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CASE REPORT

Stroke in patients with COVID associated Mucormycosis: A Report of Two Cases

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Abstract

Mucormycosis is a rare and invasive fungal disease with potentially fatal outcome. It most commonly affects patients with compromised immunity, especiallly those with poorly controlled diabetes. The incidence of mucormycosis has increased after the COVID-19 pandemic and both COVID-19 and mucormycosis are associated with an increased incidence of stroke. We present a report of two cases of COVID associated mucormycosis who had stroke. A 50-year-old patient with uncontrolled diabetes developed swelling of left eye and face ultimately leading to complete ophthalmoplegia of left eye. Imaging studies of brain revealed infarcts. MRI/MRA brain showed left internal carotid artery thrombosis, cavernous sinus thrombosis and a brain abscess in left temporal lobe. A second patient was a 65-year-old diabetic and hypertensive male who had COVID and then developed right MCA territory infarct and right sided cavernous sinus thrombosis. Diagnostic nasal endoscopy and biopsy was suggestive of mucormycosis in both the cases. Both these cases were managed with combination of tight glycemic control, antifungal therapy, and surgery. Clinicians should be aware of the association of stroke with COVID and COVID associated mucormycosis (CAM).

Key Words: Mucormycosis, COVID-19, COVID associated mucormycosis (CAM), Stroke, Cavernous sinus thrombosis,

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Introduction

Mucormycosis is a rare and potentially fatal angio-invasive fungal infection caused by Mucorales. It has drastically risen in incidence in the post COVID-19 setting. Traditional risk factors for mucormycosis include hyperglycemia, iron overload, iron chelating agents e.g, deferoxamine, and immunosuppression in hematologic malignancy. The rampant increase in the use of steroids along with an increase in non-obese diabetes due to steroids and COVID-19 associated hypoxemia is believed to have caused the recent surge in mucormycosis cases. An increase of 2.1 times has been noted in the incidence of mucormycosis in late 2020 as compared to 2019 [1].

COVID-19 has been observed to cause damage at the alveolointerstitial level leading to extensive pulmonary disease. This may predispose to invasive fungal infections of the airways including the lung and the sinuses. Moreover, COVID-19 infection causes immune dysregulation, characterized by decreased T - cells (both CD4 and CD8 cells), resulting in an altered innate immunity [2].

Pulmonary and rhino-orbito-cerebral are the two most common manifestations of mucormycosis based on the site of involvement. Its rhino-orbital variant can extend to the brain directly or via the vessels, causing protean neurological presentations. COVID-19 has been associated with several neurological manifestations, including cerebrovascular disease, encephalitis, and peripheral nervous system involvement [3].

In view of the increasing prevalence of mucormycosis cases, clinicians should actively look for signs and symptoms of mucormycosis amongst the patients with recent history of COVID-19, infection, diabetics, and patients on longer duration of steroid intake.

For added emphasis on the breakout of mucormycosis cases in COVID-19 infected individuals, most of the recent studies have reported such cases as COVID-19 associated mucormycosis (CAM). There is an increase in cerebrovascular events in CAM patients. In one study by Kulkarni et al, the incidence of stroke in CAM was found to be 11.8% [4]. Here, we present two cases of COVID associated rhino-orbito-cerebral mucormycosis presenting with stroke.

Patient 1

A 50-year-old diabetic male presented to the emergency department of a private hospital with complaints of low-grade fever associated with loose stools and shortness of breath on exertion for last 5-6 days. He was found to be positive for SARS CoV-2 by RT-PCR. He recovered after 6th day of admission and had no episodes of fever thereafter. He did not require steroids but had uncontrolled hyperglycaemia during the hospital stay. 2-3 days later, he developed dull aching pain over his left eye and left half of his face. He had a sudden onset dip in his sensorium associated with difficulty in hearing on the 10th day of admission. This was associated with slight drooping of his left eyelid. MRI brain was suggestive of an acute ischemic infarct in the temporal lobe. Vascular imaging could not be done due to financial constraints. Despite an improvement in his sensorium, his left eyelid continued drooping further such that he was unable to move it. Moreover, the lateral movements of his eyeball were restricted and he developed swelling around his left eye. A month after the initial neurological insult, he presented to our casualty with same complaints.

On arrival, his blood sugars were within the normal range. Patients' hematological and biochemical profile is summarized in Table 1. He had complete ophthalmoplegia of his left eye with no pupillary reaction to light and no light perception. There was no other focal neurological deficit. Since the swelling around his left eye and ptosis of his left eyelid were progressive and did not correlate with the infarct site (Figure 1A). ENT and Ophthalmology consultations were taken.

His NCCT head was suggestive of fresh infarcts in the left temporal lobe. His sensorium worsened during the hospital stay probably because of the fresh infarct. MRI brain done after a week revealed mucosal thickening of nasal cavity, frontal, bilateral ethmoid, sphenoid and maxillary sinuses with extra sinus extension into left orbit, left pre-antral fat and retro-antral fat, left infratemporal fossa, left inferior orbital fissure and left pterygopalatine fossa, suggestive of invasive fungal sinusitis with rhino-orbito-cerebral involvement. MR angiography showed left internal carotid artery thrombosis, and cavernous sinus thrombosis (Figure 1E). A brain abscess was present in the left temporal lobe, with peripheral diffusion restriction and low ADC values in the centre (Figure 1 B, C&D). MR spectroscopy done for the abscess revealed a trehalose peak between 3.6 and 3.8 ppm suggestive of fungal abscess (Figure 1F). Diagnostic nasal endoscopy was performed which revealed blackish necrotic debris on the nasal floor and inferior medial meatus. Fungal KOH mount was suggestive of mucormycosis.

Treatment was initiated immediately on presentation to the hospital (one month after left eye swelling) with intravenous Liposomal Amphotericin B at 5mg/kg/day, tablet Posaconazole

Table 1: Laboratory Findings

Parameter	Patient	Normal
Haemoglobin (g/dl)	9.4	>13
TLC	6080 (70/24/5/1)	4000-11000
Platelet count (Lakhs/ml)	2.72	1.5 to 4.0
Urea (mg/dl)	13	19-43
Creatinine (mg/dl)	0.5	0.7-1.3
Na^+/K^+ (mmol/l)	131/4.1	137-145/3.5-5.1
Bilirubin (mg/dl)	0.4	0.2-1.3
ALT/AST (U/ml)	20/23	5-50/17-59
HbA1C (%)	11.1%	<6.5%
LDH (U/L)	203	140-280
D-Dimer (ng/ml)	2561	<500
INR	1.14	0.8-1.2
APTT (s)	30.4	23.0-32.4
CRP (mg/L)	99	<3
HIV	Non-Reactive	
HBsAg	Negative	
Anti HCV	Negative	

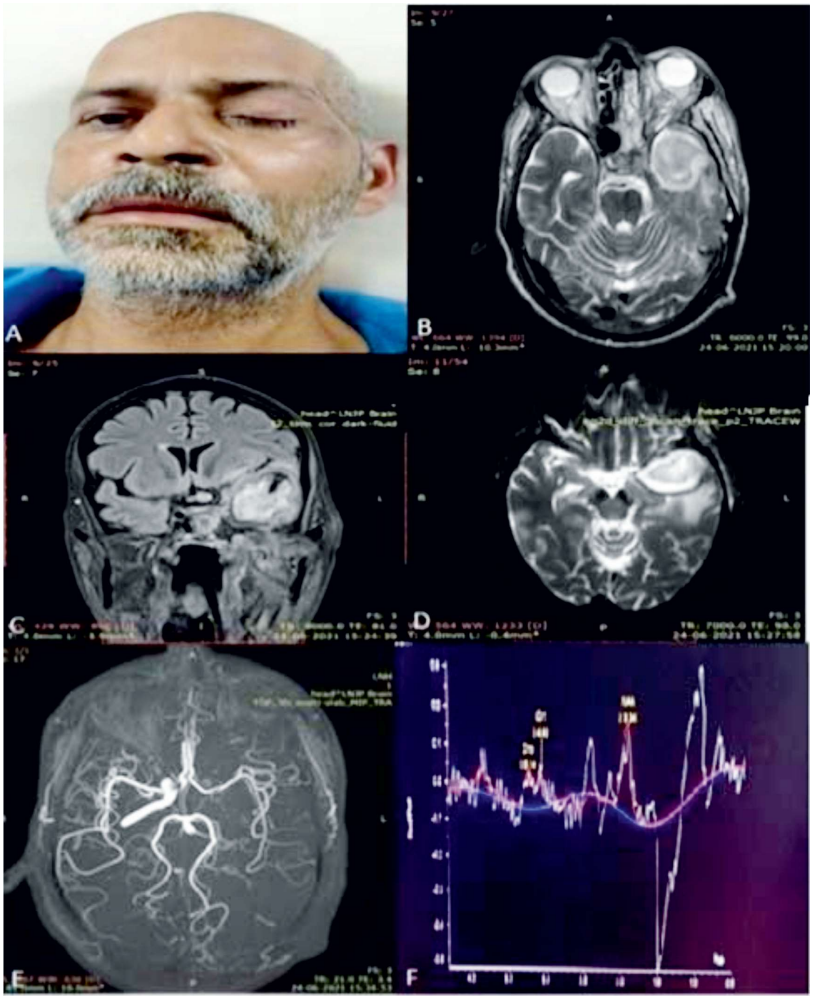

Figure 1: A - Ptosis and oedema surrounding the left eye of the patient. B - MR T2 weighted axial image showing peripheral hetero-intense ring enhancement in the left temporal lobe and left rhino-orbital involvement. C - MR T2 weighted coronal image showing left temporal lobe hyperintensity D - Diffusion MRI: Peripheral diffusion restriction. E - MRA showing Left ICA thrombosis. F - MR Spectroscopy image of the lesion showing trehalose peak between 3.6-3.8

300 mg twice daily on day 1 followed by 300 mg once daily. Once the abscess was detected, the dose of Liposomal Amphotericin B was increased to 10 mg/kg/day. Temporal abscess drainage followed by a left orbital exenteration and partial maxillectomy with debridement was done via open approach. Biopsy was taken from the abscess wall, pterygopalatine fossa and orbit which revealed broad and aseptate hyphae suggestive of mucor. Some residual abscess was still left after the drainage. Unfortunately, he developed hospital acquired pneumonia and could not be weaned off his ventilatory support and eventually succumbed to his illness.

Patient 2

A 65-year-old diabetic and hypertensive male with a recent cerebrovascular accident, presented to the casualty with the complaints of swelling around the right eye for 2 months with deterioration of visual acuity in the right eye. He also complained of numbness and pain in the right maxillary region for 2 months.

The patient had tested positive for SARS Cov-2 about 1 week prior to these symptoms, with CT Severity Score of 11/25, for which he was hospitalized. Oxygen therapy, steroids and other COVID appropriate care were given at the hospital. He had developed sudden onset of weakness of the left side of the body during his hospital stay. His NCCT head showed a large infarct in right middle cerebral artery (MCA) territory involving the frontal, parietal, and temporal regions (Figure 2 A&B). Hematological and biochemical profile of the patient are mentioned in Table 2.

CECT Nose, PNS and Orbit was done which revealed heterogeneously enhancing soft tissue contents in the right maxillary, frontal, ethmoid, and sphenoid sinuses, with extra sinus extension into the preantral space, retro antral space, sphenopalatine foramen, pterygopalatine fossa, pterygomaxillary fissure, and masticator space with bony

Table 2: Laboratory Findings

Parameter	Normal Reference Values	Week 1	Week 2	Week 3	Week 4
Haemoglobin (g/dl)	>13	8.5	7.1	8.2	9.9
TLC	4000-11000	5860	3010	2300	4080
Platelet count (Lakhs/ml)	1.5 to 4.0	410000	108000	98000	129000
Urea (mg/dl)	19-43	15	34	30	32
Creatinine (mg/dl)	0.7-1.3	0.4	0.9	0.8	0.9
Na^+/K^+ (mmol/l)	137-145/3.5-5.1	127/4.2	126/3.1	136/3.4	135/3.8
Bilirubin (mg/dl)	0.2-1.3	0.2	0.5	0.5	0.5
ALT/AST (U/ml)	5-50/17-59	19/21	25/32		38/48
D-Dimer (ng/ml)	<500	5000	1020	573	986
Ca2+/Po4 (mmol/l)	9-11/3.5-4.5	8.3/4.0	8.0/3.6		8.2/3.5
PT (s)/INR	11/1.0	13/1.1	16/1.2	16/1.2	14/1.2
Total Protein (g/dl)/Serum Albumin (g/dl)	6.2-8.3/3.5-5.5	6.0/2.6	6.0/2.7	6.2/2.8	6.4/3.0
HIV	Non-Reactive				
HBsAg	Negative				
Anti HCV	Negative				

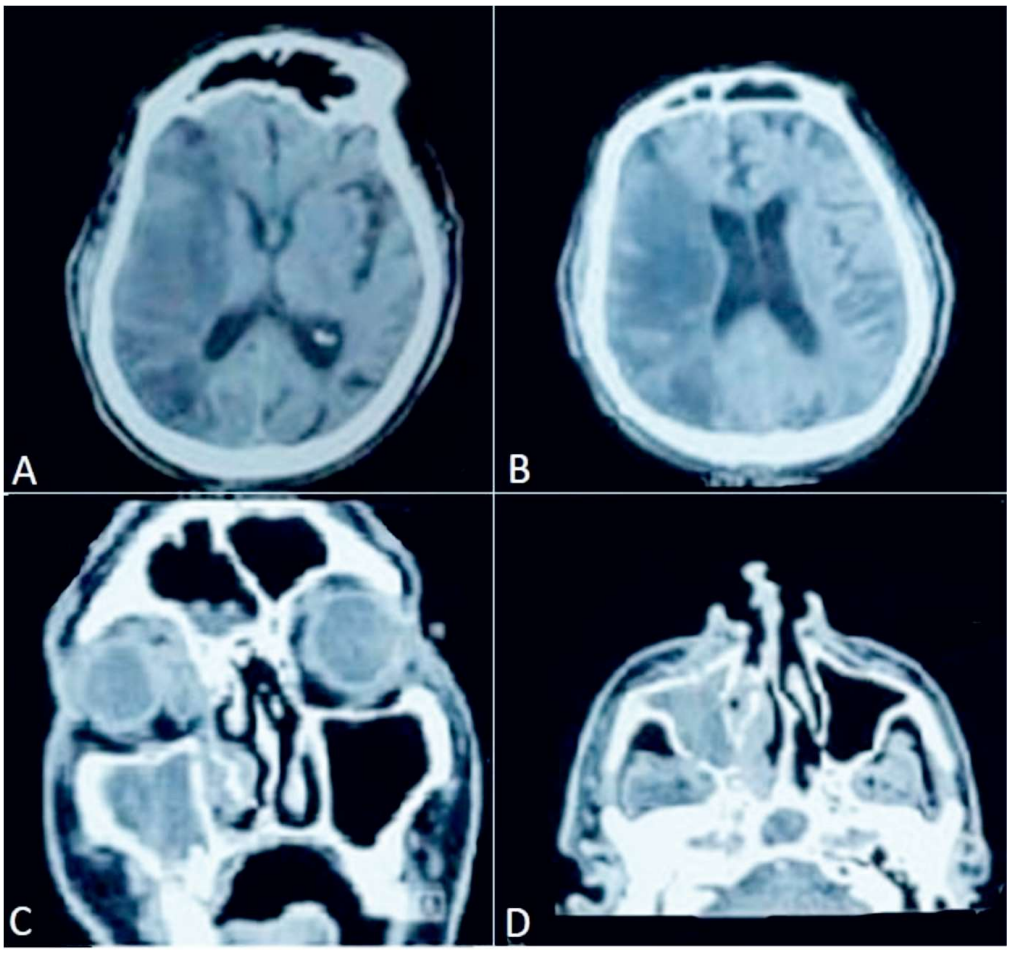

Figure 2 A&B - NCCT head showing large infarct in Right MCA territory, involving frontal, parietal, and temporal regions C&D - CECT Nose, PNS and Orbit showing heterogeneously enhancing soft tissue contents in the right maxillary, frontal, ethmoid, and sphenoid sinuses, with extra sinus extension into the preantral space, retro antral space, sphenopalatine foramen, pterygopalatine fossa, pterygomaxillary fissure, and masticator space with bony destruction.

destruction suggestive of invasive fungal rhinosinusitis. There was also intra orbital extension and right cavernous sinus thrombosis (Figure 2 C&D). Diagnostic nasal endoscopy with biopsy was done. Biopsy findings were suggestive of mucormycosis.

The patient was treated with IV Liposomal Amphotericin B at 5mg/kg body weight, tablet Posaconazole 300 mg BD on day 1 (2 months after the initial right eye swelling) followed by 300 mg OD, antibiotics, and measures to control blood pressure and blood sugar. This treatment was continued for 3 weeks but patient did not show any signs of improvement. The patient was then planned and taken up for debridement which was done successfully, after which patient's condition improved. Fever had resolved and his sensorium significantly improved. The patient was discharged on Tab Posaconazole 300mg OD, with a Ryle's tube for feeding and is following up regularly.

Discussion

Mucormycosis is a rare invasive fungal disease caused by lower fungus, belonging to the order Mucorales which has seven families which include genera like Mucor, Rhizomucor, Actinomucor, Cunninghamella, and others. A wide spectrum of clinical syndromes like pulmonary, rhino-orbital-cerebral, gastrointestinal, cutaneous, and disseminated forms are known to occur in mucormycosis.

With the documented and visible surge in mucormycosis cases, attention is now being directed towards the risk factors and presentations of mucormycosis. The incidence of CAM stands at about 3.4% in India [5].

Risk factors which are typically associated with mucormycosis include diabetes mellitus, hematological malignancy, CKD, COPD, tuberculosis and iron overload states. The reported new risk factors, responsible for the rise in incidence include hypoxemia (as a result of COVID-19), inappropriate glucocorticoid use and new onset diabetes (attributed to either steroid use or COVID-19 itself).

Cerebrovascular manifestations were reported in 6% of COVID-19 patients in a case series from Wuhan, conducted early in the pandemic. Out of these 5% patients had ischaemic stroke and <1% had intracranial haemorrhage and cerebral sinus thrombosis [6]. In one retrospective study, 2% of hospitalized patients diagnosed with COVID-19 had a stroke [7]. In a report from a neurology centre in Italy, 77% of admitted SARS-CoV-2 positive patients had cerebrovascular disease, out of which 12% had transient ischemic attacks, 81% had ischemic stroke, and 7% had hemorrhagic strokes [8]. There have been multiple case reports on Mucormycosis resulting in stroke as shown by other studies [9-11].

Both of the patients of CAM presented with cerebrovascular accident (CVA) like picture. Studies have suggested that cerebrovascular disease in COVID-19 might be due to the development of a coagulopathy. SARS-CoV-2 directly damages the vascular endothelial cells, leading to a cascade of events eventually activating inflammatory and thrombotic pathways. One plausible theory is whereby endothelial cell infection or monocyte activation by the virus, results in the upregulation of tissue factors and the release of microparticles, which activate the thrombotic pathway and cause microangiopathy [12,13]. Acute ischemic stroke could also occur due to artery-to-artery or cardio-embolism, during the early inflammatory process following SARS CoV-2 infection, resulting in carotid plaque destabilization or triggering atrial fibrillation [14]. Another explanation is that a vasculitis like process, as is seen with varicella zoster virus infections, occurs with SARS CoV-2. Viral replication in the walls of cerebral arteries triggers local inflammation and vasculitic infarcts [15]. In addition to this, Mucormycosis is known to increase the risk of stroke by direct fungal invasion of the vascular endothelium. Mucormycosis is invasive, and usually spreads through the vessels, bone (via cribriform plate, ethmoid sinus and lamina papyracea), or via the pterygopalatine fossa to reach the orbit and eye. It may also spread via the involvement of sphenopalatine and internal maxillary arteries. Involvement of the internal carotid artery by angioinvasion, and cavernous sinus thrombosis is seen late in the course of disease, resulting in stroke [16].

Mucormycosis can present as distinct clinical syndromes. Both our patients presented as rhino-orbito-cerebral mucormycosis, which is the most common overall, especially among diabetics. In such patients the initial symptoms are usually non-specific and include facial and eye pain. This may be followed by bloody nasal discharge, conjunctival suffusion and blurring of vision. Fever may be absent in half of the cases, as was the case here. Numbness of face, drooping of eyelids and inability to move eyes may be seen late in the case with a more extensive involvement. Behavioral changes, headache, vomiting other focal neurologic deficits may indicate cerebral involvement. As the initial symptoms are non-specific, in scenarios and places where there is less knowledge of such a complication, atypical presentations such as this may lead to delayed diagnosis and an ever-increasing risk of mortality [3].

A high index of suspicion is required for making timely diagnosis of mucormycosis. As the Mucorales are ubiquitous organisms, the definitive diagnosis depends on their presence in biopsy along with, either the evidence of tissue invasion or surrounding inflammation. However, their mere presence in sterile sites may be enough for sealing the diagnosis. Culture may help with the identification of definite species, though time consuming [17]. Keeping in view the high mortality associated with mucormycosis, it is recommended

that treatment be initiated based on high clinical suspicion alone.

Radiological investigations aid in supporting the diagnosis. Sinus mucormycosis can be seen as non-specific nodular thickening of mucosa with extension into the soft tissues of infra-temporal and temporal fossa. Black turbinate sign, due to small vessel occlusion, is useful for differentiation from other causes of sinusitis. Bony destruction is present in less than half of cases, thus its absence cannot be used for exclusion [18]. Orbital involvement shows edema and thickening of the muscle wall especially the medial rectus muscle, pre-septal edema, proptosis, and orbital fat infiltration especially at the apex. There are no specific features to differentiate it from bacterial orbital cellulitis. The three most common findings on imaging in intracranial mucormycosis are cavernous sinus thrombosis, brain infarction, and internal carotid artery occlusion [19]

Brain abscess may be present in few cases. As biopsy is not always practical, a combination of features in conventional MR, DWI and PMRS help in differentiation from bacterial abscess. A ring-enhancing T2 hetero-intense lesion with irregular walls, irregular projections into the cavity, low ADC, DW restriction, and no enhancement of these projections on giving contrast and no diffusion restriction of the rest of the core, makes it more likely to be fungal. Moreover, presence of trehalose peak between 3.6 and 3.8 ppm by MR spectroscopy, favored fungal abscess. The abscess in the first patient showed no DW restriction in the centre [20].

A combination of medical and surgical management needs to be implemented timely for salvaging Mucormycosis patients. Medical therapy with Amphotericin B (liposomal preferentially) with or without a combination of Posaconazole may be tried. In case of cerebral involvement, higher dose Liposomal Amphotericin B may be started (10 mg/kg) [21]. However, without debridement and drainage, the utility of a lone medical approach is doubtful. Urgent surgical intervention is thus required. Ischemic stroke is managed as per the AHA Guidelines.

To conclude, all the clinicians should be aware of increasing possibility of development of fungal infections like mucormycosis in patients with COVID-19, particularly those with comorbidities or on immunosuppressive agents, and requiring oxygen. Early recognition of such cases in any susceptible patient presenting with sinus or facial pain, bloody nasal discharge, eye selling or drooping or a neurological deficit, may help curtail the high morbidity and mortality. The risk of CVA increases in patients with CAM, especially rhino-orbito-cerebral form. Early debridement is of prime importance in managing such patients.

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References

1. 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.
2. Sarkar S, Gokhale T, Choudhury SS, Deb AK. COVID 19 and orbital mucormycosis. Indian J Ophthalmol 2021;69:1002-4.
3. AK AK, Gupta V. Rhino-orbital Cerebral Mucormycosis. [Updated 2021 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557429/
4. Kulkarni R, Pujari SS, Gupta D, Ojha P, Dhamne M, Bolegave V. Cerebrovascular Involvement in Mucormycosis in COVID-19 Pandemic. J Stroke Cerebrovasc Dis. 2022;31(2):106231
5. Mishra Y, Prashar M, Sharma D, Akash, Kumar VP, Tilak TVSVGK. Diabetes, COVID-19 and mucormycosis: Clinical spectrum and outcome in a tertiary care medical center in Western India. Diabetes Metab Syndr. 2021;15(4):102196.
6. Li Y, Wang M, Zhou Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. 2020. https://media.tghn.org/medialibrary/2020/06/Li_ 2020_ Preprint_ Acute_ cerebrovascular_ disease_ COVID19.pdf (preprint).
7. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020;191:9-14.
8. Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. Neurology. 2020 Aug 18;95(7):e910-e920.
9. Ermak D, Kanekar S, Specht CS, Wojnar M, Lowden M. Looks like a stroke, acts like a stroke, but it's more than a stroke: a case of cerebral mucormycosis. J Stroke Cerebrovasc Dis. 2014;23(8):e403-e404.
10. Nagendra V, Thakkar KD, Prasad Hrishi A, Prathapadas U. A Rare Case of Rhinocerebral Mucormycosis Presenting as Garcin Syndrome and Acute Ischemic Stroke. Indian J Crit Care Med. 2020;24(11):1137-1138.
11. Mititelu R, Bourassa-Blanchette S, Sharma K, Roth V. Angioinvasive mucormycosis and paradoxical stroke: a case report. JMM Case Rep. 2016;3(4):e005048.
12. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417-1418.
13. Lopes da Silva R. Viral-associated thrombotic microangiopathies. Hematol Oncol Stem Cell Ther. 2011;4(2):51-9.
14. Emsley HC, Hopkins SJ. Acute ischaemic stroke and infection: recent and emerging concepts. Lancet Neurol 2008;7:341–53.
15. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol 2009; 8: 731–40.
16. Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of Mucormycosis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2012;54(Suppl 1):S16–22.
17. Schelenz S, Barnes RA, Barton RC, Cleverley JR, Lucas SB, Kibbler CC, et al. British Society for Medical Mycology best practice recommendations for the diagnosis of serious fungal diseases. Lancet Infect Dis. 2015;15(4):461–74.
18. Raab P, Sedlacek L, Buchholz S, Stolle S, Lanfermann H. Imaging Patterns of Rhino-Orbital-Cerebral Mucormycosis in Immunocompromised Patients: When to Suspect Complicated Mucormycosis. Clin Neuroradiol. 2017;27(4):469–75.
19. Son JH, Lim HB, Lee SH, Yang JW, Lee SB. Early Differential Diagnosis of Rhino-Orbito-Cerebral Mucormycosis and Bacterial Orbital Cellulitis: Based on Computed Tomography Findings. PLoS ONE. 2016;11(8):e0160897.
20. Luthra G, Parihar A, Nath K, Jaiswal S, Prasad KN, Husain N, et al. Comparative Evaluation of Fungal, Tubercular, and Pyogenic Brain Abscesses with Conventional and Diffusion MR Imaging and Proton MR Spectroscopy. Am J Neuroradiol. 2007;28(7):1332–8.
21. Lanternier F, Poiree S, Elie C, Garcia-Hermoso D, Bakouboula P, Sitbon K, et al. Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis. J Antimicrob Chemother. 2015;70(11):3116–23.