ORIGINAL ARTICLE

Epidemiological Profile of Mold Infections in Coronavirus Disease 2019 Patients

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Abstract

Background: Coronavirus disease 2019 (COVID-19) has predisposed to secondary fungal infections, particularly when it is associated with varied comorbidities and immunocompromised situations.

Materials and methods: We performed a retrospective clinico-epidemiological evaluation on 45 patients with a history of COVID-19 who presented with clinical features of fungal infections and their association with preexisting comorbid risk factors. The clinico-demographic information of the patients was obtained using a *pro forma*. Samples from representative clinical sites were collected, like respiratory secretions, pus, or tissue samples from nasal cavities and paranasal sinuses. These samples were processed as per the standard mycological procedures and the fungal isolates, so obtained, were identified according to their culture and microscopic characteristics.

Results: The median time interval for the appearance of clinical features of fungal infections from the time of COVID-19 diagnosis was 17 days. Diabetes mellitus (DM) (84.44%) was found to be the leading comorbidity. History of administration of glucocorticoids was noted in 62.22% of the patients. The most frequent presentation was rhinosinusitis in 86.67% of the individuals. Different kinds of molds were isolated in 73.33% of the specimens, with Mucorales (78.89%) being the dominant one. The 32 admitted patients were managed by antifungal therapy and/or surgery. A total of nine patients did not respond to the treatment and succumbed to the disease.

Conclusion: Though the true prevalence of these mold infections is not known, but timely diagnosis and management are extremely important in view of their high mortality.

Keywords: Comorbidities, Coronavirus disease 2019, Diabetes mellitus, Mucorales, Rhinosinusitis.

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Introduction

The complete world today is facing a calamitous COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2. As of mid-May 2022, >500 million individuals are infected globally, with a mortality rate of >2%.[1] A combined interaction of components like old age; preexisting comorbidities including DM, cardiovascular disease, chronic obstructive pulmonary disease (COPD), and malignancy; administration of immunosuppressant drugs including glucocorticoids; mechanical ventilation; prolonged intensive care unit (ICU) stay; and COVID-19 induced systemic immune alteration hitherto predispose these patients to secondary bacterial or fungal infections.[2–4] Though secondary infections were infrequently documented during the initial phase of the pandemic, but they have shown a rising trend lately, especially fungal infections.[5] Nonetheless, acute respiratory distress syndrome (ARDS) induced by viral infections increases the susceptibility to secondary complications. COVID-19 associated pulmonary aspergillosis (CAPA) has been increasingly reported in many patients despite an obvious absence of the immunocompromised state.[6]

In India, mucormycosis is 80 times more prevalent than in developed countries, with a prevalence of 0.14 cases per 1,000 population.[7] Furthermore, mucormycosis is frequently observed in patients with compromised immune status, but cerebral and/or orbital complications are usually noticed in patients with DM and concomitant use of steroids. In India, mucormycosis is most commonly associated with DM.[8]

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The purpose of this study was to evaluate the epidemiological, clinical, and microbiological profile of the patients who suffered from COVID-19 and had coinfection with molds.

Materials and Methods

We performed a retrospective observational study from June 2020 to 2021 in our hospital in Delhi, India, which is a 500 bedded tertiary care center. As this was a retrospective data analysis, consent was not obtained from the patients. The study was approved by the Hospital Internal Review Board.

Inclusion Criteria

Coronavirus disease 2019 (COVID-19) positive (by polymerase chain reaction) patients with clinical and/or radiological features

suggestive of fungal infections of upper/lower respiratory tracts, paranasal sinuses, orbit, cerebrum, etc.

Patients with infections other than molds were not included in the study.

Laboratory Methods

Respiratory samples and endoscopically collected pus or tissue specimens from representative sites of nasal or sinus mucosa were processed by standard mycological procedures for microscopy and fungal culture. The tissue samples were cut into smaller fragments, mucoid part of respiratory and pus samples was examined microscopically with 40% potassium hydroxide (KOH). They were also inoculated on sabouraud dextrose agar and potato dextrose agar in sets of duplicates. Each set was then incubated at 37° and 25°C for up to 6 weeks. The fungal isolates, so obtained, were then identified by their colony morphology, growth characteristics, and microscopic features by lactophenol cotton blue preparation. In addition to the above, 28 samples were processed for histopathological examination (HPE).

The clinico-demographic information of the patients was obtained using a *pro forma*. The details included were clinical presentation, history of COVID-19 up till the preceding 1 year, its severity and management including any comorbidity, use of steroids or drugs like tocilizumab, type of presentation/categorization of fungal infection, laboratory and radiological investigations, treatment, and patient outcome.

The clinical severity of COVID-19 illness was classified as follows:

- *Mild:* Patients with uncomplicated upper respiratory tract infections may have mild symptoms without evidence of breathlessness or hypoxia (normal saturation).
- *Moderate:* Adolescents or adults presenting with clinical features of dyspnea and or hypoxia, fever, cough, including oxygen saturation (SpO_2) <94% (range 90–94%) at room air, respiratory rate (RR) ≥ 24/minute, that is, pneumonia with the absence of signs of severe illness.
- *Severe:* Adolescents or adults with characteristics of severe pneumonia and RR ≥ 30/minute, SpO_2 < 90% at room air, or severe respiratory distress.[9]

Results

Around 45 patients were included in the study. Their ages ranged from 34 to 84 years, with the median age noted as 55 years. The male:female ratio (M:F) was found to be 3.2:1.

Out of 45 patients, 34 (75.56%) were admitted and 11 (24.44%) presented to the outpatient department (OPD). The clinical criteria of the patients are enlisted in Table 1. Majority of our patients (34; 75.56%) presented after the resolution of clinical symptoms of COVID-19 disease. The median time interval of clinical presentation and COVID-19 diagnosis was observed to be 17 days in our study, ranging from as less as 13 days to a maximum of 210 days in one of the patients. Though most patients (22; 48.89%) experienced severe disease, nevertheless, many (10; 22.22%) mild cases also presented with features of fungal infection. More than half (28; 62.22%) of the patients received glucocorticoids for the treatment of COVID-19 infection. Methylprednisolone was the most common glucocorticoid used either orally or parenterally. The predominant comorbid risk factor was found to be DM (38; 84.44%), with three cases being newly diagnosed, which was followed by hypertension (HTN) (18; 40.00%).

The most prevalent clinical and/or radiological presentation in our patients were rhinosinusitis (39; 86.67%), which presented mostly with nasal discharge and stuffiness. Orbital (23; 51.11%) involvement was observed as the most frequent complication where the patients had blurring of vision, proptosis, and orbital pain. An intracranial extension was detected among three (6.67%) patients having a headache as the predominant presenting feature (Table 1).

Microscopy and fungal culture were performed for all cases, but requisition for HPE was received in 28 (62.22%) out of 45 patients. This implies that all three investigations were done in 28 (62.22%) out of 45 patients. Figure 1 shows the distribution of positive results of the various investigations done. As seen in the diagram, positive results in all three investigations were seen among 22 (78.57%) of these 28 specimens. Among these 22 patients, 13 (59.09%) cases showed concordance, where results matched in all three investigations. In the rest of the nine (40.91%) patients, all three investigations showed positive results; however, discordance among these was observed (Table 2).

Distinct genera of fungi were identified among 33 (73.33%) out of 45 samples. The most common fungal isolates belonged to order Mucorales (26; 78.79%). Mixed growth was observed in nine (34.62%) samples (Table 3).

All the OPD patients (11; 24.44%) were lost to follow-up as they did not visit our center further. Out of the remaining 34 admitted patients, two (5.88%) patients with pulmonary fungal infections passed away very soon after they were admitted. However, their clinical samples could be collected. The rest of the 32 (94.12%) were managed either with antifungal therapy and/or surgery. Depending upon the clinical features, site, and extent of disease, surgical intervention was performed in 27 (84.38%) out of 32 patients in addition to medical management. But one (3.13%) of the 32 treated patients did not receive any antifungal treatment but underwent only surgery. About 17 (53.13%) out of the 32 treated patients underwent surgery as well as received combination therapy with liposomal amphotericin B (AMB) and azoles. Posaconazole was the chief azole used in 16 of these 17 patients. About nine (28.13%) out of 32 individuals were managed with surgery and a single antifungal agent, AMB in six (66.67%), posaconazole in two (22.22%), and voriconazole in one (11.11%) of these nine people. Around five

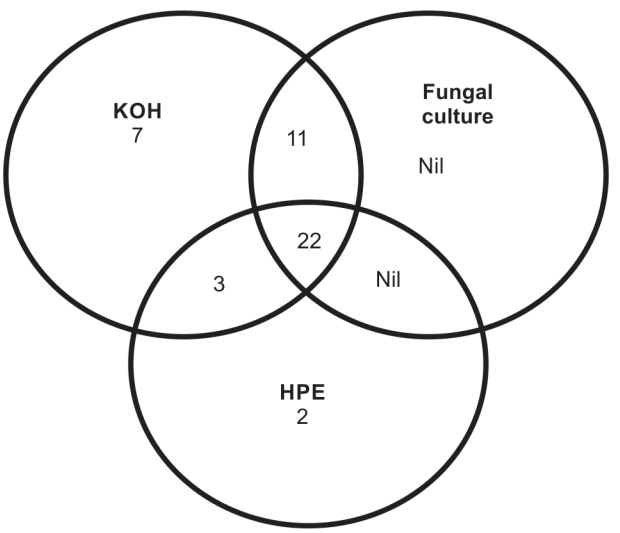

Fig. 1: Distribution of results

Table 1: Summary of the determinants of the patients

Determinants	*Values*
History of COVID-19:	
• Current	11 (24.44%)
• Previous	34 (75.56%)
COVID-19 severity:	
• Mild	10 (22.22%)
• Moderate	13 (28.89%)
• Severe	22 (48.89%)
DM:	
• Present	38 (84.44%)
• Absent	3 (6.67%)
• Not known	4 (8.89%)
Other comorbidities:	
• HTN	18 (40.00%)
• Cardiovascular disease	3 (6.67%)
• Chronic/acute renal disease	3 (6.67%)
• Posttransplant	2 (4.44%)
• Chronic liver disease	1 (2.22%)
• Hepatocellular carcinoma	1 (2.22%)
Use of glucocorticoids for COVID-19 disease:	
• Present	28 (62.22%)
• Absent	2 (4.44%)
• Not known	15 (33.33%)
Clinical presentation:	
• Rhinosinusitis	39 (86.67%)
• Rhinosinusitis (only)	15 (33.33%)
• Rhinosinusitis + orbital involvement	23 (51.11%)
• Rhinosinusitis + orbital and cerebral involvement	3 (6.67%)
• Rhinosinusitis + mandibular involvement	1 (2.22%)
• Pulmonary	5 (11.11%)
• Mandibular (only)	1 (2.22%)
No. of patients who received the treatment for fungal infections (n = 45)	32 (71.11%)
Use of adjunct surgery for the treatment (n = 32)	27 (84.38%)
Outcome (n = 45):	
• Discharged	22 (48.89%)
• Expired	9 (20.00%)
• Left against medical advice	3 (6.67%)
• Not admitted	11 (54.44%)

Table 2: Discordant results among 40% KOH mount/HPE/fungal culture

S. no.	*40% KOH mount*	*HPE*	*Culture*
1	Aseptate hyphae	Aseptate hyphae	*R. arrhizus* + *A. niger*
2	Aseptate and septate hyphae	Aseptate hyphae	*Cunninghamella bertholletiae* + *A. niger*
3	Aseptate hyphae	Aseptate hyphae	*R. arrhizus* + *A. niger*
4	Aseptate hyphae	Aseptate and septate hyphae	*R. arrhizus*
5	Septate hyphae	Aseptate hyphae	*R. arrhizus* + *A. niger*
6	Aseptate and septate hyphae	Aseptate hyphae	*R. arrhizus* + *A. niger*
7	Aseptate hyphae	Aseptate hyphae	*R. arrhizus* + *A. alternata*
8	Aseptate and septate hyphae	Aseptate hyphae	*R. arrhizus* + *F. dimerum*
9	Aseptate hyphae	Aseptate hyphae	*R. arrhizus* + *A. flavus*

(15.63%) out of 32 patients did not undergo surgery and received only antifungal therapy either by posaconazole, voriconazole, or combination therapy with AMB and posaconazole. All-inclusive AMB was given to 24 (75.00%) of the 32 treated patients.

Patients' outcome has been mentioned in Table 1. All but one (1.23%) of the nine expired patients had severe COVID-19 disease. Among these, one patient, though, did not have any comorbidity and died young (aged 35 years). The rest of the deceased patients (88.89%) were above 55 years of age and diabetic. Among these nine patients, the predominant presentation was that of rhinosinusitis found in seven (77.78%) individuals, orbital involvement was noticed in four (44.44) of them, and cerebral extension in one (11.11%). The other two (22.22%) had pulmonary symptoms. About five (55.56%) of these nine cases were diagnosed with *Rhizopus arrhizus*, two of

Table 3: Results of fungal culture

Determinants	*Values (n = 33)*
R. arrhizus	16 (48.49%)
R. microsporus	1 (3.03%)
A. flavus	2 (6.06%)
A. fumigatus	3 (9.09%)
A. alternata	2 (6.06%)
R. arrhizus + A. flavus	2 (6.06%)
R. arrhizus + A. niger	4 (12.12%)
R. arrhizus + A. alternata	1 (3.03%)
R. arrhizus + F. dimerum	1 (3.03%)
C. bertholletiae + A. niger	1 (3.03%)
No growth	12 (26.67%)

them had a dual infection, each with *Aspergillus flavus* and *Fusarium dimerum*. Both patients (22.22%) with pulmonary symptoms had invasive pulmonary aspergillosis (IPA) by *A. fumigatus*. Growth of *Alternaria alternata* was observed in one (11.11%) person who had rhinosinusitis with orbital involvement. But no fungus could be isolated in the nasal tissue of one (11.11%) individual who presented with rhinosinusitis.

Discussion

The mayhem of COVID-19 pandemic has not spared anybody across the globe. A manifold presentation and complications of this novel pandemic have already been reported, yet we witness the unfolding of several new and emerging features with each passing day. A significant surge of invasive fungal infections, especially of the maxillofacial region, namely mucormycosis and aspergillosis, had been observed.[10] Though the mechanism of COVID-19 associated mycoses is not completely understood, certain immunological processes, like the release of danger-associated molecular patterns, may be responsible for the development of CAPA and other fungal infections.[11]

Studies have reported that age was not a barrier for these COVID-19 related mycoses, it was affecting individuals of all ages, commonly males.[10,12,13] The median age in our study group was 55 years with an age bracket of 34–84 years with predominantly males (M:F = 3.2:1). Similar observations of widened age-group were also reported in other studies, while Garg et al. reviewed and documented COVID-19 associated mucormycosis (CAM) in even younger and older patients (22–86 years).[10,12,14,15]

In spite of the fact that our robust immune system has a natural defense mechanism against fungal infections, this dramatically increased incidence was observed more in patients with associated comorbid risk factors like DM, COPD, administration of immunosuppressant drugs including glucocorticoids, neutropenia, hematopoietic stem cell transplant, mechanical ventilation, ICU stay, and with cytokine storm.[2–4,11,12,16,17] The most prevalent comorbidity in our patients (Table 1) was found to be DM (84.44%), as also depicted by other authors.[10,12–15,18,19] In a multicentric study conducted in various Indian cities, CAM was observed in 60.4% of diabetic individuals. DM had already been recognized as the prime risk factor in the occurrence of zygomycosis.[20] This is due to the fact that in diabetic individuals, dysfunctional mononuclear and polymorphonuclear phagocytes are unable to inhibit the germination of fungal spores as a result of impaired chemotaxis and faulty intracellular killing mechanisms.[21,22]

The rampant and injudicious use of glucocorticoids (60–100%) and/or anti-interleukin (IL)—6 treatment with tocilizumab has possibly precipitated the upsurge of CAM and invasive aspergillosis (IA).[5,10,12,15,16,18,19] About 28 (62.22%) of our patients received glucocorticoids so as to suppress the inflammatory response, thereby reducing the mortality associated with COVID-19. We could not elicit a history of corticosteroid use in 15 patients. Due to the use of steroids as a treatment modality for severe and/or moderate COVID-19 cases, the incidence of CAPA may vary.[5,9] Higher rates were observed by White et al. after corticosteroid use, while Rutsaert et al. noticed increased incidence despite nonadministration of steroids.[23,24] Owing to their immunosuppressive and hyperglycemic effects, susceptibility to secondary fungal infections increases.[25]

The patients predominantly presented with rhino-orbital-cerebral features (88.89%). Only 11.11% of the individuals had pulmonary symptoms. The rhino-orbital-cerebral mucormycosis (ROCM) is the most frequent presentation found in Indian patients, as also documented in some multicentric studies.[10,15,26] Sharma et al. observed sinusitis as the main feature in their patients with 43.48% orbital involvement, while sino-orbital involvement was noticed in all of their patients by Sarkar et al.[18,19] In a recent multicentric study, Patel et al. observed that in diabetic individuals too, the most usual presentation is ROCM (77%).[26] In another study, DM was documented as the main risk factor in 80–100% of the cases of ROCM.[27] *Aspergillus* can exhibit diverse clinical symptoms, varying between just colonization (48.5%) on one end of the spectrum to the most severe and fulminant IA (IA; 1.6 cases/10,000 admissions) on the other end.[28] In another study, Denning observed that aspergillosis commonly manifests as IPA (80–90%).[29] Higher rates of CAPA were reported in patients with COVID-19 (3.2–33.3% in China), especially in those with induced ARDS (20–35% in a European case series).[11,25]

We noticed that the median time interval for appearance of clinical features of fungal infections in our patients was 17 days (13–210 days) after the diagnosis of COVID-19 was established. The shortest duration observed was 6 days by Revannavar et al. to that of the longest of 27 days by Patel et al.[12,14,20,30]

About 43 (95.56%) cases were diagnosed on the basis of direct microscopy by KOH mount. The rest of the two cases were diagnosed on HPE and clinico-radiological features. In our study, HPE was not done in all but 28 (62.22%) patients. The absolute corelation of HPE with fungal culture and/or KOH mount could be established in 18 (64.29%) individuals. Fungal culture positivity was observed in 33 (73.33%) of the 45 samples. Patel et al. reported 82.6% positivity in KOH mount, 90.5% in HPE, and 48.1% in fungal cultures.[20] Similar observation (42.86%) was noticed by Ahmadikia et al. in their CAM patients.[31] Negative culture outcomes could be the results of difficult recovery of zygomycetes from tissues due to their focal presence in the specimen.

Overall, Mucorales (26; 78.79%) dominated the list, followed by *Aspergillus* species (12; 36.36%). *R. arrhizus* 24 (72.72%) was the most commonly isolated among Mucorales. Two different types were observed in nine (27.27%), as shown in Table 1. Various Mucorales reported by Patel et al., were *R. arrhizus*, *Rhizomucor pusillus*, *Apophysomyces variabilis*, etc.[20] In India, the burden of CAM was found to be 47,508 cases within a span of just 3 months from May to August 2021.[32] Globally, *R. arrhizus* is the most common etiological agent of mucormycosis.[27] Overall, the leading causative organism of aspergillosis in our patients was *A. niger* (Table 1). *A. fumigatus* was reported as the most prevalent etiological agent of aspergillosis among COVID-19 patients, *A. flavus* was primarily responsible for invasive sinusitis, especially in developing countries.[16,25,33]

Treatment with liposomal AMB/azoles was administered in 32 (71.11%) patients, with adjunct surgery in 27 (84.38%) of them. Though nine (28.13%) of our 32 treated patients died, but 22 (68.75%) of them were discharged in good health. Almost similar death rates (33–44.44%) were observed by other investigators.[10,12,13,15,20] The greatest hurdle in managing these fungal infections in our country is the financial restrictions in completing the therapy due to the high-priced antifungal drugs.[26] Other factors attributing to higher deaths could be a delay in presentation, diagnosis, and hence, in treatment.[33]

The lack of uniformity in the sample testing is a major constraint while extrapolating the data to all 45 patients. The other limitations of our study were that we could not trace the history of oxygen inhalation in the patients since most of the patients presented to our hospital during the convalescent phase of COVID-19 illness. The corelation of the significance of abnormal biochemical markers, namely C-reactive protein, D-dimer, serum ferritin, and IL-6, and the development of fungal infections could not be studied due to similar reasons. The association of immunomodulators-induced immunosuppression with fungal infections could not be established as history could not be elucidated. And also, the reports of corticosteroid therapy, its dose, and duration, could not be obtained.

Conclusion

Though the definite incidence or prevalence of mucormycosis or IA is not definitely known but their higher prevalence among COVID-19 patients is noticeably evident, distinctly in association with the comorbidities like DM. Due to their invasive character and higher mortality, these fungal infections need to be timely diagnosed and treated.

Highlights

The study highlights the prevalence of fungal infections, especially Mucorales, in COVID-19 cases. *R. arrhizus* is the most common mold found in these patients. The study also features the importance of diagnostics in the management of these patients.

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