Sinonasal Mucormycosis Amidst the Second Wave of COVID-19 Pandemic; Clinical Spectrum and Outcome in a Tertiary Care Center in Nepal

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ABSTRACT

Background

Mucormycosis is an angioinvasive opportunistic fungal infection which surged during the second wave of COVID-19 pandemic.

Objective

This study assessed patient demographics, risk factors, clinical characteristics, and outcomes of sinonasal mucormycosis during the second wave of COVID-19 pandemic.

Method

The clinical records of patients with histologically proven sinonasal mucormycosis, admitted between May 2021 to October 2021, in a tertiary center were reviewed.

Result

There were 25 patients (18 males, 7 females). The age ranged from 16 to 70 years (mean 51 ± 9.5 years). Uncontrolled diabetes mellitus detected in 23 patients was the most common co-morbidity. COVID-19 infection was documented in 20 patients. The mean time of diagnosis was 12 days after the onset of COVID-19 infection. Based on the disease extent, six patients had sino-nasal, seven had rhino-orbital, and 12 had rhino-orbital-cerebral involvement. The most common first presenting symptom was orbital (17/25) followed by facial (5/25) and orodental (3/25). All patients received intravenous amphotericin B for 2 to 8 weeks. Maintenance with posaconazole ranged from 3 to 9 months. Sixteen patients underwent surgical debridement. Out of the 25 patients, 14 (56%) had good recovery. Poor outcome was observed mostly with intracranial involvement.

Conclusion

Uncontrolled diabetes mellitus was a common risk factor. Advanced disease at presentation was frequently encountered due to rapid extrasinus spread. Nearly 50% of patients had good recovery whilst poor outcome was observed, mostly with intracranial involvement. Adequate blood sugar control, early administration of antifungals, and aggressive surgical debridement are the mainstay of treatment.

KEY WORDS

COVID-19, Hyperglycemia, Mucor, Mucormycosis, Pandemic

INTRODUCTION

Invasive fungal co-infections in severe COVID-19 patients have been recognized mainly with Aspergillus and Candida with Mucor and Cryptococcus being less frequent.[1,2] Mucormycosis is a fulminant, fatal, opportunistic infection affecting immunocompromised host with characteristic angioinvasion leading to tissue infarction.[3] It can manifest as sinonasal, pulmonary, cutaneous, gastrointestinal, renal, and disseminated mucormycosis.[4]

Mucormycosis which was uncommon before the pandemic saw a rapid surge of cases in India in the second wave of the COVID-19 pandemic.[5-7] Nepal seemed to follow a similar trend as the number of sinonasal mucormycosis started rising after Nepal entered the second wave of COVID-19 in May 2021.

This study assessed the patient demographics, risk factors, clinical characteristics, and outcomes of sinonasal mucormycosis cases treated at a COVID-19 referral hospital in Nepal from May 2021 to October 2021. This is the largest cohort of this rare disease treated at a single center in the whole country.

METHODS

This retrospective, observational study was conducted in the department of ENT-HNS, Tribhuvan University Teaching Hospital, Nepal. Ethical clearance from the Institutional Review Committee (Ref 47(6-11)E2 081/082) was obtained before the study. Clinical records of 25 sinonasal mucormycosis patients managed at this center from May 2021 to October 2021 were reviewed.

Patients with histologically proven sinonasal mucormycosis were included in this study (Fig. 1). Those with invasive fungus other than mucormycosis or mucormycosis involving any sites other than the nose, paranasal sinus, orbit, and central nervous system were excluded.

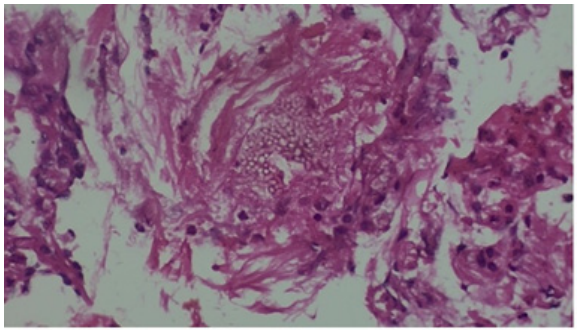


Figure 1. Non-septate, broad based hyphae with wide angle branching on H&E stain diagnostic for mucormycosis.

Patient demography, clinical features, and COVID-19 status were noted during admission. Routine blood tests were done, including C-reactive protein (CRP), Chest X-ray, and RT-PCR (Real-Time Polymerase Chain Reaction) for COVID-19 status. Nasal endoscopy was performed; samples for KOH mount and histopathological examination were taken. Computed tomography (CT) and Magnetic Resonance Imaging (MRI) of the nose, paranasal sinuses, orbit, and brain were obtained to determine disease extension.

All patients received intravenous amphotericin B mostly liposomal amphotericin B (LamB). Deoxycholate Amphotericin B (DamB) was administered whenever LamB was unavailable. Depending upon clinical and radiological findings, aggressive surgical debridement was done at the earliest possible. The necrotic tissue was debrided aggressively till bleeding was encountered, the extent was hence guided by clinical assessment and radiology. Persistence of disease in post-operative surveillance as indicated by raised CRP, a positive biopsy, and radiological evidence of disease lead to redebridement.

Once stable clinically, the patients were discharged on oral posaconazole, the duration of which was determined by clinical improvement, serial CRP, and nasal endoscopy findings in the outpatient visit.

The patient demographics, co-morbidities, COVID-19 status, clinical characteristics, and outcomes were assessed. The data was analyzed using Microsoft Excel (Version 16.49). All descriptive data were analyzed using mean, standard deviation, frequency, range, and percentages.

RESULTS

A total of 25 patients of sinonasal mucormycosis were admitted from May 2021 to October 2021 with the maximum number of admissions in June 2021 (Fig. 2). There were 18 males and seven females. The age ranged from 16 to 70 years with a mean of 51 ± 9.5 years.

Figure 2. Month-wise admission of sinonasal mucormycosis cases during the second wave of COVID-19 in Nepal

Co-morbid conditions

Uncontrolled diabetes mellitus (DM) was the most common co-morbidity detected in 23 patients of which 15 were previously known and eight were new onset. Amongst them, one had diabetic ketoacidosis. Of the two non-diabetics, one patient was on maintenance chemotherapy for Acute lymphoblastic leukemia while the other patient had no obvious co-morbidities nor documented history of COVID-19 infection (Table 1).

Sinonasal mucormycosis and COVID-19 infection

There were 20 patients with COVID-19-associated sinonasal mucormycosis (CASM) whilst five had no documented history of COVID-19 infection. Out of 20, nine patients still tested positive for COVID-19 at the time of admission whilst

11 had a history of COVID-19 in the recent past. Amongst these 20 CASM cases, 12 had been treated for COVID-19 pneumonia, seven had been observed in the hospital without oxygen and one was in home isolation. The mean time for sinonasal mucormycosis diagnosis was 12 days (2 to 45 days) after COVID-19 infection (Table 1).

Table 1. Patient demographics and systemic co-morbidities

Features	Number (%)
Age	
Range in years	16 - 70
Mean in years	51.24 (±9.5)
Gender	
Male	18 (72%)
Female	7 (28%)
Diabetes	
HbA1c	9.9 (±1.6)
Previously known	15 (60%)
New onset	8 (32%)
Non-diabetic	2 (8%)
Other co-morbidities	
Hypertension	8 (32%)
Acute kidney injury	2 (8%)
Chronic kidney disease	1 (4%)
Chronic liver disease	1 (4%)
Internal carotid artery dissection with partial Horner's syndrome	1 (4%)
Acute lymphoblastic leukemia	1 (4%)
COVID-19 status (n=25)	
Active at the time of admission	9
Recovered from COVID-19 infection	11
No documentation	5
Treatment for COVID-19 (n=20)	
Treated for pneumonia	12
Observation in hospital	7
Home isolation	1
Onset of symptoms of sinonasal mucormycosis post recovery from COVID-19 infection (n=11)	
Range in days	2 – 45
Mean in days	12
Within 14 days of recovery	8
After 14 days of recovery	3

Clinical presentation

Based on the extent of the disease clinically and radiologically, six patients had rhino-maxillary (RM), seven had rhino-orbital (RO), and 12 had rhino-orbital-cerebral (ROC) involvement (Table 3, Fig. 4). The most common first presenting symptom was orbital (17/25) followed by facial (5/25) and orodental (3/25) with other clinical features manifesting subsequently (Table 2, Fig. 3).

Table 2. Clinical presentation of sinonasal mucormycosis (N=25).

Symptoms	Signs
Orbital (19)	
Periorbital swelling (16)	Periorbital oedema (16)
Ptosis (10)	Complete ophthalmoplegia (10)
Loss of / diminished vision (9)	Loss of / diminished vision / CN II (9)
Diplopia (6)	CN VI palsy (6)
Pain (3)	Proptosis (2)
Proptosis (2)	
Facial (19)	
Numbness of cheek (17)	CN V2 Palsy (17)
Facial swelling (7)	Cheek swelling (7)
Cheek pain (6)	Cheek skin discoloration and discharging pit (1)
Painful frontal swelling (1)	Tender frontal swelling (1)
Nasal (15)	
Nasal blockage (3)	Black middle turbinate (7)
Blood mixed blackish nasal discharge (3)	Black inferior turbinate (7)
	Yellowish thick discharge with pale nasal mucosa (8)
	Black nasal discharge (4)
	Septal perforation (2)
	Blackish nasal septum (1)
Dento-alveolar (4)	
Dental pain with loosening of tooth (2)	Hypoesthesia of palate (2)
Ulcer In hard palate (2)	Hard palate ulcer (2)
Hard palate discoloration (1)	Unhealthy gums with loosening of tooth (2)
Cerebral (2)	
Disorientation and unilateral weakness of body (2)	Hemiparesis (2)

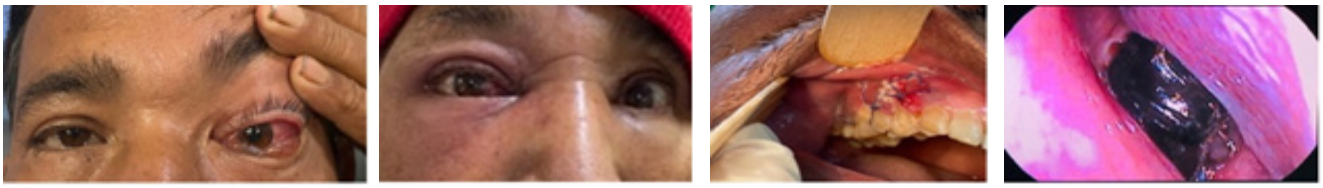
Various radiological findings were key in supporting the diagnosis of the ROC mucormycosis (Table 3).

Treatment

Nine patients received only medical treatment while 16 patients had surgical procedures combined with medical treatment. These sixteen patients underwent 26 surgical procedures. The procedures ranged from one to four per person (Table 4).

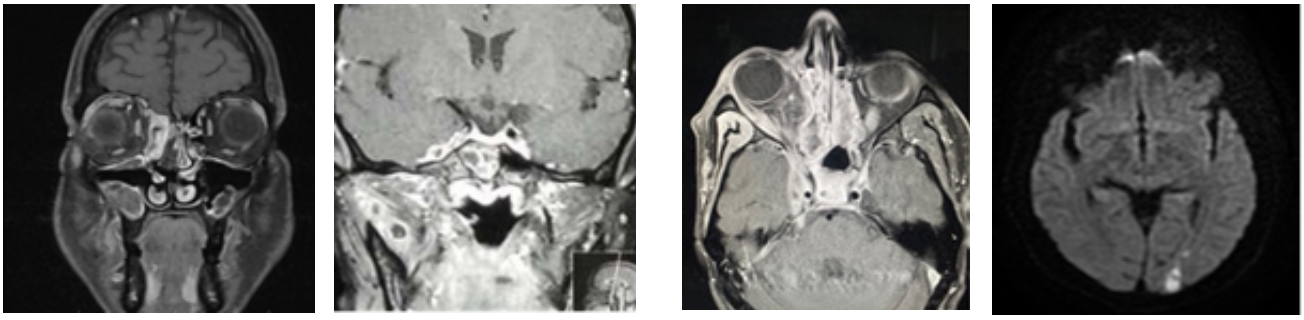
Outcome

Out of the 25 patients, 14 (56%) had good recovery. Amphotericin B was given for 2 to 8 weeks (4 weeks on average). The amphotericin B was mostly liposomal preparation which was replaced by deoxycholate form in case of unavailability of liposomal amphotericin B. Four



Left ophthalmoplegia | Right 6th nerve palsy with right periorbital swelling | Loosening of tooth | Black middle turbinate on nasal endoscopy

Figure 3. **Various clinical presentation of sinonasal mucormycosis.**



T1 with contrast - Right black middle turbinate sign | T1 with contrast -Involvement of right ITF, sphenoid sinus, cavernous sinus, right temporal lobe dural enhancement | T1 with contrast Involvement of the Right V and Meckel's cave | Diffusion weighted image Left occipital lobe infarction

Figure 4. **MRI findings in rhino-orbital-cerebral mucormycosis patients.**

Table 3. **Radiological findings in rhino-orbital-cerebral mucormycosis patients (n=12)**

Radiological findings		Number of patients
Cavernous sinus thrombosis		3
Cavernous sinus thrombosis with	Infarction of frontoparietal lobe	2
	Temporal lobe dural enhancement	1
	Meckel's cave involvement and temporal lobe dural enhancement	1
Temporal lobe dural enhancement		3
Internal carotid dissection and thrombosis		1
Frontal lobe abscess		1

Table 4. **Surgical procedures sinonasal mucormycosis patients (n=16).**

Surgical procedure	Number of patients
Endoscopic	
Modified Denkers' approach	8
Modified Denkers' approach with orbital exenteration	2
Draf IIb procedure + medial maxillectomy	1
MELP	1
Redebridement of previous cavity	9
Open procedure	
Subtotal maxillectomy	2
Total maxillectomy	2
MELP with Reidel's procedure	1

*MELP: Modified Endoscopic Lothrop Procedure

patients received Transcutaneous retrobulbar amphotericin B. Maintenance with posaconazole ranged from 3 to 9 months (5.5 months on average).

Four patients expired during their hospital stay. One patient (ROCM) had bilateral cavernous sinus involvement with infarcts in the frontal, parietal, and occipital lobe, and another (ROCM) had left ICA dissection with thrombosis with partial Horner's syndrome. These patients had received medical management only. One patient (RM) expired on the 7th postoperative day due to septic shock and another (ROCM) due to refractory hypoxemia secondary to pneumothorax during central venous catheter insertion.

Four patients with intracranial extension and hence poor prognosis were discharged on request. Three patients left the hospital against medical advice due to financial issues, therefore, the outcomes of these seven patients are unknown (Table 5).

DISCUSSION

During the second wave of the COVID-19 pandemic, a rapid surge of mucormycosis was observed. In just six months, there were 25 histologically proven sinonasal mucormycosis cases. The hospital where these patients received treatment is a tertiary care center based in Kathmandu, the capital city of Nepal. It was a designated COVID-19 hospital

Table 5. Outcomes of sinonasal mucormycosis based on disease extent (N=25).

Disease Extent	Outcomes	Number of patients
RM (6)	Recovered	3
	Left against medical advice	2
	Death (septic shock)	1
ROM (7)	Recovered	6
	Left against medical advice	1
	Death	0
ROCM (12)	Recovered	5
	Discharged on request	4 (cavernous sinus thrombosis-3, multiple infarct right frontoparietal lobe – 1)
	Death	3

*RM:Rhino-maxillary mucormycosis; ROM:Rhino-orbital mucormycosis; ROCM:Rhino-orbital-cerebral mucormycosis

then, which received a lot of referrals. The increase in the number of sinonasal mucormycosis cases in the country was reflected in the number of cases referred and admitted during the second wave of COVID-19.

Mucormycosis is caused by Mucoraceae which falls under the class of Zygomycetes. They are commonly found in the air, soil, and decaying organic material and can also be present in the nasal mucosa as commensal. It can invade the paranasal sinus and beyond if the host becomes immunocompromised such as in cases of diabetes mellitus, severe burns, or solid organ transplant.[5] The mode of infection is by inhalation of fungal spores.

The epidemiology for mucormycosis differs in developing countries as compared to Western countries. As for developing countries, uncontrolled diabetes mellitus is the main risk factor whilst hematological malignancies are predominant in developed countries.[3,4] This has been attributed to the increasing number of patients receiving intensive chemotherapy and fewer cases of uncontrolled diabetes mellitus in developed countries.[3] The clinical presentation can vary depending on the immune characteristic of the host. Diabetics tend to develop sinonasal mucormycosis with the paranasal sinus being commonly involved followed by the orbit and brain subsequently.[3,4] Sino-pulmonary mucormycosis is often seen in those with hematological malignancies with a lesser tendency for cerebral involvement. Skin and soft tissue mucormycosis often precede trauma.[3]

Patel et al. reported a prevalence of 0.27% mucormycosis among hospitalized COVID-19 patients.[8] The patients with COVID-19 associated mucormycosis had three distinct features, namely hyperglycemia, steroid use, and sinonasal involvement.[9,12] Poor glycemic control is an important factor that was observed in 23 out of 25 patients in our study. One patient had diabetic ketoacidosis. Uncontrolled sugar levels and diabetic ketoacidosis provide an ideal environment for the proliferation of fungi by various mechanisms, viz. impaired phagocytosis and chemotaxis, hyperferritinemia, and increased expression of GRP78 in the endothelial cells, which has an affinity to bind with CotH3 protein of fungal hyphae.[10,11]

COVID-19 was found to produce a severe inflammatory reaction in the human body that flared up a hyperglycemic state.[13] In addition, it acted on angiotensin-converting enzyme 2 receptors in pancreatic islet cells which led to hyperglycemia.[11,14] Furthermore, the liberal use of corticosteroids during the COVID-19 pandemic could have flared up the situation. Immunological alteration with reduced CD4/CD8 T cells during COVID-19 infection led to opportunistic infections.[11,15] The hyperferritinemic state during the COVID-19 infection not only favored fungal growth but, led to the production of reactive oxygen species and tissue damage.[11,14,16]

In our study, the onset of symptoms of sinonasal mucormycosis varied from when patients still tested positive for COVID-19 to 2 to 45 days (mean 12 days) post-recovery from COVID-19. Similarly, Sen et al. also reported the onset of sinonasal mucormycosis ranging from when the patient was still under active treatment for COVID-19 to three months post-recovery with 56% manifesting the disease within 14 days.[7] There was a lag of 20 (15 to 24) days between diagnosis of COVID-19 and sinonasal mucormycosis in the study by Bhattacharyya et al.[17] The possibility of delayed onset of the disease emphasized the need for longer follow-up of COVID-19 patients post-recovery.

Sen et al. reported a mean age of 51.9 (12 to 88) years, mostly affecting males (1993/2826, 71%).[7] Similar to the Indian scenario, sinonasal mucormycosis cases in Nepal emerged rapidly in the second wave of the COVID-19 pandemic. The age affected was similar (range 16-70 years; mean 51 years) with 72% being males in our study. Similarly, Saleeb et al. in Egypt reported a mean age of 54 years with 51.5% males.[18] Hoenigl et al. reported a similar age of 55 years (range 10 to 86 years) as the mean age of presentation and 78% of males based on the data from 18 countries.[9]

Mucor has angionvasive properties with hematogenous spread. Fungal hyphae proliferate in internal elastic lamina and cause thrombosis with tissue necrosis. COVID-19 may flare up this mechanism by thrombotic microangiopathy.[11] In the initial phase, the nasal cavity and turbinates are affected, with discoloration, and loss of sensation, indicative of tissue necrosis. This could rapidly spread to paranasal sinuses and orbit. Ethmoidal and maxillary sinuses are commonly involved.[17,19] At this stage, facial pain, orbital or facial cellulitis, ophthalmoplegia, proptosis, and loss of vision may occur.[16] Failure to adequately treat results in the spread of infection to the pterygopalatine fossa, infratemporal fossa, cavernous sinus, palate, and alveolus. Intracranial spread may occur via contiguous

spread, perineural spread especially via the maxillary nerve or the optic nerve, or rarely by hematogenous route to result in mycotic brain abscess.[20-22]

In our study, most of the patients were admitted at an advanced stage of disease. Twelve out of 25 patients had rhino-orbital-cerebral involvement, seven had rhino-orbital while only six had sinonasal involvement. The commonest presenting symptom was cheek numbness and periorbital swelling. The initial symptom of nasal blockage was seen in only three patients. This reflects the rapid spread of infection to deeper structures and the late referral of these patients to our hospital. Due to the rarity of mucormycosis, a high index of suspicion is required for early diagnosis. In a meta-analysis done by Bhattacharyya et al., rhino-orbital presentation was the most common.[17] Vision loss, ophthalmoplegia, proptosis, and lid edema were found to be the commonest orbital symptoms.[17] Desai et al. and Garg et al. reported headache and facial pain as the commonest clinical presentation.[23,24] Intracranial spread to the cavernous sinus should be suspected when III, IV, V1, V2, and VI are involved. Hemiparesis, altered sensorium, and seizures could be due to brain invasion and infarction.[3]

The black turbinate sign as indicated by non-enhancing mucosal tissue and turbinates due to small vessel occlusion and mucosal ischemia is seen on contrast MRI. Extrasinus involvement includes spread to the orbit, subcutaneous facial tissue, and the infratemporal and temporal fossa. Extension to the orbit causes thickening and lateral displacement of the medial rectus muscle, preseptal edema, proptosis, and orbital fat infiltration, particularly at the orbital apex. Cavernous sinus thrombosis, brain infarction, and internal carotid artery occlusion are common findings if the disease has spread intracranially.[3]

Since tissue necrosis is more common than bone erosion in mucormycosis, contrast-enhanced MRI is the preferred choice of imaging as soft tissue delineation is better. CT can be misleading as it can appear normal.[5] However, contrast-enhanced CT does have a role when MRI cannot be carried out. A plain CT also may be useful to assess disease extent if contrast is contraindicated.[7]

A multidisciplinary approach consisting of timely effective antifungal treatment, early surgical debridement of the necrotic tissue, and correction of the underlying immunocompromised status are crucial for positive outcomes.[3] The need for strict control of underlying medical conditions is equally important.[5] The extent of surgery depends on the disease's extent. Endoscopic debridement can address localized disease but open surgery may be needed for orbital, palatal, and intracranial extension. Repeated surgical debridement may be needed for local control of the disease.[5] Orbital exenteration although not routinely done for orbital disease, it may be life-saving at times depending on the aggressiveness of presentation, the type of underlying disease process, and response to initial therapy.[5] The patient's general condition and prognosis need to be considered especially when extensive surgery is planned.

Amphotericin B is the antifungal drug of choice with liposomal preferred over deoxycholate formulation owing to its less nephrotoxicity. However, deoxycholate or lipid complex may be used in case of unavailability of LamB.[7] Irrigating and packing the surgical site with amphotericin have also been documented.[5] Antifungals are continued till there is clinical improvement with radiological evidence of stabilization or resolution of the disease and control of the underlying immunosuppressive condition. The duration of therapy for mucormycosis may therefore vary based on the individual status.[5] For CNS mucormycosis, the ideal treatment duration is yet to be known, however, most are treated for a minimum of six months. The initial treatment includes L-AmB which is followed by maintenance treatment with less toxic azoles like posaconazole or isavuconazole.[3]

The overall mortality with orbital and intracranial involvement is 50 to 80%.[25] In our study, higher mortality was seen in patients with intracranial infection. Mortality can be reduced with rapid correction of immune imbalance, blood sugar control along with antifungals and surgical debridement. Fourteen out of 25 (56%) patients had good recovery in our study. This is similar to the findings of a meta-analysis performed by Bhattacharyya et al. with 60.8% success rate.[17] Saleeb et al. reported a mortality of 27.3% (9 out of 33 patients).[18]

The strength of this study lies in its inclusion of the largest cohort of sinonasal mucormycosis in Nepal, which was rarely encountered before the pandemic. Thus, it provides a better clinicopathological insight into this rare disease and helps raise a high index of suspicion needed to initiate intervention as early as possible for a better outcome. The limitations of this study include its small sample size and its retrospective nature.

CONCLUSION

Sinonasal mucormycosis in COVID-19 was common in uncontrolled hyperglycemic patients. Advanced disease presentation in the form of rhino-orbital-cerebral involvement was common due to rapid extrasinus spread and delay in diagnosis. Just a little more than 50% of patients had good recovery while those with intracranial involvement had poor outcomes. A high index of suspicion for diagnosis is needed. Adequate blood sugar control, early administration of antifungals, and aggressive surgical debridement are the mainstay of treatment.

REFERENCES

1. Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: we should be prepared. *J Mycol Med*. 2020 Jun;30(2):100971. doi: 10.1016/j.mycmed.2020.100971.
2. Song G, Liang G, Liu W. Fungal co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China. *Mycopathologia.* 2020 Aug;185(4):599-606. doi: 10.1007/s11046-020-00462-9.
3. Chikley A, Ben-Ami R, Kontoyiannis DP. Mucormycosis of the central nervous system. *J fungi.* 2019 Jul 8;5(3):59. doi:10.3390/jof5030059.
4. 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 Jun 1;57(4):395-402. doi:10.1093/mmy/myy060.
5. Ballester DG, González-García R, García CM, Ruiz-Laza L, Gil FM. Mucormycosis of the head and neck: report of five cases with different presentations. *J Craniomaxillofac Surg*. 2012 Oct 1;40(7):584-91. doi:10.1016/j.jcms.2011.10.015. Epub 2011 Nov 13.
6. Raut A, Huy NT. Rising incidence of mucormycosis in patients with COVID-19: another challenge for India amidst the second wave? *Lancet Respir Med.* 2021 Aug 1;9(8):e77. doi: 10.1016/S2213-2600(21)00265-4.
7. Sen M, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U, et al.. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India–Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. *Indian J Ophthalmol*. 2021 Jul 1;69(7):1670-92. doi: 10.4103/ijo.IJO_1565_21.
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 Sep;27(9):2349. doi:10.3201/eid2709.210934.
9. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, et al. The emergence of COVID-19-associated mucormycosis: a review of cases from 18 countries. *Lancet Microbe.* 2022 Jul 1;3(7):e543-52. doi:10.1016/S2666-5247(21)00237-8.
10. Alkhamiss AS, Ahmed AA, Rasheed Z, Alghsham R, Shariq A, Alsaeed T, et al.. Mucormycosis co-infection in COVID-19 patients: An update. *Open Life Sci.* 2022 Aug 10;17(1):917-37. doi: 10.1515/biol-2022-0085.
11. Das AK, Mani SK, Singh SK. Surgical management of post-COVID-19 invasive rhino-orbito-cerebral mucormycosis and its outcomes: Role of neurosurgeons in a tertiary care center. *Surg Neurol Int.* 2022;13:335. doi: 10.25259/SNI_374_2022.
12. Prabhakar A, Bansal S, Vyas S, Bhatia V, Kumar A, Patro S, et al. Clinicoradiological profile of COVID-19 associated rhino-orbital cerebral mucormycosis with a focus on computed tomography: A clinical case series and review. *Am J Trop Med Hyg*. 2023 Sep;109(3):600. doi:10.4269/ajtmh.22-0298.
13. Vadivel S, Gowrishankar M, Vetrivel K, Sujatha B, Navaneethan P. Rhino orbital cerebral mucormycosis in COVID-19 crisis. *Indian J Otolaryngol Head Neck Surg*. 2023 Apr;75(Suppl 1):1014-20. doi:10.1007/s12070-023-03474-1.
14. John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. *J fungi.* 2021 Apr 15;7(4):298. doi: 10.3390/jof7040298.
15. Mitra S, Janweja M, Sengupta A. Post-COVID-19 rhino-orbito-cerebral mucormycosis: a new addition to challenges in pandemic control. *Eur Arch Otorhinolaryngol.* 2022; 279(5): 2417–2422. doi: 10.1007/s00405-021-07010-1.
16. Pal R, Singh B, Bhadada SK, Banerjee M, Bhogal RS, Hage N, et al. COVID-19-associated mucormycosis: an updated systematic review of literature. *Mycoses.* 2021 Dec;64(12):1452-9. doi: 10.1111/myc.13338.
17. Bhattacharyya A, Sarma P, Kaur H, Kumar S, Bhattacharyya J, Prajapat M, et al. COVID-19–associated rhino-orbital-cerebral mucormycosis: A systematic review, meta-analysis, and meta-regression analysis. *Indian J Pharmacol.* 2021 Nov 1;53(6):499-510. doi: 10.4103/ijp.ijp_839_21.
18. Saleeb MF, Sabry SM, Mahmoud MS, Nassif MM. Risk factors affecting outcome of rhino-orbital-cerebral mucormycosis in COVID-19 patients. *Egypt J Otolaryngol.* 2023 Jun 7;39(1):95.
19. Joshi AR, Muthe MM, Patankar SH, Athawale A, Achhapalia Y. CT and MRI findings of invasive mucormycosis in the setting of COVID-19-19: experience from a single center in India. *AJR Am J Roentgenol*. 2021 Dec 23;217(6):1431-2. doi:10.2214/AJR.21.26205.
20. Galletta K, Alafaci C, D'Alcontres FS, Maria ME, Cavallaro M, Ricciardello G, et al. Imaging features of perineural and perivascular spread in rapidly progressive rhino-orbital-cerebral mucormycosis: A case report and brief review of the literature. *Surg Neurol Int.* 2021;12. doi: 10.25259/SNI_275_2021.
21. Hosseini SM, Borghei P. Rhinocerebral mucormycosis: pathways of spread. *Eur Arch Otorhinolaryngol.* 2005 Nov;262:932-8. doi:10.1007/s00405-005-0919-0.
22. Orguc S, Yücetürk AV, Demir MA, Goktan C. Rhinocerebral mucormycosis: perineural spread via the trigeminal nerve. *J Clin Neurosci*. 2005 May 1;12(4):484-6. doi: 10.1016/j.jocn.2004.07.015.
23. Desai EJ, Pandya A, Upadhya I, Patel T, Banerjee S, Jain V. Epidemiology, clinical features and management of rhino orbital mucormycosis in post-COVID-19 patients. *Indian J Otolaryngol Head Neck Surg.* 2022 Mar;74:103-7. doi:10.1007/s12070-021-02807-2.
24. Garg R, Bharangar S, Gupta S, Bhardwaj S. Post COVID-19 infection presenting as rhino-orbital mycosis. *Indian J Otolaryngol Head Neck Surg*. 2022 Oct;74(Suppl 2):3050-7.
25. Eker C, Tarkan O, Surmelioglu O, Dagkiran M, Tanrisever I, Yucel Karakaya SP, et al. Alternating pattern of rhino-orbital–cerebral mucormycosis with COVID-19in diabetic patients. *Eur Arch Otorhinolaryngol*. 2023 Jan;280(1):219-26.