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Invasive pulmonary aspergillosis and hyperthermia in an immunocompetent patient with COVID-19

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ABSTRACT

Severely ill influenza patients are at increased risk of invasive pulmonary aspergillosis (IPA). Previous reports suggest that Coronavirus Disease 2019 (COVID-19) patients may also be at increased risk of IPA. Here we present an *Aspergillus* co-infection in a COVID-19 immunocompetent patient, complicated by bacteremia and persistent hyperthermia. We describe the challenges in diagnosing IPA in COVID-19 immunocompetent patients and how the patient responded to the treatment.

1. Introduction

The novel virus SARS-CoV-2 causes Coronavirus Disease 2019 (COVID-19), a disease ranging from asymptomatic to critical illness, and can cause severe lung damage [1,2]. About 5% of COVID-19 patients require intensive care [3–5]. Severe COVID-19 has been suggested to be a risk factor for the development of complicating aspergillus infection. Invasive pulmonary aspergillosis (IPA) is a known complication of severe influenza pneumonia [6–8]. COVID-19 patients requiring ICU admission have a high mortality, and if they are co-infected with *Aspergillus*, the mortality rate might be even higher, as it is also seen for influenza patients [3,9].

Here we present a complicated case of COVID-19 infection, with persistent hyperthermia, bacteremia and invasive fungal co-infection, which was successfully treated and the patient is currently in rehabilitation.

2. Case presentation

A 52-year-old male was admitted with respiratory distress preceded by four days of cough and dyspnea. Past medical history included percutaneous coronary intervention (PCI), diabetes type 2, heart failure treatment with angiotensin converting enzyme (ACE) and obesity (body mass index (BMI) at 36.8). No history of cancer or immunosuppression.

The patient was afebrile, with blood pressure 149/90, respiration rate 16/min, saturation 100% with in ambient air. Reverse transcriptase polymerase chain reaction (PCR) for SARS-CoV-2 RNA and Influenza A and B was performed on a nasopharyngeal swab. All targets were negative, and the patient discharged the same day. The assumed diagnosis was decompensation.

16 days later, on day 20 after symptom onset, the patient presented again, with acute respiratory distress, cough, dehydration, and a feeling of fatigue (day 0). The patient was now febrile with a temperature of 39,2 $^{\circ}C$. A new PCR for SARS-CoV-2 was positive on a nasopharyngeal swab.

The patient rapidly deteriorated and on day 2, he was transferred to the intensive care unit (ICU) and was intubated. Computer tomography (CT)-scan showed bilateral infiltrates and broad-spectrum antibiotics (piperacillin/tazobactam and later meropenem) were initiated together with anticoagulant dalteparin due to atrial fibrillation. Hyperthermia with a body temperature above 40 $^{\circ}C$ persisted in spite of paracetamol treatment and external cooling devices. Because of the persistent hyperthermia, continuous renal replacement therapy (CRRT) was initiated on day 9–13 and lowered the temperature to around 38 °C.

On day 20, after 18 days in ICU, blood cultures were positive for *Enterococcus faecium*, catheters were changed and vancomycin added to the antibiotic treatment. Growth from the central venous catheter tip was positive for coagulase negative staphylococci, but not for *E. faecium*.

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Even though *E. faecium* was not grown from the catheter tip, it was still suspected to be the source of infection. Antibiotic treatment with meropenem and vancomycin was continued. SARS-CoV-2 PCR was repeated on tracheal aspiration and remained positive.

A bronchoalveolar lavage was performed on day 24, due to respiratory deterioration.

Aspergillus galactomannan (GM) (Platelia™, BIO-RAD, France) was positive from BAL with an index of 5.7. Blankophor microscopy of BAL revealed hyphae and spores, and culture yielded growth of *Aspergillus fumigatus* sensu stricto (identified according to morphologic criteria and MALDI-TOF). PCR for *Aspergillus* (AsperGenius, PathoNostics, The Netherlands) on BAL was positive for *Aspergillus fumigatus*. PCR was negative for the most common environmental resistance profiles, TR34/L98H and TR46/Y121F/T289A.

Hence, according to the modified AspICU criteria, the patient fulfilled the diagnosis of putative invasive pulmonary aspergillosis [6,10–13].

Aspergillus GM on serum was performed four times during the admission, and remained negative.

Antifungal susceptibility testing performed by broth microdilution according to the EUCAST guidelines showed susceptibility to voriconazole, isavuconazole, itraconazole, posaconazole and amphotericin B [14].

At the regional hospital, on day 25, targeted antifungal treatment with voriconazole 300 mg iv twice daily was initiated (weight 110 kg). Afterwards, the patient was transferred to tertiary care hospital. After 18 days of iv voriconazole, on day 43, the dose was increased to 400 mg iv twice a day due to low level of plasma concentrations of voriconazole (0.7 mg/l). At day 21 of treatment, on day 46, the patient was changed to per oral voriconazole 400 mg, twice a day.

A renewed CT-scan continued to show bilateral infiltrates with consolidation and ground glass opacity.

The patient received CRRT from day 32–34, again due to uncontrolled hyperthermia.

Antibiotics were discontinued on day 40. Antifungal therapy with voriconazole was continued, with timely therapeutic drug monitoring (TDM) ranging from to 0.7–4.8 mg/l. No dose adjustment was necessary. After a total of 41 days in ICU, on day 43, the patient was transferred to the infectious disease department for continued treatment of IPA and rehabilitation. Clinically, he suffered from a massive loss of muscle mass. During the ICU stay an overall weight loss of 18 kg occurred (14% of initial weight). Rehabilitation was challenged by persistent severe dyspnea and critical illness neuropatia.

The voriconazole treatment was well-tolerated and an initial course of 3 months' treatment was planned with subsequent lung imaging to determine overall treatment duration. Clinically the patient improved well and was discharged to a rehabilitation center on day 62 with outpatient follow up. He continued to improve and 2 months after discharge (125 days after admission) CT-scan showed regression in infiltrates and consolidations. The 6-month treatment duration was decided upon, as the follow-up CT-scan at 2 months, still showed infiltrates and consolidations. Treatment duration from 3 to >50 weeks is reported in the literature (ESCMID REF), 2016 IDSA guidelines suggests a minimum of 6–12 weeks [13,15]. However, both IDSA and ESCMID-ECMM-ERS guidelines stress that treatment duration should be guided by evidence of disease improvement, e.g. clinical response and response on imaging.

3. Discussion

COVID-19 patients have a high risk of numerous complications, especially in severe COVID-19 requiring ICU admission. These complications include a high risk of thrombosis, bacterial co-infection - and as described here - a risk of IPA. Severely ill influenza patients at the ICU have a risk of IPA of around 7–23%, with prolonged ICU stay and increased mortality [6]. It still remains unclear if COVID-19 is also associated with an increased risk of IPA. However, there have been many reports from COVID-19 patients in intensive care, highlighting a risk of IPA for COVID-19 patients [3–5].

The diagnosis of IPA can be complicated, as there are no validated guidelines for invasive fungal diseases in critically ill patients who do not fulfil the host factors as described by EORTC/MSG guidelines [16,17]. Here, putative invasive pulmonary aspergillosis was diagnosed using modified AspICU criteria [6,10–12]. If IPA is suspected, it should prompt CT or High Resolution CT scan, and BAL should be obtained for *Aspergillus* GM, blankophor microscopy, culture and PCR. Diagnostic procedures to obtain microbiologic material can be challenging due to the patient's condition, whereas imaging can assist in distinguishing COVID-19 specific changes (as ground glass opacity and crazy paving) from changes related to invasive pulmonary aspergillosis (as nodular consolidation with ground glass halo) [17,18].

BAL is an aerosol generating procedure, and there are reservations concerning health care staff and performing the procedure in an already respiratory challenged patient. However, establishing microbiological evidence for IPA is essential and as demonstrated in this case a full diagnostic work-up is feasible. Establishing a microbiological diagnosis is crucial to ensure timely and correct treatment.

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Consent

Written informed consent was obtained from the patient or legal guardian(s) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of competing interest

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