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Covid-19 and Mucormycosis: The Tole of Hyperglycemia In Viral and Fungal Coinfection †

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Abstract: A fungal infection that is difficult to diagnose and treat, mucormycosis gained prominence with the SARS-CoV-2 pandemic as the infection with the new coronavirus predisposes patients to a greater risk of developing opportunistic infections, such as that caused by the "black fungus". In order to identify the physiological changes and risk factors related to SARS-CoV-2 infection that favor the development of mucormycosis, an integrative review was carried out based on the PICO strategy in which searches in December 2021 in the Virtual Library in Health, on the PubMed portal and on the Web of Science, using the Mesh terms: COVID-19, SARS-CoV-2 Infection and Mucormycosis together with the Boolean operators "AND" and "OR". Full-text articles were included, available in journals/periodicals, published in Portuguese, English and Spanish from December 2019 to 2021 that addressed the metabolic changes caused by COVID-19 related to involvement by mucormycosis and excluded studies of review, editorials and duplicates. With the application of filters and exclusion of duplicates, 140 and 151 studies were selected by title and abstract, 113 convergent and 41 divergent; and, with the reading in full, 9 studies remained to compose the review. The results indicated a greater number of publications from India and a predominance of male and diabetic patients with elevated inflammatory markers. The results indicated a greater number of publications from India and a predominance of male and diabetic patients with elevated inflammatory markers. The higher prevalence of diabetics and hyperglycemia are in line with the hypotheses raised by other literature, given the impacts resulting from COVID-19 on glycemic control and the risks to the body from Diabetes. Thus, post-Sars-CoV-2 hyperglycemia may be a risk factor for the development of mucormycosis.

Keywords: covid-19; sars-cov-2; mucormycosis; physiology

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1. Introduction

Mucormycosis, known as "black fungus disease", is a rare and invasive opportunistic fungal infection that emerged with the second wave of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mainly in Indian territory, being caused by fungi of the order Mucorales, with the species *Rhizopus* the one that most infects humans. Such a fungal infection has become worrying because of its difficult diagnosis and treatment, in addition to having invasive signs and symptoms, such as tissue necrosis of the face, which can reach the brain and leave sequelae if not detected early. This opportunistic infection usually affects people with a weakened immune system, especially during or shortly after

infection with COVID-19, in addition to having a strong association with diabetics or those who are using corticosteroids, as they also increase serum glucose [1].

The cases of mucormycosis associated with COVID-19 have become concerning in recent years. This is due to the abrupt increase in the state of immunosuppression caused by the viral infection, with more than 3000 cases in the year 2020 alone, with a higher concentration in India. In this way, the disease presents itself as a public health emergency that requires, therefore, a standardization of protocols and treatments to deal with this infectious association. Risk factors listed in the literature include, mainly, individuals who have decompensated diabetes and who have recently used high doses of corticosteroids [2].

The hyperglycemia that predisposes to viral infection is associated with an acidosis environment conducive to fungal growth, a fact that corroborates the high number of cases in India, a country that has a significant prevalence of diabetics (15-20%) when compared to the global prevalence. (10.5%), which may explain the high probability of developing cases of mucormycosis [3,4]. Thus, the epidemiology from Indian cases suggests that patients with severe COVID-19 associated with uncontrolled diabetes is a fatal combination that easily predisposes the patient to fungal contamination, with the rhino-orbito-cerebral presentation being the most prevalent in India [5].

Therefore, this study aimed to gather information on cases of mucormycosis associated with COVID-19, especially those in which hyperglycemia played a relevant role, in addition to presenting the pathophysiology and the different courses of the disease. The information from this work can help health professionals to identify, at an early stage, the signs and symptoms of this fungal infection, as well as to know the clinical conditions of patients with COVID-19 who were infected by this opportunistic disease, to better manage the clinical outcome. and facilitate multidisciplinary management.

2. Metodology

2.1. Study

Descriptive-exploratory study, with a qualitative approach, with a method based on an integrative review. The delimitation of the guiding question was carried out from the PICO strategy: "In patients infected with SARS-CoV-2 (P), involvement by mucormycosis (I) compared to patients who did not develop mucormycosis (C) is related to metabolic changes resulting from COVID-19 (O)?".

The bibliographic survey was carried out in December 2021 by searching the Virtual Health Library (VHL), PubMed and Web of Science portals, using the Mesh terms: COVID-19, SARS-CoV-2 Infection and Mucormycosis, together with the Boolean operators "AND" and "OR", using the search strategies: ((COVID-19) OR (SARS-CoV-2 Infection)) AND (Mucormycosis).

2.2. Inclusion and Exclusion Criteria

Inclusion criteria were full-text articles, available in journals/periodicals, published in Portuguese, English and Spanish from December 2019 to 2021 that addressed the physiological changes caused by COVID-19 related to involvement by mucormycosis. Meanwhile, review, editorial and duplicate studies were excluded.

2.3. Selection and Analysis of Studies

There was a pre-selection by title, abstract and keywords, proceeding with the reading of the works in full to make their selection. The selection was performed manually and blindly by the researchers JPAC and SMGB, and SMA analyzed the conflicting articles. Subsequently, the selected studies were read in full. The review steps followed the PRISMA flowchart.

The categorization and analysis of the information was carried out through the instrument of collection of own authorship, containing the divisions: author, year, place,

level of evidence, type of study, journal of publication and main results. With the formation of an individual library, the contributions of the studies were analyzed to elucidate the guiding question, in order to enable reflection on the results and to trace relationships between the works to meet the proposed objective.

3. Results and Discussion

After screening the studies, it was observed that the majority came from India (66.6%), with the others distributed equally between the USA, Italy and Iran. Case studies (55.5%) were predominant, but there was a Case/Control Cohort study [6], which has a great impact due to its level of evidence according to the Oxford Level of Evidence [7]. The profile of patients is mostly male (69.4%) with a mean age of 53.4 years, and diabetes is still the prevalent comorbidity (83.18%). The most common form was rhino-orbital (61.5%), followed by rhino-orbital-cerebral (23.9%) [4,6,8,9,10,11,12,13].

Regarding the profile of studies and patients, the findings of this integrative review coincided with those of other literature, with a predominance of articles of Indian origin, male individuals with a mean age of 53.4 years [14,15]. As for the main results with regard to possible biochemical changes resulting from COVID-19 and that may contribute to the installation and development of mucormycosis, diabetes mellitus was a more common finding among the comorbidities found in the research, being the same reported in seven of the nine selected articles, which demonstrates how this comorbidity can favor the development of this fungal infection.

Since mucormycosis is a rare but serious invasive fungal infection, occurring mainly in immunocompromised patients, especially in individuals diagnosed with uncontrolled diabetes mellitus or hematologic malignancies [16]. This comorbidity is highly prevalent in the Indian population (15 to 20% of the population) when compared to the world average (10.5%), which generates a high probability of developing cases of mucormycosis, as evidenced [3,17].

It is also important to remember that infection by the SARS-CoV-2 virus in people with diabetes generates a stressful situation for the body, increasing the release of hyperglycemic hormones, leading, in addition to high blood glucose levels, to high variability of its values, combined with the recurrent use of corticosteroids [8]. Furthermore, we can mention the direct pancreatic damage of the virus, probably due to the interaction of the virus with the ACE-2 receptors of the beta cells [17,18].

Therefore, after searching the literature for hypotheses to support the relationship between hyperglycemia and mucormycosis infection, we can mention: i) decreased affinity of ferritin for iron when blood glucose is high, which increases serum iron levels; ii) greater expression of the GRP78 receptor, which interacts with *Rhizopus*, serving as a facilitator of endothelial injury [19,20].

4. Patents

The SARS-CoV-2 pandemic brought with it an infection by the “black fungus” or mucormycosis in worrying proportions, mainly affecting India, a country marked by a hot and humid climate and poor sanitary conditions that led to a greater spread of this fungus. However, what stands out is the high prevalence of diabetics in the country, with the hyperglycemic state being a major factor in the development of mucormycosis. Therefore, it can be concluded that the exacerbation of glycemic levels may be related to the direct impact that COVID-19 causes on the body, thus explaining the increase in the incidence of the "black fungus" during the pandemic scenario in which we live.

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References

1. Raut, Akshay; Huy, Nguyen Tien. Rising incidence of mucormycosis in patients with COVID-19: another challenge for India amidst the second wave?. The Lancet. Respiratory Medicine, **2021**. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8175046/ . Acesso em: 21/01/2022.
2. Choksi, T.; Aagrawal, A.; Date, P. Mortalidade cumulativa e fatores associados aos resultados da mucormicose após COVID-19 em um centro de atenção terciária multiespecialidade na Índia. JAMA Ophthalmol, **2021**. Disponível em: https://jamanetwork.com/journals/jamaophthalmology/fullarticle/2787145. Acesso em: 30dez. 2021.
3. Sun et al. Atlas ded diabetes da IDF: Estimativas de prevalência de diabetes em nível global, regional e nacional para 2021 e projeções para 2045. Diabetes Res. Clin. Pratique, **2021.** Disponível em: https://www.diabetesresearchclinicalpractice.com/article/S0168-8227(21)00478-2/fulltext. Acesso em: 25 jan. 2021.
4. Vare *et al*. Incidência, mortalidade cumulativa e fatores que afetam o resultado da mucormicose associada a COVID-19 no oeste da Índia. Indian Journal of Ophthalmology, V. 69, Ed. 12, p 3678-3683, dez. **2021**. Disponível em: https://www.scielo.br/j/rboto/a/pBpfxKgkh4JxGZFcJSCcVSx/?lang=pt. Acesso em: 30 dez. 2021.
5. Rastogi, S.; Verma A. Jalaneti (saline nasal irrigation) as primary intervention in suspected rhino-orbito-cerebral mucormycosis helps improving the recovery: A case report. J Ayurveda Integr Med. **2021** Nov 1;13(2). Disponível em: https://pubmed.ncbi.nlm.nih.gov/34736856/ . Acesso em: 30/12/2021.
6. Meshram, HS, *et al*. Mucormycosis as SARS-CoV2 sequelae in kidney transplant recipients: a single-center experience from India. **2021** Nov 18:1–11. Disponível em: https://pubmed.ncbi.nlm.nih.gov/34792722/. Acesso em: 30 dez. 2021.
7. Pedrosa, Karilena Karlla Amorim et al. ENFERMAGEM BASEADA EM EVIDÊNCIA: CARACTERIZAÇÃO DOS ESTUDOS NO BRASIL. Cogitare Enfermagem, [S.l.], v. 20, n. 4, dez. **2015**. ISSN 2176-9133. Disponível em: <https://revistas.ufpr.br/cogitare/article/view/40768>. Acesso em: 31 dez. 2021.
8. Gupta, S., Ahuja, P. Fatores de Risco para Procurence of Mucormycosis and its Manifestations Post Covid-19: a Single Arm Retrospective Unicentric Clinical Study. Indian J Otolaryngol Head Neck Surg, **2021**. Disponível em:https://pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/pt/covidwho-1427410. Acesso em: 30 dez. 2021.
9. Kumar H M, *et al*. Serum iron indices in COVID-19-associated mucormycosis: A case-control study. Mycoses**. 2022** Jan;65(1):120-127. Disponível em:https://pubmed.ncbi.nlm.nih.gov/34743358/. Acesso em: 30 dez. 2021.
10. 10.Arora *et al*. Post-COVID-19 mucormycosis presenting as chest wall cellulitis with mediastinitis. Lancet Infect Dis. **2021**, Nov;21(11):1611. Disponível em: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00582-X/fulltextv. Acesso em: 30 dez. 2021.
11. Ostovan, VR, *et al*.. Coronavirus disease (COVID-19) complicated by rhino-orbital-cerebral mucormycosis presenting with neurovascular thrombosis: a case report and review of literature. J Neurovirol. **2021** Aug;27(4):644-649. Disponível em: https://pubmed.ncbi.nlm.nih.gov/34342852/. Acesso em: 30 dez. 2021.
12. Revannavar, SM, P S S, Samaga L, V K V. COVID-19 triggering mucormycosis in a susceptible patient: a new phenomenon in the developing world? BMJ Case Rep. **2021** Apr 27;14(4):e241663.

13. Khan, Nariman et al. A case report of COVID-19 associated pulmonary mucormycosis. **Archive of Clinical Cases**, v. 7, n. 3, p. 46, 2020 .Disponível em:https://pesquisa.bvsalud.org/portal/resource/pt/mdl-34754927. Acesso em: 30 dez. 2021.

14. Muthu, Valliappan et al. Epidemiology and pathophysiology of COVID-19-associated mucormycosis: India versus the rest of the world. Mycopathologia, v. 186, n. 6, p. 739-754, **2021.** Disponível em: https://link.springer.com/article/10.1007/s11046-021-00584-8. Acesso em: 30 dez. 2021

15. 15.Singh, Awadhesh Kumar et al. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, **2021**. Disponível em: https://www.sciencedirect.com/science/article/pii/S1871402121001570. Acesso em: 30 dez. 2021

16. Bassetti, Matteo; Bouza, Emilio. Infecções invasivas por fungos no ambiente de UTI: complexidades e soluções, **J**ournal of Antimicrobial Chemotherapy, v. 72, Issue suppl_1, p. i39 – i47, mar **2017**. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28355466/. Acesso em: 30 dez. 2021

17. 17.Roopa R., Thanthoni, Malakordi; WARRIER, Aravind S. COVID-19 Coinfection With Mucormycosis in a Diabetic Patient. Cureus, Chennai, IND, v.13, ed.6, **2021.** Disponível em: https://pubmed.ncbi.nlm.nih.gov/34306884/. Acesso em: 30 dez. 2021.

18. Pandiar D, Kumar NS, Anand R, Kamboj M, Narwal A, Shameena PM. Does COVID 19 generate a milieu for propagation of mucormycosis? Med Hypotheses. **2021** Jul;152:110613. Disponível em: https://pubmed.ncbi.nlm.nih.gov/34087613/. Acesso em: 30 dez. 2021.

19. Baldin, Clara; IBRAHIM, Ashraf S. Molecular mechanisms of mucormycosis—the bitter and the sweet. PLoS pathogens, v. 13, n. 8, p. e1006408, **2017**. Disponível em: https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006408. Acesso em: 21/01/2022.

20. Pushparaj, Karthika et al. Mucormycosis (black fungus) ensuing COVID-19 and comorbidity meets-Magnifying global pandemic grieve and catastrophe begins. Science of The Total Environment**,** v. 805, p. 150355, **2022**. Disponível em: https://www.sciencedirect.com/science/article/pii/S0048969721054322 . Acesso em: 30/01/2021