



## Guest Editorial

# How COVID-19 Impacted on Rhino-Orbital-Cerebral Mucormycosis

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## 1. An old disease with a new risk factor

Increased number of sinu-orbital mucormycosis, just a few months after COVID-19 pandemic, has raised concerns among healthcare providers, healthcare policy makers and the community. Mucormycosis is a fungal infection caused by an angioinvasive fungus in the order of Mucorales.<sup>1</sup> The fungus spreads from the nasal and sinus to the orbit, palatine and pterygopalatine fossa. It can then invade intracranial cavity with a much higher mortality, if not controlled. This is a well-known rare disease among patients with underlying systemic disease with disturbed immunity. The known risk factors for mucormycosis are diabetes mellitus, neoplastic diseases especially hematologic malignancies, aplastic anemia, malnutrition, burns, organ transplants, immunosuppressive drugs and immunomodulating agents. Rarely, it can occur in apparently immunocompetent patients.<sup>2</sup>

Investigators and clinicians dealing with these patients noted a remarkable increase in incidence of mucormycosis since March 2020, a few months after beginning of COVID-19 pandemic.<sup>3</sup> The majority of these patients had recent COVID-19 infection, hence named as COVID-19 associated mucormycosis (CAM). It is estimated that the prevalence of mucormycosis has raised up to 2.1 during COVID-19 pandemic.<sup>4</sup> More than one risk factor can operate in CAM. It seems that COVID-19 disease can be

proposed as risk factor of sinu-orbital mucormycosis.

## 2. Significance of CAM

Rhino-orbital mucormycosis can be considered a secondary infection after SARS-CoV2 infection.<sup>3</sup> Orbital mucormycosis can be fatal if not quickly and effectively managed.

Timely diagnosis, quick, aggressive and appropriate management are the critical factors for a successful outcome. Pakdel et al. reported that the most common presenting feature among patients with COVID associated orbital mucormycosis was orbital apex syndrome.<sup>3</sup> This signifies the importance of ophthalmological evaluations in diagnostic process.<sup>3</sup>

Early symptoms of sinu-orbital mucormycosis are usually subtle and difficult to notice. Initial imaging findings are similar to a typical sinusitis with scant or no orbital findings.<sup>1</sup> External visible signs are none or minimal such as mild periorbital edema. We have observed that the early symptoms and signs have been easily ignored by patients and physicians. Later, other features of disease occur abruptly and thunderously with a sudden profound visual loss and total ophthalmoplegia. In this later phase both patients and physician know that something threatening is going on. The majority of patients with COVID-19 associated mucormycosis have diabetes mellitus.<sup>3</sup> Almost 20% of patients with COVID-19 have diabetes mellitus. Furthermore, 50% of patients hospitalized for

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COVID-19 experienced hyperglycemia.<sup>5</sup> The mechanism by which COVID-19 predisposes to mucormycosis is yet to be clarified by future studies. It can be secondary to several mechanisms. SARS-Cov-2 virus can directly damage Langerhans cells in pancreas and induce diabetes. Diabetes mellitus disturbs innate and adaptive immunity, the main defense mechanism against mucorale invasion.<sup>6</sup> Corticosteroids and immunomodulator agents including anti-interleukin 6 that are used in the inflammatory phase of COVID-19, can predispose the patients to mucormycosis.

The golden key to timely diagnosis is to remember that subtle orbital findings in a patient with predisposing factors, may be secondary to mucormycosis. Indeed, this could be reliably accomplished when both COVID-19 patients, especially those with diabetes mellitus, and physicians are instructed about the clinical findings, diagnosis and management.

Current standard diagnosis are based on clinical suspicion of the physician, tissue biopsy and mycological studies. It is essential to start medical treatments immediately at the phase of clinical diagnosis. After a clinical diagnosis of mucormycosis, antifungal agents should not be held until obtaining histopathological and mycological reports.

We found it useful to alarm emergency physicians, ophthalmologists, infectious disease specialists and COVID-19 patients about early findings of mucormycosis and the role of diabetes as a predisposing factor. Thus, we could see more patients in the earlier stages of disease. Pakdel and associates found a median interval of seven days from COVID-19 and mucormycosis.<sup>3</sup> The above finding shows the importance of this critical surveillance time for detecting mucormycosis in COVID-19 patients.

Optimal management of patients with mucormycosis needs a well-equipped hospital with highly skilled team of specialists including but not restricted to oculo-facial plastic surgeon, ophthalmologist, infectious disease specialist, ENT, endocrinologist, pathologist, mycologist, neurosurgeon, nephrologist, neuroradiologist and oncologist.

Treatment with intravenous amphotericin B and adequate sinus debridement are essentials of management plan. It has been shown that those patients that received combined intravenous amphotericin B and Posaconazole might have a higher survival rate compared to those that received only liposomal amphotericin B.<sup>3</sup>

There are few reports that found transcutaneous retrobulbar amphotericin B (TRAMB) may be associated with lower exenteration rate (RR=0.28) in patients with orbital mucormycosis.<sup>7</sup>

In summary, COVID-19 is probably an important emerged risk factor for mucormycosis. Acknowledgment

and alarming the association between SARS-Cov-2 infection and sinu-orbital mucormycosis among all physicians from different disciplines and healthcare providers is an important step to control the uprising incidence of this devastating and lethal disease. Specialists' and public awareness needs to run parallel to sensitize and alarm policymakers to provide necessary antifungal medications, immunization against COVID-19 and strategic planning for control of diabetes in the population. Further, educating patients, family and nurses about the early symptoms of CAM especially among those with diabetes, immunocompromised states and those receiving immunomodulating drugs can be useful to find and treat patients in the earlier stages of the disease. It can be hypothesized that adequate control of diabetes and judicious use of corticosteroid and immunomodulators in patients with COVID-19 may decrease the risk of mucormycosis.

### 3. Conflict of Interest

The authors declare that there is no conflict of interest.

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