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COVID-19 associated mucormycosis is not a direct consequence of SARS-CoV 2 induced immune dysfunction

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The term mucormycosis identifies the invasive infection of humans by saprophytic fungi of the order Mucorales. *Rhizopus oryzae*, formerly *R. arrhizus*, is the species present in 70% of patients [1]. Mucormycosis shows six forms of presentation: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous, the first two being the most frequent [2]. That entity, in any of its presentations, is not contagious. The spores of the saprophytic fungi that cause it are widely distributed in nature, scattered in the soil, air, food and decomposing organic debris. Due to their low virulence, these fungi may be present as commensals, for example, on the nasal mucosa of a healthy host. Under adverse conditions to the host, they can germinate, spread to neighboring tissues and cause their necrosis [3].

India has been one of the countries hardest hit by the COVID-19 pandemic. As of October 4, 2021, 33,834,702 individuals had been infected with SARSCoV-2 and 448,997 persons had died of the virus in that country [4]. Since the beginning of the second wave of the COVID-19 pandemic, which has been particularly devastating there, that country has shown a spectacular increase in the number of cases of mucormycosis in patients affected by the virus and, above all, in people recovered from severe forms of the disease. The association of COVID-19 with mucormycosis, reported much less frequently in other countries, has been documented in more than 12,000 patients in the Indian subcontinent [5-7].

Mucormycosis is typically considered an opportunistic infection, meaning it thrives when the host immune system is compromised [8]. Nevertheless, that old concept has not always been managed in the best way for understanding the association between COVID-19 and mucormycosis. Here, we comment some evidences demonstrating that COVID-19 associated mucormycosis is not a direct consequence of the SARS CoV-2 induced immune dysfunction.

The natural progression of SARS CoV-2 infection is extremely variable. It ranges between an asymptomatic course or mild clinical expression, which generally occurs in children and healthy adults, and the development of pneumonia and severe multi-organ failure, more frequent in the elderly and in patients of chronic diseases. This broad spectrum of clinical expression is the consequence of another one at immunological level: SARS CoV-2 infection activates innate and adaptive immune responses that, in the most frequent and benign of evolutions, lead to the containment of viral replication and recovery and, in the most unfavorable of sequences, can stimulate an intense pulmonary inflammatory reaction that, leading to more severe complications, can end in death [9-10].

Roughly speaking, the deregulation of immune responses that occurs in severe forms of COVID-19 is characterized by fewer important cell types (total leukocytes, T lymphocytes, CD4 + T cells, CD8 + T cells, and platelets) and, paradoxically, by an increase in the number of neutrophils. To these cellular changes is added the increase in circulation, and in the affected tissues, of inflammatory cytokines such as interleukins (IL) -2R and IL-6 and TNF-α (from the English Tumor Necrosis Factor-alpha), among others [6,9-11].

The immune deregulation that takes place in people suffering from severe forms of COVID-19, which in many cases allows the development of opportunistic infections, including fungi (pulmonary aspergillosis, oropharyngeal candidiasis, among others), has been one of the most alluded arguments to explain the association between this viruses and mucormycosis [6,12]. At least, three observations refute that direct link:

(i) The deregulation of immune responses that takes place during severe forms of SARS CoV-2 infection is universal (that is, in all geographic areas where the epidemic has reached) and the association between COVID 19 and mucormycosis has been reported in a small number of countries; beyond isolated cases, almost all of the reported series correspond to studies in India.

(ii) As mentioned above, an increase in peripheral neutrophil number has been noted in patient of COVID-19 [11]. This is beneficial for the host as far as immunity to Mucorales is concerned. The neutrophils are very effective and they readily inactivate the fungus by the generation of oxidative metabolites if the host is immunocompetent. In fact, individuals with low levels of neutrophils or with impaired function of those cells, as occur with patients of some malignant blood diseases, are at high risk of mucormycosis [13].

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(iii) As commented before, a decrease in peripheral lymphocytes number has been observed in persons affected by sever forms of SARS CoV-2 infection [6, 9-11]. However, lymphopenia does not play any significant role in increasing the host susceptibility to Mucorales [11]. Epidemiologically, this can be evidenced by the lower incidence of mucormycosis in HIV-infected patients and other lymphopenic syndromes [14].

Alternatively, and analyzing the association between COVID-19 and mucormycosis from a more holistic perspective, the epidemiologic triad formed by environment, etiological agents, and host factors may be a practical model to explain that association in India: First, the tropical weather and sanitary conditions in some areas of that country shape up a conducive environment for the growth of mucoralean spores [15]; Second, the distribution of agents causing mucormycosis varies depending on the geographic area [16]; And third, some metabolic events caused by COVID-19 comorbidities, mainly diabetes, which is particularly prevalent in India [12], could be related with the development of clinical forms of mucormycosis during and after SARS CoV-2 infection in that subcontinent [5,7,11,15].

At least, three metabolic events have been related with the development of clinical forms of mucormycosis in patient of COVID-19: (i) Increased levels of circulating glucose (as a result of previous decompensated diabetes, in response to infectious stress, and induced by steroids used in the treatment of the viruses) would damage innate immunity mechanisms, in particular migration, chemotaxis and phagocytosis of neutrophils, which are necessary for the control of fungal infection [11]. Elevated glucose levels, due to the ketoacidosis to which they lead, also interfere with the adequate physiological sequestration of serum iron by ferritin and transferrin and, with this, increase free iron levels (growth of *R. oryzae* is directly proportional to serum free iron levels) [11,17]. (ii) Low oxygen concentrations, result of invasion of tissues by SARS-CoV-2, promote a favorable environment for fungal germination and proliferation [7]. (iii) High doses of steroids frequently used in the treatment of the inflammatory phase of COVID-19, in addition to further increasing glucose levels, can lead to decreased migration, phagocytosis and microbicidal activities of macrophages, functions also necessary for the control of fungal infection [11,18].

In summary, the reemergence of mucormycosis in the setting of the COVID-19 pandemic has resulted in significant morbidity and mortality in several countries, mainly in India. Although more research is needed to obtain a better comprehension of the pathophysiologic basis of COVID-19 associated mucormycosis, some metabolic events caused by COVID-19 comorbidities, mainly diabetes, that indirectly deregulate immune responses, could be related with the development of clinical forms of mucormycosis during and after SARS CoV-2 infection in that subcontinent.

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Conflicts of interest

None.

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