

Predictors of mortality in rhinocerebral mycosis

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Introduction: Rhinocerebral mycosis is a rapidly progressive fatal opportunistic infection, predominantly affecting people in an immunocompromised state. Aggressive surgical therapy, with repeated debridement in combination with intravenous amphotericin B can lead to a high rate of cure.

Aim: To determine the predictors of mortality in rhinocerebral mycosis. **Materials and Methods:** The demographic data, clinical features, radiological (MRI/CT) findings, treatment details of patients with a diagnosis of rhinocerebral mycosis confirmed on histopathology were analyzed retrospectively. The outcome was assessed as alive and dead. Univariate analysis with odds ratio (OR) was employed in data analysis. Chi-square test was used for *P* value. **Results:** There were 38 patients. The age range was 7-82 (mean 48.68) years; 30 (79%) were males. Craniofacial pain was the most common initial presenting symptom, noted in 29 (76.3%). Rhino-orbital involvement was noted in 24 (63.2%) and 12 (31.6%) had associated focal neurological deficits. Immunocompromised state was noted in 24 (63.2%). Eighteen (47.4%) patients died. The predictors for mortality: odds ratio (95% CI) were 2.45 (1.01-3.89) for elderly age, 5.67 (4.13-7.21) for intracranial extension, 2.6 (1.26-3.94) for immunocompromised state, 2.62 (1.25-3.99) for infection with *zygomycosis* and 2.33 (1.01-3.65) for anemia. **Conclusion:** Rhinocerebral mycosis is associated with high mortality in spite of aggressive therapy. Intracranial extension with focal neurological deficits is a major predictor of mortality in rhinocerebral mycosis.

Key words: Intracranial extension, mortality, rhinocerebral mycosis

Paltau^[1] first identified rhinocerebral mycosis in 1885. He described a case of rhinocerebral *mucormycosis*. *Aspergillosis* and *zygomycosis* are the commonest causes of central nervous system (CNS) mycosis. *Cryptococcus*, *Candida*, *coccidioides*, *histoplasma* and *cladosporium* are the other fungi causing CNS mycoses. *Aspergillosis* is caused by *Aspergillus fumigatus* in the majority of cases, but *A. flavus*, *A. glaucus* and *A. niger* are not rare.

Zygomycosis includes the fungi of family *Mucoraceae*. It includes *Mucor*, *Rhizopus*, *Rhizomucor* and *Absidia*.^[2]

In rhinocerebral mycosis the disease originates in the nasal/sinus mucosae, after inhalation of fungal spores and takes a rapidly progressive course by extending to neighboring tissues including the orbit and central nervous system.^[3] The initial clinical findings in orbital involvement are most commonly headache, lethargy and facial pain. These may be rapidly followed by restriction of ocular movements, proptosis, ptosis and periorbital cellulitis. Paralysis of the third, fourth and sixth cranial nerves and visual loss due to central retinal artery occlusion is not uncommon. The fifth and seventh cranial nerves may be involved. The most serious complication of rhinocerebral mycosis is cerebral vasculitis due to direct vascular involvement.^[4]

Rhinocerebral mycosis is a rapidly progressive and fatal opportunistic infection, predominantly affecting individuals in an immunocompromised state. Occurrence in immunocompetent individuals is not uncommon.^[5] It carries a high residual morbidity and mortality due to the angioinvasive property of fungi, causing vascular occlusion and extensive tissue necrosis. Impaired delivery of the antifungal drugs to the site of infection because of vascular thrombosis and limited aggressive surgery because of the complex anatomy of the rhino-orbitocerebral region cautions for early diagnosis and aggressive management in these patients.

There are many case reports / series of rhinocerebral mycosis. The mortality in rhinocerebral mycosis ranged from 15-82% in various series.^[6-16] The predictors of poor outcome were intracranial extension of the disease,^[7,12] delayed diagnosis^[9] and hemiplegia as a neurological complication.^[11] Aggressive surgical therapy, with repeated debridement in combination with intravenous amphotericin B can lead to high rate of cure with long-term survival rate.^[10,15]

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Aim

To determine the predictors of mortality in patients with rhinocerebral mycosis.

Materials and Methods

Medical records of 46 consecutive patients with a diagnosis of rhinocerebral mycosis admitted to the Neurology department from January 1997 to December 2005 were analyzed retrospectively. All the patients had histopathological evidence of fungal infection. Functional endoscopic excision biopsy using 0 degree and 30 degree endoscopes was done. Tissues were fixed in buffered formalin and processed for paraffin embedding. Hematoxylin and Eosin stained sections were examined for tissue reaction. Fungal morphology was identified by Periodic acid Schiff (PAS) and Gomori's methenamine silver (GMS) and other appropriate special stains. 'Broad non-septate hyaline ribbon-like hyphae with irregular branching' was the basis for identification as *Zygomycetes* and narrow hyphae with distinctive septa, parallel walls and acute angle dichotomous branching, for *Aspergillus*. Melanized fungi were identified by the presence of thin branching, septate hyphae with melanin pigment. The melanin-specific Masson-Fontana stain was used for confirmation. Culture reports were obtained whenever tissue was submitted for culture. The demographic data, predisposing illness, clinical features, radiological (MRI/CT) findings, treatment details (medical and/or surgical) and outcomes were recorded.

Statistics

Univariate analysis with odds ratio (OR) was employed in data analysis. Chi-square test was used for *P* value and *P* value of < 0.05 was taken as significant.

Results

There were 46 patients with a diagnosis of rhinocerebral mycosis. Eight patients did not continue the treatment and were lost to follow-up. Hence the results were analyzed in 38 patients. Age ranged from 7-82 (mean 48.68) years; 30 (79%) were males. All the patients presented with multiple symptoms and signs. Craniofacial pain was the most common initial presenting symptom, noted in 29 (76.3%) patients. The other symptoms and signs were fever, vomiting, seizures, cranial nerve palsies, altered sensorium, meningitis and focal neurological deficits [Table 1]. At admission significant anemia (hemoglobin of <8 gm/dl) was noted in 15 (39.5%), leukocytosis in 12 (31.6%) and elevated erythrocyte sedimentation rate (ESR) in 22 (57.9%) patients.

Rhinoorbital involvement with facial edema, proptosis, chemosis and ophthalmoplegia were the commonest findings noted in 26 (68.4%) patients. Rhinoorbitocerebral

Table 1: Symptoms and signs of rhinocerebral mycosis at admission

Clinical feature	Number (%)
Craniofacial pain	29 (76.3)
Fever	14 (37)
Vomiting	7 (18.4)
Seizures	5 (13.2)
Altered sensorium	8 (21)
Meningitis	3 (7.9)
Cranial nerve palsies	
3 rd , 4 th , 6 th cranial nerves	36 (94.7)
2 nd cranial nerve	30 (78.9)
5 th cranial nerve	11 (28.9)
7 th cranial nerve	6 (15.8)
8 th cranial nerve	1 (2.6)
9 th and 10 th	2 (5.3)
11 th and 12 th	1 (2.6)
Focal neurological deficits	12 (31.6)

involvement with focal neurological deficits was seen in 10 (31.6%) patients. Sinocranial involvement with focal neurological deficits due to brain abscess was noted in two patients with mycosis due to melanized fungi. The third, fourth and sixth cranial nerves were involved in all the patients with rhinoorbital involvement and optic nerve in 30 (79%) [Table 1] patients. Two patients had bilateral rhinoorbital involvement.

Immunocompromised state was noted in 24 (63.2%); 23 had diabetes mellitus (DM) and one patient of Wegener's granulomatosis was on immunosuppressive therapy. One patient with DM had renal transplantation with hepatitis C and B virus infection and one patient with DM had HIV-1 infection. Seven patients with DM were in diabetic ketoacidosis (DKA), 12 had hyperglycemia and four were euglycemic at the time of admission. One patient had denovo DM with DKA. There were 14 (36.8%) patients with no identifiable cause for immunosuppression.

Magnetic resonance imaging (MRI) was done in all the patients. Paranasal sinusitis with orbital involvement was noted in 26 (68.4%) patients. Intracranial extension was noted in 12 (31.6%) patients. Cavernous sinus involvement was noted in six and suprasellar extension in two patients. Stroke secondary to probable vasculitis was seen in 12 patients - 11 had internal carotid artery (ICA) stroke (bilateral involvement in two) and one had posterior cerebral artery (PCA) stroke. Four patients had intracranial abscess [Figure 1] (bifrontal -one, temporal lobe-one, capsuloganglionic -one and cerebellopontine angle-one). All the patients underwent spheno-ethmoidectomy and or maxillectomy according to the involvement. Radical surgery (enucleation of eye, orbital exenteration, craniotomy with debridement, extensive craniofacial resection and reconstruction,) was done in 18 (47.4%) patients.

The diagnosis of fungal infection was based on direct microscopy of the tissue from the nasal/sinus mucosa or the intracranial mass lesion and histopathology. *Zygomycetes* and *Aspergillus* were the commonest

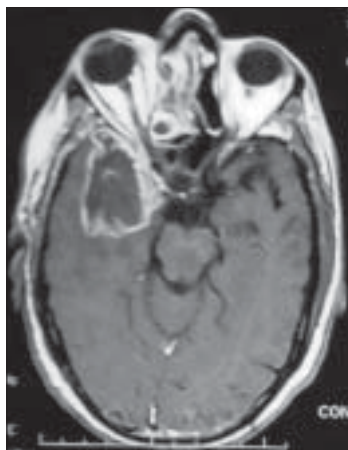


Figure 1a: MRI brain (contrast) image of a case of rhinocerebral mixed mucormycosis and *Aspergillus* infection with right temporal abscess (before treatment)

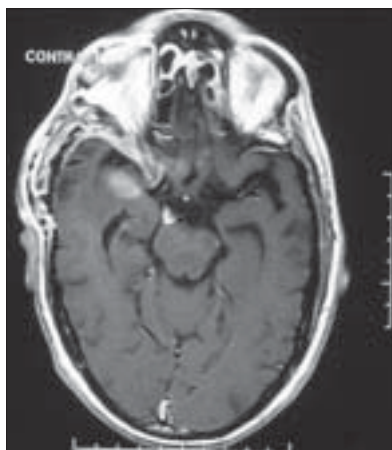


Figure 1b: MRI brain (contrast) image of a case of rhinocerebral mixed mucormycosis and *Aspergillus* infection with right temporal abscess (one year after treatment)

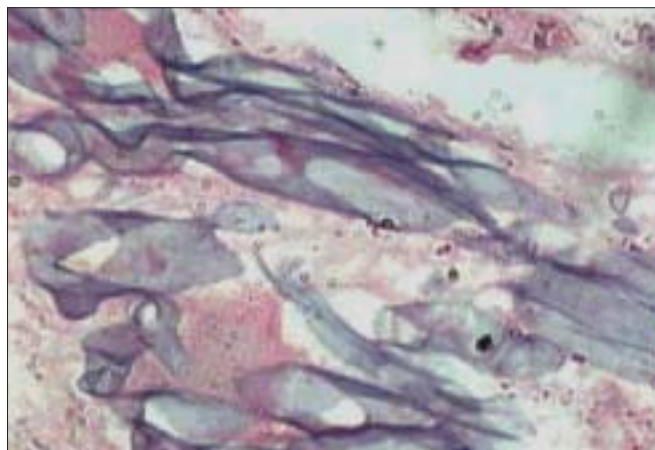


Figure 2: Photomicrograph showing broad, aseptate irregularly branching hyphae of mucormycosis (H/E, x40)

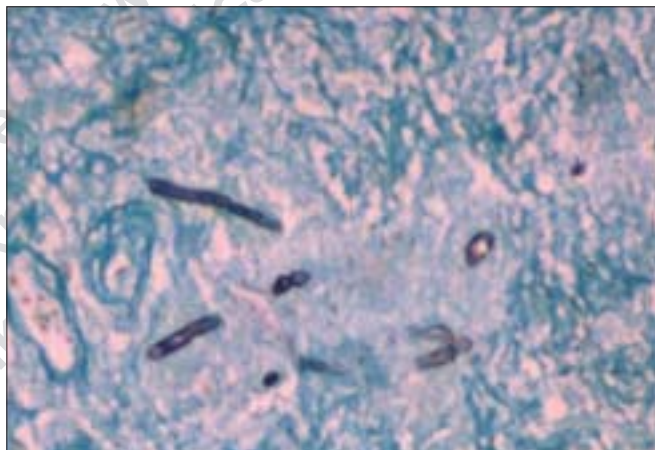


Figure 3: Photomicrograph showing slender, septate hyphae of *Aspergillus* species (Gomori's methenamine sliver, x40)

organisms found in 18 (47.4%) and 16 (42.1%), respectively [Figures 2 and 3]. Melanized fungi was found in two and mixed *Aspergillus* and *Zygomycosis* in two patients. The culture was done in 21 cases and it was positive in 12 (*aspergillus* species in five, *rhizopus* in six and *cladosporium* in one). *Aspergillus flavus* was isolated in three, *Aspergillus fumigatus* and *Aspergillus terreus* in one each. Among those with culture-positive *zygomycosis*, *Rhizopus oryzae* was isolated in five and *rhizomucor* in one patient. Culture was positive in one patient with pheohyphomycosis and basal ganglionic abscess and *cladosporium* species was isolated.

All these patients were treated with amphotericin B. In addition six patients with *Aspergillosis* received 5-fluorocytosine. The total dose of amphotericin B given ranged from 3-6 g. Liposomal amphotericin (Ambisome) was given to seven patients and the total dose given in each patient was 3 g. One patient with rhino-orbitocerebral mixed *Aspergillus* and *Zygomycosis*

infection and a temporal lobe fungal abscess, did not respond to liposomal amphotericin. Mixed *zygomycosis* and *aspergillus* infection was identified on tissue morphology, but culture isolated *Aspergillus fumigatus* only. He was given intravenous voriconazole 400 mg/day for two weeks followed by oral voriconazole 400 mg/day for six months. The patient improved markedly at the end of one year with no residual neurological deficits and near total resolution of the temporal lobe abscess on MRI [Figure 1]. The common complications during treatment with amphotericin B were hypokalemia in 30 (78.9%), acute renal failure in four (10.5%), hyponatremia in two (5.3%) and symptomatic hypomagnesemia in three (7.9%). The duration of hospital stay in the survived group was 21-123 (mean 56) days.

All the patients underwent follow-up MRI of brain and sinuses (plain and contrast) for the resolution of the lesions. Repeat biopsy/aspiration cytology was done in 12 patients who survived and no fungal elements could be demonstrated on pathology.

The follow-up ranged from one to nine years. Eighteen (47.4%) patients died. Elderly patients (age > 60 years) had a mortality of 58.3% compared to 36.4% in adults (age 17-59) and the difference was not statistically significant ($P \leq 1$). There was no statistically significant difference in mortality between males (46.6%) and females (50%) with $P \leq 1$. Patients with focal neurological deficits had higher mortality (75%) compared to those without focal deficits (34.6%) and the difference between the two groups is statistically significant ($P < 0.025$). The mortality was higher in patients with immunocompromised state (56.5%) compared to those with immunocompetent state (33.3%) but the difference was not statistically significant ($P \leq 0.2$). No significant difference in mortality was noted between the patients who underwent radical surgery (44.4%) and no radical surgery (50%), $P \leq 1$. Among the 10 patients who did not undergo radical surgery six patients died due to associated medical complications like septicemia in three, massive upper gastrointestinal bleed in one, acute renal failure in one and myocardial infarction in one. One patient had subarachnoid hemorrhage before death. The mortality was higher in rhinocerebral syndrome due to *Zygomycosis* (62.5%) than with *Aspergillus* (38.9%), but the difference was not statistically significant ($P \leq 0.2$). The mortality was 66.6% in patients with significant anemia at admission and 38.5% in those without anemia, the difference was not significant ($P \leq 1$). The predictors for mortality: odds ratio (95% CI) were 2.45 (1.01-3.89) for elderly age, 5.67 (4.13-7.21) for intracranial extension with focal neurological deficit, 2.6 (1.26-3.94) for immunocompromised state, 2.62 (1.25-3.99) for infection with *zygomycosis* and 2.33 (1.01-3.65) for anemia [Table 2]. The OR was highest for intracranial extension causing focal neurological deficit,

suggesting that it is a major predictor of mortality in rhinocerebral mycosis.

Discussion

Rhinocerebral fungal infection typically originates in the nasal or oral mucosae, spreads to paranasal sinuses and enters the orbit via the ethmoid and maxillary sinuses or via the nasolacrimal duct. Intracerebral extension may occur from the orbit via the orbital apex, orbital vessels or via the cribriform plate. Diabetes mellitus is a common predisposing factor for this infection.^[4,6-10,12,17,18] CNS mycosis is common in the setting of diabetic ketoacidosis (DKA). In our series diabetes was noted in 23 (56.5%) patients and seven were in DKA at admission. However, rhinoorbital *zygomycosis* has been reported without ketoacidosis and with well-controlled diabetes.^[19] Euglycemic state at admission was noted in four patients in our series. Post-renal transplant state and retrovirus (HIV-1) infection were the other predisposing factors similar to previous reports.^[8,20,21] Occurrence in immunologically competent patients is not uncommon^[5,22,23] and we had 14 (36.8%) patients with immunocompetent state.

Ocular and sinonasal involvement were the commonest clinical features at admission.^[6,8-10,12]

In our series rhinoorbital involvement was noted in 26 patients and 12 had rhinoorbitocerebral involvement on imaging. Cavernous sinus invasion with ICA thrombosis is a common complication, associated with high mortality.^[24-26] In the present series six patients had cavernous sinus involvement on MR imaging and two had suprasellar extension. Eleven patients had ICA stroke and one had PCA stroke, probably due to fungal vasculitis. Intracerebral abscess is another complication of invasive mycosis, especially in intravenous drug users.^[29-31] We had four patients with intracranial abscess. In two of these patients melanized fungi were identified. Fatal complications like acute subdural hematoma and intracerebral hemorrhage due to rupture of an aneurysm was reported.^[32] In the present study one patient developed subarachnoid hemorrhage during treatment and died.

Invasive diseases caused by fungi are termed mycoses. *Aspergillus* is the most common fungus in histologically verified CNS mycosis from India and presents with focal neurological signs and symptoms.^[33-36] *Zygomycosis* is infrequently reported from India and the rhinocerebral form is the commonest form of CNS *Zygomycosis*.^[37] *Aspergillus* spreads to the CNS by direct inoculation by trauma or surgery, direct extension from paranasal sinuses or eye, invasion of arteries and veins and fungemia. The inflammatory response may range from an acute exudative lesion to a calcified granulomatous lesion. *Zygomycosis* is caused by direct extension from paranasal sinuses. Characteristic morphology of the

Table 2: Predictors of mortality in rhinocerebral mycosis

Variable	Mortality %	Odds ratio (95%CI)
Age		
Elderly vs. Adults	58.3 36.4	2.45 (1.01-3.89)
Sex		
Males vs. Females	46.7 50	0.875 (0.68-2.43)
Focal neurological deficits		
Present vs. Absent	75 34.6	5.67 (4.13-7.21)
Immunocompromised state		
Present vs. Absent	56.5 33.3	2.6 (1.26-3.94)
Anemia		
Present vs. Absent	60 39.1	2.33 (1.01-3.65)
Radical surgery		
Done vs. Not done	44.4 50	0.8 (0.5-2.1)
Type of infection		
<i>Zygomycosis</i> vs. <i>Aspergillus</i>	62.5 38.9	2.62 (1.25-3.99)

fungus on histopathology invading the vessel wall with fibrin deposition, intense polymorphonuclear response and infarction of adjacent tissue help in diagnosis. Multiple melanized fungi also cause central nervous system fungal infections. *Cladosporium bantiana* is the most commonly isolated species among phaeohyphomycosis, the dark pigmented fungi. It occurs most commonly in immunocompetent patients and brain abscess is the commonest presentation. The mortality was high (70%) regardless of immune status.^[38] We identified *Cladosporium* species in one case and in the second a tissue diagnosis of melanized fungus was made. Sinocranial disease, angioinvasion on histology has been reported with *Cladosporium*.^[23] Fungus-specific virulent factors, such as expression of surface molecules allowing adhesion to endothelial and epithelial cells, the production of surface molecules mimicking host substances and thereby avoiding the host's immune response and hydrolytic enzymes are important in the pathogenesis.^[39] Biopsy/aspiration cytology will confirm the diagnosis and must be performed in all suspected cases. *Aspergillus* and *zygomycosis* are the commonest organisms causing rhinocerebral syndrome.^[5-8,12,18] In the present study *Aspergillus* was found in 47.4% and *Zygomycosis* in 42.1%. Melanized fungi was found in two and mixed *Aspergillus* and *mucor* in two patients. Mixed infection with *Aspergillus* and *Zygomycosis* has been reported earlier.^[5,40]

Contrast MRI of the brain and sinuses should be done in all patients with suspected rhinocerebral mycosis. Contrast enhancement, extension of the disease into the orbit and cranial cavity can be well delineated on MRI and may simulate malignancy.^[5] Aggressive therapy with amphotericin B, rigorous glucose control, surgical debridement and radical surgery when indicated will improve the survival in these patients.^[7-10,12,13,15,24,25,29,40] Radical surgery was performed in addition to amphotericin B therapy in 47.4% of patients in the present study. Prolonged therapy with amphotericin may be needed in some cases. Voriconazole may be tried in resistant cases of rhinocerebral *aspergillosis*.^[41] Only one patient with mixed *Zygomycosis* and *Aspergillus* infection received voriconazole in the present series and responded well. Mixed *zygomycosis* and *aspergillus* infection was identified on tissue morphology, but culture isolated *Aspergillus fumigatus* only. Several times *Aspergillus* may be misdiagnosed as *zygomycetes* on tissue morphology. The role of voriconazole in rhinocerebral mycosis needs further confirmation in a large series of patients.

Mortality is high in patients with rhinocerebral mycosis if treatment is delayed.^[7-9,35] Intracranial extensions of the disease on imaging, hemiplegia as a neurological complication and diabetic ketoacidosis at presentation are adverse prognostic factors.^[11,12,42] The

predictors of mortality in the present series were elderly age, intracranial extension, immunocompromised state, infection with *Zygomycosis* and anemia. Intracranial extension causing focal neurological deficit is a major predictor of mortality. Awareness, early diagnosis, aggressive surgical and medical management with antifungal therapy and treatment of underlying predisposing factors will improve the prognosis.

One of the limitations of the present study was that the fungus was identified on tissue sections based on morphology of fungi. *Aspergillus*, *Fusarium*, *Scedosporium*, *Pseudallescheria* species and *Chaetomium* species exhibit similar septate tissue hyphae in tissue sections. Correlation with culture results is necessary for definite identification of the species.^[43,44]

Conclusion

Intracranial extension causing focal neurological deficit is a major predictor of mortality in rhinocerebral mycosis. Aggressive medical management with prompt surgical therapy is an important factor contributing to a better outcome.

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