Fungal Keratitis

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Introduction

The significance of corneal pathology as a major cause of blindness in the world remains second only to cataract. The epidemiology of corneal disease is complicated, variable across the world, and dependent heavily on socio-economic factors, eye care services and availability of donor cornea. India has 2 million corneal blind, as much as a quarter of total corneal blindness in the world. However, the Andhra Pradesh Eye Disease Study (APEDS), the largest ever population based study in India found that 0.12% of the population is corneally blind, which if extrapolated to the entire country gives a mind boggling figure of 6.5 million. Corneal infection, often following trivial trauma is a major cause of corneal blindness. In India and South East Asia, fungal infection accounts for 40-50% of microbial keratitis, unlike the Western world. The lack of potent fungicidal agents and poor ocular penetration of existing antifungal agents, together with crunch of resources result in significant ocular morbidity and often, permanent visual loss.

Fungi are eukaryotic organisms, present almost everywhere on earth from deep sea to desert. They are genetically diverse and comprise about 1.5 million species. Like bacteria they are saprophytic and decompose organic matter. But unlike bacteria they have nuclei and other cell organelles and are closely related to animals. Fungi can reproduce asexually, by spore formation, budding, fission and fragmentation, but most commonly by the former. Most species can reproduce sexually also. The versatile mode of reproduction is also responsible for their vast occurrence.

Williamson et al isolated fungi from 2.9% of 1106 healthy conjunctival sacs, a higher incidence observed in older age groups, but could not recover the same organisms on repeat culture after few weeks suggesting that fungi are transient aerial contaminants. Ando N et al also observed similar findings and isolated fungi from 6.6% of healthy conjunctiva, more so in diseased eyes.

Classification

An overwhelming number of fungi have been reported to cause damage to the eye, however a small number of fungi have been repeatedly isolated in ophthalmic mycoses. Thomas et al who has done extensive work on fungi causing ocular infection classified into 4 categories: 1) Hyaline filamentous septate- found abundantly in soil, water, sewage, decaying vegetation. Can grow on any moist environment and are common contaminants of hospital air. All the following five species, especially Fusarium and Aspergillus commonly cause keratitis and endophthalmitis. Fusarium spp – F. solani, F. oxysporum, F. dimerum
Aspergillus spp – A. fumigatus, A. flavus, A. niger, A. terreus
Scedosporium spp - S. apiospermum [Pseudallescheria boydii], S. prolificans
Paecilomyces spp – P. lilianicus, P. variotti
Acremonium spp – A. kiliense

2) Dematiaceous (Phaeoid) fungi – All species have in common dark pigmentation of their hyphae. Keratitis caused by dematiaceous fungi – third common cause of fungal keratitis [behind Aspergillus and Fusarium]. Brown or black pigmentation of the corneal infiltrate is a characteristic feature.
   Bipolaris
   Curvularia
   Exophiala
   Lecytophora
   Phialophora
   Lasiodiplodia
   Cladosporium

3) Yeasts and Zygomycetes
   Yeasts – Candida – C.albicans,C.parapsilosis, C. guilliermondii
   Cryptococcus – C.neoformans
   Zygomycetes
   Rhizopus – R.arrhizus
   Mucor
   Rhizomucor
   Absidia
   Apophysomyces

4) Thermally dimorphic fungi – Causes lid and conjunctival lesions, granulomatous anterior uveitis, epiceritis, endophthalmitis, orbital infections, but rarely keratitis.
   Paracoccidioides - P. brasiliensis
   Coccioides - C.immitis
   Blastomyces – B.dermatitis
   Sporothrix – S.schenckii
   Histoplasma – H.capsulatum, H.duboisii

5) Of uncertain classification
   Pythium.insidiosum-resembles zygomycetes; causes severe keratitis & orbital cellulitis
Rhinosporidium – R. seeberi - not associated with keratitis
Pneumocystis – P. carinii - not associated with keratitis

Filamentous fungi are the predominant etiological agents throughout the world. The common organisms in the order of frequency in Asia and Africa are Fusarium, Aspergillus and Dematiaceous fungi. Candida is a rare fungal pathogen in India [0.7%] 8,14.

Risk factors for keratitis


Fungal keratitis tend to occur more frequently in young males, more so in winter and monsoon. Gopinathan U et al in the largest series of fungal keratitis [1354 cases] found that trauma was a predominant risk factor, seen in 54.4% of cases. Males (962) were affected significantly more (p< 0.0001) than females and 853 (64.4%) were in the younger age group.

Bharati et al in a similar series found higher incidence of corneal trauma [92%, 1009 cases] and the correlation between trauma and fungal keratitis was highly significant (P<0.0001). 671 (61.28%) patients had corneal injury with vegetative matter and this correlation was highly significant (P<0.0001). 73 (6.67%) patients had co-existing ocular diseases responsible for development of fungal keratitis. Use of corticosteroids were found in 1.12% and systemic predisposing factors in 16% of cases. Traditional eye medicines, often comprising of dried leaves or other vegetable matter dispensed in urine, saliva or breast milk offer excellent opportunity to the pathogenic organism in an eye which already has a breach in epithelial integrity. In Tanzania, as much as 25% of corneal ulcers are related to use of traditional eye medicines.

It is interesting to note that keratitis due to filamentous fungi usually occur in young healthy males with no apparent predisposing factor other than trauma. Candida infection, in contrast appears more in predisposed eyes (eg - in dry eye, lagophthalmos, eyes with a pre-existing epithelial defect like HSV keratitis or contact lens wear or systemic conditions like diabetes mellitus or immunocompromised status.

Clinical features

Typically symptoms are less compared to bacterial keratitis. Clinical picture, however depends on the type of fungus, virulence of the particular strain and host factors 14.

Common findings in fungal keratitis are

- Dry raised greyish white infiltrate
- Feathery or hyphate margins
- Satellite lesions
- Pigmentation – only for dematiaceous fungi
- Gritty feel on scraping
- Convex cheesy hypopyon
- Endothelial exudates with fibrinous extension

The first three are characteristic features of fungal keratitis.

Bharati et al in their series of 1095 culture proven cases of fungal keratitis from Tirunelveli, comprising predominantly of rural population, found dry thick raised infiltrate in 75% and hyphate edges in 72%, but satellite lesions only in 10% of fungal keratitis cases. Early fungal keratitis resembled dendritic keratitis in 4% of cases. Endothelial exudate often called posterior corneal abscess is an infrequent presenting feature [1%] of fungal keratitis. The sensitivity of clinical diagnosis by a trained ophthalmologist in this retrospective series was 94%.

Though most cases of fungal keratitis exhibit these basic features, some etiological agent may show some unique characteristics. Fusarium solani can cause severe keratitis with deep extension, endothelial exudates filling up the entire anterior chamber resulting in a fungal mass involving cornea, iris and angles. Malignant glaucoma and endophthalmitis can supervene in such cases and can result in loss of the eye 16. In contrast, certain dematiaceous fungi [Curvularia spp, Bipolaris spp] presents as a persistent, low-grade, smoldering keratitis with pigmentation on the surface of plaque on the cornea. Simple debridement may suffice for resolution in most cases. However, Lecytophora, another...
dematiaceous fungus results in severe keratitis unresponsive to medical therapy. The clinical picture of Candida spp resembles bacterial keratitis with a discrete infiltrate and slow progression usually in eyes with a pre-existing disease. 

**Diagnosis** - Though clinical presentation can be suggestive, treatment must be initiated after microbiological study. WHO guidelines [for South-East Asia region] advocate corneal scraping to be done for all cases of microbial keratitis presenting to an ophthalmologist and sent for at least 10% KOH preparation. The treatment is based on the presence or absence of fungal hyphae in smear.

Whenever possible, corneal scraping should be sent for [1] KOH preparation [2] Gram’s stain [3] Cultures – on blood agar and SDA. Corneal scraping is done with a No.15 blade or Kimura’s spatula. If the infiltrate is deep seated corneal biopsy may be required to procure the material. If endothelial exudate is present, anterior chamber tap may be taken aseptically and sent for microbiological study.

Direct microscopic evaluation - is a very useful, inexpensive and a rapid diagnostic tool for the detection of fungal filaments in corneal scraping. 10% KOH mount has a sensitivity of 90 – 99% in well-experienced hands. Gram’s stain can identify fungi in 45 to 89% of cases, Giemsa stain in 66%, Methenamine silver staining in 89% and Calcoflour white staining in 90%.

Fungal culture - Culture positivity for fungi in blood agar or Saboraud’s dextrose agar ranges from 52 to 68% and growth occurs usually within 48 – 72 hours.

Polymerase Chain Reaction [PCR] is emerging as a rapid, highly sensitive test for the diagnosis of fungal keratitis. Primer used commonly is 28S rRNA gene, common to all medically important fungi. It has a sensitivity of 70 – 89% and a specificity of 57 – 88%.

Confocal microscopy - has a definite role in the early diagnosis and follow-up of fungal keratitis in a tertiary care institute, more so being a non-invasive test. Fungal filaments are seen as interlocking white lines approximately 6 microns wide and 200 – 400 microns long mostly arranged parallel to the corneal surface. Vadavalli PK et al in a prospective double masked controlled trial observed high sensitivity (88.3%) and specificity of 91.1% in the diagnosis of fungal keratitis.

**Management**

The guidelines for management as suggested by WHO for the South East Asian Region are as follows.

At the secondary level [patient seen by an ophthalmologist] - If the 10% KOH mount is positive for fungus, treatment is started with 5% Natamycin eye drops or 0.15% Amphotericin B hourly and followed up every 2 days. Antifungal drops are continued 3 hourly for 2 weeks after healing of the ulcer.

If there is no improvement in 7 days, the case should be referred to a tertiary care centre. Immediate referral to tertiary care [at the first visit itself] is recommended if [1] one eyed [2] child [3] impending/actual perforation [4] fungal ulcer, but KOH or fungal stain not available.

If the smear is negative for fungus, it is treated as a bacterial keratitis with a combination of fortified Cefazolin [5%] and Gentamycin [1.4%] hourly.

**At the tertiary care level**

In a tertiary care centre it is recommended that a detailed proforma filled and photographic documentation done. If photographic equipment is not available, a detailed corneal diagram is made.

possible Brain Heart Infusion agar. 5% Natamycin or 0.15% Amphotericin B eye drops are started one hourly for all patients with fungal keratitis. Treatment modification is done based on response to initial treatment and microbiology.

In-patient care is recommended [1] if there is immediate threat to vision [2] if patient is a child [3] to ensure hourly treatment.

**Anti-fungal agents**

**[1] Polyenes – Amphotericin B**

*Natamycin*

*Nystatin*

The polyene antifungal agents bind with sterols in the fungal cell membrane, principally ergosterol. This changes the transition temperature (Tg) of the cell membrane, thereby placing the membrane in a less fluid, more crystalline state. As a result, the cell's contents leak and the cell dies. Animal cells contain cholesterol instead of ergosterol and so they are much less susceptible.

*Natamycin* – 5% Natamycin suspension is the drug of choice in any fungalkeratitis. It is effective only when applied locally. Due to poor corneal penetration it may be ineffective in deep stromal lesions.

*Amphotericin B* can be used as topical preparation (0.15 to 3%), intracameral (20 – 30 microgram/ ml) and through parenteral [intravenous] route. It has good activity against Aspergillus spp and Candida. However, Scedosporium and Fusarium spp are resistant. It penetrates into the deep stroma after topical application in susceptible fungi. Amphotericin B is considered as first-line treatment of keratitis in many countries where natamycin is unavailable. However it is toxic to the corneal epithelium on long-term use.

**[2] Azoles**

**Imidazoles**

- *Miconazole*
- *Ketoconazole*
- *Clotrimazole*
- *Sulconazole*

**Triazoles**

- *Fluconazole*
- *Itraconazole*
- *Ravuconazole*
- *Posaconazole*
- *Voriconazole*

The imidazole and triazole drugs are synthetic antifungal drugs that inhibit the enzyme cytochrome P450 14α-demethylase. This enzyme converts lanosterol to ergosterol, and is required in fungal cell membrane synthesis. Triazoles are newer and better tolerated.


**Fluconazole** – Poor activity against most strains of Aspergillus and fusarium spp. Poor results in the treatment of keratitis due to filamentous fungi. Good intraocular penetration after topical use. Excellent activity against Candida keratitis. Oral dose – 200 mg / day. Topical – 1 - 2 %.

**Itraconazole** – Good in vitro activity against all Aspergillus spp. Poor activity against Fusarium and Lasiodiplodia. Excellent safety profile after oral administration Oral – 200 – 400 mg /day.

**Voriconazole** – Potent fungicidal agent with broad spectrum activity [effective against Candida, Aspergillus, Fusarium solani, Scedosporium, Curvularia, Acremonium] Good intraocular penetration with low MIC. Some species of Fusarium are resistant. Oral dose – 400 mg b.i.d. Topical – 1 or 2 % ; 1% used for intracameral and intravitreal use.

**[3] Allyl amines**

- *Terbinafine*
- *Naftifine*

They inhibit ergosterol synthesis and are active against dermatophytes and candida.

**[4] Echinocandins**

- *Capsofungin*
- *Micafungin*

Inhibits glucan synthesis required for cell wall. Active against candida SPP and aspergillus spp. No documented use in keratitis

**[5] Others** – Flucytosine – inhibit nucleic acid synthesis

**Surgical Management**

**[1] Tissue adhesive application**[n-butyl cyanoacrylate] may be done for tectonic support if there is impending or actual perforation. For perforation larger than 2.5 mm usually therapeutic keratoplasty is required.

**[2] Keratoplasty** is again resorted to if keratitis worsens on medical management. It is known fact that about 15 - 25% of fungal keratitis does not respond to medical management. Early therapeutic keratoplasty can eradicate infection and ensure better long-term visual outcome in such cases. Though there are a few reports of successful Deep Anterior Lamellar Keratoplasty, penetrating keratoplasty would be the preferred procedure as fungal filaments can extend beyond the area of visible corneal infiltrate. The area of recipient bed trephination must be at least 0.5 mm beyond the area of visible infiltrate. During keratoplasty, fungal filaments on the
iris, angles and lens should be peeled off and washed with Amphotericin-B[0.15%] to minimize the chances of recurrent infection.

[3]Anterior chamber wash – Infrequently while treating keratitis, one comes across some patients with a non-progressing corneal infiltrate but with increasing endothelial exudate. Mechanical removal of endothelial exudates by anterior chamber wash followed by intracameral injection of 0.1 ml of 0.15% Amphotericin B is seen to be effective in controlling the infection in this subset of patients. It is likely that, in such cases, there is good response to topical antifungal [natamycin] treatment, but progression of endothelial exudate occurs as adequate anti-fungal concentration was not achieved in the anterior chamber.

Conclusion - Fungal keratitis accounts for a substantial load of corneal blindness in a country like ours dependent heavily on agricultural income. Preventive strategies need to be directed at the villagers and socioeconomically deprived, who are the usual hapless sufferers. Medical management of fungal keratitis is expensive, time-consuming and only partially effective in limiting visual loss. Although newer drugs like voriconazole show promise, there is need for more efficacious drugs, which work well against filamentous fungi especially Fusarium spp. As fungal keratitis is too miniscule a problem in the developed world, the initiative needs to come from countries like India.

References