

Covid 19 Associated Mucormycosis: An Epidemic

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Abstract

Patients with Coronavirus disease (COVID-19) are commonly treated with broad spectrum antibiotics, glucocorticoids and/or immune modulators. This has led to development/exacerbation of opportunistic fungal infections. Mucormycosis is one such disease that complicates the course of severe COVID-19. Here we present a study of 15 patients and their epidemiology who were diagnosed with Covid19 Associated Mucormycosis (CAM) at our institute - the highest number of cases in literature.

Keywords: Mucormycosis; COVID19; Immunosuppression

Introduction

The coronavirus disease 2019 (COVID-19) infection caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been declared a global pandemic and has been posing major health related issues. These problems may be attributed to the wide range of disease pattern, bacterial and fungal co-infections or adverse reactions to the drugs used in treatment. There also may preexist co-morbidities (diabetes mellitus, lung disease) that adds to the burden of primary disease management.

Systemic glucocorticoids have been shown to improve survival in COVID-19 infected patients. Unfortunately, the widespread use of glucocorticoids can lead to secondary bacterial or fungal infec-

tions. However, Mucormycosis is uncommonly suspected or diagnosed.

India is witnessing a major surge in the number of cases of Mucormycosis and many states, including Rajasthan, has declared it as an epidemic and falls under the category of Notifiable Diseases. The primary reason that appears to be facilitating Mucorales spores to germinate in people with COVID-19 is an ideal environment of low oxygen (hypoxia), high glucose (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), high iron levels (increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-

mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators.

There are only a few case reports found on CAM in literature and the aim of this study was to report the pattern of CAM in this part of the country and discuss the various aspects of etiopathogenesis of CAM for the benefit of fellow practitioners. Here we present the largest number of cases reported in literature of patients diagnosed with CAM.

Materials and Methods

The study was conducted at the department of Otorhinolaryngology and Head and Neck Surgery, American International Institute of Medical Sciences, Udaipur, Rajasthan. It was a prospective study conducted where first 15 patients of CAM were included in the study. These patients were studied on the bases of their age, sex, complaints on presentation, status of Covid19 infection, history of hospitalization in recent past, history of Diabetes Mellitus (type I/type II), use of steroids/immunomodulators/monoclonal antibodies in recent past, involvement of orbit/brain, base line haemoglobin, blood glucose levels, SpO₂, primary site of infection and fungal culture reports. These values were then tabulated and appropriate test were applied to evaluate significance.

Results

We included total 15 patients in this study. There were 4 females and 11 males. There were maximum 9 patients in the age group of 21 - 40 years, while only 2 patients in the age group 41 - 60 (Graph 1). According to history, the most common presenting complaint was facial pain while pus discharge from gums was the east common complaint (Graph 2). 7 out of 15 patients were Positive on RTPCR test for COVID 19 infection on admission while only 8 had negative RTPCR test (Graph 3). All these 15 patients had history of hospitalization for COVID 19 infection in the last 1 month. On asking for history of Diabetes Mellitus, 11 patients had history of DM type II, 1 patient had DM type I, 2 patients were recently diagnosed DM type II after COVID 19 infection, while 1 patient had no history of DM (Graph 4). On evaluating their previous treatment history, 14 out of 15 patients were administered steroids for their treatment of COVID 19 infection while 1 patient was undergoing local treatment by a village quack (documents unavailable). 6 patients out of 15 had some involvement of orbit (reduced visual

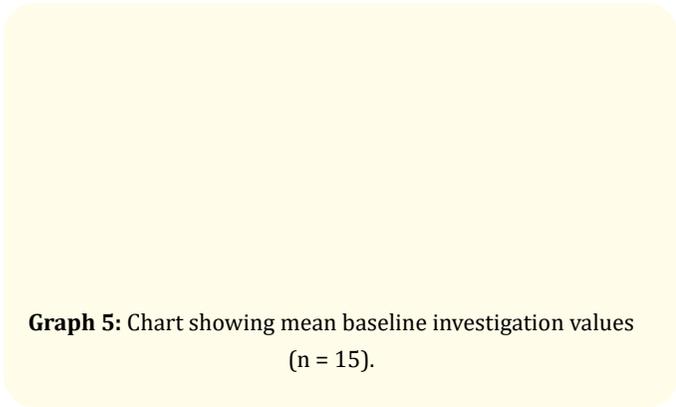
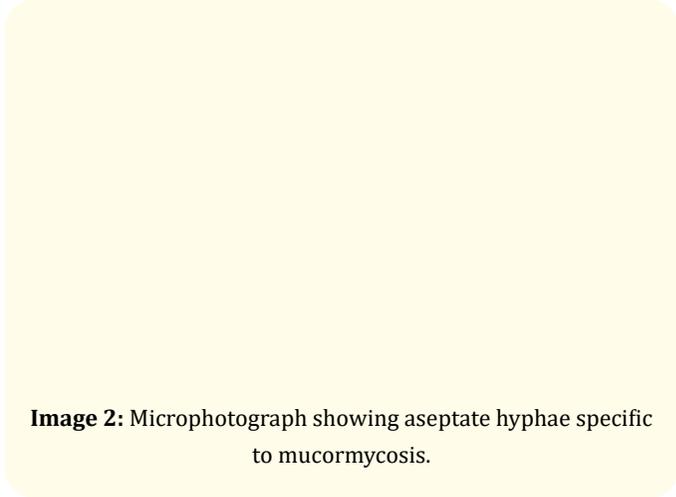
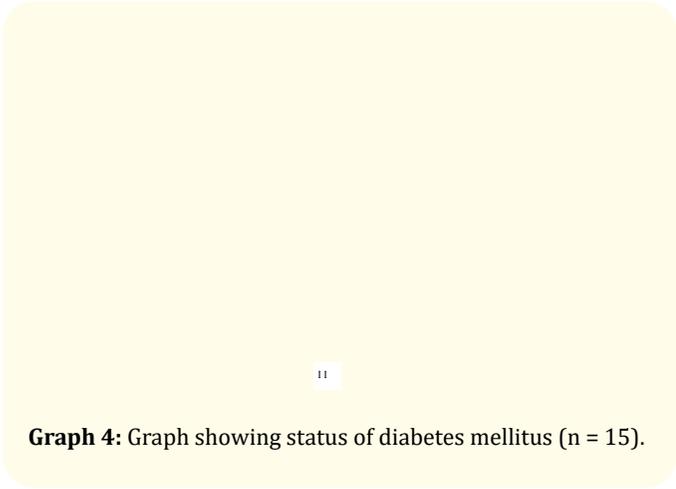
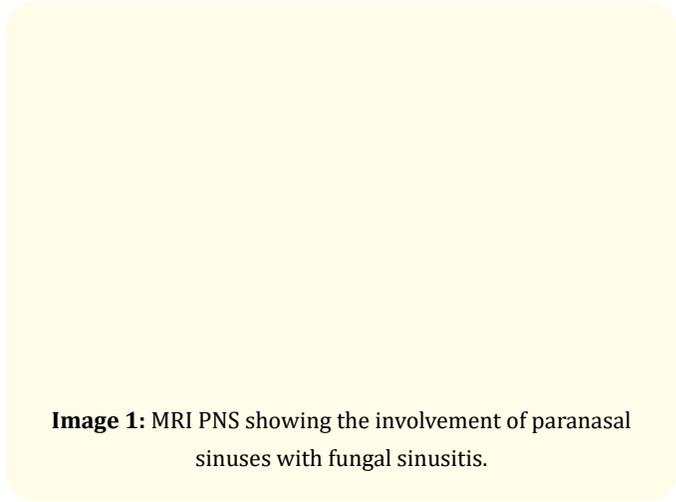
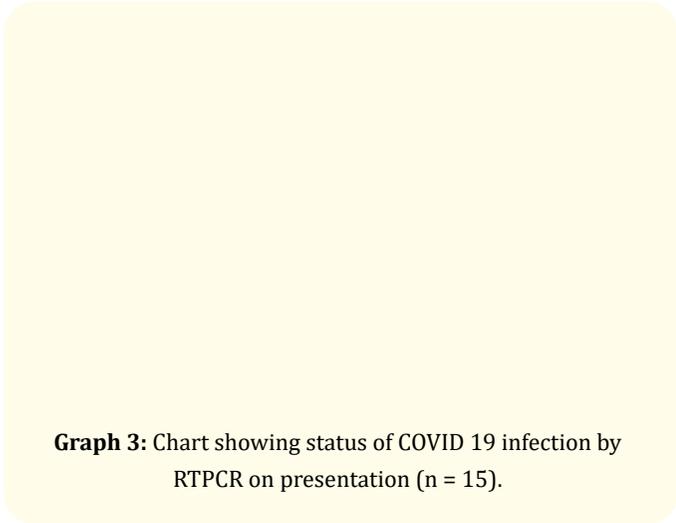
acuity, restricted movement or complete loss of vision) while rest had no visual symptoms. The average baseline haemoglobin, blood glucose levels and SpO₂ are depicted in graph 5. The commonest site of involvement of mucormycosis was paranasal sinuses (commonest maxilla) followed by orbit and then palate (Image 1). The culture tissue of all the patients tested positive for Aseptate hyphae specific to mucormycosis on KOH study (Image 2).

Discussion

The impact of COVID 19 infection has been severe across the globe. While physical health has taken a troll, mental, economic

Graph 1: Distribution of cases according to age in years (n = 15).

Graph 2: Distribution of cases according to chief presenting complaint (n = 15).



and social imbalances have affected every individual in varying degrees of magnitude [1]. Healthcare workers have been exposed to various challenges in treating these patients, mainly due to shortage of drugs and oxygen in recent times, often referred to as second wave of the said disease. The recent development of emergence of opportunistic infections has posed a new threat to healthcare workers in the treatment of COVID 19 infection.

A complex interplay of factors, including preexisting diseases, such as diabetes mellitus, CKD, HIV AIDS, previous respiratory pathology, use of immunosuppressive therapy, the risk of hospital-acquired infections, and systemic immune alterations of COVID-19

infection itself may lead to secondary infections, which are increasingly being recognized in view of their impact on morbidity and mortality [2]. In a recent review, 62/806 (8%) patients had secondary bacterial or fungal infections during hospital admission [3].

Current guidelines in India recommend intravenous methylprednisolone 0.5 - 1 mg/kg/day for three days in moderate cases and 1 - 2 mg/kg/day in severe cases [4]. 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 [5]. The guidelines specifically mention the risk of developing a secondary infection [6].

There are specific pathophysiologic features of COVID-19 that may permit secondary fungal infections, including a propensity to cause extensive pulmonary disease and the subsequent alveolo-interstitial pathology that may enhance the risk of invasive fungal infections. Second, the immune dysregulation associated with COVID-19, with reduced numbers of T lymphocytes, CD4+T, and CD8+T cells, may alter innate immunity [7].

Mucormycosis is an acute opportunistic infection caused by several fungi belonging to phylum Glomeromycota. These saprophytic fungi are found ubiquitously in the soil and environment. The alarming rise in the number of cases of Rhino-orbital-cerebral mucormycosis has been attributed to rampant use of industrial oxygen, poor hygienic condition of humidifiers and immune dysregulation as mentioned above. This has led to declaration of CAM as an epidemic in many parts of India, including Rajasthan.

Although there is no gender predisposition of mucormycosis, we have seen a significant difference between males and females. Males are affected more than females in our study. This is similar to the finding reported by Singh A., *et al.* in a systemic review of COVID 19 associated Mucormycosis [8]. In the current study, no patient was seen less than 20 years of age, while there were 9 patients in the age group of 21 - 40 years, 2 patients between 41 - 60 years while 4 patients more than 61 years. Mucormycosis is known to affect elderly patients as Diabetes, CKD and use of immunomodulators for chronic illnesses is common in patients more than 50 years of age. But the contrary pattern seen in current study could be due to 2 reasons- 1) increasing number of cases of juvenile DM (type I) and early onset of DM type II in recent years due to changing

lifestyles and 2) increasing number of severe COVID 19 infection in young individuals due to nationwide vaccination drive targeting senior citizens.

CAM is reported to have occurred in patients who have recovered from COVID 19 infection. But in our study, 7 patients were found to be COVID positive on RTPCR test. This poses a therapeutic challenge as treatment armamentarium includes steroid therapy which increases the spread of fungus. Poor pulmonary function of these patients makes them unfit for surgical debridement. The commonest site of infection is paranasal sinuses, commonest being maxilla and ethmoid. This can be correlated with facial pain and swelling being the commonest symptoms on presentation. Orbital invasion is the next common site of involvement followed by palatal erosion. This is why eye pain and swelling, visual disturbance and pus discharging gums and palate are the subsequent presenting feature. These patients also complained of occasional nasal stuffiness or blood stained discharge from nose. This is consistent with the findings of Singh A., *et al.* Mucormycosis 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-orbital-cerebral Mucormycosis is the commonest variety seen in clinical practice world-wide [9].

The baseline haemoglobin and SpO₂ levels of all the patients was found to be above average. Mean haemoglobin in our study was 12.6 gm% while all patients except 1 had more than 95% oxygen saturation levels. The blood glucose levels, however, was deranged in all 17 patients suggesting a strong correlation between deranged blood glucose levels and occurrence of fulminant opportunistic infections.

Early surgical debridement and antifungal treatment (Amphotericin B) remains to be the mainstay of treatment for CAM and we also follow the standard protocols. The epicentre surgical debridement is partial maxillectomy with pan sinus debridement. This may be achieved endoscopically (modified Denker's approach) or open approach (Weber Ferguson's approach). Orbital exenteration is adjuvant in cases with patients with complete vision loss. Amphotericin B (liposomal) is administered in the dose of 5 mg/kg/day for minimum 3 weeks and daily renal function and electrolyte monitoring. The above patients are still under treatment and the final survival outcome is yet to be evaluated.

Conclusion

In conclusion, there are various opportunistic infections that pose major health problem in patients with infections like COVID-19 or patients with immunosuppression. Mucormycosis is a life threatening disease and only timely diagnosis and treatment can save the lives of such patients. Thus, primary treating physicians should be aware of such infections and any unexplained symptom must be evaluated. Also these patients must be regularly monitored for any derangement in body fluid profile that may give these infections a chance to dwell. If diagnosed with CAM, early debridement and antifungal therapy remains to be mainstay of treatment to save lives.

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