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## **Mycological study of Zygomycosis in patient suffering from suspected Mucormycosis during COVID-19 pandemic at IGIMS, Patna**

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**Abstract**--Aim: To study the speciation of zygomycosis, associated risk factors and spectrum of other fungus isolated in patients of suspected mucormycosis. Methodology: A prospective observational cross-sectional study was conducted for duration of 6 months in the Department of Microbiology, IGIMS, Patna. All the patients suspected clinically with mucormycosis visiting IGIMS, Patna were included in this study. Patient details were taken from lab investigation form after taking informed consent form from the patients or close relatives. Specimens were collected and routine microscopy (KOH mount), grams stain and culture was done for all samples. All the demographic details, laboratory results, clinical symptoms, COVID-19 status,

systemic history, treatment history details were collected and analysed. Results: Out of 203 patients, 72.4% were males and 27.6% were females. Mean age of the patients was  $50.19 \pm 3.08$  years. 51.2% were KOH positive and 48.8% were KOH negative. In culture method, 28.6% had Rhizopus spp, 17.7% had Aspergillus spp, 17.7% had Candida spp, and 43.8% had no growth. 27.1% patients were either COVID positive during examination or had COVID history in recent time. Out of 55 patients (27.1%) having/had COVID history, only 54.5% were KOH positive and 41.8% were Rhizopus spp positive culture. On systemic examination, 81.8% had diabetes and 49.1% had hypertension. 69.1% patients were on steroid therapy and 34.5% were on oxygen therapy recently. 32.7% patients were admitted to the hospitals during COVID. In 63.6% patients, eyes were involved followed by PNS (60%), nose (25.4%), and brain (16.4%). Most common clinical manifestations were headache (50.9%), orbital pain (38.2%), proptosis (32.7%), nasal discharge (23.6%), dec vision (21.8%), fever (18.2%), blindness (10.9%), and jaw pain (7.2%). Conclusion: From this study, it can be concluded that KOH smear and culture examination are approximately equally diagnostic in COVID-19 affected patients. The COVID-19 affected patients who are more susceptible to these infections are immunocompromised, have diabetes, and are prescribed steroids. Eyes are affected more commonly than any other organ in most of the patients.

**Keywords**---Zygomycosis, mucormycosis, diabetes, Rhizopus, proptosis.

## Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by newly discovered novel severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), affecting more than 10 million people worldwide. There have been a variety of complications reported during and post COVID infection [1]. The coronaviruses are enveloped, positive-sense single-stranded viruses that utilize the human angiotensin-converting enzyme 2 (ACE2) receptors located on cells in many organs/tissues, including the lung, heart, kidney, bladder, eyes, nasal and oral cavities, brain, thyroid, liver, gallbladder, stomach, pancreas, intestine, reproductive system of males and females, and skin, to gain entry and trigger a range of clinical manifestations [2]. Recently, several cases of mucormycosis in people with COVID19 have been increasingly reported world-wide, in particular from India.

Phycomycosis or zygomycosis was first described in 1885 by Paltauf [3] and later coined as Mucormycosis in 1957 by Baker [4], an American pathologist for an aggressive infection caused by Rhizopus. 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 [5]. The Rhizopus soryzae is most common type and

responsible for nearly 60% of mucormycosis cases in humans and also accounts Journal Pre-proof for 90% of the Rhino-orbital-cerebral (ROCM) form [6]. Mode of contamination occurs through the inhalation of fungal spores.

Severe COVID-19 disease is associated with an increase in pro-inflammatory markers, such as IL-1, IL-6 and tumor necrosis factor alpha, less CD4 interferon-gamma expression, and fewer CD4 and CD8 cells; this, therefore, increases the susceptibility to bacterial and fungal infections [7]. Mucormycosis is an opportunistic fungal infection that belongs to the zygomycete family and is ubiquitous in the environment. The major route of infection is via inhalations of spores, which then spread to the paranasal sinuses and lungs. Mucormycosis is non-pathogenic in immunocompetent individuals as a result of the presence of an intact immunity via neutrophils which hence permit the elimination of these spores [8]. However, in immunocompromised patients such as those with uncontrolled diabetes mellitus, diabetic ketoacidosis, presence of an open wound, HIV/ AIDS, cancer, and organ transplant, mucormycosis can result in a severe invasive fungal infection [9].

Infection with mucormycosis is associated with high mortality primarily due to complications such as cavernous sinus thrombosis, disseminated infection, osteomyelitis, and death. Diagnosis is made via routine blood work, biopsy, and radiological imaging. The standard protocol for the management is primarily reversal of risk factors, surgical debridement as well as intravenous antifungal medication such as Amphotericin B [9]. Infection with SARS-CoV-2 drastically impacts the immune system via induction of an inflammatory storm, an increase in neutrophil count as well a decrease in lymphocyte count, specifically CD4+ and CD8+ T cells. Neutrophils ensure the immunocompetence of individuals, so one would expect an even more increased immune response against mucormycosis fungi when reading that neutrophil numbers are rising during SARS-CoV-2. Consequently, these patients are at increased susceptibility of developing opportunistic infections such as mucormycosis, due to decreasing lymphocyte cells [8]. Hence the present study was conducted with the aim to study the speciation of zygomycosis, associated risk factors and spectrum of other fungus isolated in patients of suspected mucormycosis.

## **Materials and Methods**

A prospective observational cross-sectional study was conducted for a duration of 6 months in the Department of Microbiology, IGIMS, Patna. All the patients suspected clinically with mucormycosis visiting IGIMS, Patna were included in this study. Patient details were taken from lab investigation form after taking informed consent form from the patients or close relatives. Confidentiality was maintained and no personal details (such as name of the patients) were included in this study. Sample processing:

- In the microbiological laboratory, the samples were processed immediately as a routine procedure according to the standard operating procedures (SOP) of the department.
- Specimens were collected aseptically in sterile containers. Routine microscopy (KOH mount), grams stain and culture was done for all samples according to SOP.

All the demographic details, laboratory results, clinical symptoms, COVID-19 status, systemic history, treatment history details were collected and analysed.

## Results

Samples of 203 patients suspected with mucormycosis processed in the department of Microbiology, IGIMS, Patna, Bihar, India. Out of 203 patients, 72.4% were males and 27.6% were females. Mean age of the patients was  $50.19 \pm 3.08$  years. Out of 203 patients, 51.2% were KOH positive and 48.8% were KOH negative. In culture method, 28.6% had rhizopusspp, 17.7% had aspergillus spp, 17.7% had candida spp, and 43.8% had no growth. 27.1% patients were either COVID positive during examination or had COVID history in recent time.

Table 1  
Demographic details, microbiological examination, and COVID details of the enrolled patients

Variables		Number (n=203)	%
Gender	Male	147	72.4
	Female	56	27.6
Mean age (in years)		$50.19 \pm 3.08$	
KOH	Negative	99	48.8
	Positive	104	51.2
Culture	Negative	89	43.8
	Rhizopusspp	58	28.6
	Aspergillus spp.	36	17.7
	Candida spp.	16	7.9
	Others	4	2.0
COVID-19 status	Confirmed Positive/ Post-COVID	55	27.1
	Negative/ Not known	148	72.9

Table 2  
Microbiological examination details, associated risk factors, clinical manifestations and organ involvement in COVID-19 confirmed cases

Variables		Number (n=55)	%
KOH positive		30	54.5
Rhizopusspp positive		23	41.8
Diabetes	Yes	45	81.8
	No	10	18.2
Steroid therapy	Yes	38	69.1
	No	17	30.9
Oxygen therapy	Yes	19	34.5
	No	36	65.5
Hypertension	Yes	27	49.1
	No	28	50.9

Hospital stay during COVID	Yes	18	32.7
	No	37	67.3
Organ involved	Eye	35	63.6
	Nose	14	25.4
	PNS	33	60.0
	Brain	9	16.4
Clinical manifestations	Orbital pain	21	38.2
	Nasal discharge	13	23.6
	Proptosis	18	32.7
	Dec vision	12	21.8
	Fever	10	18.2
	Headache	28	50.9
	Blindness	6	10.9
	Jaw pain	4	7.2

Out of 55 patients (27.1%) having/had COVID history, only 54.5% were KOH positive and 41.8% were rhizopus spp positive culture. On systemic examination, 81.8% had diabetes and 49.1% had hypertension. 69.1% patients were on steroid therapy and 34.5% were on oxygen therapy recently. 32.7% patients were admitted to the hospitals during COVID.

In 63.6% patients, eyes were involved followed by PNS (60%), nose (25.4%), and brain (16.4%). Most common clinical manifestations were headache (50.9%), orbital pain (38.2%), proptosis (32.7%), nasal discharge (23.6%), dec vision (21.8%), fever (18.2%), blindness (10.9%), and jaw pain (7.2%).

## Discussion

Although mucormycosis is an extremely rare in healthy individuals but several immunocompromised conditions predispose it. This includes uncontrolled DM with or without DKA, hematological and other malignancies, organ transplantation, prolonged neutropenia, immunosuppressive and corticosteroid therapy, iron overload or hemochromatosis, deferoxaminetherapy, severe burns, acquired immunodeficiency syndrome (AIDS), intravenous drug abusers, malnutrition and open wound following trauma [10]. In our study also, out of COVID positive patients suspected for mucormycosis, 81.8% had diabetes and 49.1% had hypertension. 69.1% patients were on steroid therapy and 34.5% were on oxygen therapy recently. 32.7% patients were admitted to the hospitals during COVID.

Mucormycosis can involve nose, sinuses, orbit, central nervous system (CNS), lung (pulmonary), gastrointestinal tract (GIT), skin, jaw bones, joints, heart, kidney, and mediastinum (invasive type), but ROCM is the commonest variety seen in clinical practice world-wide [10]. It should be noted that term ROCM refers to the entire spectrum ranging from limited sino-nasal disease (sino-nasal tissue invasion), limited rhinoorbital disease (progression to orbits) to rhino-orbital-cerebral disease (CNS involvement) [11]. In our study, eyes were involved in 63.6% patients followed by PNS (60%), nose (25.4%), and brain (16.4%). Most common clinical manifestations were headache (50.9%), orbital pain (38.2%),

proptosis (32.7%), nasal discharge (23.6%), decreased vision (21.8%), fever (18.2%), blindness (10.9%), and jaw pain (7.2%).

A 2019 nationwide multi-center study of 388 confirmed or suspected cases of mucormycosis in India prior to COVID-19, Prakash et al found that 18% had DKA and 57% of patients had uncontrolled DM [12]. The predisposing factors associated with mucormycosis in Indians include DM (73.5%), malignancy (9.0%) and organ transplantation (7.7%) [13]. Presence of DM significantly increases the odds of contracting ROCM by 7.5-fold (Odds ratio 7.55,  $P = 0.001$ ) as shown in a prospective Indian study, prior to COVID-19 pandemic [14].

In a recent systematic review conducted by John et al [15] that reported the findings of 41 confirmed mucormycosis cases in people with COVID-19, DM was reported in 93% of cases, while 88% were receiving corticosteroids. These findings are consistent with our findings, where out of 55 confirmed COVID cases with suspected mucormycosis, 81.8% had diabetes and 49.1% had hypertension, and 69.1% patients were on steroid therapy.

## Conclusion

From this study, it can be concluded that KOH smear and culture examination are approximately equally diagnostic in COVID-19 affected patients. The COVID-19 affected patients who are more susceptible to these infections are immunocompromised, have diabetes, and are prescribed steroids. Eyes are affected more commonly than any other organ in most of the patients. This study is intended to raise awareness for early detection and treatment of high mortality fungal infection i.e. mucormycosis, in COVID-19 patients to reduce the risk of mortality.

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