

Predictors of Mucormycosis in COVID-19

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ABSTRACT

Background and Aims: Mucormycosis, a serious angioinvasive infection caused by common filamentous fungi, that is, mucormycetes, constitutes the third most common invasive fungal infection, following aspergillosis and candidiasis. Although a rare infection, in recent times we witnessed a sudden surge of mucormycosis cases post-COVID-19 (coronavirus disease 2019). The present study was carried out to understand its relation to COVID-19, inflammatory markers, steroid use during COVID-19 treatment, clinical course and outcome of the disease. **Material and methods:** The present study was conducted at RNT Medical College, Udaipur over a period of 1 month. Written and informed consent from patients were taken. In this study, 15 patients admitted in COVID wards, medical wards, mucormycosis ward and ICU were included if fungal hyphae were found on potassium hydroxide (KOH) mount and there was a history of COVID-19 illness; negative KOH mount patients were excluded. **Results:** In the present study, on admission, out of 15 patients, 7 (46.7%) were admitted with mean neutrophil-to-lymphocyte ratio (NLR) >5.5, mean C-reactive protein (CRP) 126, mean interleukin (IL)-6 82.4, mean lactate dehydrogenase (LDH) 528, mean ferritin 662, mean D-dimer 1760; 5 (33.3%) patients were admitted with mean NLR 3.5-5.5, mean CRP 68, mean IL-6 39.6, mean LDH 336, mean ferritin 448, mean D-dimer 780; and 3 (20%) patients were admitted with mean NLR <3.5, mean CRP 16, mean IL-6 12.8, mean LDH 172, mean ferritin 226, mean D-dimer 430. Out of the 7 patients who were admitted with NLR >5.5, 3 (42.8%) were admitted with orbital cellulitis and 4 (57.2%) with invasive sinusitis. Out of 5 patients admitted with NLR 3.5-5.5, 3 (60%) were admitted with orbital cellulitis and 2 (40%) with invasive sinusitis. Out of 3 patients admitted with NLR <3.5, 1 (33.3%) patient had orbital cellulitis and 2 (66.7%) had invasive sinusitis. Out of total 7 patients who were admitted with orbital cellulitis, in 71.4% patients, steroid was used during COVID-19 treatment and out of 8 patients who were admitted with invasive sinusitis, in 62.5% patients, steroid was used during COVID-19 treatment. In the present study, 68% patients were male and 32% were female. Around 78% patients were from rural area and 22% patients were from urban area. Overall, 74% cases were treated with amphotericin B. Among these, 36% cases were diagnosed with orbital cellulitis and 38% cases were diagnosed with invasive sinusitis. Around 26% cases were treated with posaconazole, and among these 9% were orbital cellulitis cases and 17% were invasive sinusitis cases. About 85.72% cases of orbital cellulitis and 75% cases of invasive sinusitis improved. Nearly 42.86% cases who were admitted with NLR >5.5 did not improve with treatment. **Conclusion:** As per present study, inflammatory markers of COVID-19, NLR and history of steroid use during treatment can be considered as predictors of mucormycosis occurrence and their outcome.

Keywords: COVID-19, NLR, CRP, LDH, IL-6, mucormycosis

Mucormycosis is an angioinvasive infection caused by filamentous fungi mucormycetes. It is the third most common invasive fungal infection after aspergillosis and candidiasis.¹ The pathogens can result in infections with high mortality in immunocompromised individuals, particularly in

diabetes patients and people taking steroids.² Although a rare infection, in recent times we witnessed a sudden surge of mucormycosis cases post-COVID-19 (coronavirus disease 2019). Mucorales includes different species associated with rhinocerebral, pulmonary, skin and gastrointestinal infections and some other less frequently encountered infections in immunocompetent and immunocompromised people. Members of the genus *Rhizopus* are the most commonly isolated pathogens in a clinical setting, with *Rhizopus arrhizus* being the most common. Irrespective of the route of infection, whether inhalation of spores, ingestion or direct skin inoculation, the mucor hyphae eventually invade blood vessels, causing tissue infarction and necrosis.³ Risk factors for the infection include long-term neutropenia, use of steroid therapy, hematological

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malignancies, aplastic anemia, myelodysplastic syndromes, solid organ or hematopoietic stem-cell transplantation, human immunodeficiency virus (HIV) infection, diabetic and/or metabolic acidosis, intravenous substance abuse, prematurity and older age.^{4,6} The rhinocerebral type is the most commonly reported form of the infection, others being cutaneous, gastrointestinal, pulmonary and disseminated infections.⁷

MATERIAL AND METHODS

The present study was conducted at RNT Medical College, Udaipur, Rajasthan. This study was done over a period of 1 month after getting approval from Institutional Ethics Committee. Written and informed consent from patients were taken. In this study, 15 patients admitted in COVID wards, medical wards, mucormycosis ward and ICU were included if fungal hyphae were found on potassium hydroxide (KOH) mount and there was a history of COVID-19 illness; negative KOH mount patients were excluded.

RESULTS

In the present study, 68% patients were male and 32% patients were female. Around 78% patients were from rural area and 22% patients were from urban area.

On admission, out of 15 patients, 7 (46.7%) were admitted with mean neutrophil-to-lymphocyte ratio (NLR) >5.5, mean C-reactive protein (CRP) 126, mean interleukin (IL)-6 82.4, mean lactate dehydrogenase (LDH) 528, mean ferritin 662, mean D-dimer 1760; 5 (33.3%) patients were admitted with mean NLR 3.5-5.5, mean CRP 68, mean IL-6 39.6, mean LDH 336, mean ferritin 448, mean

D-dimer 780; and 3 (20%) patients were admitted with mean NLR <3.5, mean CRP 16, mean IL-6 12.8, mean LDH 172, mean ferritin 226, mean D-dimer 430.

Table 1 summarizes the distribution of patients as per mean NLR, CRP, IL-6, LDH, ferritin and D-dimer level on admission.

Out of the total 7 patients who were admitted with NLR >5.5, 3 (42.8%) were admitted with orbital cellulitis and 4 (57.2%) with invasive sinusitis. Out of 5 patients who were admitted with NLR 3.5-5.5, 3 (60%) were admitted with orbital cellulitis and 2 (40%) with invasive sinusitis. Out of 3 patients who were admitted with NLR <3.5, 1 (33.3%) patient was admitted with orbital cellulitis and 2 (66.7%) with invasive sinusitis (Table 2).

Out of total 7 patients who were admitted with orbital cellulitis, in 71.4% patients, steroid was used during COVID-19 treatment and out of 8 patients who were admitted with invasive sinusitis, in 62.5% patients, steroid was used during COVID-19 treatment (Table 3).

Around 74% cases were treated with amphotericin B, and among these, 36% were diagnosed with orbital cellulitis and 38% were diagnosed with invasive sinusitis. About 26% cases were treated with posaconazole, and among these 9% were orbital cellulitis cases and 17% were invasive sinusitis cases.

Nearly 85.72% cases of orbital cellulitis improved and 75% cases of invasive sinusitis improved (Table 4).

Additionally, around 42.86% cases who were admitted with NLR >5.5 did not improve with treatment (Table 5).

Table 1. Distribution of Patients as per Mean NLR, CRP, IL-6, LDH, Ferritin and D-dimer Levels on Admission

Mean NLR	N	Mean CRP	Mean IL-6	Mean LDH	Mean ferritin	Mean D-dimer
<3.5	3	16	12.8	172	226	430
3.5-5.5	5	68	39.6	336	448	780
>5.5	7	126	82.4	528	662	1760

Table 2. Prevalence of Orbital Cellulitis and Invasive Sinusitis in Patients Based on NLR Value on Admission

NLR	Orbital cellulitis (N) (%)	Invasive sinusitis (N) (%)	Total (N) (%)
<3.5	1 (33.3)	2 (66.7)	3 (100)
3.5-5.5	3 (60)	2 (40)	5 (100)
>5.5	3 (42.8)	4 (57.2)	7 (100)

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Table 3. Steroid Use in Patients with Orbital Cellulitis and Invasive Sinusitis

Steroid	Orbital cellulitis (N) (%)	Invasive sinusitis (N) (%)
Used	5 (71.4)	5 (62.5)
Not used	2 (28.6)	3 (37.5)
Total	7 (46.7)	8 (53.3)

Table 4. Outcome in Patients with Orbital Cellulitis and Invasive Sinusitis

Improved	Orbital cellulitis (%)	Invasive sinusitis (%)	Total (%)
Yes	85.72	75	80
No	14.28	25	20

Table 5. Outcome in Patients with Treatment Based on NLR on Admission

NLR	Orbital cellulitis (N) (%)	Invasive sinusitis (N) (%)	Improved with treatment (%)	Did not improve with treatment (%)
<3.5	1 (33.3)	2 (66.7)	100	-
3.5-5.5	3 (60)	2 (40)	100	-
>5.5	3 (42.8)	4 (57.2)	57.14	42.86

DISCUSSION

In the present study, more patients were male and from rural background, and more number of patients were admitted with severe COVID-19 disease with NLR >5.5, mean CRP >50, mean IL-6 >50, mean LDH >300, mean ferritin >400 and mean D-dimer >1000. More number of cases were diagnosed with invasive sinusitis than orbital cellulitis and in these cases more number of patients were admitted with severe COVID-19 disease. Mucormycosis developed more commonly in patients

who were admitted with severe form of COVID-19 illness with cytokine storm and were treated with steroid during their COVID illness. Amphotericin B was used more commonly than posaconazole in mucormycosis treatment. Around 80% patients improved with treatment and they were of mild and moderate severity, while 20% patients did not improve, who were admitted with severe form of COVID-19 illness with cytokine storm.

CONCLUSION

As per present study, inflammatory markers of COVID-19, NLR and history of steroid use during treatment can be considered as predictors of mucormycosis occurrence and their outcome.

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ECTRIMS and EAN Issue Statement on COVID Vaccination in MS Patients

The ECTRIMS and the European Academy of Neurology (EAN) have released a joint position statement on COVID-19 vaccination among patients with MS. It states that the COVID-19 vaccines currently available are safe for patients with MS. It also mentions that the vaccines provide the same protection to patients with MS as to the general population. However, there may be exceptions, such as patients taking the S1P modulator fingolimod and anti-CD20 drugs. Antibody responses have been found to be reduced in these patients. Presenting the statement at the 37th Congress of ECTRIMS 2021, held online, Mauricio Farez said that no specific contraindications for any COVID-19 vaccines in MS patients have been reported thus far... (Source: Medscape)

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