Medical Mycology Case Reports 31 (2021) 6–10

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

CAPA Case Report

COVID-19 associated pulmonary aspergillosis (CAPA): An Australian case report

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ARTICLE INFO

Keywords:
COVID-19 associated pulmonary aspergillosis (CAPA)
ARDS
ICU
Fungal infection

ABSTRACT

As the COVID-19 pandemic has developed, concern for invasive fungal infections in critically ill COVID-19 patients with acute respiratory distress syndrome (ARDS) has emerged. We describe a clinical case of coronavirus disease (COVID-19) associated pulmonary aspergillus (CAPA) infection and acute respiratory distress syndrome (ARDS) with a good clinical outcome, in a previously well, non-immunocompromised Australian woman.

1. Introduction

Co-infection with *Aspergillus* spp. in critically ill ventilated patients and in association with severe viral pneumonia, including influenza and SARS, is well described [1,2]. Influenza associated invasive pulmonary aspergillosis (IAPA) may occur in the absence of other known predisposing host risk factors, and influenza infection may be an independent risk factor for invasive aspergillosis, with an incidence of 19% compared to 5% in a matched comparison of patients in ICU with pneumonia, with and without influenza respectively [1].

The observation of aspergillosis in cases of severe COVID-19 pneumonia has been highlighted in emerging reports and observational case series from China and Europe [3,4]. Koehler et al. described 5 cases of putative invasive pulmonary aspergillosis in 19 patients with ARDS and severe COVID-19 in Germany [5]. A prospective observational study of COVID-19 in France reported putative invasive aspergillosis in 9 of 27 ventilated cases (33%) [6]. Early COVID-19 reports from China reported 7 of 221 ICU patients with aspergillosis [7]. Whether SARS-CoV-2 predisposes the host to invasive aspergillosis as an independent host factor is not known yet, and the true incidence, outcomes and pathophysiological mechanisms for invasive disease have not been elucidated in this setting [8].

Diagnosis of aspergillosis requires a high level of suspicion as clinical and radiological signs may be similar to those of COVID-19, and sampling and safe laboratory processing of respiratory cultures is required. The positive predictive value of upper respiratory tract *Aspergillus* spp. cultures for true invasive disease is not known, as tracheal colonisation is well recognized [8]. Screening and early diagnosis might be enhanced with non-culture methods as recommended by Gangneux et al. [9]. However the sensitivity and performance of serum galactomannan assays, *Aspergillus* PCR and 1,3-B-D-glucan assay may be variable in non-immunocompromised cases and in early reports of CAPA [5,6,8,10].

Treatment of critically ill COVID-19 patients with evidence of *Aspergillus* spp. in bronchoalveolar lavage or serum is supported by expert groups in Europe pending further research [8]. Experience with empirical or directed use of antifungal agents in the setting of COVID-19 is required, particularly in regards to efficacy, duration of treatment and possible adverse drug reactions in the setting of hepatotoxicity (a not uncommon feature of severe COVID-19), renal compromise, renal dialysis, arrhythmias, and electrolyte imbalance. Drug interactions with concurrent critical care agents or new or proposed COVID-19 specific therapies may influence the choice of an antifungal agent.

2. Case report

A 66-year-old woman presented with fever after close contact with a confirmed COVID-19 case in April 2020. SARS-CoV-2 RNA was detected

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https://doi.org/10.1016/j.mmcr.2020.06.002
Received 3 June 2020; Received in revised form 9 June 2020; Accepted 9 June 2020
Available online 18 June 2020

in nasopharyngeal and throat swab by RT-PCR method described by Corman [11] (E-gene Ct 22.04 & RdRp Ct 35.09, Roche LightCycler 480). Initial supportive treatment for COVID-19 was supervised at home.

On day+8, symptoms of fever, headache, fatigue, muscle aches, mild abdominal pain, diarrhoea, and vomiting developed, and the patient presented to hospital. Medical history was significant for hypertension and osteopenia. Prescribed medications included Perindopril/Amlodipine and Cholecalciferol (vitamin D3). She was a recent ex-smoker of 20 pack years. There was no history of immunosuppression, no chronic organ dysfunction, nor a history of fungal colonisation on respiratory culture performed in 2017. She was independent in her activities of daily living (see Fig. 1).

Features on examination were fever (40 °C), respiratory rate 26/min, pulse 80/min, blood pressure 120/70 mmHg, with low oxygen saturation (SpO2 89% on room air). There was increase in work of breathing and bibasal coarse crepitations noted on lung auscultation. The remainder of the physical examination was normal. Arterial blood gas sampling on room air demonstrated pH of 7.44, PaO_2 70 mmHg; (PaO_2/FiO_2 = 334), PaCo2 34 mmHg, lactate 0.9 mmol/L. The white blood cell count (WCC) was 5.3 × 10^9/L, with a neutrophil differential count 3.9 × 10^9/L, and lymphocyte count 1.2 × 10^9/L. Liver function tests demonstrated AST 52U/L, ALT 32 U/L, GGT 61U/L, and LDH 429 U/L. Renal function was normal. Blood cultures performed on admission isolated *Facklamia hominis* and urine culture isolated *Escherichia coli*; both organisms were susceptible to Ceftriaxone. Chest radiology demonstrated poorly defined pulmonary opacities bilaterally, located principally in the lower lung fields and the right mid lung field (Fig. 2a).

The patient was admitted to a dedicated COVID-19 respiratory ward as she had risk factors associated with worse COVID-19 outcomes (age >60 years, hypertension, and the history of smoking) and met clinical criteria for severe COVID-19 pneumonia [7,12,13]. Ceftriaxone 1g daily and Azithromycin 500mg daily was commenced for possible bacterial co-infection in addition to supplemental oxygen and subcutaneous enoxaparin sodium for venous thromboembolism prophylaxis. No specific therapy targeting COVID-19 infection was initiated (as per local guidelines).

On day+10 of illness the patient's condition deteriorated rapidly with progressive dyspnoea and increasing oxygen requirement. She was admitted to a newly commissioned COVID-19 intensive care unit (ICU) for supportive management. On examination, temperature was 39.5^{O}C, respiratory rate 40/min, oxygen saturation 91% on high flow nasal prongs (HFNP) with FiO_2 40%, and 40 L/m of airflow with a moderate increase in her work of breathing. No clinical signs of heart failure were detected. A trans-thoracic echocardiogram was performed and demonstrated normal biventricular function with mild right ventricular dilatation. Arterial blood gas on FiO_2 of 40% demonstrated pH 7.46, PaO_2 59 mmHg (PaO_2/FiO_2 = 148) and $PaCO_2$ 31 mmHg suggestive of moderate acute ARDS. Awake prone positioning [14] was performed for alveolar recruitment with no significant improvement in oxygenation, therefore elective endotracheal intubation and mechanical ventilation were instituted. Post intubation, she was managed with lung-protective ventilation (Tidal volume 4–6 ml/kg, PEEP 12 cmH_2O and Plateau pressure <30 cmH_2O) aiming for PaO_2>60 mmHg and pH > 7.2 as per ARDS net protocol [15]. There was further deterioration in ventilatory parameters, and she fulfilled the severe ARDS criteria as per Berlin definition (PaO_2/FiO_2 = 82 mmHg, PEEP = 12 cmH_2O) [16].

On day+16 of illness, worsening respiratory function and hypercapnoea were observed. Fever was absent, but increased inflammatory markers were observed: C reactive protein 351mg/L, deranged LFTs (ALT = 125 U/L, AST = 154 U/L, GGT = 611 U/L, ALP = 229 U/L), raised ferritin (1295 μg/L), raised D-dimer 0.99mg/L and fibrinogen 5.8g/L. Chest radiology revealed significant progression of bilateral consolidative opacities (Fig. 2b). Respiratory tract specimens were obtained by non-bronchoscopic endotracheal aspirate (ETT) to assess for presence of persistent SARS-CoV-2 RNA and to exclude ventilator-associated pneumonia, and a 7-day course of Piperacillin/Tazobactam was initiated. Based on anecdotal evidence from the PROSEVA trial, prone ventilation was initiated, and some improvement in ventilatory parameters was noted [17]. Microbiology results revealed persistent SARS-CoV-2 RNA on RT-PCR (Corman method) [11]. No viral culture or quantitative viral load was performed. Fungal elements were seen on Gram staining of the ETT sample. Green colonies of *Aspergillus fumigatus* complex were isolated at 48 hours on Horse blood agar and Chocolate agar, demonstrating uniseriate conidial heads with phialides limited to the upper two thirds of the vesicle (culture mount stained with lactophenol cotton blue). Three subsequent ETT cultures isolated *Aspergillus fumigatus* complex, increasing the clinical suspicion for invasive aspergillosis. On day+20, with new onset of fever, and progressive bilateral consolidation seen on chest radiography (Fig. 2c), the decision was made to initiate a cautious trial of intravenous Voriconazole (6 mg/kg loading followed by 3mg/kg twice daily), despite concerns regarding abnormal liver function tests.

The patient was observed to make rapid clinical and radiological progress over the next 7 days (Fig. 2d). Fevers settled, inflammatory markers improved, and liver function normalized. Steady-state

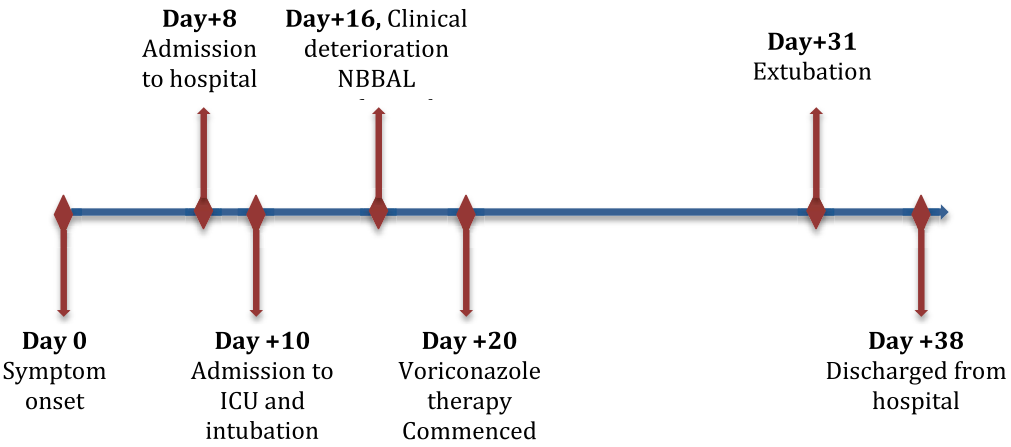

Fig. 1. Timeline depicting the clinical course.

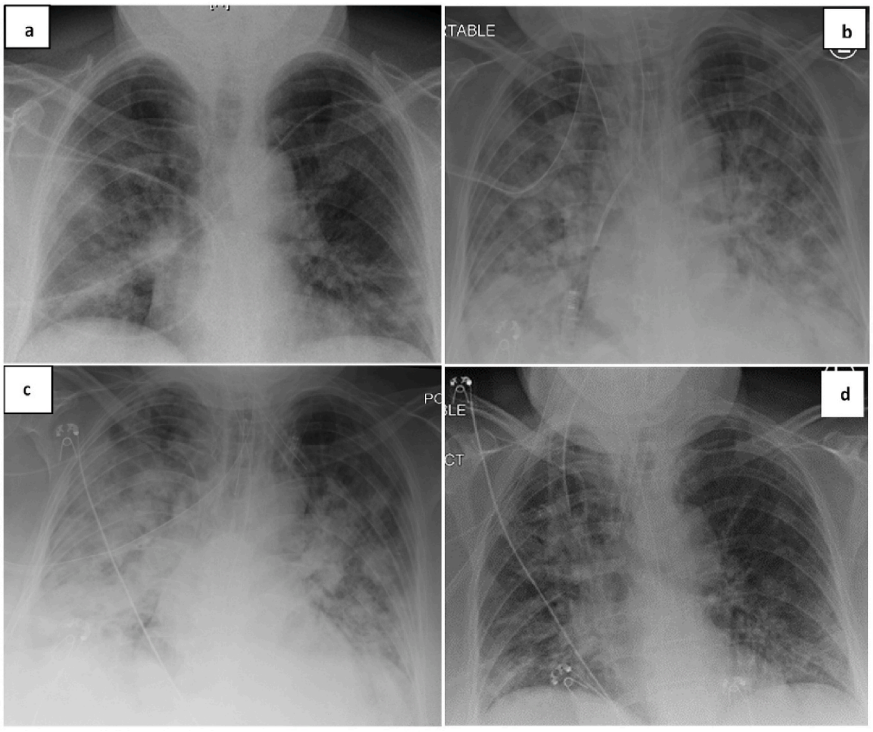

Fig. 2. a: Chest radiograph day+8 showing poorly defined pulmonary opacities bilaterally, located principally in the lower lung fields and right mid lung field. SARS-CoV-2 detected on nose and throat swab. **b:** Chest radiograph day+16 showing significant progression of bilateral consolidative opacities, worse in the lower zones. *Aspergillus fumigatus* complex isolated from ETT, and SARS-CoV-2 RNA detected by PCR on ETT sample. **c:** Chest radiograph on day+21 showing increased confluent right lung consolidation and persistent focal nodular consolidation in the left mid to lower zones. Voriconazole treatment day+1. **d:** Chest radiograph on day+27 showing overall improvement.

Voriconazole trough levels were observed (2.72mg/L). She was extubated on day +31. Treatment was de-escalated to oral Voriconazole (300mg twice daily) once tolerating oral diet. After a period of ward rehabilitation and two negative SARS-CoV-2 RT-PCR clearance swabs as per local public health guidelines, the patient was discharged home on day +38.

On day+45, a contrast-enhanced computed tomography (CECT) of the chest was performed to assess for disease progression and complications. CECT demonstrated bilateral organising pneumonia and fibrosis (Fig. 3) with a probable small segmental pulmonary embolism in the left upper lobe, which are known sequelae of COVID-19 pneumonia. Voriconazole was ceased at that stage (total duration of treatment was one month), due to the risk of drug-drug interaction with proposed anticoagulation therapy (Apixaban) and abnormal liver function testing (Voriconazole trough level 3.6mg/L). At the time of this report the patient remains well, off anti-fungal therapy, with mild dry cough and improved effort tolerance, and no systemic features.

3. Discussion

This report illustrates the successful management of a case of severe COVID-19, in a well-prepared intensive care unit and with the benefit of the published experience of other groups. The diagnosis of aspergillosis in this case was confounded in the presence of viral pneumonitis and inflammation, ARDS, vascular thrombosis, and highly transmissible virus.

The bilateral pulmonary opacities on CECT would be consistent with pulmonary infection however the radiographic appearance cannot determine the causative pathogen. Routine computed tomography (CT) imaging is generally not recommended by most radiology societies and was not utilized in this case for practical reasons. CT appearances of COVID-19 pneumonia may be considered typical, indeterminate or atypical. CT may help distinguish between “typical” COVID pneumonia (bilateral peripheral ground glass opacity which may be rounded or associated with intralobular septal thickening giving a crazy paving

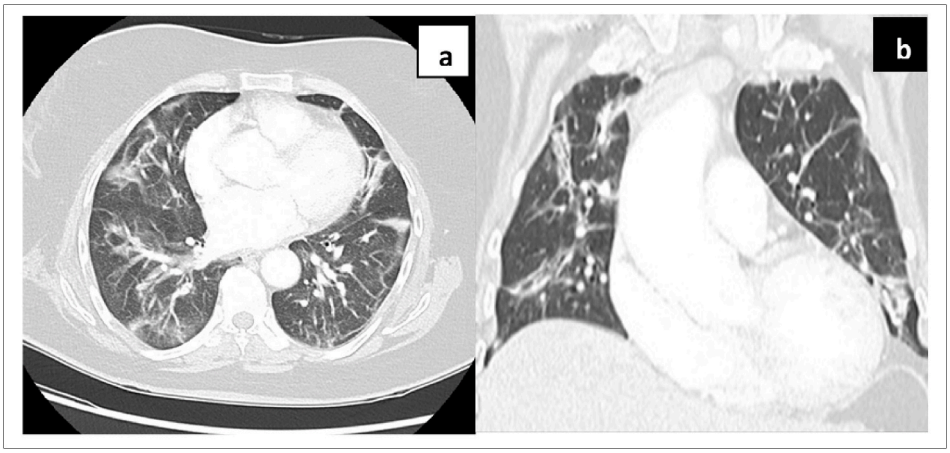

Fig. 3. Contrast-enhanced computed tomography chest on day+45 showing organising pneumonia with mild scarring anteriorly in the upper lobes and left lingula.

pattern) and "typical" invasive pulmonary aspergillosis (nodular consolidation with a ground glass halo) [5,18].

Revised EORTC/MSG guidelines for the diagnosis of invasive fungal disease are not validated in critically ill patients in the absence of a recognized predisposing host factor [19]. An alternative clinical algorithm to identify putative invasive aspergillosis and discriminate between significant infection and tracheal colonisation in critically ill patients was evaluated by Blot et al. [20] in the *Asp*ICU Study, and modified for influenza by Schauwvlieghe et al. [1] and has been utilized for CAPA by Koehler et al. [5]. Fungal culture in upper respiratory tract samples and tracheal aspirates has low sensitivity and specificity for invasive fungal disease, but bronchoscopy in the presence of SARS-CoV-2 infection may increase the risk of virus aerosolisation and transmission, and may increase the risk of pulmonary de-recruitment and was therefore not performed. This case did not fulfil all criteria for proven or putative invasive fungal infection, as bronchoscopic sampling for culture, cytology, fungal PCR or galactomannan was not performed, and serum galactomannan or other non-culture techniques or biopsy were not done. Diagnostic discrimination between putative invasive aspergillosis and tracheal colonisation, or earlier diagnosis may have been enhanced with serum galactomannan testing.

The decision to initiate an anti-fungal agent was made on clinical grounds of worsening respiratory function in spite of appropriate antibiotics and increasing ventilatory support, with evidence of colonisation with *Aspergillus fumigatus* complex isolated from multiple tracheal aspirate samples. No SARS-CoV-2 viral culture or vial load was performed, and the persistent detection of SARS-CoV-2 by RT-PCR does not necessarily correlate with underlying infectious process. Although a compelling clinical response was observed after antifungal therapy was initiated, this may reflect the natural course of severe COVID-19 recovery and the role of supportive ICU measures including empiric treatment of sepsis and prone ventilation. Radiological improvement was more rapid than may be expected for true invasive fungal infection. Voriconazole was well tolerated initially, with acceptable steady-state therapeutic trough levels but hepatotoxicity was noted after four weeks of therapy, and influenced the decision to cease treatment.

No recognized predisposing host factor or acquired immunosuppression, other than severe COVID-19 infection with ARDS was identified. The environmental source of infection was not determined, and the protective or predisposing role of facemask use prior to illness or a negative air pressure environment has not been assessed. No concurrent cases of invasive aspergillosis or fungal colonisation were noted in other ventilated COVID-19 patients on screening with ETT sputum cultures (three patients), and no clusters or increased incidence of invasive aspergillosis cases have been observed hospital-wide, preceding this case or subsequently.

We believe that in the absence of clear diagnostic criteria, consideration should be given to anti-fungal directed therapy if aspergillosis is suspected in severe COVID-19 associated pneumonia. Prompt notification and identification of co-infections in COVID-19 in critical care settings may be enhanced with multi-disciplinary and collaborative case discussions including clinicians, microbiologists, and radiologists.

To our knowledge, this is the first case report of COVID-19 associated pulmonary aspergillosis in NSW, Australia. Registries and larger case series are required to better identify and characterize the incidence, pathogenesis, geographical variation, diagnostic criteria, and treatment and prevention strategies.

Declaration of competing interest

The Authors declare no conflict of interest.

Acknowledgements

Authors acknowledge David Pham and Lyn Doan for microbiology assistance. No funding to declare.

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