Case Report

Critical COVID-19-associated pulmonary mucormycosis: The underreported life-threatening spectrum of the mucormycosis epidemic

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ABSTRACT

The explosive rise in angioinvasive mucormycosis (MM) in India and other parts of the world has been described as the "epidemic following the COVID-19 pandemic," with the majority being rhino-orbital-cerebral MM. We report a case series of five COVID-19-associated pulmonary MM (CAPM) with an aggressive clinical course. Clinical and radiological clues were limited, and the initial suspicion of CAPM was the morphological appearance on bronchoscopy, which led to the diagnosis. Histopathology was consistently positive in all cases, while other microbiological and molecular tests had varying sensitivity. Most patients had a fulminant and fatal course. Also noted was dual fungal infection in 3/5 cases with coexisting multidrug resistant bacterial infection in all cases. CAPM is the hidden part of the COVID-MM epidemic and warrants a high degree of suspicion with early diagnosis and treatment.

KEY WORDS: Bronchoscopy, COVID, COVID fungal infection, COVID-19-associated pulmonary mucormycosis, mucormycosis, pulmonary mucormycosis

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INTRODUCTION

COVID-19 is associated with an increased incidence of mucormycosis (MM) in adults with multisystem involvement, predominantly rhino-orbital-cerebral MM (ROC-MM).[1,2] More than 30,000 COVID-associated MM (CAM, largely ROC-CAM) cases have been reported in the current wave of COVID-19 in India.[3] We report the first case series of COVID-19-associated pulmonary MM (CAPM) detected with advanced diagnostic strategies, with a high mortality.

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CASE REPORTS

Case 1

A 60-year-old diabetic female, glycosylated hemoglobin (HbA1C) 10.2 and COVID-19 infection 35 days ago treated with prolonged corticosteroids [Table 1], was referred with respiratory distress and was mechanically ventilated. Chest radiograph (CXR) showed a right lower lobe (RLL) and left upper lobe dense consolidation with right empyema-intercostal chest drainage was inserted.

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Table 1: Clinical and laboratory details of the patients with COVID-19-associated pulmonary mucormycosis

Age	Sex	HbA1C	Comorbidities	Time since symptom onset (days)	Steroid Dosage	Radiology-CXR/CT	Morphology of airways	BAL KOH	Fungal culture	Fungal PCR	HPE	BAL GM	BAL COVID19 RT-PCR	Bacterial culture
60	Female	10.2	DM/HTN	35	MPS 120 mg x 5 days, f/b 60 mg x 15 days	CXR: RLZ/LUZ consolidation Right empyema	Extensive endobronchial necrosis RLL/LUL apical	Aseptate hyphae	Negative	Negative	MM	1.75	Negative	MDR *K. pneumonia*
70	Male	8.4	CKD	12	MPS 80 mg x 10 days	CXR: LUZ/LMZ dense consolidation	Thick purulent secretions, with airway necrosis	Aseptate + septate hyphae	Aspergillus fumigatus + Mucor	*R. delemar*	MM + Aspergillus	1.45	Positive	MDR *Acinetobacter baumannii*
67	Male	9.9	DM/HTN/IHD	21	Dexamethasone 8 mg x 21 days	CXR: Bilateral lower zone opacities	Thick purulent secretions	Aseptate hyphae + Aspergillus sporulation	Aspergillus fumigatus	Negative	MM + Aspergillus	3.28	Negative	MDR *K. pneumonia*
46	Female	14.6	DM	23	MPS 80 mg x 14 days	CXR: Left lung collapse with bronchus cut-off	Tracheal thick secretions, distal tracheal→LMB mass with erosion into cartilage	Aseptate hyphae	Mucor	*R. oryzae*	MM	0.57	Negative	MDR *K. pneumonia*
63	Male	9.2	DM	38	Prednisolone 60 mg x 7 days	CT: LLL cavity with fungal growth	Minimal secretions	Negative	Negative	Not done	MM + Aspergillus	2.75	Negative	MDR *K. pneumonia*

K. pneumonia: Klebsiella pneumoniae, R. delemar: Rhizopus delemar, R. oryzae: Rhizopus oryzae, DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischemic heart disease, CKD: Chronic kidney disease, RUZ: Right upper zone, LUZ: Left upper zone, LMZ: Left mid zone, RMZ: Right mid zone, RLZ: Right lower zone, LLZ: Left lower zone, LLL: Left lower lobe, MDR: Multidrug resistant, LMB: Left main bronchus, GM: Galactomannan, MM: Mucormycosis, HbA1C: Hemoglobin A1C, CXR: Chest radiograph, RLL: Right lower lobe, LUL: Left upper lobe, BAL: Bronchoalveolar lavage, RT-PCR: Reverse transcription polymerase chain reaction, CT: Computerized tomography, KOH: Potassium Hydroxide

Bronchoscopy showed purulent, cheesy secretions, extensive necrosis of the RLL segments [Figure 1], and KOH mount of the washings suggested MM confirmed on histopathology (HP). Liposomal amphotericin B (LAmpB) was started but she expired within 48 h.

Case 2

A 70-year-old male with chronic kidney disease (CKD) had COVID-19 infection for 12 days treated with intravenous steroids, presented with respiratory failure, and was mechanically ventilated. CXR showed bilateral lower zone dense consolidations. Bronchoscopy showed thick purulent secretions with mucus plugging and microbiology and HP confirmed *Aspergillus fumigatus* and *Mucor spp*. Bronchoalveolar lavage (BAL) panfungal polymerase chain reaction (PCR) grew *Rhizopus delemar*. He was started on LAmpB, went into progressive septic shock, and expired after 3 days.

Case 3

A 67-year-old diabetic male with HbA1C 9.9 and COVID-19 infection 21 days ago treated with steroids was referred for worsening respiratory distress and ventilated. CXR showed bilateral lower zone patchy opacities. Bronchoscopy showed purulent secretions with mucosal ulcerations and microbiology grew *Aspergillus flavus*, while endobronchial biopsy showed dual infection with *Aspergillus* and *Mucor spp*. After initial improvement, he worsened rapidly and expired 4 days later.

Case 4

A 46-year-old female uncontrolled diabetic with HbA1C 14.2 with COVID-19 23 days prior treated with high dose steroids was referred for respiratory distress with left lung collapse and was ventilated. Bronchoscopy showed purulent tracheal secretions and a necrotic mass at distal trachea/carina eroding the posterior tracheal wall [Figure 1]. Cryoadhesion was used to remove the mass. KOH mount showed aseptate hyphae, BAL fungal PCR grew *Rhizopus oryzae*, and HP showed angio-invasive

Figure 1: Bronchoscopic, radiological, and histopathological images of COVID-19-associated pulmonary mucormycosis

Mucor spp. [Figure 1]. She was initiated on LAmpB but expired 48 h later.

Case 5

A 63-year-old male diabetic treated for severe COVID pneumonia 3 weeks ago presented with a left tension pneumothorax, and a chest drain was inserted. Computed tomography (CT) chest showed diffuse fibrosis and a left LL cavity with a fungal ball [Figure 1]. BAL and transbronchial biopsy confirmed *Aspergillus* and *Mucor* dual infection. L-Amp B was started and he stabilized.

All patients had additional multidrug-resistant (MDR) bacterial infection. Table 1 summarizes the demographic, radiological, and clinical details of the patients.

DISCUSSION

This case series describes critical CAPM as an important subset of the CAM epidemic in India. CAPM appears to be difficult to suspect, is often diagnosed late, and has limited treatment options with a bad outcome.

The main risk factors postulated for the CAM epidemic in India are extensive corticosteroid usage and uncontrolled DM.[1,2,4,5] In our series, 4/5 patients were uncontrolled diabetics with a mean HbA1c of 10.46%. One patient had CKD, and all patients received high dose (equivalent of methylprednisolone >80 mg/day) and long-term corticosteroids – median steroid treatment was for 21 days (range 9–31 days).

The diagnostic tools for CAPM include radiology, followed by appropriate microbiology and HP. CXR findings are nonspecific and described CT findings for CAPM include the "reverse halo" sign, nodular infiltrates, dense consolidation, cavitation, and pleural effusion.[6] However, CT scan is not always feasible in these unstable ventilated patients, and in addition, CT findings have a low specificity. Significant challenges are there with microbiological tests, due to varying sensitivity, specificity, and turnaround time, with treatment and outcome implications. Guidelines recommend demonstration of aseptate fungal hyphae on direct microscopy, culture, and HP. PCR-based tests have a moderate recommendation due to nonstandardization, despite high sensitivity.[6] Bronchoscopy, though challenging, is useful to obtain BAL/biopsy samples, as sick patients are often unable to expectorate.[7]

In our series, in 4/5 patients, the most common CXR finding was patchy dense consolidation, with 1 empyema. One patient had a cavity with COVID fibrosis with the differential of CAPM or COVID-associated pulmonary aspergillosis (CAPA). None of these patients were able to produce sputum. CT could not be done in 4/5 patients, and CAPM was therefore not suspected. Bronchoscopy done in 4/5 patients for worsening infiltrates revealed unsuspected CAPM on visual inspection of necrotic/mass lesions. KOH mount of the BAL/biopsy was positive with a rapid turnaround time. HP was consistently positive in all cases, fungal culture was positive in 3/5 cases, and fungal PCR was positive in 2 cases. Bronchoscopy was the pivotal test for diagnosis and sample acquisition in this cohort. Bronchoscopically visualized necrosis with anatomical obliteration was paradoxically an adverse prognostic factor in 4/5 patients, as none of them were candidates for surgery. Dual infection with *Aspergillus* and *Mucor spp.* was also seen in 3/5 patients.

Historically, the prognosis of pulmonary MM is poor, with mortality as high as 87%.[8] Early diagnosis and therapy with appropriate antifungals (amphotericin B, LAmpB) and aggressive surgery (debridement and debulking) can significantly reduce mortality.[9] These concepts have been extended to CAPM management,[10] with significant limitations mentioned below.

All patients were initiated on LAmp B but could not be operated due to instability, extensive disease, and fibrosis– this feature seems to be unique to CAPM. The fulminant course led to demise within 4 days of diagnosis in 4/5 patients. Dual infection with MDR bacterial infection was another concern which may have added to mortality.

CONCLUSION

This series highlights that CAPM is infrequently reported, may co-exist with CAPA, and is the worrisome subset of the CAM epidemic. It presents enhanced challenges from both aspects – diagnosis and therapy. CAPM needs a higher index of suspicion, and often bronchoscopy is needed for diagnosis. Visual necrosis appears to be an adverse factor with imminent mortality, and dual fungal with MDR bacterial co-infection has can further worsen outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, *et al*. Multicenter epidemiologic study of coronavirus disease-associated mucormycosis, India. Emerg Infect Dis 2021;27:2349-59.
2. Garg D, Muthu V, Sehgal I, Ramachandran R, Kaur H, Bhalla A *et al*. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM):

Case Report and Systematic Review of Literature. Mycopathologia 2021;186:289-98.
3. Available from: https://www.deccanherald.com/national/in-the-wake-of-india-s-covid-crisis-a-black-fungus-epidemic-follows-999682.html. [Last accessed on 2021 Jul 21].
4. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021;15:102146.
5. Patel A, Kaur H, Xess I, Michael J, Savio J, Rudramurthy S *et al*. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clinical Microbiology and Infection 2020;26:944.e9-944.e15.
6. Cornely OA, Arikan-Akdagli S, Dannaoui E, Groll AH, Lagrou K, Chakrabarti A, *et al*. European society for clinical microbiology and infectious diseases (ESCMID) and European confederation of medical mycology (ECMM): Joint clinical guidelines for the diagnosis and management of mucormycosis. 2013.
7. Al-Abbadi MA, Russo K, Wilkinson EJ. Pulmonary mucormycosis diagnosed by bronchoalveolar lavage: A case report and review of the literature. Pediatr Pulmonol 1997;23:222-5.
8. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, *et al*. Epidemiology and outcome of zygomycosis: A review of 929 reported cases. Clin Infect Dis 2005;41:634-53.
9. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis 2008;47:503-9.
10. Sun HY, Aguado JM, Bonatti H, Forrest G, Gupta KL, Safdar N, *et al*. Pulmonary zygomycosis in solid organ transplant recipients in the current era. Am J Transplant 2009;9:2166-71.