CASE REPORT

Case Report: Diagnostic challenge of COVID-19 associated pulmonary aspergillosis (CAPA) [version 1; peer review: 1 approved with reservations]

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Abstract

Background: Coronavirus disease 2019 (COVID-19) was declared a pandemic in March 2020 by the World Health Organization (WHO). Severe COVID-19 is represented with acute respiratory distress syndrome (ARDS) that requires mechanical ventilation. Moreover, recent studies are reporting invasive fungal infection associated with severe COVID-19. It is unclear whether the prescription of immunotherapies such as corticosteroids, or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection itself is risk factor for COVID-19-associated invasive pulmonary aspergillosis (CAPA). Hence, fungal infections present an additional uncertainty in managing COVID-19 patients and further compromise the outcome.

Case study: Here we report a case of SARS-CoV-2 complicated by invasive pulmonary aspergillosis (IPA) in a patient with no traditional risk factors for IPA. Admitted to ICU due to ARDS on mechanical ventilation, the patient deteriorated clinically with unexplained increased of fraction of inspired oxygen (FiO₂) requirement from 50% to 80%. Investigations showed borderline serum galactomannan, nonspecific radiological findings reported to be atypical for COVID-19, and the respiratory sample grew *Aspergillus* spp.

Main diagnosis: COVID-19 related fungal infection. The patient was treated with antifungal therapy for four weeks. He improved clinically after one week of starting antimicrobial treatment. After a prolonged ICU stay (87 days) due to infection control precaution, he was discharged from the ICU and moved to a long-term facility for further management and support.

Conclusions: This case highlights the diagnostic challenge in such cases. and the importance of early recognition of CAPA which can optimize therapy by administration of appropriate antifungal agents that may impact mortality.

Open Peer Review

Approval Status ? ✓

	1	2
version 2 (revision) 07 May 2021		✓ view
version 1 01 Feb 2021	? view	

1. **Ali S. Omrani**, Hamad Medical Corporation, Doha, Qatar
2. **Hamid Badali** , Mazandaran University of Medical Sciences, Sari, Iran

Any reports and responses or comments on the article can be found at the end of the article.

Keywords

COVID, SARS-CoV2, Aspergillosis, Invasive, Pulmonary, Critical.

This article is included in the **Emerging Diseases and Outbreaks** gateway.

This article is included in the **Coronavirus** collection.

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Author roles: **Albasata H:** Writing – Original Draft Preparation; **Alamri MM:** Writing – Original Draft Preparation; **Almuhaidb SA:** Writing – Original Draft Preparation; **Aljebreen AM:** Writing – Review & Editing; **Almaghrabia RS:** Writing – Review & Editing

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Background

Invasive pulmonary aspergillosis (IPA) is typically thought to cause disease in immunocompromised hosts, particularly in neutropenic patients. In the last two decades, it has been more commonly recognized in critically ill patients, particularly those with severe acute respiratory distress syndrome (ARDS)¹. An increasing number of IPA cases complicating severe influenza have been reported following the H1N1 influenza pandemic in 2009. Vanderbeke *et al.* described 128 cases published between 1952–2018². In late December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a public health emergency and has spread globally³. Co-infections among patients with coronavirus disease 2019 (COVID-19) are currently well described in the literature. *Chlamydomyces pneumoniae*, *Mycoplasma pneumoniae*, and human metapneumovirus are among the common pathogens identified⁴. Intensive care unit admission is required in around 5–30% of patients with COVID-19. IPA has started to be recognized in severe COVID-19 infection, with multiple case series of severe COVID-19 pneumonia complicated by IPA having been reported since the start of the pandemic^{5–10}. Here we report a case of IPA that was diagnosed in a patient with severe COVID-19 infection.

Case

We report the case of a 29-year-old Saudi male security guard known to have diabetes mellitus and chronic kidney disease. He was admitted to hospital at the end of May 2020 as a case of COVID-19 pneumonia that was complicated with diabetic ketoacidosis and required admission to the intensive care unit (ICU). He rapidly deteriorated with progression to ARDS, requiring intubation and mechanical ventilation. He also suffered a cardiac arrest that required resuscitation for 12 minutes. He received Lopinavir/Ritonavir and Ribavirin along with Ceftriaxone in the referring hospital (dosage unknown). He was then transferred to the King Faisal Specialist Hospital and Research Centre (KFSHRC) around six days after his initial diagnosis for further management.

On day 0 of ICU admission at KFSHRC the patient was deeply sedated on intravenous (IV) propofol 150mg/hour and fentanyl 100mcg/hour, measured temperature 34.7 °C, intubated on pressure control ventilation requiring FiO₂ 50% and positive end-expiratory pressure (PEEP) 8 cm H₂O. He required IV norepinephrine 0.02– 0.2 mcg/kg/min to maintain his mean arterial blood pressure above 65 mmHg. His blood workup on day 0 was white blood cell count (WBC) 8.28 x10⁹ / L (3.9–11 x 10⁹ / L), absolute lymphocytes count 0.5 x10⁹ / L (1.50– 4.30 x 10⁹ / L), platelet 54 x10⁹ / L (155– 435 x 10⁹ / L), creatinine 603 umol/L (64 – 115 umol/L), and galactomannan antigen (AG) 0.48 (>0.5 reactive). A beta D-glucan test was not done as it was not available.

The patient was started on continuous renal replacement therapy (CRRT); his clinical status deteriorated with increased ventilation requirement of FiO₂ 50% to 80%, PEEP 8 to 16 cm H₂O on day 4. A chest X-ray showed multiple bilateral ill-defined patchy opacities in the right lower lung zone (Figure 1). A

computed tomography (CT) scan for his chest was done and showed multiple bilateral patchy ground-glass opacities (Figure 2, Figure 3). Bilateral lower lobe consolidations with air bronchogram showed greater involvement of the right lower lobe, while an unenhanced CT of the brain demonstrated hyperdense foci seen in the left inferior frontal, right parietal lobes with surrounding edema, and right central sulcus compatible with intra-parenchymal hemorrhage and subarachnoid hemorrhage, respectively. A follow-up MRI of the brain was obtained, showing an increased gyral pattern of T1 and FLAIR sequence, as observed in the bilateral occipital, bilateral frontal, and

Figure 1. Chest radiograph anteroposterior (AP) view. The radiograph shows multiple bilateral ill-defined patchy opacities more in the right lower lung zone.

Figure 2. Computed tomography (CT) scan of the chest (sagittal view). The scan shows a right middle lobe central ground-glass density with surrounding consolidation (arrow), giving the appearance of reversed halo sign 'atoll-sign'. A peripheral ground-glass density (curved arrow) is seen in the right lower lobe; a typical picture of coronavirus disease 2019 (COVID-19).

Figure 3. Computed tomography (CT) scan of the chest (axial view). The scan shows a left lower lobe nodule (arrow) with surrounding faint ground-glass densities giving halo sign appearance.

right parietal lobes, likely related to laminar necrosis from the anoxic- ischemic event. Gradient recalled echo (GRE) sequence showed scattered areas of blooming artifacts that are likely to be related to recent extensive hemorrhage. The brain findings were suggestive of hemorrhage and hypoxic injuries of vascular causes of previous cardiac arrest events.

On day 0, the patient was started on hydroxychloroquine 400mg orally every 12 hours for 1 day, followed by a maintenance dose of 200mg every 12 hours and azithromycin 500mg orally once followed by a maintenance dose of 250mg daily, respectively, for a total duration for 5 days. His antimicrobial therapy was escalated to Meropenem 0.5 gm IV every 12 hours. He continued to worsen, and thus his septic screen was repeated. His blood and urine culture remained negative.

Tracheal aspirate culture on day 0 grew *Aspergillus fumigatus* and *Aspergillus flavus* (Figure 4a, Figure 4b, Figure 5a, Figure 5b). Bronchoscopy was considered; however, it was not done due to concerns of COVID-19 transmission to the house staff. The patient was then started on dual antifungal therapy (day 4) for 1 week; Voriconazole 400mg orally every 12 hours as a loading dose, then 200mg every 12 hours as maintenance. In addition, the patient was given Caspofungin 70mg IV as a loading dose, followed by 50mg daily. After this Voriconazole monotherapy therapy (200mg orally every 12 hours) for a total duration of four weeks was completed in the hospital. One week after starting antifungal therapy (day 10 in the ICU), the secretions improved and the ventilator setting was decreased to FiO₂ 30%. Unfortunately, the patient on day 5 of ICU admission was found to be in a vegetative state secondary to anoxic brain damage post-cardiac arrest. The Glasgow Coma Scale was GCS 10/15 on tracheostomy.

The patient had a prolonged ICU stay due to infection control precaution; his stay was complicated with rhabdomyolysis, difficulty to wean him from ventilation, nosocomial infection

Figure 4a. *A. flavus* culture on sabouraud's dextrose agar. Olive-lime green colony morphology on sabouraud's dextrose agar.

Figure 4b. Microscopic examination of *A. flavus* from culture. Radiate, biserial conidia.

Figure 5a. *A. fumigatus* culture on sabouraud's dextrose agar. Gray-green colony morphology on sabouraud's dextrose agar.

after 30 days of ICU admission, and persistent COVID-19 virus shedding up to 73 days. The patient was then moved to a long-term facility (on day 87) after discharging him from the ICU.

Discussion

This case further supports the association between IPA and severe COVID-19 infection. It highlights the importance of early diagnosis and treatment of this serious complication that

Figure 5b. Microscopic examination of *A. fumigatus* from culture. Uniseriate conidiophore with columnar conidia.

can impose increased mortality. The diagnosis of IPA in patients in ICU without classical risk factors like neutropenia remains challenging¹⁻⁹.

Multiple studies from China have reported different rates of *Aspergillus* infections among patients with COVID-19. The estimated rates of *Aspergillus* co-infection in these combined studies are as follows: in Jiangsu province, 60/257 (23.3%), Zhejiang province, 8/104 (7.7%); and lastly, Wuhan, 13/48 (27%). All these reported CAPA cases lack standardization in diagnostic criteria and use specific definitions to identify and define CAPA^{10,11}. A European case series reported severe COVID-19 pneumonia complicated by IPA. All 27 cases were for patients admitted to the ICU, the majority of whom were intubated. The median duration between CAPA diagnosis and symptom onset was six days. Aspergillosis diagnosis was as early as three days post ICU admission or as late as 28 days¹⁰. Of the 27 patients, 12 (44%) received corticosteroids during their ICU stay, and 19 (70%) were treated with mould-active antifungal medication⁵⁻⁸. Bartoletti and colleagues found 22 (73%) of the 30 patients who were diagnosed with CAPA received Tocilizumab, and 18 (60%) received corticosteroids⁹.

Mixed fungal infection similar to our case was reported in two patients in a study from Pakistan, one with *A. falvus* and *A. fumigatus* diagnosed as CAPA, while a second patient was thought to be colonized with *A. falvus* and *A. nigar*¹². Diagnosis is challenging due to the difficulty in differentiating between colonization and active disease in positive culture cases. Recently Arastehfar *et al.* suggested that galactomannan (GM) testing of bronchoalveolar fluid (BALF), or even of tracheal aspirates, may support CAPA's diagnosis¹¹, though the test has not been validated for these specimens and cut-off values are not yet established.

Spanish tertiary hospitals carried out a retrospective study in patients with confirmed SARS-CoV-2 by PCR who isolated *Aspergillus* spp. in respiratory samples from bronchial aspirates (BAS) and bronchoalveolar lavages (BAL). Galactomannan assays were performed in serum and/or BAL with a cut-off index of 0.5 for both samples. COVID-19 associated IPA cases were

classified according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group EORTC/MSG criteria¹³ and *Aspergillus* algorithm for use in critically ill patients AspiCU algorithm¹⁴. *Aspergillus* spp. were grown in ten patients from respiratory samples. Seven patients were intubated in the ICU. All isolates were detected from deep respiratory samples: eight BAS one sputum and one BAL. Galactomannan analyses were run in only three patients, one with positive values in both serum and BAL ((1.97, 3.87) and another with repeated positive values in BAL samples (2.16, 1.11). The third patient had a negative serum galactomannan test (0.22)¹⁵.

Performing bronchoscopy and obtaining a bronchial wash is challenging in patients with COVID-19. It carries a significant risk of transmission to healthcare workers, which further complicates the diagnosis of IPA in this patient population¹⁶. A surveillance strategy for fungal co-infections in intubated patients with COVID-19 was done by Brown *et al.*¹⁷ utilizing weekly serum 1-3- β -D-glucan, galactomannan *Aspergillus* enzyme immunoassay (EIA) and *Aspergillus* PCR from bronchoalveolar lavage or endotracheal aspirates. A total of 62 patients were examined, and a galactomannan test of tracheal aspirates was performed for 85 samples; positive results were seen in six out of 62 patients, of which positive *Aspergillus* PCR was seen in five out of the six, and two grew *Aspergillus fumigatus* in culture. CAPA was clinically suspected in two patients. One of these patients' GM from BAL was not performed. Whether galactomannan positivity of endotracheal aspirates is a marker for CAPA or reflects upper airway colonization is not clear. It should be noted that none of their cases met the definition of CAPA¹⁷.

The radiological differentiation between IPA and COVID-19 is often complex, as the radiological changes in IPA in non-neutropenic patients are diverse and non-specific. For instance, ground-glass opacities and dense consolidation are often found in COVID-19 and IPA¹⁸⁻²⁰.

To the best of our knowledge, this is the first reported case of mixed fungal infection in COVID-19 in the Middle East region. This case report further supports published data about severe COVID-19 and invasive fungal infection. Diagnosis of IPA in critically ill patients with COVID-19 in ICUs remains a challenge. The difficulties we faced were that the CT chest scan showed left lower lobe nodules with surrounding faint ground-glass densities which are not sufficient to define CAPA, while tracheal aspirate cultures positive for the presence of *A. fumigatus* and *A. flavus* cannot differentiate between colonization or true invasion. Obtaining future tests from BAL to support the diagnosis is complicated by the restriction in performing bronchoscopy in patients with COVID-19 due to the risk of aerosol generation. The accuracy of serum galactomannan to diagnose IPA would increase if consecutive tests were performed to override its poor sensitivity in IPA detection in

non-neutropenic patients in ICUs. Lastly, repeated chest imaging to assess clinical response of the patient with IPA after completion of antifungal therapy unfortunately was not done, as the patient was kept on conservative and minimal intervention management.

Conclusions

IPA can complicate severe COVID-19 pneumonia. The diagnosis of CAPA is often challenging and requires a high index of suspicion. A constellation of clinical, biochemical, microbiological, and radiological criteria needs to be incorporated

to establish the diagnosis. Timely diagnosis and management are required for better outcomes.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the relative of the patient.

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Open Peer Review

Current Peer Review Status: ?

Version 1

Reviewer Report 24 February 2021

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Ali S. Omrani

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An interesting report on an emerging clinical problem in the context of the ongoing SARS-CoV-2 pandemic. The authors describe the case in reasonable detail, its clinical progression and outcome. The discussion included a good contextualization of the case in the light of the salient knowns in the area. I suggest the authors consider the following comments to further improve their manuscript:

1. The first letter of an antimicrobial agent's generic name should not be capitalized when mentioned mid-sentence (examples from the manuscript: caspofungin, voriconazole, meropenem, lopinavir/ritonavir, ribavirin, and ceftriaxone).
2. SARS-Co-2 is the virus, while COVID-19 is the disease. The following expressions are incorrect: "COVID-19 transmission", "persistent COVID-19 virus shedding", "COVID-19 infection".
3. Was the patient intubated in the referring hospital? If so, what was the timeframe between intubation and day 0 ICU in KFSHRC?
4. Did the patient receive corticosteroids, tocilizumab, sarilumab, or baricitinib in the referring hospital or in KFSHRC? It should be possible to obtain those details from the referring hospital? State if none was given.
5. It would be useful to comment in the discussion on the isolation of *Aspergillus* species from baseline BAL (day 0).
6. It would be useful to comment on combination AFT for IPA.
7. What are the prevailing *Aspergillus* species in Saudi Arabia? Is the isolation of *A. flavus* unusual?
8. Are there any other reports of CAPA from the Middle East or the Gulf region?

9. The article below is a comprehensive review of CAPA reports up to August 2020¹. The authors might find it useful for their discussion.

Thank you

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Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases in immune compromised hosts and critically ill patients

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 12 Mar 2021

Hanan AlBasata, King Faisal Specialist Hospital and research center, Riyadh, Saudi Arabia

Thank you for your review and comments, the following has been done in response to your valuable input:

Comment 1: edited.

Comment 2: Changed.

Comment 3: added.

Comment 4: Yes, he did receive dexamethasone in KFSH, added to the manuscript.

Comment 5: Added.

Comment 6: Added.

Comment 7: A paragraph was added for the most prevalent spp. locally and globally.

Comment 8: At the time of the writing no reported cases, however recently a case series in Kuwait was published and this was added in the discussion.

Competing Interests: No competing interests were disclosed.

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