

Case Series:

Intracranial Mass Lesion Due to Fungal Infection: A Case Series and Review of Literature



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ABSTRACT

Background and Importance: Fungal infections of the Central Nervous System (CNS) usually present as subacute meningitis or intracranial space-occupying lesion with mass effect on surrounding structures and consequent focal neurological deficits. Intracranial fungal granulomas are often misdiagnosed clinically and radiologically as neoplastic lesions. Biopsy of the lesion is the only reliable technique to establish the correct diagnosis as well as to detect the causative fungal species. Voriconazole (VZ) is a broad-spectrum triazole antifungal agent. It can be given orally and intravenously and has lesser adverse effects.

Case Presentation: In this article, we report a series of 6 cases of biopsy-proven fungal granuloma with varied clinical and radiological presentations who were given treatment with voriconazole for 6 months and demonstrated favorable response. Out of 6 patients (4 males and 2 females), 1 was immunocompromised Diabetes Mellitus (DM) with uncontrolled hyperglycemia). Headache was the most commonly observed symptom. Paranasal sinus and anterior cranial fossa were the most commonly affected site. Four patients received voriconazole therapy for 12 months and 1 received the same for 6 months before showing clinical resolution of disease. There was 1 death in the study group from non-related medical complications.

Conclusion: Our series focuses on the correct diagnosis of fungal granuloma which can be achieved by biopsy and clinical evidence of the efficacy of voriconazole against intracranial fungal granuloma.

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Highlights

- Intracranial fungal infections frequently masquerade as neoplastic lesions.
- Paranasal sinus infection with contiguous spread to the intracranial compartment is the most common pattern.
- Biopsy is essential to establish the diagnosis.
- The mortality rates seen in the literature review vary from 15% to 95%.
- Multimodality approach consisting of conservative surgical debridement with anti-fungal chemotherapy produces favorable results (mortality rate 18%).

Plain Language Summary

Fungal infection of the central nervous system is an increasingly common entity not limited to the immunocompromised population. The clinical and radiological presentations are unremarkable and biopsy is the only way to establish the diagnosis. The prognosis of the disease is generally poor with no standard recommended treatment protocol. Multimodality treatment consisting of surgical debridement of the fungal mass lesion with intravenous followed by long-term oral voriconazole therapy provides favorable results.

1. Background and Importance

Fungal infection of the central nervous system is a relatively rare entity, commonly seen to occur in groups with compromised immune status [1]. Organ transplant recipients, patient on chemotherapy, intensive care unit hospitalization, comorbid condition, and hematological malignancies predispose the patients to acquire intracranial fungal infection and may increase the morbidity and mortality. Intracranial fungal infections are seen in all age groups but most commonly occurs in the 3rd to 5th decades of life. The clinical presentation can be varied and non-specific but they are broadly classified into 3 clinical subtypes depending on the nature of the disease [2-4]:

1. Involvement of cranial nerves I-VI with sinonasal and orbital symptoms.
2. Focal neurological deficits due to the involvement of Central Nervous System (CNS).
3. Stroke-like syndrome with acute onset hemiparesis.

These patients can also present with features suggestive of raised intracranial pressure, seizures, altered sensorium, and meningoencephalitis. Meningitis is the most frequent presentation of CNS fungal infections but filamentous fungal infections cause granuloma or brain

abscess more commonly than meningitis [5]. Zygomycetes and *Aspergillus* may invade blood vessels, leading to thrombosis [6]. Although mechanical barriers protect the CNS against fungal invasion, it can cause CNS infection through 3 different routes:

1. Hematogenous spread from the remote extracranial focus;
2. Direct extension from sinonasal disease ;
3. Iatrogenic inoculation by neurosurgical procedure [7].

The most common risk factor for intracranial fungal infection is uncontrolled diabetes with most infections spreading from a contiguous site. Fungal granuloma is the most common pathological finding seen with these lesions [8]. Aspergillosis, mucormycosis, cryptococcosis, and candidiasis are common fungi causing intracranial granuloma [9, 10].

Understanding the radiological appearance of Central Nervous System (CNS) fungal infections is indispensable because early diagnosis helps to plan appropriate and timely treatment strategy which otherwise can prove to be a fatal diagnosis [11]. Even though classical teaching suggests that aggressive surgical management of Intracranial Fungal Mass (IFM) is associated with a better outcome, radical surgery might not always be feasible due to the location of IFMs in deep or eloquent regions

or contraindicated due to poor general condition of patients [2, 12-14, 15]. Siddiqui et al. had also suggested that a more conservative approach can be an equally good alternative with comparable results [16].

IFMs are commonly caused by Aspergillosis, Histoplasmosis, Blastomycosis, Mucormycosis, Cryptococcosis, etc. Aspergillosis and mucormycosis initially colonize paranasal sinuses from where they spread and invade CNS and infect the subjacent meninges and brain parenchyma producing frontal-temporal IFMs. Hematogenous spread of other fungi from their primary focus commonly produce parietal granulomas. Small IFM can be managed with antifungal chemotherapy (amphotericin B, voriconazole (VZ), or other newer agents) along with supportive care. However, large lesions causing mass effect are subjected to surgical treatment. The mortality of intracranial fungal granulomas has been reported to be as high as 63% [17, 18]. Squash cytology has been an extremely useful tool for intra-operative decision-making due to the problems with frozen sections in neuropathology [19].

Fungal granuloma on MRI is characterized by a thin peripheral “weak ring” enhancement with reduced diffusion restriction [20]. In some cases, enhancement may even be absent.

Amphotericin B remains as one of the most efficacious and commonly used broad-spectrum antifungals. But due to its extensive list of side effects and limitations, the azole group of antifungal medications are being increasingly used as first-line therapy. Their main advantages being ease of administration, high bioavailability, water-soluble, low protein binding, relatively low toxicity, and longer half-life. Triazoles demonstrate a broad-spectrum activity against most of the commonly encountered pathogenic fungal species, e.g., *Aspergillus*, *Blastomyces*, *Candida*, *Cryptococcus*, *Coccidioides*, *Histoplasma*, etc.

Voriconazole is a broad spectrum second-generation triazole antifungal which has potent activity against Aspergillosis. It acts against various fungi including *Aspergillus* species [21]. It is available as oral and Intravenous (IV) preparation. It has a bioavailability of 95% with distribution into most of the body fluids including CSF (cerebrospinal fluid). It rapidly attains high CSF concentration (0.08-3.93 µg/ml) in patients with fungal meningitis (CSF: serum ratios= 0.22-1) [22]. It has fewer adverse effects like photopsia, rash, and hepatitis. Its efficacy against Aspergillosis has been reported to be better than amphotericin in terms of clinical response rate, survival, safety, and tolerability [23].

2. Case Presentation

This retrospective study included symptomatic patients diagnosed with intracranial fungal granuloma on histopathology presenting to our neurosurgical department between 2015 and 2018. The patients underwent radiological evaluation using CT and MR imaging and a treatment plan was formulated. The patients were initially planned to undergo surgical treatment to achieve gross total excision. In a case where the aim of gross total excision could not be realized due to difficult access or proximity to eloquent regions, surgical decompression of lesion with biopsy was done. After confirmation of fungal pathology in the histopathology report, the following voriconazole treatment regimen was started: injection voriconazole IV for 2 weeks, starting with 3 mg/kg at 12-hour intervals followed by oral voriconazole in a dose of 200 mg twice a day for 6 to 12 months [24]. Patients were followed up monthly with clinical assessment and routine blood investigations. At the 6-month post-operative interval, a radiological assessment was done besides routine follow-up.

A total of 6 patients were enrolled in the study, out of whom 4 were males and 2 females with ages ranging from 10 to 55 years. All were immunocompetent except a single patient (case 5, Table 1) who was suffering from diabetes mellitus with uncontrolled hyperglycemia. All patients had non-specific neurological symptoms and signs referable to IFM. The patients' characteristics, clinical, and radiological findings are summarized in Table 1, Figure 1 and Figure 2. Headache was the most common symptom seen in all 6 patients. Other commonly seen symptoms were nasal obstruction in 3 patients, vomiting in 3 patients, fever in 2 patients, hemiparesis in 1 patient, papilloedema in 3 patients, ptosis, and vision loss in 1 patient each. The histopathology was s/o aspergillosis granuloma in 4 out of 6 cases with 1 reported case each of mucormycosis and cryptococcus. The most commonly affected areas were the paranasal sinus and anterior cranial fossa.

Voriconazole treatment regimen was started for all the cases according to the defined treatment protocol and the decision to continue the same was guided by the clinical response. One patient died after 3 months of surgery from the complication of his medical morbidity. The evaluation was repeated for the rest of the patients at 6 months and a further treatment plan was decided accordingly. Oral voriconazole was continued for another 6 months for those patients suffering from rhinocerebral variant of the disease. However, 1 patient with intracerebral disease showed good clinical and ra-

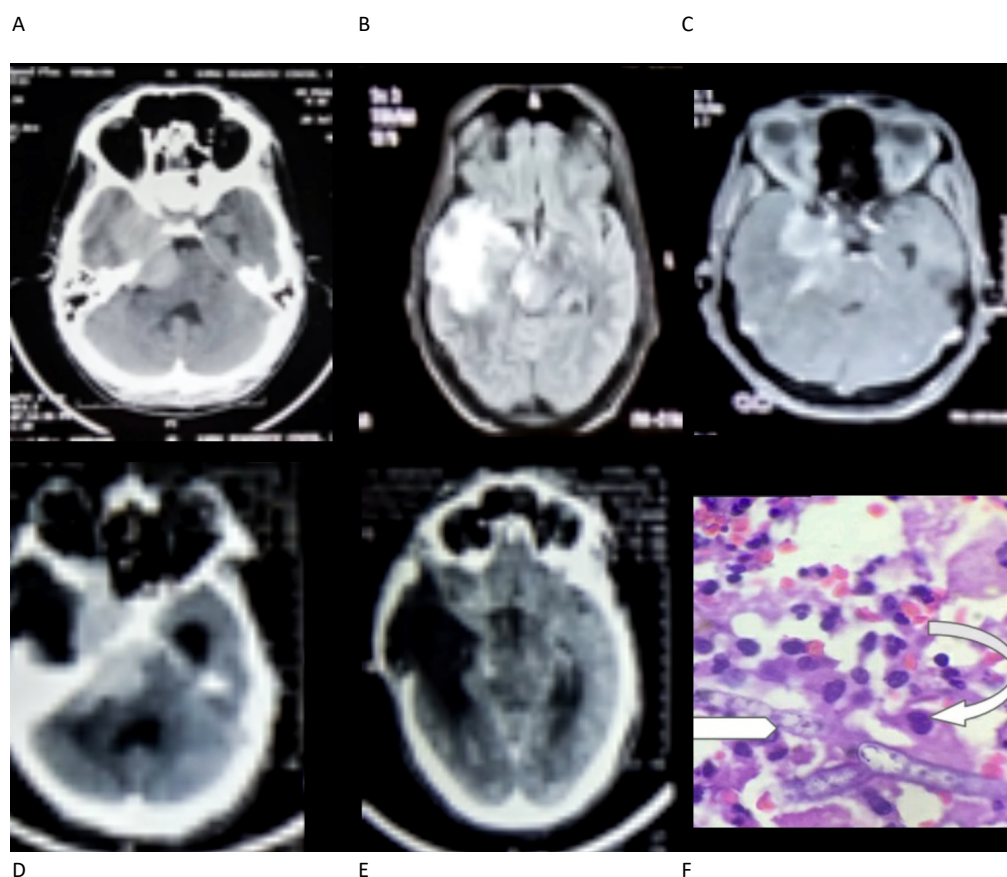


Figure 1. A 38-year-old male patient presented with a non-specific headache with no neurological deficit



A. Head CT showing revealed large soft tissue mass near the lesser and greater wing of sphenoid extending into the right cavernous sinus, middle temporal fossa and sphenoid sinus causing mass effect on the right temporal lobe; B. FLAIR image showing hyperintense signal in a right temporal region extending to a suprasellar and crural cistern; C. T1-contrast enhanced MR sequence showing mild peripherally enhancing mass in the right temporal and petroclival region; D. Post-operative head CT showing a hyperdense lesion in right side medial temporal region and petroclival region; E. Repeated head CT performed at 6 months showing radiological resolution of the fungal mass; F. Histopathological examination showing necrosis, inflammatory cells, giant cells with fungal hyphae (straight arrow) and spores (curved arrow).

diological response hence received only 6 months of voriconazole therapy.

3. Discussion

CNS fungal infection (IFMs, granulomas, and abscesses) is an uncommon entity but it is being increasingly seen in clinical practice possibly because of rising cases of Human Immune deficiency Virus (HIV) infections, increasing survival of organ transplant patients with the use of immunosuppressants and immunomodulators, cancer chemotherapy and the ever-increasing numbers of Diabetes Mellitus (DM) patients. Based on the radiological involvement of the paranasal sinus, IFM can be classified into:

1. Rhinocerebral;
2. Purely intracranial.

This can further be divided into:

1. Intra-cerebral (intraaxial),
2. Extra-cerebral (extraaxial) [2].

In our study, fungal granulomas were more commonly found in an immunocompetent patient with only 1 patient suffering from DM. Our findings correlated with those reported in other studies which also found 50% of IFG patients without evident association with predisposing conditions or any evidence of immunosuppression [2, 12-14, 16, 25]. In a study done by Naik et al., the majority of the 66 patients had no predisposing illness [24].

The mean age of our patient was 35.33 years which is almost similar to 40.2 years, 32.5 years, and 28 years reported by Mishra et al., Naik et al., and Sharma et al., respectively in their studies [2, 24, 25]. The clinical

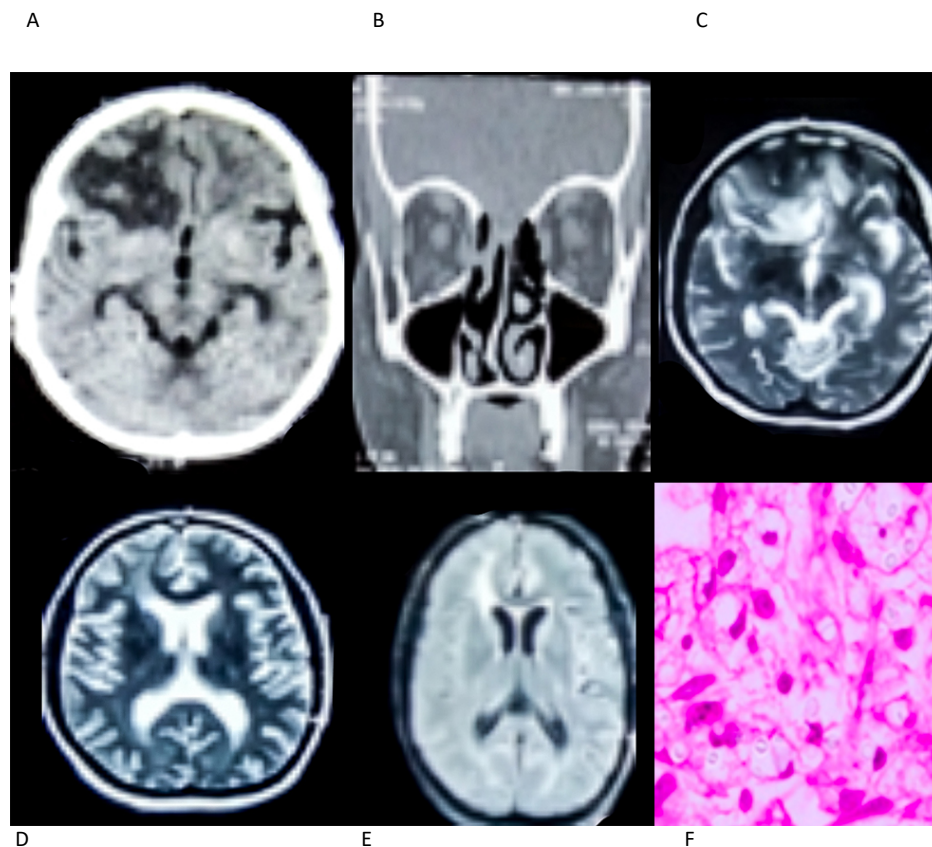


Figure 2. A 35-year female presenting with headache, vertigo, and vomiting

A. CT head showing hypodense lesion with small specks of hyperdensity present in right frontal region; B. CT PNS showing erosion of skull base in the ethmoid region with extension to the nasal cavity; C. T2 MRI sequence showing a heterogenous predominantly hyperintense lesion in the right frontal region; D and E. Voriconazole chemotherapy was started following endoscopic endonasal biopsy. MRI imaging was done at 6 months interval showing altered intensity in the right frontal region, resolution of lesion size compared with the pre-operative scan; F. Histopathological section with H&E stains showing necrosis and yeast structure of *Cryptococcus*.

presentation (headache, vomiting, and cranial nerve involvement) was also found to be similar to that reported in the literature [12]. Anterior cranial fossa and Paranasal Sinus (PNS) were similarly found to be the most common site of involvement probably due to the proximity of the PNS and frontal base [2, 12, 24].

Aspergillosis was found to be the most common fungal organism in our study, similar to other previous studies [2, 8, 12, 24]. *Aspergillus* spores can be found in both air and soil and they spread via the inhalational route to the sphenoid and paranasal sinus. Consequently, gardeners and farmers have increased chances of exposure to those spores leading to a higher incidence of disease in that population. Patients with impaired drainage and clearance of sinus due to occlusion of their natural ostia are thought to be more susceptible to infection [19].

Jamjoom et al. reported on a possible relationship between IFM and snuff abuse. In immunocompetent pa-

tients, inhalation and snorting opium is a defined risk factor [13]. In our series, 4 out of 6 patients were rhinocerebral type and 2 were purely intracranial (Table 1).

The radiological findings of IFM in our series were not consistent (Table 1). There is always a diagnostic dilemma with these lesions, they may mimic intracranial neoplasms (Table 2). Differential diagnosis of intracranial fungal granulomas includes brain metastasis, brain abscess, infarction, toxoplasmosis, demyelinating disease, and enlarged perivascular space. The rhinocerebral fungal granuloma is commonly associated with higher morbidity and mortality probably due to insufficient penetration and concentration of antifungal drugs in the granuloma because of a thrombotic blood vessel. Moreover, the anatomy of the rhino-orbito-cerebral region with the resulting exposure and access makes radical surgery difficult [28]. In our study, there was 1 mortality, intracerebral IFM due to associated co-morbid conditions. Kourkoumpetis et al. suggested that patients who underwent surgical excision achieved better out-

Table 1. Summary of presentation of intracranial fungal disease with treatment received and histopathology report

No.	Age/Sex	Site of Lesion	Type of Lesion	MRI Features	Intervention Done	VZ GIVEN*	Histopathology Report
1	38Y/M	Right sphenoid sinus, right cavernous sinus, and middle cranial fossa	Rhinocerebral	T1 isointense T2 hypointense Contrast enhancing	Endoscopic endonasal trans-sphenoidal decompression f/b transcranial excision with MPVP shunt	Yes 3 mg/kg IV for 2 weeks followed by 200 mg BD for 1 year	Inflammatory granulation tissue with hyphae and spore s/o aspergillosis
2	35Y/F	Right ethmoidal and bilateral frontal sinus and anterior cranial fossa	Rhinocerebral	T1 hypointense T2 isointense Non-enhancing on contrast	Endoscopic endonasal biopsy	Yes 3 mg/kg IV for 2 weeks followed by 200 mg BD for 1 year	Hydrated thick capsule s/o cryptococcus
3	40Y/M	Left ethmoidal sinus and anterior cranial fossa and left cavernous sinus	Rhinocerebral	T1T2 Isointense	Endoscopic endonasal biopsy	Yes 3 mg/kg IV for 2 weeks followed by 200 mg BD for 1 year	Long, narrow, septate branching fungal bodies s/o aspergillosis
4	34Y/M	bilateral ethmoidal sinus and left cavernous sinus	Rhinocerebral	T1 hypointense T2 hyperintense enhancement on contrast	Endoscopic endonasal biopsy	Yes 3 mg/kg IV for 2 weeks followed by 200 mg BD for 1 year	Broad pleomorphic hyphae that branch at right angle s/o mucormycosis
5	55Y/F	Right parieto-occipital lobe	Intracerebral	T1, T2 hyperintense contrast enhancement present	Right parieto-occipital craniotomy with gross total excision	Yes 3 mg/kg IV for 2 weeks followed by 200 mg BD for 3 months (died)	Chronic inflammatory cells with fungal hyphae and spore s/o Aspergillosis
6	10Y/M	Left cerebellar hemisphere	Intracerebral	T1 isointense T2 hyperintense Peripheral contrast-enhancing	Left suboccipital craniectomy with gross total excision	Yes 3 mg/kg IV for 2 weeks followed by 200 mg BD for 6 months	A large number of hyphae with angulation and spore s/o aspergillosis



comes than those receiving only medical treatment [29]. Therefore, timely diagnosis and management in these patients are imperative to achieve a better outcome [29, 30].

We adopted a multimodality management approach for our patients- surgical excision followed with long-term anti-fungal chemotherapy with voriconazole guided by the clinical and radiological response. Open

craniotomy is the preferred approach for suspected IFMs that are in relatively accessible and non-eloquent regions of the brain when a radical excision is expected to be feasible and safe. In the case of rhinocerebral type of disease, endonasal biopsy is a feasible alternative. In our series, 4 patients were subjected to endonasal biopsy and the remaining 2 were treated with craniotomy and excision. One patient from the endonasal biopsy

Table 2. Differential diagnosis of IFM with their differentiating features

Differential Diagnosis	Radiological Features
Brain metastasis	Thicker ring enhancement: usually no reduced diffusion in the necrotic center
Infarction	Gyral enhancement or no enhancement: distribution conforms to a vascular territory
Bacterial abscess	Thicker ring enhancement: reduced diffusion in the necrotic center
Toxoplasmosis	Thicker ring enhancement: usually no reduced diffusion in the necrotic center
Demyelinating lesion	Incomplete ring enhancement: usually no reduced diffusion or leading-edge reduced diffusion
Enlarged perivascular space	No enhancement, characteristic distribution



group later presented with an intracranial extension of granuloma with a mass effect which was managed with craniotomy and surgical excision. Post-operatively, voriconazole was given as the primary antifungal agent to all patients. Intracerebral fungal infections showed a good clinical response within 6 months compared with rhinocerebral infection which demonstrated resolution with 12 months of voriconazole therapy.

Satisfactory clinical response was observed in 5 out of 6 patients with single mortality. The literature review on mortality in IFM shows a declining trend over time. In 1985 Yanai et al. and Young et al. reported a mortality rate of more than 95% and 62.8%, respectively [31, 32]. Similar rates were reported by Dubey et al. in 2005 (65%) and 36.4% by Naik et al. in 2015 [12, 24]. Siddiqui et al. in his series reported lower mortality of 15% which is similar to our study [32]. The improving trend in overall mortality is possibly due to better imaging modalities and improved resolution leading to early diagnosis with consequent early and aggressive multimodality treatment.

4. Conclusion

Intracranial fungal granulomas are uncommon intracranial space-occupying lesions having a wide spectrum of presentation from rhinocerebral to purely intracranial IFM. Radiologically, they are a heterogeneous group of a lesion with variable features which can mimic neoplastic lesions in immunocompromised as well as immunocompetent subjects. Surgical excision with histopathological confirmation is done when feasible followed by long-term antifungal chemotherapy with oral voriconazole. The sole endoscopic endonasal procedure with decompression and biopsy of the lesion may be a viable alternative if followed by appropriate antifungal treatment to ensure a good treatment outcome.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed about the purpose of the research and its implementation stages. Written informed consent was obtained from all participants.

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Authors' contributions

Conceptualization and supervision: Ashok Gandhi, Sapna Gandhi, Shashikant Jain; Methodology: Ashok Gandhi, Sapna Gandhi, Shashikant Jain; Original draft and writing: Keshav Mishra, Surrendra Jain; Review & editing: All authors; Data collection: Keshav Mishra, Surrendra Jain; Data analysis: All authors.

Conflict of interest

The authors declared no conflict of interest.

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