Short Communication

Ashok kumar Ahirwar*, Kirti Kaim, Pradeep Ahirwar and Rajani Kumawat

The second wave of COVID-19 results in outbreak of mucormycosis: diabetes and immunological perspective

<https://doi.org/10.1515/hmbci-2021-0072>

Received August 6, 2021; accepted December 3, 2021;

published online December 16, 2021

Abstract

Objectives: To evaluate the potential relationship between COVID-19 pandemic and mucormycosis outbreak.

Methods: PubMed, Embase, Cochrane Library and Google Scholar were searched for the term “COVID-19 and mucormycosis” up to May 31, 2021.

Results: After the second wave of COVID-19, the mucormycosis outbreak complicates the natural course of COVID-19. COVID-19 patients with uncontrolled diabetes mellitus with diabetic ketoacidosis, excessive glucocorticoid use, prolonged neutropenia, malnutrition and any underlying immunocompromised conditions are at risk of developing mucormycosis.

Conclusions: Hyperglycaemia impairs the motility of phagocytes and also decreases the oxidative and non-oxidative mechanism of killing the causative pathogen. Chronic hyperglycemia also leads to the formation of advanced glycation end-products (AGE), which leads to cross-linking between key proteins of inflammation and connective tissue such as collagen which makes tissue susceptible to immunological dysregulation. The receptor for AGE (RAGE) is expressed on various inflammatory cells including neutrophils and its activation by AGEs leads to

activation of many down signaling pathways which ultimately leads to impairment of the inflammatory response. Hyperglycemia also increases serum Nitric Oxide (NO), which decreases neutrophil motility and reduces the synthesis and release of various inflammatory mediators such as TNF- α and IL-1 β , IL-6. It also decreases the expression of adhesion molecules such as LFA-1 and ICAM-2, on neutrophils. Steroids cause immunosuppression majorly by inhibiting the NF- κ B pathway which is a transcription factor involved in the synthesis of many immunological mediators such as Interleukins, cytokines, chemokines, etc., and various adhesion molecules.

Keywords: COVID-19; diabetes mellitus; diabetic ketoacidosis; mucormycosis; steroid.

After the second wave of COVID-19, the mucormycosis outbreak complicates the natural course of COVID-19 worldwide. Mucormycosis also commonly known as ‘black fungus’ is a life threatening rare fungal infection caused by mucormycetes. COVID-19 patients with uncontrolled diabetes mellitus with diabetic ketoacidosis, excessive glucocorticoid use, prolonged neutropenia, malnutrition and any underlying immunocompromised conditions are at risk of developing mucormycosis [1]. Even its diagnosis is challenging due to lack of clinical suspicion, late presentation, and non-availability of rapid diagnostic services leading to underdiagnosis of mucormycosis and grave prognosis in COVID-19 patients [2].

The characteristic feature of mucormycosis is angioinvasion which leads to the formation of microthrombi and ultimately necrosis. Angioinvasion is responsible for the hematogenous spread of mucormycetes that leads to local and systemic dissemination as shown in Figure 1 [3].

Hyperglycaemia in diabetes mellitus impairs the motility of phagocytes and also decreases the oxidative and non-oxidative mechanism of killing the causative pathogen. The impaired function of phagocytes is thought to be due to metabolic reprogramming. Activated macrophages utilize glycolytic pathway for energy required to support

*Corresponding author: Dr. Ashok Kumar Ahirwar, MD, Assistant Professor, Department of Biochemistry, University College of Medical Sciences, New Delhi, 110095, India, Phone: +919654210832, E-mail: drashoklhmc@gmail.com

Kirti Kaim, ESI Hospital, Rohini, New Delhi, India, E-mail: kirti.kaim@gmail.com

Pradeep Ahirwar, Department of Radio-Diagnosis, Index Medical College, Hospital & Research Centre, Indore, Madhya Pradesh, India, E-mail: pradeepahirwar21@gmail.com

Rajani Kumawat, Department of Biochemistry, All India Institute of Medical Sciences, Bathinda, Punjab, India, E-mail: dr.rajanikumawat@gmail.com

Figure 1: Mechanism of mucormycosis in diabetes.

immunological action, instead of Krebs's cycle and mitochondria's ETC. Glycolysis pathway intermediates are utilized in the synthesis of amino acids, ribose, and NADPH, which are necessary for the synthesis of DNA, various inflammatory mediators, reactive oxygen species, etc. In diabetics, the glycolytic pathway is impaired that leads to the impairment of the classical function of macrophages against the pathogen. Hyperglycemia also increases oxidative stress which leads to defective chemotaxis of neutrophils, further diminishing the inflammatory response of immune cells against mucormycetes [4].

Chronic hyperglycemia also leads to the formation of advanced glycation end-products (AGE) which are produced by a non-enzymatic reaction between excessive glucose, and amino acids of various proteins. AGEs lead to cross-linking between key proteins of inflammation and connective tissue such as collagen which makes tissue susceptible to immunological dysregulation. The receptor for AGE (RAGE) is expressed on various inflammatory cells including neutrophils and its activation by AGEs leads to activation of

many down signaling pathways which ultimately leads to impairment of the inflammatory response [4].

Some studies show that hyperglycemia also increases serum Nitric Oxide (NO), which decreases neutrophil motility. Hyperglycemia induced NO also reduces the synthesis and release of various inflammatory mediators such as $\text{TNF-}\alpha$ and $\text{IL-1}\beta$, IL-6 . It also decreases the expression of adhesion molecules such as LFA-1 and ICAM-2, on neutrophils. All these pathological changes lead to impaired inflammatory response against pathogens [5].

Steroids are usually used in complicated and severe cases of COVID-19. The steroid reduces the dysfunctional immunological and hyper inflammation response commonly known as 'cytokine storm' and improves the outcome in COVID-19. But excessive steroid use also increases the risk of various opportunistic infections such as mucormycosis by decreasing the immunological response. Steroids cause immunosuppression majorly by inhibiting the NF- κ B pathway which is a transcription factor involved in the

synthesis of many immunological mediators such as Interleukins, cytokines, chemokines, etc., and adhesion molecules. Steroid use also directly inhibits the genes which synthesize various cytokines such as IL-1, 2, 3, 4, 5, 6, 8 and IFN- γ . It also induces apoptosis of T cells, thus decreasing the T cell response against the pathogen. It also decreases the synthesis of end products of inflammation like prostaglandins and leukotrienes [4].

Diabetic Ketoacidosis or any systemic acidosis condition increases the availability of iron due to its displacement from the binding site in the presence of excessive H^+ ion. Excess of iron decreases the phagocytic activity of monocytes and macrophages, altering the activity of T cells and their subsets which further leads to inadequate immune response [5].

Although the presence of various risk factors complicates mucormycosis in COVID-19 patients, its early diagnosis and timely management is of utmost importance to improve the prognosis in COVID-19. Diagnosis of mucormycosis usually based on clinical history, physical and histopathological examination. Biochemical tests are not commonly used in routine clinical practice but molecular tests based on detecting mucormycosis species by next generation DNA sequencing based on bar code genes, such as 18S, ITS, 28 s, or rDNA are available in limited specialized laboratories [1]. The sample for laboratory investigations includes sputum, tissue lesions, secretions and are mostly based on direct microscopy or fluorescent microscopy examination. There is a need for developing tests that can detect mucormycetes DNA in the biological fluid and increase the turnaround time (TAT) to manage the COVID-19

associated mucormycosis appropriately [1]. There is also a need of the hour to develop a POCT test which could detect mucormycosis at the community health centre and primary health centre of India.

Acknowledgments: Authors are grateful to Dr. Puja Kumari Jha, Department of Biochemistry, UCMS, New Delhi.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Not Applicable.

Ethical approval: Not Applicable.

References

1. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, et al. Coronavirus disease (Covid-19) associated mucormycosis (CAM): case report and systematic review of literature. *Mycopathologia* 2021;186:289–98.
2. Spellberg B, Edwards J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clin Microbiol Rev* 2005;18:556–69.
3. Insuela D, Coutinho D, Martins M, Ferrero M, Carvalho V. Neutrophil function impairment is a host susceptibility factor to bacterial infection in diabetes. *Cells Immune Syst* 2019;1–22. <https://doi.org/10.5772/intechopen.86600>.
4. Strehl C, Ehlers L, Gaber T, Buttgerit F. Glucocorticoids—All-Rounders tackling the versatile players of the immune system. *Front Immunol* 2019;10:1744.
5. Walker EM, Walker SM. Effects of iron overload on the immune system. *Ann Clin Lab Sci* 2000;30:354–65.