COVID-19 Associated Mucormycosis (CAM): A Single Hospital-Based Study

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Abstract

Background: Opportunistic fungal infections like Mucormycosis in Coronavirus Disease 2019 (COVID-19) patients have posed a great challenge to health care professionals, especially in developing countries like India. Hence, there is a need to understand the biological behaviour of COVID-19 associated Mucormycosis (CAM) to establish standard treatment Protocols and to reduce mortality.

Aims: This study aims is to assess the type of Mucormycosis among COVID-19 patients in study population and compare the findings with clinical, radiological and haematological parameters along with treatment and surgical management.

Methods and Material: This retrospective, observational study included 60 cases of CAM reported to the Department of Oral and Maxillofacial Surgery at the tertiary care centre, Karnataka Institute of Medical Sciences, Hubli. Data about various parameters were tabulated and analysed statistically.

Statistical Analysis Used: Bivariate analysis was done using the Chi-Square test to assess the relationship between the type of Mucormycosis and other variables. Spearman’s Correlation test was used to assess the correlation between types of Mucormycosis with the other variables. Linear regression analysis was performed to assess the response variable related to the type of Mucormycosis.

Results: About 50% of subjects presented with “Rhino orbital” type of Mucormycosis. Palatal discoloration and palatal erosion was the most common oral manifestation among “only Sinus” and “Rhino orbital” types of Mucormycosis \( (P = 0.00) \). Significant association \( (P = 0.29) \) was found between the type of Diabetes mellitus and Mucormycosis.

Conclusions: The study indicates that DM is the most commonly associated comorbidity in CAM patients. Hence, a thorough understanding of the underlying comorbidity and its close monitoring during and after COVID-19 infection is mandatory for successful treatment outcomes.

Keywords: COVID-19, diabetes, mucormycosis

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has gripped the world for more than a year creating havoc and global health crisis. While still dealing with the management of COVID-19, various secondary bacterial and opportunistic fungal infections have emerged. Among these, the rare fungal infections linked to COVID-19 are COVID-19-associated pulmonary aspergillosis and COVID-19-associated Mucormycosis (CAM). The ballooning of CAM during the second surge of the COVID-19 is a matter of apprehension. In India, with in a matter of 3 months, 47,000 CAM cases were reported.

Mucormycosis is an angioinvasive opportunistic infection caused by order Mucorales with a worldwide distribution. The genera responsible for human infection are Rhizopus, Mucor and Rhizomucor; Cunninghamella, Lichtheimia and Apophysomyces. These ubiquitous filaments normally occur in soil, manure, fruits, and decaying matter. These fungal spores can cause aggressive and life-threatening disease in immunocompromised hosts but is harmless in healthy individuals. These invasive Mucorales can provoke infections in immunosuppressed individuals, especially in those with uncontrolled Diabetes mellitus (DM) haematological malignancy, chronic malnutrition, chronic liver diseases and hematopoietic stem cell transplantation patients. Clinically, CAM can be categorised into Rhino-Orbital, Paranasal Sinus, Rhino-Cerebral, Rhino-Orbital-Cerebral, Oral, Pulmonary, Gastrointestinal, Cutaneous, and disseminated. The most common being the Rhino-cerebral and the most common oral manifestation being palatal ulceration or necrosis and later palatal perforation due to the spread of infection from the nasal cavity or paranasal sinuses via palatal vessels. Hence, the dental surgeon’s need has aroused to be able to identify the oral manifestation at an early stage to plan the treatment protocol to prevent its rapid spread leading to fatality. However, a link between COVID-19 and Mucormycosis need to be unearthed.

Aim: Our aim was (1) Assessment of type of Mucormycosis among COVID-19 patients in north Karnataka population reported at Department of oral and Maxillofacial Surgery, Tertiary care centre, Karnataka Institute of Medical Sciences, Hubli. (2) To compare the type of Mucormycosis across the demographic variables, oral manifestations, vaccination status, Diabetes type, diabetes status, comorbidities, radiological features, haematological factors, treatment, and surgical management.

Methodology: This was a retrospective, observational study carried out in COVID-19 cases confirmed either by Real-Time reverse transcriptase Polymerase chain reaction or Rapid antigen test in North Karnataka Population at the tertiary care centre, Karnataka Institute of Medical sciences, Hubli, reported between June 1, 2021, to September 31, 2021. A total of 60 cases of CAM were included in this study and reported to the Department of Oral and Maxillofacial Surgery after magnetic resonance imaging, functional endoscopic sinus surgery and confirmed histopathological report of Mucormycosis [Figure 1]. Data about demographics, oral manifestations, comorbidities, radiological features, haematological investigations, treatment, surgical management and prognosis was collected after obtaining informed consent from all patients. The study was accepted by the institutional ethics committee.

Statistics: The data obtained were compiled systematically in a Microsoft Excel sheet and subjected to statistical analyses using Statistical package for social sciences software version 20. The significant level was fixed at $P < 0.05$. Descriptive statistics were generated in terms of frequencies or percentages. Bivariate analysis was done using the Chi-Square test to assess the relationship between the type of Mucormycosis and other variables. Spearman’s correlation test was used to assess the correlation between types of Mucormycosis with the other variables. Linear regression analysis was performed to assess the response variable related to the type of Mucormycosis.

RESULTS

Table 1: Among the 60 COVID-19 positive patients, 21 (35%) patients had “only Sinuses” type of Mucormycosis, 30 (50%) patients suffered from “Rhino orbital” type of Mucormycosis followed by only 9 (15%) were with “Rhino orbito cerebral” type of Mucormycosis.

![Figure 1: Photomicrograph of Mucormycosis showing non-Septate Hyphae (H & E stain, 40X)](image_url)
Table 2: There was a significant association found between the type of Mucormycosis and the appearance of oral manifestation \((P = 0.00)\). Among which palatal discoloration and palatal erosion [Figure 2] was common and higher in “only Sinus” and “Rhino orbital” type of Mucormycosis followed by occurrence of draining sinus in “Rhino orbital” type of Mucormycosis. Similarly, when compared with the type of DM and Mucormycosis, a significant association was also found \((P = 0.29)\). But the frequency of occurrence of different types of Mucormycosis was found to be high in an uncontrolled type of DM patients and the frequency of “Rhino orbital” type of Mucormycosis was high among controlled diabetes mellitus patients.

Table 3: Depicts the spearman’s correlation between the type of Mucormycosis and demographic variables, oral manifestations, vaccination status, comorbidity, type and status of DM. A significant correlation \((P = 0.000)\) was seen between oral manifestation and type of Mucormycosis and also significant correlation \((P = 0.038)\) was seen between the type of associated Illness and Type of Mucormycosis.

Table 4: Depicts the relationship between the type of Mucormycosis with Altered signal density. A significant relationship was noticed between the type of Mucormycosis and altered signal density of Sinus with a \(P\) value of 0.021.
DISCUSSION

India, being one of the most affected countries by COVID-19 infection has witnessed a rapid surge in opportunistic infections like Mucormycosis during the second wave. A distinctive characteristic of Mucormycosis is angioinvasion followed by thrombosis and tissue necrosis. Inherent thermotolerance, swift growth, an affinity for endothelial cells and aptitude to gain iron from the host makes these Mucorales aggressive.[8] Various contributing factors have been suggested for CAM. Hence to analyse the profile of patients affected by CAM and understand the pathogenesis, this hospital-based study was conducted.

In this observational study at the tertiary care centre, the most common type of Mucormycosis observed in the present set of patients was Rhino-orbital form (50%) [Table 1]. Jose et al. also have found most of the cases in the rhino-orbital

Figure 2: Clinical Image showing the denuded area in the right maxilla of an edentulous patient

Table 9: Describes the relationship between Type of Mucormycosis and the number of days of administration of Oxygen Supplements. Eleven, Fourteen, and one patient of ‘Only sinus type’, Rhino-orbital type, and Rhino-orbital cerebral type respectively received oxygen supplements. But no significant relationship was seen between them.

Table 8: Describes the relationship between Types of Mucormycosis and the number of days of administration of Steroid therapy. Although a large number of patients, that is, 11 patients of “only Sinus type” of Mucormycosis received steroid therapy for a range of duration, it did not illustrate a statistically significant relation.

Table 7: Divulges descriptive analysis between the span of COVID and Type of Mucormycosis. Meantime span of COVID-19 and the appearance of CAM was 37.93 ± 25.41 days. There is no significant relationship observed.

Table 4: Altered signal density of nasal cavity, maxilla, mandible, and maxillary sinus across the type of Mucormycosis of Steroid therapy. Although a large number of patients, that is, 11 patients of “only Sinus type” of Mucormycosis received steroid therapy for a range of duration, it did not illustrate a statistically significant relation.

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region. In the literature, it has been reported that the Rhino-orbito-cerebral form is most common followed by other variants (like Cutaneous, pulmonary, disseminated and gastrointestinal types).\(^9\)

In our study, the majority of CAM-affected patients were between the 2nd and 7th decades of life with a maximum number of cases above the age of 40 years [Table 2]. Similar studies have also reported analogous findings. The maximum number of patients included in the present study were males (n = 43). This is in accordance with previous reports.\(^{10,11}\) This might be due to the fact that most of the COVID-19 affected patients globally are males. Mucormycosis has not shown any gender predilection both in COVID-19 and non-COVID-19 era; however, it has been suggested that oestrogen might protect females from systemic fungal infections.\(^4\)

In our study, CAM was more commonly seen in the bilateral maxilla (n = 31) compared to the right, left, or anterior Maxilla, as SARS-COV-2 is transmitted through aerosols and droplets to the nasal and oral cavity.\(^{12}\) Thus, this rapidly spreading aggressive fungal infection involves the bilateral maxilla swiftly. Frequently seen oral manifestation here were Palatal discoloration (n = 22) and Palatal erosion (n = 20) [Table 2]. Similar findings were noted by Janjua et al.\(^{13}\) There was also a significant correlation between oral manifestation and Type of Mucormycosis with a P value of 0.000 [Table 3] suggesting the palate is an untimely involved structure in the oral cavity.

With respect to vaccination status, most of the CAM patients did not receive the COVID-19 vaccine (n = 48) [Table 2]. The study by Petrikkos et al.\(^{14}\) also found that most of their patients were not vaccinated for COVID-19. Although it has been observed that vaccination reduces the severity of the disease, only 3% of the population was vaccinated\(^{11}\) during the second wave, and its role in the occurrence of CAM cannot be commented upon.

Among the comorbidities, DM (n = 60) was the most commonly associated illness in CAM patients and most of them had uncontrolled DM (n = 40) which was statistically significant with a P value of 0.029 [Table 2]. This is in accordance with studies both in Pre-COVID-19 and COVID-19 era.\(^{10,11,14}\) Literature reports indicate DM to be

### Table 5: Relationship between the type of Mucormycosis with an altered signal density of nasal cavity, maxilla, mandible, and maxillary sinus

| Spearman’s Correlation value (rho) | P       |
|-----------------------------------|---------|
| ASD NASAL                        | 0.006   |
| ASD MAX                          | 0.156   |
| ASD MAN                          | 5.72639 |
| ASD SINUS                        | 0.262   |

### Table 6: Comparison of the difference in haematological parameters across the type of Mucormycosis

| Lab Parameters | Type of Mucormycosis | n | Mean | SD | SEM | t | df | P | Mean difference | 95% CI Lower | 95% CI Upper |
|----------------|----------------------|---|------|----|-----|---|----|----|----------------|-------------|-------------|
| N_L            | "only sinuses"       | 21 | 2.5848 | 1.0116 | 0.22065 | -1.86 | 48.354 | 0.069 | -0.60237 | 1.2528 | 0.04813 |
| D_dimer        | "only sinuses"       | 30 | 3.1871 | 1.29642 | 0.23669 | 1.161 | 37.21905 | 0.370 | -0.133 | -0.153 |
| Ferritin levels| "only sinuses"       | 21 | 507.2857 | 157.72639 | 34.41872 | 0.904 | 49 | 0.370 | -0.133 | -0.153 |
| CRP            | "only sinuses"       | 21 | 54.1905 | 25.10502 | 5.47836 | 0.278 | 49 | 0.782 | 1.89048 | -11.7782 | 15.55919 |

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|----------------|----------------------|---|------|----|-----|---|----|----|----------------|-------------|-------------|
| N_L            | "Rhino orbital"      | 21 | 2.5848 | 1.0116 | 0.22065 | -1.86 | 48.354 | 0.069 | -0.60237 | 1.2528 | 0.04813 |
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|----------------|----------------------|---|------|----|-----|---|----|----|----------------|-------------|-------------|
| N_L            | "Rhino orbito cerebral" | 21 | 2.5848 | 1.0116 | 0.22065 | -1.86 | 48.354 | 0.069 | -0.60237 | 1.2528 | 0.04813 |
| D_dimer        | "Rhino orbito cerebral" | 30 | 3.1871 | 1.29642 | 0.23669 | 1.161 | 37.21905 | 0.370 | -0.133 | -0.153 |
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an independent risk factor for Mucormycosis.\[11\] The effects of DM like; Neutrophil dysfunction, that is, impaired chemotaxis and phagocytosis have been suggested for this association. It is also postulated that SARS-CoV-2 results in the dysfunction of β cells of the pancreas leading to insulin resistance by binding to ACE-2 receptors of pancreatic β cells. This is exaggerated by a cytokine storm caused by SARS-COV-2.\[14-18\] DKA was seen in 36 patients, Patel et al.\[19\] found DKA to be less frequent in CAM patients compared to non-CAM patients. Acidosis-associated with DKA has the following effects: (a) stimulates the expression of GRP78 and coat protein homologue CotH. These proteins of Mucorales attach to the GRP78 endothelial receptors of the host, (b) increases levels of free-iron by a detachment of iron-protein complexes, thus favoring the growth of Mucorales.\[11,14,15,20,21\] Most of the CAM patients did not have any illness at the time of CAM (n = 38), and very few of them were hypertensive [Table 2]. This finding in our study is in contrast to the observations made by Patel A et al.\[19,22\] wherein they reported that 58.6% of patients had more than one comorbidity.

All 60 cases of CAM in this study were reported to the Department of Oral and Maxillofacial Surgery after Magnetic resonance imaging, functional endoscopic sinus surgery, and confirmed histopathological report of Mucormycosis. Altered signal density in nasal cavity (n=30), maxilla (n=21), mandible (n=2) and Maxillary sinus (n=40) was noted. Altered signal density in the maxillary sinus showed a significant P value of 0.021 [Table 4]. This finding is in accordance with Mehta S et al.\[23\] suggestive of maxilla being the most commonly involved structure. Rhino-orbital-cerebral mucormycosis usually affects the maxillary sinus with the involvement of maxillary teeth, orbits, and ethmoidal sinuses. According to Sanghvi et al.,\[24\] contrast-enhanced magnetic resonance imaging (MRI) is the best mode of choice for the demonstration of CAM. Black turbinate is the classical imaging sign but there was no positive correlation seen between the type of Mucormycosis with an altered the signal density of nasal cavity, maxilla, mandible and maxillary sinus [Table 5].

The NLR is an easily accessible biological marker to assess the severity of the disease and can serve as an early warning signal. The mean NLR among various types of Mucormycosis was 2.9880 in our study [Table 6]. It has been hypothesized that COVID-19 may act on T lymphocytes,
Steroid therapy causes disruption of glycemic control and poor response of pulmonary macrophages in the prevention of growth of spores of Mucorales. The National Institute of Health, pulmonary macrophages in the prevention of growth of spores of Mucorales. The National Institute of Health, disruption of glycaemic control and poor response of who received steroids. Most of the studies have reported CAM cases in patients presented with CAM without steroid treatment [Table 8]. In our study, 31 patients received steroids, and 29 patients close follow-up for control of DM is recommended. Mucormycosis and tapering of steroid levels along with should observe the patients for the occurrence of mucormycosis was 37.93 days and there was no significant correlation. Serum Ferritin level and D dimer are the two commonly used diagnostic tools to determine the extent of inflammation. The mean of Ferritin levels among various types of Mucormycosis in our study was 399 micrograms per litre [Table 6]. Although Ferritin levels were higher in CAM patients, it was not statistically significant. Cantinieaux et al.[26] suggested an increase in iron concentration promotes fungal growth by decreasing phagocytosis and IFN production. Free iron is a must for Mucorales species for their biological processes, thus iron availability might represent an essential mechanism involved in the pathogenesis of CAM.[27] D dimer is a fibrin degradation product, a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis.[28] High levels of these indicate active clot formation. Our study showed a mean D dimer range of 474 ng/ml. Although the D dimer range was higher in CAM patients, it was not statistically significant [Table 6]. CRP is a non-specific, annular pentameric protein found in plasma, whose circulating concentration increases in response to inflammation. COVID-19 patients demonstrate elevated levels of CRP, hence can be used as an aid in triage, diagnosis, and prognosis.[29] Mean range of CRP levels in CAM patients in our study were 52.6 mg/L. Although there was an increase in CRP levels, it was not statistically significant [Table 6]. The mean time interval between the COVID-19 and Occurrence of mucormycosis was 37.93 days and there was no significant correlation was found [Table 7]. It is suggested that during the recovery period, the clinicians should observe the patients for the occurrence of Mucormycosis and tapering of steroid levels along with close follow-up for control of DM is recommended.[10] In our study, 31 patients received steroids, and 29 patients presented with CAM without steroid treatment [Table 8]. Most of the studies have reported CAM cases in patients who received steroids.[10,11,14] Steroid therapy causes disruption of glycemic control and poor response of pulmonary macrophages in the prevention of growth of spores of Mucorales. The National Institute of Health, conferring on the Randomized Evaluation of COVID-19 In therapy (“RECOVERY”) collaborative group, recommended that the use of steroids must be reserved only for patients on supplemental oxygen or ventilator and not in milder cases. In addition, the risk of secondary infection is also specified.[11,30] About 33 patients in our study received oxygen supplements during the treatment for COVID-19 [Table 9], and most of them presented with a Rhino-orbital form of Mucormycosis. However, there was no significant correlation.

**Management**

The management of mucormycosis is a multidisciplinary approach involving neurosurgery, ophthalmology, ENT surgeon, oral and maxillofacial surgeon, oncosurgery, plastic surgery, critical care, and pathology. Due to blood vessel thrombosis and tissue necrosis, the antifungal agents have poor penetration in the affected site in Mucormycosis. So, debridement of involved tissue is necessary to maximise the outcomes of disease. Biopsy from the nasal mucosa and/or sinuses can help achieve the diagnoses. The use of an intraoperative frozen section can be a great aid in deciding the surgical extent.[31]

Orbital exenteration along with debridement of the pterygopalatine fossa and inferior orbital fissure should be performed in patients with progressive ocular involvement to reduce the fungal load and to prevent further extension of disease to the cranium. Functional endoscopic surgery has been routinely performed as a successful treatment option in treating mild and early rhinocerebral Mucormycosis in selected patients.[32] Orbital exenteration is although life saving, not necessary in all patients and is a case-by-case base.[33] The decision of Orbital exenteration is based on the progression of disease, involvement, and response to anti-fungal treatment. Surgical treatment must be always associated with systemic antifungal agents (polyenes, azoles, etc.) for better outcomes. In the case of vital structures where vital tissue cannot be completely resected, the anti-fungal agents can be used to control the infection.[34]

The only signs and symptoms of isolated pterygopalatine fossa involvement is limited to the nasal cavity and sinuses. In such cases, endoscopically guided debridement along with anti-fungal therapy can control mucormycosis. Occasionally sphenopalatine foramen is also involved and in such instances, the foramen must be debrided or resected. The spread of mucormycosis can involve a greater palatine canal after involving pterygopalatine fossa with the invasion of nasopalatine and descending palatine vessels causing black necrosis of the palate or erosion of the hard palate. The involvement of internal maxillary artery and
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its tributaries can cause complete necrosis of the maxilla and palate.\[^{33}\] The surgical intervention may range from simple alveoloplasty to radical maxillectomy along with palatal debriement. The vitality of the palatal flap plays an important role in primary closure. The surgical options for a maxillofacial surgeon are maxillary sinus debriement via the Caldwell-Luc approach, marginal maxillectomy, Hemi maxillectomy, partial maxillectomy, complete and radical maxillectomy along with hard palate debriement. The surgical access can be gained by crestal incision, vestibular gloving incision, lateral rhinotomy with subcilliar or supra orbital, and Weber Ferguson approaches.\[^{34}\]

The maxillary sinus, hard palate, and infratemporal fossa should be inspected and debrided if necessary. After the resection of involved tissue, the tissue defects can be closed by means of primary closure, obturators, and local pedicled flaps, such as Galealfrontalis-peri cranial nasolabial flap temporalis muscle flap, sub-mental flap, or facial artery island flap. Large defects can be reconstructed with free flaps such as anterolateral thigh flap, fibula osteocutaneous flap latissimus dorsi free flap, radial forearm free flap, scapula osteocutaneous free flap, reverse rectus abdominis musculocutaneous flap, vascularized iliac osteocutaneous flap, and chimeric flaps. Immediate reconstruction is not recommended in hemodynamically unstable patients, cellulitis, aggregated infections, incomplete resection, and when the recipient’s vessels are involved and unhealthy.\[^{37}\]

Cavernous sinus and central nervous system (CNS) involvement can develop after the invasion of the orbital apex. Extension from the sphenoid sinus, frontal sinus, and cribiform plate to the CNS is rare. Signs and symptoms of involvement of CNS and cavernous sinus are unilateral headache, loss of consciousness and unilateral neurological signs on the opposite side, and seizures. Craniotomy and partial or complete lobectomy is advised in advanced diseases, although it is associated with some form of neurological deficit.\[^{38}\]

To conclude, the above findings indicate that there are multiple factors that can be linked to the occurrence of mucormycosis in COVID-19 patients. The effect on the immune system of various suggested contributing factors results in CAM. The present study indicated that the factors may act independently (mainly DM) or jointly to cause CAM. Hence, the CAM cases must be addressed by a multidisciplinary team focussing on the control of co-morbidities, judicious use of steroids; zinc supplements, and so on, along with appropriately planned individualized treatment modalities.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Narayanan S, Chua JV, Baddley JW. COVID-19 associated mucormycosis (CAM): Risk factors and mechanisms of disease. Clin Infect Dis 2021;74:1279‑83.
2. Muthu V, Rudramurthy SM, Chakrabarti A, Agarwal R. Epidemiology and Pathophysiology of COVID-19-Associated Mucormycosis: India Versus the Rest of the World. Mycopathologia 2021;186:739‑54.
3. Sivapathasundaram B. Shafer’s Textbook of Oral Pathology. 8th ed. New Delhi, India: Elsevier; 2012. p. 435‑6.
4. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Review Epidemiology and outcome of zygomycosis: A review of 929 reported cases. J Clin Infect Dis 2005;41:634‑53.
5. Rodriguez-Morales AJ, Sah R, Millan-Oñate J, Gonzalez A, Montenegro-Idrogo JJ, Scherger S, et al. COVID-19 associated mucormycosis: The urgent need to reconsider the indiscriminate use of immunosuppressive drugs. Ther Adv Infect Dis 2021;18:2049936121102765.
6. 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;64:1452‑9.
7. Doni BR, Peerapar BV, Thotappa LH, Hippiargi SB. Sequence of oral manifestations in rhino-maxillary mucormycosis. Indian J Dent Res 2011;22:331‑5.
8. Kamar M, Datar U, Byakodi S, Kamat S, Vimal Kumar V. COVID-19-associated mucormycosis of head-and-neck region: A systematic review. J Clin Transl Res 2022;8:31‑42.
9. Jose A, Singh S, Roychoudhury A, Khokhriya Y, Arya S, Roychoudhury S. Current understanding in the pathophysiology of SARS-CoV-2-associated rhino-orbito-cerebral mucormycosis: A comprehensive review. J Maxillofac Oral Surg 2021;20:373‑80.
10. Sen M, Lahane S, Lahane TP, Parekh R, Honavar SG. Mucor in a viral land: A tale of two pathogens. Indian J Ophthalmol 2021;69:244‑52.
11. Ibrahim AS, Kontoyiannis DP. Update on mucormycosis pathogenesis. Curr Opin Infect Dis 2013;26:508‑15.
12. Roopa R, Thanthony M, Warrier AS. COVID-19 coinfection with mucormycosis in a diabetic patient. Cureus 2021;13:e15820.
13. Janjua OS, Shaikh MS, Fareed MA, Qureshi SM, Khan MI, Hashem D, et al. Dental and oral manifestations of COVID-19 related mucormycosis: Diagnoses, management strategies and outcomes. J Fungi (Basel) 2021;7:34‑49.
14. Petrikos G, Tsioitis C. Recent Advances in the pathogenesis of mucormycoses. Clin Ther 2018;40:894‑902.
15. Alekseyev K, Didenko I, Chaudhry B. Rhinocebral mucormycosis and COVID-19 pneumonia. J Med Cases 2021;2:85‑9.
16. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: Understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol 2020;8:782‑92.
17. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: An analysis from 1990 to 2025. Sci Rep 2020;10:14790.
18. Montefusco L, Ben Nasr M, D’Addio F, Loretelli C, Rossi A, Pastore I, et al. Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. Nat Metab 2021;3:774‑85.
et al. Multicenter epidemiologic study of coronavirus disease-associated mucormycosis, India. Emerg Infect Dis 2021;27:2349‑59.
20. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: Pathophysiology, presentation, and management. Clin Microbiol Rev 2005;18:556‑69.
21. Waizel‑Haiat S, Guerrero‑Paz JA, Sanchez‑Hurtado I, Calleja‑Alarcon S, Romero‑Gutierrez L. A case of fatal rhino‑orbital mucormycosis associated with new onset diabetic ketoacidosis and COVID‑19. Cureus 2021;13:e13163.
22. 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. Clin Microbiol Infect 2020;26:944.e9‑15.
23. Mehta S, Pandey A. Rhino‑orbital mucormycosis associated with COVID‑19. Cureus 2020;30:e10726.
24. Sanghvi D, Kale H. Imaging of COVID‑19‑associated craniofacial Mucormycosis: A black and white review of the “black fungus. Clinical Radiology 2021;76:812‑9.
25. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil‑to‑lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med 2020;18:206.
26. Cantinieaux B, Janssens A, Boelaert JR, Lejeune M, Vermeylen C, Kerrels V, et al. Ferritin‑associated iron induces neutrophil dysfunction in hemosiderosis. J Lab Clin Med 1999;133:353‑61.
27. Reid G, Lynch JP 3rd, Fishbein MC, Clark NM. Mucormycosis. Semin Respir Crit Care Med 2020;41:99‑114.
28. Asakura H, Ogawa H. COVID‑19‑associated coagulopathy and disseminated intravascular coagulation. Int J Hematol 2021;113:45‑57.
29. Stringer D, Braude P, Myint PK, Evans I, Collins JT, Verdur A, et al. The role of C‑reactive protein as a prognostic marker in COVID‑19. Int J Epidemiol 2021;17:420‑9.
30. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: A deadly addition to the pandemic spectrum. J Laryngol Otol 2021;135:442‑7.
31. Spellberg B, Ibrahim AS. Recent advances in the treatment of mucormycosis. Curr Infect Dis Rep 2010;12:423‑9.
32. Alobid I, Bernal M, Calvo C, Vilaseca I, Berenguer J, Alós I. Treatment of rhino‑cerebral mucormycosis by combination of endoscopic sinus debridement and amphotericin B. Am J Rhinol 2001;15:327‑31.
33. Rapidis AD. Orbitomaxillary mucormycosis (zygomycosis) and the surgical approach to treatment: Perspectives from maxillofacial surgeon. Clin Microbiol Infect 2009;15:98‑102.
34. Ferguson BJ: Mucormycosis of the nose and paranasal sinuses. Otolaryngol Clin North Am 2000;33:349‑65.
35. Kyrmizakis DE, Doxas PG, Hajioannou JK, Papadakis CE. Palate ulcer due to mucormycosis. J Laryngol Otol 2002;116:146‑7.
36. Hosseini SM, Bonghei P. Rhinocerebral mucormycosis: Pathways of spread. Eur Arch Otorhinolaryngol 2005;262:932‑8.
37. Palacios JJ, Hanson EV, Rendon MA, Infante RS. Reconstruction of head and neck mucormycosis: A literature review and own experience in immediate reconstruction. J Reconstr Microsurg Open 2019;4:e65‑72.
38. El‑Naaj IA, Leiser Y, Wolf A, Peled M. The surgical management of rhinocerebral mucormycosis. J Craniofac Surg 2013;41:291‑5.