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**Original Research Article**

# COVID associated mucormycosis and its etiopathological correlation

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## ABSTRACT

**Background:** During COVID-19 pandemic, patients with diabetes mellitus (DM) and immunocompromised condition were at risk of opportunistic infections among which mucormycosis came with most dreadful consequences. Mucormycosis is a potential life-threatening, opportunistic fungal infection caused by fungi belonging to the order mucorales. Most vulnerable patients at risks are observed to be patients with uncontrolled blood sugar and diabetic ketoacidosis (DKA), patients with immunocompromised state, severe neutropenia in viral infections, on steroid therapy, oxygen therapy, chemotherapy. Despite aggressive and disfiguring surgeries paired with antifungal therapy, the mortality and morbidity rate are high. The mentioned epidemiological factors were observed and correlation between these were analysed to avoid the predisposing factors in future.
**Methods:** The study was conducted over 160 patients as prospective cross-sectional design, admitted in mucor ward of NSCB and MCH, Jabalpur. Patients were assessed clinically with related investigations. Consent was taken after explaining the nature and purpose of study.
**Results:** In our study, mucormycosis was found to affects elderly males more commonly, with immune-compromised state especially in diabetic population, received unsupervised steroid or oxygen therapy in unhygienic setups.
**Conclusions:** To ensure better outcome, along with early surgical intervention and medical management, environmental predisposing factors must be taken care of. Immunocompromised state especially uncontrolled diabetes and acidosis should be corrected, judicial use of steroids, healthy life style, oxygen supplementation with aseptic masks and tubings, use of distilled water in humidifiers, immunity build-up may bring a major change in prognosis.

**Keywords:** Post-COVID mucormycosis, DM, Steroid therapy, Oxygen supplementation, Immunocompromised status

## INTRODUCTION

Mucor mycosis is an angioinvasive fungal infection belonging to phylum zygomycetes including mucor, apophysomyces, rhizomucor, rhizopus, absida.[1] Invasive zygomycosis followed by aspergillosis is an important concern in India as highest number of cases being reported from here. It is often mis diagnosed or delayed in diagnosis consequently causing higher morbidity and mortality. The unprecedented rapid surge of this devastating fungus during active second wave of COIVD-19 (Delta virus) pandemic forced government of India to declare it as epidemic, on May 10, 2021.

Inhaled fungal spores converted from saprophytic to pathogenic fungi in nasal blockage and zygospore germinate to produce hyphae in presence of sinus obstruction with impaired sinus ventilation. Following spores inhalation, the fungus germinates and invades neural and vascular structures consequently leading to

vessel thrombosis and causes mucosal necrosis and further more deep bony destruction.[2,4,7]

The fungus is ubiquitous and can cause disease in an altered immunity status. Patients that are more vulnerable to get the disease are the ones who are post COVID, having uncontrolled diabetes with or without DKA, other than that, immune-compromised state, iatrogenic immunosuppression either unsupervised steroid therapy or chemotherapy with neutropenia, prolonged antibiotics, patients who received oxygen therapy, iron supplements, or had undergone dental extraction recently without proper asepsis seem to be get affected by disease comparatively more than general population.[3,5,6,19-25] DM patients are particularly prone to zygomycetes infection as these organisms has an active ketone reductase system and they used to thrive in increased glucose acidotic condition, which is favoured by DM with DKA patients.[8-10] Also, in hyperglycaemia and low pH, phagocytes are dysfunctional and have impaired chemotaxis and intracellular killing mechanism.[8,9] Rhizopus requires iron for its growth so patients having iron overload by any means are prone to get disease, nonetheless disrupted skin/mucosal barrier in burns and trauma also is a provoking factor.[7,11] The usage of contaminated oxygen masks due to patient overload and unmet requirements, also seen to play important role in dissemination of infection by inhalation of large amount of causative agent.

Clinical features may vary depending upon the site of invasion distributed among, cutaneous, pulmonary, gastrointestinal, rhino-orbital-cerebral sites.[12-15] Nasal symptoms vary from nasal discharge, loss of sensation, discoloration of nasal mucosa, granulation, ulceration, crusting to disruption and osteolytic lesions in paranasal sinuses bony walls. Orbital symptoms range from periorbital discoloration, diplopia, proptosis, decreased vision to complete loss of vision, ophthalmoplegia can spread the infection to cavernous sinus by various ways and the consequences of same in the form of central or brainstem infection, may present as headache, neurological deficit, seizures, coma. Angioinvasion manifested as blackish discoloration of affected part.in pulmonary mucor mycosis, in general cough and fever are common, along with pleuritic chest pain and dyspnoea.[16] In case angioinvasion occurs then massive haemoptysis can occur eventually followed by dissemination of disease.

In radiological examinations gadolinium enhanced both T1, T2 weighted MRI images should be obtained as it helpful in planning surgery. Heterogenous intensity mass extending to variable structures, black turbinate sign commonly seen.

The disease must be treated by multidisciplinary approach, along with aggressive surgical debridement and Amphotericin B with other supportive management and regular follow-up.

## METHODS

### *Study area and target population*

Out of 240 admitted mucor patients in NSCB medical college and hospital, Jabalpur (MP) India, between time period of May 2020 to July 2020, the study was conducted over 160 patients who has given consent for participation, with keen observation and required investigations.

Surgical management done, paired with medical management, samples sent for related postoperative investigations.

### *Study design*

We have followed prospective cross sectional study design.

### *Inclusion criteria*

Patients giving consent having symptoms and signs of mucormycosis in early or in advanced stage were included.

### *Exclusion criteria*

Patients with allergic rhinitis and patients with history of sinusitis due to nasal polyp or mass were kept apart from study.

### *Data collection*

Based on detailed history, clinical examination, endoscopic examination, pathology investigations including fungal culture, KOH mount, HPR findings with other related blood and radiological investigations. Data was analysed and was presented in the form of frequency and percentage shown by bar and pie charts.

### *Ethical approval*

Ethical approval was obtained from the ethics committee.

### *Statistical analysis*

The data of 160 participants was collected, was entered in Microsoft excel and thoroughly analysed. Findings and patterns were been noticed and presented in the form of pie and bar charts.

## RESULTS

A total number of 160 patient with related sign and symptoms admitted in tertiary care centre in central India were included in this study. In the study population we observed that 127 patients (79.4%) came to hospital with suspected mucormycosis were either recovered from

COVID-19 or were suffering from both the diseases simultaneously. The rest of the 33 patients (20.6%) were negative for COVID-19 RTPCR test, but had suffer flu like symptoms from past 1 to 2 months and were symptomatically treated as covid suspects.

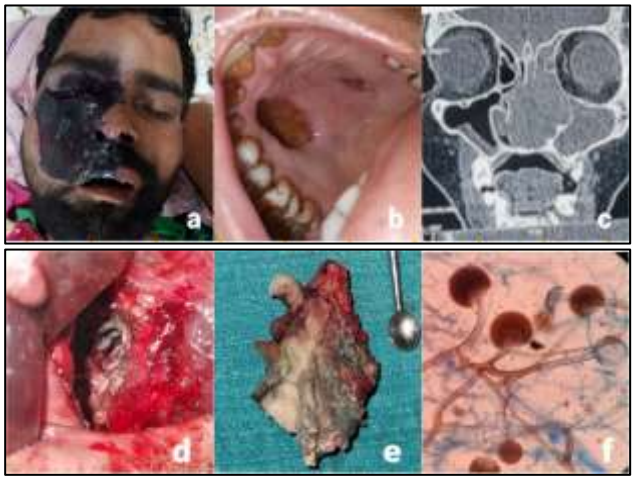



**Figure 1 (a-f): Cutaneous mucormycosis, palatal lesion, heterogenous mass in MRI, endoscopic picture, debrided tissue and microscopic picture of fungus.**

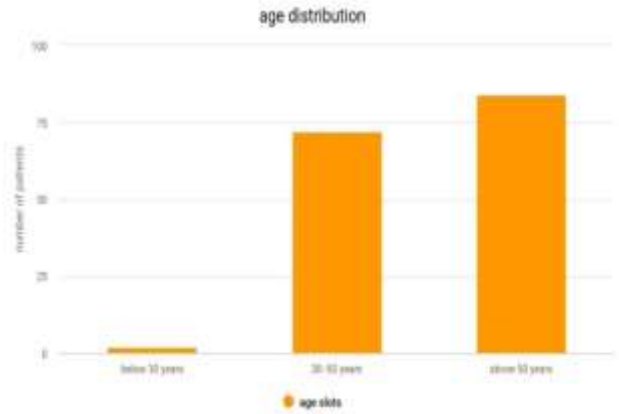
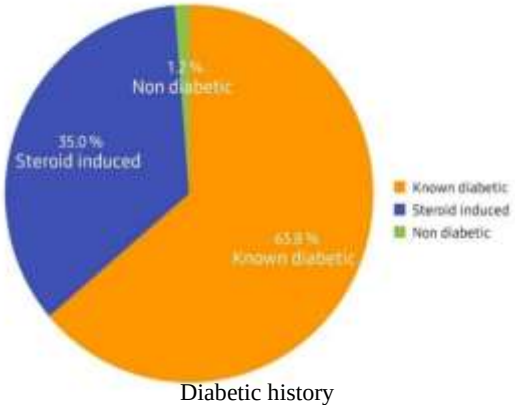
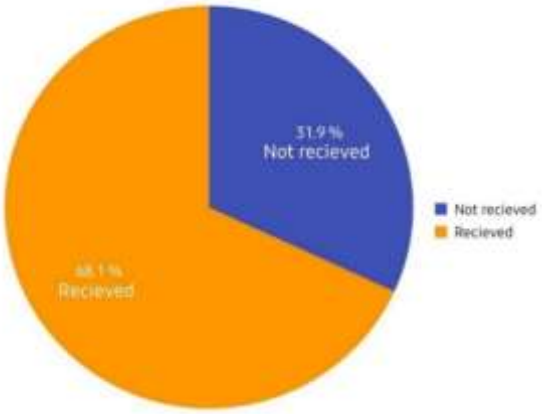



**Figure 2: Distribution according to age.**




Diabetic history

**Figure 3: Distribution according to diabetic history.**




History of oxygen supplementation

**Figure 4: Distribution according to oxygen therapy received.**

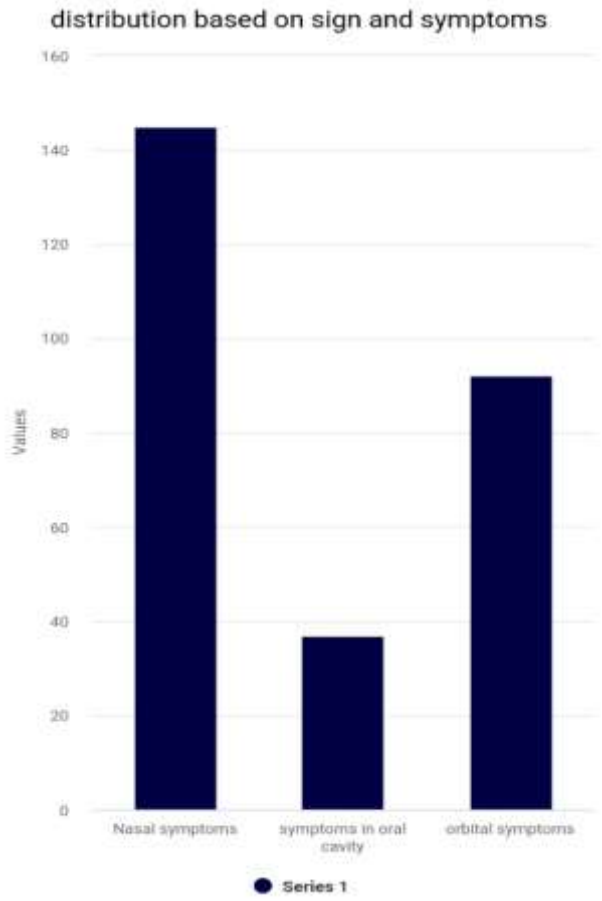



**Figure 5: Distribution according to sign and symptoms.**

Out of 160, 106 (66.2%) patients were hospitalized for covid treatment while rest of them were in home isolation and treated as outpatient.

The 89 patients (55.6%) belong to urban and 71 (44.4%) belongs to remote/ rural location.

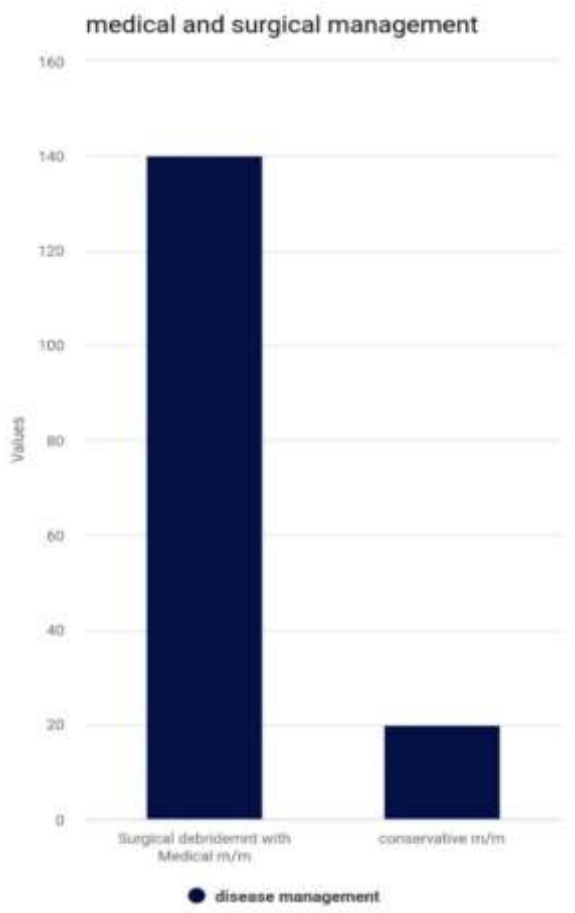



**Figure 6: Distribution according to management.**

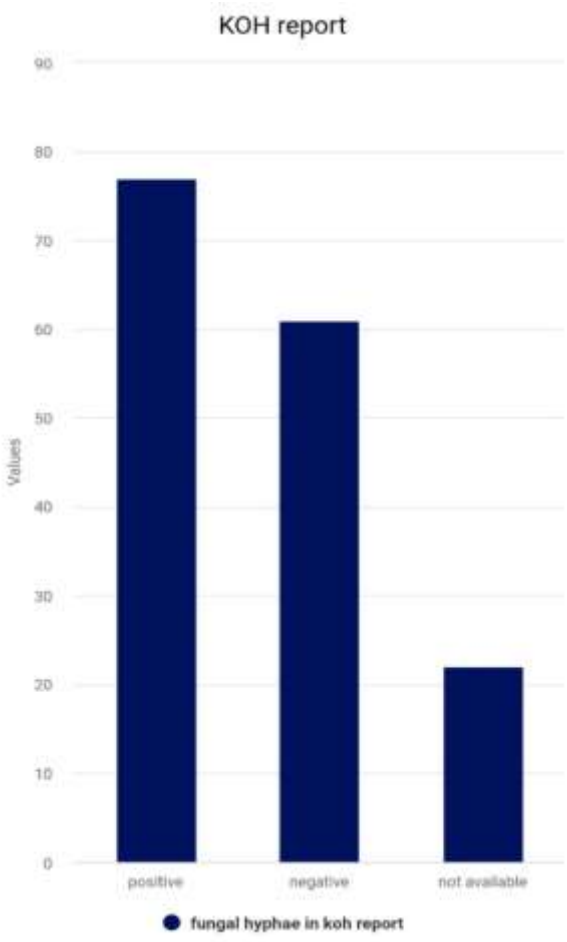



**Figure 7: Distribution according to the KOH reports.**

Age was categorized into 3 groups ,1st ranging below 30 years, 2nd from 30 to 50 years, whereas 3rd is above 50 years. Out of 160 patients, age group 3 contains 86 patients (53.8%), followed by age group 2 containing 72 patients (45%), Only 2 patients are in 1st age group (1.2%). So, younger population is more resistant.

Out of 160 patients 118 male patients contributed major portion (73.8%) whereas 42 patients were female (26.2%).

In an overlapping manner, patient presented in OPD with variable nasal, oral, orbital symptoms and signs. A spectrum of Nasal symptoms observed in 145 (90.6%) patients with complaints of mucoid/ black/ blood-tinged discharge, crusting, discoloration, pain over dorsum of nose, paranasal sinus tenderness or oedema, discoloration, black eschar etc.

With combination of nasal symptoms patient also presented with a range of oral cavity lesions. The 29 (18.1%) patients came with hard palatal ulcer/ erosion, 8 patients had dental pain, 2 got their tooth extracted. Patient also developed covid tongue, aphthous ulcer, oral/oesophageal candidiasis during covid treatment course.

Patient also came with a wide spectrum of orbital symptoms ranging from 9 (0.05%) patients with complete vision loss/dead eye, 19 patients developed reduced vision by the time, out of total 92 (57.5%) patient had orbital symptoms commonest being proptosis, lagophthalmos, some patient had chemosed eye.

Out of 160 patients, 102 patients (63.8%) were known diabetics, with uncontrolled blood sugar level ranging from 200 to 550 mg/dl, the other 56 patients (35%) were newly diagnosed diabetics after receiving steroids during covid treatment, the rest of 2 patients were non diabetics.

A total of 88 (55%) patients had received steroid therapy as covid positive or as covid suspect, before getting admitted to mucor ward, the rest of 72 patients had not received steroids before (45%).

A total number of 109 patients out of 160 (68.1%) had received oxygen supplementation during covid treatment, whereas number of patients not receiving the same was 51 (31.9%).

Among 160 patients, surgical management was done in 140 (87.5%) patients; rest of the 20 (12.5%) patients either came in inoperable status or died before intervention, unwilling for operation or had non-invasive

disease thus managed conservatively. KOH mount, fungal culture and tissue sample for HPR sent.

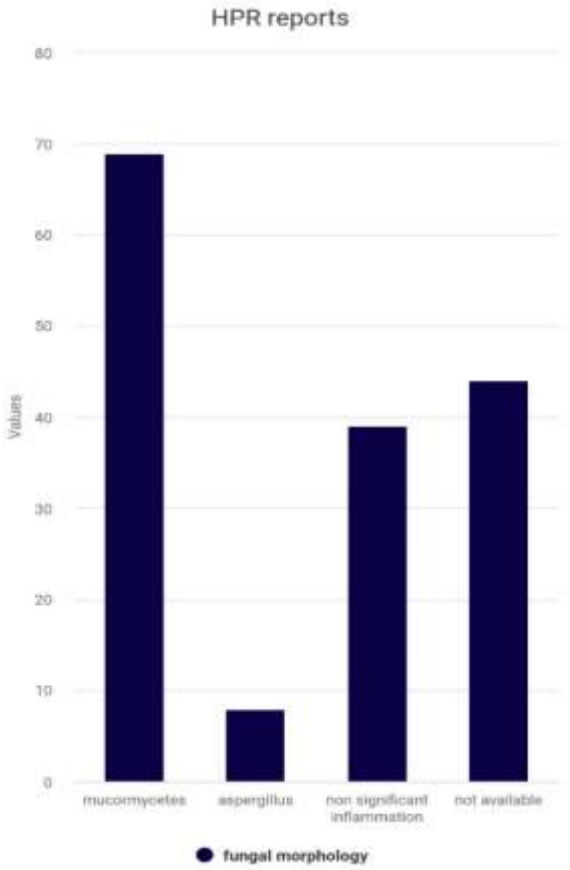



**Figure 8: Distribution according to the HPR reports.**

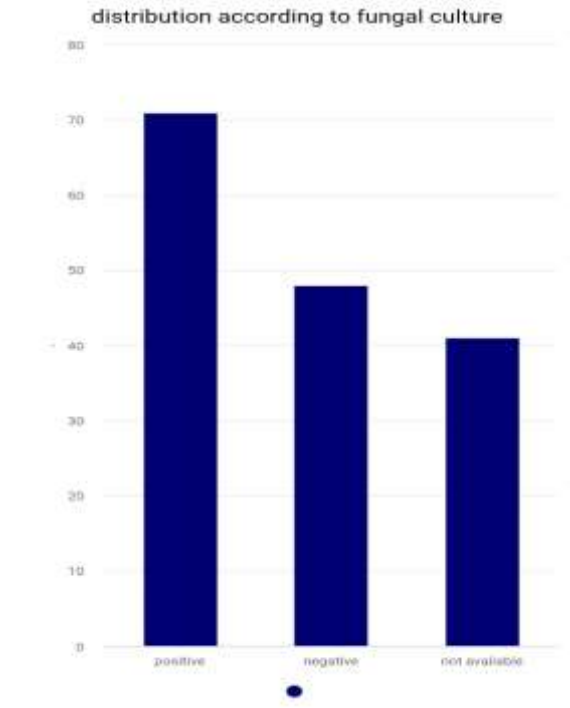



**Figure 9: Distribution according to fungal culture.**

Out of 160 patients, 77 (48.1%) patients were reported positive for fungal hyphae in KOH reports, 61 (38.1%) were negative and report of 22 patients couldn't be obtained due to various reasons.

In HPR report, 69 (43.1%) patients were reported as mucormycosis case, 8 were labelled as aspergillus variety, 39 patients report shown as non-significant inflammation only.

Fungal culture report was positive for fungal element in 71 patients (44.3%), whereas negative in 48 patients (30%) patients although 41 reports couldn't be obtained due to various reasons.

## DISCUSSION

Mucormycosis is a potentially fatal opportunistic infection caused by saprophytic fungus of class phycomycetes, the most common pathogen behind is rhizopus, rhizomucor and absida. Fungal sinusitis classified into acute fulminant, chronic invasive and chronic granulomatous. Invasive mucormycosis is classified according to their occurrence in anatomical sites as rhino-orbito-cerebral, pulmonary, gastrointestinal, cutaneous, and disseminated. Mucormycetes characterised by presence of broad aseptate hyphae and formation of zygospores.[16,17]

The portal of entry may be different, fungal spores may enter through inhalation, through injured skin, through contaminated oxygen masks, catheters, syringes, or contaminated food. The most commonly observed conditions predisposing to disease are immunocompromised state ,the underlying cause may be known uncontrolled diabetes particularly with ketoacidosis ,or steroid induced poorly controlled blood sugar, neutropenia causing conditions, as they all leading to impaired host defence, and better nutrients and favourable acidotic environment to grow, iron overload due to haematological diseases as they provide required micronutrients for fungus growth, breached skin and mucosal barrier due to burn or trauma, also adds on to disease invasion comparatively easy, dental extraction with improper asepsis and lack of compliance to medicines also follows same and giving access to infection for further invasion into maxillary antrum and mandible and so on.[8,18,19] Once the fungus makes it to nasal cavity, it forms thrombus, occludes blood vessels, causes avascular tissue necrosis; the consequence would be fungal invasion through mucosal lining from maxillary antrum to Pterygopalatine fossa and adjacent structures, involving foramen rotundum with running vessels and nerves ultimately reaching cavernous and intracranially, if not been treated on time.[20,21] Initially, the infected mucosa may appear normal, discharge, erythema only but progressively with thrombosed blood vessels and invaded nerves apparently healthy mucosa will turn into black, necrotic nasal /palatal eschar secondary to avascular tissue necrosis.

The maximum number of cases came during summer in the period between mid-May to July in advanced stage with history of mucormycosis sign and symptoms since 15-20 days. It has been postulated that hot, dusty, arid conditions predispose to rhinitis and recurrent sinusitis, as this environmental condition believed to produce mucositis and allows ingrowth and tissue damage by fungus and its metabolites, causes blocked sinus ostium and promoting further fungal growth.[20]

The major number of patients (66.2%) had been hospitalized earlier for treatment as covid positive or covid suspect, and thus had already received prolong multiple antibiotics, steroid and oxygen therapy. Elderly males found to be more prone for the disease. Also, a slight raised % of patient seen to be come from urban area that reflects better awareness in urban population.

The disease found to affects age group of above 50 years more, younger age is comparatively resistant.

Majority of patient presented to mucor ward with variety of nasal symptoms commonest being nasal discharge/crusting, and PNS tenderness, followed by orbital and least with oral cavity lesions.

In our study we observed that a major portion of study population was immunocompromised, either they were post covid, or with uncontrolled diabetes with or without DKA or developed iatrogenic immunocompromised state by receiving steroid therapy during covid treatment or antibiotics for longer period, or chemotherapy with neutropenia. Diabetics with DKA has serum acidosis that inhibits transferrin capacity to bind iron, thus allows Rhizopus to use available iron for its growth. Also, in diabetics impaired neutrophil and macrophage function in deranged pH may contributes to increased risk of mucormycosis.

The other predisposing factors might be contaminated oxygen portals in humid tropical weather. The unhygienic oxygen delivery to hypoxic patients, usage of oxygen cylinders with uncleaned mask and tubings in covid crisis, usage of tap water/ contaminated water in humidifiers, usage of same mask for multiple patients in emergencies are the probable causes for exponential rise in nosocomial mucor infection. As the fungal spores are ubiquitous, with favourable environment they get converted into pathogenic from sporophytic fungi and thrives in presence of occluded sinus ostium due to inflamed mucosa in arid hot weather.

In our study, it was found that KOH mount investigation is a sensitive tool for detecting fungus, but HPR and fungal culture should be used next for confirmation.

## CONCLUSION

Early diagnosis is of prime importance in mucormycosis treatment, correcting predisposing factors is the essential step to improve the treatment outcome. As it was seen that immunocompromised state especially uncontrolled diabetes plays important role, this must be alleviated, hyperglycaemia and acidosis should be corrected, judicial use of steroids, with healthy life style, use of oxygen in needy patients in hygienic condition with aseptic masks and tubings, use of distilled water in humidifiers, immunity build-up may bring a major change in prognosis.

Early surgical intervention and appropriate debridement of affected area often prevents the infection from progressing further with less mortality. A multidisciplinary approach paired with surgical intervention, medical management including intravenous antifungal drugs is equally essential to ensure successful outcome. Taking into account of nosocomial infection, better hygiene, following sterile and aseptic precautions during treatment, can reduce the further incidences. To improve survival rates, clinicians must be aware of the disease manifestations, with good access to mycology and pathology labs for rapid diagnosis and confirmation.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

## REFERENCES

1. Hibbett DS, Binder M, Bischoff JF, et al. A higher-level phylogenetic classification of the Fungi. Mycol Res. 2007;111:509-47.
2. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev. 2000;13:236-301.
3. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev. 2005;18:556-69.
4. Roden MM, Zaoutis TE, Buchanan WL. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41:634-53.
5. Sugar AM. Agents of mucormycosis and related species. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and practice of infectious diseases. 6th ed. Philadelphia, PA: Elsevier. 2005;2979.
6. Ibrahim AS, Edwards JE, Filler SG. Zygomycosis. In: Dismukes WE, Pappas PG, Sobel JD, eds. Clinical mycology. New York, NY: Oxford University Press. 2003;241-51.
7. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2002;34:909-17.
8. Chinn RY, Diamond RD. Generation of chemotactic factors by Rhizopus oryzae in the presence and absence of serum: relationship to hyphal damage mediated by human neutrophils and effects of

hyperglycemia and ketoacidosis. Infect Immun. 1982;38:1123-9.
9. Lamaris GA, Ben-Ami R, Lewis RE, Chamilos G, Samonis G, Kontoyiannis DP. Increased virulence of Zygomycetes organisms following exposure to voriconazole: a study involving fly and murine models of zygomycosis. J Infect Dis. 2009;199:1399-406.
10. Chakrabarti A, Sharma SC, Chander J. Epidemiology and pathogenesis of paranasal sinus mycoses. Otolaryngol Head Neck Surg. 1992;107:745-50.
11. Veress B, Malik OA, Tayeb AA, El Daoud S, El Mahgoub S, El Hassan AM. Further observations on the primary paranasal Aspergillus granuloma in Sudan. Am J Trop Med Hyg. 1973;22:765-72.
12. Chakrabarti A, Sharma SC. Paranasal sinus mycoses. Indian J Chest Dis Allied Sci. 2000;42:293-304.
13. Chamilos G, Luna M, Lewis RE, et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989-2003). Haematologica. 2006;91(7):986-9.
14. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston VI. Zygomycosis in the 1990s in a tertiary care cancer center. Clin Infect Dis. 2000;30:851-6.
15. Talmi YP, Goldschmeid-Reouven A, Bakon M. Rhino-orbital and rhino-orbito-cerebral mucormycosis. Otolaryngol Head Neck Surg. 2002;127:22-31.
16. Funada H, Matsuda T. Pulmonary mucormycosis in a hematology ward. Intern Med. 1996;35:540-4.
17. Prabhu RM, Patel R. Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. Clin Microbiol Infect. 2004;10(1):31-47.
18. Fogarty C, Regennitter F, Viozzi CF. Invasive fungal infection of the maxilla following dental extractions in a patient with chronic obstructive pulmonary disease. J Can Dent Assoc. 2006;72(2):149-52.
19. Tugsel Z, Sezer B, Akalin T. Facial swelling and palatal ulceration in a diabetic patient. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;98:630-6.
20. Kwon-Chung KJ, Bennett JE. Mucormycosis. In: Medical mycology. Philadelphia, PA: Lea and Febiger. 1992;524-59.
21. Gartenberg G, Bottone EJ, Keusch GT, Weitzman I. Hospital-acquired mucormycosis (Rhizopus rhizopodiformis) of skin and subcutaneous tissue: epidemiology, mycology and treatment. New Engl J Med. 1978;299:1115-8.

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