Orbital Exenteration in Rhino-Orbito-Cerebral Mucormycosis: A Prospective Analytical Study with Scoring System

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Abstract Mucormycosis is an uncommon, rapidly progressive, angio-invasive, commonly fatal, opportunistic fungal infection. The most critical decision in the management of rhinoorbital mucormycosis is whether the orbit should be exenterated. (1) To layout the indications of orbital exenteration in patients with rhino-orbito-cerebral mucormycosis. (2) To devise a scoring system that predicts the stage at which the exenteration needs to be carried out. A scoring system was devised by a team of experienced Otorhinolaryngologists and Ophthalmologists from prior experience in managing mucormycosis. All patients of mucormycosis visiting our hospital were admitted and included in the study. A total of 15 patients were included. The scoring system is based on 3 main criteria, namely: (1) clinical signs and symptoms. (2) Direct and Indirect Ophthalmoscopy. (3) Imaging. The Sion Hospital Scoring System is an accurate and promising measure to solve the

dilemma that is associated with orbital exenteration in orbito-rhino-cerebral mucormycosis.

Keywords Mucormycosis · Orbital exenteration · Amphotericin

Introduction

Mucormycosis is an uncommon, rapidly progressive, angio-invasive, commonly fatal, opportunistic fungal infection. The most critical decision in the management of rhino-orbital mucormycosis is whether the orbit should be exenterated. The literature fails to provide a broad base of information of how clinicians determine the need for exenteration in daily practice. The decision for exenteration often depends on the judgment of the treating otolaryngologist and the ophthalmologist. This prompted us to devise a scoring system which efficiently tracks the orbital involvement by the disease and also lay down the indications of orbital exenteration in rhino-orbito-cerebral mucormycosis.

Aims and Objectives

1. To layout the indications of orbital exenteration in patients with rhino-orbito-cerebral mucormycosis.
2. To devise a scoring system that predicts the stage at which the exenteration needs to be carried out.

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Materials and Methods

A scoring system was devised by a team of experienced Otorhinolaryngologists and Ophthalmologists from prior experience in managing mucormycosis. All patients of mucormycosis visiting our hospital were admitted and included in the study. A total of 15 patients were included. Routine history taking, clinical examination and diagnostic nasal endoscopy were performed in all the patients. This was followed by the radiological investigation. CT PNS (Plain and Contrast) was performed in all the patients and MRI Brain with orbit was done in patients in whom intracranial or intra-orbital spread of the disease was suspected. Ophthalmologist's opinion was taken irrespective of the ocular status. Direct and Indirect Ophthalmoscopy was performed in all the patients. The scoring system was applied on the patients. Depending on the score, surgical debridement from the nasal/paranasal/oral region $\pm$ orbital exenteration was carried out within a period of 24–36 h of admission. Inj Amphotericin-B intravenously was started after an initial sensitivity test dose at strength of 1 mg/kg/day and continued till a total dose of 2–3 g was completed.

To monitor the nephrotoxicity a daily Amphotericin-B chart was maintained. Daily input/output ratio was calculated with monitoring of blood sugar levels. Serum Creatinine, Urea, Sodium, Potassium and Magnesium along with complete blood count were measured twice a week. Patients were given 500 ml of normal saline before and after Amphotericin-B injection to maintain hydration. They were also encouraged to have 2–3 l of oral fluids along with coconut water. Any ion deficit was corrected promptly.

A repeat nasal endoscopy was performed and tissue from the suspected diseased area was sent for microscopic examination on KOH mount. If KOH mount was found negative, Amphotericin-B was stopped. Patients were then discharged and followed up on OPD basis.

The scoring system is based on 3 main criteria, namely:

1. Clinical signs and symptoms
2. Direct and Indirect Ophthalmoscopy

3. Imaging.

Based on the vision, salvage ability of the eye, likelihood of further spread and cosmesis, different number of points were given to different findings which are listed below

How the score was given

- 1 point = Mild symptoms/signs
- 2 points = Moderate symptoms/signs
- 3 points = Severe symptoms/signs

- A. Clinical
- B. Ophthalmology
- C. Imaging

Observations and Results

A total of 15 patients visited our hospital with mucormycosis in the last 6 months. These patients were scored accordingly.

Table 1 showing the presentation of patients.

Based on the scoring system, it was observed that those patients who crossed a score of 23 were eligible candidates for orbital exenteration as agreed upon by the Otorhinolaryngologist and Ophthalmologists. It was found that most of these patients were in turn positive for mucormycoses on histopathology and are stable now after completion of Amphotericin therapy (Tables 2, 3, 4 and 5).

Discussion with Review of Literature

Microscopy

Mucormycosis is any fungal infection caused by the order *Mucorales* and the common species culpable are *Mucor*, *Rhizopus*, *Abidia* and *Cunninghumella*. These fungi are ubiquitous and are present in the soil and decaying matter. Humans are exposed to these fungi on a routine basis but rarely suffer any disease as their virulence is very low. Thus, it mainly affects those who are immunocompromised

Table 1 Clinical symptoms

	0	2	3
Vision	Normal or same as prior to other symptoms	Decreased vision after developing other symptoms	Total blindness
Pupil	Normal	RAPD	Fixed
Ocular motility	Normal	Extra-ocular muscle palsy/Diplopia	Fixed eyeball
Proptosis	Absent	–	Present
Intracranial spread	Normal	Headache, projectile vomiting, confusion	Altered consciousness, Pulsatile Exophthalmos, coma

Table 2 Ophthalmology

Fundus changes	Points
Normal	0
Cotton wool spots	1
Congested tortuous retinal blood vessels	2
Optic disc oedema	2
Central retinal vein occlusion	2
Central retinal artery occlusion	2
Retinal detachment	2
Choroidal folds	2
Optic disc pallor	2
Total	15

Table 3 Imaging

Orbital involvement by the disease (globe/muscles/fat)	3
Intracranial spread/superior orbital fissure/inferior orbital fissure involvement	3
Optic neuritis	3
Sphenoid sinus involvement	2
Frontal sinus involvement	1
Ethmoidal sinus involvement	1
Infra-temporal fossa involvement	1
Maxillary sinus involvement	1

with Diabetes Mellitus being the most common pre-disposing factor as it was present in around 50–71% of the reported mucormycosis cases around the world. The other pre-disposing diseases that may contribute to mucormycosis are prior steroid therapy, lymphomas, renal failure, liver cirrhosis, neutropenia, Desferioxamine therapy, malnutrition (particularly GI mucormycosis) and AIDS.

Mode of Infection

The most common mode of spread of these fungi is through inhalation of fungal spores or *conidia*. The other modes of spread are traumatic inoculation into the skin or nasal mucosa or via ingestion [1]. The most common site for infection is the nose and the paranasal sinuses; however cerebral, pulmonary and cutaneous mucormycosis have been reported too [2]. These Mucoraceae are molds in the environment and become hyphae once they infest the tissues. Once these spores enter the tissues, they find their way into the blood vessels and get lodged there. This then induces an inflammatory reaction which leads to formation of a thrombus which enlarges in size and ultimately leads to compromised blood supply of the tissues and thence causes ischaemic necrosis. The necrosis is responsible for the blackening of the tissues which is characteristic of Mucormycosis [3–5].

The spread of mucor from nose and PNS to the orbit occurs through lamina papyracea, infra-temporal fossa, inferior orbital fissure, superior orbital fissure or the orbital apex. Depending upon the site of entry of infection into the orbit and the structure involved, the first symptoms the patients experience are decreased vision and mono-muscular palsy leading to diplopia. Late features include complete blindness, chemosis/proptosis, total ophthalmoplegia and optic atrophy on ophthalmoscopy. Further spread intra-cranially may lead to headache, altered consciousness and death.

Management

The management of limited sino-nasal mucormycosis is pretty straightforward. Surgical debridement of all the necrosed tissue along with Inj Amphotericin-B (1 mg/kg/day for a total dose of 2–3 g) is the treatment of choice. However, when the orbit is involved the decision making is not as direct. The vision is arguably the most important sensation of a human being. The decision to either preserve the eye or exenterate it as a part of surgical debridement has to be taken jointly by the otolaryngologists and the ophthalmologists [6]. All efforts should be made to preserve the eye for as long as possible. It needs to be highlighted that the eye not only provides vision but the removal of the same causes significant psycho-social problems as well. Dogbe et al. performed a study on ten post-exenteration subjects and found that 50–60% of patients were strongly uncomfortable with the cosmetic effects of the surgery, suffered unwelcome comments and unpleasant stare from close friends and relatives which made them uncomfortable in their company. Thus, there are long term ophthalmic, cosmetic as well as psychological repercussions of exenteration. Thus, the decision has to be a close balance between preserving the eye or preventing further intra-cranial spread and eventually death.

Unfortunately, the literature fails to provide any set criteria for the stage at which the exenteration needs to be carried out. This prompted us to lay out a scoring system that accurately directs the clinician to either perform or avoid orbital exenteration. This scoring system has been devised by a team of Otorhinolaryngologists and Ophthalmologists with years of experience in managing this disease and promises to accurately predict the stage at which the exenteration should be carried out. It is so devised that any practitioner with access to radio-diagnostic facilities can use it.

Orbital Exenteration with Enucleation

Exenteration was carried out under GA. First the enucleation was done by the Ophthalmologist. A 360°

Table 4 Observation

Patient	Predisposing condition (s)	Presenting symptoms	Clinical findings	Radiographic manifestations	Antimicrobial treatment (dose; duration)	Length of follow-up
Patient 1	Diabetes mellitus	Head ache, nose block, proptosis, facial pain and diminision of vision which progressed to total loss of vision	nasal mucosa necrosis with eschar, chemosis with proptosis	Mildly enhancing heterogenous lesion present in the nasal cavity and PNS. Proptosis present	Amphotericin 2.2 g	6 months
Patient 2	None	nose block, proptosis, facial pain, fixed eyeball, diminision of vision which progressed to total loss of vision	Total ophthalmoplegia, fixed pupil, PR vision, black eschar in nose and PNS, erosion of hard palate present	Enhancing lesion in nose, PNS, proptosis, optic neuritis present, lesion involving SOF, ITF and reaching up to lateral wall of cavernous sinus	Amphotericin 2.8 g	6 months
Patient 3	Diabetes mellitus	Headache, loss of vision, epiphora, proptosis, periorbital pain	Nasal mucosa necrosis, black eschar formation, orbital cellulitis, proptosis, chemosis, ophthalmoplegia, fixed pupil with no vision	Lesion involving region of right optic canal, greater wing of sphenoid, extra and intradural extension present with evidence of skull base osteomyelitis	Amphotericin 2.5 g plus Oral Posaconazole for 10 days	6 months
Patient 4	Diabetes mellitus	Head ache, nose block, proptosis, facial pain and diminision of vision which progressed to total loss of vision	nasal mucosa necrosis with eschar, chemosis with proptosis	Mildly enhancing heterogenous lesion present in the nasal cavity and PNS. Proptosis present	Amphotericin 2.2 g	6 months
Patient 5	Diabetes mellitus	Nasal block with discharge, hyposmia	Black necrotic mass seen in nasal cavity, ethmoidal, maxillary and sphenoid sinuses with sinusitis	Enhancing lesion seen in nasal and paranasal sinuses	Amphotericin 2.2 g	8 months
Patient 6	Diabetes mellitus	Nasal block with discharge	Black eschar seen in nasal cavity	Enhancing lesion confined to nasal cavity	Amphotericin 1.8 g	6 months
Patient 7	Diabetes mellitus	Nasal block, anosmia and proptosis with loss of vision	Total ophthalmoplegia, proptosis fixed pupil, PR vision, black eschar in nose and PNS	Proptosis with thickening of optic nerve present. Swelling of the orbital soft tissues present. Nose and PNS involved	Amphotericin 2.8 g	6 months
Patient 8	Diabetes mellitus	Nasal discharge, facial pain, retro-orbital pain, proptosis and diminution of vision which progressed to complete loss of vision	Conjunctival chemosis, fixed pupil, black eschar in nose and PNS, hard palate and mucosa	Thickening of optic nerve present. Swelling of the orbital soft tissues present. Nose and PNS involved, erosion of hard palate and adjoining alveolus present	Amphotericin 2.5 g	6 months
Patient 9	Diabetes mellitus	Nasal block and facial pain	Nasal mucosa necrosis and crust formation present	Lesion confined to nasal cavity	Amphotericin 2 g	Expired
Patient 10	Diabetes mellitus	Nasal block and facial pain with anosmia and headache	Nasal mucosa necrosis and eschar formation	Lesion confined to nasal cavity	Amphotericin 2.0 g	6 months
Patient 11	Diabetes mellitus	Nasal discharge, facial pain, retro-orbital pain, proptosis and diminution of vision which progressed to complete loss of vision	Conjunctival chemosis, fixed pupil, black eschar in nose and PNS, hard palate and mucosa	Proptosis with thickening of optic nerve present. Swelling of the orbital soft tissues present. Nose and PNS involved, erosion of hard palate and adjoining alveolus present	Amphotericin 2.5 g	6 months

Table 4 Observation

Table 4

Patient	Predisposing condition (s)	Presenting symptoms	Clinical findings	Radiographic manifestations	Antimicrobial treatment (dose; duration)	Length of follow-up
Patient 12	Diabetes mellitus	Nasal block and discharge	Nasal mucosa necrosis and crust formation present with sinusitis	Lesion confined to nose, ethmoidal, frontal and sphenoid sinus	Amphotericin 2.4 g	6 months
Patient 13	Diabetes mellitus	Nasal block and facial pain with anosmia and headache	Nasal mucosa necrosis and eschar formation	Lesion confined to nasal cavity	Amphotericin 2.0 g	6 months
Patient 14	Diabetes mellitus, HTN and hypothyroidism	Nasal block with discharge, hyposmia, decreased vision with chemosis	Blackish crust present in nasal cavity, involving the inferior turbinate, middle turbinate and middle meatus	Mildly enhancing heterogenous lesion present in the nasal cavity and PNS. Optic nerve bulky. Proptosis present. Lesion reaching lateral wall of cavernous sinus along the orbital apex	Amphotericin 2.8 g	Lost to follow up
15	DM	Nasal block and anosmia with headache	Pansinusitis with crusting, total ophthalmoplegia with fixed pupil	Pansinusitis, orbital apex inflammation present with frontal lobe abscess	Amphotericin 1 g	Present

conjunctival periotomy dissection and separation of recti muscle from the eyeball was done. This was followed by removal of the eyeball. Exenteration was done by the Otorhinolaryngologist. Incision was taken with a monopolar cautery just below the tarsal plate and deepened to the bone. Periosteum was elevated against the orbital cavity all around. Dissection too was done with the monopolar cautery. The extra-conal muscles were identified and elevated from the orbit along with the periosteum. Dissection was continued posteriorly. Anterior ethmoidal artery was identified and cauterised. After reaching the posterior most part of the orbit and lifting the periosteum; superior orbital fissure and inferior orbital fissure were identified and cauterised. Optic nerve was identified and cut sharply. The entire specimen was removed in total. The specimen (orbital tissues and eyeball) was sent for HPER and KOH mount. Cavity was washed with povidone iodine and vaseline pack was kept inside the orbit which was removed after 5 days. Lateral tarsorrhaphy was done. A medial window of about 5 mm was kept open for pack removal and examination post-operatively via endoscope.

Endoscopic Orbital Exenteration

This is a newer concept where the orbit is exenterated via the trans-nasal route. It offers the advantage that the uninvolved superior and lateral periorbital can be preserved which helps in post-op mucosalization of the cavity and obviates the need for packing or tissue-grafting the cavity. It also helps in direct trans-nasal cauterization of the Ophthalmic artery as it emerges from the Optic foramen and better visualization of the Ocular pathology [7].

This however is a young concept and has a steep learning curve and may require facilities like Neuro-navigation which are not available in all the hospitals.

Amphotericin-B

Obtained from *Streptomyces Nodosus*, it was the first antifungal to be discovered in 1953. It is a polyene amphoteric macrolide with internal cyclic ester and 4–7 conjugated double bonds. The hydrophobic polyene domain makes it poorly soluble in aqueous media [8]. The mode of administration is parenteral and four formulations are available commercially. These are:

- Conventional Amphotericin-B
- Amphotericin-B Colloidal Dispersion
- Liposomal Amphotericin-B
- Amphotericin-B Lipid complex.

The highest plasma concentration achieved by these formulations in decreasing order is Liposomal Amphotericin-B > Amphotericin-B Colloidal Dispersion > Conventional Amphotericin-B > Amphotericin-B Lipid Complex.

The best formulation is considered to be Liposomal Amphotericin-B in terms of therapeutic efficacy and safety margin. In our centre, Conventional Amphotericin-B was used due to financial constraints.

Some fungi have been reported to develop resistance to the drug by replacing the ergosterol by other sterols. But this is mostly seen in *Candida lusitanae*, *Aspergillus terreus* and *Aspergillus nidulans*.

The adverse drug reactions of Amphotericin-B are either infusion related or drug related. The infusion related

Table 5 Results after applying the scoring system

Patient	Score	Exenteration performed	Histopathology of the orbital mass for Mucor	Patient current condition
Patient 1	28	Yes	Negative ^a	Stable
Patient 2	32	Yes	Positive	Stable
Patient 3	25	Yes	Positive	Not known
Patient 4	37	Yes	Positive	Recurrence of disease in the palate with bony erosion
Patient 5	2	No	–	Stable
Patient 6	0	No	–	Expired due to other medical conditions
Patient 7	28	Yes	Positive	Stable
Patient 8	24	Yes	Positive	Stable
Patient 9	2	No	–	Expired due to other medical conditions
Patient 10	5	No	–	Expired
Patient 11	33	No	–	Patient dies within 2 days of admission. So any surgical intervention was not possible
Patient 12	4	No	–	Stable
Patient 13	13	No	–	Stable
Patient 14	36	Yes	Positive	Expired due to other medical conditions
Patient 15	26	Yes	Positive	Stable

^aA special needs to be made about Patient number 1 who was negative on histopathology for mucormycosis after exenteration. When the patient was diagnosed of mucormycosis, he had normal vision on the affected side. He underwent endoscopic nasal debridement for mucormycosis. However, inspite of the debridement and being on Amphotericin B for 7 days, his orbit got clinically involved. He initially had restriction of extra ocular movements and later developed vision loss with proptosis on the affected side. Hence, in clinical suspicion (in consultation with two Ophthalmologists), his dose of Amphotericin B was stepped up and a second anti-fungal (Posaconazole) was added. However, there was no clinical improvement over the next 48–72 h and hence he was offered orbital exenteration surgery for his non-functioning and clinically diseased eye. The fact that the affected eye was negative for mucormycosis on microbiology is probably the reason that his condition did not worsen further and he is currently alive and well

adverse reactions are fever and chills (most common), tachypnea, stridor, hypotension, anaphylaxis and bronchospasm (rare). To minimise these infusion related drug reactions, pre-medication with anti-pyretics, antihistamines and corticosteroids should be given. Further giving a prior test dose of 1 mg IV and giving the infusion slowly may prevent these reactions too.

The drug related reactions are:

Nephrotoxicity

Azotaemia occurs in 80% of individuals which is dose dependent and transient, however the histopathological changes are permanent. There is increased for those who are on concurrent nephrotoxic drugs, have altered RFT, co-existing kidney disease or those who receive more than 3–4 grams of the drug. Patient should be loaded with 1 litre of normal saline prior to infusion to reduce the nephrotoxicity. Hypokalaemia, hyponatremia and hypomagnesaemia should be treated as soon as possible [9].

Haematological

Amphotericin-B causes anaemia by decreased Erythropoietin production. This however is reversible on stopping the drug and recombinant EPO should be used whenever necessary. This is less observed with lipid formulations. Other haematological complications are leucopenia and thrombocytopenia.

The other complications are nausea, vomiting, malaise and weight loss.

Do's and Don'ts

- Never use electrolyte containing IV fluids for infusion
- Flush IV line with D5W/D10W before AMB infusion/ use separate IV line for AMB
- Do not use if precipitate/foreign matter is present
- Do not freeze
- Protect from heat and sunlight.

Other Medical Management Options

Posaconazole is a new triazole that has been shown to have good activity against some strains of Mucorales. Studies have shown that it is an effective alternative in patients with severe Amphotericin-B nephrotoxicity and those who are unresponsive to Amphotericin-B. Pitisuttithum et al. conducted a study in 2005 where they tested Posaconazole oral suspension at a dose of 800 mg/day in patients of CNS fungal infections and obtained successful results in 48% (14 out of 29) patients [10–12]. Toben et al. reported a patient with mediastinal fungal infection caused by *Rhizopus* who was previously operated for dual heart and kidney transplant and had Diabetes Mellitus. Posaconazole

was given after 6 weeks of unresponsive Amphotericin-B treatment and there was significant clinical improvement as early as 7 days into the treatment with continued improvement for 23 weeks of therapy and no adverse reactions attributable to Posaconazole.

HBO2 and G-CSF are the other medical management options that have shown some promise. They act by enhancing the leukocyte killing capacity and increase oxygen delivery to the tissues. Their role is however only additive to systemic anti-fungals.

Orbital Reconstruction

In our centre, the orbit is reconstructed with a prosthetic eye 3–4 months after cure of disease. A galeal frontalis-pericranial flap from the mid-forehead region can also be used for the reconstruction of the orbit.

Conclusion

The Sion Hospital Scoring System is an accurate and promising measure to solve the dilemma that is associated with orbital exenteration in orbito-rhino-cerebral mucormycosis.

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