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Letter to the Editor

COVID-19-Associated Mucormycosis in Diabetic Patients: The Tip of an Iceberg

Amirhossein Parsaei [1], ***Ashkan Mohammadi Kooshki*** [2], ****Hamid Nasri*** [3,4], ***Shakiba Hassanzadeh*** [4]

1. *Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
2. *Department of Infectious Diseases, Iran University of Medical Sciences, Tehran Iran*
3. *Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran*
4. *Nickan Research Institute, Isfahan, Iran*

***Corresponding Author:** Email: hamidnasri@med.mui.ac.ir

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Dear Editor-in-Chief

Mucormycosis (MM) is a rare opportunistic fungal infection mostly seen in immunocompromised patients. The incidence of MM has recently increased during the COVID-19 pandemic (1). Poorly controlled diabetic patients, mostly in developing countries, have been more affected by the SARS-CoV-2 infection (2). Sustained hyperglycemic state, stress- or steroid-induced impaired immune responses and long-term admission at the intensive care unit (ICU) have made the COVID-19-infected diabetic patients more vulnerable to fungal infections, especially the lethal mucormycosis (2).

Both *Rhizopus arrhizus* and SARS-CoV-2 bind to the glucose-regulated protein 78 (GRP78); an overexpressed receptor observed in long-term hyperglycemia (3). On the other hand, the treatment of COVID-19 could also trigger COVID-19-associated mucormycosis (CAM). As a high-risk group, diabetic patients with COVID-19 infection are more susceptible to receiving intensive steroid therapy, antiviral drugs, or immunomodulatory agents, and usually have longer ICU admission (4). Therefore, diabetic patients require more consideration regarding this opportunistic infection during the COVID-19 pandemic.

The longer duration of the COVID-19 pandemic, the more threat of opportunistic infection. The challenge of managing DM has changed during the quarantine era. Lifestyle changes due to social isolation and restricted access to physicians for periodic follow-ups have already raised concerns about controlling the blood glucose of patients with DM (5). In addition, corticosteroid therapy seems to be inevitable in the management of COVID-19 symptoms. The dose of these immunosuppressive agents may be increased in diabetic patients that are re-infected with the new SARS-CoV-2 variants (6). As the virus replicates, the risk for mutations increases as well. Consequently, these mutations may develop a more deadly or transmissible variant that could even be able to penetrate the immune barrier of vaccinated individuals.

The diagnosis of MM is challenging. In addition, the negative impact of COVID-19 infection on the immune responses could make the diagnosis more difficult. Delayed diagnosis of MM and the

lack of effective prophylactic and therapeutic methods could increase the mortality in susceptible patients. Therefore, immediate management of opportunistic infections seems critical and urgent.

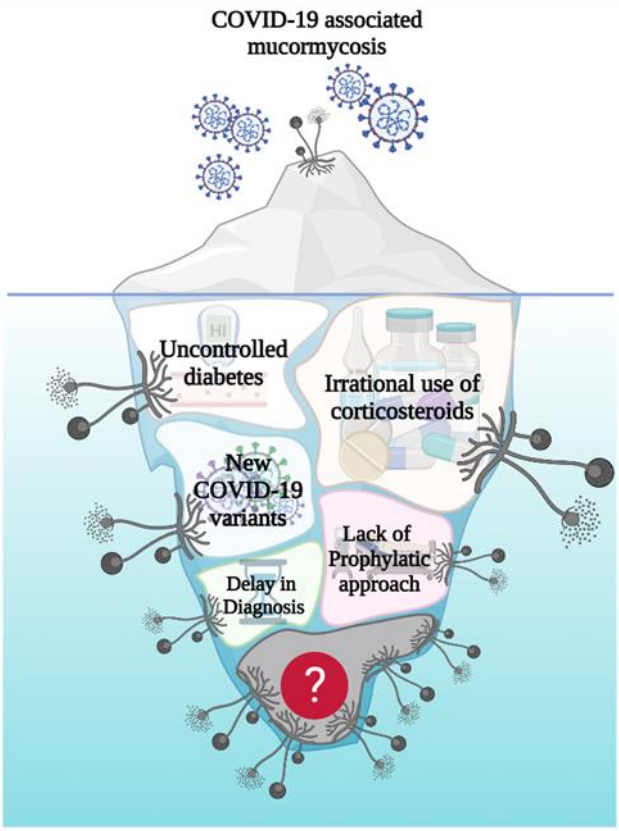

Fig. 1: COVID-19-associated mucormycosis (CAM) is the tip of an iceberg

MM has a high mortality rate in diabetic patients; however, it is controllable with the proper approaches. Since therapy with high dose corticosteroid makes diabetic patients with COVID-19 infection more susceptible to MM, they may significantly benefit from a comprehensive guideline on corticosteroid use. In addition, tight control of blood glucose levels, limited ICU stay, and a second thought on the benefit of immunomodulatory drugs can lead to better outcomes (2). The delay in diagnosing MM usually results in the lack of administrating prophylactic antifungal agents. Prompt antifungal combination therapy (with amphotericin B, posaconazole, and caspofungin) in susceptible patients resulted in a 100% survival rate (7).

Diagnosis of MM, as a highly lethal disease, is quite challenging. Although a 12-hour delay in diagnosing MM can be fatal (8), the average time of diagnosing MM is 12 days after admission (7). MM has a rapidly progressive nature and only half of the patients are diagnosed before death (9). Therefore, prompt diagnosis of MM and immediate treatment within the first two weeks are important in patients with CAM.

CAM in diabetic patients is the tip of an iceberg (Fig. 1), especially since the emergence of COVID-19 variants of interest such as B.1.1.7, B.1.617.2, and other variants of concern that cause

severe COVID-19 infection. Moreover, the currently available vaccines have faced questions regarding their sufficient efficacy in diabetic patients (10). There will probably be more cases of severe COVID-19 infections in diabetic patients. Due to the current limitations in diagnostic and treatment options, this population has an increased risk for CAM. We believe that the inevitable surge in the incidence of CAM in diabetic patients is only preventable through immediate prophylactic action such as administrating a combination of antifungal drugs.

It seems that more cases of CAM will be reported in this pandemic. The main involved factors include the irrational use of corticosteroids, uncontrolled blood glucose levels, new emerging variants, lack of clear guidelines on prophylactic approaches, delayed diagnosis, and a variety of other unknown factors

Conflict of interest

The authors declare that there is no conflict of interest.

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