



CLINICAL STUDY OF INVASIVE MUCORMYCOSIS PATIENTS ADMITTED IN TERTIARY CARE HOSPITAL

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ABSTRACT **Background & objective** - Mucormycosis is an emerging angioinvasive infection caused by the ubiquitous filamentous fungi of the Order Mucorales and class of Mucormycetes. Since last months higher number of Mucor mycosis cases were found to be associated with recent COVID 19 infection. This association may be due to steroid use in these patients in turn causing hyperglycaemia . But very limited data was available in this context . **Method-** We conducted a retrospective study of 50 patients who were diagnosed as having mucormycosis in a tertiary care hospital during January 2021 to May 2021. Data was collected and analysed in standard proforma. **Results** - The mean age of study population was found to be 40 years. Sixty percent (60%) patients were farmers by occupation from rural area. Most common presenting complaint was Nasal blockage in 70% patients followed by orbital pain and eye swelling in 60%. Headache was present in 40%, Ophthalmoplegia, Proptosis and facial palsy in 20%, toothache in 20% and Hemiparesis in 10%. History of use of steroid was present in 80% patients. 45 (90%) patients were diabetic. COVID infection is associated in 47 patients. Rhino-orbital was the most common site involved in 80% patients. **Conclusion** - Combination of surgery and medical treatment with amphotericin B was associated with better outcome. Mucormycosis has become a serious health issue in India. High index of suspicion, early diagnosis, timely management with judicious use of Steroids, strict Blood sugar control are essential to decrease the burden of Mucormycosis in Indian population.

KEYWORDS : Mucormycosis, Amphotericin B, Rhino-orbital, Ophthalmoplegiabelonging to the order

Mucormycosis is caused by the fungus belonging to the order Mucorales. Humans acquire the infection predominantly by inhalation of sporangiospores while working in the farms, occasionally by ingestion of contaminated food or traumatic inoculation. *Rhizopus Arrhizus* is the most common agent causing mucormycosis across the globe, followed by *Lichtheimia*, *Apophysomyces*, *Rhizomucor*, *Mucor* and *Cunninghamella* species]. Mucormycosis is associated with angio-invasion leading high mortality [1]. The infection is increasingly reported across the globe in patients with diabetes mellitus, haematological malignancies, solid organ transplants, and immunosuppressive therapy. A similar rise in prevalence had been reported in a few studies from India . A recent study from India reported a rise of mucormycosis cases from 24.7 cases per year (1990–2007) to 89 cases per year (2013–2015) at a single tertiary-care hospital [2]. In a multicentre study from Indian ICUs, mucormycosis has been reported as 24% of all invasive mould infections [3].

In last one and half years world is facing CORONA Virus pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARSCoV-2), and has proved to be the most common risk factor for invasive mucormycosis. Till date, the COVID-19 has rapidly spread to 212 countries and caused nearly 170 million laboratory-confirmed cases and more than 3.6 million deaths globally.(4) The disease pattern of COVID-19 can range from asymptomatic, mild to life-threatening pneumonia with development of cytokine storm. Due to the associated comorbidities (e.g., diabetes mellitus, chronic obstructive pulmonary disease) and immunocompromised conditions (e.g. corticosteroid therapy, ventilation, intensive care unit stay), these patients are prone to develop severe opportunistic infections. There are reports of the development of severe opportunistic infections such as oropharyngeal candidiasis, pneumocystis jiroveci pneumonia, pulmonary aspergillosis, bloodstream candida infections, etc., in patients affected with COVID-19 disease.[5] There are also few isolated case reports of rhino-orbital mucormycosis in COVID-19 disease from India. Sen et al recently reported a series of six cases of COVID-19 disease with rhino-orbital mucormycosis.(6)

Consortium (EORTC/MSGERC) consensus, prolonged use of corticosteroids at a therapeutic dose of ≥ 0.3 mg/kg for at least three weeks in the last 60 days is considered a risk factor for invasive fungal diseases [7]. In COVID-19 positive diabetic patients inappropriate & overuse of steroids not only increases the risk of developing severe disease, but also predisposes them to invasive fungal infections [8].

Uncontrolled hyperglycaemia and precipitation of DKA is often observed due to corticosteroid intake. Low pH due to acidosis is a fertile media for mucor spores to germinate. Moreover, steroid use reduces the phagocytic activity of WBC (both first line and second line defence mechanism), causes impairment of broncho alveolar macrophages migration, ingestion, and phagolysosome fusion, making a diabetic patient exceptionally vulnerable to mucormycosis. [8].

Furthermore, IL-6-inhibiting drugs such as Tocilizumab, Itolizumab, Bevacizumab, IV Immunoglobulins, immunomodulators like Baricitinib used in treatment of cytokine storm in COVID 19 may cause immune dysregulation and increase the risk of secondary infections without providing substantial clinical benefit in patients with COVID-19 [9]. COVID-19 patients with acute respiratory distress might be susceptible to secondary infections as a result of immune dysregulation [10]. Patients infected with SARS-CoV-2 have declined levels of circulating lymphocytes and T cell subsets, resulting in suboptimal cell-mediated immune responses [11]. With these in mind, one can anticipate that critically ill patients with COVID-19 are at increased risk of developing severe invasive fungal infections.

Mucormycosis is an invasive fungal infection. It can involve nose, sinuses, orbit, central nervous system (CNS), lung (pulmonary), gastrointestinal tract (GIT), skin, jaw bones, joints, heart, kidney, and mediastinum (invasive type), but Rhino-Orbito-Cerebral mucormycosis (ROCM) is the commonest variety seen in 80%. [12]. It is often seen in patients with diabetic ketoacidosis or with uncontrolled diabetes mellitus. This intracranial involvement by mucormycosis has very high mortality.

However, in developing countries the existing data about Mucormycosis is inadequate and comes from small studies. Herein,

According to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research

We analysed the mucormycosis cases at tertiary care centre in Western Maharashtra. We retrieved the clinical details of all the patients of proven mucormycosis cases admitted at our hospital over the period of five months, from 1 January 2021 to 31 May 2021. The data was analysed to determine demographic characteristics, risk factors, comorbidities, site of infection, association with Covid 19 Infection & outcome of these patients. We also evaluated the outcomes of the patients who were treated with combined surgical and chemotherapeutic approach.

Methods

We conducted a retrospective observational study from 1 January 2021 to 31 May 2021 at tertiary-care centre in Maharashtra. The study was approved by the Institute Ethics Committee.

All the patients with proven/probable mucormycosis admitted during the above period were enrolled in this study. We defined proven mucormycosis as those individuals with clinically compatible disease and the demonstration of fungi in the tissue (or body fluids) either by direct microscopy (broad ribbon like aseptate hyphae), culture or molecular methods. The probable were defined as clinically compatible disease with relevant radiological findings on CT PNS / MRI Brain & orbit.

Study procedure

We collected the following information on a standardized case report form which includes: -

- (1) demographic details; (2) clinical features; (3) predisposing factors; (4) Association with COVID infection , (5) Details of Treatment received during COVID; (6) site of involvement; (7) BSL levels and ketoacidosis (8)Microbiological/ Radiological Findings (9) Treatment received at Tertiary care centre for Mucormycosis (10) Outcome.

Results –

Data of 50 patients admitted over the period from 1 January 2021 to 31 May 2021 at tertiary-care centre in Maharashtra with Mucormycosis was analysed during the study period. The proportion of male (n= 30) patients was higher than female patients (n= 20). The mean age of study population was found to be 40 years.

Sixty percent (60%) patients were farmers by occupation from rural area. Most common presenting complaint was Nasal blockage in 70% patients followed by orbital pain and eye swelling in 60%. Headache was present in 40%, Ophthalmoplegia, Proptosis and facial palsy in 20%, toothache in 20% and Hemiparesis in 10%. Two patients were having only symptom as vision loss.

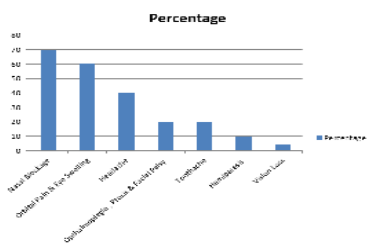


Figure 1: Symptomatology of mucor-mycosis

History of use of steroid was present in 80% patients while 20% denied steroid use. Out of 50 cases, 45 (90%) patients were diabetic, two patients were on immunosuppressant drugs for malignancy, 6 patients had additionally chronic kidney disease, 2 patients were without any comorbidity. On admission, 38 patients (76%) were having uncontrolled BSL levels (>200 mg/dl) and 14 patients (28%) were having Diabetic Ketoacidosis, 4 CKD patients were in fluid overload and in acute left ventricular failure.

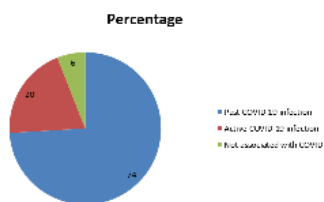


Figure 2: Association of COVID infection and Mucor-mycosis

Thirty-seven mucormycosis patients were having history of past COVID 19 infection in last one month. Amongst these, 31 patients were hospitalized and 6 were treated at home. All 31 patients were treated with steroids, either Methylprednisolone or Dexamethasone for an average duration of 20 days. Twenty patients received 5 doses of Remdesivir, 6 patients received Tocilizumab and 10 patients received Favipiravir. Four patients received both Remdesivir and Tocilizumab. Twenty six patients were on Oxygen Therapy for an average of 4 days and 2 patients were on Non Invasive Ventilation (NIV) support for 6 to 8 days.

Ten (20%) mucormycosis patients were having active COVID 19 infection. Amongst them 6 patients had moderate oxygen requirement and received Remdesivir. Symptoms of mucormycosis i.e. nasal blockage and pain over sinuses, redness of eyes, toothache started on an average of 6th day of diagnosis and treatment of covid 19 illness.

Rhino-orbital was the most common site involved in 80% patients followed by Rhino-orbito-cerebral in 12 % patients. Pansinusitis in 2% and palatal involvement in the form of palatal erosions was present in 2% patient. Pulmonary involvement was present in 4% patients.

KOH mount was positive in 40% patients. Other patients were diagnosed on basis of characteristic clinical features and radiological imaging studies (CT Chest/CT PNS+Orbit and MRI Brain + Orbit + PNS).

Forty four patients were started on conventional Amphotericin treatment with 1 mg /kg dose, while 6 CKD patients were started on Liposomal Amphotericin 3mg – 5 mg /kg dose. FESS procedure was performed on 40 patients, 2 underwent Partial Maxillectomy and 2 patients underwent eye exenteration.

Ten Mucormycosis patients (20%) succumbed during treatment due to intracranial extension and sepsis while 12 patients were discharged on oral Posaconazole maintenance treatment. Remaining 38 patients were still hospitalized and receiving Amphotericin treatment.

Discussion

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, the most important reasons being, negligence about the health, high prevalence of undiagnosed diabetes mellitus and poor monitoring and follow up.

Prior to COVID 19 Pandemic , In a multicentric study of 388 confirmed or suspected cases of Mucormycosis , Prakash et al found that 18% had DKA and 57% of patients had uncontrolled DM at the time of diagnosis [1]. Similarly, in a data of 465 cases of mucormycosis , Patel et al [2] have shown that rhino-orbital presentation was the most common (67.7%), followed by pulmonary (13.3%) and cutaneous type (10.5%). The predisposing factors associated with mucormycosis in Indians include DM (73.5%), malignancy (9.0%) and organ transplantation (7.7%). Presence of DM significantly increases the odds of contracting ROCM by 7.5-fold as shown in a prospective Indian study, prior to COVID-19 pandemic.

Whereas in COVID 19 Pandemic study by Satish et al [13] reported 11 case-series of mucormycosis in people with COVID-19 showed mucormycosis was predominantly seen in males (78.9%), both in people who were active (59.4%) or recovered (40.6%) from COVID-19. Hyperglycemia at presentation (due to pre-existing DM or new-onset hyperglycemia or new-onset diabetes or diabetic ketoacidosis [DKA]) was the single most important risk factor observed in majority of cases (83.3%) of mucormycosis in people with COVID-19, followed by cancer (3.0%). Pre-existing DM accounted for 80% of cases, while concomitant DKA was present in nearly 15% of people with mucormycosis and COVID-19. History of corticosteroid intake for the treatment of COVID-19 was present in 76.3% of cases, followed by remdesivir (20.6%) and tocilizumab (4.1%). Commonest organ involved with mucormycosis was nose and sinus (88.9%), followed by rhino-orbital (56.7%) and ROCM type (22.2%). Overall mortality was noted in 30.7% of the cases.

Also, other case series of COVID 19 and Mucormycosis reported from different parts of India also showed male predominance with mean age of 60 years with uncontrolled BSL and steroid use in 90% patient. (Sen

et al & Moorthy et al) (14) Mishra et al reported case series of 10 patients with Rhino-orbito cerebral mucor-mycosis in COVID 19 patients showed high mortality of 40% despite of Surgical and medical management. (15)

Sharma et al study in 23 COVID 19 with Mucormycosis patients showed Intracranial spread of 8.69%. (16)

Our study is having similar finding consistent with above studies.

We would like to note a few extra findings here. We observed that significant number of patients were farmers and most likely had daily exposure to mucor through soil, manure, decomposing vegetables. We also noted that the mean age of our patients was about 40 years which is almost 10 years younger than other studies. This finding may reflect the immunosuppression caused by steroids rather than only diabetes mellitus.

Despite the lack of published well-designed randomised clinical efficacy trials, it is generally agreed that appropriate and repeated aggressive surgical debridement coupled with effective antifungal medications is the cornerstone of management. Appropriate surgery is essential, particularly in rhino-orbito-cerebral disease and soft-tissue infections as Intracranial spread increases mortality by 10 fold.

The higher number of Mucor mycosis cases were found to be associated with recent COVID 19 infection. This association may be due to steroid use in these patients in turn causing hyperglycaemia (New as well as worsening of pre-existing DM) and may be due to immunosuppression caused by COVID 19 itself. Although the last point needs further elaboration and research.

Conclusion –

Next to COVID 19, Mucormycosis has become a serious health issue in India. High index of suspicion, early diagnosis, timely management with judicious use of Steroids, strict Blood sugar control are essential to decrease the burden of Mucormycosis in Indian population.

Financial support & Sponsorship: NIL

Conflicts of interest: NIL

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