



COVID -19 ASSOCIATED RHINO ORBITAL AND CEREBRAL INVASIVE FUNGAL INFECTIONS - 1 YEAR STUDY FROM TERTIARY CARE CENTRE.

Pathology

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ABSTRACT

India is struggling against a rapid increase in Covid-19 cases, but a nasty and rare fungal infection affecting some coronavirus patients is dealing the country a double blow. Reports suggest the number of cases is now much higher, which is unsurprising given the current wave of Covid-19 infections in India. Coronavirus disease 2019 (COVID-19) infections may be associated with a wide range of bacterial and fungal co-infections.

KEYWORDS

COVID 19, Fungal infection, Mucormycosis, comorbidity

INTRODUCTION

COVID -19 has taken a toll on health care system in India. With this viral infection the otherwise less infective fungal infections have superseded causing more morbidity and mortality. More than 4,300 people have died of the deadly "black fungus" in India in a growing epidemic that mainly affects Covid-19 patients.

The two worst-affected states are Maharashtra and Gujarat, where 1,785 people have died from mucormycosis.

The coronavirus disease 2019 (COVID-19) infection caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be associated with a wide range of disease patterns, ranging from mild to life-threatening pneumonia. A wide range of bacterial and fungal co-infections may exist and may be associated with preexisting morbidity (diabetes mellitus, lung disease) or may develop as a hospital-acquired infection such as ventilator-associated pneumonia.[1]

The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), high iron levels (increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators.[2]

Mucormycosis is an uncommon but a fatal fungal infection that usually affects patients with altered immunity. Mucormycosis is an angioinvasive disease caused by mold fungi of the genus *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella* and *Absidia* of Order-Mucorales, Class-Zygomycetes.[3]

The *Rhizopus Oryzae* is most common type and responsible for nearly 60% of mucormycosis cases in humans and also accounts for 90% of the Rhino-orbital-cerebral (ROCM) form.[4] Mode of contamination occurs through the inhalation of fungal spores.

Both *Aspergillus* and *Candida* have been reported as the main fungal pathogens for co-infection in people with COVID-19 [2].

Phycomycosis or zygomycosis was first described in 1885 by Paltau [3] and later coined as Mucormycosis in 1957 by Baker, an American pathologist for an aggressive infection caused by *Rhizopus*. [4]

Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000) in India compared to developed countries, in a recent

estimate of year 2019–2020 [2]. In other words, India has highest cases of the mucormycosis in the world. Notwithstanding, India is already having second largest population with diabetes mellitus (DM) and was the diabetes capital of the world, until recently [2]. Importantly, DM has been the most common risk factor linked with mucormycosis in India, although hematological malignancies and organ transplant takes the lead in Europe and the USA [2]. Nevertheless, DM remains the leading risk factor associated with mucormycosis globally, with an overall mortality of 46% [2]. Indeed, presence of DM was an independent risk factor (Odds ratio [OR] 2.69; 95% Confidence Interval 1.77–3.54; $P < 0.001$) in a large 2018 meta-analysis of 851 cases of rarely occurring mucormycosis, and the most common species isolated was *Rhizopus* (48%) [2]. While long term use of corticosteroids have often been associated with several opportunistic fungal infection including aspergillosis and mucormycosis, even a short course of corticosteroids has recently been reported to link with mucormycosis especially in people with DM. A cumulative prednisone dose of greater than 600 mg or a total methyl prednisone dose of 2–7 g given during the month before, predisposes immunocompromised people to mucormycosis [2].

There are few case reports of mucormycosis resulting from even a short course (5–14 days) of steroid therapy, especially in people with DM. Surprisingly, 46% of the patients had received corticosteroids within the month before the diagnosis of mucormycosis in the European Confederation of Medical Mycology study. [2]

These findings need a relook in the context of COVID-19 pandemic where corticosteroids are often being used. There has been a steep rise in case reports/series of mucormycosis in people with COVID-19 especially from India. Similarly, many cases are being reported from other parts of globe. Several anecdotal cases are also being reported in grey literature such as the print and electronic media. These findings are unprecedented and carry an immense public health importance, primarily because fatality rate with mucormycosis is pretty high. Especially the intracranial involvement of mucormycosis increases the fatality rate to as high as 90% [2]. Moreover, rapidity of dissemination of mucormycosis is an extraordinary phenomenon and even a delay of 12 h in the diagnosis could be fatal, the reason 50% of cases of mucormycosis have been historically diagnosed only in the post-mortem autopsy series [2].

This prompted us to conduct a systematic review of published case reports/series of mucormycosis in people with COVID-19, to know its temporal associations in relation to comorbidities, association with drugs being used in COVID-19 and overall characteristics of patients with its outcome.

We additionally postulated a mechanistic explanation as to why mucormycosis could be increasingly linked to COVID-19 and is being reported increasingly from India.

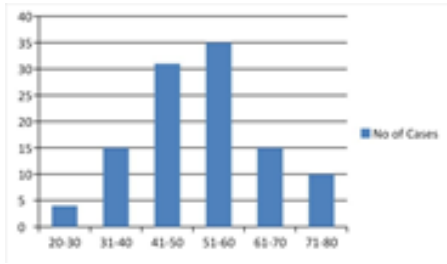


Chart 1 Age distribution

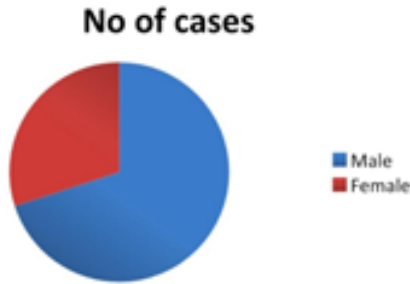


Chart 2 Sex Distribution

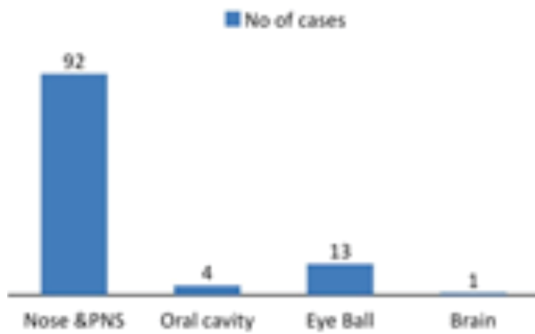


Chart 3 Site of involvement

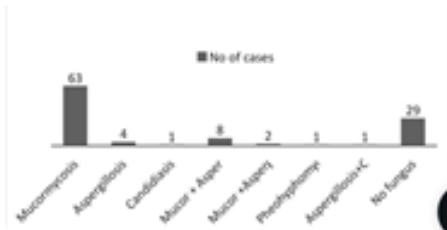


Chart 4 Fungus

Case Study:

Method

We hereby present a compile data of cases of post covid rhino orbital and cerebral fungal infections in a tertiary care centre in Maharashtra over a period of 1 year.

RESULTS

A total of 107 cases of post COVID 19 fungal infections were studied in 1 year duration. Study shows male preponderance with predominantly nasal and para nasal sinuses involvement followed by eye ball invasion. The most common fungus isolated was mucormycosis. Other less common cases included aspergillosis, candidiasis and an uncommon fungus condiobolus coronatus. Mixed infection was also reported. Most of the patients belong to age group of 40-60 years with pre-existing comorbidities. All the cases were treated with anti fungal and showed good response to treatment.

CONCLUSIONS

COVID 19 treatment which includes O2 therapy, steroids and ventilators with pre existing Co- morbidities was considered to be the cause of increase in fungal infections in patients. Judicious use of steroids and sterilizing the ventilators with improving health status can overcome this morbid fungal infection.

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