Review Article

COVID-19 associated pulmonary mucormycosis: A systematic review of published cases with review of literature

Deependra K. Rai

Additional Professor & Head, Department of Pulmonary Medicine, All India Institute of Medical Sciences, Patna, Bihar, India

Abstract

Background: There is sharp rise in cases of Coronavirus disease 2019 (COVID-19)-associated mucormycosis worldwide and specially during second wave of COVID-19 pandemic. This systemic review was conducted to characterize pulmonary mucormycosis associated with COVID-19 infection. **Materials and Methods:** A systematic literature search was conducted in the electronic database of PubMed and Google Scholar from 1st January 2020 to June 5, 2021 using keywords. Details of all the cases that reported pulmonary mucormycosis in people with COVID-19 so far, were retrieved and analyzed. **Result:** Total 9 articles of pulmonary mucormycosis with COVID-19 infection were reported in the database of PubMed and Google Scholar. Only one case till date was reported from India, others are from USA (n-3), Italy (n-2), France (n-1), UK (n-1), and Arizona (n-1). Pooled data from this study showed mucormycosis was predominantly seen in males (8 male, 1 female). The most common comorbidities associated were diabetes (n-3), hematological malignancy, (n-2) and end-stage renal disease (n-2), while 2 cases did not show any associated comorbidity. All the cases were having severe COVID-19 infection and 7 out of 9 patients were in ICU and on mechanical ventilation at the time of diagnosis. None of the cases associated with rhino-orbital-cerebral mucormycosis (ROCM) except 1 patient with sinus involvement. Mortality was found in 7 out of 9 patients. **Conclusion:** There is a need to keep a high index of suspicion in patients with severe COVID-19 infections, diabetic, and received treatment in ICU with ventilator support for early diagnosis and treatment. Although Mucor is less common than Aspergillus infection, it is associated with higher mortality.

Keywords: COVID-19, mucormycosis, pulmonary, pulmonary cavity, SARS COV-2

Introduction

COVID-19 disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first time was detected in December 2019 in Wuhan, China.[1] Studies have shown that 14% of COVID-19 pneumonia cases progress to become severe, and 5% of infected patients require intensive care unit (ICU).[2] Once disease becomes severe, COVID-19 cases may present with features of acute respiratory distress syndrome (ARDS), multi-organ dysfunction, and finally death. Although super added infections were rarely reported in the early phase of pandemic, now there are several reports of fungal infection associated with COVID-19 infection. Especially critically ill patients who were admitted to the intensive care unit (ICU) and required mechanical ventilation, or those who have longer hospital stays, were more likely to develop fungal coinfections.[3] There are lots of literature described about COVID-19 associated pulmonary aspergillosis (CAPA) and Candida infection but few cases of pulmonary mucormycosis. Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported, especially in second wave of pandemic in India. It is important for primary care physician to aware about this fatal opportunistic infection, especially in patient recovered from severe COVID-19 infection. Although very few cases of COVID-19 associated pulmonary mucormycosis (CAPM) have been described, how these cases presented, importance of

Address for correspondence: Dr. Deependra K. Rai, Additional Professor & Head, Department of Pulmonary Medicine, All India Institutes of Medical Sciences, Phulwarisharif, Patna - 801 505, Bihar, India.
E-mail: deependra78@gmail.com

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early treatment, and there outcome must be aware by primary physician.

The classical risk factors predisposing patients to mucormycosis are uncontrolled diabetes mellitus, neutropenia, hematological malignancies, organ transplantation, trauma and burn, and use of immunosuppressant such as corticosteroids.[4-9] Furthermore, diabetes is one of the most common comorbidity complicating COVID-19 management.[2] Other factors in COVID-19 could be low oxygen (hypoxia), hyperglycemia, acidic medium (metabolic acidosis), and increased ferritins promote infection by Mucor.

Mucormycosis word generally exchange with zygomycosis is an angioinvasive disease caused by mold fungi of the genus Rhizopus, Mucor, Rhizomucor, Cunninghamella, and Absidia of Order- Mucorales, Class-Zygomycetes.[10] The *Rhizopus Oryzae* is most common type and responsible for almost 60% of mucormycosis cases in humans.

In immunocompromized patients, the main route of infection seems to be through inhalation of spores causing pulmonary infection. Pulmonary mucormycosis typically develops in patients with profound neutropenia and graft-versus-host disease, while diabetic patients typically present with rhino orbital disease. This infection causes angioinvasion leading to thrombotic infarction and necrosis of lung parenchyma.[11] It has rapid course and thus can spread locally to surrounding structures like lymph nodes, chest wall, mediastinum, and diaphragm.[12] There are lots of case series of rhinoorbital cerebral mucormycosis with COVID-19 infection but hardly any case series characterized pulmonary mucormycosis with COVID-19 infection. This systemic review was conducted to find out a patient's characteristics having pulmonary mucormycosis and COVID-19 infection.

Materials and Methods

A systematic literature search was conducted in the electronic database of PubMed and Google Scholar from 1st January 2020 to June 5, 2021 using keywords "COVID-19", "SARS CoV-2", and Pulmonary or Lung or LUNG and "Mucormycosis" or Zygomycosis. Details of all the cases that reported pulmonary mucormycosis in people with COVID-19 so far, were retrieved. Patients with rhino orbital cerebral mucormycosis without pulmonary involvement were excluded. Characteristics of each patient were collected on excel sheet and analyzed on various endpoints and outcomes. Two authors independently checked the quality of data.

Results

Total 9 articles (case report) of pulmonary mucormycosis with COVID-19 infection were reported in the database of PubMed and Google Scholar in given defined time frame.[13-21] Clinical characteristics of all cases are summarized in Tables 1 and 2. All the cases were confirmed cases of COVID-19 infection positive by RTPCR of Nasopharyngeal sample. Only one case is reported from India till now; others are from USA (n-3), Italy (n-2), France (n-1), UK (n-1), and Arizona (n-1). Pooled data from this study showed mucormycosis was predominantly seen in males (8 male, 1 female), both in people who were active (n-2) or recovered (n-7) from COVID-19. Recovered COVID-19 was defined as those who were either discharged from hospital or in-hospital but 2 weeks had passed post-detection, although there was some overlap across the cases. The most common comorbidities associated were diabetes (n-3), hematological malignancy (n-2), and end-stage renal disease (n-2), while 2 cases did not show any comorbidity. All the cases were having severe COVID-19 infection and 7 out of 9 patients were in ICU and on mechanical ventilation before got the diagnosis of mucormycosis. History of parenteral steroid administration was found in 6 patients, remdesivir in 4 patients, and 2 patients received tocilizumab for COVID-19 infection. Radiological suspicion for COVID-19 infection started with development of cavity in 5 patients. Bronchoalveolar lavage (BAL) sample was used for Mucor diagnosis in 4 patients, sputum in 2 patients, 1 patient in thoracotomy sample, and 2 patients were diagnosed after autopsy. Three cases were found also suffering with Aspergillus coinfection. Seven out of nine cases could not survive.

Discussion

Mucormycosis represents a group of fungal infections caused by member of the order Mucorales, which can affect organs such as skin, paranasal sinuses, orbits, brain, lungs, and gastrointestinal tract. Rhino-orbital-cerebral (ROCM) form is the most common variety seen in clinical practice world-wide.[22] Pulmonary mucormycosis was described in 22% in one of the case series of 116 mucormycosis cases.[23] In another case series which include 101 cases of COVID-19 with mucormyciosis, pulmonary mucormycosis was reported in 7 cases.[24] Several risk factors have been described for COVID-19 associated with mucormyciosis like poor controlled diabetes mellitus, diabetic ketoacidosis, chemotherapy, hematological malignancies (leukemia and lymphoma), immunosuppressive therapy, acquired or congenital neutropenia, antibiotic therapy, renal failure, a prolonged post-operative course or hospital stay, solid organ transplantation, and burns.[25-27] Some risk factors predispose for particular site of mucormycosis like ROCM are frequently observed in association with poorly control diabetes and diabetic ketoacidosis (DKA), whereas lung involvement occurs in patients having neutropenia, bone marrow and organ transplant, and hematological malignancies. This case series also showed diabetes and hematological malignancy as the most common underlying risk factors predisposing for pulmonary mucormycosis. In one of the largest case series of pulmonary mucormycosis of 87 patients before this pandemic, male predominance (3:1) and underlying risk factors such as diabetes in 56% and hematological malignancy in 32% patients were found.[28] Incidence of mucormycosis has risen sharply during the second wave compared with the first wave of COVID-19 in India and reason for which are not clear. One theory given that SARS CoV-2 infection by itself can induce an

Table 1: Summary of 9 pulmonary mucormycosis cases in COVID-19 reported till June 5, 2021

Author (Country)	Age range Sex (M/F)	Comorbidity	COVID-19 diagnosis (active/ recovery)	ICU admission	Clinical condition	Mucor diagnosis method	CT features (Halo sign/ reverse halo sign/Cavity	Diagnosis (Confirm/ probable)	Other organs involved* (N, S, O, C)	Other Fungus	Drugs** (C,T,R)	Outcome: Alive/Dead
Pasero *et al.*[13] (Italy)	66, M	Hypertension	Recovery (3rd week)	Y	On mechanical ventilation, post trachesostomy, on RRT	BAS and BAL	Cavity	Probable	Nasal	-	-	Dead
Khan *et al.*[14] (USA)	44 F	Diabetes	Active (2nd week	Y	On mechanical ventilation	Tracheal aspirate, BAL	Cavity	Probable	-	Aspergillus flavus, Candida	C,R	Dead
Johnson *et al.*[15] (USA)	76 M	Diabetes, Hypertension	Recovery (5th week)	Y	On mechanical ventilation for 2 weeks	BAL	Cavity	Probable	-	Aspergillus	C,R	Alive (on vent support)
Kanwar *et al.*[16] (USA)	55 M	ESRD	Recovery (3rd week)	N	Readmitted with right-sided consolidation with cavitation and hemoptysis	Sputum Pleural fluid	Cavity	Probable	-	-	C, T	Dead
Garg *et al.*[17] (India)	55 M	Diabetes, Hypertension, ESRD, Cardiomyopathy	Recovery (3rd week)	N	Cough with expectoration, at room air	Sputum	Cavity	Probable	-	-	C, R	Alive
Hanley *et al.*[18] (UK)	22 M	-	Active	Y	Y	Autopsy	-	Confirm	-	-	-	Autopsy
Placik *et al.*[19] Arizona	49 M	-	Recovery (3rd week)	Y	On mechanical ventilation, Right-sided pneumothorax	Thoracotomy	-	Confirm	-	-	C,R	Dead
Bellanger *et al.*[20] (France)	55 M	Lymphoma (Auto-HCT)	Recovery (3rd week)	Y	On mechanical ventilation	BAL, tracheal aspirate	-	Probable	-	*Aspergillus fumigatus*	N/A	Dead
Zurl *et al.*[21] (Italy)	53 M	Leukemia	Recovery (4th week)	Y	On mechanical ventilation	Autopsy	-	Confirm	-	-	C,T	Autopsy

•N - Nose, S - Sinus, O - Orbital, C- Cerebral, ** C - Corticosteroid, R - Remdesivir, T - Tocilizumab

Table 2: Clinicodemographic characteristics of COVID-19 patients with pulmonary mucormycosis

Characteristics	Total (09)
Age in years (range)	22-66
Male:Female	8:1
Diabetes	3
Hypertension	3
ESRD	2
Hematological malignancy	2
No comorbidity	2
Coinfection with Aspergillus	3
Mortality	7
Confirm diagnosis	3

immunosuppressive state that exposes the patient to the risk of developing opportunistic infections. The most common factors attributed to the rise of mucormycosis in COVID-19 patients are uncontrolled diabetes, the excessive use of corticosteroids for immunosuppression, and prolonged stays in the intensive care unit. Other factors could be immune dysregulation caused by the virus itself and the use of concurrent immunomodulatory drugs such as tocilizumab.[29,30] Fungal infections by *Aspergillus* are more common than mucormycosis in COVID-19 infection and have been reported in almost 14% of ICU patients.[31] Both Aspergillus and Mucor have been recognized as secondary complications of coronavirus disease 2019 (COVID-19), especially among critically ill patients in the intensive care unit (ICU).[31,32] Reports have shown that up to 35% of these patients have invasive pulmonary aspergillosis, which has been associated with previous corticosteroid usage and has led to higher mortality.[32] In contrast, the incidence of invasive pulmonary mucormycosis following COVID-19 is rare, with only 9 cases currently reported.[33] Primary care physician should be aware that invasive pulmonary aspergillosis and pulmonary mucormycosis share similar risk factors, clinical presentation, and radiology and so differentiation is always challenging. Even differentiating bacterial pneumonia from secondary fungal infection is challenging. Hence, a lack of clinical suspicion and difficulty in isolating the causative fungi might contribute to the underdiagnoses of mucormycosis. Three out of 9 published case reports had additional Aspergillus infection. The major challenge in diagnosis of pulmonary mucormycosis is the avoidance of respiratory samples or bronchoscopy in COVID-19 patient as aerosol generating procedure. COVID-19 associated pulmonary mucormycosis CAPM should be suspected in patients with risk factors such as hematological malignancy, solid organ transplantation, autoimmune diseases, pulmonary cavities or multiple nodules on imaging would signal the cases to look more carefully for other characteristic imaging signs, and not to be confused with COVID-19 radiological features. Another issue in diagnosis as there is no marker for invasive pulmonary mucormycosis in compare invasive pulmonary aspergillosis is easily diagnosed by serum or BAL galactoman, or beta-d-glucan**.** This case series highlights difficulty in diagnosis and 6 out of 9 patients treated on the basis of probable diagnosis. Out of 9 patients in this case series, 2 patients were diagnosed only after autopsy. Most of the patients were diagnosed in this cases series during routine sample processing for fungal hyphae stain and culture. RCOM involvement is not common in patients with pulmonary mucormycosis and in this case series, only one case[13] showed involvement of sinus. European Organization for Research and Treatment of Cancer/Mycosis Study Group defined invasive fungal infection as confirm or probable.[34] Confirm PM was defined by histological evidence of tissue invasion consisting of nonseptated, right-angle branching filamentous fungi plus recovery of Mucorale species by culture of specimens from pulmonary tissue or positivity for immune histochemical staining with anti-Rhizopus arrhizus monoclonal antibody, while probable PM was defined as the presence of host factors together with one or more clinical indications, such as dense, well-circumscribed lesions with or without a halo sign, and an air-crescent sign or cavity on CT, and mycological evidence of Zygomycetes in sputum or BAL fluid culture. In this systemic review of 9 cases, only 3 patients had confirm pulmonary mucormysosis as tissue diagnosis was not made in others; confirmation was made in 2 patients after autopsy and 1 patient after thoracotomy. The most common samples for fungal evaluation in this case series were sputum, tracheal or bronchial aspirate, and BAL. Imaging of pulmonary mucormycosis is mostly nonspecific. An abnormal chest roentgenogram is shown in >80% of pulmonary mucormycosis patients,[17] which include consolidation, cavitation, the air-crescent sign, the halo sign, the reversed halo sign, lung nodules or masses, bronchopleural fistulae, lymphadenopathy, and pleural effusion. Cavitation is observed in 40% of cases, but the air-crescent sign is not found commonly. Cavity was found in 5 out of 9 patients (55.5%) in this case series. It is important to rule out a more common cause of lung cavitation such as tuberculosis, bacterial and more common fungal infection by Aspergillus as invasive pulmonary or necrotizing pulmonary aspergillosis.

Pulmonary mucormycosis associated with high mortality rate could be related to delays in diagnosis, compromized immune system and a poor host response, as well as to the complexity of the treatment that includes a combination of antifungal therapy, availability of thoracic surgeon. A recent paper highlighted pulmonary involvement by Mucor associated with higher mortality compared to nonpulmonary Mucor infection in COVID-19.[35] Early referral by primary physician to center with thoracic expertise may change the prognosis of patient.

Conclusion

There is a need of a high index of suspicion required to diagnose pulmonary mucormycosis in COVID-19 infection. All the severe COVID-19 patients requiring ICU care with cavitary lesion on imaging should be evaluated for mucormycosis. COVID-19 associated pulmonary aspergillosis (CAPA) is more common that COVID-19 associated pulmonary mucormycosis (CAPM) and presence of one cannot rule out others. It is important at primary care physician level for early referral to expertise center.

Take home message

The current article reviewed all published case reports of pulmonary mucormycosis associated with COVID-19 infection. It is important to keep high index of suspicion for early treatment initiation as it is associated with high mortality. In the presence of dual infection by Aspergillus and Mucor, treatment should be targeted to Mucor by injectable amphotericin rather than voriconazole, which is not effective against Mucor. Primary healthcare physicians are the first contact with health services; hence, their knowledge is of utmost important to disseminate the knowledge about this fatal disease.

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Conflicts of interest

There are no conflicts of interest.

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