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Original Research Article

A Clinicopathological Study and Management of Fungal Corneal Ulcer in a Tertiary Care Hospital

Dr. Santosh Jajodia[1], Dr. Sushree Sagarika Sahoo[2,] Dr. Prasanta Kumar Nanda[3]

[1]Associate Professor, Department of ophthalmology, Hi-tech Medical College and Hospital, Pandara: Bhubaneswar, Odhisa, India.
[2]Final Year Postgraduate, Department of ophthalmology, Hi-tech Medical College and Hospital Pandara: Bhubaneswar, Odhisa, India.
[3]Professor & HOD, Department of ophthalmology, Hi-tech Medical College and Hospital Pandara, Bhubaneswar, Odhisa, India.

Corresponding Author
Dr. Santosh Jajodia, Associate Professor, Department of ophthalmology, Hi-tech Medical College and Hospital, Pandara: Bhubaneswar, Odhisa, India.

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ABSTRACT

Background
In this study we wanted to assess the prevalence of specific fungal pathogens, analyze the influence of demographic factors on the spectrum of fungal species responsible for fungal corneal ulcers and also determine the effectiveness of treatment.

Methods
This was a prospective study carried out over a period of two years involving 53 corneal ulcer patients. Corneal scraping materials collected from the patients were sent for a 10% KOH/NaOH stain and Sabouraud dextrose agar for culture and sensitivity by micro-broth dilution technique. All the patients who were KOH stain positive and/or culture positive in Sabouraud medium were considered for the study. The patients were emperically treated with Topical Natamycin 5percent eye drop. As per culture and sensitivity report, voriconazole (1%), topical amphotericin-B or a systemic anti-fungal drug like Itraconazole (200 mg) was added. All patients were followed up daily for one week, every one week up to one month, and every two weeks up to three months till the epithelium healed, as evidenced by the negative FL stain and disappearance of signs and symptoms. The collected data was tabulated and analyzed using SPSS (Statistical Package for Social Science) version 22.0. For statistical analysis, mean, frequency, percentage and Pearson's chi-square test were performed; a p-value <0.05 was considered to be statistically significant.

Results
The maximum number of cases were seen in males in the range of 51- 60 years and in females aged 41-50 years, who were mostly involved in outdoor work. Males were more affected (62.26%) than females (37.73%). 52.83% were agricultural workers or farmers, with vegetative matters (39.60%) being the most common traumatic agent. 26.4% of study subjects were diabetics and 13% had a history of using topical steroids. A central location for corneal ulcers was present in 50.9% of cases, and a paracentral location was present in 39.6% of cases. In 77.4% of patients, the ulcer was ≤6 mm. 35 (66%) out of 53 study subjects fell within the range of 34%-67% depth of corneal involvement. 50.94% of study subjects had visual acuity between <6/60 and >1/60. All study subjects had a 10% KOH smear positive. 31 study subjects had a positive SDA culture, the rest had negative and variable reports. Aspergillus was the predominant organism in 45 (84.9%), followed by fusarium in 8 (15.1%). All fungal ulcers were sensitive to natamycin (100%) with a

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variable sensitivity to voriconazole 17 (32.1%), amphotericin B 7 (13.2%) and itraconazole 15 (28.3%).

Conclusion

The present study has brought to light again the fact that fungal keratitis continues to be a major concern for loss of sight, especially in the rural, agricultural population. Goals directed towards proper education, early recognition and appropriate treatment will go a long way towards mitigating the problem of this potentially sight-threatening condition.

Keywords: Corneal Ulcer, Corneal Scraping, Filamentous Fungi, Aspergillus, Fusarium.

INTRODUCTION

Despite advances in the medical field, blindness remains a major public health problem. Among the different causes of visual impairment, corneal ulcers, which lead to corneal opacity, are the second most avoidable cause of impairment, followed by cataract.[1]

A corneal ulcer is defined as a breach in the corneal epithelium with a superadded infection. Among the infective causes of corneal ulcers, fungal corneal ulcers are more virulent and sight-threatening, i.e., worsening of visual outcome, which, if not treated properly, can lead to a higher rate of corneal perforation, corneal opacity, panophthalmitis and monocular blindness. Early diagnosis and management are therefore essential to prevent long-term complications including blindness.[2]

The incidence of fungal keratitis has been increasing for the past 30 years. It accounts for about 40-50% of all microbial keratitis.[3] Common organisms responsible for fungal corneal ulcers include species of aspergillus, fusarium, carvularia, candida and penicillium. The specific type of fungus responsible for fungal corneal ulcers depends on global distribution; generally, aspergillus and fusarium species are common in tropical and subtropical regions and candida are dominant in temperate areas.[4] Fungal corneal ulcers are endemic in warmer climates like India. Our country is an agriculture-dependent country with a majority of people, i.e., about 40% to 80% dependent on farming.

As per the literature, the most common risk factors for fungal corneal ulcers are trauma with vegetative material like crop leaf, thorn, straw or animal origin, i.e., cow tail, or contaminated mud and wood. Besides those other personal risk factors, i.e., unhygienic conditions, indiscriminate use of topical steroids and immunocompromised states like diabetes mellitus. Increased use of contact lenses with improper or contaminated solutions used for storage is also a major risk factor.

Fungal corneal ulcers are mostly treated with timely and suitable antifungal medication. Since the corneal epithelium serves as a barrier to the penetration of most topical antifungal agents, debridement of the corneal epithelium is an essential component of medical management. Some of the topical agents used are natamycin 5% suspension, amphotericin B, fluconazole, econazole, clotrimazole, voriconazole etc.

India being an agricultural country, many people are victims of fungal corneal ulcers dueto trauma from agricultural products and other risk factors. There are very few studies done about fungal corneal ulcers in India. The purpose of this study was to assess the prevalence of specific fungal pathogens, analyse the influence of demographic factors on the spectrum of fungal species responsible for fungal corneal ulcers and also determine the effectiveness of treatment.

MATERIALS & METHODS

This was a prospective study involving 53 corneal ulcer patients reporting to the Department of Ophthalmology at Hi-Tech Medical College Hospital, Bhubaneswar, Odisha, between October 2020 and September 2022. Corneal scraping materials collected from the patients were sent for a 10% KOH/NaOH stain and Sabouraud dextrose agar for culture and antifungal susceptibility test by micro-broth dilution technique.All the patients who were KOH stain positive and/or culture positive in Sabouraud medium were considered for the study. Patients with perforated corneal ulcers, peripheral ulcerative keratitis, sterile neurotrophic ulcers, ulcers associated with

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autoimmune conditions and those with pre-existing corneal disorders were excluded from the study.

The patients were treated based on clinical suspicion and KOH result with Natamycin 5./. Thereafter as per culture in SDA medium and antifungal sensitivity report done by micro-broth dilution technique i.e., amphotericin B (0.15%), voriconazole (1%) or a systemic anti-fungal drug like itraconazole (200 mg) was added according to the response tothe treatment.

All patients were followed up daily for one week, every one week up to one month and every two weeks up to three months till the epithelium healed as evidenced by the negative FL stain and disappearance of signs and symptoms.

The collected data was tabulated and analysed using SPSS (Statistical Package for Social Science) version 22.0. For statistical analysis, mean, frequency, percentage and Pearson's chi-square test were performed; a p-value <0.05 was considered to be significant.

RESULTS

Demographic Profile

The majority of the patients, 28.30%, belonged to the 51–60 year age group, followed by 41–50 years (24.52%). Males made up 33 (62.26%) of the 53 study participants, while females made up 20 (377.3%). Among male patients, a majority, i.e., 27.27%, belonged to 51–60 years old, followed by 21.21% to 31–40 years old. Among females, 35% belonged to 41–50 years, followed by 30% belonging to 51–60 years. The predominant group affected were agricultural workers 15 (28.3%), followed by farmers 13 (24.5%) and labourers 9 (17.0%). 88.68% belonged to low socioeconomic groups.

Aetiology

Out of 53 cases, the commonest mode of injury causing corneal ulcers were vegetative materials 21 (39.6%), followed by animal tails 7 (13.2%), leaf 6 (11.3%), mud 5 (9.4%), unknown 5 (9.4%), wood 4 (7.5%), finger nail 3 (5.7%), contact lens 2 (3.8%).

Ulcer Characteristics

Out of 53 study subjects, the frequency of keratitis in the right eye was 30 (56.6%) and the frequency in the left eye was 23 (43.4%). The maximum frequency of the site of the corneal ulcer was observed at central location 27 (50.9%) and the minimum frequency was seen at periphery 5 (9.4%). The size of the ulcer was ≤6 mm in 41 (77.4%) and >6 mm in 12 (22.6%). With respect to the depth of invasion, the frequency of 0-33% invasion was 17 (32.1%), of 34-67% invasion was 35 (66%) and of 68-100% invasion was 1 (1.9%). Of the 53 study subjects, hypopyon was present in 14 (26%) cases and absent in 39 (74%) cases.

Clinical Features

As shown in Table 1, out of 53 study subjects, the number of cases with visual acuity <1/60 was5 (9.43%), >1/60 to <6/60 was 27 (50.94%) and ≥6/60 was 21 (39.62%).

Visual Acuity	Frequency	Percent
<1/60	5	9.43
>1/60 TO <6/60	27	50.94
s≥6/60	21	39.62
Total	**53**	**100.00**

Table 1: Visual Acuity at the Time of Presentation Wise Distribution

As shown in Table 2, the frequency of cases with an IOP less than 20 mmHg was 47 (89%)and those with an IOP greater than 20 mmHg had a frequency 6 (11%).

IOP (mmHg)	Frequency	Percent
< 20	45	84.90
≥ 20	8	15.10

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Total	**53**	**100**
Table 2: IOP Wise Distribution		

Diagnosis

Table 3 shows the distribution of a 10% KOH-stained smear and SDA culture growth of the fungal agent. Out of 53 study subjects, the frequency of 10% KOH smear positives was 53 (100%). The frequency of SDA culture positive were 31 and negative were 22.

Lab Test	**Positive**	**Negative**
10% KOH	53	0
SDA Culture	31	22
Table 3: 10% KOH and SDA Culture Report Wise Distribution		

In the present study, the frequency of aspergillus species was 45 (85%) and the frequency of fusarium species was 8 (15%) (Table 4)

Fungal Agent	**Frequency**	**Percent**
Aspergillus	45	84.9
Fusarium	8	15.1
Total	53	100.0
Table 4: Fungal Agent Wise Distribution		

Treatment

Table 5 shows that **in** 41 (77.4%) of patients, natamycin topical eye drops were only used, while in 8 (15.1%) of patients, natamycin topical eye drops when used along with oral itraconazole were found to be effective, and in 4 (7.5%) of patients, natamycin topical eye drops were used along with voriconazole topical eye drops.

Treatment	**Frequency**	**Percent**
Nata+Itrac	8	15.1
Nata+Vori	4	7.5
Natamycin	41	77.4
Total	53	100.0
Table 5: Treatment Wise Distribution		

Table 6 shows that all lesions were sensitive to natamycin, while 17 (32.1%) were sensitive to voriconazole, 7 (13.2%) were sensitive to amphotericin-B, and 15 (28.3%) were sensitive to itraconazole.

Drug	**Sensitivity**	
	Frequency	**Percent**
NATA	53	100
VCZ	17	32.1
AMB	7	13.2
ITCZ	15	28.3
Table 6: Sensitivity to Drug Wise Distribution		

As shown in Table 7, out of 53 study subjects, 33 (62.26%) Aspergillus fungal ulcer caseswere treated with only natamycin, 8 (15.09%) cases treated with natamycin with itraconazole, and 4 (0.75%) cases treated with natamycin with voriconazole. All eight fusarium fungal ulcer cases (15.09%) treated with only topical natamycin.

Fungal Agent	**NATA**	**NATA+ Itra**	**NATA+Vori**
Aspergillus	33	8	4
Fusarium	8	0	0
Table 7: Distribution of Treatment to the Fungal Agents			

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Outcome

As shown in Table 8, cases in which <33% of the depth of the cornea was involved healed with a scar within a range of 3 to 9 weeks, 34 to 67% of the depth involved healed within 6 to 12 weeks, and the rest, i.e., >=68% of the depth involved, needed >12 weeks.

Depth (in %)	Duration of Healing in Weeks
<33	3 to 9
34 to 67	6to 12
68 to 100	>12

Table 8: Distribution of Depth of Ulcer to Time of Healing

DISCUSSION

A dangerous infection that can impair vision, fungus corneal ulcers typically arise from trauma or damaged corneal surfaces. Over the past 20 years, there has been a rise in the prevalence of fungal keratitis due to the widespread and increased use of corticosteroids and antibiotics.

Reports of incidence range from 17% to 36% globally. Even though fungal keratitis maynow be diagnosed and treated medically, 15 to 27% of patients still need surgery, such as therapeutic penetrating keratoplasty, enucleation, or evisceration, depending on how advanced their condition is or how well their previous treatments worked. The prevalence of fungal pathogens in South India is significantly greater. A report from South India found that about 44%of all corneal ulcers are caused by fungi. In southern, western, north-eastern, and northern India,the prevalence of mycotic keratitis has been found to be 36.7%, 36.3%, 25.6%, and 7.3%, respectively. In the present study, the maximum number of study subjects were males in the rangeof 51- 60 years and females 41-50 years, who were mostly involved in outdoor work. Males were more affected (62.26%) than females (37.73%), probably attributed to males being more engagedwith outdoor activities. 52.83% of the study subjects were agricultural workers or farmers prone to fungal corneal ulcers, traumatised most commonly by vegetative matters (39.60%) followed by animal tail.

A comparable investigation of 1354 fungal corneal ulcer eyes over a 10-year period was carried out by Usha Gopinathan et al.[3] The results showed that males (962) were substantially more afflicted ($p<0.0001$) than females (390). 853 (64.4%) of the 1,352 patients belonged to the younger age group (16–49 years). Of the 1,354 eyes, 736 (54.4%) were prone to infection due to ocular trauma.

Consistent with our research, Anuradha Chowdhary, Kirti Singh, et al.[5] also noted that fungal keratitis afflicted males (68%) more frequently than women (32%). Young people between the ages of 31 and 40 made up the largest age group (36%). 79% of patients had predisposing risk factors identified, including contact lens usage (25%), corneal trauma (42%), and topical corticosteroids (21%). Aspergillus species made up 78 (41%) of the isolated fungus, followed by curvularia species in 55 (29%).

Additionally, the incidence of fungal keratitis differs by geography. An investigation into475 suspected instances was done by Yamini Tawde et al.[6] Fungal keratitis was identified in 337 (71%) cases (median age: 50 years; 77.2% men). In North and Northeast India, respectively, aspergillus sp. (52.1%) and fusarium sp. (47.61%) were the most common etiological agents recovered from patients. India is located in a tropical area, which means that the country has year-round favorable climatic conditions for the growth of fungi. In India, the prevalence of FK varies from 25.6 to 36.7%. FK prevalence ranges from 7.3 to 25.6% in North and Northeast India, 36.3% in West India, and a higher prevalence of 36.7% in Southern India.

Given that agriculture is the most prevalent employment in North and Northeast India, a higher susceptibility to fungal infection is linked to activities connected to agriculture, which increases fungal exposure from the surrounding environment. There are nearly 100 genera of filamentous fungus, 18 genera of yeasts or yeast-like fungi, and 6 genera of dimorphic fungi

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among the at least 166 genera and 144 species of fungi that have been linked to human FK.

In the present study, the maximum number of fugal agents isolated were aspergillus, in 45 (84.9%), followed by fusarium in 8 (15.1%). All were filamentous fungi. Basak et al. (2005) documented the epidemiological pattern and risk factors for suppurative corneal ulceration in eastern India, which are comparable to the current investigation.[7] 1198 individuals with suppurative keratitis were assessed during a three-year period.

In 994 (82.9%) individuals, ocular trauma was the most frequent predisposing factor ($p<0.0001$), with topical corticosteroid usage coming in second with 231 (19.28%) patients. Of the patients, 811 (67.7%) had positive cultures. Of the patients with culture-positive results, 509 (62.7%) had infections caused by pure fungi ($p<0.001$), 184 (22.7%) had pure bacterial infections, and 114 (14.1%) had a combination of bacterial and fungal infections. Of the patients, 4 (0.49%) had acanthamoeba. Aspergillus spp. was the most prevalent fungal pathogen, accounting for 373 (59.8%) of all positive fungal cultures ($p<0.0001$), with fusarium spp. following in 132 (21.2%) cases.

Leck and associates[4] 1090 individuals with possible microbial keratitis were assessed in multicenter research conducted in Ghana and southern India. Filamentous fungus accounted for 42% of the causal microorganisms in both locations. The most often isolated fungus species were aspergillus and fusarium species.

In a clinico-demographical investigation carried out in North India by Gupta et al.[8] 209 cases of keratitis were examined; in 80 of those instances (38.3%), a culture revealed growth. Fungi were detected in 77.5% and bacteria in 22.5% of these 80 instances of growth. Similar to our investigation, the spectrum of keratomycosis included Aspergillus flavus (22.5%), Fusarium solani (16.1%), A. fumigates (11.3%), and Candida albicans (6.4%).

In a prospective research, 434 patients with central corneal ulcerations were assessed by Srinivasan et al.[1] A prior history of ocular damage was found in 65.4% of the patients. 68.4% of cornea cultures were positive. 46.8% of the people whose cultures came out positive had just fungal illnesses. Fusarium spp. accounted for 47.1% of all positive fungal cultures and were the most frequently identified fungal pathogen, followed by Aspergillus spp. (16.1%).

All the study subjects in the current study had a 10% KOH smear positive. 31 study subjects had SDA culture positive. In the rest, culture reports were negative or had variable reports, which may be due to an insufficient sample, previous treatment, improper procedure or equipment malfunction.

In the Srinivasan et al. study[1] fungus was found in 1,219 (91.0%) and 1,224 (91.4%) of the potassium hydroxide preparation (KOH), Calcofluor white (CFW), Gram, and Giemsa- stained smears. 1,139 (85.1%) and 1,181 (88.2%) eyes, in that order. Fusarium (506, 37.2%) and aspergillus species (417, 30.7%) dominated the hyaline fungal spectrum (1,133), with curvularia species (39, 2.8%) being the highest among the dematiaceous isolates (218).

While amphotericin B, miconazole, ketoconazole, itraconazole, and fluconazole can be delivered in many ways, natamycin can only be applied topically. For infections caused by Candida and related fungus, topical amphotericin B (0.1–0.3%) is usually the recommended course of treatment; for keratitis caused by filamentous fungi, topical natamycin (5%) is the recommended course of action. Surgical intervention may become necessary if medical therapy fails. Fungal infections affecting the cornea remain a significant contributor to ocular morbidity, especially in underdeveloped countries where agriculture is the main industry. The prognosis of this illness will be enhanced by a thorough understanding of the agent and host variables contributing to these infections.

In the present study, all fungal agents were found to be sensitive to natamycin (100%), with variable sensitivity to voriconazole 17 (32.1%), amphotericin-B 7 (13.2%) and itraconazole 15 (28.3%). The maximum number of aspergillus species-associated fungal corneal ulcers were treated with natamycin only, i.e., 41 (77.4%). But those who had size >5 mm and depth > 50% were treated with a combination of drugs, i.e., topical natamycin (5%) with topical voriconazole (1%) in 4 cases and topical natamycin (5%) with oral itraconazole 200 mg in 8 cases. A 5% natamycin eye drop was used to treat all cases of fungal corneal ulcers caused by fusarium species.

This was consistent with the MUTT (Mycotic Ulcer Treatment Trial), a randomised study

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carried out by Prajna et al. that compared voriconazole with natamycin.[9] Regression coefficient = 0.18 log MAR; (95% CI, 0.30 to 0.05; P=.006) showed that cases treated with natamycin had significantly better 3-month best spectacle-corrected visual acuity than cases treated with voriconazole. Additionally, the group receiving natamycin treatment had a lower likelihood of perforation and needed less therapeutic penetrating keratoplasty (odds ratio = 0.42; 95% CI, 0.22 to 0.80; P = .009). While non-Fusarium patients fared equally, Fusarium cases responded better to natamycin than to voriconazole. The study discovered that natamycin treatment led to much better clinical and microbiological outcomes than voriconazole treatment for smear-positive filamentous fungal keratitis. The main reason for this difference was better outcomes in fusarium.

In addition, a randomised clinical study comparing 5% natamycin with 2% voriconazole for the treatment of fungal keratitis was carried out by the same authors. When it came to success (defined as a healed or healing ulcer) at the last visit, there were no significant differences between the two groups at baseline (p = 0.79). As a result, 2% voriconazole and 5% natamycin seemed to be equally successful in treating mycotic keratitis.

In the present study, all the ulcers were healed. Those in which the ulcers involved <33% depth healed within 3-9 weeks, 34-67% depth involved within 6-12 weeks and those with > 68% depth involved healed in >12 weeks, indicating the effectiveness of early recognition and timely intervention.[10]

CONCLUSION

The present study has brought to light again the fact that fungal keratitis continues to be a major concern for loss of sight, especially in the rural, agricultural population. Goals directed towards proper education, early recognition and appropriate treatment will go a long way towards mitigating the problem of this potentially sight-threatening condition.

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