

## Diagnostic Dilemma of Intracranial Fungal Granuloma Risk Versus Benefit Assessment Before Neurosurgical Management

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### Abstract

**Objective:** MRI and outcome based learning experience in the management of intracranial fungal granulomas and atypical brain infections (IFG) considering risk versus benefit before neurosurgical interventions.

**Methods:** We performed a retrospective analysis of all patients with diagnosed IFG or anticipated diagnosis based predominantly on imaging from 2011 to 2019 collected data included clinical history, lab results treatment and review of all imaging studies performed. Among these cases, one case required additional consideration of histopathological confirmation due to refractory response to anti-fungal medication and subsequent deterioration of neurology of patient hence neurosurgical intervention was done in that individual case. The variables were symptoms and signs at presentation, predisposing factors, location of granuloma, involvement of paranasal sinuses, diagnostic studies including blood and urine cultures, septic profile, surgical procedure performed along with histopathology treatment and prognosis. Computed tomography and magnetic resonance imaging scans were performed.

**Results:** Predominant symptoms included headache (83%) vomiting proptosis (48%) and visual disturbances. Other symptoms were fever, nasal congestion and seizures (18%). Common signs included papilledema with cranial neuropathy I, III, IV, VI and V in patients respectively. Predisposing factors were diabetes and immunocompromise status related to renal dialysis, transplant and tumor. Location was primarily frontal 1 parasellar sellar 1 involvement. One patient underwent frontal craniotomy for resection of fungal granuloma abscess histopathology revealed aspergilloma. All patients treated with itraconazole. Few were offered fluconazole, flucytosine and amphotericin B for a brief period. Mortality 1 secondary to meningoencephalitis.

**Conclusion:** Early diagnosis, risk versus benefit assessment oriented surgical decompression and prophylactic anti-fungal course according to variability of case with prompt initiation of antifungal therapy showed better outcome. Preoperative oral administration of itraconazole therapy improve clinical outcome in patients with aspergillosis. Larger prospective clinical studies are required to make firm clinical therapeutic recommendations.

Medical therapy with anti-fungal agents is required for prolonged periods following surgery in patients with IFM. In spite of several advances in imaging and surgical techniques and the advent of some newer antifungal agents, the prognosis for patients with IFM continues to remain grim and mortality rates range between 40 and 90% [1].

**Keywords:** Intracranial Fungal Granuloma (IFG); Antifungal Therapy (AFT); Rhino-orbital Cerebral Mucormycosis (ROCM)

### Introduction

Fungal infection of the central nervous system are rare clinical entities presenting with protean clinical manifestation difficult diagnostic dilemma and special therapeutic challenge [2,3].

Rhino-orbital-cerebral mucormycosis (ROCM) is an uncommon acute and aggressive fungal infection occurring in several immunocompromised states including diabetes, which is the most common (60% - 80%) predisposing factor [4,5].

The disease originates in the nasal, sinus mucosa after inhalation of fungal spores and takes a rapidly progressive course extending to neighboring tissue, including the orbit and sometimes brain. Gregory, *et al.* in 1943 reported three cases of ROCM in patients with uncontrolled diabetes with unilateral orbital cellulitis, complete ophthalmoplegia, cerebral invasion and death [6]

ROCM causes very high residual morbidity and mortality due to the angioinvasive property of the fungus, thereby causing vascular occlusion and consequently resulting in extensive tissue necrosis [7]. Impaired delivery of the antifungal drug to the site of infection because of vascular thrombosis and limited aggressive surgery because of complex anatomy of rhino-orbital region cautions for early diagnosis and aggressive management of these patients.

Many case studies have revealed the involvement of nasal, paranasal sinuses orbit and sometimes cerebral tissue by mucorales in patients with diabetes or aspergillus in patients on dialysis with high morbidity and mortality. We present the complete profile and treatment outcome of sporadically 10 fungal cases and an atypical bacterial case in our tertiary care teaching centers.

### Case Reports

#### Case 1

9 yrs old male patient was on dialysis presented with complain of headache fever and visual deterioration. During his stay in the hospital he had undergone complete workup in terms blood biochemistry septic profile and Magnetic resonance imaging which revealed as frontal lobe lesion. Frontal craniotomy and excision of frontal mass was done and biopsy showed fungal lesion and isolation of *Aspergillus*. Hence patient was kept on antifungal medications after consultation by infectious department and continued for about five years in two phases. In the Initial phase amphotericin B was given in the ICU setting and after couple of weeks therapy due to emerging toxic effects of drug patient was kept on itraconazole for a about five year in close follow up. Later on he developed hydrocephalus and was treated by performing diversion procedure.

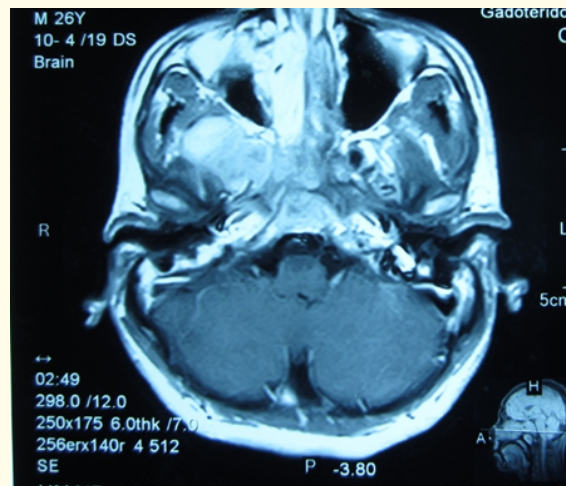
#### Case 2

26 years old male patient presented with complain of headache, proptosis right eye and diminution of vision. Magnetic resonance imaging revealed parasellar mass extending in the orbit with the invasion of paranasal sinuses. He was kept on itraconazole for a period of 9 months within a phase of two to three months he responded well in terms of resolution of proptosis and improvement in symptoms. He stopped taking anti-fungal medications and lost to follow up. Then he reappeared with limping gait after a period of 4 to 5 months secondary to persistent signs and symptoms subsequent to discontinuation of anti-fungal treatment. Repeat scanning revealed expansion of lesion and involvement of brain stem hence the patient was again kept on antifungal treatment (itraconazole) with more vigilance and close follow ups. Patient responded well in terms of improvement of gait within the period of 6 months to one year.

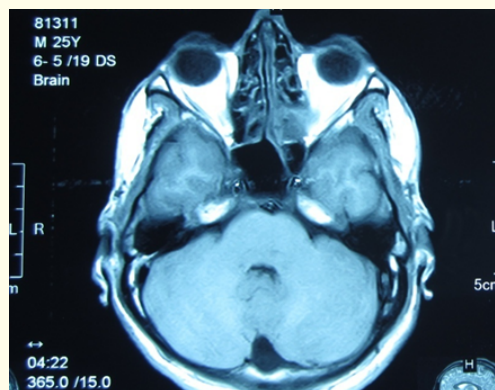
#### Case 3

8 years old girl presented with complaint of fever, headache and fits. On enquiry there was a history of fall from stairs. MRI brain revealed right occipital uneven rim enhancing lesion. After optimization of patient, informed consent was obtained.

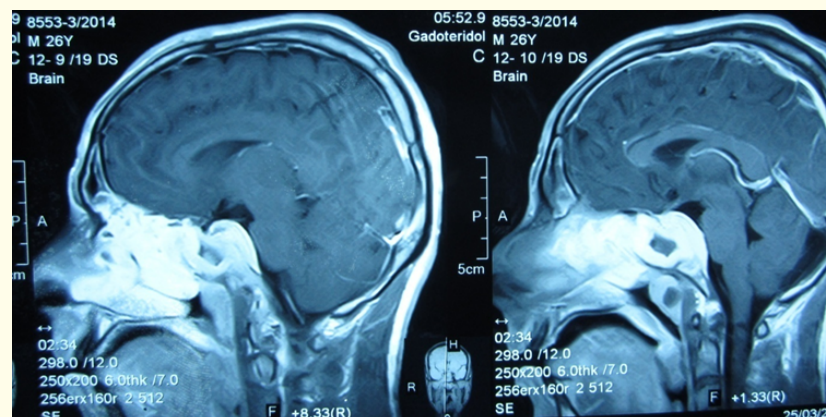
There after the lesion was accessed by proper right occipital broad based craniotomy, frank yellow colored pus was drained after localization of lesion by the help of brain needle and the debris cavity was identified and washed with antibiotic mixed saline multiple times. After homeostasis closure was performed. Pus was sent for gram stain AFB culture and fungal smears. Tissue was also sent for histopathology. Results revealed bacteria growth and sensitive antibiotics hence patient was kept on antibiotics accordingly for a period of more than 3 months with uneventful recovery. The patient remains in close follow up for more than 3 years without any recurrence.



**Figure 1:** Pre-treatment imaging filling ethmoid and sphenoid sinuses.



**Figure 2:** Post treatment imaging showing clear ethmoid and sphenoid sinuses.



**Figure 3:** Pre-treatment of same patient with involved all sinuses extending up to clivus and brain stem.



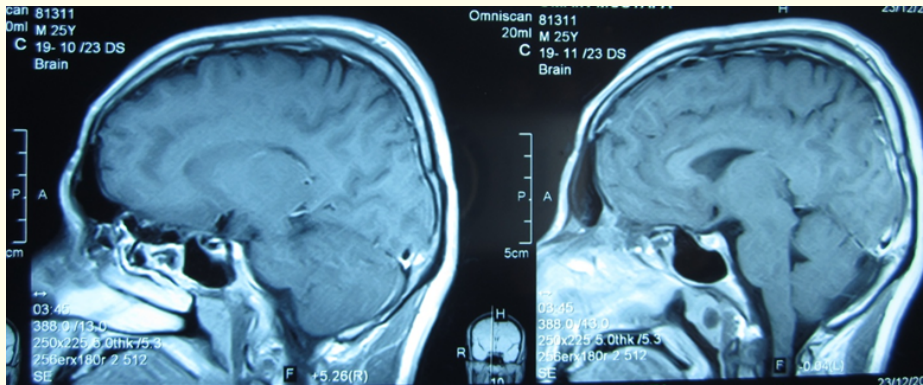


Figure 4: Post treatment of same patient clearance of pathology from all involved areas.

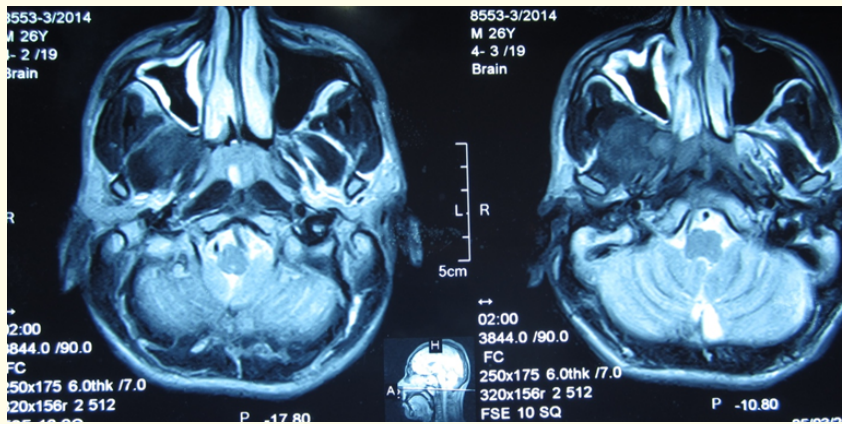


Figure 5: Pre-treatment involved maxillary sinus

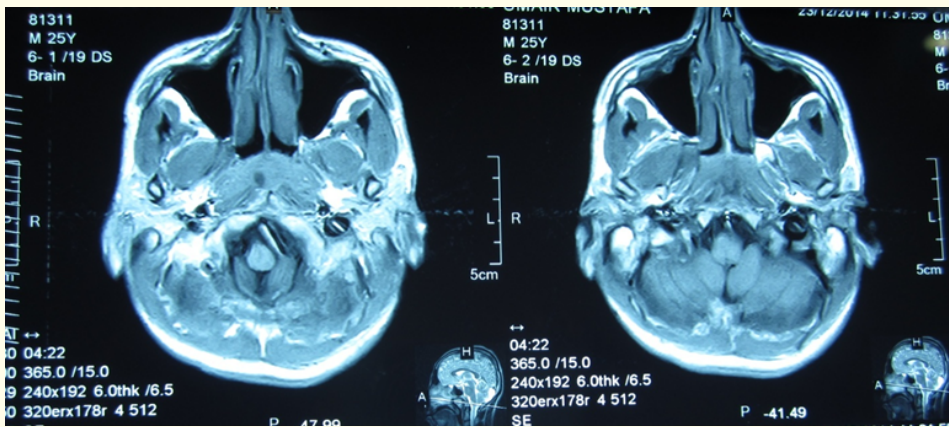


Figure 6: Post treatment clear maxillary sinus.

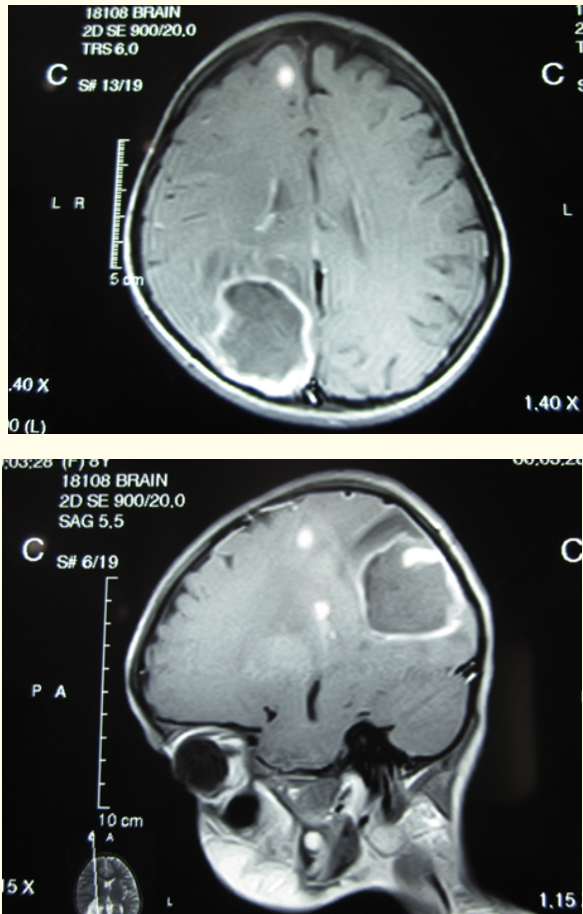
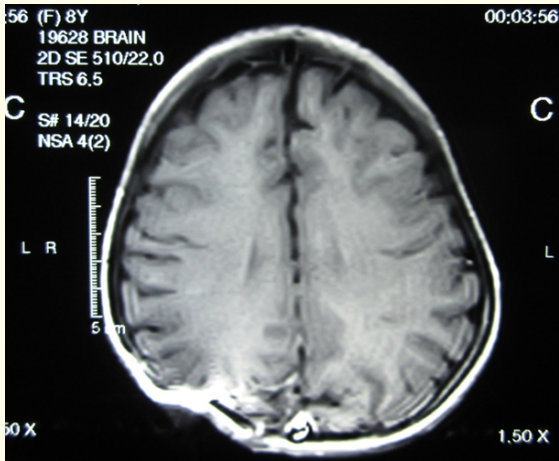
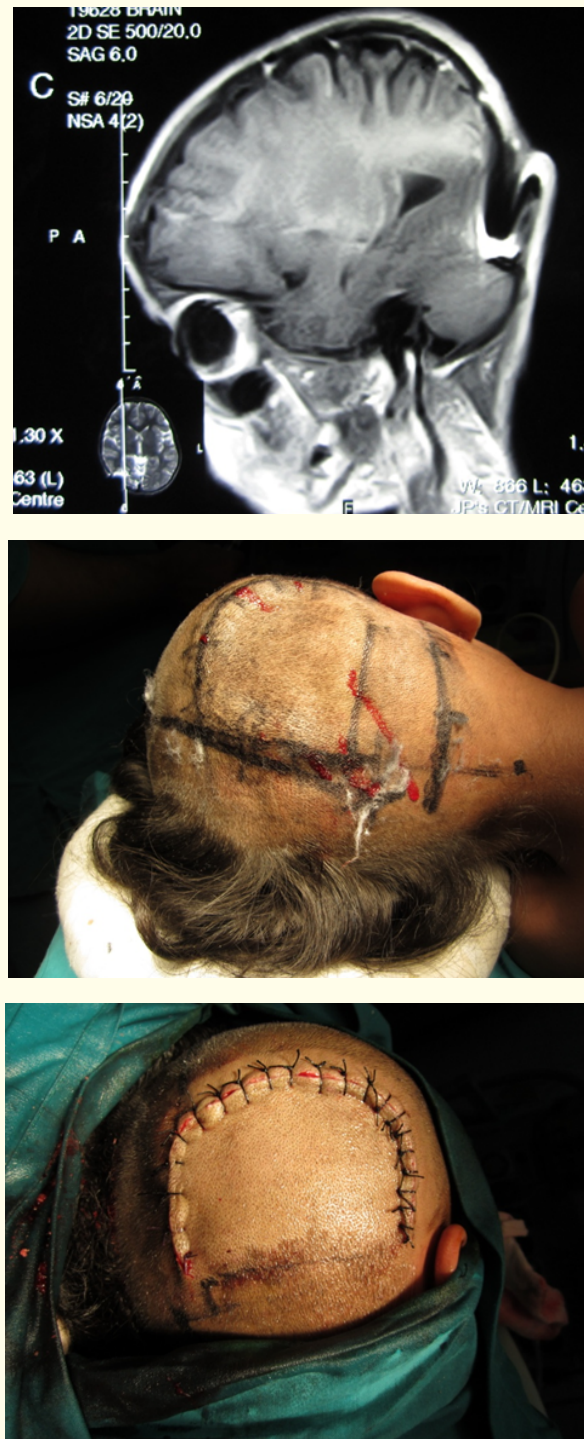


Figure 7: Pre intervention occipital uneven rim enhanced lesion.





**Figure 8:** Post intervention excision of lesion with resolution of lesion.



## Discussion

In the view of these findings, we reviewed the clinical courses of ten assessable patients based on MRI and CT scan clearance along with clinical improvement, unchanged and worsening status. All these patients were kept on itraconazole due to tentative diagnosis based on MRI findings like involvement of nasal, para-nasal sinuses, intracranial extension or rhino-orbital penetration. In one of ten patients the combination of amphotericin B and itraconazole was given pre-operatively by the consultation of infectious disease department. The prompt neurosurgical intervention results in eradication of intracranial fungal abscess with isolation of *Aspergillus* and subsequent development of hydrocephalus which was dealt by the help of diversion procedure. That vary patient was kept on antifungal therapy for prolong period.

In 3 of 10 patients single itraconazole therapy along with close follow up and monitoring successfully eradicated the mycosis with improvement of clinical symptom. Although one patient developed relapse due to abrupt discontinuation of antifungal therapy (itraconazole) after resolution of symptoms, hence he was offered a combination therapy of flucytosine and itraconazole. He had also attained complete recovery. Before prescribing flucytosine the whole workup for immunocompromised status was done including cbc, septic profile (ESR CRP), LFT and HIV screening. On enquiry that patient was taking steroids for the purpose of body building. Remaining patients were kept on single itraconazole therapy and they responded well. Except two patients who could not survive due to sudden deterioration despite continuing anti-fungal treatment secondary to other factors like cancer. In the literature review it is well documented due to severe adverse effects of different anti-fungal medications it is always necessary to monitor drug levels [8-11] if needed, more over Alt, Ast, Alkaline phosphatase, anemia, granulocytopenia and thrombocytopenia should also be considered while continuing flucytosine therapy [12,13].

Due to the aforementioned monitoring adverse effects and multiple risk involvement we had to discontinue flucytosine. Moreover, the availability of flucytosine was also become difficult for single patient of our series.

In this study, there was a limited usage of flucytosine as it was offered to only single patient due to relapse of disease and immunocompromised status confirmation. Hence some larger studies will be more appropriate in deciding the cause and effect of application of this combination antifungal therapy.

In the literature review it is well documented that intracranial fungal masses can be seen at any age but most patients are in the third, fourth and fifth decades of life. There are reported cases in neonates, infants and young children [14].

The duration of symptoms can vary from days to several months or even years [15-17].

The clinical presentation can be categorized in to three groups:

1. Involvement of cranial nerves 1 to 6,
2. Focal neurological deficit,
3. Stroke like presentation with sudden onset of hemiparesis.

There are other possibilities like altered sensorium and seizures. Rarely, patients with fungal aneurysm present with subarachnoid hemorrhage. Fever has also been observed with Intracranial fungal masses but in only 10 - 31% of patients [18].

Based on the presence or absence of radiological evidence of CNS disease. IFM were in to two types 1. Rhino cerebral type 2. Pure intracranial type further divided in to intra cerebral or extra cerebral form.

Moreover, some of the patients with intracranial fungal masses also presented with fever ranging 10 - 31% of patients. While in our series we could find out such clinical picture among few cases.

The largest case series reported to date has 40 patients gathered over 22 years from four centers one in India and the other in the United States [15].

Even in the afore mentioned research article it is demonstrated that due to the reason of immunocompromised issues fungal infection rate is increasing as compared to previous era. Moreover, it is also well documented that despite having large series of patients in a long span period of time, management of intracranial fungal granuloma has not been standardized. Although anti-fungal medication is the primary treatment but the role of surgery in terms of minimally invasive biopsy, craniotomy (open excision biopsy), FESS (fibro-optic endoscopic sinus surgery) and ventriculo peritoneal shunt placement is mandatory in selected cases and produces rewarding outcome. The duration of antifungal antibiotic therapy has not been clearly elucidated in the literature. This article will be helpful in reviewing the prognostic factor and outcome based role of surgery reported in literature. It may give an idea as to how long the antifungal treatment should be continued if the literature review high lights this aspect of the challenging rare disease.

In our case series we had continued anti-fungal therapy for about 1 to 5 years depending on the clinical response and radiological images resolution of the disease, more over some large clinical trials would be more beneficial in addressing about duration of therapy.

High mortality and morbidity have been uniformly reported in almost all series of patients with intra cranial fungal granuloma. The mortality rate of 63 percent was reported by Dubey, *et al.* [15] in their series of 40 patients with intracranial fungal masses. Two third of patients had predisposing illness (diabetes, tuberculosis, renal transplant and dialysis). Mortality in immunocompetent patients with intra cerebral aspergillosis was 66.7% in the series reported by Siddiqui, *et al.* [17], while in our series of 10 patients we found 20% mortality.

Similarly, in our small case series of 10 patients over the time span of approximately 9 years. We found that one was reported Rhino cerebral type with frontal lobe involvement and *Aspergillus* species was the causative agent. Who required abscess drainage by proper craniotomy and subsequent ventriculoperitoneal shunt placement due to post craniotomy development of hydrocephalus. Afterwards the patient was kept on prolong antifungal therapy along with short duration initial phase of combination amphotericin B antifungal therapy in Intensive Care Unit setting. While in rest of cases, temporal lobe, frontal lobe, seller and para seller areas were found to be involved on imaging

### Conclusion

Early diagnosis, risk versus benefit assessment oriented surgical decompression and prophylactic anti-fungal course according to variability of case with prompt initiation of antifungal therapy showed better outcome. Preoperative oral administration of itraconazole therapy improve clinical outcome in patients with aspergillosis. Larger prospective clinical studies are required to make firm clinical therapeutic recommendations.

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