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Original Research Paper

Pathology

HISTOPATHOLOGICAL SPECTRUM OF COVID -19 ASSOCIATED RHINO ORBITAL AND CEREBRAL INVASIVE FUNGAL INFECTIONS - 1 YEAR STUDY FROM TERTIARY CARE CENTER.

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ABSTRACT **Background:** 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. **Aims And Objectives:** To study the histopathological spectrum of COVID -19 associated rhino orbital and cerebral invasive fungal infections. **Methodology:** We hereby present a compile data of cases of post covid rhino orbital and cerebral fungal infections in a tertiary care center in Maharashtra over a period of 1 year. **Results:** A total of 75 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 conidiobolus 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 antifungal and showed good response to treatment. **Conclusion:** COVID 19 treatment which includes O2 therapy, steroids and ventilators with preexisting comorbidities were 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.

KEYWORDS : COVID 19, mucor, paranasal sinuses, invasion, angio invasive, steroids, judicious, death, ethmoid, histopathology.

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 With this viral infection the otherwise less infective fungal infections have superseded causing more morbidity and mortality.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 Paltauf [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 finding 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.

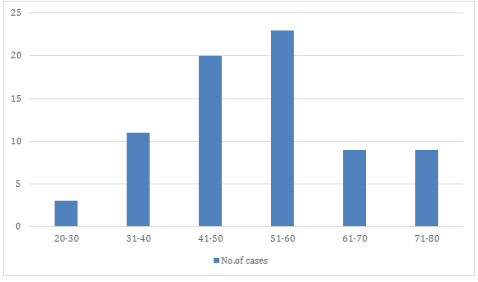

Chart 1 Age distribution

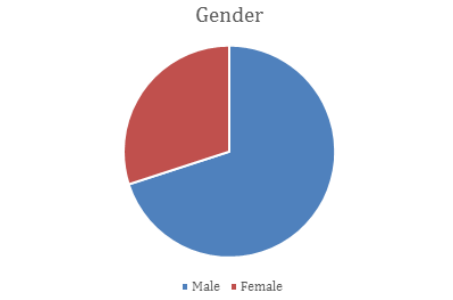

Chart 2 Gender Distribution

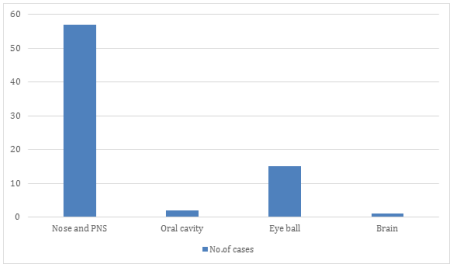

Chart 3 Site Of Involvement

Methodology And Inferences

Age	Sex	Nature of specimen	Histopathological diagnosis	Comorbidity
41	M	Necrotic bone	Fungal infection suggestive of mucormycosis	DM
72	M	Crust with tissue of left ethmoidal and sphenoidal sinus	Mucormycosis	DM
72	M	Necrotic bone	Suggestive of mucormycosis	DM
34	F	Nasal crust	Suggestive of mucormycosis	NIL
53	M	Anterior ethmoid and orbit	Mucormycosis	DM
54	M	Soft tissue maxilla, nasal septum, orbital rim,	Fungal infection suggestive of mucormycosis	NIL
48	F	Tissue from nasal cavity	Suggestive of pheohyphomycosis	DM
54	M	Tissue from nasal cavity	Suggestive of mucormycosis	NIL
70	M	Nasal crust	Fungal infection suggestive of mucormycosis infected granulation	DM,HTN
54	M	Crust from nasal cavity, nasal polyp, nasal septal cartilage	Infective fungal sinusitis suggestive of mucormycosis	DM
59	M	Nasal mucosa	Fungal infection suggestive of mucormycosis	DM
48	M	Nasal crust	Mucormycosis	NIL
37	M	Necrosed mucosa from right nasal cavity, black crust from right nasal cavity	Nasal mucosa- mucormycosis, anterior ethmoid and maxillary sinus- invasive fungal infection	DM
55	F	Tissue from nasal cavity, tissue from anterior ethmoid, tissue from maxillary sinus	Nasal cavity?, lwft eyeball mucormycosis	NIL
80	M	Biopsy from nasal cavity, left eye orbital extension, left eye ball specimen	Mucormycosis	DM
50	M	Necrotic tissue from right nasal cavity	Right maxillary tissue- aspergillous and mucor seenno fungal element seen	DM
50	M	Right maxillary tissue, right ethmoidal polypoidal tissue	No fungal element seen	NIL
64	F	Nasal crust with mucosa- polypoidal tissue in left nostrial	No fungal element seen	NIL
47	M	1. Necrotic biopsy from right maxillary	Chronic inflammatory	DM,HTN

		sinus, 2. Biopsy from right maxillary and ethmoidal sinus	pathology	
45	F	Left maxillary sinus soft tissue	No fungal element seen	DM
42	M	Nasal crust	1. Mucormycosis , 2. No fungus, 3. Mucormycosis	NIL
38	M	1. Necrotic tissue - left maxilla, 2. Left necrotic polypoidal tissue, 3. Right necrotic tissue from all sinuses	No fungal element seen	DM
48	F	Left anterior ethmoidal tissue	Mucormycosis	DM,HTN
32	F	Nasal polyps	1,2,3-mucormycosis	NIL
57	M	1. Right nasal cavity necrotic and polypoidal tissu, 2. Necrotic septum, 3. Left nasal cavity and sinuss	Mucormycosis	DM
69	M	1. Inflammatiry poly tissue from right maxillary, ethmoid, 2. Infected polyp tissue from left maxillary, ethmoid and sphenoid	1. No fungal element, 2. Mucor	DM
56	F	Right inflammatory tissue from maxillary, ethmoid sinus	Mucormycosis with panophthalmitis	DM
59	M	Enucleation of left eye ball	1,2,3-mucormycosis,4-mucor + aspergilluos, 5.-mucormycosis	DM
37	F	1. Right nasal polyp, 2. Right nasal tissue, 3. Palatal tissue, 4 left nasal tissue, 5. Right nostril septum	1&2- mucor + aspergillous	NIL
61	M	1. Left septum with tissue, 2. Right septum with tissue	1. Mucor + aspergilous, 2	DM
30	M	1. Right maxillary sinus, 2. Right ethmoidal & sphenoidalsinus	1. No fungal element, 2. Mucor	NIL
56	F	1. Right nasal necrotic tissue, 2. Left nasal necrotic tissue	1.mucor, 2. Mucor +asprgillous	DM
71	M	1. Left nasal cavity & paranasal sinuses, 2. Right nasal cavity sinus	Candidiasis	NIL
70	F	Nasal crust	Optic nerve invasion by fungus s/o mucor	DM
60	F	Left eye ball	Chronic inflammation	DM
43	M	Right maxillary nasal crust	No fungus element seen, s/o chronic inflammation	NIL
63	F	Right nasal crust	Mucormycosis with chronic inflammation	DM
56	M	1. Nasal biopsy from right nostril, 2. Nasal biopsy from left nostril	S/o mucormycosis	NIL
66	M	Left nasal tissue	1 & - chronic inflammation	NIL
41	M	1. Left maxillary soft tissue, 2. Right soft tissue	Mucormycosis	DM
45	F	Eye ball and optic nerve	1&2- no fungal elememt seen	HTN
50	M	1. Soft tissue from left nostril all sinuses, 2. Soft tissue from right nostril + all sinuses	Mucormycosis	DM
72	F	Nasal crust	S/o mucormycosis	DM
72	F	Right eyeball	1. Mucor + aspergilous, 2. Mucor	DM
50	M	1. Necrotic and polypoidal tissue from nasal cavity and all sinuses, 2. Polypoidal tissue from all sinuses from left nasal cavity	Chronic inflammation	NIL
47	M	Left polyp with paranasal sinuses	1,2& - no mucormycosis seen	NIL
52	M	1. Polypoidal tissue from right maxillary sinus, 2. Polypoidal tissue from left maxillary sinus, 3. Septal cartilage	1&2. Chronic inflammation	DM
55	F	1. Right maxillary sinus tissue + all sinuses tissue, 2. Nasal cavity and pus tissue	1. Chronic inflammation, 2. Mucormycosis	NIL
50	F	1. Necrotic tissue from right midle turbinate and right nasal cavity, 2. Necrotic tissue from middle turbinate left maxilla, frontal sinus	1&3-aspergillous + mucormycosis	NIL
52	F	1. Polypoidal tissue from right sphenoidal sinus, 2. Polypoidal tissue from right ethmoid, 3. Polypoidal tissue from right maxillary asteomeatal complex	S/o mucormycosis	DM
56	F	Left nasal cavity tissue	1. Mucormycosis with panopthalmitis with optic neuritis, 2&3-.	DM

			Chronic inflammation	
40	M	1. Left eye ball, 2. Left posterior orbital fat, 3. Left phenoidal tissue	Panopthalmitis	DM
48	M	Left enucleated eye	Chronic inflammation	NIL
66	M	1. Right side nucosal polypoidal tissue, 2. Left side mucosal polypoidal tissue	Acute inflammatory pathology	NIL
26	M	Left nasal cavity crust	Invasive sinusitis s/o mucormycosis	DM
47	M	1. Right nasal biopsy, 2. Left retromolar triagone biopsy, 3. Left nasal biopsy	Mucormycosis	DM
33	M	Left maxillary sinus soft tissue	Chronic inflammatory pathology	DM
55	F	1. Left maxillary polipoidal tissue, 2. Right maxillary polypoidal tissue	1&2. Chronic inflammation	DM
55	M	1. Right maxillary sinus tissue, 2. Left maxillary sinus tissue	Acute on cchronic inflammatory pathology	NIL
54	M	Left nasal cavity crust	1. Consistent with inflammatory polyps, 2,3,4-chronic inflammatory pathology	DM
73	M	1. Nasal cavity soft tissue ,2. Ethmoidal tissue right,3. Left ethmoidal tissue,4. Left frontal sinus tissue	Mucormycosis	DM
30	M	Left sided nasal mass	1&2-inflammatory polyps, 2-adenoid normal histology, 3= consistent with nasal septum	DM
40	F	1. Right maxillary polypoidal tisssue,2. Left maxillary polypoidal tissue, 3. Adenoid, 4. Nasal septum	S/o mucormycosis with chronic inflammation	DM
66	M	Right maxillary crust	Chronic inflammation	DM,HTN
54	F	Left maxillary crust	1- inflammatory polyps, 2-consistent with nasal septum	DM
53	M	1. Left maxillary polypoidal tissue. 2. Septum	S/o mucormycsis	DM
42	F	Nasal crust	Mucormycosis	DM,HTN
60	M	Slough over vocal cord	Mucor with aspergillosis	DM
73	M	Pansinusitis with bony erosion	Mucormycosis	DM,DM NEPHR OPATHY
39	M	Nasal crust	Mucormycosis	DM
44	M	Biopsy from right nostril	Mucormycosis	DM
60	M	Biopsy from left nostril	Mucormycosis	DM
55	M	Right nostril nasal tissue	Fungal infection suggestive of mucormycosis of the left eyeball	DM,HTN
35	M	Left exenterated eyeball	Fungal infection suggestive of mucormycosis of the right eyeball	DM
32	M	Right exenterated eyeball	Right and left nasal cavity mucormycosis	DM
72	M	Right nostril nasal tissue	Mucormycosis	DM

REFERENCES:

1. Kubin C.J., McConville T.H., Dietz D. Open Forum Infectious Diseases; (2021). Characterization of bacterial and fungal infections in hospitalized patients with COVID-19 and factors associated with healthcare-associated infections.201. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
2. Awadhesh Kumar Singh, Ritu Singh, Shashank R. Joshi, and Anoop Misra. Mucormycosis in COVID-19 (May 2021) : A systematic review of cases reported worldwide and in India. Published online [PubMed] [Google Scholar]
3. Eucker J., Sezer O., Graf B., Possinger K. (2001). Mucormycoses. Mycoses;44(7):253–260. [PubMed] [Google Scholar]
4. Sugar A.M. In: Mandell, Douglas, and Bennett's principles and practice of infectious diseases.(2000) Fifth ed. Mandell G.L., Bennett J.E., Dolin R., editors. Churchill Livingstone; New York, USA:. [Google Scholar]