

A study on clinical presentation of rhino orbital cerebral mucormycosis associated with COVID-19 infection

¹Dr. Bomma Vijay Kumar, ²Dr Naresh Mogilicharla, ³Dr. Potlacheruvu Nagaraju,
⁴Dr. Moota Madhuri, ⁵Dr. A Shobhan Babu

¹Assistant Professor, Department of E.N.T, Gandhi Medical College, Secunderabad, Telangana, India

²Senior Resident, Department of E.N.T, Government Medical College, Kothagudem, Telangana, India

^{3,4}Junior Resident, Department of E.N.T, Gandhi Medical College, Secunderabad, Telangana, India

⁵Professor and HOD, Department of E.N.T., Gandhi Medical College and Hospital, Secunderabad, Telangana, India

Corresponding Author:

Dr. A Shobhan Babu (shobhanaachi@gmail.com)

Abstract

Background and aims: During the second wave of coronavirus disease 2019 [covid-19] in India, there is a rapid surge of opportunistic fungal infections among covid-19 patients. Rhino-Orbito-Cerebral mucormycosis is the most common disease among these patients apart from pulmonary aspergillosis. The study aims to determine the clinical presentation, signs, and symptoms in patients with rhino-orbito-cerebral mucormycosis associated with coronavirus disease in the present scenario.

Methods: It is a retrospective observational study. The Clinical history of 100 patients from medical records with Rhino-Orbito-Cerebral mucormycosis associated with covid-19 during the months of May and June 2021 is collected and analyzed.

Results: In our study on 100 patients with mucormycosis infection 95 patients were diagnosed with covid-19 infection and 82 patients were diabetic. Among the diabetic group, 53 were chronic diabetic and 29 were detected denovo. The disease is seen most prominently in the people of the age group between 30-60yrs. Males are more affected. The urban population represented 67 percent. The chief complaints of the patients with mucormycosis related covid-19 are pain (88%), swelling/edema (79%), visual disturbance (51%), numbness over the face (47%), nasal discharge (45%). Clinical findings of the disease are, ptosis (52%), blurring/absent vision (51%), proptosis (41%), ophthalmoplegia (33%), discoloration over the face (26%) and necrosis of the soft tissues (8%).The percentage of people presented with mucormycosis between diagnosis of covid-19 infection and onset of symptoms of mucormycosis is observed to be 72% within two weeks and 89% within three weeks. Regarding the covid-19 symptoms, mild symptoms were seen in 59.9%, moderate symptoms in 29.4% and severe symptoms in 10.5% of patients. 76 patients were on corticosteroid therapy and 35 patients were oxygen-dependent.

Conclusion: Clinical features like unilateral facial pain, facial and periorbital edema, nasal discharge, and numbness over the face within 3 weeks of covid-19 infection should raise suspicion. Early signs and symptoms should be identified and the diagnosis of mucormycosis

should be done. Histopathology and radiological findings should be done to confirm the diagnosis. Uncontrolled blood sugar levels and immunosuppression are the contributing factors for mucormycosis. Blood sugar levels have to be controlled and judicious administration of corticosteroids is recommended.

Keywords: Clinical, orbital cerebral, mucormycosis, COVID-19, coronavirus

Introduction

Mucormycosis is a rare fungal infection caused due to fungi of the order Mucorales (Skiada *et al.*, 2020). Among Mucoraceae, *Rhizopus oryzae* is the most common cause of infection (Ribes *et al.*, 2000). In the second wave of covid-19 in India during the months of May and June 2021, there is a sudden rise in this rare form of fungal infection associated with coronavirus. It is mostly seen in immunocompromised patients like patients with uncontrolled diabetes mellitus, a history of corticosteroid use, malignancies, and organ transplant patients (Petrikos *et al.*, 2012). The presentation of the disease is usually rhino-orbito-cerebral, cutaneous, renal, pulmonary and gastrointestinal in decreasing order among Indian patients (Chakrabarti *et al.*, 2001). Angioinvasion and vessel thrombosis resulting in necrosis of the infected tissues is the prominent feature of this disease (Bouchara *et al.*, 1996). The clinical manifestations and disease progression are quite different with covid related mucormycosis when compared to covid-19. The disease progress rapidly and there is a need for aggressive management of these patients with medical and surgical modalities. Diagnosis is made by clinical manifestations, imaging and histopathology (Skiada *et al.*, 2020) (Prakash & Chakrabarti, 2021). Studies that were done in India before the pandemic treated this disease as a rare fungal infection, but during the second wave of covid, India reported thousands of mucormycosis cases. Most of these cases are related to covid-19 infection either in covid recovered patients or patients with active covid infection. The disease presentations in these patients should be studied in relation to covid-19 infection to diagnose them early and manage these cases to decrease the mortality among these patients.

Methods

We retrospectively studied the medical records of 100 patients admitted with mucormycosis associated with covid-19 infection at a public hospital in the state of Telangana, India. Data regarding the age distribution, sex ratio, signs and symptoms, comorbidities, and covid-19 associated factors are collected. The time period is taken between May and June 2021 during the second wave of covid-19 in India, where there was a surge in mucormycosis related covid-19. The data was analyzed and conclusions were made accordingly.

Results

Demography

Out of 100 patients 67 were males and 33 were females. The age group extended from 18yrs to 75yrs and most of the affected were between 30-60yrs of age. The urban population represented a major proportion of the patients.

Age group

Table 1

Age group										
1-10yrs	11-20yrs	21-30yrs	31-40yrs	41-50yrs	51-60yrs	61-70yrs	71-80yrs	81-90yrs	91-100yrs	Total
0	1	3	24	35	28	6	3	0	0	100

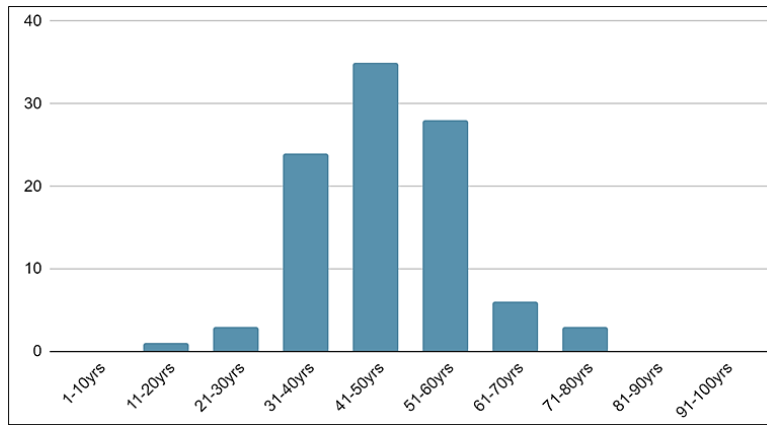


Diagram 1: No of patients

Table 2

Total	100
Urban	67
Rural	33

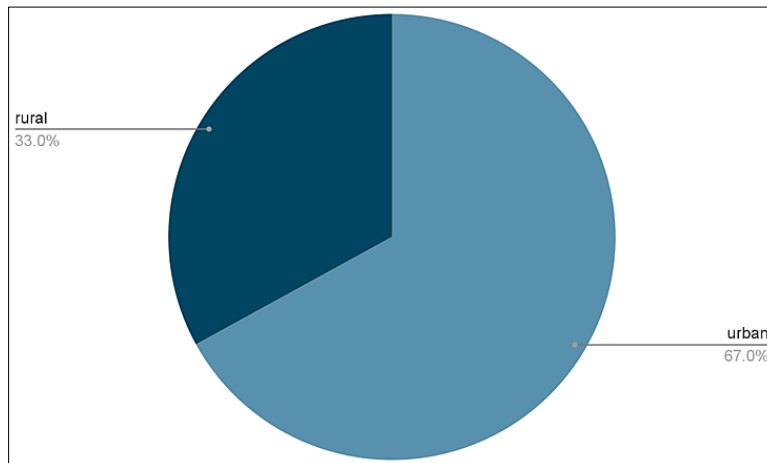


Diagram 2: Sex ratio

Table 3

Sex ratio		
Male	Female	Total
67	33	100

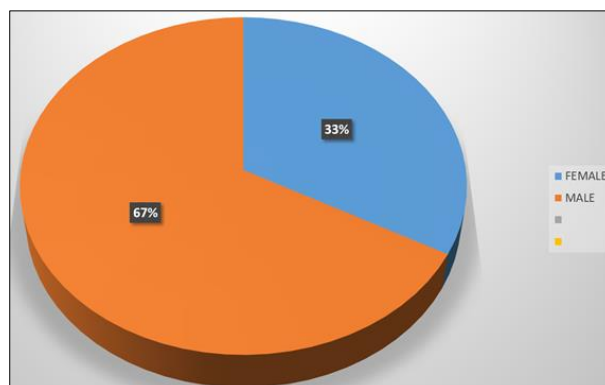


Diagram 3: Sex ratio
1990

Signs and symptoms

Patients presented with pain, edema over the face and periorbital region, visual disturbances, numbness over the infraorbital region, bloody nasal discharge, skin discoloration over the face, and necrosis over the hard palate. Pain is a major complaint of patients with mucormycosis. out of 100 patients, 88 complained of pain. Mostly presented with facial pain over maxillary, alveolar, periorbital regions, and headache. Unilateral pain is seen in the majority of patients.

Table 4

Total no of patients	100
Patients with pain complaints	88
Facial pain	70
Periorbital pain	67
Headache	64

Swelling of the soft tissues due to inflammation is also an important sign with nasolabial and periorbital regions involving the most. out of 100 patients, 79 patients presented with edema over the face i.e, periorbital edema and edema over the nasolabial region.

Table 5

Total no of patients	100
swelling/edema over face	79
Nasolabial and periorbital region	36
Periorbital edema only	24
Nasolabial edema only	19

47 patients complained of numbness over the infraorbital region, palate, and alveolus. Numbness over the unilateral infraorbital region is seen in most of the patient's

Table 6

Total no of patients	100
Patients complaining of Numbness	47
Numbness over the face	42
Numbness of teeth/alveolus	12

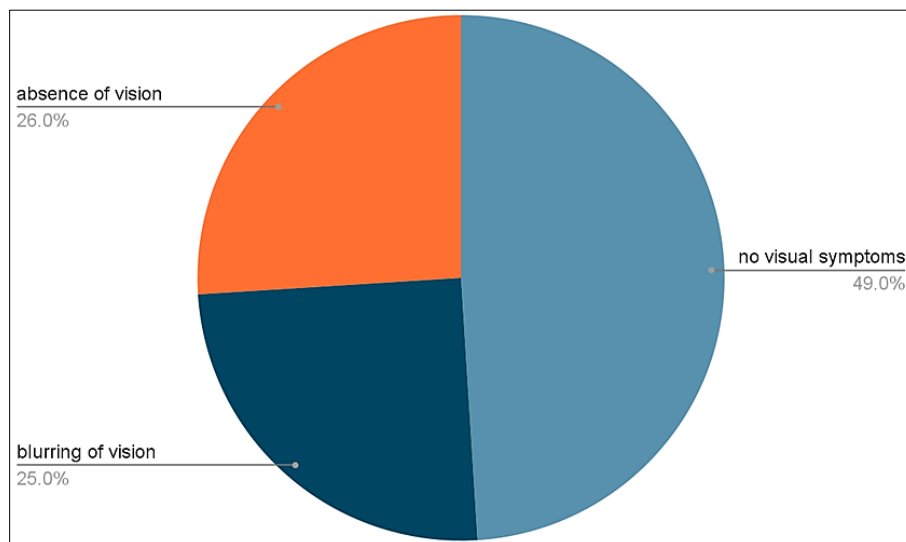
51 patients presented with visual disturbances in the form of blurring of vision in 25 patients and loss of vision in 26 patients. The visual disturbances are associated with proptosis and limitation of movement of the eyeball. Most of the patients presented with unilateral symptoms while bilateral symptoms were seen in only 2 patients.

Table 7

Total	100
Visual disturbance	51
proptosis	41
Limitation of movement of eyeball	33
ptosis	52

Table 8

Total	100
Visual disturbance	51
Blurring of vision	25
Absence of vision	26

**Diagram 4**

Nasal discharge is seen in 45 patients out of which 27 complain of bloody nasal discharge while others are blackish and mucoid nasal discharge.

Table 9

Total no of patients	100
Pt's with Nasal discharge	45
Bloody discharge	27
Blackish discharge	9
Mucoid discharge	9

Other significant signs and symptoms are discoloration over face, nasal obstruction, cough, shortness of breath, fever, loosening of teeth, throat pain, necrosis over hard palate, and altered sensorium.

Table 9

Total	100
Discoloration over face	26
Nasal obstruction	24
Cough	23
Shortness of breath	19
Fever	17
Loosening of teeth	11
Throat pain	11
Palatal necrosis	8
Altered sensorium	8

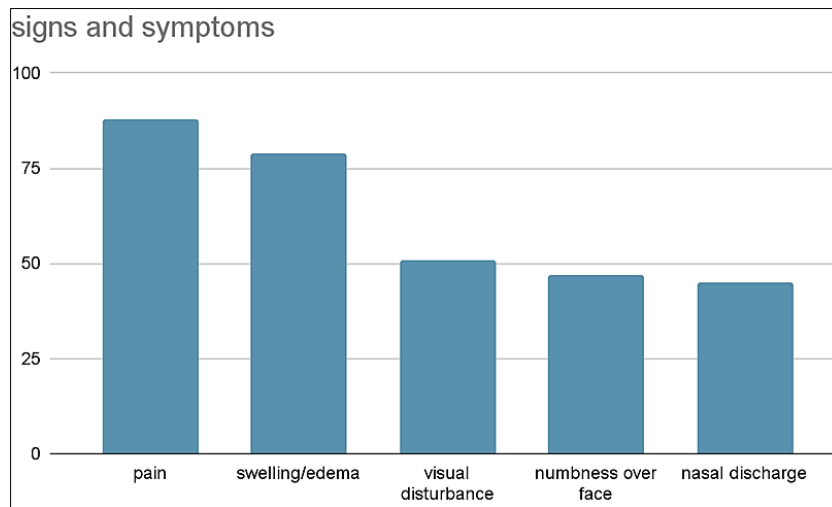


Diagram 5

Comorbidities

82 out of 100 patients were diabetic and 33 out of 100 were hypertensive. Among the diabetic group of 82 patients, 53 patients were chronic diabetics and 29 patients were detected denovo. Out of 33 hypertensive patients, 28 were having diabetes mellitus. Other comorbidities like obesity, hypothyroidism, cardiovascular disease, chronic kidney disease, and malignancy were noted.

Table 10

Total no of patients	100
Diabetes mellitus	82
hypertension	33
Obesity	6
Hypothyroidism	5
Cardiovascular disease	4
Chronic kidney disease	3
Malignancy	3

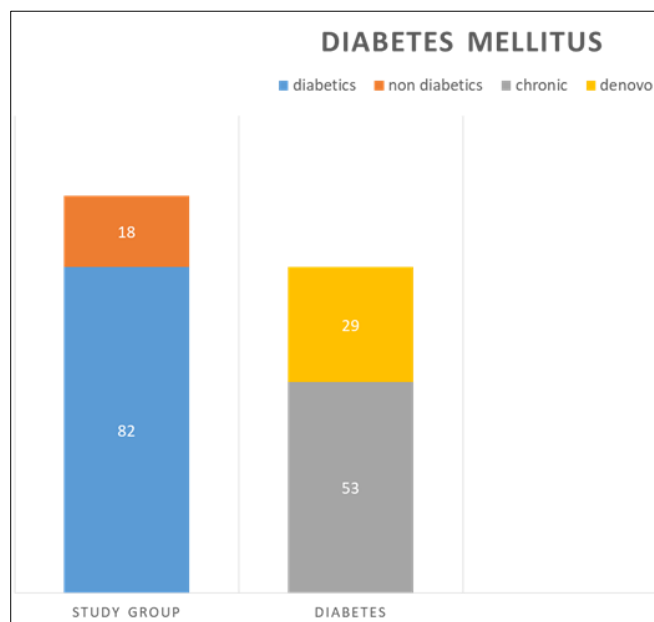


Diagram 6

Table 11

Patients with diabetes	82
chronic	53
Denovo detected	29

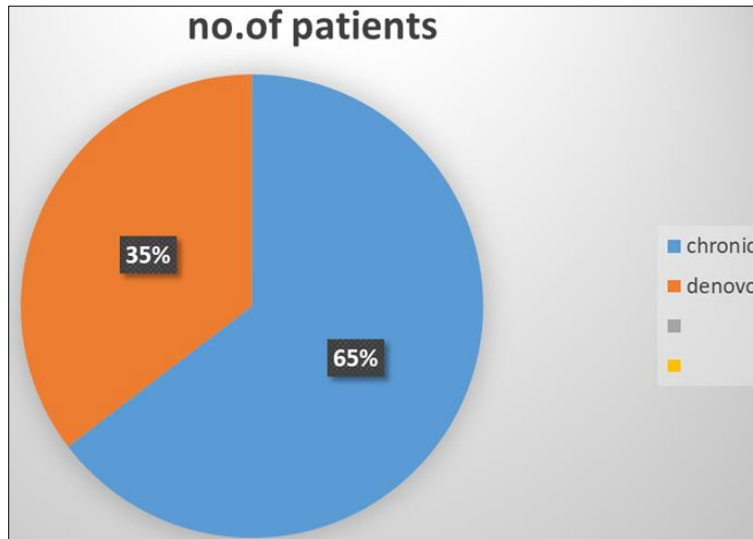


Diagram 7

Covid-19 history

95 except 5 were either active covid-19 cases or with covid-19 recovered cases. Out of 95 patients 48 patients presented with mucormycosis symptoms within one week of covid-19 diagnosis and 24 patients during the second week. Majority of cases were seen during the first two weeks of covid-19 infection. 57 patients were having mild covid symptoms, 28 patients were with moderate covid symptoms, and 10 patients with severe covid symptoms. Out of the 5 covid negative patients, 3 patients were chronic diabetic and hypertensive and 2 patients were nondiabetic & nonhypertensive. Their age group range is from 35yrs to 41yrs.

Table 12

Total no of mucormycosis patients	100
Covid-19 positive	95
Covid-19 negative	5

Table 13

	Duration between covid-19 and mucormycosis symptoms
Total no's of covid-19 patients	95
0-7 days	48
8-14days	24
15-21days	17
22-28days	3
29-35days	2
36-42days	0
43-49days	1

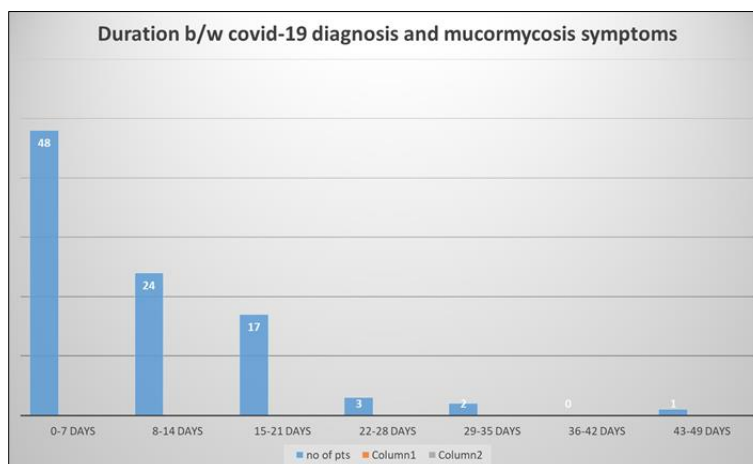


Diagram 8

Table 14

Total covid-19 patients	95
Mild	57
Moderate	28
Severe	10

76 patients had a history of treatment with corticosteroids and 35 patients were oxygen-dependent during the covid treatment.

Discussion

Mucormycosis was a rare fungal infection but the scenario changed during the covid-19 pandemic. In many of the covid-19 patients during the phase of active viral infection and the recovery phase, there is a surge of co-infection with mucormycosis. Most of the covid-19 patients were treated with antivirals and corticosteroids. Usually, humans have humoral immunity for preventing the germination of fungal spores and the growth of hyphae (Waldorf A.R., 1989) (Waldorf *et al.*, 1984). Neutrophils and monocytes or macrophages act on aspergillosis and mucormycosis (Waldorf A.R., 1989) (Waldorf *et al.*, 1984). In diabetics, the ability of macrophages to prevent spore germination is disabled thus making the diabetic population more prone to mucormycosis (Waldorf *et al.*, 1984). The relation between covid-19 and mucormycosis as direct causative factors is not proven in any study till now. Diabetes mellitus is considered an independent risk factor in both these conditions. In our study on 100 patients of covid-19 related mucormycosis infection, 95 patients were diagnosed with covid-19 infection. 82 patients had a history of diabetes. Among the diabetic group, 53 were chronic diabetic and 29 were detected denovo. In the covid negative group with 5 patients, 3 patients had a history of chronic diabetes. Mucormycosis in non-diabetic covid patients has to be further studied with a larger population group. The disease is seen most prominently in the people of age group between 30-60yrs. males are more affected (67%). The urban population represented 67 percent. Chief complaints of the patients with covid-19 related mucormycosis are pain (88%), swelling/edema (79%), visual disturbance (51%), numbness over the face (47%) and nasal discharge (45%). clinical findings of the disease are, ptosis (52%), blurring/absent vision (51%), proptosis (41%), ophthalmoplegia (33%), discoloration over the face (26%) and necrosis of the soft tissues (8%). similar findings were noted in studies done prior to covid in India (Bala *et al.*, 2015) (Patel *et al.*, 2020) (Sungurtekin *et al.*, 2021). The percentage of people presented between the diagnosis of covid-19 infection and onset of symptoms of mucormycosis is observed to be 72% within two weeks and 89% within three

weeks. Regarding the covid-19 symptoms, mild symptoms were seen in 59.9%, moderate symptoms in 29.4%, and severe symptoms in 10.5% of patients (protocol for COVID-19., 2020). Out of 100 patients, 76 patients were on corticosteroid therapy and 35 patients were oxygen-dependent. There is a need to be aware of the clinical findings of covid-19 related mucormycosis and act as early as possible to manage the disease to reduce mortality. Early findings in covid patients like unilateral facial pain, periorbital swelling, and bloody nasal discharge should raise suspicion of mucormycosis. Blurring of vision is an imminent sign of orbital cellulitis and if delayed, will progress to loss of vision. Diagnosis should be confirmed by histopathology and radiological imaging. Patients are managed by surgical debridement of the necrotic tissue followed by medical management with antifungal therapy along with covid treatment.

Conclusion

During the Covid-19 pandemic, there was a lot of confusion among the medical practitioners which led to the indiscriminate use of corticosteroids. Uncontrolled blood sugar levels and immunosuppression are the contributing factors for mucormycosis. Early signs and symptoms should be identified and a diagnosis of mucormycosis should be done. Clinical features like unilateral facial pain, facial and periorbital edema, nasal discharge, and numbness over the face should raise suspicion. Histopathology and radiological findings should be done to confirm the diagnosis. Blood sugar levels have to be controlled and judicious use of corticosteroids should be administered to covid-19 patients. Aggressive management with surgical debridement followed by administration of antifungals is of utmost importance to reduce the mortality of the disease.

References

1. Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: An update. *Journal of Fungi*. 2020;6(4):265. <https://doi.org/10.3390/jof6040265>
2. Chakrabarti A, Das A, Sharma A, Panda N, Das S, Gupta KL, *et al*. Ten years' experience in zygomycosis at a Tertiary Care Centre in India. *Journal of Infection*. 2001;42(4):261-266. <https://doi.org/10.1053/jinf.2001.0831>
3. Petrikos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. *Clinical Infectious Diseases*. 2012;54(1):S23-S34. <https://doi.org/10.1093/cid/cir866>
4. Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. *Microorganisms*. 2021;9(3):523. <https://doi.org/10.3390/microorganisms9030523>.
5. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. *Clinical Microbiology Reviews*. 2000;13(2):236-301. <https://doi.org/10.1128/cmr.13.2.236>.
6. Bouchara JP, Oumeziane NA, Lissitzky JC, Larcher G, Tronchin G, Chabasse D. Attachment of spores of the human pathogenic fungus *Rhizopus oryzae* to extracellular matrix components. *European journal of cell biology*. 1996;70(1):76-83.
7. Waldorf AR. Pulmonary defense mechanisms against opportunistic fungal pathogens. *Immunology series*. 1989;47:243-271.
8. Waldorf AR, Ruderman N, Diamond RD. Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against *Rhizopus*. *Journal of Clinical Investigation*. 1984;74(1):150-160. <https://doi.org/10.1172/jci111395>
9. Bala K, Chander J, Handa U, Punia RS, Attri AK. A prospective study of mucormycosis in north India: experience from a tertiary care hospital. *Medical mycology*. 2015;53(3):248-257. <https://doi.org/10.1093/mmy/myu086>.

10. 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. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* 2020;26(7):944.e9-944, e15. <https://doi.org/10.1016/j.cmi.2019.11.021>.
11. Sungurtekin H, Sargin F, Akbulut M, Karaduman S. Severe rhinocerebral mucormycosis case developed after COVID-19. *J Bacteriol. Parasitol.* 2021;12:100-0386.
12. Clinical management protocol for COVID-19. [Jul; 2020]; <https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19.pdf> 2020.