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Mucormycosis in COVID-19 Patients- A case series

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Abstract

Mucormycosis is an opportunistic fungal infection caused by fungi classified within phygomycetes, subclass Zygomycetes, order Mucorales, family Mucoraceae.

Corona virus disease 2019 (Covid 19) is a contagious infection caused by SARS- COV-2.

During the second wave of Covid-19, India experienced an epidemic of mycormycosis in Covid 19 patients.

In this paper, we report 8 cases of mucormycosis associated with Covid 19 over a period of 6 months and the risk factors associated with it. Diabetes mellitus and steroid treatment were identified as major risk factors for Covid associated mucormycosis in our study. However other risk factors also described in literature, which are associated with mucormycosis such as renal failure, organ transplant, immunosuppressive therapy, AIDS, malignancy.

Early diagnosis, control of risk factors and early management is required for better outcome in these cases.

Keywords: Covid – 19, Mucormycosis, Diabetes mellitus, Corticosteroid therapy.

Introduction

The pandemic corona virus disease (Covid 19) is caused by novel severe acute respiratory syndrome corona virus 2. (SARS- COV-2), has affected millions of people worldwide. Covid 19 has been associated with several opportunistic bacterial and fungal infections. [1]

During the second wave of Covid 19, several cases of Covid 19 associated mucormycosis (CAM) have been reported from various parts of the world, particularly from India. [2]

In May 2021, the Government of India declared mucormycosis as a modifiable disease in many states, under the Epidemic Diseases Act 1897. [3]

Mucormycosis is an opportunistic fungal infection caused by genus Rhizopus, Mucor, Rhizomucor, Cunningamella, Licthemia, Syncephalastrum, Sakseneae and Cokeromyces of order Mucorales and class Zygomycetes.

These are saprophytic fungi found in soil and environment.[4]

The clinical types of mucormycosis include pulmonary mucormycosis, gastrointestinal mucormycosis, cutaneous mucormycosis, rhino-orbito-cerebral mucormycosis and disseminated mucormycosis.[5]

It is an acute opportunistic and aggressive fulminant invasive infection that can occur in immunocompromised patients such as uncontrolled diabetes, renal failure, organ transplant, long term corticosteroid and immunosuppressive therapy, AIDS, malignancy and corona virus disease 2019 (Covid 19) infections. [6]

In the paper we report 8 cases of rhino-orbital mucormycosis (ROM) and other fungal infection associated with mucormycosis in Covid 19 patients on histopathology in specimens received in department of pathology, at a tertiary care centre of Navi Mumbai, India during the year 2021.

Case Presentation

Sn.	Age In Years	Sex M/F	Symptoms	Post Covid	H/O Diabetes	H/O Steroid Treatment	Organs Involved	Special Stain	Diagnosis
1	65	M	Nasal obstruction, Loss of vision in right eye	Yes	Yes	No	Middle & inferior nasal turbinate, Eye ball	PAS positive	Mucormycosis
2	47	M	Facial Pain. Headache	Yes	Yes	Yes	Left & right nasal cavity and sinuses	PAS & GMS positive	Mucormycosis
3	70	M	Pus drainage from anterior maxillary alveolus	Yes	Yes	Yes	Maxilla	PAS & GMS positive	Mucormycosis. Maxillary bone involved
4	62	M	Left eye proptosis, vision loss, CNS involvement	Yes	Yes	Yes	Left eye ball segment of maxillary sinus, Wall of orbit, left and right nasal cavity	Pas and GMS positive	Mucormycosis & Aspergillosis. Angioinvasion and bony invasion noted
5	47	M	Nasal blockage	Yes	Yes	Yes	Right and left maxillary sinus, Right Turbinate, Left inferior & middle Turbinate	Pas and GMS positive	Mucormycosis and Aspergillosis
6	49	M	Polypoidal mass arising from left middle turbinate & Nasal obstruction	Yes	Yes	No	Left middle turbinate	Pas and GMS positive	Mucormycosis
7	73	M	Right nasal block with nasal discharge	Yes	No	No	Right nose	Pas and GMS positive	Mucormycosis
8	54	F	Nasal blockage	Yes	No	No	Nasal tissue	Pas positive	Mucormycosis

We received 8 specimens for histopathology in department of pathology, two were from orbit, rest 6were tissues from nasal cavity and sinuses along with clinical history. All the cases seen in patients between 49 to 75 year. Maximum cases were found in male patients. Two cases were seen in patients with loss of vision and proptosis. Majority of cases presented with nasal blockage. All the cases were developed in covid patients during therapy. Six of the eight patients were having history of diabetes. Four of the eight patients were having history of steroid therapy during covid. All the cases were belonging to Rhino – orbital Mucormycosis. On H&E section, Broad pauciseptate ribbon like hyphae was seen with irregular branching amidst areas of necrosis. PAS stain showed irregular pink color fungal hyphae. GMS stain demonstrated black color fungal hyphae. In one of the case mucormycosis was associated with Aspergillosis, in which we could demonstrate characteristic fruiting bodies. Two of the cases showed bony invasion by fungus and one case showed Angioinvasion.

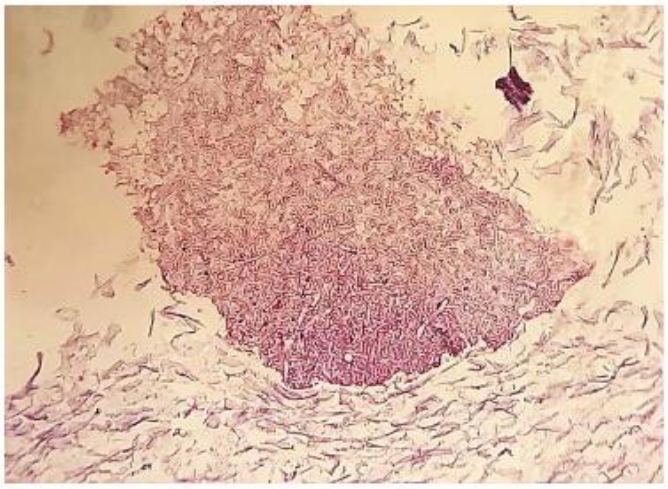

Figure 1: H & E; 10x, Colony of fungal hyphae

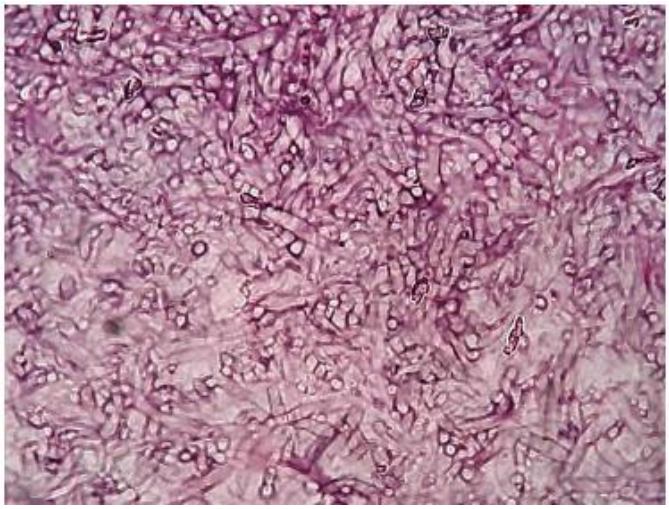

Figure 2: H & E; 40x, wide non-septate hyphae with irregular branching

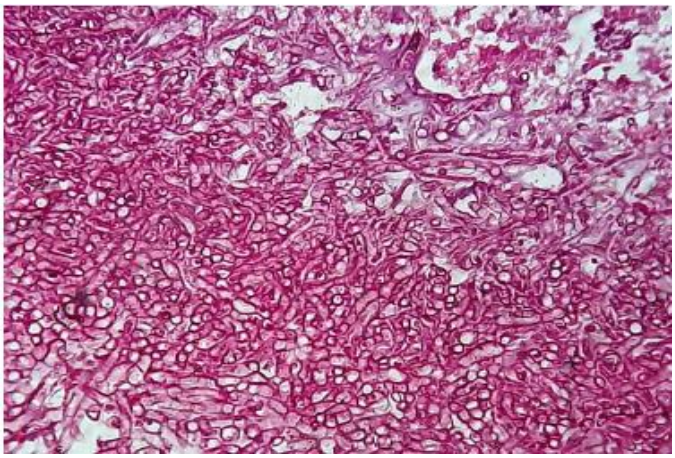

Figure 3: PAS stain; 40x: Broad, irregular branching hyphae

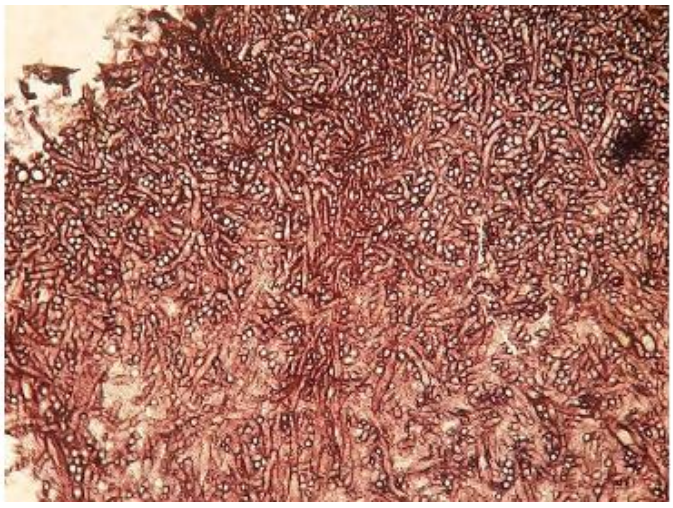

Figure 4: GMS Stain; 40x, Black colored hyphae

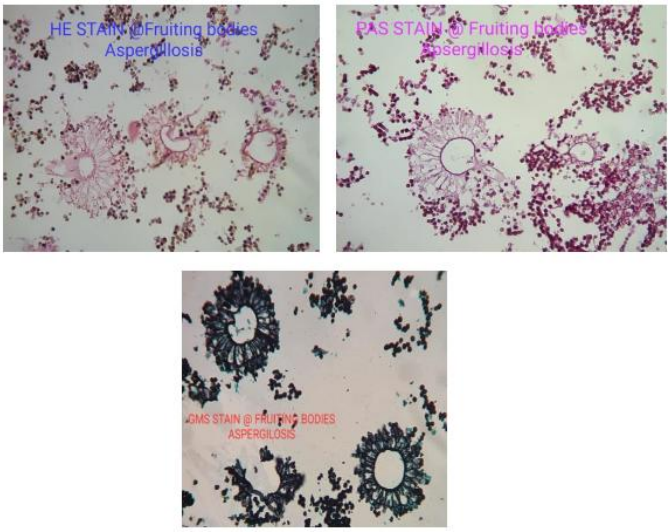

Figure 5: H&E, PAS &GMS Stain; Fruiting bodies of Aspergilus.

Discussion

In pandemic of Covid 19, with the absence of an effective vaccine or antiviral therapy, supportive treatment with glucocorticoids and remdesivir played a vital role in Covid 19management. [6]Steroids can cause drug induced hyperglycaemia by making liver resistant to insulin, and exacerbate hyperglycaemia in patients of diabetes mellitus. Higher blood sugar levels and more acidic blood creates a fertile environment for fungi to thrive. [7,8]Glucocorticoids increase the risk of secondary infections. The immune dysregulation caused by reduced numbers of T lymphocytes, CD4+ and CD8+ T cells by the virus, further increase the risk of infections in COVID 19 patients. [9, 10]

Diabetes mellitus can cause mucormycosis by the following ways:

1. Diabetes is the chronic inflammatory state causing endothelial dysfunction. High blood glucose increases the expression of glucose regulatory protein 78 (GRP 78) receptor in human endothelial cells. GRP 78 serves as a receptor for vascular invasion by mucorales. [11] The endothelial invasion by mucorales is mediated by spore cot protein homologs (COtH) which act as a ligand for GRP 78. [12]
2. High blood glucose causes glycosylation of transferring and ferritin which results in reduction in iron binding capacity and increases free iron. Free iron supports the growth of Mucorales. The acidosis in diabetic ketoacidosis (DKA) decreases the binding of iron to transferring and increases free iron in circulation. [13] High glucose and high iron content seen in DKA also causes over expression of GRP 78 which results in further endothelial invasion by mucorales. [14]

COVID 19 can cause mucormycosis by the following ways

1. SARS COV- 2 infection causes endothelial dysfunction due to direct viral invasion and host inflammatory responses. [15] Endothelial damage promotes the invasion of mucorales.
2. COVID 19 often causes immunosuppression by impairment of CD4+ cells, CD8+ cells and antigen presenting dendritic cells, which results in secondary or opportunistic fungal infections like mucormycosis. [13]

COVID 19 and diabetes have bidirectional relationship. On one hand, diabetes mellitus can cause severe COVID 19 due to impairment of immune responses which results in poor ability to fight against infection. On the other hand, COVID 19 complicates diabetes mellitus in the following two ways.

1. COVID 19 causes poor glycaemic control having insulin resistance and impaired insulin secretion which leads to diabetic ketoacidosis. [16]
2. The SARS COV-2 enters into host cells using Angiotensin Converting Enzyme 2 (ACE 2) receptors. [14] ACE 2 receptors present in the

pancreas allow the entry of SARS COV-2 into beta cells. The damage of beta cells promotes diabetes mellitus. [17]

In our case series, 6 of 8 patients had history of diabetes mellitus.

Four patients received corticosteroids for treatment.

However, we could not assess the dose and duration of steroids, since most of the patients in our study were treated for COVID 19 elsewhere. Our case series supports the study conducted by Patel et al [6] and Rashbi et al [18] that diabetes mellitus and corticosteroids are the prime factors predisposing covid associated mucormycosis.

Mucormycosis infections are characterized by extensive Angioinvasion that results in vessel thrombosis and subsequent tissue necrosis. Ischemic necrosis of infected tissues can prevent delivery of leukocytes and antifungal agents to the foci of infection.

This angioinvasion likely contributes to the capacity of the organism to hematogenously disseminate to other target organs.[19] In our series, one case showed angioinvasion. Data from observational studies have suggested that patients who were receiving metformin as treatment for diabetes at the time of their Covid-19 diagnosis had a lower risk of progressing to severe Covid-19.[20] So Proper control of Diabetes mellitus is required. Rudramurthy et al reported high fungal spore count in hospital air. The outbreak of CA Min India may be due to combined action of COVID 19, high burden of uncontrolled diabetes mellitus, inappropriate corticosteroid therapy, along with high fungal spore count in Indian hospital environments.[21]Early diagnosis and treatment is required for optimal management of these patients so histopathological examination is the best tool to diagnose these cases. Diagnosing mucormycosis almost always requires Histopathologic evidence of fungal invasion of the tissues. Culturing organisms from a potentially infected site is rarely sufficient to establish the diagnosis of mucormycosis because the causative agent is ubiquitous, may colonize normal persons, and is a relatively frequent laboratory contaminant. Additionally, the organism may be killed during tissue grinding, which is routinely used to process tissue specimens for culture. Thus, a sterile culture does not rule out the infection. Furthermore, waiting for the results of the fungal culture may delay the institution of appropriate therapy.[22]

The mainstay of treatment of mucormycosis is use of amphotericin B and surgical debridement. In this scenario, histological examination can result in optimal uses of such nephrotoxic drug and radical surgeries. [6]

Conclusion

The study of series of our cases concludes that Diabetes mellitus and Corticosteroid therapy are two major risk factors for the outbreak of mucormycosis in Covid – 19 Patients. Therefore Control of blood sugar level in Diabetes and judicious use of steroids are required for prevention of mucormycosis in these patients.

Early diagnosis of mucormycosis is important to start the appropriate treatment at the earliest and to prevent disabilities and complications related to it. One has to keep in mind, that like Covid 19 infection, other viral infections will be going to occur in future so we must be aware of risk factors associated with debilitating fungal infections.

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