

How We Do It.....

A protocol for management of Rhino-cerebral Mucormycosis.

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Key Messages

1. Rhino-orbital symptoms and signs in an immunocompromised patient along with fat stranding in CT scan are strongly suggestive of RCM.
2. Sinoscopy under anesthesia may be required for definitive diagnosis of RCM as nasal examination can be completely normal in early stages.
3. Liposomal Amphotericin along with other supportive measures and strict fluid/ electrolyte balance can reduce mortality significantly
4. Topical conventional Amphotericin packaging is an important adjunct to systemic therapy.

Keywords: Rhino-cerebral Mucormycosis, Mucormycosis, Fungal Sinusitis

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Introduction

Rhino-cerebral Mucormycosis (RCM) is an invasive fungal infection caused by filamentous fungi of the Mucoraceae family ^[1,2]. Majority caused by organisms in the genera *Rhizopus* (70%), to a lesser extent by *Lichtheimia* and *Mucor* and rarely by *Rhizomucor*, *Apophysomyces* and *Saksenea* ^[3,4]. The disease is commonly associated with an immunosuppressive state and most commonly seen amongst diabetic patients⁵.

RCM becomes common in Anuradhapura during rainy seasons and currently we are facing the worst epidemic experienced during last 5-6 years. RCM has a very high mortality rate which is typically more than 50%⁵. A retrospective study carried out at teaching hospital Anuradhapura in 2018 (12 patients from 2015 -2017) has shown a mortality rate of more than 65% in spite of treatment. Therefore, we have taken some important steps to try and decrease mortality and come up with a departmental protocol. With this we have experienced a remarkably low mortality rates and we are yet to see any deaths managed using this protocol during this year (7 cases).

The key points of our departmental protocol are

1. Early diagnosis (clinical, radiological and laboratory)
2. Aggressive endoscopic debridement
3. Liposomal Amphotericin
4. Fluid, electrolyte balance and other supportive measures
5. Follow up endoscopic examination/debridement and topical treatment

Early diagnosis

Because of the relative low incidence of the invasive fungal sinusitis, a high index of suspicion must be maintained to arrive at an early diagnosis ^[6]. This is a key factor leading to a better prognosis. RCM usually presents with headache, retro-orbital/orbital pain, fever, nasal discharge, proptosis, ophthalmoplegia, loss of vision ^[6]. Our previous study showed that unilateral headache as the commonest presentation and most have developed multiple cranial nerve palsies during the course of the illness.

An urgent CT scan of nose paranasal sinuses with fine cuts will be carried out, sometimes even before endoscopic examination. Intravenous contrast is indicated whenever possible especially when intracranial or intra-orbital extension is suspected. Otherwise a non-contrast CT is adequate in most instances. Mild to moderated unilateral mucosal thickening is usually a common initial finding. Infiltration of peri-antral fat planes (fat standing) is an initial CT sign of invasive fungal sinusitis ^[7]. There may be focal bony erosions, air fluid levels, obstruction of osteo-meatal complex, heterogeneous opacifications with focal areas of high signal intensity. CT may be normal in about 12% especially when disease is limited to nasal cavity. ^[8]



Fig1: Infiltration of peri-antral fat planes in CT

Endoscopic examination and aggressive debridement

Immunocompromised patients with localized sino-nasal and orbital symptoms are urgently examined at our department with nasal endoscopy to rule out RCM. Rigid nasal endoscopic evaluation may only show subtle changes or it can be normal initially. Therefore, we tend to do this under general anesthesia and keep a low threshold for sinostomies (middle meatal antrostomy and/or sphenoidotomy) depending on CT findings. Alteration in the appearance in the mucosa is the most striking feature. Normal typical pinkish appearance in nasal mucosa can be replaced by discoloration, ulceration or granulation. Angioinvasion will cause a tissue ischemia and mucosa will appear whitish, and later it will become blackish due to the tissue necrosis. Nowadays we see quite a number of patients with normal nasal mucosa but pale sinus walls on sinostomies. This is probably due to high index of clinical suspicion and early endoscopy.

Nasal mucosal abnormalities, when present, most commonly appear on middle turbinate (67%), followed by septum (24%), palate (19%) and inferior turbinate (10%) [8]. Reduced mucosal sensation and decreased mucosal bleeding can also be noted.



Fig 2: This pale sinus wall is seen only after an antrostomy and in this case nasal endoscopy was completely normal.

Aggressive surgical debridement of all necrotic tissue is done until normal well-perfused bleeding tissue edges are seen. Sometimes this requires entering into pterygopalatine fossa, infratemporal fossa or orbital decompression. We try to do maximum surgical debridement during the initial surgery. It reduces the fungal load and provide samples for fungal studies. Surgery can reduce and halt the progression of the disease.

Samples are taken from suspicious areas for fungal studies, cultures and histology. We have established a system to transport samples urgently to Medical Research Institute, Colombo for urgent microscopic examination and cultures. Direct smear will demonstrate hyphal forms within the submucosa with or without angiocentric invasion in mucormycosis.

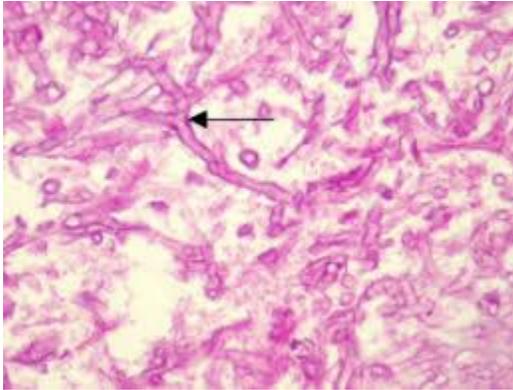


Fig 3: Zygomyces fungi under microscopy

Liposomal Amphotericin

Amphotericin B is the drug of choice for this disease. However, unfortunately we have experienced serious side effects including deaths with conventional Amphotericin B. Even though Liposomal Amphotericin B is significantly more expensive compared to conventional form we have experienced significantly low side effect profile and very good response to treatment. This fact is well established in the literature. [9]

We emphatically start intravenous liposomal Amphotericin B on clinical suspicion. Baseline renal functions and liver functions are done prior to starting Amphotericin. The standard dose is 3mg/Kg bodyweight [10] after a test dose. However, 2013 ESCMID and ECMM (European Society for Clinical Microbiology and Infectious Diseases and European Confederation of Medical Oncology) joint clinical guidelines for the diagnosis and management of mucormycosis recommends 5mg/kg body weight except when CNS involvement is present [11]. However, a dose of 3mg/kg appears to be adequate for our patients, especially in the context of significant financial burden to the health care system.

According to the literature, usual recommendation is to give a total accumulated dose of 2.5 to 3g of Amphotericin B. However, there are some reports of loading 5-6g [12]. We usually give Liposomal amphotericin for total duration of 4-6weeks depending on the severity of the case. This means we load a total of 4.2 -6.3g of Amphotericin into our patients. Our patients appear to tolerate this regimen very well and we will be reporting a case series to determine its long-term outcome

Conventional Amphotericin B is used only when Liposomal form is not available. After a test dose conventional form is given by a gradually increasing dosage and given at a dose of 1mg kg BW. It is not recommended to be increased to more than 1.5mg/Kg due to its side effects, especially the risk of sudden cardio- respiratory events.

We routinely obtain nephrology opinion when serum creatinine goes up and sometimes Amphotericin is temporarily withheld when serum creatinine doubles from the baseline value. There are concurrent bacterial infections and relevant intra venous antibiotics are given during initial period.

Fluid, electrolyte balance and other supportive measures

Hydration with normal saline is done before and after the Amphotericin infusion- usually 250 ml is infused before and after. Strict Fluid balance charts are maintained and about 2500-3000 ml of fluid intake is maintained. Serum Creatinine and serum electrolytes are done daily afterwards. CRP, FBC, serum Magnesium, serum calcium is done about every other day. Serum phosphate is done about every 5th day. Electrolyte abnormalities (hypokalemia, hypocalcemia and hypomagnesaemia) are common with amphotericin due to renal tubular acidosis. Electrolyte abnormalities are treated accordingly and investigations need to be done more frequently when they are low.

Tight glycemic control is achieved using insulin and help of the endocrinologist sought early. Any other immunosuppressive states are also addressed. Nutrition levels of these patients are optimized with the help of nutritionist.

Follow up endoscopic examinations and topical treatment

Rigid nasal endoscopic examinations are done about twice a week. Debridement of necrotic materials mostly done under local anesthesia and sometimes under general anesthesia. We tend to limit aggressive debridement procedures under general anesthesia when electrolyte abnormalities are present. Other than intravenous Amphotericin, we carry out local packing of the sinuses and nasal cavity with conventional Amphotericin B soaked nasal packs every third day. We have also been trying douching and irrigation with conventional Amphotericin to give some packing free intervals.

After the completion of 4-6 weeks' treatment we perform a follow up CT to exclude any progression and repeat samples are sent for fungal studies to exclude any active infection. These along with endoscopic finding and CRP levels are used to make a decision to stop treatment. However, we closely monitor them inward for about a week even after stopping treatment. This is because half-life of Amphotericin increases with long term use. Then we review them weekly with RNE for about a month then interval is increased.

Conclusion

We can achieve a remarkably low mortality in patients with RCM with early diagnosis, aggressive surgical debridement, liposomal amphotericin, topical Amphotericin therapy, control of underlying comorbidities and other supportive measure with close monitoring. High index of suspicion must be maintained in at-risk populations, in order to rapidly execute a multifaceted approach.

Departmental Protocol for management of Rhino-cerebral Mucormycosis

- Urgent CT and RNE
- Aggressive surgical debridement and sent samples for direct smear, culture & histology
- Start IV Liposomal Amphotericin B - 3mg /Kg BW daily after test dose as soon as possible.
Can increase up to 5mg /Kg BW
(Reconstitute the Amphotericin vial strictly according to manufactures advices)
- Hydrate with 250 ml of normal saline before and after IV amphotericin.
- IV Ceftazidime, or relevant IV antibiotic.
- Baseline renal function and liver functions
- Daily serum creatinine and serum electrolytes.
- CRP, FBC, serum Magnesium, serum Calcium, BU every other day, serum Phosphate every 5th day.
- Correct electrolyte abnormalities accordingly & repeat Ix more frequently if they are abnormal
- Maintain daily IP/OP chart.
- When serum creatinine level doubles Amphotericin is usually withheld until it becomes to baseline value.
- Maintain tight glycemic control.
- Frequent RNE and debridements of necrotic tissue
- Local packing with Amphotericin packs every third day

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