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Original Research Article

Invasive fungal rhinosinusitis associated with COVID-19: An observational study

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ABSTRACT

Objectives: Respiratory Viral infections predispose patients to various coinfections and this may lead to enhanced disease severity and mortality. Despite the proven importance of co-infections, these are understudied during the large outbreaks of respiratory infections. Occurrence of invasive fungal respiratory superinfections in patients with COVID-19 has gained increasing attention recently. This study aims to assess Clinical & Microbiological profile of patients with invasive sinusitis in setting of COVID-19 disease at our institute Study Design: A retrospective observational study.

Materials and Methods: Study included patients diagnosed with acute invasive fungal rhinosinusitis (AIFR) suffering from or having a history of coronavirus disease infection over the period of three months.(April 21 – June 21). The patients' presentation details, imaging findings, co-morbidities, management details, and follow-up information were obtained, recorded and analysed.

Results: A total of 32 patients with AIFR with a mean age of 54.46±13.13 years old were included. Most common associated disease was diabetes mellitus (62.5%). Mycological analysis revealed most common fungi isolated from these patients were Mucor species.(56.25%) followed by Aspergillus species(15.62%) while coinfection with both of these species was seen in 5 patients.(15.62%) Candida species was isolated from samples of 4 patients (12.5%). Radiological studies of nose and paranasal sinuses showed that ethmoid (62.5%) and maxillary (46.87%) sinuses being the most commonly affected sinuses followed by Frontal (31.25%) and sphenoid (21.87%) sinuses. Peri-orbital invasion was seen in 5 (15.62%) cases whereas intracranial involvement was seen in 1 patient.(3.12%) In 8 (25%) patients only medical line of treatment was sufficient whereas 20 (62.5%) patients required surgical debridement during the treatment. 4 patients were lost to follow up. Overall survival was 90.62% (29/32) at the conclusion of the study.

Conclusion: We are still learning the new and long-term complications of COVID- 19.The puzzle still remains unsolved about the cause and increased prevalence of invasive fungal infections in post-covid-19 population. High clinical suspicion and early and accurate diagnosis of AIFR in COVID-19 patients are essential for better prognosis.

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1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become wide-ranging across the globe.¹

Old age, diabetes, hypertension, chronic obstructive pulmonary disease and cardiovascular disease are the main risk factors attributed for severity and mortality in COVID-19.^{2,3} It is found that COVID-19 patients have immune-suppression accredited to a decrease in CD4+T and CD8+T cells. This results in a wide range of bacterial and fungal infections that can co-exist with possible association with

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a preexisting co-morbid conditions (diabetes mellitus, lung disease) or can develop as a hospital-acquired infection.⁴ Since most of the hospitalized COVID-19 patients are under severe medication care, like intubation/mechanical ventilation, they are potentially vulnerable for acquiring hospital infections. Aligned to this assertion, broad-spectrum antibiotics were prescribed in 75% of COVID-19-infected patients who were admitted to intensive care units (ICU).⁵

Acute invasive fungal rhinosinusitis is described by a time course of <4 weeks with predominant vascular invasion. Mucormycosis infection of the sinuses is a type of fatal invasive fungal rhino-sinusitis caused by Mucorales species of the phylum Zygomycota. It commonly occurs in patients with immune-compromised status such as hematological malignancies, uncontrolled diabetes mellitus,

following transplant, AIDS, immunosuppressive, and chemotherapeutic drugs and recently, COVID-19. The histopathology demonstrates hyphal invasion of blood vessels, hemorrhage, tissue infarction, and acute neutrophilic infiltrates.^{6,7} Tissue necrosis is a hallmark of Mucormycosis but it is often a late sign.

The prevalence of Mucormycosis in Indian population is 0.14 per 1000, which is about 80 times higher than developed countries.⁸ Overall a fatality rate of mucormycosis is 46%. However, with intra-orbital and intracranial complications the mortality rate can go as high as 50–80 per cent. Therefore a high suspicion for this condition must be well thought-out especially in patients who have immunosuppression.

Herein, the primary objective of this study is to demonstrate mucormycosis in relation to COVID-19 pandemic and its aspects and clinical management at our institute.

2. Materials and Methods

2.1. Study design

Retrospective Observational study Setting-Tertiary Referral Centre.

2.2. Participants

Patients diagnosed with Acute Invasive Fungal Rhinosinusitis associated with a recent COVID-19 infection were included in the study. All participants had a definite diagnosis of COVID-19 by PCR (Polymerase chain reaction). Diagnosis of invasive fungal rhinosinusitis was done according to the recent guidelines.⁷

2.3. Study procedure

The patients presenting clinical details, imaging findings, co-morbid illnesses, details of treatment given, and follow-up information were obtained, recorded and analysed.

2.4. Processing of samples

We recorded variety of samples such as excised or biopsied tissue, BAL, Sputum, nasal swabs etc.

These samples were subjected to conventional microscopy, culture, histopathological examination. Microscopy was performed using the KOH (10%) mount method. The patient samples were also inoculated onto two sets of Sabouraud dextrose agar with chloramphenicol, one tube was kept at room temperature (RT) and the other one was incubated at 37°C. The positive cultures were identified by their macroscopic and microscopic characteristics.

KOH wet mount of Mucor species shows characteristic broad, non-septate, ribbon-like hyphae with wide-angle or right-angle branching at irregular intervals.

The colonies are rapidly growing, with mycelia elements expanding to cover the entire plate in only a few (1 to 7) days showing dense and have hairy appearance described as cotton-candy growth. At mature growth, the mycelium tends to be quite high, with some isolates reaching the lid of the petri dish. It is this vigorous growth characteristic that is responsible for the group being called as “lid lifters”

These organisms are hyaline, with the reverse side of the tube demonstrating light coloration (tan to yellow for most species).

KOH wet mount of Aspergillus species shows narrow, septate hyphae with dichotomous branching that is progressive and primarily at acute angles of around 45°.

Macroscopic features in species identification were the colony diameter, color (conidia and reverse), exudates and colony texture. Microscopic characteristics of LPCB mount for the identification were conidial heads, stipes, color and length vesicles shape and seriation, metula covering, conidia size, shape and roughness.

Candida species show yeast cells 4–8 μm with budding and pseudohyphae. Presence of pseudohyphae denotes tissue invasion hence their demonstration in direct microscopy from the tissue sample is highly significant.

On fungal culture, the colonies of Candida species appear in 3–4 days as cream colored, smooth and pasty.

The samples submitted for histopathological examination were examined using haematoxylin & eosin stain.

3. Results

A total of 32 patients presented; 24 of these were male and 8 were female. The mean age was 54.46 ± 13.13, years ranging from 28 to 77 years.

Four of the patients were COVID-19 positive at the time of presentation and the remaining 28 had been infected earlier and had recovered.

Patients' demographic, clinical data, and comorbidities are listed in Table 1.

Table 1:

Total cases	32	100%
Age (Years)(Mean±SD)	54.46±13.13	
Sex (Male/Female)	24/08	75/25
Comorbidities		
DM	20	62.5
HTN	5	15.62
CKD	1	3.12
Solid organ transplant	2	6.25
Clinical Extension		
Ethmoid Sinus	20	62.5
Maxillary Sinus	15	46.87
Frontal Sinus	10	31.25
Sphenoid Sinus	07	21.87
Orbital Invasion	5	15.62
Intracranial	1	3.12
Steroids received during COVID19 treatment	24	75
Oxygen /Mechanical ventilation needed	06	18.75
Organism		
Mucor sp.	18	56.25
Aspergillus sp.	5	15.62
Mucor+Aspergillus	5	15.62
Candida sp.	4	12.5
KOH positive but Culture Negative For Mucor	04/18	22.23
Treatment given		
Medical	8	25
Surgical	20	62.5
Patients lost to follow up	04	12.5
Outcome		
Survival	29	90.62
Death	3	9.37

The most common associated disease was diabetes mellitus (DM) (62.5%) and hypertension (15.62%). 2 patients had a history of renal transplant (6.25%). 1 patient had a chronic kidney disease as a comorbidity.(3.12%).

Radiological studies reveal that the most common sinus involved is Ethmoidal sinus(62.5%) followed by Maxillary (46.87%), Frontal(31.25%) and Sphenoid sinus (21.87%). Peri-orbital invasion was seen in 5 (15.62%) cases whereas intracranial involvement was seen in 1 patient (3.12%).

24 out of 32 patients (75%) received steroids during the treatment of COVID19 while 06 patients gave the history of receiving oxygen or mechanical ventilation during the treatment of COVID19 (18.75%).

Histopathological and fungal culture data showed that the most common fungi isolated from these patients were Mucor species.(56.25%) followed by Aspergillus species (15.62%) while co-infection with both of these species was seen in 5 patients (15.62%).

Candida species was isolated from samples of 4 patients (12.5%).

We have also found that 4 out of 18 samples (22.23%), microscopy with KOH was indicative of Mucor sp but cultures turned out to be negative.

In 8 (25%) patients only medical line of treatment was sufficient whereas 20 (62.5%) patients required surgical debridement during the treatment.4 patients were lost to follow up (12.5%).

Overall survival was 90.62% (29/32) at the conclusion of the study.

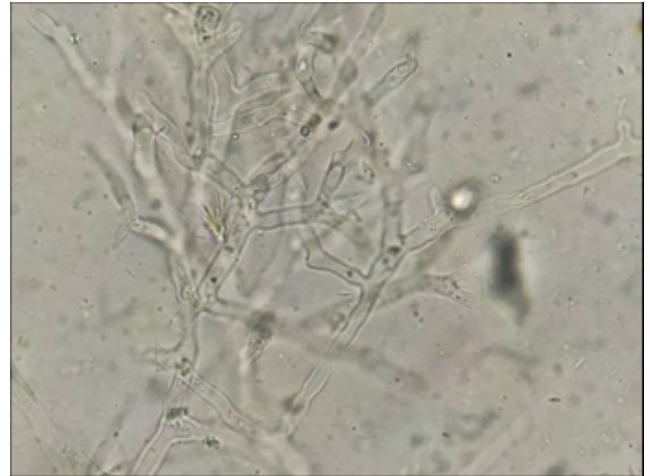


Fig. 1: KOH wet mount from the tissue showing characteristic broad, non-septate, ribbon-like hyphae with wide-angle or right-angle branching at irregular intervals, s/o zygomycetes.

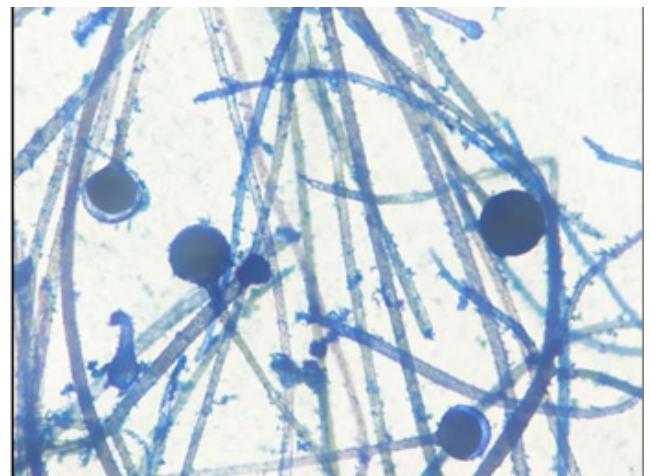


Fig. 2: LPCB mount of Mucor sp. showing non-septate hyphae with globose, smooth walled sporangia.

4. Discussion

The latest threat to global health is the ongoing outbreak of the respiratory disease that was recently given the name Coronavirus Disease 2019 (Covid-19).

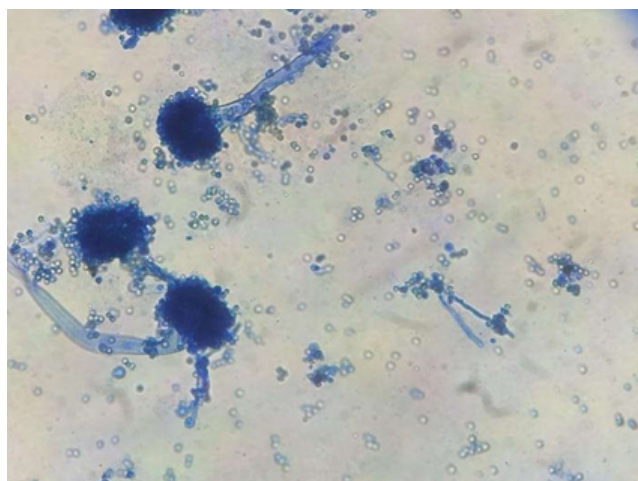


Fig. 3: LPCB mount of *Aspergillus* sp. showing conidiophores, vesicles and conidia

Along with diffuse alveolar damage, there are specific pathophysiologic features of COVID-19 that may permit secondary fungal infections, including severe pulmonary vascular endothelial injury that may enhance the risk of invasive fungal infections. Second, there is an immune dysregulation in COVID-19, with reduced numbers of T lymphocytes, CD4+T, and CD8+T cells, which may alter innate immunity and may lead to secondary mould infections.^{9,10}

In earlier studies, fungal infections were observed in SARS patients and were considered the leading cause of death in 25% to 73.7% of patients. Similarly, SARS-CoV-2 causes lower respiratory infection and can lead to Acute Respiratory Distress Syndromes (ARDS).¹¹ Based on this experience, it is critically important to pay attention to the probability of fungal infections accompanying COVID-19.

The standard definition of AIFR includes hyphal invasion of blood vessels, tissue infarction and acute neutrophilic infiltrates. It is a time-sensitive condition with clinical course of less than 4 weeks which must be diagnosed and treated promptly to avoid life-threatening complications.

In present study we observed 32 cases of fungal sinusitis out of 100 samples (32%) received for fungal microscopy and culture at our institution over the period of 3 months during second wave of COVID-19 in India.

Many fungal species, *Rhizopus*, *Mucor*, *Rhizomucor*, *Aspergillus* and *Candida* are known to cause AIFR.¹² Microbiology culture and Histopathologically confirmed fungal species in the present study were *Mucor* species (56.25%) *Aspergillus* species (16.67%), co-infection with *Mucor* species and *Aspergillus* species (16.67%) and *Candida* species (13.34%). Similar pattern of fungal species isolation in patients with COVID-19 infection was observed in different studies across the globe.^{1,4,8,9,13}

Invasive fungal infection due to *Candida* is also seen in patients of COVID-19. *Candida albicans* is the most common species isolated in our study. Similar reports are found from western part of the world in post covid patients.¹⁴

There are various possible reasons for association between Invasive fungal infections and covid-19. One of them could be the immunosuppression caused by Covid-19 infection and disease process, or the extensive use of steroids and broad-spectrum antibiotics in the management of Covid-19, leading to the development or exacerbation of a pre-existing fungal disease.

Studies done by El-Kholy et al., Sharma S et al., in post COVID patients shows that the most common associated comorbidity was DM and HTN. D. Garg, V.Muthu et al., Teny M John et al., also denoted that DM in post COVID patients poses the perfect condition for Mucormycosis. This is in accordance with results in our study as the most common associated disorder was diabetes mellitus (62.5%) followed by hypertension (16.67%).

We also found that 2 patients presented with acute invasive fungal rhinosinusitis at comparatively younger age of 28 and 32 had a history of solid organ transplant. A Multivariate analysis indicates a significantly higher risk for solid organ transplant recipients.⁶

Radiological studies of nose and paranasal sinuses showed different patterns. Those patterns range from mucosal thickening of the involved sinus mucosa, deviation of nasal septum, atrophy of the nasal turbinates, osteomyelitis of the related bone.

24 patients (75%) amongst the study have received one or other form of steroids during the course of treatment of Covid-19. Current guidelines in India recommend not to give Systemic oral steroids in mild disease. Intravenous methylprednisolone 0.5-1 mg/kg/day for 5-10 days in moderate cases and 1-2 mg/kg/day in severe cases.^{15,16} The National Institute of Health recommends the use of dexamethasone (6 mg per day for a maximum of 10 days) in patients who are ventilated or require supplemental oxygen but not in milder cases.¹⁷ The guidelines specifically mention the risk of developing a secondary infection.

One important observation in diagnostic point of view which we observed in our study is that, out of 18 diagnosed patients for Mucormycosis, samples from 4 (22.23%) showed characteristic microscopic features in KOH and histopathology but fungal cultures turned out to be negative. Although the mucormycetes are not fastidious fungi still they fail to grow sometimes during primary isolation.

In about 50% of cases there is no growth despite direct demonstration of the fungi. The reason is that these are sparsely septate fungi and while handling or processing of biopsy entire cytoplasm oozes out losing viability of the organism.¹⁸

Regarding AIFS, 7(23.3%) patients were treated with medical management while in 19 (63.3%) patients surgical approach had to be considered.

Overall survival was 90.62% at the conclusion of the study. 3(9.37%) patients died.

Our study has limitations. It is retrospective and single-centered. A prospective design would have allowed us to be comprehensive on certain aspects of the study. Also the samples were only tested for fungal pathogens based upon clinical discretion.

5. Conclusion

We are still learning the new and long-term complications of COVID-19. The puzzle still remains unsolved about the cause and increased prevalence of invasive fungal infections in post-covid-19 population. A multi-centric study is needed for the same. Till then a high clinical suspicion and early and accurate diagnosis of AIFR in COVID-19 patients are essential for better prognosis.

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7. Conflicts of Interest

The authors declare no potential conflict of interest with respect to research, authorship, and/or publication of this article.

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