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Pandemic Within Pandemic – Histopathological Features Of Mucormycosis In Post Covid 19 Patients In A Tertiary Care Hospital - South India

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Abstract

Mucormycosis is a currently emerging opportunistic infection caused by fungi of the order Mucorales. This infection had created a pandemic within a pandemic. Mucormycosis infection had received scarce attention earlier but the emergence of the SARS-CoV-2 disease (COVID-19) had increased the attention of this fungal infection. Being a deadly Angio invasive infection, appropriate and timely treatment of mucormycosis is required to reduce mortality rate, which can be achieved by early detection and intervention. This is the aim & target of the current research. Covid infected patient with risk factors like Diabetes(DM), prolonged hospitalization, immunosuppressive drugs and oxygen therapy has been a fertile area for the growth of mucormycosis. Even-though molecular methods is definitive for diagnosis the classical histomorphological detection of fungal elements and their specific histological changes in the surgical specimen is still promising in diagnosis of mucormycosis. Special fungal stains like Periodic Acid Schiff (PAS) and Grocott's-Gomori Methamine Silver Stain (GMS) add up in the specific diagnosis. In this paper we have studied about patients who were infected or recovered from SARS-CoV-2 disease(COVID-19) along with multiple risk factors. The specimens taken from various areas were examined and were confirmed as mucormycosis with its classic histomorphological feature by using standard haematoxylin and eosin stain (H&E) as well with fungal stains – PAS, GMS.

Keywords: Black fungus, COVID -19 complications, Mucormycosis, Opportunistic infection.

Introduction

The first discovered human corona virus were HCoV-229e and HCoV-OC43 from the nasal cavities of humans patients who are suffering from common cold in 1960s [(6)].Phycomycosis or zycomycosis was first described in 1885 by Paltauf [(1)] and later coined as mucormycosis in 1957 by Baker an American pathologist for an aggressive infection caused by Rhizopus[(2).]

Mucormycosis is a deadly Angio invasive infection caused by fungi of the order Mucorales. As per recent reports in India, recently there is an increase in incidence of this infection in the past 2 years [(3)] .Experts are referring it as "pandemic within COVID-19 pandemic"[(4,5)].Yet this number is underestimated [(5)]. Earlier to this incidence of mucormycosis infection, Mucorales had received mere attention due to the low number of cases compared to other much frequent fungal infection. Current pandemic with SARS-Co-2 had raised the occurrence and incidence with this infection more than 50 times than in the past. Hussian et al in 2021 had highlighted about the need for the better understanding of this infection so

that the associated risk with mucormycosis can be better managed [6,7] .

The incidence of black fungus has increased in covid 19 patients who were hospitalized or have recovered [8] .This mucormycosis infection were noticed during the second wave of Covid- 19 than the first wave with an increased mortality rate. India has contributed to almost 70% of the global cases of mucormycosis since the emergence of Covid-19 [9].

Clinical implication of mucormycosis

Mucormycosis is an opportunistic fungal infection caused by the spores / moulds of the order Mucorales. These Mucorales are ubiquitous in the environment found in soil, plants, manure, decaying fruits and vegetables. Mucorales affects people with altered immunity and causes fatal infection in immunocompromised individuals but these moulds are non-pathogenic in immunocompetent individuals. The major route of entry of this organism is via aerosol. These spores / moulds invades sinus tissues within 3-4 weeks and manifest as severe sinusitis, nasal blockage, crusting, facial oedema, proptosis, chemosis, ophthalmoplegia, headache fever and other neurological features [10,11].

Pathogenesis of mucormycosis and factor contributing its growth

Patients with decreased phagocytes or having impaired phagocytic function and patients with severe neutropenia are at increased risk of black fungus infection[12]. In contrast as in HIV/AIDS patient did not seem to be at increased risk depicting that the neutrophils play a key role in inhibition of fungal spore proliferation, but not necessarily T lymphocytes. Eg: In Diabetic ketoacidosis (DKA) patients phagocytes are dysfunctional and have impaired chemotaxis and defective intracellular killing by both oxidative and non-oxidative mechanisms.

Patients with ketoacidosis present with low cytosolic pH which aids in the growth of mucor spores and corticosteroid usage further decreases the immune response to the fungus [12,13]. High blood sugar levels lead to transferrin and ferritin to glycosylate, which lowers iron coupling and allows free iron, which ultimately causes tissue damage due to generation of large amounts of reactive oxygen species. And one of the essential elements for cell growth and development is iron. Therefore, pathogens use some process for obtaining iron from the host, which is proved as a unique host defence mechanism against bacteria, virus and fungus especially Rhizopus or mucor because they cannot be grown in laboratories with normal serum unless iron is added exogenously.

There are several hypothesis as to what else may contribute to mucormycosis infection, which are yet to be proved, such as the use of industrial oxygen or ventilation system , age related immune complications and use of non-sterile water in oxygen humidifier and steam inhalation which may play a role by impacting the mucosa. Providing zinc supplement in covid infected patients may act as a fungal growth promoter [14]. Other factors like prolonged hospital stay (more than 5 days) admission in ICU requiring a ventilator, increased IL-1,6 and TNF alpha with persistent lymphopenia may also play a role in black fungus infection [15,16] . As fungus enters an individual via aerosol the rhino-orbital-cerebral is the commonest site of this infection followed by cutaneous, pulmonary, disseminated, gastrointestinal and others in that order [17].

Investigation

Clinically suspicious cases of mucormycosis are subjected to radiological investigation like CT scan and MRI scan to the affected areas. KOH Mount test and fungal culture were also done. As mucormycosis is a fatal and life threatening Angio invasive infection with high mortality rate, it needs emergency intervention like surgical debridement and administration of parenteral antifungal medication.

Diagnosis

The non-invasive radiological investigation may provide a clue for the diagnosis while KOH mount test may show positive in case of fungal infections but may not be confirmatory to subclassify the subspecies of Mucorales. Fungal cultures take longer time for results hence histopathological and microscopical examination of the **BLACK ESCHAR** or tissue bits of debridement showing broad aseptate fragile hyphae branching at obtuse angles with areas of necrosis, thrombosis, haemorrhage, acute neutrophilic infiltrates characterize the fungal type and give a confirmed diagnosis of mucormycosis. Further fungal presence can be confirmed by special stains like **PAS** and **GMS**.

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With recent advancements in molecular diagnosis cell free DNA (cf DNA), Polymerase Chain Reaction(PCR), Next Generation Sequencing(NGS), CRISPR-cas test would aid in detection and sub-classifying the species causing the infection.

Aims And Objectives Of The Study

1. To study the histomorphological features of mucormycosis in post covid 19 patients.
2. To evaluate the risk factors and various clinical manifestations for mucormycosis in covid-19 infected patients.
3. To correlate clinical and histopathological diagnosis of mucormycosis

Limitations Of The Study

1. Smaller sample size.
2. All samples were received as small biopsies, hence in some cases the fungal infection site might have been missed and only necrotic or devitalized tissues were sent for histopathological examination.
3. Empirical antifungal treatment prior to surgery in patients suspected for mucormycosis may also mask the diagnosis.

Study Setting

- **Study design:** This is a retrospective case study done in patients presented to ENT, ophthalmology department and pulmonary medicine patients and clinically diagnosed as of rhino-orbit cerebral mucormycosis or pulmonary mucormycosis.
- **Inclusion and exclusion criteria**: Patients with post COVID 19 infection/recovery follow up in a tertiary care hospital, Vizianagaram, AP from May2021 to September, 2021 were included in the study. Covid negative cases were excluded from the study
- **Data collection:** The medical records from ENT, Ophthalmology and Pulmonary department were retrieved and the demographic findings along with clinical data were reviewed.
- **Sample size:** 24

Material And Methods

- **used**: All the patients underwent radical surgical debridement of devitalised tissue by endoscopic denker's approach and CT-guided small lung biopsies. The tissues were received in histopathology department for processing.
- **Methods:** These were small biopsies and thus whole of the specimen was processed and stained with routine H&E stain and special stains like PAS and GMS.

Results

Post covid-19 follow up of patients from ENT, Ophthalmology and Pulmonary medicine department with more than 1 risk factors and also with any of the above symptoms were clinically diagnosed as Rhino-orbital mucormycosis or pulmonary mucormycosis. These clinically suspected patients had undergone surgical debridement by FESS(ENT) or small biopsy(Lung) and sent for histopathological examination and the results obtained are given below

1.Sex and age distribution:

In our study predominantly affected population were male with M:F ratio of 7:5. The age affected were ranging from 27-69 years and maximum patients were belonging to 4^{th} and 5^{th} decade of life. Among the cases studied 10/24 cases (42%) belong to age group of 41-50 years, 8/24 (34%) were belonging to 41-50 years, 6/24 other cases (8%) were distributed equally distributed in 21-30, 31-40 and 61-70 years of age.

2.Various clinical manifestations in patients

Post covid- -19 infection, follow up of the patients who presented to ENT and Ophthalmology department with symptoms like facial pain, orbital pain, headache, blurred vision and black nasal discharge were clinically suspected as Rhino orbital mucormycosis. Cough and dyspnoea were the common presenting symptom in patients with pulmonary mucormycosis. These symptoms were not a single complaint but were in various combination especially in Rhino-orbital mucormycosis. Facial pain was the predominate symptom (75%)18/24 patients, the next frequent symptom observed was orbital pain and headache contributing to (41.6%) 10/24 patients. Two out of 24 (8.3%) patients presented with blurred vision and (4.1%) one out of

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24 patients presented with black nasal discharge to ENT department.

3. Risk factors for mucormycosis.

All the patients were covid 19 positive and had been hospitalized for prolonged period of time. The major risk factors for mucormycosis were diabetes mellitus accounting to 16/24 (66.6%) patients, 20/24 (83.3%) patients were given oxygen therapy during the hospital stay. One patient (4.1%) had hypertension and another patient (4.1%) had multiple systemic risk factors like valvular heart disease and old pulmonary tuberculosis.

Table 1: Risk factors of mucormycosis

S.NO	RISK FACTOR	NO.OF CASES
1.	COVID -19 INFECTION	24
2.	DIABETES(past & de novo)	16
3.	OXYGEN THERAPY	20
4.	PROLONGED HOSPITALIZATION	24
5.	HYPERTENSION OR OTHERS	2

Clinico-pathological correlation:

Clinically suspected Rhino-orbital mucormycosis patient who underwent surgical debridement 14/24 (58.32%) showed broad, obtuse angled fragile aseptate hyphae along with areas of necrosis and neutrophilic infiltration and was confirmed as mucormycosis on histopathological examination. 5/24 cases (20.8.%) were diagnosed with non-specific inflammation, 4/24 cases (16.6%) diagnosed as pulmonary mucormycosis and 1/24 (4.1%)case was diagnosed as pigmented fungi (Phaeohyphomycosis).

Table 2 : Clinical-pathological correlation of mucormycosis

S.NO	CLINICAL DIAGNOSIS	HISTOPATHOLOGICAL DIAGNOSIS	NO.OF CASES
1.	RHINO-ORBITAL MUCORMYCOSIS	MUCORMYCOSIS	14
2.	RHINO-ORBITAL MUCORMYCOSIS	PIGMENTED FUNGAL INFECTION	1
3.	RHINO-ORBITAL MUCORMYCOSIS	NON-SPECIFIC INFLAMMATION	5
4.	NON-RESOLVING PNEUMONIA	MUCORMYCOSIS	4

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Figure 1A& B: Clinical picture of a patient with orbital oedema, redness and discharge from the right eye and conjunctival chemosis

Figure 1A **Figure 1B**

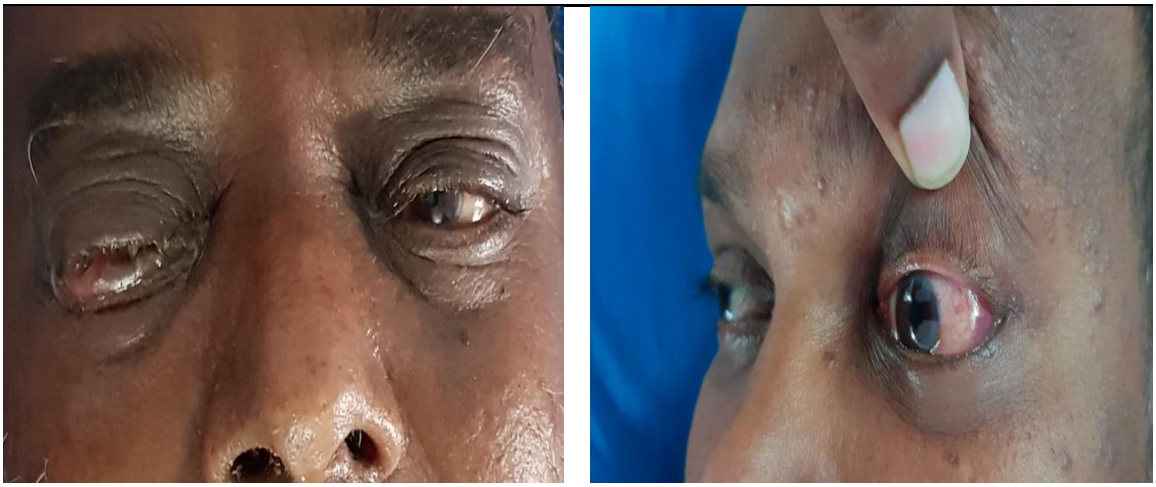

Figure 2: Cytology image from an imprint smear of a lung biopsy stained with Haematoxylin and Eosin stain at 400x magnification showing broad fungal hyphae in clusters

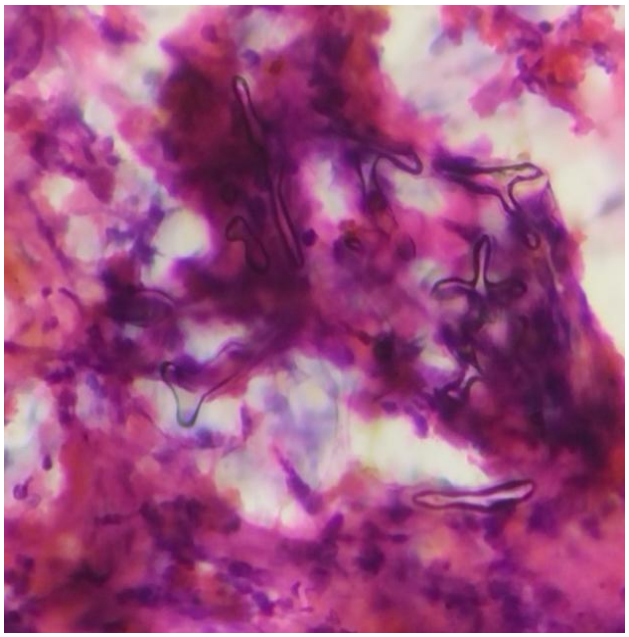

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Figure 3 A&B : Histopathological images with Haematoxylin and Eosin stain at 400x magnification showing broad aseptate fragile fungal hyphae in singles and clusters

Figure 3A.

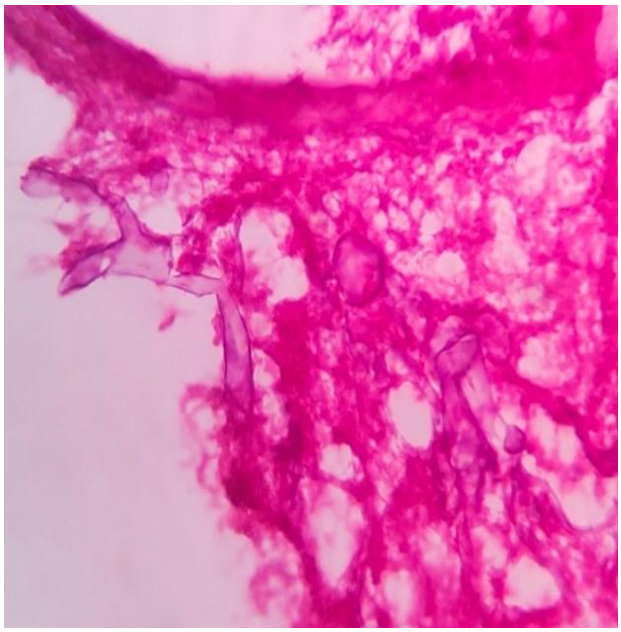

Figure 3B

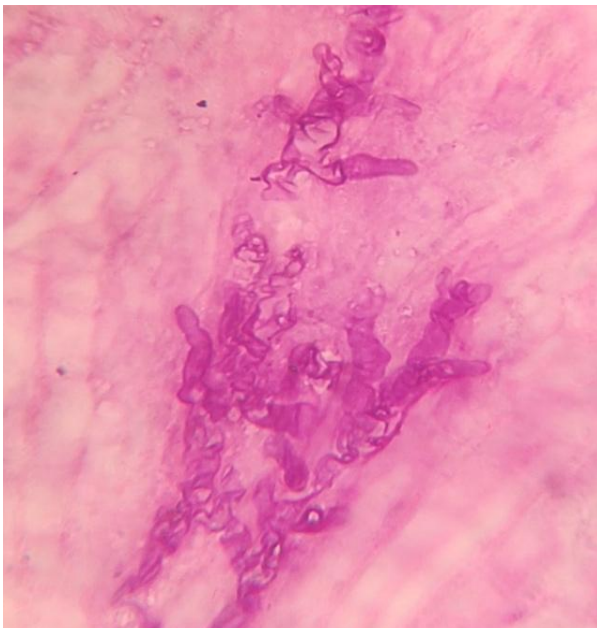

Figure 4 A&B: Special stain with PAS shows fungal elements GMS at 400x magnification showing fungal elements.

Figure 4A: PAS

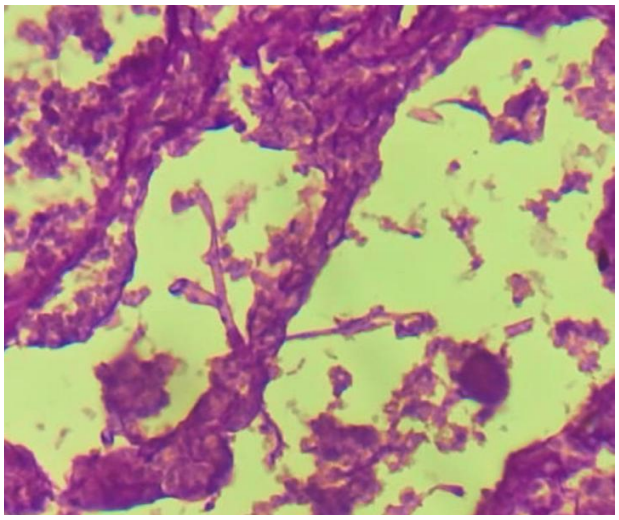

Figure 4B: GMS

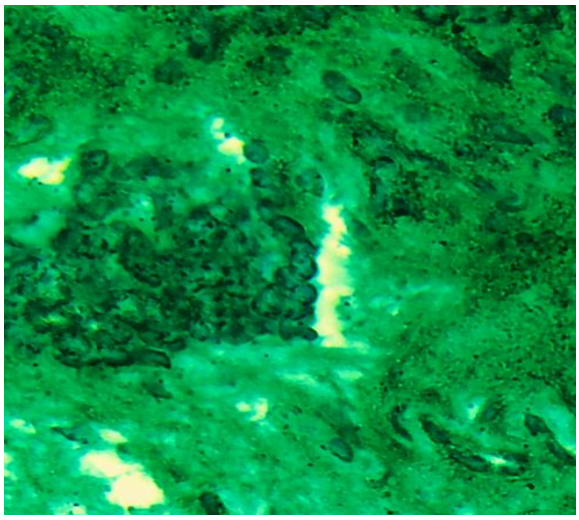

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Table 3: Comparison of mucormycosis cases in South India during pandemic covid-19 with the present study.

S. no	Author	Place of report	No of cases	Age	Co-morbidity DM	Confirm /suspect	Treatment Steroid	Treatment Antiviral	Confirm	Site Rhino-orbital	Site others
1.	MISHRA et al [18]	Bangalore	10	37-78yrs M-9 F-1	Y-8 N-2	C-10	Y-6 N-4	Y-6 N-4	ALL	ALL	-
2.	SARKAR et al [19]	Puduch erry	10	27-67yrs M-8 F-2	Y-10 DKA-9	C-10	Y-10 N-	Y-5 N-5	C-6 S-4	ALL	CNS
3.	SEN et al [20]	Mumbai	6	46.2-73.9 yrs M-6	Y--all	C-all	Y- all	NIL	C-5 S-1	ALL	CNS
4.	MOOETHY et al [21]	Bangalore	17	39-73yrs M-15 F-2	Y-15 N-2	17	Y-15 N-2	NIL	C-ALL	ALL	CNS
5.	PRESENT STUDY	Vizianagaram	12 M=7 F=5	27-69yrs M-7 F-5	DM-8 Others-4	C-8 S-4	Y-8 N-3	NIL	C-8 S-3	7	LUNG-2

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Table 4: Comparison of mucormycosis cases worldwide during pandemic covid-19 with the present study

S.no	Author	Place of report	No. of cases	Age	Co-morbidity DM	Confirm/ Suspect	Treatment steroid	Treatment Antiviral	Confirmed	Site Rhino-orbital	Site-others
1.	DALLELZADEH et al (22)	USA	2 M-36, F-48	36-48	Y-2 DKA-2	C-2	Y-2	Y-2	C-1 S-1	Y-2	CNS
2.	HANLEY et al (23)	UK	M-2	22	nil	C-1	NIL	NIL	C-1 AUTOPSY	N	LUNG
3.	PASERO et al (24)	ITALY	M-66	66	NIL	C-1	NIL	NIL	C-1	N	LUNG
4.	VEISSE et al[25]	IRAN	2 M-1,F-1	40-54	Y-1 N-1	C-2	NIL	NIL	C-2	Y-2	YES
5.	BELLANGA et al (26)	FRANCE	1 M-55	55	LYMPHOMA	C-1	NIL	NIL	C-1	NIL	LUNG
6.	SARGIN et al (27)	TURKEY	1 F-56	56	Y-1 DKA	C-1	Y-1	NIL	C-1	Y-1	CNS
7.	WAIZEL et al (28)	MEXICO	1 F-24	24	Y-1 DKA	C-1	Y-1	NIL	C-1	Y-1	nil
8.	ZURLET etal (29)	AUSTRIA	1 M-53	53	LEUKEMIA	C-1	NIL	NIL	C-1 AUTOPSY	NIL	LUNG
9.	PRESENT STUDY	INDIA	12 M-7, F-5	27-69	Y-8 N-4	C-8 S-4	Y-8 N-4	NOT KNOWN	C-8 N-4	Y-7	LUNG-2

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Discussion:

Mucormycosis is a dreadful angioinvasion infection of immunocompromised people. Early detection and timely management would prevent morbidity and mortality. Patients with risk factors like diabetes, prolonged hospitalization, requiring oxygen therapy, immunosuppressive therapy and on mechanical ventilators should have a clinical suspicion of black fungus infection and especially when these patients have symptoms like sudden onset of facial pain, diplopia, headache which is not subsiding with supportive therapy. Such patients should be investigated to rule out invasive fungal infection. If accompanied by black nasal discharge they have to be undergo emergency debridement and sent for histopathological examination, which may aid in confirmatory diagnosis. These patients post debridement may also be started on empirical parenteral antifungal therapy.

We have compared the present study with the mucormycosis cases in covid affected patient in studies presented as case report/case series in other states of South India and also with other countries internationally. In south India a study was done by Mishra et al in Bangalore on covid-19 positive patients(10) with multiple risk factors. Results of the study showed that cases were of male predominance with a M:F ratio of 9:1 and were belonging to age ranging 37-78yrs which are almost similar to our study. The risk factors in their study included DM in (80%) of cases ,steroid use in (60%) and all the cases were confirmed as Rhino-orbital mucormycosis. Another study done in Puducherry by Sarkar et al on covid positive cases(10) had male predominance also all the patients had DM(100%) and steroid(100%) use as risk factors were confirmed as Rhino-orbital mucormycosis with Central nervous system(CNS) involvement. Sen et al from Mumbai conducted a study on 6 covid positive cases who were males, diabetic and were on steroids as treatment, were confirmed as Rhino-orbital-cerebral-mucormycosis with CNS involvement. The above mentioned studies done in covid-19 patients diagnosed as mucormycosis had DM and steroid use as risk factors, which were in concordance with the present study.

Studies done in other countries like USA by Dallazadeh et al on 2 covid -19 positive cases(M-1,F-1) were diabetic with DKA and were on steroids. Both the cases were confirmed as Rhino-orbital-cerebral-mucormycosis. Sargin et al from turkey presented a case report of a 56 year old covid positive patient with DKA treated with steroids also was confirmed as Rhino- -orbital-cerebral-mucormycosis

Study done by Zurlet et al in Austria on a 53 year old covid positive patient with leukaemia as a risk factor, was confirmed with pulmonary mucormycosis on autopsy. Bellanga et al from France reported a 55year old male covid positive patient with lymphoma as risk factor had been confirmed as pulmonary mucormycosis on autopsy. In the present study 2 covid positive cases on follow up for non-resolving pneumonia with hypertension, valvular heart disease and tuberculosis as risk factors were confirmed as pulmonary mucormycosis. These 2 patients improved with parenteral antifungal therapy. These studies and comparative results are also presented in a table format. Studies done in other countries also showed that the paranasal sinus and orbit (Rhino-orbital mucormycosis) was the commonest site affected followed by paranasal sinus and central nervous system (Rhino-orbital-cerebral- mucormycosis) and followed by lung, which is in concordance with our study.

Conclusion:

Mucormycosis a life threatening opportunistic infection. High risk patients with DM, prolonged hospitalization, on steroids or any form of clinical suspicion should be evaluated and intervention is mandatory. Early detection and timely treatment would prevent morbidity and mortality. Patient with Covid-19 are immunocompromised due to the infection as well as the medication used as the supportive care during the hospital stay which plays a vital role for the ubiquitous fungal organism to grow. Any post covid-19 patients with symptoms like facial pain, orbital pain, diplopia, headache and non-resolving respiratory symptoms should prompt the treating physician to suspect mucormycosis. Along with the basic investigations, fungal culture and debridement of the devitalized tissue sent to histopathological examination would provide the direct visualization of fungal elements and the associated changes. Further fungal presence can be confirmed by fungal special stains like PAS and GMS. With recent advancements in molecular

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diagnosis cell free DNA (cf DNA), PCR, NGS, CRISPR-cas test would aid in detection and sub classifying the species causing the infection. In spite of these expensive investigations the gold standard and cost effective investigation for mucormycosis is the histopathological examination.

Mucormycosis predominantly affecting sites are Rhino-orbit, Rhino-orbital-cerebral and followed by lung. Patient with risk factors like DM and steroids responded to antifungal better than the patients with other risk factors like lymphoma and leukaemia. Involvement of lung and other organs were fatal compared to the Rhino-orbit or the Rhino-orbital-cerebral mucormycosis.

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