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Case Series

# COVID-19 associated with pulmonary mucormycosis; a case series

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ABSTRACT

*Introduction:* Coronavirus disease 2019 (COVID-19) has evolved as a result of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). With the rise of cases worldwide, plenty of potential COVID-19 complications have emerged, including increased susceptibility to subsequent bacterial and fungal infections. This study aims to report four cases of COVID-19 associated with pulmonary mucormycosis.

*Method:* This is a multi-center case series study. Diagnosis of COVID-19 was confirmed by reverse transcriptase-polymerase chain reaction.

*Result:* A total of 4 patients infected with SARS-CoV2 were involved in this study. The majority of the cases were female, aged >42 years old. All patients developed severe symptoms. All of the patients had received steroids, half of them had co-morbidities. The most common computerized tomography (CT) scan findings were pulmonary cavitation and empyema. All of the cases were treated with a combination of surgery and antifungal treatment.

*Conclusion:* As the number of COVID-19 cases rises, enhanced surveillance for co-infections with unusual pathogens should be continued. Clinicians should raise awareness of these deadly infections, which can further aggravate severe COVID-19.

## 1. Introduction

Coronavirus disease 2019 (COVID-19) has evolved as a result of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) [1]. It was initially detected in Wuhan, Hubei Province, China, and soon spread to other areas of the world, resulting in a global pandemic [2]. Until September 5, 2021, there have been more than 235 million verified cases with approximately 5 million deaths [3].

Most patients with SARS-CoV2 infection are asymptomatic or have very mild symptoms, such as fever and dry cough. However, in extreme situations, particularly in the elderly patients, hypertensive, and diabetic individuals, it can cause severe acute respiratory syndrome (SARS) [4]. SARS-CoV-2 is most commonly associated with a lung infection, resulting in pneumonia; but the latest researches have revealed that many other organ systems, including the cardiovascular, immunological, neurological, and gastrointestinal systems, can be involved [5].

With the rise of cases worldwide, plenty of potential COVID-19 implications have emerged, including increased susceptibility to subsequent bacterial and fungal infections [6]. Both Aspergillosis and Candida have been identified as the most common fungal infections associated with COVID-19 co-infection [7]. COVID-19 has generated an inflammatory storm that has weakened individuals' immune system, resulting in the occurrence of mucormycosis [8]. COVID-19 associated with pulmonary mucormycosis is a rare condition with only a few cases reported [9].

This study aims to report four cases of critically ill COVID-19 patients associated with pneumonia and complicated by pulmonary mucormycosis. The article was reported in line with PROCESS 2020 guideline

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[10].

## 2. Method

**Registration:** The research was registered in Research Registry. The registration number is researchregistry7474.

The link is Browse the Registry - Research Registry.

### 2.1. Case 1

A 56-years-old female presented with fever, dyspnea, and cough for 5 days. She was confirmed as a case of COVID-19 by reverse transcriptase-polymerase chain reaction (RT-PCR).

On general examination, she was well-nourished (BMI:20.4 kg/m2), well oriented to time, place, and person, and was able to speak comfortably. Her vital signs at the time of presentation were as follows: Heart rate (HR) (98 beats/min), blood pressure (BP) (150/90 mmHg), respiratory rate (RR) (24 breaths/min) and oxygen saturation was 94% without oxygen supply.

On systemic examination, she had decreased breath sounds over the left side of the lung with normal vesicular breath sounds over the right side. On cardiovascular examination, there was nothing significant.

Laboratory tests were significant for underlying infection with a total leucocyte count of (16,420) with neutrophils (88%) and lymphocytes (7%), hemoglobin (10.6 g/dL), and platelet count (328 x 109/L). The renal function test and coagulation profile were within the normal range. ECG showed normal sinus rhythm.

She was admitted to the ward and treated according to the local protocol (which contains steroids) but she hadn't improved after two weeks. A high-resolution computerized tomography (HRCT) scan of the chest was performed. It showed right-sided empyema. The decision was made to perform decortication of the lung via a classical postero-lateral thoracotomy at the fifth intercostal space. During surgery, the involved lung had a greenish-black discoloration with extensive damage to the lung so the decision was made to carry on three segmentectomies to control the numerous air leaks facing the surgical team. The hertopathologic results confirmed the diagnosis of mucormycosis. Postoperatively, the patient was kept on mechanical ventilation and treated with antifungal therapy. However, despite relative improvement in her lung status the patient developed multiple organ dysfunction syndrome (MODS) and died on the third postoperative day.

### 2.2. Case 2

A 42-year-old man presented with fever and dry cough of one week duration. He was a non-smoker and had a negative past medical history. Chest CT revealed bilateral ground-glass opacities. The diagnosis of COVID-19 was confirmed by RT-PCR. Subcutaneous heparin and oral dexamethasone were administered for 5 days; he was discharged on day eight of admission. Four days after discharge, the CT showed bilateral consolidations. One week later, he experienced hemoptysis and was sent for imaging. Chest CT showed a cavitary lesion with an air-fluid level involving the middle lobe. During surgery, the middle lobe was completely destroyed, so middle lobectomy was eventually performed. Histopathology of the surgical specimen confirmed mucormycosis. Postoperatively, the patient was weaned from mechanical ventilation on the third postoperative day and was kept in the intensive care unit (ICU) for an additional couple of days. His recovery period was uneventful, and he was discharged home after one week. Follow-up after six weeks showed progressive improvement in his condition with no major drawbacks.

### 2.3. Case 3

A 72-year-old woman with diabetes mellitus (DM) presented to the emergency department with shortness of breath. She was diagnosed with COVID-19 by RT-PCR one week prior. Chest CT revealed bilateral peripheral infiltrates and areas of consolidation. She was intubated because of respiratory failure caused by COVID-19 pneumonia in the intensive care unit and was treated with medications that included methylprednisolone (1000 mg), favipiravir, and RNA polymerase inhibitor. On admission, her clinical condition improved but was still dependent on a high concentration of oxygen.

New HRCT of the chest revealed collapse consolidation of both right middle and lower lobes in addition to empyema. The decision was made to do lung decortication. During surgery, both involved lobes were severely destructed and bi-lobectomy was done. Histopathological examination confirmed mucormycosis. She was kept on mechanical ventilation for 3 days and remained in the ICU for an additional 2 days. She was later transferred to the ward where she remained for a week. During that period, she was kept on strict glycemic control using soluble insulin subcutaneously which was crucial to her improved clinical condition and her eventual discharge from the hospital.

### 2.4. Case 4

A 67-year-old female presented to the hospital with shortness of breath of two days. The condition started two weeks prior with a high fever, shortness of breath, myalgia, and cough. She was confirmed as a case of COVID-19 with an RT-PCR test. She is a known case of DM, ischemic heart disease (IHD), and hypertension (HTN). Her condition deteriorated, and she was placed on continuous positive airway pressure (CPAP). She was treated as a severe case of COVID-19 with steroids, antibiotics (AB), and antivirals like remdesivir. After two weeks, her condition deteriorated further. A new CT scan of the chest showed cavitary pulmonary lesion and empyema. She was henceforth referred to the cardiothoracic surgery department for possible decortication. After optimizing her medical condition, a thoracotomy was performed. The right lower lobe was found to be completely destructed by the cavitary lesion and had a very repulsive, strange odor. Air leak control and complete decortication were performed. Histopathology confirmed the diagnosis. She was then moved to the ICU department. Histopathological examination confirmed the diagnosis of pulmonary mucormycosis. Antifungal treatment was prescribed. She was kept on mechanical ventilation for two days. Four days after extubation, she was transferred to the ward.

## 3. Discussion

Mucormycosis, often known as 'black fungus' in India, is a fungal illness caused by molds from the mucormycetes family, which are common decomposers of organic wastes found in soil and dust. Mucormycetes is a fungus that has at least 20 pathogenic species classified into 12 genera. Rhizopus is the genus that has been associated with the majority of mucormycosis cases reported in the literature [11]. It is characterized by ischemia and necrosis of the host tissue due to the invasion of its vascular lamina by hyphae [12]. Progressive tissue necrosis can develop at many anatomical regions based on the mode of fungal exposure, which includes inhalation, ingestion, direct contact, and traumatic injection [13]. Mucormycosis mostly affects the head and neck, with the nose being the most commonly affected region; however, the illness can extend to the paranasal sinuses, orbit, facial bones, and cranial cavity. It can also involve the respiratory and central neurological systems, the gastrointestinal tract, and other organ systems [14]. A complex interplay of factors including DM, hematological malignancy, solid-organ transplant recipients on immunosuppressive therapy, iron overload, extensive skin injury, human immunodeficiency virus (HIV) infection, and peritoneal dialysis are associated with increased risk of developing mucormycosis [15]. The most prevalent comorbidities in this study besides COVID-19 infection were DM, HTN, IHD, and a high BMI, with two patients having no comorbidities at all.

Previous researchers found that fungal infections were more likely to

occur in the advanced stages of COVID-19 infection [16]. During COVID-19 recovery period, patients are immunocompromised due to viral infection, steroid usage, and the widespread use of broad-spectrum AB, and this may possibly be a risk factor [17]. COVID-19 possesses particular pathophysiologic characteristics that may allow secondary fungal infections, such as a tendency to produce severe lung disease and subsequent alveolar-interstitial pathology which may increase the risk of invasive fungal infections. Secondly, the immunological dysregulation associated with COVID-19, which includes lower numbers of T lymphocytes, CD4+T cells, and CD8+T cells, may affect innate immunity [18]. There has been an unexpected increase in COVID-19-associated mucormycosis, with the majority of patients displaying rhino-orbital involvement, whereas evidence on COVID-19-associated pulmonary mucormycosis is rare [9]. Mucormycosis has been found in less than 1% of hospitalized COVID-19 patients, with COVID-19-associated pulmonary mucormycosis accounting for 9% of all COVID-19-associated mucormycosis [9].

Seventy percent of rhino-orbital-cerebral mucormycosis patients have been observed to be diabetic individuals, the majority of whom had also experienced ketoacidosis at the time of presentation [19]. Half of the cases of this series had DM. Facial discomfort, nasal blockage or congestion, and bloody/brown/black discharge with or without local sensitivity or pain are early warning symptoms of COVID-19-associated mucormycosis. This is often accompanied by fever, nausea, and headache. Nasal ulcers or crusts that become black later in the course of the disease are frequently observed. Furthermore, when the maxillary, frontal, or ethmoidal paranasal sinuses are involved, patients may have facial numbness or edema. Palatal involvement can be seen as an ulcer over the upper palate that leads to a black necrotic region [20]. It may also manifest as toothache, loosening of maxillary teeth, and limitation of jaw mobility, which were not observed prior to COVID-19 [21]. Werthman-Ehrenreich reported a case with left-sided ptosis and proptosis with impaired sensorium [19].

Many radiological characteristics of pulmonary mucormycosis coincide with those of other fungal pneumonia, such as pulmonary aspergillosis, making the diagnosis challenging. Pulmonary mucormycosis is frequently accompanied by the reversed halo sign [22]. When there is a thick-walled lung cavity, numerous nodules, and pleural effusion, mucormycosis should be suspected [23]. The CT findings of this study were pulmonary cavitation and empyema in two patients and collapse consolidation in one patient. Histopathological analysis of tissues taken from various lesions can provide a definite diagnosis. They have distinctive wide aseptate or pauci-septate hyphae with hyphae folding to provide a ribbon-like appearance [rudramurthy2021]. The final diagnosis of all cases of this study was confirmed as COVID-19-associated pulmonary mucormycosis through histopathologic examination postoperatively.

The appropriate and timely antifungal medication, as well as surgical excision, when possible, are found to be crucial in the treatment of mucormycosis. The medication of choice is liposomal amphotericin B [21]. Triazoles, such as posaconazole and isavuconazole, are usually applied during the consolidation phase or as salvage treatment [23]. Evidence does not clearly support the role of combined antifungal therapy in mucormycosis, but the combination of surgery and antifungal treatment was linked to improved survival [12,21]. Cornely et al. stated that for local management of mucormycosis, early and vigorous surgical resection and debridement of the afflicted tissues is required [23]. In the current series, all cases were treated with a combination of surgery and antifungal treatment.

As stated in the previous studies, failure to identify and treat COVID-19 infection complications will most probably result in higher mortality [24]. Even with adequate treatment, rhino-orbital mucormycosis has a poor prognosis, with a mortality rate of up to 50% [19]. Because of its severe clinical course in pulmonary involvement, it has a mortality rate of up to 80% [25]. The high death rate in pulmonary localization may be due to diagnostic delays, an imbalanced immune system, and a poor host response, as well as the complexity of the treatment, which involves a combination of antifungal medication and a high-risk surgical operation [26]. In this study, three patients recovered from the disease and one died on the third postoperative day.

In conclusion, as the number of COVID-19 cases rises, enhanced surveillance for co-infections with unusual pathogens should be continued. Clinicians should raise awareness of these deadly infections, which can further aggravate severe COVID-19. Early, adequate and vigorous therapy is required for a favorable result of mucormycosis.

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## Ethical approval

The manuscript approved by ethical committee of the University of Sulaimani.

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## Author contribution

Okba F.Ahmad, Saoud Al-Neaimy, Fahmi H.Kakamad: cardiothoracic surgeons who manages the cases, follow up, and final approval of the manuscript., Razhan k. Ali: literature review, writing the manuscript, final approval of the manuscript. Tomas M. Mikael, Ahmed Gh. Hamasaeed, Shvan H. mohammed, Rawezh Q. Salih, Muhammed Gh. Hamasaeed: literature review and final approval of the manuscript. Abdulwahid M. Salh: major contribution of the idea, final approval of the manuscript.

## Consent

Consent has been taken from the patients and the family of the patients.

## Registration of research studies

Researchregistry7474.
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## Guarantor

Fahmi Hussein Kakamad is Guarantor of this submission.

## Declaration of competing interest

There is no conflict to be declared.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103434.

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