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The association of mucormycosis co-infection in patients with COVID-19 pneumonia: experience at tertiary care hospital in India

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ABSTRACT:

Objective: We performed this study to explore the impact of multiple co-morbidities, different treatment strategies and vaccination in patients diagnosed with mucormycosis co-infection during the ongoing COVID-19 pandemic.

Patients and methods: This is an observational study of 60 patients out of 3000 admitted from March 2021 to May 2021 for treatment of COVID-19 pneumonia, with confirmed diagnosis of opportunistic fungal infection. Characteristics like age, antibiotic usage, steroid usage, and associated co-morbidities, need of oxygen or ventilator support and status of vaccination were studied.

Results: Out of 60 patients studied, maximum 37 (61.6%) belonged to 40 to 60 years age group and 38 (63.3%) were male. Fifty-two (86.6%) patients had one or other co-morbidities, while 56 (93.3%) of these patients received steroids in oral or intravenous form. Fifty-one (85%) patients received one or more than one higher grade antibiotics during treatment in hospital. Forty-two (70%) patients required Intensive Care Unit (ICU) admission out of which 4 (6.7%) required ventilator support, 10 (16.6%) required Non-Invasive Ventilation (NIV) while 28 (46.6%) were managed with high flow oxygen.

Conclusions: Our observations suggest for judicious use of steroids and higher antibiotics during treatment of COVID-19 pneumonia as it is associated with increased risk of opportunistic fungal infections. Strict control of blood glucose levels, multidisciplinary approach to reduce the impact of opportunistic fungal infection on patient morbidity and widespread vaccination especially among patients with co-morbidities will help in mitigating the impact of opportunistic fungal infections in patients with COVID-19 pneumonia.

Keywords: COVID-19, Mucormycosis, Fungal osteomyelitis prevention, Treatment.

INTRODUCTION

Around the end of year 2019, a number of patients with symptoms of pneumonia of unknown cause were detected in Wuhan, China. A novel coronavirus was identified as the causative pathogen, provisionally named as 2019 novel coronavirus (2019-nCoV) by the World Health Organization (WHO)[1,2]. Within two years this virus has spread from China to the whole world affecting more than 150 countries across all continents and causing morbidity and mortality across all age groups. This human-to-human transmitted disease, coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been an emerging global public health event.

SARS-CoV-2 is mainly a lower respiratory tract infection causing Acute Respiratory Distress Syndromes (ARDS)[3]. In addition to widespread alveolar damage

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and inflammatory exudation, COVID-19 patients also develop immunosuppression due to a reduction in CD4 T and CD8 T cells. Such patients turn critical rapidly and require intensive care unit (ICU) admission along with mechanical ventilation[4]. These patients stand a very high risk of developing fungal co-infections. Many studies[5-7] have demonstrated multiple fungal co-infections like *Aspergillus flavus*, *A. fumigates*, *Candida albicans*, *C. Grabrata* in COVID-19 patients.

Mucormycosis is a type of opportunistic fungal infection caused by micro-organisms belonging to the phylum glomeromycota. Once a rare fungal infection, it is now seen as emerging threat in the wake of increased incidence of opportunistic fungal infections in COVID-19 patients[8]. Mucormycoses are life-threatening fungal infections mostly affecting diabetic, patients on immunosuppressant and solid organ recipients. Mucormycosis infection is characterised by infarction and necrosis of host tissues that results from invasion of vasculature by hyphae. Mucormycosis is most commonly present as rhino-orbito-cerebral and pulmonary infection[8,9]. In this short period of time, no studies have been conducted that determine the incidence of mucormycosis infections in COVID-19 patients and also the causative factors leading to a sudden increase in incidence[10,11]. Hence, we performed a study in the Indian population where the caseload of COVID-19 infections is extremely high.Our aim was to calculate the incidence of mucormycosis co-infection in patients suffering from COVID-19 pneumonia by finding the risk factors associated with increased incidence of mucormycosis co-infection in COVID-19 pneumonia, to determine the effectiveness of current treatment protocol of mucormycosis co-infection and to determine whether COVID-19 vaccination is effective in preventing fungal co-infections.

PATIENTS AND METHODS

This observational descriptive type of study was carried out over a period of three months from March 2021 to May 2021 and the patients admitted in Mahatma Gandhi Mission Hospital and Medical College, Aurangabad, Maharashtra for treatment of COVID-19 pneumonia were included in our study.

The inclusion criteria for our study were patients with confirmed diagnosis of COVID-19 pneumonia by RT-PCR test with testing device INSTA Q 9 (Equipment Number: ML01 – manufactured by Himeda Serial Number HN550988). Patients with proven diagnosis of fungal co-infection on laboratory tests (potassium hydro-oxide KOH mount of scrapping from infected tissue).

Exclusion criteria for our study were patients with history of fungal infection in the past and patients with fungal infection but not associated with COVID-19 infection.

A total of 3000 patients with confirmed diagnosis of COVID-19 pneumonia were admitted from March 2021 to May 2021. Amongst these patients those developing clinical symptoms of fungal infection and proven as mucormycosis infection on direct examination in 10% potassium hydro-oxide (KOH) of sample from scrapping of infected tissue, histopathology and culture reports were studied. A total of 60 patients were diagnosed with mucormycosis co-infection over a period of 3 months and these patients were followed up regularly throughout their course of disease.

When the patient first arrived in the fever clinic of our hospital (during COVID-19 pandemic special fever clinic and emergency section were established in our hospital campus to segregate patients with acute onset high grade fever with/without breathing difficulty from other emergency patients) an exhaustive history was taken regarding the type, severity and duration of symptoms. Specific information was obtained regarding the presence of co-morbid conditions, its duration and the type of treatment that is being carried out. A thorough general and system specific examination was then carried out with special attention towards the respiratory system for severity of symptoms. As soon as the patient was admitted a nasal swab was sent for RT-PCR which detects the spike gene and the N gene on viral RNA and is considered gold standard for diagnosing the presence of COVID-19 pneumonia[12]. Apart from this a battery of laboratory and radiological investigations comprising of Complete blood count, Renal Function Test, Liver Function Test, Serum Electrolytes, CReactive Protein, Serum ferritin, Arterial blood analysis, Erythrocyte sedimentation rate,X-ray chest, High resolution computed tomography of chest were done to assess severity of the disease and plan an appropriate course of action for the same. Patients who developed symptoms of fungal co-infection in addition to above investigations also underwent tests like direct microscopy of KOH mounted samples taken from specific sites of suspected infection, fungal cultures for detection of causative organism and magnetic resonance imaging of the brain, orbit or paranasal sinuses to evaluate of extent of disease.

Patients developing mucormycosis after admission for COVID-19 pneumonia had symptoms of lid edema and soft tissue swellings along the para nasal sinuses. Severe cases present with orbital cellulitis, para nasal sinusitis with osteomyelitic changes or neurological symptoms if the infection spreads to the brain. Mucormycosis was detected on nasal and conjunctival swabs subjected to direct microscopy and fungal cultures. MRI of the brain as well as orbit and para nasal sinuses gave an idea about the extent of spread of infection.

The treatment protocols for COVID-19 pneumonia are not well documented but the basic regime followed in our hospital included supportive treatment including intravenous fluids and oxygen support. According to the severity of the symptoms patients were started on oral or intravenous steroids, as well as antiviral drugs like Remdesevir with dosage – Day 1: Inj. Remdesivir 200 mg in 100 ml NS IV OD, Day 2 to 5: Inj. Remdesivir 100 mg in 100 ml NS IV OD. As a cover to protect the patients from secondary bacterial infections broad spectrum antibiotics and higher antibiotics like Meropenem (Inj. Meromac 500 mg IV in 100 cc NS IV BD), Tigecycline (Inj. Teganex 100 mg IV od followed by Inj.

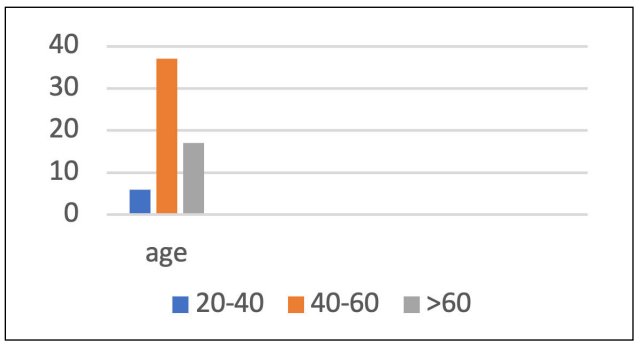

Figure 1. Age wise incidence of fungal osteomyelitis.

Teganex 50 mg BD) and Piperacillin tazobactum (In. Piptaz 4.5 gm iv TDS) were given. Enoxaparin (Inj. Clexane 0.4 cc or 0.6 SC HS) and other anti-thrombotic agents (Tab. Ecosprin 75 mg or 150 mg HS) were given to the patients to prevent life-threatening thrombotic events. In cases of fungal co-infections patients were started on antifungal like Amphoterecin B-Inj. Liposomal Amphotericin 5 amp 250 mg in 250 ml D5 IV OD for 21 days or Inj. Amphotrate (1 amp) 150 mg in 250 ml D5 OD for 21 days under all photosensitivity precautions and Posaconazole-Tab. Posaconazole 300 mg OD for 3 months. Surgery for the infected paranasal sinuses and orbital cellulitis was reserved for cases not responding to medical treatment or as a salvage procedure.

RESULTS

There were a total of 3000 patients admitted in our hospital for COVID-19 pneumonia out of which 60 patients suffered from Mucormycosis within a time period of 3 months with an incidence of 2%. Among these 60 patients there were 6 (10%) patients in the age group of 20-40, 37 (61.6%) patients belonged to the age group of 40-60 and17 (28.3%) patients above the age of 60 years who suffered from mucormycosis (Figure 1). Total 38 (63.3%) patients were male and 22 (36.7%) were female with a male to female ratio of 1.7:1 (Figure 2).

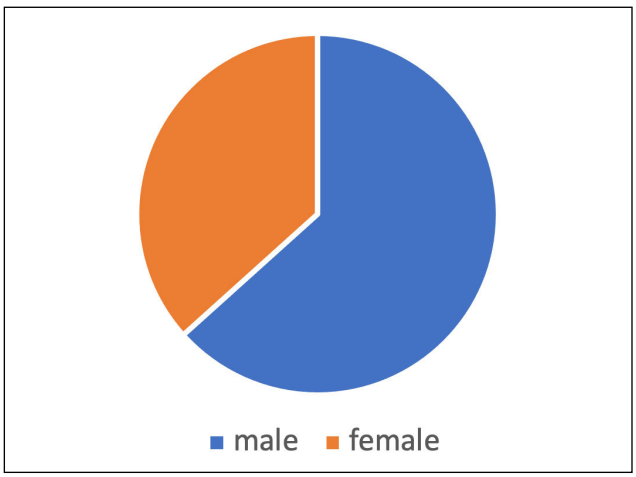

Figure 2. Sex wise incidence of fungal osteomyelitis.

From a total of 60 patients who suffered from fungal infections, 52 (86.6%) patients had presence of co-morbidities. Amongst these, diabetes mellitus was the most common co-morbidity seen in 34 (65.3%) patients with mucormycosis infections, followed by hypertension seen in 19 (36.5%) patients (Figure 3). There were also 14 (26.9%) patients who suffered from a combination of co-morbidities.

Steroids were one of the first line drugs used to counter the inflammatory response of the body to COVID-19 pneumonia and were administered either orally or intravenously in 56 (93.3%) of the 60 patients suffering from mucormycosis (Figure 4). Most of these patients received steroids for more than 5 days amongst which 8 patients consumed oral dexamethasone while 48 patients were administered IV methyl prednisolone.

The viral pneumonia affecting the lungs increased the susceptibility of patients to various super added bacterial infections. These infections were treated using both broad spectrum and higher antibiotics. Amongst the 60 patients maximum, 25 (41.66%) were treated with high end antibiotics like Inj piperacillin tazobactum, Inj meropenem in 9 (15%) patients and Inj tigecycline in 2 (3.33%) patients (Figure 5). Broad spectrum antibiotics like ceftriaxone, doxycycline or azithromycin were

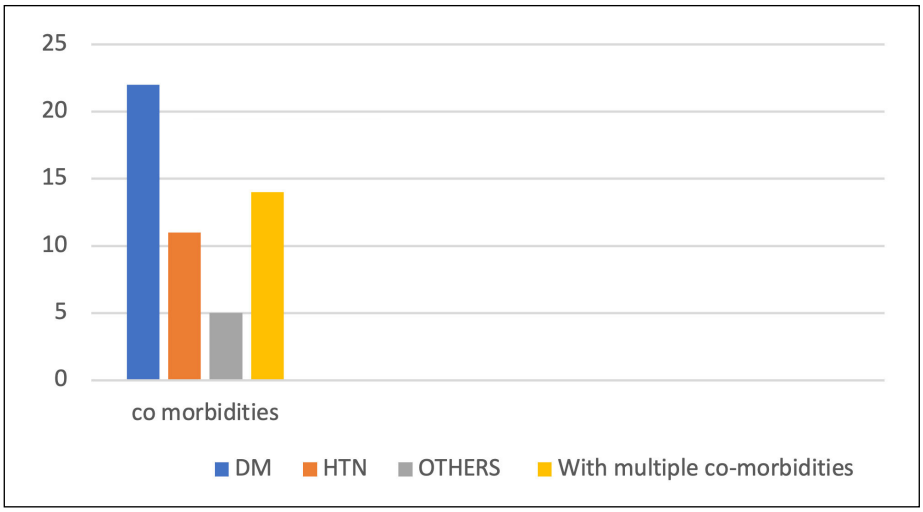

Figure 3. Incidence of co-morbidities in patients with mucormycosis.

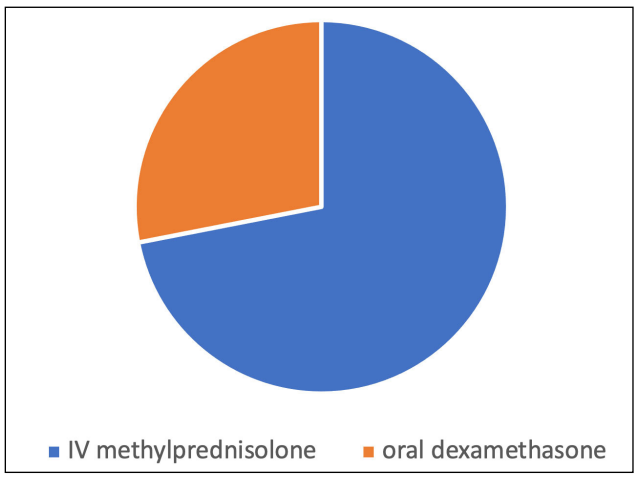

Figure 4. Steroid use.

used in 17 (28.33%) patients. Seven (11.66%) patients received a combination of above antibiotics.

In our study amongst 60 patients who suffered from COVID-19 pneumonia, 42 (70%) patients required ICU admission at some point in their course of disease. Four (6.7%) patients had to be put on ventilator support, 10 (16.6%) patients required non-invasive ventilation and 28 (46.6%) patients needed high flow oxygen with canula or reservoir bag (Figure 6). The rest 18 (30%) patients were treated in ward with intermittent need for O_2 support.

The role of vaccines in preventing COVID-19 infections has not yet been proven but studies suggest that previously vaccinated individuals are more likely to suffer from a mild illness without any serious complications. An observation was made that from the 60 patients who suffered from Mucormycosis only 9 patients had taken at least one dose of COVID-19 vaccine before suffering from the disease and amongst these only 3 patients required intensive care with others being managed in the ward on intermittent oxygen support.

Out of 60 patients in our study 9 (15%) patients died during course of follow-up, 4 (6.66%) patients required re-exploration surgery for residual infection, while 47 (78.33%) patients had an uneventful recovery at 3 months follow-up.

Mucormycosis occurring as a result of COVID-19 infection mainly affected the face with the nasal sinuses being the most common site of fungal infection seen in 36(60%) patients followed by orbit in 9 patients (15%) and brain in 6 (10%) patients (Figure 7). Nine (15%) patients presented with fungal infections in more than one site, the orbit and para nasal sinuses being the most common sites.

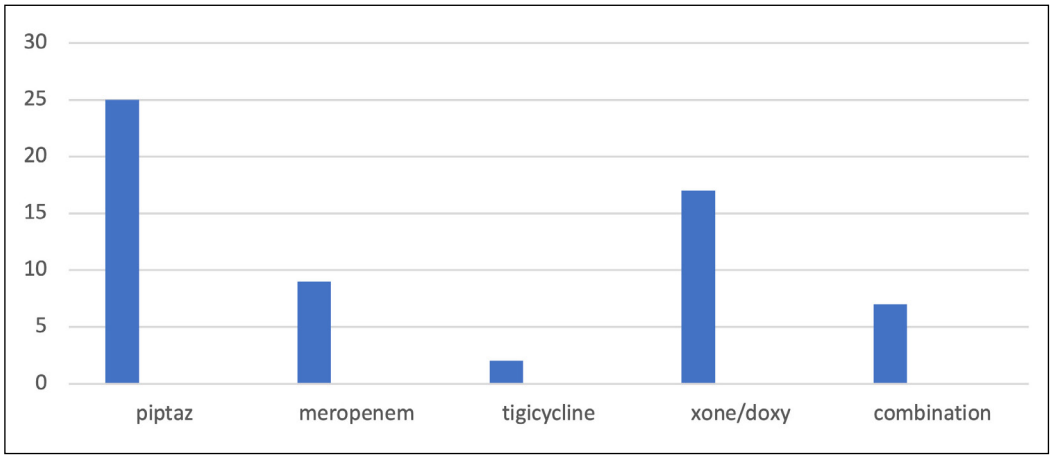

Figure 5. Antibiotics used.

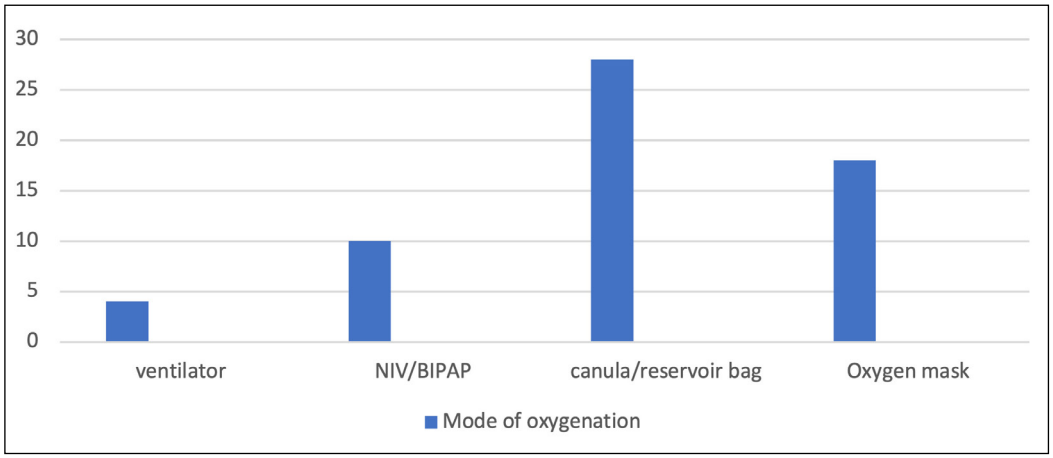

Figure 6. Oxygen support.

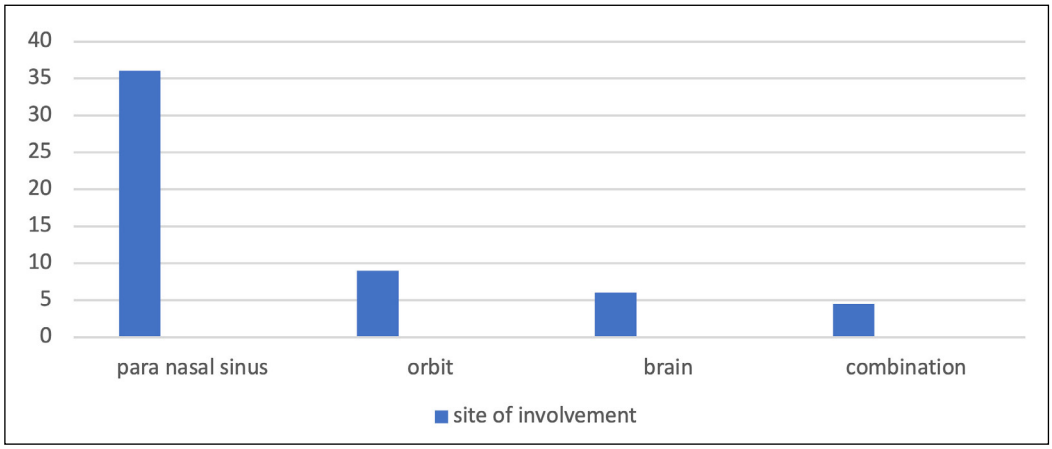

Figure 7. Site of occurrence of mucormycosis.

DISCUSSION

Mucormycosis is a deadly opportunistic fungal infection caused by fungus originating from mucorales order and includes Mucor, *Rhiopus*, *Rhizomucor*, *Abdidia*, *Apophysomyces* and *Cunninghumella*. Fungal spores enter *via* inhalation and then reach up to paranasal sinuses. Spores may also be acquired by contaminated food ingestion. Affected individuals usually present with acute sinusitis, fever, nasal congestion, purulent nasal discharge and headache[16]. If not treated early, contiguous spread to adjacent structures may occur, resulting in various clinical symptoms[16]. The orbital cavity is accessible through the ethmoid bone *via* the lamina papyracea, infratemporal fossa, inferior orbital fissure or orbital apex. Contiguous intracranial extension can occur through the ethmoid cribriform plate, supraorbital fissure and perineural routes[17]. Cavernous sinus or sagittal sinus thrombosis, carotid occlusion, cerebral infarction, intracranial aneurysm, intracranial haemorrhage and cerebral abscesses are potential *sequelae*[17-24].

In our study conducted over a period of 3 months there were a total of 3000 patients admitted in our hospital from which 60 patients developed Mucormycosis as a complication with an incidence of 2%. Jeong et al[14] in their study found an incidence a rate of 0.005-1.7 per million population globally. Alanio et al[25] screened 135 adults with COVID-19 infection and reported an incidence of invasive fungal infections of 26.7%. Patients with invasive fungal diseases had higher mortality (53% with *vs.* 31% without), which was significantly reduced by appropriate therapy. Corticosteroid therapy and a past history of chronic pulmonary disease were associated with a higher risk of invasive fungal disease[25]. Similarly, high incidences have been observed in Pakistan (23/147, 15.6%) and Italy (30/108, 27.7%), and with the authors suggesting that the development of invasive fungal infections alters the natural history of the disease[26,27].

In our study the para nasal sinuses were the most common site of affection for the fungal spores followed by the orbit and then brain. Similar results were observed in studies conducted by Selarka et al[28] where the most common site was rhino-cerebro-orbital (44%-49%), followed by cutaneous (10%-19%), pulmonary (10%-11%), disseminated (6%-11%) and gastrointestinal (2%-11%).

Mucormycosis is known to affect immunocompromised patients especially those with diabetes mellitus, prolonged corticosteroid use, solid organ transplant recipients, neutropenia and haematological malignancies[29-31]. The overall immunity of the patient suffering from COVID-19 infection has been observed to decline due to a decrease in CD4 and CD8 counts which is further aggravated by medical co-morbidities such as diabetes mellitus, hypertension and bronchial asthma. Diabetes mellitus is known to cause microangiopathy reducing tissue perfusion[13-15]. So, the deadly triad of diabetes mellitus, rampant use of steroids in the background of COVID-19 infection appears to increase risk of mucormycosis. All efforts should be made to maintain optimum glucose levels along with judicious use of steroids in COVID-19 treatment. In our study 52 patients were suffering from one or more co-morbidities with diabetes mellitus being the most common, 34 (56.66%) patients playing a major role in the severity of infection. In a cohort study presented by Erener et al[32] amongst patients diagnosed with COVID-19 pneumonia and mucormycosis, about three-quarters had a pre-existing history of diabetes mellitus along with a poor glycaemia control at presentation. The excessive use of broad spectrum antibiotics and immunosuppressive agents such as steroids and Remdesevir has also adversely affected the immunity of the individual. In our study, almost 93% of the patients suffering from Mucormycosis had received steroids for more than 5 days and almost all the patients had received complete courses of higher end antibiotics and Remdesivir to tackle the COVID-19 infection, all laying foundation for opportunistic infections like Mucormycosis. In addition, COVID-19 patients were more prone to develop secondary infections if they had decompensated pulmonary functions or required invasive mechanical ventilation. Our study showed that 42 patients required ICU admission with half of them requiring either ventilatory or non-ventilatory support of oxygen which was similar to studies conducted by Sharma et al[17] showing 82% of their study population required large amounts of oxygen through ventilator support.

The role of vaccination in preventing COVID-19 infection is still debatable but observations from our study show that Mucormycosis was fairly more common in individuals who had not received any previous dose of vaccinations and the severity of infection was comparatively lesser in those patients that had been vaccinated previously.

LIMITATIONS

Some limitations in our study were that the data represented the experience of loading in a single tertiary care centre, which often treat most of the sick patients with severe complications. Thus, the data may not be generalisable. Second, we could not perform blood investigations in all study participants due to lack of affordability by the patients, as well as limited availability of test kits among rapidly rising cases of COVID-19 patients. Third, a case series of 60 patients might be considered a small sample size and various associations could not be evaluated. However, given the rarity of the disease, it still accounts for a large case series. In fact, according to the published literature, 101 cases of mucormycosis in patients with COVID-19 have been reported so far, of which 82 cases belong to India[30]. Lastly, being an observational study, there is no control group to evaluate reliable differences and association.

CONCLUSIONS

The incidence of mucormycosis in the COVID-19 pandemic is likely to increase and can result in significant morbidity and mortality. While treating COVID-19 patients, we should have a high index of suspicion of mucormycosis especially when corticosteroids are used during the course of disease. Optimised glycaemic control should be achieved to control mucormycosis. Comprehensive monitoring of blood sugar levels on daily basis should be encouraged. Use of antifungal therapy with surgical debridement of affected tissue together should be undertaken and it remains the mainstay of treatment. Precautions need to be practised with regard to the widespread usage of corticosteroids and broad-spectrum antibiotics, with an emphasis to administer corticosteroids only in severe COVID-19 pneumonia and to reduce super-infections. Excessive use of corticosteroids should be restricted. A multidisciplinary approach involving an intensivist, diabetologist, otolaryngologist, ophthalmologist, infectious diseases specialist, neurologist and/or neurosurgeon is needed for the management of mucormycosis. An accelerated COVID-19 vaccination programme should be the highest priority in a country with high prevalence of diabetes and relatively poor resources to avoid massive outbreaks, morbidity and mortality during the current pandemic.

Conflicts of Interest:
The authors declare that they have no conflict of interests.

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