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CLINICAL STUDY

Post-traumatic fungal endophthalmitis—a prospective study

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Abstract

Purpose **To study the incidence, clinical presentation, and the response of anti-fungals in cases of fungal endophthalmitis following open globe injury.**
Methods **This is a prospective study of eight cases of post-traumatic fungal endophthalmitis among 110 patients who presented to us with open globe injury between August 2003 and January 2005. Patients with panophthalmitis were eviscerated and rest received intravitreal amphotericin B. Pars plana vitrectomy along with intravitreal miconazole was given in patients with inadequate response to intravitreal amphotericin.**
Results **Two patients had panophthalmitis at the time of presentation and were eviscerated. Six different organisms were isolated from the culture of intraocular specimen of eight patients. The yield of vitreous aspirate was 87.5% and that of aqueous aspirate was 66.6%. *Aspergillus* sp. and *Fusarium* sp. were isolated in 62.5% of cases. Minimum inhibitory concentration of amphotericin B and miconazole was less than 3 μg/ml for all organisms except for *Paecilomyces lilacinus* and *Fusarium solani*, respectively. In total, 37.5% of patient had final visual acuity of 20/400 or better.**
Conclusions **Fungal endophthalmitis is a relatively rare complication of open globe injury. The final visual outcome after fungal endophthalmitis is dismal. *Aspergillus fumigatus* was found to be the most virulent organism. All organisms were found to be sensitive to amphotericin B, except *P. lilacinus*, which was sensitive to miconazole. Repeated intravitreal injection may be required to control the infection. The virulence of the organism and the site of injury are the main determinants of final visual outcome.**
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Keywords: open globe injury; fungal endophthalmitis; amphotericin sensitivity; intravitreal miconazole; minimum inhibitory concentration

Introduction

Exogenous fungal endophthalmitis is a rare complication of open globe injury.[1] There is usually a latent period of weeks to months in fungal endophthalmitis as compared to bacterial endophthalmitis, which usually presents within days. Fungal endophthalmitis tends to be more localized, often confined to the anterior chamber, pupillary space, or anterior vitreous, and is not associated with much ocular discomfort.[2,3]

The optimum therapy for exogenous fungal endophthalmitis is not well established, particularly with regard to the selection, route of administration, and dosage of anti-fungal agents. Visual prognosis is generally poor in these patients.[4]

Patients and methods

Our study included patients developing fungal endophthalmitis following open globe injury who presented to us between August 2003 and January 2005. Patients with age more than 15 years were included in the study. Fungal endophthalmitis was defined by positive fungus culture from the specimen obtained either from anterior chamber or vitreous.

The size and position of the laceration was noted in all cases and emergency repair of the corneoscleral laceration was undertaken. The corneal laceration was sutured using 10-0 nylon sutures, whereas scleral laceration was sutured with 8-0 nylon sutures. Iris was abscised in cases with associated iris prolapse; however, choroid was reposited back in cases with

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posterior scleral laceration with choroidal prolapse. Aqueous aspirate (0.1 ml) was sent for microbiological workup in cases of injuries involving the anterior chamber or if exudates were present in the anterior chamber alone. Prolapsed vitreous was cut flush to the wound with a cellulose sponge and was sent for microbiological evaluation in cases with posterior segment injury. However, for obtaining vitreous samples after the development of endophthalmitis, 21 G needle mounted on the tuberculin syringe was used to enter the vitreous transconjunctivally 4 mm from the limbus. The needle was directed into the mid-vitreous cavity and 0.2 ml of vitreous was withdrawn gradually. Vitrector was used to obtain the sample, if vitreous could not be aspirated with the needle.

Cultures were considered positive when there was growth of the same organism on two or more solid media at the inoculation site or when the organism grew on one culture and was also noted on stained smear (Gram, Giemsa, or Gomori methenamine silver).[5] Anti-fungal sensitivity testing was performed using a broth dilution method on frozen stored isolates from all the patients. The frozen specimens were defrosted and plated on Sabouraud's agar. After 48 h of growth, the fungal hyphae and spores were suspended in sterile saline and adjusted to a final concentration of 10^5 colony-forming unit. Tubes containing serial dilution of the anti-fungal were inoculated with the fungus and incubated for 48 h. The tubes were then examined for growth and the minimum inhibitory concentration (MIC) was determined.[6]

Intraocular antibiotics were given in accordance to the following protocol:

- Vancomycin (1000 μm) and amikacin (400 μm) at the time of initial repair of corneoscleral laceration, if the eyes had clinical evidence of infection like hypopyon or exudates in the pupillary area or in the vitreous.
- Intravitreal amphotericin (5 μm) if the clinical signs of infection persisted for more than 48 h and staining or culture showed evidence of fungal growth.
- Repeat intravitreal amphotericin (5 μm) was given after 72 h of the previous injection if the clinical signs of infection persisted.
- Pars plana vitrectomy along with 40 μm miconazole (or according to the sensitivity pattern of the organism) at the end of the procedure, if the signs of infection persisted after 72 h of the second intravitreal amphotericin injection.
- Intracameral amphotericin (5 μm) was given if the clinical signs of anterior chamber infection like hypopyon or exudates were present or if aqueous aspirate was positive for fungal filaments.
- Cultures were obtained before each procedure.

Systemically, all patients received a loading dose of oral fluconazole 800 mg, in two divided doses for 3 days followed by 400 mg in two divided doses for 3 weeks after the baseline liver function tests.[7] Topically, 5% natamycin eyedrops were instilled two-hourly. Subconjunctival injection of amphotericin on alternate days was given if anterior chamber exudates persisted. Response to the treatment was monitored clinically and by ultrasound B-scan.

Results

Clinical data

Of the 110 patients with open globe injuries who presented to us during the study period, eight patients developed fungal endophthalmitis. The size, extent of laceration, and associated uveal prolapse are given in Table 1. The time lapse before presentation varied from 3 to 22 days following injury. Seven eyes had the clinical evidence of infection, such as hypopyon, or exudates in the pupillary area or in the vitreous. One patient (Case 7) did not show any clinical evidence of infection, but developed endophthalmitis after 8 days of initial treatment.

Two patients had panophthalmitis at the time of presentation and were eviscerated as these patients had no hope of getting back any useful vision. Microbial evaluation of the intraocular contents of these patients revealed *Aspergillus fumigatus* as the causative organism.

Five out of the remaining six eyes were given intravitreal vancomycin (1000 μm) and amikacin (400 μm) in accordance to the protocol, as they had evidence of infection at the time of presentation. Subsequent positive fungal culture showed them to harbour fungal endophthalmitis. These six patients received intravitreal amphotericin of which four had to be given a repeat of intravitreal amphotericin (Table 2). Two out of these four patients were taken up for pars plana vitrectomy with intravitreal miconazole as these patients did not respond to intravitreal amphotericin adequately. Four eyes were given intracameral amphotericin in accordance to the protocol. Repeat intracameral amphotericin was not required. Subconjunctival amphotericin or miconazole was given in patients with persistent anterior chamber exudates. These patients were followed up for a minimum of 6 months (range 6–9 months).

Culture data

Six different organisms were obtained from eight patients (Table 3). Culture of anterior chamber aspirate was performed in six cases (two eyes with panophthalmitis were excluded), whereas vitreous aspirate culture was performed in all cases. Four out of

Table 1 Summary of the clinical features of the patients

Case no.	*Age/ sex*	*Time lapse before presentation (days)*	*Object of injury*	*Visual acuity at presentation*	*Site and size of injury*	*Final visual outcome*	*Cause of decrease in vision*
1	68/M	14	Assault with a fist	PL negative	Scleral laceration of 1.5 mm, 4 mm behind limbus with choroidal prolapse at 11 o'clock	Eviscerated	
2	35/M	22	Stone	PL negative	Scleral laceration of 4 mm circumferential to limbus, 5 mm behind the limbus superiorly	Eviscerated	
3	16/M	5	Iron object	PL positive	Corneoscleral laceration of 6 mm perpendicular to limbus with iris prolapse at 1 o'clock	20/200	Corneal astigmatism, persistent macular oedema, and scarring
4	48/M	16	Bull gore	PL positive	Corneoscleral laceration of 10 mm from 8 to 1 o'clock across the visual axis with iris prolapse and extending 3 mm onto the sclera	FC at 2ft	Developed glaucoma with persistent corneal oedema
5	60/M	3	Thorn	PL positive	Scleral laceration circumferential to limbus from 9 to 1 o'clock and then 3 mm perpendicular to limbus with uveal prolapse	Phthisical	Developed retinal detachment
6	39/M	16	Iron rod	HMCF	Corneoscleral laceration of 7 mm perpendicular to limbus from the centre of cornea to limbus and 2 mm beyond at 6 o'clock with iris prolapse	20/100	Corneal astigmatism and epiretinal membrane over the macula
7	42/M	12	Bark of a tree	FC at 2ft	Corneoscleral laceration of 7 mm perpendicular to limbus at 2 o'clock with uveal prolapse	Phthisical	Developed retinal detachment
8	18/M	3	Bull gore	PL positive	Radial scleral laceration of 5 mm starting at 7 mm behind limbus with uveal prolapse	20/400	Epiretinal membrane over the macula and optic atrophy

PL: perception of light; HMCF: hand movement close to face; FC: finger counting.

Table 2 Summary of treatment

Case no.	*Intravitreal injections of anti-fungals*			*Subconjunctival injections*	*Intracameral injections*
	First	*Second*	*After pars plana vitrectomy*		
3	AMP	NA	NA	NA	NA
4	AMP	AMP	NA	AMP	AMP
5	AMP	AMP	NA	AMP	AMP
6	AMP	NA	NA	AMP	AMP
7	AMP	AMP	MIC	MIC	NA
8	AMP	AMP	MIC	AMP	AMP

Cases 1 and 2 were eviscerated.
Cases 7 and 8 underwent pars plana vitrectomy.
NA: not applicable; AMP: amphotericin B; MIC: miconazole.

six anterior chamber aspirates and seven out of eight vitreous aspirates were positive for fungal culture. One eye had anterior chamber aspirate culture positive but negative vitreous aspirate culture. In patients with both aqueous and vitreous showing fungal growth, the organisms obtained were the same. Repeated cultures of vitreous were obtained in cases in which repeat intravitreal injection was given. The causative fungal organisms were found to be *Aspergillus fumigatus* and *Fusarium solani* in two cases each, whereas *Candida*

Table 3 Summary of repeated cultures

Case no.	*Vitreous cultures*			*Aqueous cultures during repair of open globe injury*
	During initial repair of open globe injury	*During first intravitreal injection*	*During second intravitreal injection (if required)*	
1	*Aspergillus fumigatus*	NA	NA	NA
2	*Aspergillus fumigatus*	NA	NA	NA
3	*Candida parapsilosis*	Same	NA	Negative
4	*Fusarium solani*	Same	Same	Same
5	*Fusarium solani*	Same	Same	Same
6	Negative	*Aspergillus flavus*	NA	*Aspergillus flavus*
7	*Paecilomyces lilacinus*	Same	Same	Negative
8	*Acremonium curvulum*	Same	Same	Same

Note: Cases 1 and 2 were eviscerated. NA: not applicable.

Table 4 Anti-fungal sensitivity

Organisms	*Number of cases*	*Minimum inhibitory concentration (μg/ml)*		
		Amphotericin B	*Miconazole*	*Ketoconazole*
Aspergillus fumigatus	2	1.50	0.78	2.00
		2.00	1.50	NA
Aspergillus flavus	1	0.310	1.50	1.50
Candida parapsilosis	1	2.50	0.75	1.50
Fusarium solani	2	0.62	12.50	25.00
		1.50	25.00	25.00
Acremonium curvulum	1	2.50	0.19	1.50
Paecilomyces lilacinus	1	20.00	0.78	1.50

NA: not available.

parapsilosis, *Aspergillus flavus*, *Paecilomyces lilacinus*, and *Acremonium curvulum* was seen in one case each. Fungal hyphae were noted in diagnostic staining in only three (37.5%) out of eight patients.

Sensitivity of the organisms to different anti-fungal agents was obtained (Table 4). MIC of different isolates of the same organism (*Aspergillus fumigatus* and *F. solani*) differed. *P. lilacinus* had a very high MIC (20.0 μg/ml) for amphotericin B.

Discussion

Injuries with vegetable matter, stone, or mud particles increase the risk of fungal infection. The presenting complaint in 50% of our patients was poor vision and redness rather than pain as described by Theodore.[8] However, two patients had ocular pain as their chief complaint. Two cases in our series developed endophthalmitis within 1 week of trauma instead of the usual period of weeks to months.[10] The usual clinical feature in fungal endophthalmitis is infiltrates localized to the anterior chamber, pupillary space, or anterior vitreous.[2,8] Although four patients had similar presentation, two patients had diffuse intraocular inflammation resembling bacterial endophthalmitis. This variability in presentation of fungal endophthalmitis stresses the need of consideration of fungal aetiology even if the clinical findings suggest bacterial aetiology, and thus cultures of the intraocular specimens for both bacteria and fungus should be carried out, regardless of the presenting clinical signs.

Aqueous aspirates were negative in two cases despite positive vitreous cultures, which may be due to improper sampling or low infective inoculum in the anterior chamber. There was one case with positive anterior chamber aspirate but negative vitreous culture. This has been reported in earlier studies also.[9] This may be due to poor penetration of the fungus in the vitreous cavity unlike bacteria.[3] Hence, anterior chamber aspirate should always be obtained along with the vitreous aspirate for microbiological workup.

Only in cases with early evidence of endophthalmitis after trauma or severe diffuse intraocular inflammation, use of intravitreal vancomycin and broad-spectrum aminoglycoside like amikacin during initial repair is justified.[10,11] On the other hand, routine use of intravitreal amphotericin is not justified as fungal infections are relatively rarer.

Fungal organisms are more virulent than bacteria, but virulence level differs among different fungi. Unlike

other studies, both cases of *Aspergillus fumigatus* in this series developed panophthalmitis.[1] *F. solani* is associated with poor visual outcome as it causes extensive ocular damage by liberating proteolytic enzymes.[12] It is also difficult to eradicate this organism after it has spread to the vitreous cavity.[13] In contrast, a different filamentous organism with similar morphology, *Acremonium curvulum* has a relatively better outcome. *P. lilacinus* infection has been described following use topical corticosteroids, which was also seen in our case.[14] Thus, care should be taken before starting steroid therapy in cases with open globe injury especially if the infection is suspected. The visual outcome was relatively better in eyes with infections due to *C. parapsilosis* and *Aspergillus flavus*. Similar outcome has been noted in other studies also.[1] This may be due to the susceptibility of the isolates to intravitreal amphotericin and systemic fluconazole.[15,16]

MIC of different isolates usually differs due to dissimilarity in the genes encoding for the proteins conferring sensitivity to the anti-fungals. The sensitivity pattern in *Aspergillus fumigatus* differs in accordance to the pattern of cytochrome *b* gene sequences.[17] Simultaneous institution of multiple anti-microbial agents may lead to overexpression of some proteins, which may decrease the sensitivity of the isolate to the anti-fungals and thus the MIC differs.[18] An anti-fungal agent with MIC greater than 3 μg/ml against a particular isolate is unlikely to be effective *in vivo*.[19] In our case series, all organisms other than *P. lilacinus* had amphotericin B MIC less than 3 μg/ml. Thus, intraocular miconazole (40 μg) should be considered for endophthalmitis caused by *P. lilacinus* (MIC for miconazole: 0.78 μg/ml), or in cases with failures with amphotericin.[20]

Six out of eight patients in our series had poor visual outcome. This may be related to the severity of injury (posterior scleral tears resulting in retinal detachment) and the virulence of the fungal organisms. Altogether, the overall visual outcome in cases of post-traumatic fungal endophthalmitis is dismal. We could salvage some vision in four out of eight eyes. Fungal infections associated with trauma with organic matter (stick, stone, bark, etc) are difficult to treat. Response to presently available anti-fungal agents is slow and suboptimal. Early diagnosis (with a high index of suspicion) and prompt treatment may improve visual outcome.

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