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"A DEADLY COMBINATION OF MUCORMYCOSIS AND COVID-19": A RETROSPECTIVE STUDY FROM TERTIARY CARE INSTITUTE IN KOTA, SOUTH–EAST RAJASTHAN, INDIA

Dr. Seema Malav[1], Chetna Jangid[2] and Dr. Bhupendra Kumar Mandawat[3*]

[1]Senior Demonstrator, Department of Microbiology and Immunology, Government Medical College, Kota, Rajasthan, India.

[2]M.Sc. Medical Microbiology, Department of Microbiology and Biotechnology, University of Kota, Kota, Rajasthan, India.

[3]Professor, Department of Microbiology and Immunology, Government Medical College, Kota, Rajasthan, India.

***Corresponding Author: Dr. Bhupendra Kumar Mandawat**

Professor, Department of Microbiology and Immunology, Government Medical College, Kota, Rajasthan, India.

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ABSTRACT

Background: COVID-19 is associated with an increased risk of secondary infections.The recent rise in the number of cases of COVID-19 during the second wave of pandemic has been associated with a rise in cases of fungal infections such as Mucormycosis(MM) especially among critically ill patients. **Objective:** Main aim of this study is to find out occurrence of infection by mucorales group, Aspergillus and other groups of fungus and find out clinical features, site involvement of body with underlying risk factors in CAM patients. **Method:** This is a retrospective observational study of 214 cases of Mucormycosis in COVID-19 patients. The collected data had detailed age, gender, RT-PCR for COVID-19, underlying disease, uncontrolled diabetes, use of steroid, broad-spectrum antibiotics and method of oxygen delivery system. We did direct KOH and culture on SDA for clinically diagnosed cases Mucormycosis who are RT-PCR COVID-19 positive or history of RTPCR positive a few days back. **Result:** Out of 214 clinically defined cases of Mucormycosis in COVID-19 patients Males were 63% whereas females were 37% and Male to female ratio was 1.7:1. Mean age of the patient was 43± 11 years in the present study. 45% cases of Mucormycosis were COVID-19 RT-PCR positive. 47.2% were positive for direct KOH, 33.18 % positive for culture on SDA. In growth isolates 50.70 % were Rhizopus sp, 21.13 % were specified Mucorales, 28.17% were non specified Mucorales and 18.31 % has mixed growth of Rhizopus and Aspergillus sp. Most of the patients presented in OPD with complaints of headache lethargy and mild body ache. Most common co-morbidity was in COVID-19 RT-PCR positive Mucormycosis cases were Diabetes mellitus as compared to malignancy and other kidney diseases 72% patients have uncontrolled diabetes and Most common site of involvement is rhinoorbital sinusitis. **Conclusion:** Mucormycosis gained attention for its wide spread existence during this period of the second wave of COVID-19. In COVID-19 pandemic surge of cases of Mucormycosis in COVID-19 positive patients were especially with uncontrolled diabetes mellitus and on treatment with steroids and immunosuppressive drugs.

KEYWORDS: RT-PCR (Reverse transcriptase polymerase chain reaction), Mucormycosis (MM), CAM (COVID-19 Associated Mucormycosis), DM (Diabetes Mellitus), KOH (Potassium hydroxide), SDA (Sabouraud Dextrose Agar)

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causative agent of Coronavirus disease 2019 (COVID-19) is an emergency global pandemic. Other than Acute respiratory distress syndrome (ARDS) COVID-19 patients were found to have immune-suppression with low CD4+T and CD8+T cells.[1] This results in a diverse range of bacterial and fungal infections that may co-exist with possible association with a preexisting morbidity (diabetes mellitus, lung disease) or may develop as a hospital-acquired infection. The complications are very commonin both current cases and recovered cases of COVID-19 infections. Most common secondary complication are bacterial and fungal infection.[2] The most common risk factor associated with Mucormycosis is diabetes mellitus in India.[2] In Rajasthan many cases of systemic Mucormycosis are reported. In tissue these fungal infection are seen as broad non septate hyphae with predilection to invade deep blood vessels causing embolism formation leading

to extensive necrosis of surrounding area. Common fungus species are from order Mucorales like Rhizopus, Mucor, Rhizomucor, Cunninghamella and Absidia. The prevalence of Mucormycosis in India is approximately 0.14 cases per 1000 population, about 80 times the prevalence in developed countries.[3] There are some preexisting conditions increases prevalence of fungal infection in COVID-19 patients theses are indiscriminate use of antimicrobial agents like imipenem and glucocorticoid drugs. Occasional reports of COVID-19–Associated Mucormycosis (CAM) from various centers and a series of 18 cases from South India increased our concerns about CAM.[4] After increased incidence of candidemia and invasive aspergillosis in COVID-19 patients awareness of possible fungal co-infections increased among clinicians and microbiologists. India is one of the countries worst affected by the COVID-19 pandemic. Thus, we would expect India to have many CAM cases.[5,6] One study reported invasive fungal infections in ≈6% of hospitalized COVID-19 patients (6). A 2019 nationwide multi-center study of 388 confirmed or suspected cases of mucormycosis in India prior to COVID-19, (Prakash et al) found that 18% had DKA and 57% of patients had uncontrolled DM.[7] Similarly, in a data of 465 cases of mucormycosis without COVID-19 in India, (Patel et al) has shown that rhino-orbital presentation was the most common (67.7%), followed by pulmonary (13.3%) and cutaneous type (10.5%).[8] Presence of DM significantly increases the odds of contracting ROCM (Rhino-Orbito-Cerebral Mucormycosis) by 7.5-fold (Odds ratio 7.55, P ¼ 0.001) as shown in a prospective Indian study, prior to COVID-19 pandemic[8,9] Many studies suggest a familiar connection of mucormycosis, diabetes and steroids, in people with COVID-19.[10]

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 compared to developed countries, in a recent estimate of year 2019-2020.[11,12,13,20] Mucormycosis is more often seen in immunocompromised individuals and complications of orbital and cerebral involvement are likely in diabetic ketoacidosis and with concomitant use of steroids. The epidemiology of Mucormycosis is evolving as new immunomodulating agents are used in the treatment of cancer, COVID-19 and autoimmune diseases. The modern diagnostic tools lead to the identification of previously uncommon genera/species such as Apophysomyces or Saksenaeacomplex. In addition, new risk factors are reported from Asia, including post-pulmonary tuberculosis and chronic kidney disease. New emerging species include Rhizopus homothallicus, Thamnostylumlucknowense, Mucor irregularis and Saksenaeaerythrospora. Global mortality of Mucormycosis is 46% (Chander et al).[12] Diagnosis of Mucormycosis remains challenging. Clinical approach to diagnosis has a low sensitivity and specificity, it helps however in raising suspicion and prompting the initiation of laboratory testing. Histopathology, direct examination and culture remain essential tools, although the molecular methods are improving. In other words, India has highest cases of the Mucormycosis in the world. Notwith-standing, India is already having second largest population with diabetes mellitus (DM) and was the diabetes capital of the world, until recently.[14] India has a high burden of Mucormycosis among patients with uncontrolled diabetes mellitus, and many severe COVID-19 patients have diabetes.

AIMS AND OBJECTIVES

1. Occurrence of infections by Mucorales group of fungus, Aspergillus and other groups of fungus in COVID-19 positive patients.
2. To find out clinical features, site involvement of body with underlying risk factors in CAM (COVID-19 Associated Mucormycosis) patients.

MATERIALS AND METHODS

Study design: We conducted a retrospective observational based study at Government Medical College Kota, Rajasthan, India from May 2020 to April 2021. All demographic and clinical data of clinically suspected cases and culture confirmed cases of Mucormycosis from the mycology laboratory of MBS hospital were collected and documented in pre-structured Performa. Study Objectives was to find the rise of cases of Mucormycosis during the second wave of pandemic in hospital-based population.

Sample Processing: Tissue biopsies, nasal scrapings, nasopharyngeal swabs from Mucormycosis-affected anatomical sites were used for conventional microscopy and fungal culture. Direct microscopy performed by using direct KOH mount. For keratinized tissue and plucked hair use KOH 10% for few minutes, for nails use 20% KOH and for soft tissue and bone we did overnight incubation. The samples were inoculated on 2 sets of Sabouraud dextrose agar media (HiMedia) (pH 5.5) and incubated at 25°C and 37°C. Positive cultures were identified by macroscopic and microscopic characteristics. Culture on SDA at 25 C reveals white cottony woolly colonies with bottle filled colonies also known as lid lifters after sporulation colonies become brown black later give salt and pepper appearance. In the case of aspergillus, the colony is smoky green velvety to powdery or black depending on species reverse is white. In lactophenol cotton blue (LPCB) mount broad aseptate hyaline hyphae with big sporangiophore are seen. Rhizopus bears rhizoid and mucor no rhizoid and in some isolates we seen septate branched delicate hyphae with acute angle branching seen.

Compilation of Data: All demographic and clinical data was collected and documented in pre-structured Performa.

Statistical Analysis of Data: Collected Data was entered into Microsoft Excel spreadsheet. Categorical variables

were expressed as percentage basis and analyzed as a chi-square test, continuous data expressed as mean and Standard deviation and p value less than 0.05 was taken as statistically significant for all statistical analysis done using epi infotm.

RESULT

We studied 214 cases of clinically suspected and culture confirmed case of COVID-19 Associated Mucormycosis (CAM). Males were 63% whereas females were 27% and Male to female ratio was 1.7:1. Range of patient's ages was from 26 years to 73 years. Most of the patients are above 50 year no one below 26 years. Mean age of the patient was 43± 11 years in the present study. A total of 214 samples were included in this study in which 106 (49.53%) samples were positive for fungal filaments in either KOH mount or fungal growth on SDA. Out of 214 only 101 were Direct KOH pofsitive, 73 had Broad aseptate hyphae, 17 had septate branched hyphae and 11 had Mixed septate and aseptate hyphae and 71 were culture positive. 45% cases of Mucormycosis were COVID-19 RT-PCR positive. Our study showed that most common co-morbidity in Mucormycosis are Diabetes mellitus followed by COVID-19 RT-PCR positive cases as compared to malignancy and other kidney diseases.

Table 1: Gender Distribution of Study Population.

Gender	No. of patients N=214	%
Male	135	63.00 %
Female	79	37.00 %
Total	214	100 %

Table 2: Age Distribution of Study Population.

Age	No. of patients N=214	%
1-20 years	00	00 %
21-40 years	45	21.03 %
41-60 years	111	51.87 %
>61 years	58	27.10 %
Total	214	100 %

Table 3: KOH mount test and Fungal culture growth results of Study Population.

Total no. of patients N=214			
Name and Type of test	**Fungal Culture Positive (+ve) on SDA media**	**Fungal Culture Negative (-ve) on SDA media**	**Total**
KOH Test Positive (+ve)	66	35	101 (47.20%)
KOH Test Negative (-ve)	05	108	113 (52.80%)
Total	71 (33.18%)	143 (66.82%)	214 (100%)

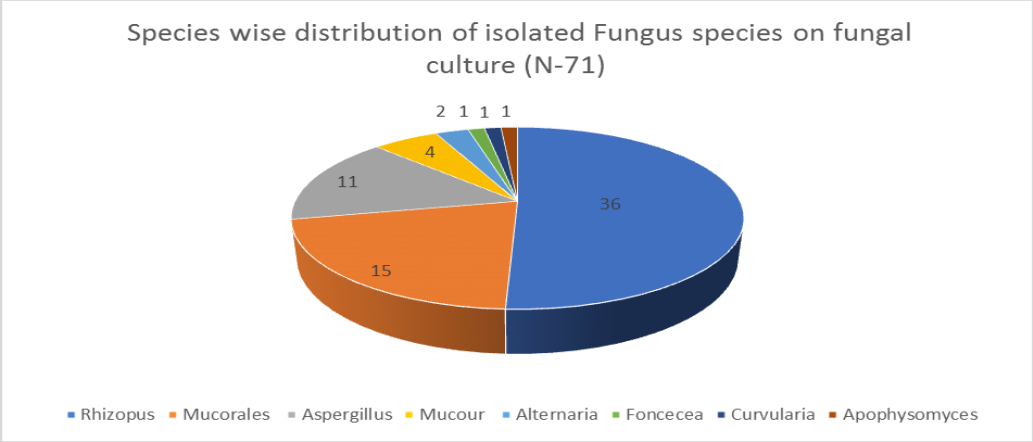
Table 4: Characteristic morphology observed in KOH mount test.

Observation	No. of patients N=101	%
Broad aseptate hyphae	73	72.28 %
Septate branched hyphae	17	16.83 %
Mixed septate and aseptate hyphae	11	10.89 %
Total	101	100 %

Table 5: Species wise distribution of isolated Fungus species grown on fungal culture.

Type of fungus	*No. of total growth N=71*	*%*
Rhizopus	*36*	*50.70 %*
Mucorales	*15*	*21.13 %*
Aspergillus	*11*	*15.49 %*
Mucour	*4*	*5.63 %*
Alternaria	*2*	*2.82 %*
Foncecea	*1*	*1.41 %*
Curvularia	*1*	*1.41 %*
Apophysomyces	*1*	*1.41 %*
Total	*71*	*100 %*

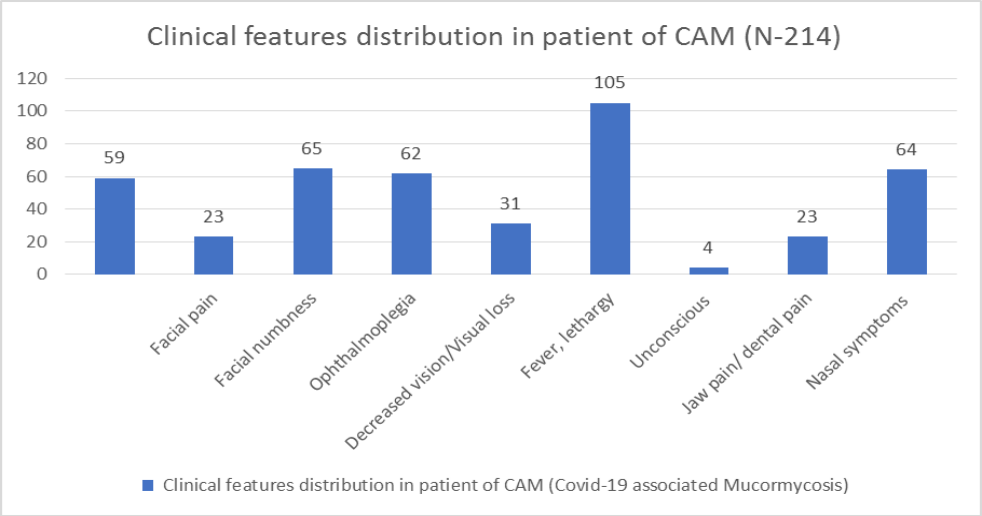
#Mixed growth was occurring in 13 samples that was Rhizopus plus Aspergillus.



Graph 1: Species wise distribution of isolated Fungus species grown on fungal culture.

Table 6: Clinical features distribution in patient of CAM (COVID-19 Associated Mucormycosis).

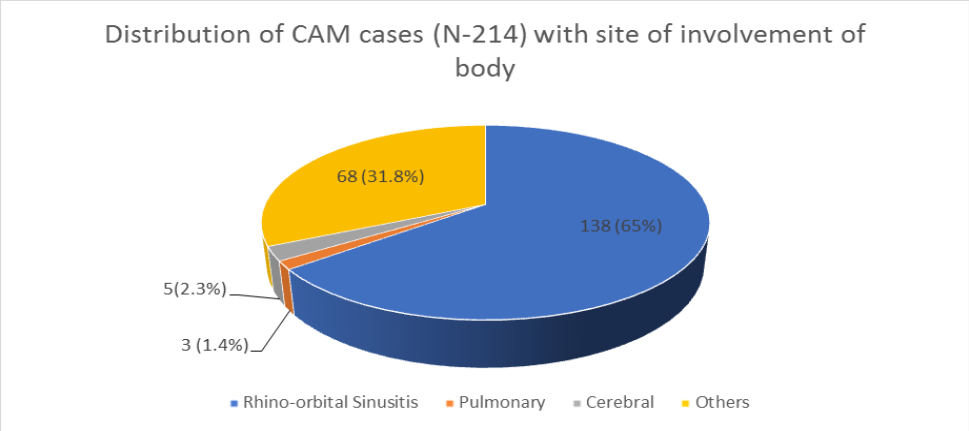
Clinical features	No. of patients N=214	%
Asymptomatic, mild body ache, headache	59	27.5 %
Facial pain	23	10.7 %
Facial numbness	65	30 %
Ophthalmoplegia	62	29 %
Decreased vision/Visual loss	31	14.5 %
Fever, lethargy	105	49 %
Unconscious	4	1.8 %
Jaw pain/ dental pain	23	10.7 %
Nasal symptoms (congestion, rhinorrhoea, epistaxis, black discharge)	64	29.9 %



Graph 2: Clinical features distribution in patient of CAM (COVID-19 Associated Mucormycosis).

Table 7: Distribution of CAM cases (COVID-19 Associated Mucormycosis) with site of involvement of body.

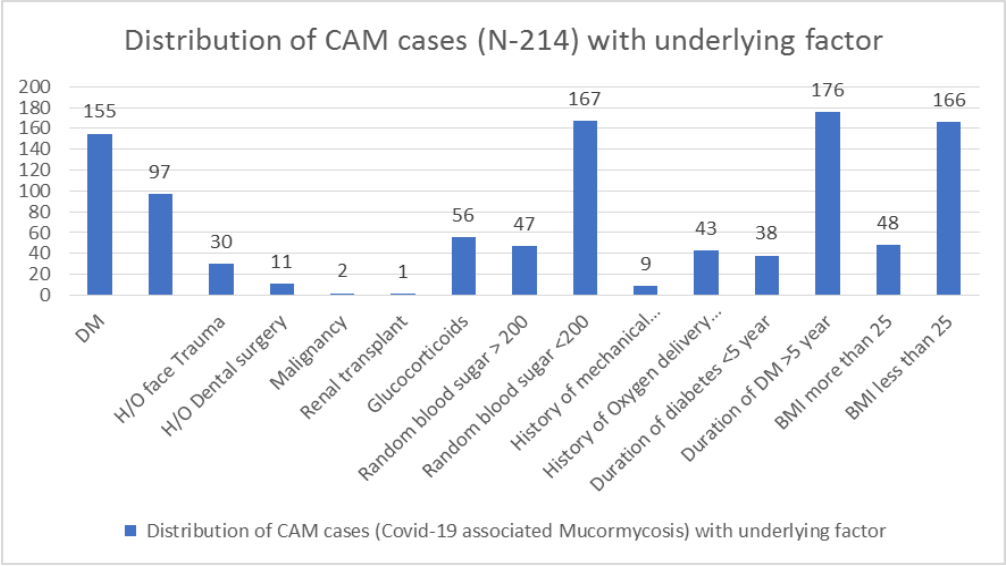
Site of involvement	**No. of patients N=214**	***%***
Rhino-orbital Sinusitis	*138*	*65 %*
Pulmonary	*3*	*1.4 %*
Cerebral	*5*	*2.3 %*
Others (GIT, skin, jaw, bone, joint, heart, kidney)	*68*	*31.8 %*
Total	*214*	*100 %*



Graph 3: Distribution of CAM cases (Covid-19 Associated Mucormycosis) with site of involvement of body.

Table 8: Distribution of CAM cases (COVID-19 Associated Mucormycosis) with underlying factor.

Underlying disease	**No. of patients N=214**	*%*
Diabetes Mellitus (DM)	*155*	*72 %*
COVID-19 RT-PCR positive (currently or within one month)	*97*	*45 %*
H/O face Trauma	*30*	*14 %*
H/O Dental surgery	*11*	*5 %*
Malignancy	*2*	*0.9 %*
Renal transplant	*1*	*0.4 %*
Glucocorticoids	*56*	*26 %*
Random blood sugar > 200	*47*	*22 %*
Random blood sugar <200	*167*	*68 %*
History of mechanical ventilation	*9*	*4 %*
History of Oxygen delivery by face mask	*43*	*20 %*
Duration of diabetes <5 year	*38*	*17.7 %*
Duration of DM >5 year	*176*	*82 %*
BMI (Body Mass Index) more than 25	*48*	*22 %*
BMI (Body Mass Index) less than 25	*166*	*77 %*



Graph 4: Distribution of CAM cases (COVID-19 Associated Mucormycosis) with underlying factor.

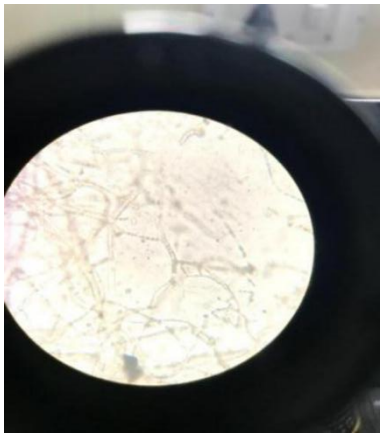


Fig. 1: KOH mount (broad aseptate hyphae)

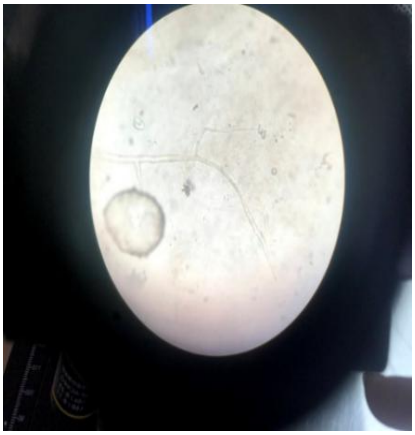


Fig. 2: KOH mount (wide angle branching 90degree)

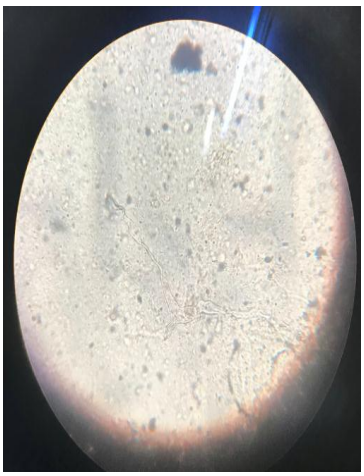


Fig. 3: KOH mount broad (aseptate ribbon like hyphae)

Fig 4: Mucorales growth on SDA.

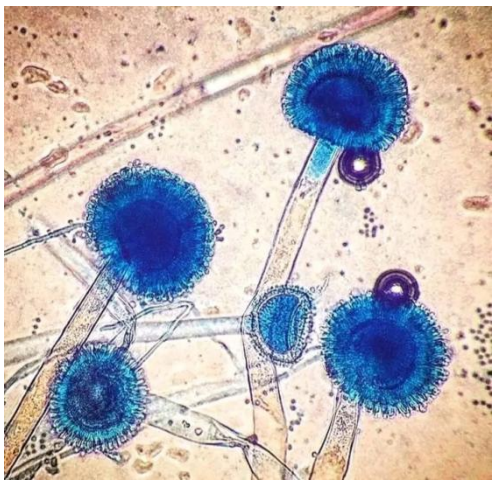


Fig. 5: LCB (Lactophenol Cotton Blue)Staining-Aspergillus flavus. Fig. 6: LCB (Lactophenol Cotton Blue) Staining-Aspergillus niger.

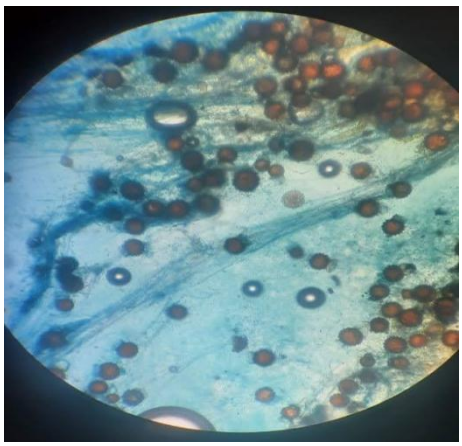


***Fig. 7: LCB(Lactophenol Cotton Blue)Staining-Rhizopus homothalicus. Fig. 8: LCB (Lactophenol Cotton Blue) Staining*-Rhizopus with rhizoid.**

DISCUSSION

Mucormycosis by black fungus is a lethal opportunistic disease with yearly incidence of 0.005 to 1.7 cases per one million population.[20,22] We studied 214 suspected and confirmed cases of Mucormycosis most of the patients are above 50 year no one below 26 years. Range of patients' ages was from 26 years to 73 years. Males were 63% whereas females were 27% and Male to female ratio was 1.7:1. Mean age of the patient was 43± 11 years. Before the COVID-19 era, Mucormycosis is known for its poor prognosis, especially with delayed management may lead to a high mortality rate. Noha et al reported mean age 52± year[21] and one other study reported 54 years. In our study most patients came to hospital OPD with complaints of lethargy and inactiveness followed by fever, facial numbness, loss of taste, ophthalmoplegia and loss of smell. 14% of patients start to lose their vision before coming to the doctor. Four patients came in unconscious state in which two had diabetic ketoacidosis. In present study most common form of Mucormycosis was rhino-orbital -sinusitis 64% followed by others which includes gastrointestinal, joints heart kidney skin palatal osseous and disseminated. noha et al reported 100% cases of sinunasal Mucormycosis A 2019 nationwide multi-center study of 388 confirmed or suspected cases of Mucormycosis in India prior to COVID-19, (Prakash et al) found that 18% had DKA and 57% of patients had uncontrolled DM.[7] Similarly, in a data of 465 cases of mucormycosis without COVID-19 in India, (Patel et al) has shown that rhino-orbital presentation was the most common (67.7%), followed by pulmonary (13.3%) and cutaneous type (10.5%).[8] In this study 50% cases of growth positive isolates were Rhizopus, 18% were mixed growth Rhizopus and aspergillus. Noha et al reported 77% cases of mixed growth of Aspergillus and muco**.** Similar to our study Chakrawati et al reported 76% case of Mucormycosis in COVID-19 cases most common cause Rhizopus arrhizus, patel et al 2020 reported DM in 73% rinoorbital 67% mc sp Rhizopus 74.7.[19,13] In the present study 45% cases of MM were COVID-19 RT-PCR positive. There are many studies reporting incidence of fungal infection in COVID-19 positive patients. COVID-19 increases the chance of thrombosis and mucor is a saprophytic fungus that has a tendency to grow on dead and ischemic tissue. In China there are some studies supported the theory that COVID-19 patients has high tendency for mucormycosis Chen et al. found five cases of pulmonary fungal infection in COVID-19 patients.[15] Yang et al. found 3% patients with pulmonary fungal co-infection in 52 critically ill patients.[16] A German study found COVID-19-associated invasive pulmonary aspergillosis in 26.3% of critically ill patients with moderate to severe ARDS.[18-22] In another study from Netherlands, out of 31 ICU patients, there were six patients (19.4%) presumed invasive pulmonary aspergillosis.[19-22] Severe respiratory infection by COVID-19 leads to immunological dysrregularities and risk factor like uncontrolled diabetes excessive use of steroid and brad spectrum antibiotics haematological malignancy make patient is vulnerable history of oxygen delivery system. In the present study 20% of patients had a history of oxygen delivery by oxygen face mask. Main oxygen delivery system among the patient was reported that they never clean the face mask used for oxygen therapy according to guidelines according to some reports unclean and filthy method of giving oxygen to patient resulted in increased cases of CAM Arora et al.[18] Our study showed that most common co-morbidity is in Mucormycosis with COVID-19 RT-PCR cases is Diabetes malitus as compared to malignancy and other kidney diseases. India already has large population of diabetes which seems as important risk factor of CAM. 22% patient random blood sugar is more than 200 mg/dl. 82%had DM from more than 5 year, and 46% had BMI more than 25kg/mt2, A k singh et al a large meta-analysis reported DM as independent risk factor for CAM in 2018. Prevalence DM in India 11% 79 million people affected by DM john et el reported 94% cases of DM,[10] The major 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 (Odds ratio 7.55, P ¼ 0.001) as shown in a prospective Indian study, prior to

COVID-19 pandemic.[8,9] In a recent systematic review conducted in 2021 by John et al.[10] that reported the findings of 41 confirmed Mucormycosis cases in people with COVID-19, DM was reported in 93% of cases, while 88% were receiving corticosteroids. These findings are consistent with our findings of even larger case series of 101 Mucormycosis cases (95 confirmed and 6 suspected) in Covid-19, where 80% cases had DM, and more than two-third (76.3%) received a course of corticosteroids. Collectively, these findings suggest a familiar connection of Mucormycosis, diabetes and steroids, in people with COVID-19.[10], in other studies with pre-COVID-19 pandemic in non covid patient still DM is most commonly associated. One study reported presence of diabetes, hematologic malignancies, and corticosteroid use in most of the patients India has a high prevalence rate of type 2 diabetes mellitus, it is also a well-known risk factor for developing fungal infections.[22] This is in accordance with results in our study as the most common associated disorder was diabetes mellitus (27.8%), In this study 26% patients received glucocorticoid therapy during COVID-19 infection. Corticosteroids are an important predisposing factor for CAM. They are potent immunosuppressants with a wide range of effects on various aspects of immunity.[8] Additionally, hyperglycemia induced by corticosteroids further increased the risk.[9] Corticosteroids impair the ability of phagocytes to clear the fungi. Dexamethasone and other corticosteroids are widely used to manage COVID-19, and their contribution to the pathogenesis of CAM appears undeniable A K singh et al.[17] However few deaths were also occurs in our referal centre but due to Central and State government policy we have not mentioned here. The Diagnosis of Mucormycosis remains challenging. Clinical approach to diagnosis has a low sensitivity and specificity, it helps however in raising suspicion and prompting the initiation of laboratory testing. Histopathology, direct examination and fungal culture remain essential tools, although the molecular methods are improving. In second wave of COVID-19 pandemic there are surge of cases of Mucormycosis in COVID-19 patients from India in our institute we also had a spike in number of Mucormycosis cases in this retrospective study we collect the data of CAM to understand more about underlying risk factor.

LIMITATION OF STUDY

Limitations of this study include this study is a retrospective study so we are unable to assess the exact incidence and prevalence of CAM in different risk groups although we describe those risk factors and could not properly evaluate the causal effect relationship. We exclude some patients from study due to incomplete data.

SUMMARY AND CONCLUSION

In COVID-19 pandemics has lead to increase prevalence of Mucormycosis due to some common risk factor such as DM, corticosteroid therapy, immunosuppressed, condition long use of broad spectrum antibiotics and corticosteroid therapy, uncontrolled DM most common form of rhinoorbital sinusitis and most common cause is rhizopus. Invasive mould infections can lead to fatal outcomes, if not detected timely. Morbidity and mortality can be reduced by ensuring access to appropriate diagnostic testing and access to specialty care, including surgical intervention when appropriate. One must bear in mind the possibility of mould infection in post-COVID patients with associated risk factors and co- morbidities, who are more prone to develop such deadly infections. Management of COVID-19 should also involve avoiding inappropriate steroid therapy and strict attention to glycemic control.

DECLARATIONS

Conflict of interest: The authors have no conflict of interest.

Human and Animal Rights and Informed Consent: This article does not contain any studies with human or animal subjects performed by authors.

Bio-Safety: All standard precautions, bio-safety measures & Biomedical Waste Management in our study according to Biological Waste Management's Rules 2016 and its new amendment were observed.

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