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Post COVID- 19 Mucormycosis- Systematic Review

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ABSTRACT

Introduction: For the management of the COVID-19, systemic glucocorticoids are given. The fungal infections of these patients are increasingly being reported. Hence in this study we intend to conduct a systemic review about the cases reported of the Mucormycosis.

Material and method: Online data was collected from the search engines of EBSCO, Pubmed, Google Scholar, Scopus. The searched terms were COVID 19, CORONA, SARS-CoV-2, fungal infections, Mucormycosisetc. The study articles were collected that from Jan 2020 to May 2021. Based on the PICOS guidelines the systemic review was performed.

Results: From a total of 20 articles on the post COVID fungal infections, only 9 articles were considered for the study that fit the criteria of mucormycosis. There was a significant association seen between the comorbidities and the treatment done for the COVID19 that may have been resulted in the fungal infection.

Conclusion: Patients with diabetes mellitus and multiple risk factors may be at a greater risk for being infected with the mucormycosis. Simultaneous glucocorticoid

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therapy may increase the risk of mucormycosis. A high index of suspicion and aggressive management is required to improve outcomes.
Keywords: COVID19, Mucormycosis, Diabetes Mellitus, Corticosteroids.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic continues to impact life worldwide. While various treatment options have been appraised, none except glucocorticoids have been shown to be better for the survival. But the injudicious use of the glucocorticoids may lead to secondary bacterial or fungal infections. Invasive pulmonary aspergillosis complicating the course of COVID-19 is widely seen;[1] but, mucormycosis is uncommonly diagnosed. It is clear from the present studies that there is a great variation in the sociodemographic, clinical course, and the prognosis.[2-5] A thorough understanding of these features is necessity for the proper treatment planning and establishing a strategy for facing future pandemics.In this study we conducted a systematic review of literature to identify cases of COVID-19 associated mucormycosis (CAM) and describe their clinical features, risk factors, and outcome.

MATERIAL AND METHODS

Online data was collected from the search engines of EBSCO, Pubmed, Google Scholar, Scopus. The searched terms were COVID 19, CORONA, SARS-CoV-2, fungal infections, Mucormycosisetc. The study articles were collected that from Jan 2020 to May 2021. Based on the PICOS guidelines the systemic review was performed. Total participants, sociodemographic, study type, clinical features, comorbidities, treatment given were noted for all the studies. The studies that included the any other fungal infections were excluded.

RESULTS

Of the nine cases reported thus far 3 from the United States of America and 2 from India. One case each was reported from Brazil, Italy, and the UK. The mean age was 57.5 years, and 7 were male. Diabetes mellitus was the most common predisposing condition. Increased serum creatinine was noted in majority. Usually it was seen after 2 weeks. The most common site of involvement by mucormycosis was rhino-orbito-cerebral (n = 3), pulmonary (n = 3), gastric (n = 1), and disseminated (n = 1). Invasive fungal infections like mucormycosis share similar risk factors, clinical presentation, and radiology.

Table 1 Comparison of the variables among the various included studies.

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Hanley et al/ UK[6]	22/male	Obesity (BMI 48.8)	COVID ARDS (mechanically ventilated)	None mentioned	Linezolid	Lymphocyte count and serum creatinine, not provided	No (Autopsy diagnosis)	Lungs	Died (D27)	No traditional risk factors
		Hypothyroidism	Pulmonary emboli	Remdesivir	Meropenem			Hilar lymph nodes		
					Caspofungin			Heart and pericardium		
								Brain		
								Kidney		
Wertheman-Ehrenreich/ USA[10]	33/female	Hypertension	Altered mentation, proptosis	Remdesivir	Vancomycin	Lymphopenia (5.9%)	Yes (suspected at presentation)	Rhino-orbito-cerebral	Died (D26)	-
		Asthma	DKA and rhino-orbital mucormycosis	Convalescent plasma	Piperacillin tazobactam	Elevated serum creatinine (2.28 mg/dL)				
		Previously undiagnosed diabetes mellitus		No mention of glucocorticoids	Amphotericin B (formulation not mentioned)					
Mehta et al/ India[7]	60/male	Diabetes mellitus	COVID ARDS requiring mechanical ventilation	Inj methylprednisolone 40 mg BD	Meropenem	Lymphopenia (9.60%)	Yes (Symptoms developed at D10)	Rhino-orbital	Died	-
		Peripheral vascular disease due to diabetes		Dexamethasone 4 mg BD	Oseltamivir	Elevated serum creatinine (1.57 mg/dL)				
				Tocilizumab 400 mg	Amphotericin (0.5 mg/ kg/day, conventional)					

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Author/country	Age in years/sex	Comorbid illness	Clinical presentation	Treatment for COVID-19	Other treatments	Investigations	Antemortem diagnosis of CAM	Organs involved by CAM	Outcome	Remarks
Hanley et al./ UK[6]	22/male	Obesity (BMI 48.8)	COVID ARDS (mechanically ventilated)	None mentioned	Linezolid	Lymphocyte count and serum creatinine, not provided	No (Autopsy diagnosis)	Lungs	Died (D27)	No traditional risk factors
		Hypothyroidism	Pulmonary emboli		Meropenem			Hilar lymph nodes		
					Caspofungin			Heart and pericardium		
								Brain		
								Kidney		
Werthman-Ehrenreich/ USA[10]	33/female	Hypertension	Altered mentation, proptosis	Remdesivir	Vancomycin	Lymphopenia (5.9%)	Yes (suspected at presentation)	Rhino-orbito-cerebral	Died (D26)	-
		Asthma	DKA and rhino-orbital mucormycosis	Convalescent plasma	Piperacillin tazobactam	Elevated serum creatinine (2.28 mg/dL)				
		Previously undiagnosed diabetes mellitus		No mention of glucocorticoids	Amphotericin B (formulation not mentioned)					
Mehta et al./ India[7]	60/male	Diabetes mellitus	COVID ARDS requiring mechanical ventilation	Inj methylprednisolone 40 mg BD	Meropenem	Lymphopenia (9.60%)	Yes (Symptoms developed at D10)	Rhino-orbital	Died	-
		Peripheral vascular disease due to diabetes		Dexamethasone 4 mg BD	Oseltamivir	Elevated serum creatinine (1.57 mg/dL)				
				Tocilizumab 400 mg	Amphotericin (0.5 mg/ kg/day, conventional)					

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Monte junior ESD et al./Brazil[8]	86/male	Hypertension	COVID ARDS and diarrhea	Hydrocortisone	Ceftriaxone	Lymphopenia (5.3%)	No	Gastric (presentation with melena, drop in hemoglobin, and large ulcers identified on endoscopy)	Died (D5)	No traditional risk factors
					Azithromycin	Elevated serum creatinine (2.34 mg/dL)				
					Oseltamivir					
Placik et al/ USA[9]	49/male		COVID ARDS	Remdesivir	Ceftriaxone	Lymphocyte count and serum creatinine, not provided	Yes (D14 developed spontaneous pneumothorax)	Pulmonary mucormycosis with bronchopleural fistula and pneumothorax	Died (D21)	Surgery and amphotericin for mucormycosis (6 days)
				Tocilizumab	Azithromycin					
				Dexamethasone	Amphotericin B (formulation not mentioned)					
Mekkawy et al/ USA[11]	60/male	Diabetes mellitus (HbA1C 14%)	COVID ARDS (mechanically ventilated)	Remdesivir	Cefepime	NA	Yes (D10 of hospitalization)	Rhino-orbital	Died (D31)	The patient had symptoms suggestive of mucormycosis on D2 of hospitalization (D8 of illness)
		Asthma		Dexamethasone (6 mg)	Vancomycin					
		Hypertension		Convalescent plasma therapy (single session)	Amphotericin B (liposomal)					
					Endoscopic surgical debridement					

DISCUSSION

More than 10 lakh lives were taken away by the COVID19 and the related events. So far only the prevention may be suggested from all the agencies for the COVID-

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19. Remdesivir and the Glucocorticoids perhaps are the only drugs proven to be useful in COVID-19. Glucocorticoids are cheap, easily available, and have been shown to lower death rate in hypoxemic patients. [3-5] But, glucocorticoids may lead to secondary infections. Furthermore, the immune dysregulation caused by the virus and the use of concurrent immunomodulatory drugs such as Tocilizumabamy increase the risk of infections in COVID-19 patients.[4-9] A lack of clinical suspicion and difficulty isolating the causative fungi might add to the under diagnosis of Mucormycosis. The biomarkers like beta-d-glucan and galactomannan, that help in the diagnosis of the invasive aspergillosis, are not available for Mucormycosis. Diabetes mellitus has been connected with severe COVID-19. Those with diabetes are at an increased risk of death than those without.[10-15] Further, poorly controlled diabetic patients may also have renal dysfunction. The incidence of multiple risk factors or comorbid illnesses in severe COVID-19 patients, along with the added immunosuppression caused by glucocorticoids, rises the net state of immune suppression, thereby predisposing them to invasive mold infections. Glycated hemoglobin becomes undependable in the presence of severe anemia, especially in patients undergoing hemodialysis.[16] Preceding studies have shown that Amphotericin B is usually well-tolerated and can be safely given in subjects undergoing dialysis.[17, 18] The current guideline for the management of mucormycosis recommends liposomal amphotericin B at a dose of 5–10 mg/kg per day. In the absence of central nervous system involvement, a dose of 5 mg/kg is suggested.[19] In a randomized controlled trial of 201 patients with invasive mold disease, liposomal amphotericin used at 3 mg/kg/day was effective but safer and better tolerated than 10 mg/kg/day dose amphotericin.[20] The time and the continuation of the treatment is based on the status of the patient.Pulmonary mucormycosis is diagnosed readily, and mortality has improved over time.[20] Control of hyperglycemia, early treatment with liposomal amphotericin B, and surgery are essential for the successful management of mucormycosis.[19, 22, 23] Firstly, hyperglycemia is aggravated by the most effective therapy for severe COVID-19, namely glucocorticoids. Coexisting ARDS and multiorgan dysfunction preclude timely diagnostic imaging and testing.[13] Finally, the hospitals are overwhelmed by COVID-19 patients, and essential services, including diagnostics and surgeries, could be significantly shortened.[24] Henceforth, the mortality due to fungal infections maybe even higher than that observed in non-COVID patients.[21, 23, 25].The development ofMucormycosis may possibly be attributed to the use of glucocorticoids and proposes a need for their judicious use. Therefore, the use of glucocorticoids in mild COVID-19 cases (without hypoxemia) or the utilization of higher doses of glucocorticoids should be evaded. Additionally, in the absence of a clear benefit, drugs targeting immune pathways such as Tocilizumab should be avoided.[5].

CONCLUSION

It can be concluded that the doctors caring for critically ill COVID-19 patients must

be conscious of serious infections that can confound the course of COVID-19. A high degree of clinical suspicion is essential to diagnose pulmonary mucormycosis. Prompt diagnosis and timely management are essential to improve outcomes in pulmonary mucormycosis.

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