Original Article

International Journal of Neurology and Neurosurgery
Volume 14 Number 3, July– September 2022
DOI: http://dx.doi.org/10.21088/ijnns.0975.0223.14322.7

Fungal Space Occupying Lesions in Brain after COVID-19: A Double Attack

Shripad S Pujari[1], Rahul V Kulkarni[2], Dulari Gupta[3], Kaustubh Dindorkar[4], Chandrashekhar Raman[5], Nilesh Palasdeokar[6], Rushikesh Deshpande[7], Bharat Purandare[8], Parikshit Prayag[9], Ameet Dravid[10], Sampada Patwardhan[11], Pradnya Jawalekar[12]

How to cite this article:
Shripad S Pujari, Rahul V Kulkarni, Dulari Gupta, et al./Fungal Space Occupying Lesions (SOLs) in Brain after COVID-19: A Double Attack/Int J Neurol Neurosurg.2022;14(3): 81-86.

Abstract

Context: COVID-19 predisposes to rhino-orbito-cerebral mycosis (ROCM) which can further form fungal space occupying lesions (SOLs) in the brain.

Aim: To study the clinico-radiological profile, type of fungus, response to treatment, outcomes and prognostic factors in patients with COVID-19 associated mucormycosis (CAM) who suffered fungal space occupying lesions (SOLs) in the brain.

Results: Twelve subjects with CAM and intracranial SOLs were studied. Brain scans were performed in all patients at rhino-orbital stage, even before appearance of brain symptoms. The localized pus collections manifested as either parenchymal abscesses (N=10) or subdural empyema (N=2). In addition to involving the brain adjacent to the rhino-orbital disease, abscesses were also seen to form in areas distant to the primary site of infection. Abscesses developed in two regions, in the midline at the base of the skull, around the cavernous internal carotid arteries or the basilar arteries and in the lateral frontal, parietal and occipital lobes. Mucormycosis was identified in all patients and dual infection with aspergillus was encountered in 25%. Treatment involved combination of anti-fungal agents and early excision surgery and the mortality was 33%.

Conclusion: Fungal abscesses form in the brain at sites contiguous to the rhino-orbital disease and also at distance sites via hematogenous route. These pus collections can be diagnosed early by screening the brain while undertaking the scan of orbits and paranasal sinuses. Mortality is high if pus spreads around the cavernous portion of the internal carotid or the basilar artery. Dual infection with mucorales and aspergillus can be seen. Early aggressive treatment can improve outcome and reduce mortality.

Keywords: rhino-orbito-cerebral mycosis (ROCM), pus collection, parenchymal abscess, subdural empyema, contiguous spread, hematogenous spread.

Key Message: Pus collections due to rhino-orbito-cerebral mycosis (ROCM) in patients with COVID-19 manifests as either parenchymal abscesses or subdural empyema. Abscess may spread contiguously to the adjacent tissue or via hematogenous route. Early and aggressive treatment can improve outcomes and reduce mortality.

Author's Affiliation: [1,2,3,7]Consultant Neurologist, Department of Neurology, [4]Consultant Neurosurgeon, Department of Neurosurgery, [8,9]Infectious Disease Consultant, Department of Infectious Diseases, [11]Microbiologist, Department of Microbiology, Deenanath Mangeshkar Hospital and Research Centre, Pune 411004, Maharashtra, India; [5]Consultant Neurosurgeon, Department of Neurosurgery, [6]Consultant Neurologist, Department of Neurology, [10]Infectious Disease Consultant, Department of Infectious Diseases, [12]Microbiologist, Department of Microbiology, Noble Hospital, Hadapsar, Pune 411013, Maharashtra, India.

Corresponding Author: Shripad S. Pujari, Consultant Neurologist, Department of Neurology, Deenanath Mangeshkar Hospital and Research Centre, Pune 411004 Maharashtra, India.

E-mail: drshripadpujari@gmail.com

Received on: 29.06.2022 **Accepted on:** 30.07.2022

INTRODUCTION

COVID-19 is a risk factor for rhino-orbito-cerebral mycosis (ROCM).[1-3] The cerebral involvement by the fungus presents as either space occupying lesions (SOLs), meningitis or cerebrovascular event.[4] We have come across SOLs that can be brain parenchymal abscesses or subdural collections. Abscesses may form at sites non-contiguous to the initial rhino-sino-orbital disease and subdural collections can appear in patients who have had initial sinus and/or orbital debridement surgery and are receiving anti-fungal therapy. Prior to the COVID-19 pandemic, very few case reports of mucormycosis causing intracranial SOLS have

been reported.[5-7] During the COVID-19 pandemic, there has been a spurt of COVID-19 associated mucormycosis (CAM) cases.[2-4,8] However only few single case reports of CAM causing intracranial SOLs have been published to date.[9-12] Thus, we present our experience of CAM causing intracranial SOLs from 2 centers in Pune in Western India. So far, India has reported the second highest number of COVID-19 cases in the world after the US.[13] The city of Pune has reported the second highest number of COVID-19 cases in India after the capital city of New Delhi.[14]

SUBJECTS AND METHODS

This was a prospective observational study conducted in 2 tertiary care private hospitals in Pune, Western India. The first hospital is a 900 bedded referral center for the state of Western Maharashtra which caters to around 4,00,000 out-patients and 68,000 in-patients being treated each year. The second hospital is a 330 bedded which serves around 1,90,000 out-patients and 13,000 in-patients each year.

Patients who suffered from CAM who went on to develop fungal SOL (pus collection) in the brain were included in the study. The study was conducted between March 2021 to February 2022. Information including demographics, risk factors for COVID-19 and fungal infection, clinical details during their admission for COVID-19 and fungal infection, investigations, medical and surgical treatment was collected. Outcome was described in terms of survival or death until end of February 2022. This study was approved by the institutional ethics committee (Ethics Committee Approval Number IHR_2020_Aug_RK_378). Since the data was completely anonymized, a consent waiver was granted.

OBSERVATIONS AND RESULTS

Clinical data, investigations and surgical treatment

Twelve patients (9 males and 3 females; age 34 to 73 years, mean: 50.75 years) who suffered COVID-9 associated Mucormycosis (CAM) and went on to develop fungal SOLs in brain as a complication of ROCM. Demographics, risk factors and details during admission for COVID-19 are presented in the Table 1. Four patients had pre-existing DM, three were newly detected DM and five had hypertension (HT) as pre-existing risk factors. The mean C reactive protein (CRP), ferritin and d-dimer values were 47.2 (<6 mg/L), 706 (20-263 ng/ml) and 596 (<198 ng/ml) respectively during their admission for COVID-19. Eleven had to be admitted for their respiratory symptoms whereas one was home quarantined and received oral steroid and favipiravir. The eleven admitted patients received supplemental oxygen, injectable steroids, remdesivir and two had to be also given tocilizumab.

Table 1: Baseline characteristics of patients during COVID admission

Characteristic	Number (N=12)	Percentage
Age	50.75 +/-12.5 (range 34-73)	
Sex	Male: 9 Female: 3	Male: 75, Female: 25
Risk factors		
Pre-Existing diabetes	4	33.3
New onset Diabetes	3	25
Hypertension	5	41.5
Investigations		
CT Chest	11 +/-4.17 (6-18)	
Mean CRP (mg/L)	47.2 +/-25 (3-97)	
Mean Ferritin (mcg/L)	706 +/-537 (222-2000)	
Mean D Dimer (ng/ml)	596+/-411 (164-1513)	
Treatment of COVID		
Supplemental Oxygen	11	91.7
Antivirals	Remdesivir 11, Favipiravir 1	91.7, 8.3
Steroids	12	100
Tocilizumab	2	16.7

Age, CRP, ferritin and d dimer values are expressed as mean along with standard deviation and ranges in the parentheses.

Table 2 displays clinical manifestations, investigations, treatment and outcomes during their admission for fungal SOLs in brain. Average interval between COVID-19 admission and second admission for fungal infection was 18 days. The important presenting symptoms in our patients were headache, orbital/ facial pain, focal neurological deficits (hemiparesis with/without aphasia) and symptoms related to the orbital apex and orbital involvement in the form of red eye, vision loss and ophthalmoplegia. Two patients also suffered ischemic stroke in the right centrum semiovale and left fronto-parietal areas, while evidence of meningitis, either in the cerebrospinal fluid (CSF) analysis or on a contrast brain MRI (meningeal enhancement) was a seen in four patients. Depending upon the location of pus collection, there were two types of presentations: brain parenchymal abscess (BPA) and subdural empyema (SDE). Ten (83.3%) showed BPAs where has 2 (16.7%) had SDE. Out of the ten parenchymal abscesses, the abscesses were located in the lateral frontal/ parietal/ occipital lobes in six patients. In four patients, the abscesses were located in the deep areas of brain, which were the anterior temporal lobes, deep nuclei or the cerebellum. In six out of twelve patients, the focal pus collection was picked up before the appearance of any symptoms suggestive of intra-cranial involvement. In these patients, the brain scan was performed along with orbit/paranasal sinuses imaging to look for early/ asymptomatic brain involvement. Ten underwent functional endoscopic sinus surgery (FESS). Both presentations are described separately hereafter.

Table 2: Clinical manifestations, investigations, treatment of fungal SOLs and outcomes

Characteristic	Number (N=12)	Percentage
Onset of fungal abscess after COVID	**Median 18 days (IQR 7.75-30 days)**	
Clinical Presentation		
Headache	10	83.3
Orbital Pain	4	33.3
Facial Pain	7	58.3
Red Eye	5	41.7
Loss of Vision	4	33.3
Ophthalmoplegia	4	33.3
Focal Neurological Deficits	7	58.3
Stroke	2	16.7
Meningitis	4	33.3
Fungal SOL Classification		
Brain Parenchymal Abscess	10	83.3
Sub Dural Empyema	2	16.7
Location of brain parenchymal abscesses (total=10)		
Frontal/ parietal/ occipital lobes	6	
Anterior temporal lobe, deep nuclei, cerebellum	4	
Stage at which fungal SOL was picked up		
Before appearance of focal symptoms	6	50
After appearance of focal symptoms	6	50
Microbiology		
Mucor alone	9	75
Mucor and Aspergillosis together	3	25
Surgical Management of Abscess		
FESS	10	83.3
Orbital Surgery	4	33.3
Craniotomy with excision of abscess	10	83.3
Medical Management of Abscess		
Amphotericin B alone	3	25
Amphotericin B and Posaconazole	9	75
Outcomes		
Survived	8	66.7
Death	4	33.3

Presentation 1: Brain parenchymal abscess (BPA)

Ten patients suffered BPA. MRI brain and orbits revealed abscesses in cerebral lobes, basal ganglia, cerebellum and/ or brainstem (extending into the cerebellar peduncles). In nine patients, pus was contiguous with the rhino-sino-orbital region from where it spread to the parenchyma (MRI of one of such patients displayed in Figure 1A), but it was distant from the area of primary infection (left high parietal) one patient (Figure 1B). Pachy-meningeal enhancement was seen in two patients. FESS (N=8), orbital surgery (N=2) and craniotomy with drainage and/or excision of abscess (N=8) was performed. The abscess in one patient was large, involving basi-frontal region as well as basal ganglia and was deemed inoperable by the neurosurgeon because of the extensive involvement of the deep nuclei. Another patient had a small 5 X 4 mm abscess in the left high parietal region distant from the rhino-orbital site. Since it did not cause any compressive symptoms, it was treated medically.

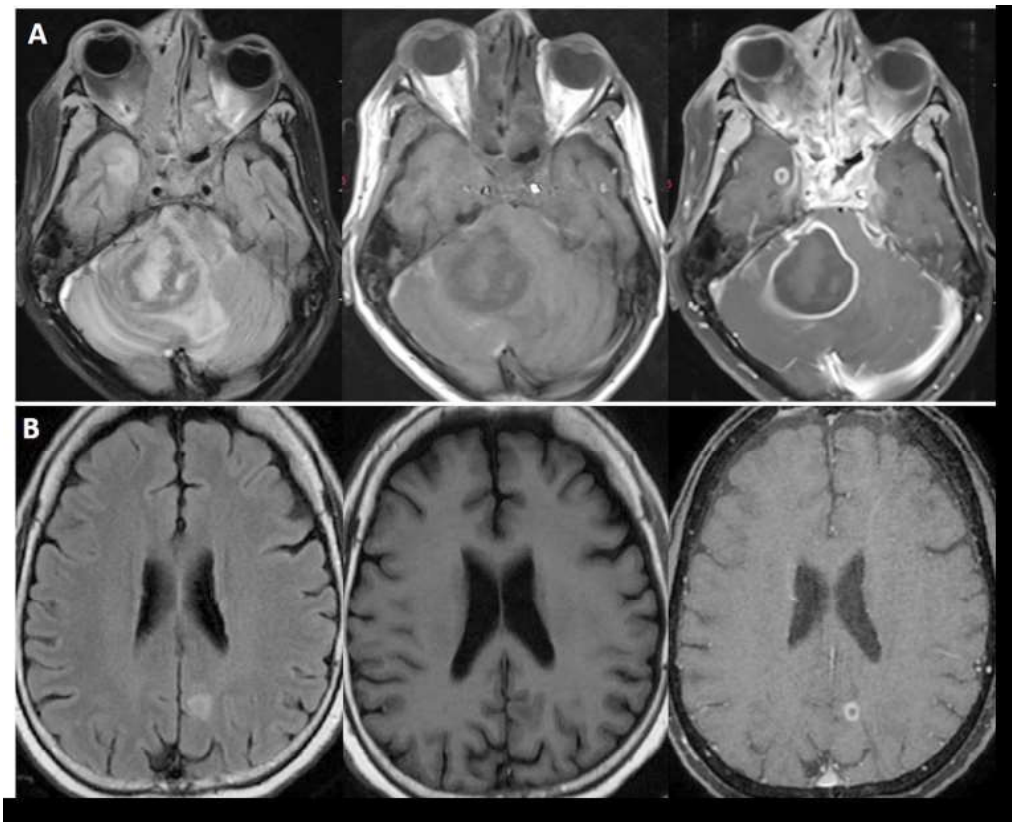

Fig. 1: FLAIR, T1W and T1W contrast axial MRIs. A: a well defined FLAIR iso-hyperintense fungal abscess involving ventrolateral aspect of right cerebellar hemisphere, right pons, middle cerebellar peduncle with peripheral enhancement, mass effect and compression of fourth ventricle. It is contiguous with the right cavernous sinus involvement. Smaller abscess is seen the right anterior temporal lobe. B: a small abscess in the left parietal lobe (non-contiguous to the rhino-orbital disease)

Presentation 2: subdural empyema (SDE)

After recovering from COVID-19, two patients got readmitted with symptoms suggestive of ROCM. One of them also developed sudden onset mild right hemiparesis due to a left fronto-parietal infarct. MRI brain and orbits showed rhino-orbital soft tissue with cavernous sinus involvement in both patients. Both underwent FESS, exenteration surgery of the eye and one patient also had a partial maxillectomy. Mucormycosis was isolated and amphotericin and posaconazole was started in both. After initial improvement for two weeks, their headache worsened and a repeat MRI revealed subdural collections at the skull base in basi-frontal region under the gyrus rectus (Figure 2).

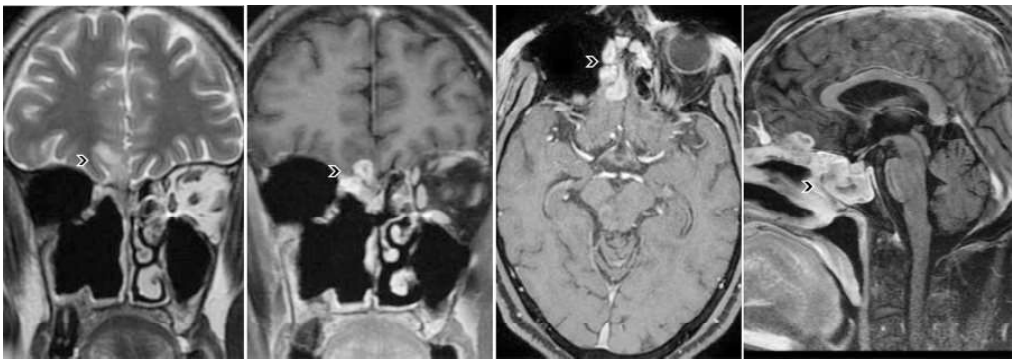

Fig. 2: MRI brain T2W coronal, T1W coronal, axial and sagittal contrast sequences of a patient showing subdural empyema collection in the right basi-frontal region under the gyrus rectus

They underwent drainage of this empyema, completed the course of anti-fungal drugs and both of them have improved.

Type of fungi, anti-fungal drug therapy and outcomes

Mucorale alone was isolated in nine (75%) and dual infection with aspergillus was found in three (25%) patients. All received amphotericin, nine also received posaconazole. Four (33%) patients died, one of them was considered inoperable, three died in spite of surgical excision. Out of the eight who have survived, four were left with an exenterated eye, two had hemiparesis and the rest still have malaise and generalized weakness.

DISCUSSION

Amongst all brain abscesses, fungal abscesses are uncommon. While the most common organisms causing fungal abscess are aspergillus and candida,[15] mucormycosis is a rare cause of abscess. There are isolated case reports, mostly in uncontrolled diabetics mellitus and immunocompromised patients presenting with cerebral abscess due to mucormycosis.[5,16-18]

There has been manifold increase in ROCM in the post COVID-19 era.[1,3] Intra-cranial involvement is uncommon in ROCM.[4] Intra-cranial lesions can present both as intra-parenchymal brain abscesses and also as sub-dural empyema collections.

Our patients presented at median of 18 days after recovering from COVID-19. Similar time interval has been described in literature.[1] Symptoms related to focal lesions were headache, pain and focal deficits.[1] Mortality of 52% has been mentioned in literature.[19] We observed a lower mortality at 33%. This could be because of high levels of awareness among the general public due to print and electronic media in India especially during the second wave of the COVID-19 pandemic. This helped patients report to hospital very early after onset of symptoms. Increased awareness about this illness amongst specialists and stringent monitoring of the disease course both clinically and with periodic orbit and brain scans also helped reduce mortality. In the four patients who died, lesions were seen in the deep anterior temporal lobe, deep nuclei and/ or cerebellum whereas lesions in patients who survived were more superficial in the frontal/ parietal/ occipital lobes. Thus, lesions infiltrating the base of the skull around the cavernous carotid artery region or basilar artery had a poor survival.

Half of our patients had developed a focal pus collection even before the appearance of symptoms suggestive of intra-cranial involvement. A brain scan needs to be performed in all patients presenting with rhino-orbital fungal syndromes to help pick up brain lesions early.[9] Mortality of ROCM is high, especially in patients who develop intra-cranial involvement. If the SOL is picked up early and treated aggressively, the morbidity and mortality can be reduced.[4,10,19-22]

In some patients, abscess forms intra-cranially in a non-contiguous fashion by spreading via hematogenous route.[1,20] This point has to be remembered that CNS involvement can occur even when the soft tissue has not yet reached the skull base.

CONCLUSION

Pus collections due to ROCM can be seen as parenchymal abscess and subdural empyema. They commonly collect in areas adjacent to the rhino-orbital disease but may also form in areas distant to the first site of infection, due to hematogenous spread. These collections may be asymptomatic at the outset and, can be picked up early by screening

the brain during imaging of paranasal sinuses and orbits. Early aggressive debridement and/ or excision along with appropriate anti-fungal therapy can improve the prognosis in this disease. Abscesses infiltrating the base of the skull around the cavernous carotid artery region or basilar artery have a very high mortality.

REFERENCES

1. John TM, Jacob CN, Kontoyiannis DP. When Uncontrolled Diabetes Mellitus and Severe COVID-19 Converge: The Perfect Storm for Mucormycosis. J Fungi (Basel). 2021 Apr 15;7(4):298.
2. Sarkar S, Gokhale T, Choudhury SS, Deb AK. COVID-19 and orbital mucormycosis. Indian J Ophthalmol. 2021;69(4):1002-1004.
3. KulkarniR, Pujari S, Gupta D, Advani S, Soni A, Duberkar D, et al. Rhino-orbito-cerebral mycosis and COVID-19: From bad to worse? Ann Indian Acad Neurol. 2022;25:68-75.
4. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: a deadly addition to the pandemic spectrum. J Laryngol Otol. 2021;135(5): 442-447.
5. Uraguchi K, Kozakura K, Oka S, Higaki T, Makihara S, Imai T. et al. A case of rhinocerebral mucormycosis with brain abscess drained by endoscopic endonasal skull base surgery. Med Mycol Case Rep. 2020;30:22-25.
6. Choir HY, Lew JM, Jackson IT. Rhinocerebral mucormycosis combined with brain abscess. European Journal of Plastic Surgery. 1992;15(3):146-50.
7. Meyerowitz EA, Sanchez S, Mansour MK, Triant VA, Goldberg MB. Isolated Cerebral Mucormycosis in Immunocompetent Adults who Inject Drugs: Case Reports and Systematic Review of the Literature. Open Forum Infect Dis. 2020 Nov 13;7(12):ofaa552.
8. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr*. 2021;15(4):102146.
9. Alekseyev K, Didenko L, Chaudhry B. Rhinocerebral Mucormycosis and COVID-19 Pneumonia. J Med Cases. 2021;12(3):85-89.
10. Verma V, Acharya S, Kumar S, Gaidhane SA, Thatere U. Rhinocerebral Mucormycosis With Brain Abscess Presenting as Status Epileptucus in a COVID-19-Infected Male: A Calamitous Complication. Cureus. 2022;14(1):e21061.
11. Sargin F, Akbulut M, Karaduman S, Sungurtekin H. Severe rhinocerebral mucormycosis case developed after COVID 19. J Bacteriol Parasitol. 2021;12:386.
12. Zhang GJ, Zhang SK, Wang Z, Zhu YX, Kong J, Huang LL, et al. Fatal and Rapid Progressive Isolated Cerebral Mucormycosis Involving the Bilateral Basal Ganglia: A Case Report. Front Neurol. 2020 Apr 21;11:295.
13. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020;20:533-4.
14. Bogam P, Joshi A, Nagarkar S, Jain D, Gupte N, Shashidhara LS, et al. Burden of COVID-19 and case fatality rate in Pune India: An analysis of First and Second wave of the Pandemic. medRxiv 2021.06.21.21259225.
15. Chakrabarti A. Epidemiology of central nervous system mycoses. Neurol India. 2007;55(3):191-7.
16. Rumboldt Z, Castillo M. Indolent intracranial mucormycosis: case report. AJNR Am J Neuroradiol. 2002;23(6):932-4.
17. Jiang N, Zhao G, Yang S, Lin J, Hu L, Che C, et al. A retrospective analysis of eleven cases of invasive rhino-orbito-cerebral mucormycosis presented with orbital apex syndrome initially. BMC Ophthalmol. 2016;16:10.
18. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41(5):634-53.
19. Patel A, Kaur H, Xess I, Michael JS, Savio J, Rudramurthy S, et al. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Microbiol Infect. 2020 Jul;26(7):944.e9-15.
20. Prakash H, Chakrabarti A. Global Epidemiology of Mucormycosis. *J Fungi (Basel)*. 2019;5(1):26.
21. Sen M, Lahane S, Lahane TP, Parekh R, Honavar SG. Mucor in a Viral Land: A Tale of Two Pathogens. Indian J Ophthalmol. 2021;69:244-2.
22. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. Am J Emerg Med. 2021 Apr;42:264.e5-264.e8.