Saudi Journal of Biological Sciences 28 (2021) 6461–6464

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Review

Post-Covid alliance-mucormycosis, a fatal sequel to the pandemic in India

Manjusha Nambiar [a], Sudhir Rama Varma [b,c,*], Marah Damdoum [b]

[a] Department of Periodontics, Sri Rajiv Gandhi College of Dental Sciences and Hospital, Banguluru, Karnataka State 560032, India
[b] Department of Clinical Sciences, Ajman University, Ajman, United Arab Emirates
[c] Center of Medical and Bio-allied Health Sciences Research, Ajman University, Ajman, United Arab Emirates

ARTICLE INFO

Article history:
Received 21 May 2021
Revised 23 June 2021
Accepted 4 July 2021
Available online 10 July 2021

Keywords:
COVID-19
Mucormycosis
Black fungus
Zygomycosis
Rhinoorbitocerebral mucormycosis
Post Covid 19

ABSTRACT

As the battle against the deadly Covid-19 pandemic is still continuing worldwide, several complications are being reported in patients who have recovered post-covid. One such lethal complication being reported in patients in India in recent times, who have tested positive for Covid-19 and are gradually recovering, is a fungal disease called Mucormycosis or the black fungus. With several hundreds of cases being reported all over the country, it has triggered an additional wave of panic among the general public. Post-Covid-19 patients who are more vulnerable to Mucormycosis are those with a history of poorly controlled diabetes mellitus and also those who are immuno-compromised and have been treated with steroids and other drugs for Covid-19. The aim of this short review is to briefly cover the epidemiology of mucormycosis, its possible pathophysiology in Post Covid scenario, the clinical presentation and its diagnosis and management.

Contents

1. Introduction

As the battle against Coronavirus disease 2019 (Covid-19) continues in India, physicians have noticed an upsurge in the incidence of Post - Covid 19 complications. Secondary infections occur mainly after severe disease and in ICU treated cases of Covid-19, comprising around 10–30% of cases. Patients with serious illness are ten times more prone to develop bacterial or fungal secondary infections than secondary viral infections (Medpage, 2021).

* Corresponding author at: Department of Clinical Sciences, College of Dentistry, Ajman University, Ajman, United Arab Emirates.
E-mail address: s.varma@ajman.ac.ae (S.R. Varma).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2021.07.004
1319-562X/

2. Epidemiology of mucormycosis

Mucormycosis (earlier called Zygomycosis) is a rare but severe fungal infection caused by a group of molds called mucoromycetes. It is a potentially lethal infection occurring primarily in immunocompromised patients, particularly in those with diabetes mellitus, hematological malignancy, hematopoietic stem cell transplantation, and solid organ transplantation (Jeong et al., 2019). The Leading International Fungal Education (LIFE) portal calculated the load of serious fungal infections worldwide and reported an annual prevalence of around 10,000 cases of Mucormycosis globally, excluding India. However, after the inclusion of data collected from India, the estimate of Mucormycosis drastically rose to 910,000 cases globally (Prakash and Chakrabart, 2019). According to the Epidemiology of Mucormycosis in India reported in 2021, the estimated prevalence of Mucormycosis was at an alarming rate of nearly 70 times higher than the global data (Prakash and Chakrabarti, 2021).

According to The US Centre for Diseases Control and Prevention (CDC), an overall all-cause mortality rate of 54% was reported for Mucormycosis. The mortality rate depends upon the underlying condition of the patient, fungus type, and affected site in the body (for example, the mortality rate reported was 46% for patients with sinus infections, 76% for pulmonary infections, and 96% for disseminated mucormycosis) (CDC, 2021). The difficulty and delay in diagnosing Mucormycosis affects the outcome of the disease and may lead to poor prognosis because of its high invasiveness and its intrinsic low susceptibility to antifungal agents. Therefore, early diagnosis and treatment are necessary.

Several hospitals across India have reported an increased incidence of Post Covid Mucormycosis cases, with deaths being reported from Jabalpur in Madhya Pradesh and Thane in Maharashtra. In the second wave of Corona in India, the cases of Mucormycosis have drastically increased, with approximately 2–3 cases being reported daily. Also, more people are losing their vision in the second wave. Though no official number has been published yet about the post covid mucormycosis cases in India, the Figure illustrated arbitrarily summarises the number of cases reported in various media print sources up to 17 May 2021 (see Fig. 1).

3. Covid 19 and mucormycosis: The pathophysiology

Rhino-Orbito-Cerebral Mucormycosis (ROCM) is the most common form, and it is usually seen in diabetic ketoacidosis or poorly controlled diabetes mellitus. A study from India has estimated that 88% of the patients with ROCM had diabetes mellitus[3]. In susceptible hosts, standard defense mechanisms slows down. For example, in diabetic ketoacidosis, the serum pH is acidic and leads to the dissociation of free iron from sequestering proteins. This release of free iron results in rapid fungal growth. Altered mechanisms of phagocytic defense like neutropenia or functional defects due to corticosteroids or hyperglycemia and acidosis due to diabetic ketoacidosis allow proliferation of the fungus. Eventually, adherence to and damage of the endothelial cells caused by the fungus allows fungal angioinvasion and vessel thrombosis leading to subsequent tissue necrosis and dissemination of the fungal infection (Spellberg et al., 2005).

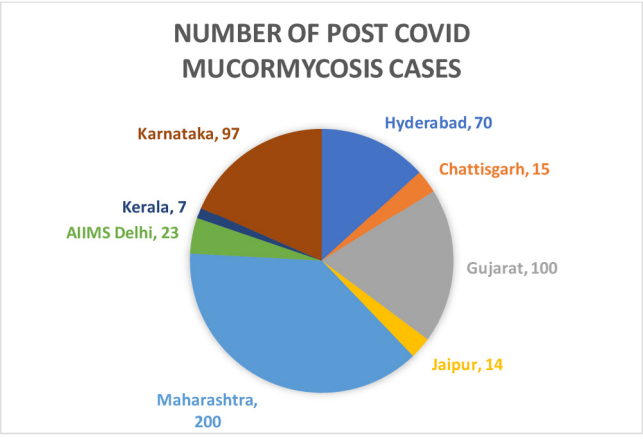

Fig. 1. Number of Post Covid Mucormycosis cases reported in India as of 17 May 2021.

Post-Covid 19 patients who are at an increased risk to develop Mucormycosis are those with a history of poorly controlled diabetes mellitus and the patients who are treated with steroids and other drugs to manage Covid 19 that may reduce their ability to fight environmental pathogens. If fungal spores are inhaled from the atmosphere, lungs or sinuses of such individuals may get affected. A defective innate immune response, dysfunction of the ciliary activity, cytokine storm, thrombo-inflammation, microvascular coagulation, which will eventually lead to impairment of the immune response, are several of the mechanisms elucidated. These events result in secondary bacterial and fungal infections, especially in critically immunocompromised patients subjected to invasive emergency procedures such as mechanical ventilation, Continuous Renal Replacement Therapy (CRRT), Extracorporeal membrane oxygenation (ECMO), inadequate nursing ratios, extended hospital stays, and breaches in asepsis (Soman and Sunavala, 2021). Furthermore, diabetic Covid 19 patients receiving corticosteroids or other immunosuppressants are exceptionally prone to Mucormycosis development.

For any patient who received oxygen support during their hospital stay, it becomes essential to observe any black pigmentation in their nostrils or mouth. Even the slightest color change or pigmentation should be reported immediately without neglect. Sanitization of the oxygen supply system in hospitals is also an area of concern. Though distilled water is recommended for hydrating oxygen, most of the time, this is neglected, which can give rise to serious concerns. Therefore, this crucial aspect of oxygen supply system in hospitals should not be overlooked. The health ministry, in its advisory, has instructed the hospitals to provide a pamphlet of mucormycosis-related symptoms, cure, and preventive measures along with the discharge papers (ICMR, 2021).

4. Clinical manifestations and diagnosis

The symptoms of Mucormycosis depend on where the fungus is growing within the body. The two most important types of Mucormycosis in this scenario are rhino-orbital-cerebral and pulmonary. Diagnosis is based on the clinical and imaging findings, along with the association of potential risk factors and the nature of disease development or progression (Soman and Sunavala, 2021).

The clinical hallmark of invasive mucormycosis is necrosis of tissue due to angioinvasion and subsequent thrombosis. The early symptoms of Rhino-Orbito-Cerebral Mucormycosis are similar to sinusitis and periorbital cellulitis and may report eye and/or facial pain and numbness followed by blurred vision. Signs and symptoms suggestive of Mucormycosis in susceptible individuals includes multiple cranial nerve palsies, unilateral periorbital facial pain, edema of eyelids, orbital inflammation, blepharoptosis, proptosis, acute ocular motility changes, internal or external ophthalmoplegia, headache, and acute vision loss (Petrikkos et al., 2012). Clinicians should also check for the development of black lesions

or discharge on the nasal bridge or upper inside part of the mouth that may quickly progress and become more severe.

COVID-19 associated pulmonary aspergillosis (CAPA) is a condition that has received attention worldwide. The clinical features and chest images of pulmonary mucormycosis are not specific and challenging to distinguish from pulmonary aspergillosis. Patients usually report prolonged fever (>38 degrees Celsius) that is not responsive to broad-spectrum antibiotics. A dry cough is another common symptom. In rare cases, especially in patients with diabetes, pulmonary mucormycosis may present as an endobronchial or tracheal lesion. Researchers have noticed that the CT finding of a reversed halo sign is more common in patients with mucormycosis than other invasive pulmonary fungal infections (Petrikkos et al., 2012).

An improper or missed diagnosis coupled with antibacterial and steroid use, worsens the condition. Although a challenge, the need to distinguish Mucormycosis from other bacterial infections and aspergillosis is very crucial. A circulating antigen detection test (similar to galactomannan detection for invasive aspergillosis) is not available to diagnose mucormycosis. Therefore biopsy of specimens from clinically affected sites is necessary for diagnosis (Skiada et al., 2013). If a biopsy is not possible, the available specimens like sputum should be used for direct examination and culture. Sinus biopsies are required in cases of sinusitis. Ear, nose, and throat endoscopy helps to assess and re-evaluate the treatment response. If pulmonary involvement is evident and sputum analysis is negative, bronchoalveolar lavage or pulmonary biopsies should be carried out based on the radiological findings obtained by CT scans (Skiada et al., 2013). The surgeons should carefully manage the material taken from biopsies not to crush the specimen because Zygomycetes are fragile, and culture may thus report negative.

Demonstration of hyphae by direct microscopy in clinical samples is essential because it is rapid and highly suggestive of the disease. Specimens can be observed after treating with Potassium hydroxide, staining with an optical brightener (Calcofluor white), or with Gomori methaminesilver (Skiada et al., 2013). Immunohistochemistry with Antizygomycete antibodies that are commercially available may also occasionally help in the diagnosis. Molecular identification of mucormycosis agents helps identify the fungus at the genus and species level and will also aid in confirming the diagnosis. Different techniques like DNA probes targeting 18S subunit, ITS1 sequencing after polymerase chain reaction (PCR) with pan-fungal primers, 18S-targeted semi-nested PCR, and real-time PCR targeting cytochrome *b* gene have been reported to aid in diagnosis (Dannaoui, 2009).

5. Management with emphasis on dental triage

Antifungal therapy, along with control of the predisposing condition and surgical management, are the cornerstones of the treatment. First-line chemotherapy involves liposomal amphotericin B and amphotericin B lipid complex. Options for second-line treatment include Posaconazole and combination therapy of liposomal amphotericin B or amphotericin B lipid complex with caspofungin (Skiada et al, 2013; Prakash, 2021) Surgery is indicated when there is rhinocerebral and skin/soft tissue involvement. Elimination of underlying risk factors (diabetes control, discontinuation/tapering of glucocorticosteroids, reduction of immunosuppressants) is vital in the treatment of mucormycosis. Antifungal treatment should be continued for at least 4–6 weeks and is guided by the resolution of all associated symptoms and findings. Furthermore, instituting antifungal and steroids as an empirical therapy requires antifungal stewardship. Maintenance therapy is necessary for long-term immunocompromised patients (Skiada et al., 2013).

Dentists should be aware of the increased incidence of mucormycosis in Post Covid patients, especially in poorly controlled diabetes and other immunocompromised individuals. Symptoms such as atypical facial or sinus pain, blackish discharge, unexpected toothache should make the dental practitioners alert and vigilant (Papadogeorgakis et al., 2010). A thorough intraoral examination is recommended in all post-Covid patients visiting the dental OPD for early diagnosis of any oral mucocutaneous lesions. Surgical approach is crucial and it should involve excision and debridement of all infected and necrotic tissues, based on the disease progression. In some cases, referral to maxillofacial surgeon is mandatory as radical resection may be required, which can include partial or total maxillectomy and mandibulectomy (Bakathir, 2006). Therefore, surgical debridement and anti-fungal treatment can be considered the key to controlling and eliminating mucormycosis.

6. ICMR guidelines: Evidence-based advisory in the time of Covid-19

The Indian Council of Medical Research, in May 2021, came up with guidelines for the screening, diagnosis, and management of mucormycosis in the time of Covid 19. The chief warning signals to suspect Mucormycosis in Covid 19 patients, people with diabetes, and immunosuppressed individuals enlisted include sinusitis, nasal congestion, blackish or bloody nasal discharge, local pain on the cheekbone, unilateral facial pain, numbness or swelling, blackish discoloration over nasal bridge/palate, toothache, teeth loosening, jaw involvement, blurred or double vision with pain, fever, skin lesion, thrombosis and necrosis (eschar), chest pain, pleural effusion, hemoptysis and worsening of respiratory symptoms (ICMR, 2021).

7. Conclusion

Vigilance among the clinicians and spreading awareness in the public health care system remains crucial in successfully managing Mucormycosis and subsequent reduction of mortality. Several hospitals in India have opened Outpatient Departments (OPD) for Mucormycosis to monitor all the Covid 19 recovered patients from 10 days to 6 weeks when they are most vulnerable to the fungal infection. Patients are asked to report to the nearest Urban Primary Health Centre or the designated OPDs in hospitals in case of any symptoms. ICMR has recommended a multidisciplinary team approach including specialists from the medical and dental fraternity for the early diagnosis and management of Mucormycosis.

CRediT authorship contribution statement

Manjusha Nambiar: Conceptualization, Methodology, Formal analysis, Investigation, Writing-orginal draft, Writing-review & editing. **Sudhir Rama Varma:** Conceptualization, Methodology, Formal analysis, Investigation, Writing-orginal draft, Writing-review & editing. **Marah Damdoum:** Conceptualization, Methodology, Formal analysis, Investigation, Writing-orginal draft, Writing-review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Not applicable.

Funding

Not applicable.

References

Bakathir, A.A., 2006. Mucormycosis of the jaw after dental extractions: two case reports. Sultan. Qaboos Univ. Med. J. 6 (2), 77–82.

Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED). https://www.cdc.gov/ncezid/dfwed/index.html (Accessed 17 May 2021).

Dannaoui, E., 2009. Molecular tools for identification of Zygomycetes and the diagnosis of Zygomycosis. Clin. Microb. Infect. 15 (Suppl 5), 66–70. https://doi.org/10.1111/j.1469-0691.2009.02983.x.

ICMR GUIDELINES: EVIDENCE-BASED ADVISORY IN THE TIME OF COVID-19 (Screening, Diagnosis & Management of Mucormycosis). https://www.icmr.gov.in/pdf/covid/techdoc/Mucormycosis_ADVISORY-FROM-ICMR-In-COVID19 (Accessed 17 May 2021).

Jeong, W., Keighley, C., Wolfe, R., 2019. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clin. Microbiol. Infect. 25 (1), 26–34. https://doi.org/10.1016/j.cmi.2018.07.011.

Papadogeorgakis, N., Parara, E., Petsinis, V., Vourlakou, C., 2010. A case of successfully treated rhinocerebral mucormycosis: dental implications. Int. J. Dent. 2010, 273127. https://doi.org/10.1155/2010/273127. Epub 2011 Feb 15. PMID: 21350609; PMCID: PMC3042627.

Petrikkos, G., Skiada, A., Lortholary, O., Roilides, E., Walsh, T.J., Kontoyiannis, D.P., 2012. Epidemiology and clinical manifestations of mucormycosis. Clin. Infect. Dis. 54 (Suppl 1), S23–S34. https://doi.org/10.1093/cid/cir866.

Prakash, H., Chakrabart, i.A.,2019. Global Epidemiology of Mucormycosis. J. Fungi. (Basel). 5(1), 26. http://dx.doi.10.3390/jof5010026.

Prakash, H., Chakrabarti, A., 2021. Epidemiology of Mucormycosis in India. Microorganisms. 9 (3), 523. https://doi.org/10.3390/microorganisms9030523.

Skiada, A., Lanternier, F., Groll, AH., 2013. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). Haematologica. 98(4), 492–504. http://dx.doi.10.3324/haematol.2012.065110.

Soman, R., Sunavala. A., 2021. Post COVID-19 Mucormycosis - from the Frying Pan into the Fire. J. Assoc. Phys. India. 69 (ISSN 0004-5772).

Spellberg, B., Edwards Jr., J., Ibrahim, A., 2005. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin. Microbiol. Rev. 18 (3), 556–569. https://doi.org/10.1128/CMR.18.3.556-569.2005.

Superinfections and coinfections in COVID-19, MedPage Today. https://www.medpagetoday.com/infectiousdisease/covid19/86192 (Accessed 17 May 2021).