases with slow tapering of the medication as ulcer showed signs of improvement. In the presence of epithelial plaque or pigments on the ulcer surface, debridement of the ulcer was done from time to time. Oral antifungal, fluconazole 300 mg once a day was started for any one or more of the following situations: large ulcers, deep ulcers, ulcers with hypopyon, ulcers not responding to topical antifungals alone, ulcers extending in the limbus and those associated with endophthalmitis. Intracameral and/or intrastromal injection of amphotericin B or voriconazole was given to non-responding ulcers. This group of patients also received topical voriconazole 1%. Intravitreal antifungal was given in case of association with endophthalmitis. Outcome of the infection was categorized as:

a. "Healed" when patients had followed up till complete resolution of infiltrate, hypopyon and closure of the epithelial defect
b. "Responded to treatment" if there was decrease in size of epithelial defect, hypopyon, and infiltrate but could not be followed up till healing because they preferred to follow up in other centers. Cases in this group were advised to come back promptly if untoward problems occurred
c. "Ulcers not responding to treatment" when they needed therapeutic keratoplasty or evisceration (when the eye was not salvable)
d. "Lost follow up" when patients were lost to follow up without being able to know whether they are getting better or worse.

Ethical consideration

Approval to conduct the study was taken from the institutional review board of the institute (Ref No. 24/2021).

Data management and analysis

For the categorical data analysis, Chi-square/Fisher's exact test were used wherever applicable and $P<0.05$ was considered statistically significant.

RESULTS

A total of 168 fungal ulcers were included in the study. 145 cases had grown fungus in culture and 23 cases showed fungus only in KOH mount. Figure 1 shows fungal keratitis presenting in various seasons. Table 1 shows the types of fungus isolated. 7 out of 145 of the culture-positive fungal ulcers have concomitant bacterial growth. The average age of the patients under study was 46.7 years. 55.3% (n=93) were male. 106 (62.5%) subjects were illiterate. 75% (n=126) were agricultural workers. Out of 168 fungal ulcers, 85.1% (n=143) were from rural region, 11 (6.5%) were from city area and 14 (8.3%) were from North India.

47.3% of 168 ulcers were first treated by either primary eye health worker or by an ophthalmologist (including 14 cases that came to our institute at firsthand); 40.7%

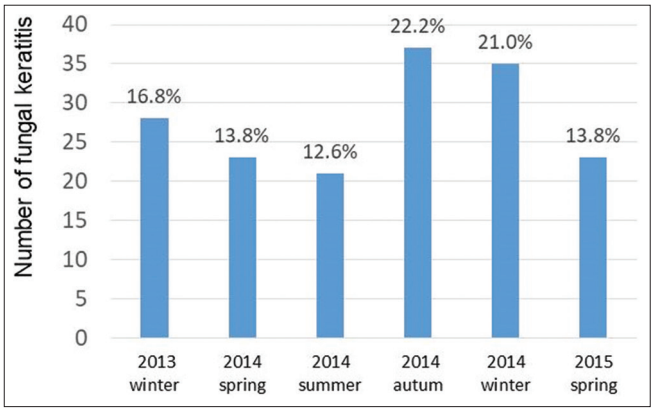

Figure 1: Seasonal distribution of fungal keratitis

had gone to pharmacy shop; 10.2% in general health post and 1.8% were seen by traditional healers in the beginning. Overall, cases had sought medical help at an average of 4.9 days of symptoms, but those who were referred to our institute (n=154) had an average duration of symptoms of 23.6 days.

127 out of 168 (75.6%) of ulcers involved the visual axis (central 4 mm diameter of the pupillary area). 112 (66.7%) cases had infiltrate size of ≤¼ of corneal surface; 20.2% had ulcer size between ¼ and ½ of corneal surface and 13.0% had very large infiltrate of size >½ of the corneal surface. In total, 94 (55.9%) cases were with hypopyon. 12 cases (7.1%) were perforated at the time of presentation which underwent either urgent therapeutic penetrating keratoplasty (TPK) or evisceration. The predisposing factor for ulcers could not be detected in 31.5% (n=53) of cases; 96 (57.1%) cases were found to possess one risk factor and 19 (11.3%) cases were having more than one risk factor for ulcers. History of trauma was present in 85 (50.6%) of fungal ulcers (in 70 cases, trauma was the single risk factor and in 15, it was associated with other risk factors). Use of topical steroid was present in 21 (12.5%) cases (in 9 cases topical steroid was the only risk factor and in 12, associated with other risk factors). 7.7% (n=13) were diabetics (in 5 cases, diabetes was the only risk factor, in 8, associated with other risk factors). Either singly or in combination with other risk factors herpetic keratitis and immunocompromising systemic illness was present as risk factor in 4.8% and 2.4% of cases respectively. 84.7% (n=72) of trauma was with vegetative matter.

Table 1: Fungal isolates

Fungi	Pure isolates	Mixed with bacteria	Total (%)
Aspergillus species	39	2	41 (28.3)
Aspergillus flavus	23	1	24 (16.6)
Aspergillus fumigatus	14	1	15 (10.3)
Aspergillus niger	1	-	1 (0.7)
Aspergillus terreus	1	-	1 (0.7)
Fusarium species	41	-	41 (28.3)
Curvularia species	16	2	18 (12.4)
Exserohilum species	4	-	4 (2.7)
Bipolaris species	3	-	3 (2.1)
Acremonium species	3	-	3 (2.1)
Cladosporium species	2	-	2 (1.4)
Scedosporium species	1	-	1 (0.7)
Colletotrichum species	-	1	1 (0.7)
Candida albicans	1	-	1 (0.7)
Unidentified dematiaceous fungus	9	-	9 (6.2)
Unidentified hyaline fungus	19	2	21 (14.4)
Total (%)	138	7	145 (100.0)

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111 out of 168 cases (66.1%) responded well to medical treatment, 43 cases (25.6%) had to undergo surgical intervention, whereas the outcome was unknown in 14 cases because they did not follow-up (Table 2). Visual outcome of cases (n=111) which has healed or responded to treatment is shown in Table 3. Table 4 shows outcome with respect to ulcer characteristics. Smaller size ulcers (≤¼ of corneal surface) were more likely to heal, less likely to need TPK or evisceration than larger ulcers with statistical significance. Ulcers without hypopyon were more likely to heal and less likely to undergo TPK than those with hypopyon. Similarly, ulcers presenting earlier (within 7 days or less) had a higher chance of healing and less chance of undergoing TPK than those presenting later than 7 days with statistical significance.

The average number of visits of fungal patients in the hospital was 3.8 and average duration of treatment had been 26.9 days. The sensitivity, specificity, and the predictive value of KOH mount has been calculated and discussed in our previous paper.[5]

DISCUSSION

Mycotic keratitis is observed worldwide, but it occurs more frequently in tropical zones with warm and wet climate than in temperate zones which has cold and dry climate.[6] Fungal keratitis constitutes up to 80% of infective keratitis in hospital-based studies in tropical regions where the type of fungus causing keratitis is mostly filamentous.[6] In the temperate zone, the causative fungus in keratitis is mostly yeast.[6] In our institute, 168 out of total of 602 presumed microbial keratitis (27.9%) were due to fungus. In India, fungal keratitis accounted for 26.4–38.06% of the total

Table 2: Outcome of the fungal keratitis

Outcome events	Number (%)
Healed (n=70) or responded to treatment (n=41)	111 (66.1)
Needed TPK* (27 cases were perforated ulcers and 10 were non-healing ulcers)	37 (22.0)
Eviscerated	6 (3.6)
Lost follow up	14 (8.3)
Total	168 (100)

*TPK: Therapeutic penetrating keratoplasty

Table 3: Best-corrected vision of cases that had healed or responded to treatment

Vision	Number (%)
≥6/18	39 (35.1)
<6/18≥6/60	19 (17.1)
<6/60≥3/60	7 (6.3)
<3/60	46 (41.4)
Total ulcers healed	111 (100)

Table 4: Outcome of fungal keratitis with respect to clinical parameters

Characteristics of ulcer	Healed or responded to treatment	Needed TPK*	Needed evisceration	Lost to follow up
Ulcer size ≤1/4 of corneal surface (n=112)	90 (80.4%)	13 (11.6%)	1 (0.9%)	8 (7.1%)
Ulcer size >1/4 of corneal surface (n=56)	21 (37.5%)	24 (42.9%)	5 (8.9%)	6 (10.7%)
p-value	<0.001	<0.001	0.016	0.555
Presence of hypopyon (n=94)	51 (54.3%)	27 (28.7%)	5 (5.3%)	11 (11.7%)
Absence of hypopyon (n=74)	60 (81.1%)	10 (13.5%)	1 (1.4%)	3 (4.1%)
p-value	<0.001	0.018	0.23	0.095
Duration of symptoms ≤7 days (n=28)	23 (82.1%)	2 (7.1%)	0 (0.0%)	3 (10.7%)
Duration of symptoms >7 days (n=140)	88 (62.9%)	35 (25.0%)	6 (4.3%)	11 (7.9%)
p-value	0.049	0.037	0.591	0.706

microbial keratitis.[7-9] *Aspergillus* species and *Fusarium* species were isolated in equal proportion, 28.3% each as shown in Table 1. In Eastern and Southern India also, *Aspergillus* species and *Fusarium* species were two predominant fungi.[9,10] However, in China and South Florida, *Fusarium* species were more commonly isolated (41–57%) in culture.[11,12] There had been only one case of *Candida* species (0.6% of fungal isolates) in our study. In China, *Candida* species were reported in 0.4% of fungal ulcers, but none was reported by in South India.[10,11] In other reports of Nepal and North India, *Candida* species had been isolated in 4 to 6% of fungal keratitis.[4,13] In South Florida, *Candida* species were isolated in 14% of fungal isolates.[12] 4.8% of culture-positive fungal ulcers had concomitant bacterial growth in culture in our Institute. Other reports showed mixed infection in 9.9–17%.[4,9]

In fungal keratitis, the male preponderance of 64–79% was seen in most of the studies including ours (55.3%).[7-9,12-15] This could be because men are more likely to be involved in outdoor activities and hence are prone to trauma and environmental exposure to the fungus. Our mean age of patients (46.7 years) was similar to the average age of 41–48 years, reported in Singapore, South Florida, and South India.[10,12,15] In our study, majority of the subjects (85.1%) were from rural region and 75% of patients were farmers by occupation. In the study of Rautaraya et al.,[9] 96% of patients with fungal keratitis belonged to rural regions and 28.4% of total patients were farmers. In Central China and South India, 92% and 64.7% were farmers respectively.[8,11]

We had more cases of fungal keratitis in autumn and winter (August–January) as shown in Figure 1. A very similar pattern was seen in India and Central China.[11,13,16] From these reports, it was observed that the fungal keratitis cases peaked during the months of high agricultural activities.

In our study, 91.6% of cases had treatment before visiting our hospital and they came at average of 23.6 days after the onset of symptoms. Only 16.6% of total cases had come to our Institute within 7 days. A large proportion of patients coming late may reflect economic and transportation difficulties to reach the city for tertiary care. In South India, 46.6% of cases of fungal ulcers reached tertiary hospital within 7 days for treatment.[8]

In our study, 50.6% cases gave a history of trauma preceding the ulcer. In other studies of fungal keratitis, trauma was reported in 40–92%.[9,8,15,17] In our study, 84.7% of trauma were due to vegetative matter. Around 60% of trauma was due to vegetative matter in the studies done in South Florida and South India.[8,12] 12.5% had history of steroid use in our study. Wong et al.,[15] mentioned 24.1% of fungal keratitis cases were using steroids in the study. In our study, 7.7% of patients were diabetics and another 2.4% were having a systemic disease such as Rheumatoid arthritis, Steven Johnson syndrome, Behcet's disease, cancers on chemotherapy. Wong et al.,[15] mentioned 20.8% of subjects were having systemic disease with immunosuppression. In other studies, 3.3–15.7% of fungal ulcers were having diabetes.[8,9] In fact, people with diabetes and immunocompromised state are more prone to fungal keratitis when they have ocular trauma.[18]

In our study, 77.2% had involvement of the central cornea and 13% had infiltrate size more than half of the cornea. Wong et al.,[15] mentioned 68.9% of fungal ulcers were with central involvement and 10.3% were with diffuse infiltrate in the cornea.

Bharathi et al.,[8] reported that hypopyon was present in 55.62% of patients, similar to our study (56%) but patients presenting with corneal perforation reported by them was 1.37% versus 7% in our study. This implies more severe cases presenting in our Institute.

The outcome of fungal keratitis in various studies is compared in Table 5 which shows the healing rate in fungal keratitis as 40.5–72.8%, rate of TPK as 19.7–59.4%, and that of evisceration as 1.4–10.3%. Variations in spectrum of fungus, treatment regimen, and method

Table 5: Comparison of outcome of fungal keratitis in various studies

Place of study and sample size	Predominant fungus isolated	Antifungals used	Outcome events		
			Healed or improved with medical treatment alone	Needed surgical intervention	Lost follow up or outcome unknown
Our study (Nepal) (n=168)	*Aspergillus*, fusarium, unidentified hyaline fungus	Mostly Gtt NT and Gtt FLU, oral FLU in severe cases Gtt NT and Gtt VC in few cases	66.1%	TPK (22%), EV (3.6%)	8.3%
Singapore (n=29) Wong et al.[15]	*Fusarium*, *Aspergillus*, *Candida*	Gtt APH in most cases, Gtt NT in some cases, systemic antifungal (APH, FLU, KTC or ITC) in severe cases	68.9%	TPK (24%), EV (6.8%)	N/A
Paraguay (n=23) Sonego-Krone et al.[14]	*Acronium*, *Fusarium* and *Curvularia*	Gtt FLU for all, Oral KTC in severe cases	70%	30%	N/A
China (n=65) Gong and Gong[19]	Not mentioned	Gtt FLU and Gtt NT for all	72.3%	27.6%	N/A
West Bengal, India (n=110) Saha et al.[7]	*Aspergillus*, *Candida*, *Fusarium*	Gtt NT or Gtt VC or Gtt APH, Oral KTC for all	40.5%	TPK (59.4%)	N/A
South Florida, USA (n=84) Iyer et al.[12]	*Fusarium*, *Candidia* and *Curvularia*	Gtt NT and Gtt APH, Oral ITC or FLU in 25% of cases	#72.8%	#TPK (25.7%), #EV (1.4%)	#14
Eastern India (n=264) Rautaraya et al.[9]	*Aspergillus*, *Fusarium* and *Acremonium*	Gtt NT, Oral KTC or FLU or ITC	54.5%	TPK (19.7%), EV (3.4%)	22.3%
South India, (n=140) Lalitha et al.[10]	*Aspergillus*, *Fusarium*, other filamentous fungi	Gtt NT for all, Oral FLU for large ulcers	#68.7%	#31.3%	#25

Gtt: Guttae, TPK: Therapeutic penetrating keratoplasty, EV: Evisceration, N/A: not applicable, NT: natamycin, FLU: fluconazole, ITC: itraconazole, KTC: ketoconazole, APH: amphotericin B, VC: voriconazole, #Cases that were "lost to follow up or outcome unknown" were excluded from total ulcers while calculating the percentage of outcome events

of analysis among different studies as shown in Table 5 make it difficult to infer about the outcome of fungal keratitis and to know about the suitable regimen of treating fungal ulcers. Sonego-Krone et al[14] and Gong et al[19] had a similar protocol of treatment as ours and had reported success in 70–71% of fungal keratitis. In our study, late presentation of the fungal keratitis, larger sized and complicated ulcers (as of 7.1% of ulcers are already perforated) at presentation had been the limiting factors for a better outcome. If these perforated ulcers which underwent TPK straight away are kept aside, the treatment efficacy of the regimen in our study could be as high as 73.2%. In severe fungal keratitis, it may be beneficial to begin with two different antifungal agents because fungal pathogens differ in their response to antifungal agents and microbiology laboratories do not routinely perform antifungal sensitivities.[12]

In our study, when analyzed independently, smaller-size ulcers, ulcers without hypopyon, and those presenting within 7 days were found to have better healing rates (>80%) with statistical significance as shown in Table 4. Prajna et al.,[20] mentioned risk of needing TPK was significantly related to presence of hypopyon, size, and depth of infiltrate but the duration of symptoms was not related to happening of perforation. Larger ulcer size had more risk of perforation in fungal ulcer in the study of Wong et al.,[15] In the study of Rautaraya et al.,[9] significantly higher surgical interventions were needed in cases which presented beyond 10 days. This shows the importance of early diagnosis and treatment of fungal ulcers.

The randomized control trial (Mycotic ulcer treatment trial)[21] showed that in filamentous fungal keratitis, particularly the *Fusarium* species, patients treated with natamycin had a better outcome than those treated with voriconazole. The differences in outcome in other species were not significant. Voriconazole should not be used as monotherapy in the treatment of Fusarium keratitis.[21]

Another randomized prospective study in India by Koul et al.,[22] concluded that the treatment efficacy of the combined therapy of natamycin 5% eye drops and fluconazole 0.3% was better than the monotherapy with natamycin 5% alone for deep filamentous fungal ulcers. This could be due to the ability of fluconazole to penetrate the deeper corneal layers as compared to natamycin.[22]

Limitations of the study

Outcome of cases that had undergone TPK has not been analyzed in this study. Cases which were lost during follow up had not been traced.

CONCLUSION

Protective measures have to be undertaken to prevent agriculture-related trauma. A study done in our Institute about the outcome of TPK for infective keratitis had shown that fungal keratitis undergoing TPK had less satisfactory outcome compared to that done for bacterial keratitis.[23] So prevention, early diagnosis, correct treatment, and timely referral are the mainstay of combating fungal keratitis in developing countries. At least a facility of KOH mount examination should be made available in secondary centers as KOH mount has good sensitivity, specificity, and predictive values.[5] Antifungal medications should be available in all the primary and secondary eye care centers. Fluconazole and natamycin eye drops can be easily made available in rural regions in our settings and do not need formulation. Fluconazole 0.3% and natamycin 5% combination with oral fluconazole severe cases had a quite good success rate in treating fungal ulcers presenting within 7 days, smaller ulcer size, or ulcers without hypopyon.

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LB- Concept, design, intellectual content, literature review, data acquisition and analysis, manuscript writing (major) and manuscript review; **ARB**- Data acquisition and analysis, literature review, manuscript writing; **RG**- Critical analysis of the manuscript.

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