# The mucormycosis and stroke: The learning curve during the second COVID-19 pandemic

Dileep Ramachandran, DM Neurology,[a] Aravind R, MD General Medicine,[b] Praveen Panicker, DM Neurology,[c] Jayaprabha S, MS ENT,[d] MC Sathyabhama, MD Microbiology,[e] Abhilash Nair, DM Endocrinology,[f] Raj S. Chandran, Mch Neurosurgery,[g] Simon George, MS Opthalmology,[h] Chintha S, MD Community Medicine,[i] and Thomas Iype, DM Neurology[j]

*Background:* The Angio-invasive Rhino-orbito-cerebral mucormycosis (ROCM) producing strokes is a less explored entity. Our hospital, a stroke-ready one, had an opportunity to manage mucormycosis when it was identified as the nodal center for mucormycosis management. We are sharing our experiences and mistakes in managing the cerebrovascular manifestations of ROCM. *Methods:* We conducted a prospective observational study during the second wave of the COVID-19 pandemic from 1st May 2021 to 30th September 2021, where consecutive patients aged more than 18 years with microbiologically confirmed cases of ROCM were included. Clinical details (timing of stroke onset after ROCM symptoms, GCS, NIHSS), imaging findings (ASPECTS, the territory of stroke, the pattern of infarct, hemorrhagic transformation, cavernous sinus thrombosis), angiogram findings, management details (IV thrombolysis), and outcomes (mRS at discharge and duration of hospital stay) were documented. We also compared the demographics, clinical features (NIHSS), radiological findings, treatment details, duration of hospital stay, and functional outcome at the discharge of the ROCM stroke patients with stroke patients without ROCM. *Results:* Stroke developed in 42% of patients with ROCM, predominantly anterior circulation border zone ischemic infarcts. Strokes occurred after a median of five days from the onset of ROCM symptoms. The most common vessel involved was the ophthalmic artery, followed by the cavernous ICA. We could not thrombolyse ROCM stroke patients. ROCM patients who developed stroke compared with patients without stroke had a more infiltrative fungal infection and higher inflammatory markers. Mucormycosis associated stroke patients had higher in-hospital mortality and poor functional outcomes.T *Conclusion :* Due to delayed recognition of stroke symptoms, none received reperfusion strategies, leading to poor functional outcomes. For early stroke detection, ROCM cases need frequent monitoring and education of patients and their relatives about

*Abbreviations:* ROCM, Rhino orbital cerebral mucormycosis; CTA, CT angiogram; ASPECTS, Alberta Stroke Program Early CT Score; ECASS, European Cooperative Acute Stroke Study; MCA, Middle cerebral artery; JCA, Internal cerebral artery

From the [a]Associate Professor, Department of Neurology, Government Medical College, Thiruvananthapuram, Kerala, India; [b]Head of Department, Department of Infectious Disease, Government Medical College, Thiruvananthapuram, Kerala, India; [c]Assistant Professor in Neurology, Government Medical College, Thiruvananthapuram, Kerala, India.; [d]Professor in ENT, Government Medical College, Thiruvananthapuram, Kerala, India; [e]Associate Professor, Department of Microbiology, Government Medical College, Thiruvananthapuram, Kerala, India; [f]Assistant Professor, Department of Endocrinology, Government Medical College, Thiruvananthapuram, Kerala, India; [g]Professor in Neurosurgery, Government Medical College, Thiruvananthapuram, Kerala, India; [h]Professor in Ophthalmology, Regional Institute of Ophthalmology, Government Medical College, Thiruvananthapuram, Kerala, India; [i]Associate Professor in SPM, Government Medical College, Thiruvananthapuram, Kerala, India; and [j]Professor and Head in Neurology, Government Medical College, Thiruvananthapuram, Kerala, India.

Received April 14, 2022; revision received September 28, 2022; accepted September 29, 2022.

Corresponding author. E-mail: drthomasiypeneuro@gmail.com.

1052-3057/$ - see front matter

© 2022 Elsevier Inc. All rights reserved.

https://doi.org/10.1016/j.jstrokecerebrovasdis.2022.106819

the ALS acronym (loss of ambulation, limb weakness, and loss of speech).
**Keywords:** Mucormycosis—COVID-19—Hospital Mortality—Pandemics—Stroke—Thrombolytic Therapy—Reperfusion
© 2022 Elsevier Inc. All rights reserved.

## Introduction

India witnessed a surge in mucormycosis cases during the second wave of the COVID-19 pandemic.[1,2] Concurrently, the state of Kerala in India also saw a rise in mucormycosis from May 2021. In response to the mucormycosis epidemic, the Government designated Government Medical College Thiruvananthapuram as the nodal center to manage cases from southern Kerala. A multidisciplinary team consisting of an Ear Nose Throat surgeon, infectious disease specialist, neurologist, neurosurgeon, endocrinologist, and ophthalmologist managed the patients at the nodal center.

Mucor, a fatal angio-invasive saprophytic environmental fungus of mucorale order (Mucor, Rhizopus, Absidia, Rhizomucor), depending on the site, can be classified into rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated.[1] The most common form, rhino-orbital-cerebral mucormycosis (ROCM), usually originates from the paranasal sinuses.[2] Orbital spread occurs through the medial orbital wall (favored by thin lamina papyracea, congenital dehiscence in the medial wall, and fenestrations in the medial wall by arteries and veins) and through the nasolacrimal duct. The cerebral invasion can be a direct invasion through the cribriform plate, superior orbital fissure, or basal foramina.

Angio invasion, which is a characteristic of this fungus, can lead to ischemic and hemorrhagic stroke.[3] The cerebrovascular involvement of ROCM was a less explored entity. Many times, strokes in Mucor patients are overlooked. We plan to share our experiences and mistakes in managing the cerebrovascular manifestations of ROCM.

## Methods

We conducted a prospective observational study during the second wave of the COVID-19 pandemic from 1st May 2021 to 30th September 2021 after getting Institutional Human ethics committee approval. Consecutive patients aged more than 18 years with microbiologically confirmed cases of ROCM were included in the study after obtaining informed written consent.[4]

We noted the basic demographic details, presence of diabetes (duration, control, and diabetic ketoacidosis), and COVID-19 status (category of COVID-19, number of days after which ROCM developed, steroid usage). All patients underwent blood investigations: ESR, CRP, Neutrophil Lymphocyte ratio, Ferritin, D-dimer, glycated hemoglobin. We documented mycological data and the radiological extent of involvement(sinus involvement, orbital involvement, orbital apex involvement, cavernous sinus involvement, intracranial involvement). Patients underwent endoscopic debridement and received antifungals. The type and dose of antifungals received and the timing and the extent of endoscopic debridement were noted.

Acute stroke in ROCM was diagnosed based on history, examination and radiology (CT or MRI). Patients who developed stroke were shifted to the Stroke Unit. Stroke details recorded were the timing of stroke onset after ROCM symptoms in days, the Glasgow coma score(GCS), and the National Institute of Health Stroke Scale Score (NIHSS).[5]

All Stroke patients underwent CT Brain and a CT angiogram. An MR TOF(Time of flight) angiogram without contrast was performed instead of a CT angiogram in patients with impaired renal function. Baseline ASPECTS (Alberta Stroke Program Early CT Score) was recorded on CT/MRI.[6] We also noted the territory of stroke (anterior or posterior circulation), the pattern of infarct (lacunar/wedge-shaped / territorial / watershed), site and volume of intracerebral hemorrhage, presence of hemorrhagic transformation assessed by ECASS criteria[7], and the presence of cavernous sinus thrombosis. In the angiogram (CT angiogram or MR angiogram), we looked for the vessel involved (cavernous ICA, cervical ICA, supraclinoid ICA, basilar artery, ophthalmic artery) and the pattern of vessel involvement (stenosis/occlusion/aneurysm). Etiological evaluation of stroke was completed in all patients (echocardiography, ECG, 24 h Holter monitoring). Details of management included the use of IV thrombolysis, antiplatelets, anticoagulants, and decompressive hemicraniectomy were documented. The outcomes included the modified Rankin scale at discharge and the duration of hospital stay.[8]

We compared the demographics, clinical features (NIHSS), radiological findings, treatment details, duration of hospital stay, and functional outcome at the hospital discharge of the ROCM stroke patients with stroke patients without ROCM. They were admitted to the Stroke ICU during the same period (from 1st May 2021 to 30th September 2021). Data were entered in Microsoft Excel and analyzed using IBM-SPSS v.27. Continuous variables were summarised as mean and standard deviation and median and interquartile ranges based on data distribution. The Chi-square test was used to analyze categorical and t-test for continuous variables. A p-value less than 0.05 was considered significant.

## Results

### *Characteristics of patients with ROCM*

During five months of the second pandemic wave (1st May 2021 to 30th September 2021), we had 26

microbiologically confirmed cases of ROCM in our center. The demographics, risk factor profile, clinical features, laboratory and imaging findings, the outcome of these patients are depicted in Table1. All patients had diabetes with poor glycaemic control indicated by high HbA1C. Ketosis was seen in a third and acidosis in a quarter of patients at admission. Half of the patients had received steroids before the symptoms. Four patients had no history of COVID infection. The most common presenting symptom was drooping of eyelids, and the sign was ptosis. The most common cranial nerve involved other than 3,4,6 cranial nerves was the trigeminal nerve's maxillary division. All inflammatory markers were elevated. The ethmoid was the most frequent sinus involved, followed by the maxillary and sphenoid sinus. A subset of patients had an intracranial extension involving the orbital apex, cavernous sinus, cerebritis, and meningeal enhancement. The most common organism isolated was Rhizopus. Mean hospital stay was around a month, with a mortality of 58%.

### *Characteristics of stroke in ROCM*

Eleven out of twenty-six ROCM patients developed stroke. (Table 2) Ten patients developed ischemic stroke, and one developed intracerebral hemorrhage. The median time from the onset of ROCM symptoms to stroke development was five days. The majority was in the anterior circulation territory, and the most common pattern of infarct was watershed infarct, especially the internal watershed infarct. A cerebral angiogram was done in all patients, and the most common finding was ophthalmic artery occlusion followed by cavernous ICA involvement. No patient received IV thrombolysis, and mortality rates were high (73%).

### *ROCM patients with stroke Vs. ROCM patients without stroke*

Table 3 compares ROCM patients who developed stroke with those who did not. Demographic and risk factor profile was similar between the two groups. Clinical features were identical between the two groups except for proptosis, chemosis, and ophthalmoplegia which was more common in mucormycosis associated stroke patients. ROCM patients who developed stroke had higher HbA1C and admission RBS but was not statistically significant. ROCM patients with stroke had more elevation in inflammatory markers like CRP, ESR, and TLC than ROCM patients without stroke. Only negligible frontal sinus involvement was observed in ROCM stroke patients. Higher in-hospital mortality and poor functional outcomes were also noted in stroke patients.

### *ROCM stroke versus non-ROCM strokes*

From 1st May 2021 to 30th September 2021, 104 acute stroke patients were admitted to the Stroke Unit, Government Medical College, Thiruvananthapuram. Table 4 shows the comparison of these stroke patients with ROCM stroke patients. All non-ROCM strokes were COVID 19 negative. Compared to non ROCM Strokes, ROCM stroke patients more frequently had diabetes with poorer glycaemic control and fewer smokers. The type of stroke and stroke severity assessed by NIHSS were similar between the two groups. Multiple territory infarcts were more found in ROCM stroke patients. Around half of non-ROCM stroke patients received intravenous thrombolysis, while no ROCM patients received the lytic drug. Inflammatory markers (ESR, CRP, TLC, NLR) were elevated in Mucormycosis associated stroke patients. ROCM stroke patients stayed in the hospital for a prolonged time with higher mortality and had poor functional outcomes at discharge.

## Discussion

We observed a two-fold rise in ROCM cases in India during the second wave of the COVID-19 pandemic.[9] Our institution was strategically placed to drain most cases from south Kerala and adjacent districts of neighboring Tamilnadu, being declared the nodal center for treatment of mucor. In addition, the institution was a stroke-ready hospital, which is being upgraded to a Comprehensive Stroke Centre.

Clinical features were similar to a previous study, and ocular symptoms were more common.[10] Orbital involvement occurs due to local or hematogenous spread from the ethmoidal and maxillary sinus. Diabetes mellitus was universal in our patients with ROCM, mostly poorly controlled. Before the COVID pandemic, diabetes had emerged as the leading risk factor for ROCM, especially in Asia.[11] Diabetes in the case of Mucormycosis associated stroke has contributed to vascular pathology as a direct risk factor and indirect risk factor to mucor, which is angioinvasion. Studies on Mycobacterium tuberculosis have shown an impaired immune response in diabetes mellitus, which could explain the increased risk to other infections: impaired phagocytic activity, impaired cellular activation resulting in impaired production of chemokines and cytokines, and impaired antigen-presenting cell (APC) recruitment.[12] The overall risk of diabetes was 56.8%, and diabetic ketoacidosis 18% in mucor. ROCM patients had 65.7% diabetes in a multicenter study in India.[13] Four patients with ROCM in our series had no history of COVID infection but had poorly controlled diabetes. Co-existing COVID infection, as well as steroids, could have contributed to the risk of ROCM in our patients.

We found that 42% of patients with ROCM developed stroke, mostly border zone ischemic infarcts in the anterior circulation. We did a CT angiogram in all patients with stroke; the most common finding noted was occlusion of ophthalmic artery occlusion followed by stenosis

and occlusion of cavernous ICA. The infected tissue near the vessels can explain this type of vascular involvement. We had a lower proportion of patients with occlusion of intracranial ICA (18.2%) than 62% reported by Kulkarni et al.[3] Direct involvement of the ophthalmic artery may have partly contributed to visual loss in these patients. The watershed infarct, especially internal watershed infarct, reflects the hypoperfusion produced by the cavernous ICA involvement. Only one patient with ROCM had basilar artery involvement. The basilar artery gets involved when the infection spreads from the sphenoid sinus to the clivus. We had three patients with multiple territory infarcts. Since multiple territory infarcts usually indicate proximal embolic sources, especially cardioembolic or prothrombotic states, we evaluated all three cases for a cardioembolic source (Transthoracic echocardiogram and 24 h Holter); but did not reveal any potential cardioembolic source. So possible mechanism could be a prothrombotic state contributed by the post-COVID inflammatory state. Another reason for multiple area infarcts is mucormycosis associated vasculitis.

Stroke is reported in 11.8% of Mucormycosis patients from Maharashtra.[3] The presence of exclusively ROCM patients, with the proximity of infection to cerebral vessels, possibly explains the higher incidence (42%) of stroke in our patients. The same explanation may hold good for our shorter median days (5 days) to stroke symptom after symptom onset compared to the experience of Kulkarni (8 days).[14] Strokes in Mucormycosis occur partially due to angioinvasion and hematogenous spread(14). Hypha can directly infiltrate the vessel wall and spread through the vessel wall. Angioinvasion is due to interaction with coat (CotH) protein on the surface of spores with Glucose Regulated Protein -78 (GRP-78) receptor on the endothelial cells.[15] This interaction is enhanced by hyperglycaemia and COVID which cause GRP-78 overexpression.[16]

Even though we continued to thrombolyse acute stroke patients during this period, we could not thrombolyse the ROCM stroke patients due to delayed recognition of strokes outside the window period of 4.5 h. The delay in recognizing the stroke symptoms is due to the restricted mobility of ROCM patients due to prolonged IV infusions and the preoccupation with the nasal and orbital symptoms. Hence, for early recognition of stroke, all cases of ROCM must be frequently monitored for new neurological symptoms and signs. Education of patients and their relatives about the symptoms like loss of ambulation, limb weakness, and loss of speech -ALS acronym rather than FAST is paramount in picking up strokes early.

ROCM patients who developed stroke compared with patients without stroke had a more infiltrative fungal infection of either cavernous sinus, orbital apex, or orbit as revealed by clinical presentation (more proptosis, chemosis, and ophthalmoplegia) and orbital apex involvement by imaging. Inflammatory markers were higher in ROCM stroke patients, either due to the inflammatory milieu produced by ROCM favoring a stroke-prone environment or the inflammation occurring after stroke.[17] Mucormycosis associated stroke patients had higher in-hospital mortality and poor functional outcomes. This excess mortality and the poor functional outcome may be contributed by co-existent stroke. Duration of hospital stay was more in mucormycosis associated stroke than non-mucormycosis associated stroke because of the need for debridement and a prolonged course of antifungals. Our stroke patients with ROCM had higher mortality rates (73%) than previous reports.[13,18]

Once patients with ROCM developed a stroke, their morbidity and mortality worsened. So prevention of strokes in ROCM is of paramount importance. Hence, further studies are needed to see if we can predict patients at risk for stroke using serial non-invasive vessel imaging, preferably MRI TOF (Time of flight imaging). In addition, once vessel involvement is documented, we could study whether they benefit from prophylactic antithrombotic agents. The major limitation of our study was the small number of cases; a multicentre study would be helpful.

## Conclusion

ROCM causes more ischemic strokes involving intracranial cerebral vessels, especially cavernous ICA and ophthalmic artery. ROCM causing strokes were associated with poor functional outcomes and higher mortality. Early identification of stroke symptoms in a patient with ROCM may provide a window of opportunity for reperfusion strategies to improve functional outcomes. Educating the patient and relatives regarding the ALS acronym will be helpful to detect strokes early. Whether serial vessel imaging predicts stroke and antithrombotic can prevent a stroke from occurring in ROCM must be studied.

## Sources of funding

None.

## Disclosures

None.

**Acknowledgments:** We thank all the Staff of the Stroke unit of our hospital. Dr.Dileep Ramachandran conceptualized the study. Drafting was done by Dr.Dileep Ramachandran and Dr.Thomas Iype. Dr. Dileep Ramachandran analyzed with the help of Dr.Praveen Panicker. All authors reviewed and approved the final article.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2022.106819.

## References


1. 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.
2. Pal P, Chatterjee N, Ghosh S, Ray BK, Mukhopadhyay P, Bhunia K, et al. COVID associated mucormycosis: a study on the spectrum of clinical, biochemical and radiological findings in a series of ten patients. J Assoc Physicians India 2021;69(10):11-12.
3. Skiada A, Lass-Floerl C, Klimko N, Ibrahim A, Roilides E, Petrikkos G. Challenges in the diagnosis and treatment of mucormycosis. Med Mycol 2018;56(suppl_1):93-101.
4. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. Stroke 1994;25(11):2220-2226.
5. Barber PA, Demchuk AM, Zhang J, Buchan AM. Group AS. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. Lancet 2000;355(9216):1670-1674.
6. Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Larrue V, Lesaffre E, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. Stroke 1999;30(11):2280-2284.
7. Van Swieten J, Koudstaal P, Visser M, Schouten H, Van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19(5):604-607.
8. Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al. Multicenter epidemiologic study of coronavirus disease-associated mucormycosis, India. Emerg Infect Dis. 2021;27(9):2349-2359.
9. Alloush TK, Mansour O, Alloush AT, Roushdy T, Hamid E, El-Shamy M, et al. Rhino-orbito-cerebral mucormycosis during the COVID-19 third wave in 2021: an Egyptian preliminary report from a single tertiary hospital. Neurol Sci 2021;43(2):799-809.
10. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi 2019;5(1):26.
11. Ayelign B, Negash M, Genetu M, Wondmagegn T, Shibabaw T. Immunological impacts of diabetes on the susceptibility of mycobacterium tuberculosis. J Immunol Res 2019;2019:6196532.
12. Prakash H, Ghosh AK, Rudramurthy SM, Singh P, Xess I, Savio J, et al. A prospective multicenter study on mucormycosis in India: epidemiology, diagnosis, and treatment. Med Mycol 2019;57(4):395-402.
13. Kulkarni R, Pujari SS, Gupta D, Ojha P, Dhamne M, Bolegave V, et al. Cerebrovascular involvement in mucormycosis in COVID-19 pandemic. J Stroke Cerebrovasc Dis 2022;31(2):106231.
14. Padma Srivastava MV, Vishnu VY, Pandit AK. Mucormycosis epidemic and stroke in india during the COVID-19 pandemic. Stroke 2021;52(10):e622-e623.
15. Gebremariam T, Liu M, Luo G, Bruno V, Phan QT, Waring AJ, et al. CotH3 mediates fungal invasion of host cells during mucormycosis. J Clin Investig 2014;124 (1):237-250.
16. Gumashta J, Gumashta R. COVID19 associated mucormycosis: is GRP78 a possible link? J Infect Public Health 2021;14(10):1351-1357.
17. Montaño DE, Voigt K. Host immune defense upon fungal infections with mucorales: pathogen-immune cell interactions as drivers of inflammatory responses. J Fungi 2020;6(3):173. https://doi.org/10.3390/jof6030173.
18. Dave TV, Gopinathan Nair A, Hegde R, Vithalani N, Desai S, Adulkar N, et al. Clinical presentations, management and outcomes of rhino-orbital-cerebral mucormycosis (ROCM) following COVID-19: a multi-centric study. Ophthalmic Plast Reconstr Surg 2021;37(5):488-495.