

COVID-19-associated rhino-orbital-cerebral mixed mycoses with intracranial fungal granuloma – An aggressively managed rare entity

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Rhino-orbital-cerebral mucormycosis (ROCM) with intracranial extension is a fatal disease. A case of extensive ROCM, with rare intracranial fungal granuloma, seen in a COVID-19 positive young male is described. A successful therapy consisting of a multidisciplinary approach for sinuses debridement, orbital exenteration, and intracranial granuloma excision was done. Nonseptate hyphae of Mucor and septate filamentous Aspergillus grew concurrently from exenterated orbital specimen.

Key words: Aspergillus, intracranial fungal granuloma, Mucor, rhino-orbital-cerebral mucormycosis

Rhino-orbital-cerebral mucormycosis (ROCM) is a rare fulminate fungal infection recognized since a century, primarily in immune deficient with an underlying pathology.^[1] Incidence rate of this

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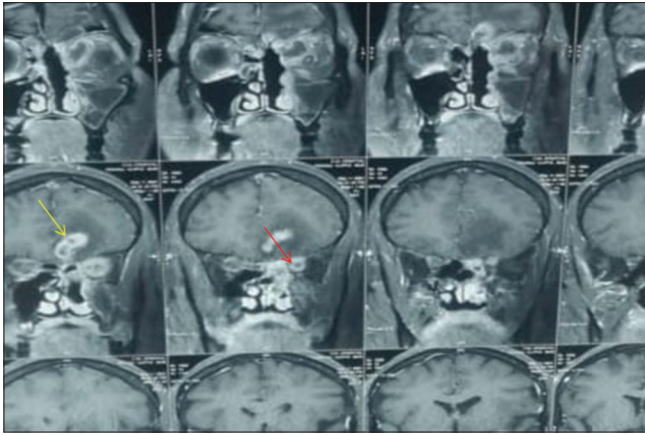


Figure 1: Coronal T1-weighted MR scan shows inhomogeneous enhancing mass in the left basifrontal region (yellow arrow) and supero-medial part of the left orbit (red arrow)

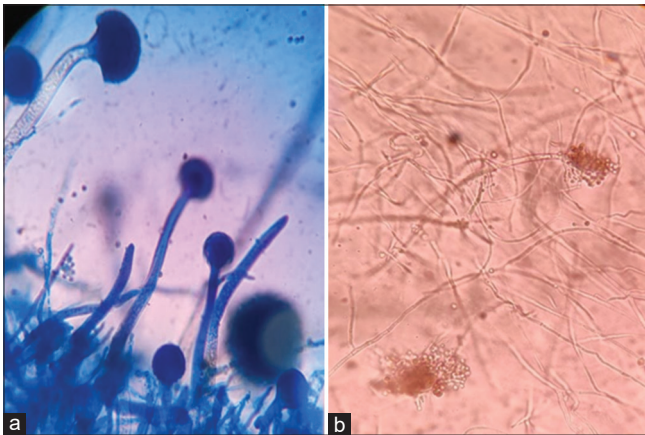


Figure 2: (a) Lactophenol cotton blue staining shows broad aseptate hyphae with aggregation of spongiospores consistent with *Mucor*. (b) KOH mount shows acute angled branching septate hyphae and conidia consistent with *Aspergillus*

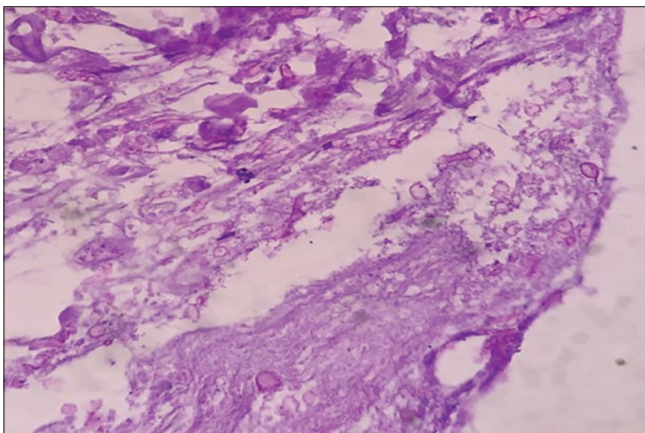


Figure 3: Histological sections of intracranial granuloma show extensive inflammatory cells with fungal colonies. PAS stain highlighted the thinned septate hyphae of *Aspergillus* spp

rare infection has risen to a worrisome scale in COVID-19 era. India contributed to large number of COVID-19-associated ROCM worldwide. A recently published large multicentric study

from India – COSMIC Report 1 – has studied the association of COVID-19 and ROCM vastly and determined risk factors as well as clinical profile.^[2] The disease once considered almost fatal has shown a steady climb in survival rate up to 47–75% with early diagnosis and prompt treatment.^[3] Nevertheless, intracranial progression of disease remains a poor prognostic factor.^[1] Among numerous manifestations, intracranial fungal granuloma (IFG) is a rare clinical entity. This case report describes an advanced case of ROCM with an IFG successfully treated with multidisciplinary intensive therapeutic strategies. Our objective is to highlight the survivability with aggressive treatment in case of intracranial involvement with IFG.

Case Report

A 36-year-old male presented with a complaint of bloody secretion from nose and vision loss in left eye since 2 days following discharge from hospital after 11 days stay for acute respiratory distress syndrome treatment. His past records revealed positive RT-PCR for SARS-CoV-2 and chest HRCT score 18 based on 25 points CT severity score assessment.^[4] He had received intravenous dexamethasone 6 mg once daily for 6 days, intravenous Remdesivir 200 mg on day 1 followed by 100 mg daily for 4 days, and intravenous Meropenem 500 mg thrice daily for 7 days. He had no prior comorbidity. He was not a known diabetic but had new onset of uncontrolled blood sugars (400 mg/dl) during the treatment for COVID-19. Glycemic control was achieved by initiation of oral hypoglycemic drugs. On comprehensive ophthalmic examination, the left eye had no perception of light, complete ophthalmoplegia, and disc pallor on fundoscopy. Right eye findings were unremarkable. Initial diagnosis was ROCM Stage 3c according to recent proposed staging.^[5] Anterior rhinoscopy and nasal swab sample culture confirmed mucormycosis. Contrast enhancing MRI imaging revealed densities in frontal, maxillary, and sphenoid sinuses bilaterally. Inflammatory changes in intraconal and extraconal tissues of the left orbit seen. Few nonenhancing areas of necrosis were noted in the left medial orbit. The basifrontal region of the brain had changes of acute infarct. The primary procedure including left-sided sinus debridement and left orbital decompression was done. Induction therapy with intravenous liposomal amphotericin B (L-AMB) 5 mg/kg body weight daily was started. Post 12th day of the treatment, the patient developed headache and seizures. Repeat contrast MRI showed progression of disease in sinuses, orbit, and brain extension. The superomedial region of the left orbit showed an abscess measuring 3.0 × 1 × 2.0 cm. The basifrontal region showed discrete heterogeneous contrast enhancing granulomatous lesion measuring 2.1 × 2.4 × 1.9 cm [Fig. 1]. Disease had progressed to stage ROCM 4c. In view of progression of disease, aggressive surgical treatment was planned. “Triple intervention” was carried out – craniotomy and stereotactic excision of granuloma by a neurosurgeon, orbital exenteration by an oculoplasty surgeon, and repeat sinuses irrigation by an otolaryngologist in similar order in the same sitting. Culture from orbital specimen showed both *Mucor* spp and *Aspergillus niger* [Fig. 2a and b]. The histopathology examination of excised frontal lobe lesion was suggestive of fungal granuloma having septate thinned fungus hyphae consistent with *Aspergillus* [Fig. 3]. Antibiotic and intravenous L-AMB therapy was continued for 3 weeks postoperatively. The patient is currently on concurrent

posaconazole regime. On serial follow-up for 2 months with radio imaging, the disease appeared regressed.

Discussion

The development of cerebral mucormycosis is cited as ominous complication of rhino orbital mucormycosis. The secondary invasion of CNS occurs through contiguous spread from the primary entry portal of paranasal sinuses. The direct local infiltration and intravascular propagation via network of valveless emissary veins gets the CNS involved in 70% of cases.^[3]

Fungal infections in the brain can simulate benign lesion, pyogenic abscess, or tumor and poses a diagnostic challenge to radiologists and clinician. In the present case, the frontal lobe infarct stand out as granulomatous lesion on subsequent radioimaging, well correlated with developing clinical symptom of headache and seizures. Zimmerman *et al.*^[6] documented the evolution of nonspecific cerebritis to an encapsulated brain abscess through serial radioimaging. The granuloma formation in the brain implies a relatively chronic confined condition and preserved host immunity rather than much deleterious meningoencephalitis seen in poor immune host. Histopathology of excised IFG documented hyphae of *Aspergillus* spp. alone. However, the exenterated orbital specimen had considerably significant growth of both *Mucor* and *Aspergillus* on culture. Although *Aspergillus* spp. is the most common recovered organisms from IFG followed by *Mucorales*,^[7] the mixed infection in orbit is of interest for its rarity. Combined infections in the rhino-oculo-cerebral region are described in Castleman disease and diabetes mellitus in the limited available literature; however, none in ophthalmic journal.^[8]

In the present case, the disease progressed in all related anatomical compartments despite continued systemic antifungal drug therapy and primary extensive sinus debridement. Brain involvement is a poor prognostic factors but an early aggressive surgical approach dramatically impacts the prognosis. Antifungal therapy alone may not be adequate in setting of substantial necrosis caused by mucormycosis angioinvasion. Moreover, fibrosis observed in *Aspergillus* granuloma has therapeutic relevance in limiting the penetration of systemically administered antifungal drug, thus necessitate its excision.^[9] The single-staged triple surgery in our case was a salvageable procedure aiming at reducing fungal load and improving antimicrobial penetration for obtaining local ROCM control. Case studies have reported better chance at survival with early radical surgery than the repeated subradical resection in ROCM with associated brain involvement.^[10,11]

Conclusion

An optimal outcome achieved with radical surgery in a case of ROCM with rare complication of IFG is reported here. Timely aggressive surgical intervention is a plausible approach in intracranial extended ROCM. The case is also unique in

reporting a combined *Mucor* and *Aspergillus* infection in orbit, not reported before from ophthalmic perspective.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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