

Clinical characteristics, predisposing factors, and treatment outcome of *Curvularia* keratitis

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Purpose: To report clinical characteristics, predisposing factors, and treatment outcome of *Curvularia* keratitis. **Methods:** Retrospective chart review of consecutive culture-proven *Curvularia* keratitis patients who presented to a tertiary eye care center in north India. Patients with mixed infections with *Curvularia* as one of the pathogens were also included. Standard case report form was developed to capture demographic information, clinical features, etiology, treatment, and outcome. Binary logistic regression was done to ascertain the effect of identified variables on final visual acuity. **Results:** Medical records of 97 patients of *Curvularia* keratitis were reviewed. Median age of patients was 45.3 years. Seventy-nine (79.4%) patients presented during the months of September to November. History of corneal trauma was present in 69.1%. Trauma from sugarcane leaf was identified in 66.1% of cases with corneal trauma with vegetative matter. Presenting visual acuity was worse than 20/60 in 57.8% of patients. Hypopyon and pigmented plaque-like infiltrate was present in 16.5% and 28.8% of patients, respectively. Mixed infection was reported in 14.4% of cases. Median time of antifungal therapy was 24.5 days. Surgical intervention was required in 18.5% cases. Of all, 11.1% patients achieved final VA of more than 20/200 who were managed surgically as compared to 68 (86%) patients who were managed medically. Younger age, absence of comorbidities, and lesser infiltrate size were found associated with good final visual acuity. **Conclusion:** Working males were most affected by *Curvularia* keratitis. Corneal trauma with sugarcane leave was the most common predisposing factor in the study area. Most of the cases presented with worse visual acuity but could be managed medically.

Key words: *Curvularia* sp. trauma, hypopyon, keratitis, pigmented plaque, sugarcane, Uttar Pradesh

Curvularia is a dematiaceous fungus found ubiquitously in soil. It is a facultative pathogen of many plant species and of the soil, but can also be isolated from air, animals, and humans. Many species of this genus have been reported as human pathogens ranging from mild skin and nail infections to severe invasive disease.^[1-3] Corneal infection due to *Curvularia* was first reported in 1959.^[4] *Curvularia* is characterized by the production of sympodial conidiophores with tretic, terminal and intercalary conidiogenous cells and elongate, transversely septate conidia with a dark basal scar. Conidia are often curved at an asymmetrically swollen intermediate cell, but species with straight conidia also have been described.^[5,6] Identification of *Curvularia* relies upon the direct examination of sporulating structures under a microscope.^[7] The key microscopic feature of *Curvularia* spp. is the presence of true septate conidia (cross-wall).^[7]

Fungal keratitis is one of the major causes of corneal blindness in tropical and subtropical countries.^[8] There is very little data available on the incidence of fungal keratitis from north India. According to one retrospective incidence study conducted in south India, the estimated annual incidence of fungal keratitis was 11.3 per 10,000 population.^[9] Over

the past decade, published reports on microbial keratitis from India identified *Curvularia* as one of the major fungal pathogens.^[10-14] However, in all these reports, the clinical characteristics, predisposing factors, and treatment outcomes were not reported exclusively for *Curvularia* keratitis.^[10-14] Till date, there has been only one case series of *Curvularia* keratitis published almost two decades ago from United States.^[15] The purpose of this case series was to report clinical characteristic, predisposing factor, and treatment outcome of consecutive patients diagnosed with *Curvularia* keratitis over a period of five years from July 2012 to June 2018. This is the first case series on *Curvularia* keratitis to be published from India. Authors believe that this study will give more insight in the management of these patients.

Methods

It is a retrospective, noncomparative, observational case series. The study was approved by institutional ethics committee and adhered to the principles of the Declaration of Helsinki. Clinical records of all consecutive patients with laboratory proven

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diagnosis of *Curvularia* keratitis, who presented to the cornea services, CL Gupta Eye Institute, Moradabad (India) from July 2012 to June 2018 were included. Patients with mycotic keratitis due to other fungi were excluded from this study.

A detailed examination of both eyes was performed using the slit-lamp biomicroscope. Standard case report form was developed to capture details of each patient including sociodemographic information clinical findings, predisposing factors, history of corneal trauma, nature of agent causing trauma, associated ocular conditions, other systemic diseases, use of steroid eye drops, therapy received prior to presentation, and visual acuity at the time of presentation. Symptoms and size of an epithelial defect, with or without hypopyon, and infiltrate as measured by the variable slit on the biomicroscope were also recorded.

For laboratory diagnosis, corneal scrapings were obtained from the base and edge of the ulcer using a sterile surgical blade (# 15 on a Bard-Parker handle) under topical anesthesia (0.5% proparacaine hydrochloride) under slit-lamp magnification. Gram stain and 10% potassium hydroxide mount were included as a part of the standard protocol for microscopic evaluation of corneal smears on the first visit. Gram-stained smears were examined at $\times 400$ and $\times 1000$ magnification; the KOH preparations were examined at $\times 200$ and $\times 400$ magnification under light microscope. Scrapings for smears were also collected along with those for culture.

For culture, the material was inoculated on to Chocolate agar, Blood agar, Brain heart infusion broth, Thioglycolate broth and incubated at 37°C and Sabouraud dextrose agar (SDA) at both 25°C and 37°C . Cultures were examined daily during 1st week, twice weekly for next 3 weeks, and discarded after 3–4 weeks if there was no growth. *Curvularia* was identified by their colony characteristics on SDA and by the morphological appearance of the spores in Lactophenol cotton blue stain, and in some cases by slide culture method. All laboratory methods were performed under standard protocols, which have been discussed in detail in the previous studies.^[10-12,16,17]

The eyes were treated initially based on the clinical evaluation and microbiological smear examinations. The eyes were treated with 5% natamycin suspension on an hourly basis. Topical voriconazole 1% (Vozole, Aurolab, India) was supplemented for larger and deeper ulcers. Adjuvant therapy of cycloplegics and analgesics was given to all patients. Indication of tissue adhesive and bandage contact lens was impending perforation or perforation of less than 2 mm. Indication for therapeutic penetrating keratoplasty was corneal perforation of more than 2 mm or infiltrate not responding to the therapy.

Statistical analysis

The statistical analysis was performed with SPSS 17.0 software (SPSS Inc, Chicago, IL, USA). Descriptive statistics were obtained to determine the frequency and proportions. Mean and standard deviation were calculated for continuous variables. Depending on the type of data, Independent t-test, Mann–Whitney U test, Chi-square test, and Fisher's exact test were used for comparison between groups.

All cases were divided into two groups based on their final visual acuity. Group one included patients with final visual acuity better than equal to 20/200 and group two had cases

with final visual acuity worse than 20/200. Univariate and multivariate analyses were done to assess the effect of variables like age, presence of trauma, prior medications, systemic illnesses, comorbidities, hypopyon, pigmented plaque, and visual acuity at presentation. Univariate analysis was done by Chi-square and multivariate analysis was done by binary logistic regression model. Covariates were retained in the model if their *P* value was <0.05 . The primary outcome measure was the final visual acuity $\geq 20/200$ and $<20/200$. A Hosmer–Lemeshow test was used to test the goodness of fit of the model.

Results

A total of 97 patients were found eligible for the study. Sixty-three patients (64.9%) were men and 34 (35.1%) were women. The median age of patients was 45.3 ± 12.2 years (interquartile range 11–75 years). Left eye was involved in 33 (54.6%) patients and right eye was involved in 44 (45.4%) patients. Seventy-seven (79.4%) cases were presented from September to November [Fig. 1].

Predisposing factors: Corneal trauma was sustained in 69.1% ($n = 67/97$) patients prior to onset of the ulcer. Of them, 70.1% patients were male. A total of 53 ($n = 53/67$; 79.1%) patients suffered traumatic corneal injury with vegetable matter. Sugarcane leaf ($n = 35/53$; 66.1%) was the most common cause among vegetative injuries followed by wood stick injury ($n = 4/14$; 28.5%). Dust particle ($n = 6/14$; 42.8%) was the main nonvegetative cause of corneal trauma. Six patients ($n = 6/97$; 6.2%) were using topical steroids at the time of presentation. Systemic illness was present in 8 ($n = 8/97$; 8.2%) patients. Concurrent systemic diseases were hypertension ($n = 3$), diabetes ($n = 1$), asthma ($n = 2$), coronary artery disease ($n = 1$), and thyroid ($n = 1$). History of prior medication was present in 81 ($n = 81/97$; 83.5%) patients. Twenty-six ($n = 26/81$; 32.1%) of them were using topical antibiotics. Rest 55 ($n = 55/81$; 67.9%) patients did not remember the name of medication they were using. No patient gave clear history of prior steroid use.

Clinical characteristics

The presenting visual acuity of affected eye was more than 20/30 in 19 (19.6%) eyes, less than 20/30 to 20/60 in 22 (22.7%) eyes, less than 20/60 to 20/200 in 18 (18.6%) eyes, and less than 20/200 in 38 (39.2%) eyes. Ocular comorbidity like ectropion, dry eye, and trichiasis was present in 5 ($n = 5/97$; 5.2%) eyes. The median infiltrate size was 7.5 mm^2 (IQR: 13.2 mm^2).

At presentation, yellow-colored infiltrate was noted in 60 eyes (61.8%), gray-colored in 10 (10.3%) eyes, and brown pigmented plaque in 27 (27.8%) eyes. Infiltrates were fluffy in 51 (52.6%) eyes, plaque-like in 29 (29.9%) eyes, an unusual long branching with reticular pattern in 14 (14.4%) eyes which we had not seen in other fungal keratitis cases, and satellite lesions were seen in 3 (3.1%) eyes. Margins of infiltrate was feathery in 78.3%, edematous in 14.4%, and scarred in 7.2% of eyes. Depth of infiltrate was anterior stromal in 70.1%, mid stromal in 15.4%, and total stromal in 14.4% of cases. Location of infiltrate was central in 76.3%, paracentral in 20.6%, and peripheral in 3.1% of eyes [Fig. 2].

Hypopyon was present in 16 ($n = 16/97$; 16.5%) eyes. The mean infiltrate size was $18.15 \pm 15.4 \text{ mm}^2$ of eyes with hypopyon and $10.2 \pm 12.1 \text{ mm}^2$ of eyes without hypopyon ($P = 0.006$;

Independent sample Mann–Whitney U test). Patients with hypopyon had worse presenting visual acuity as compared to patients without hypopyon ($P = 0.0$; Fisher's exact test). Surgical intervention was needed in 6 ($n = 6/16$; 37.5%) eyes with hypopyon as compared to 12 ($n = 12/81$; 14.8%) eyes without hypopyon ($P = 0.04$; Pearson Chi-Square).

Only *Curvularia* sp. infection was reported in 83 (85.6%) patients and mixed bacterial/fungal infection was reported in 14 (14.4%) patients. In patients with mixed infection, bacterial isolates were *Streptococcus* sp. ($n = 9$), *Acinetobacter* sp. ($n = 1$), *Corynebacter* sp. ($n = 3$), and *Pseudomonas* sp. ($n = 1$). The presenting visual acuity in patients with mixed infection was worse as compared to patients without mixed infection ($P = 0.021$; Fisher's exact test)

Management

The median time for which antifungal therapy given was 24.5 days (IQR: 33.25 days). Ninety-two patients were initially treated with topical natamycin drops on an hourly basis and 5 patients with voriconazole eye drops also was added on

first visit. Of the ones on only natamycin, after one week, if the desired response was not seen, an additional topical antifungal drug (voriconazole) was added in 24 (24.7%) patients. Natamycin in combination with voriconazole was used in 29 (31.5%) patients. Corneal thinning was present in 7 (7.2%) eyes and corneal perforation in 6 (6.2%) eyes. In this series, 18 (18.5%) eyes needed surgical intervention. Tissue adhesive and bandage contact lens (TA + BCL) was applied in 12 (12.3%) eyes, therapeutic penetrating keratoplasty (TPK) was performed in 5 (5.2%) eyes, and evisceration was done in 1 (1%) eye. Recurrence of keratitis was seen in 1 (1.03%) eye. Mean infiltrate size of patients managed surgically was $20.1 \pm 15.4 \text{ mm}^2$ and of patients who were managed medically was $9.6 \pm 11.6 \text{ mm}^2$ ($P = 0.002$; Independent sample Mann–Whitney U test). Two (11.1%) patients achieved final VA of more than 20/200 who were managed surgically as compared to 68 (86%) patients who were managed medically.

Characteristics of patients needed TPK and Evisceration: Of five patients who needed TPK, 4 had history of ocular trauma. All patients had a central ulcer. The mean size of the infiltrate prior to therapeutic penetrating keratoplasty was 31.05 mm^2 . Two patients had hypopyon of 1.5 and 2.5 mm. A pigmented plaque was noted in one patient. Four patients had history of prior medication. None of them were using steroids. Of all, four patients had presenting BCVA of less than 20/200 and one had presenting BCVA of 20/60. Days of antifungal therapy ranged from 7 to 90 days. Indications for therapeutic penetrating keratoplasty were total infiltrate threatening to involve the limbus, corneal perforation of $>2 \text{ mm}$, and infiltrate not responding to intensive medication for 1–2 weeks. Graft size ranged from 9 to 11 mm. Of all eyes, 4 eyes had complete eradication of fungus and one eye developed recurrence. Recurrence of fungal infection was noted after 45 days. Culture of half corneal button of the eye that developed recurrence revealed a coinfection with *Staphylococcus* sp. The eye that underwent evisceration had copious corneal endothelial

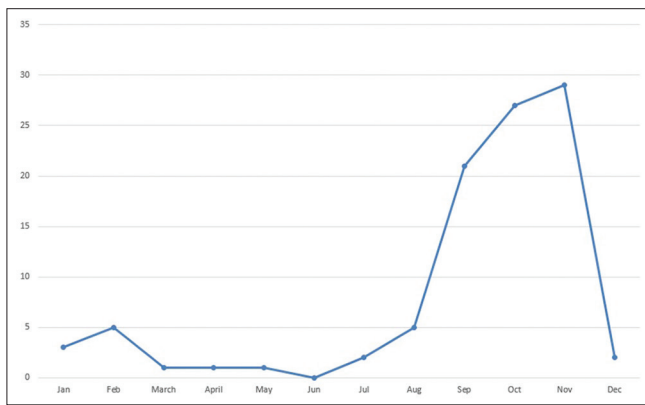


Figure 1: Month wise trend of *Curvularia* keratitis

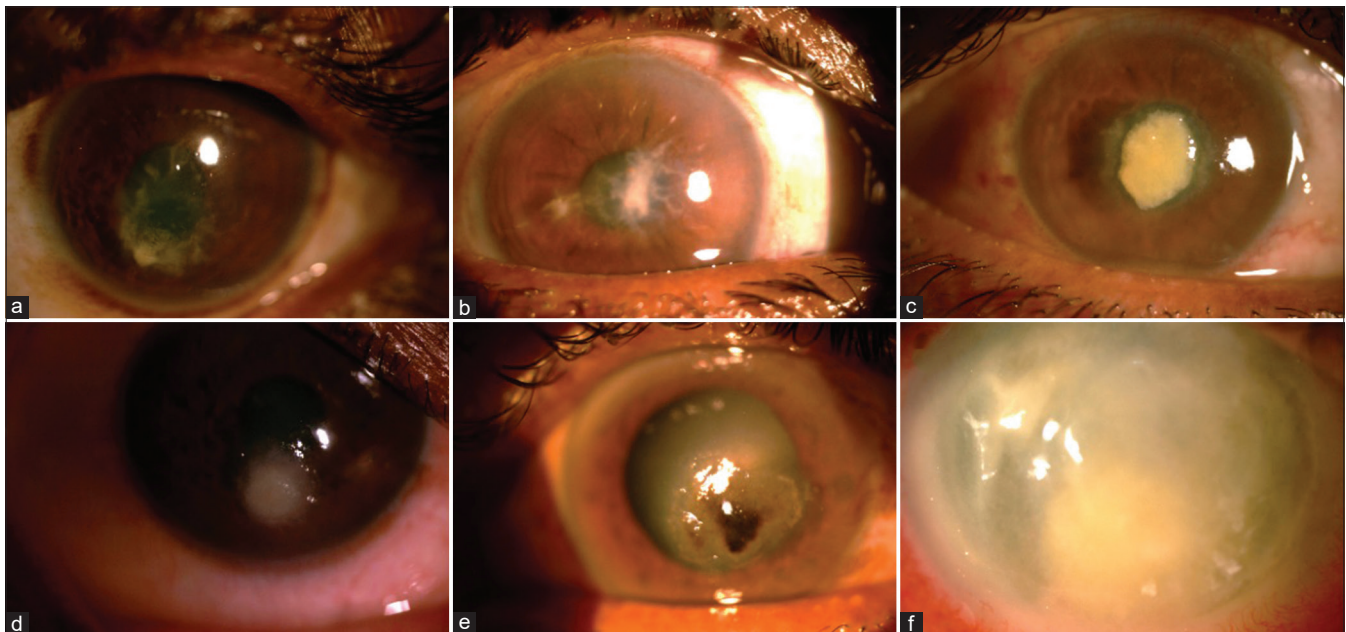


Figure 2: Clinical characteristics of *Curvularia* keratitis (a and b) Branching pattern, (c) Nonpigmented plaque, (d) Feathery edges, (e) Pigmented plaque, (f) Total infiltrate

exudates with large hypopyon with severe endophthalmitis. Patient had history of corneal trauma with stick 15 days before presentation.

Outcome

Resolution by tissue scar replacing stromal infiltrate appeared in 40 (41.2%) patients. The median time for scar appearance was 10 days (IQR: 11.5 days). Complete resolution of keratitis was seen in 41 (42.3%) eyes. Visual acuity at last follow-up was improved or remain unchanged in 89 (n = 89/97; 91.5%) patients, and decreased in 8 (n = 8/97; 8.2%) patients. A comparison between presenting visual acuity and visual acuity at last follow-up is shown in Table 1. There was a statistically significant difference in final visual acuity between patients with comorbidities and patients without comorbidities like trichiasis, dry eye, etc., (P = 0.05; Fisher's exact test).

Multivariate analysis

Final visual acuity ≥20/200 was reported in 70 cases (72.1%) and <20/200 poor in 27 cases (27.8%). Variables found to be associated with visual outcome in the univariate analysis are shown in Table 1. The binary logistic regression model was statistically significant, $\chi^2 = 56.1$, P = 0.00. The model correctly classified 85.6% of cases. Younger age (P = 0.00), absence of comorbidities (P = 0.01), and lesser infiltrate size (P = 0.00) were found associated with good final visual acuity of ≥20/200. A Hosmer–Lemeshow goodness of fit test showed that the binary regression model was good fit to the data (P = 0.23) [Table 2].

Table 1: Univariate analysis

	Total n	Final VA outcome %		P
		≥20/200	<20/200	
History of ocular trauma				
Yes	67	71.6	28.4	1.0
No	30	73.4	26.6	
Systemic Illness				
Yes	8	87.5	12.5	0.43
No	89	70.7	29.3	
Presence of comorbidity				
Yes	5	20.0	80.0	0.02
No	92	75.0	25.0	
Prior medication				
Yes	81	72.8	27.2	0.76
No	16	68.7	31.3	
Presence of Hypopyon				
Yes	16	43.7	56.3	0.01
No	81	77.7	22.3	
Presenting VA				
>20/30	19	100	0	0.86
20/30-20/60	22	90.9	9.1	
<20/60-20/200	18	88.8	11.2	
<20/200	38	39.4	60.5	
Infiltrate size (mm)				
Small (≤1.4)	16	93.7	6.3	0.00
Medium (1.5-4.9)	22	95.4	4.6	
Large (≥5.0)	59	57.6	42.4	

Discussion

In this series, the majority of the patients with *Curvularia* keratitis presented between September to November and sugarcane leaf injury was the most common cause of vegetative trauma. This period is the harvesting season of sugarcane in Uttar Pradesh, India. The tall and pointed leaves of sugarcane are close to eye level of an average height person. This increases the chance of corneal trauma if they do not wear protective glasses. Ghosh *et al.* also reported a peak in the incidence of fungal keratitis in north India during post-monsoon season (September to November).^[18] Wilhelmus reported that in Gulf of Mexico *Curvularia* keratitis appeared to occur more frequently during the hotter, moister, summer months, possibly because of an increase in airborne *Curvularia* spores during these months.^[19] Most of the patients with prior corneal trauma were male as culturally men work more in fields in the study area. 83.5% of patients were already using medications. None of the patients had a prior microbiologic examination. By the time patients have presented to our cornea facility, they were taking treatment either from a local doctor, or purchased medications directly from a medical store. Limited availability of cornea specialist in the study area has also been contributing to this low eye care seeking behavior. Large-scale public education programs to increase awareness about possibility of vegetative trauma causing serious keratitis are required in the study area (especially in sugarcane field workers) to encourage its prevention. Education of general physicians, health workers, as well as general ophthalmologists can ensure timely diagnosis and referral to a cornea specialist.

Men were more commonly affected by fungal keratitis than women. Patients between 30 and 40 years of age (62.8%) were more affected. This was also reported previously in almost every case series on keratitis.^[12] Hypopyon was present in eyes with large lesion size. Presenting visual acuity was also significantly less in eyes with large lesion size/presence of hypopyon. Surgical intervention was more common in cases with hypopyon. In this series, the majority of the cases are successfully managed medically with antifungal eye drops. Surgical interventions are required in a significant number of cases to control the infection. Lalitha *et al.*^[20] reported worse outcomes with larger ulcers with *Aspergillus* sp. In their study of the factors predictive for visual outcome, size of infiltrate and age of patients were found significantly associated with good visual outcome (VA >20/200). In our study clinical characteristics commonly described for dematiaceous fungal ulcer is the form of brownish plaque was found in only 28.4%. In addition, an unusual long branching with reticular pattern was seen in 14 (14.4%) eyes which we had not seen earlier in other fungal keratitis cases.

In our study, therapeutic penetrating keratoplasty was required in 5 (5.2%) patients. Mundra *et al.* reported 11.9% of fungal keratitis patients underwent therapeutic penetrating keratoplasty.^[21] However, *Curvularia* spp. were identified in only 2 (1%) eyes in their study.^[21] In our study, only one eye developed recurrence as compared to 10.1% of fungal keratitis patients in the study by Mundra *et al.*^[21]

However, in this series, resolution of infiltrate and scar formation was seen in 42.3% patients. In the previous study by Garg *et al.*,^[16] on dematiaceous fungal keratitis, resolution

Table 2: Binary logistic regression for visual outcomes

	Odds ratio of better outcome	Binary logistic regression 95% Confidence interval		P
History of ocular trauma				
Yes	Reference			
No	1.5	0.35	6.5	0.57
Systemic Illness				
Yes	Reference			
No	0.11	0.01	1.8	0.12
Presence of comorbidity				
Yes	Reference			
No	136.1	2840	6523	0.01
Prior medication				
Yes	Reference			
No	0.51	0.06	3.9	0.52
Presence of Hypopyon				
Yes	Reference			
No	1.2	0.25	5.7	0.81
Infiltrate size (mm)	0.82	0.74	0.91	0.00
Age of patient	0.89	0.83	0.96	0.02

of infiltrate and scar formation was reported in 72% patients. In their series, 22.7% patients were identified with *Curvularia* keratitis. Similarly, in a recent study from north India, resolution of stromal infiltrate with corneal scarring was reported in 80% patients.^[22] Although the frequency of dematiaceous fungi species was different in the above studies, this series report outcome of only *Curvularia* keratitis. This suggests that the outcome of *Curvularia* keratitis could be poorer as compared to other fungal keratitis but it may be out of the scope of this study to draw such comparisons.

In this study, topical natamycin suspension (5%) was used to treat the majority of patients. Efficacy of topical natamycin in cases of dematiaceous fungal keratitis has been reported in the previous studies.^[15,23] Natamycin is considered the most effective medication against *Fusarium* and *Aspergillus*.^[24] In a controlled trial of patients with fungal keratitis treated with natamycin 5% eye drops hourly compared with itraconazole 1% eye drops hourly, in the *Curvularia* specific keratitis subgroup, favorable responses occurred in both groups (patients receiving natamycin and in patients receiving itraconazole).^[25] The number of patients in both the groups in this subgroup analysis was few.^[25] However, in our study, topical itraconazole was not used. Voriconazole is safe and effective against the major ocular fungal infections.^[26] A double-blinded RCT conducted to compare safety, efficacy, and cost-effectiveness of voriconazole with natamycin found no significant difference between the two agents. The outcomes of our study suggest good response to natamycin and voriconazole combination in 29 cases. Surgical intervention was required in patients with severe fungal infection. The previous studies have reported penetrating keratoplasty as an effective procedure for severe cases of fungal keratitis.^[22] Final visual outcome in cases of *Curvularia* keratitis was worse after surgical intervention as compared to cases who were managed medically in our series which could be because the criteria for considering for surgery were later in the course of disease when significant damage due to inflammation had

already occurred. The outcomes of early surgery in these cases need to be evaluated.

In this series, 14.4% of *Curvularia* keratitis had a co-infection with *Streptococcus* sp., *Acinetobacter* sp., *Corynebacter* sp., and *Pseudomonas* sp. The visual outcome was worse in these cases. Gupta *et al.* also reported one case of Acanthamoeba keratitis with *Curvularia* co-infection.^[27] There are many case reports of *Curvularia* endophthalmitis^[28-30] and following laser *in situ* keratomileusis.^[31] However, in our series, only one case of *Curvularia* endophthalmitis but no case following LASIK was reported.

Conclusion

In conclusion, *Curvularia* keratitis was found to be associated with corneal trauma with sugarcane leaves. Males were more affected. Almost all patients had received prior medication. Presenting visual acuity was less than 20/60 in approximately 50% cases. A typical pigmented plaque was seen in only 28.1% cases. Unusual long branching with reticular pattern in some eyes should also raise a suspicion of *Curvularia* keratitis. Most patients of *Curvularia* keratitis can be treated with natamycin. Surgery may be required in patients with severe infection.

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Conflicts of interest

There are no conflicts of interest.

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