Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Microbiology and Infection 27 (2021) 147–148

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

Invasive aspergillosis in patients with severe COVID-19 pneumonia

Marie Helleberg [1,*], Morten Steensen [1], Maiken Cavling Arendrup [2]

[1] Copenhagen University Hospital, Rigshospitalet, Denmark
[2] Statens Serum Institut, Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 23 April 2020
Received in revised form
30 June 2020
Accepted 30 July 2020
Available online 5 August 2020

Editor: A. Kalil

To the Editor

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes viral pneumonia and can be complicated by acute respiratory distress syndrome (ARDS) which is similar to that seen in severe influenza. Approximately 5% of patients with SARS-CoV-2 disease (COVID-19) are treated in intensive care units (ICUs) because of respiratory failure. In recent years it has been recognized that rates of invasive aspergillosis are high (19%) among patients admitted to the ICU with severe influenza, including those without other risk factors for invasive fungal infections (14%) [1]. Influenza-associated aspergillosis is diagnosed at a median of 3 days after admission to the ICU and is associated with increased mortality (51% versus 28%, p 0.0001) [1]. Other severe viral pneumonias also may significantly increase the risk of invasive aspergillosis [2–4]. Recently a few case reports of COVID-19-associated *Aspergillus fumigatus* infection have been published, but the incidence of invasive aspergillosis in COVID-19 patients with critical illness is unknown [5,6].

Rigshospitalet is a tertiary referral university hospital, and one of two centres for extracorporeal membrane oxygenation (ECMO) in Denmark. We have treated eight COVID-19 patients with ECMO in the period 15th March 2020 to 11th April 2020. Two of the eight patients were diagnosed with plausible pulmonary aspergillosis due to worsening of respiratory insufficiency, pulmonary infiltrates despite antibacterial therapy, and positive *Aspergillus* cultures and galactomannan antigen (GM) tests on samples of serum or lower respiratory tract secretion. Biopsy or bronchoalveolar lavage (BAL) was not performed to confirm the diagnosis of pulmonary aspergillosis to reduce the risk of aggravation of respiratory failure and the risk of transmission of SARS-CoV-2. Thus, the diagnosis of pulmonary aspergillosis was plausible but not proven. However, a therapeutic BAL was performed later in the course of the disease for one of the patients, and GM testing of the BAL fluid yielded a positive result. Clinical and mycological characteristics, treatments and outcomes of the two patients are summarized in Table 1. Both patients were middle-aged females. One had a history of asthma and was treated with systemic corticosteroids (methylprednisolone 80 mg intravenously for 2 days then oral prednisolone 37.5 mg for 4 days) upon admission; the other patient had no classical risk factors for invasive aspergillosis. The ICU algorithm for the diagnosis of putative invasive aspergillosis require (a) an *Aspergillus*-positive lower respiratory tract specimen culture, (b) compatible symptoms, (c) abnormal chest x-ray/CT scan, and (d) either a host factor or a positive BAL culture and microscopy [7]. Patient 2 fulfilled all four criteria, while criterion 4 was not fulfilled for patient 1. However, patient 1's BAL and serum tested positive for GM. GM tests on BAL or serum are included in the updated EORTC diagnostic criteria for probable invasive aspergillosis and in the diagnostic criteria in the study of influenza-associated aspergillosis by Schauwvlieghe et al. [1,8]. Because diagnostic BAL was not feasible, we used the GM test on tracheal secretion in patient 1, although the assay is not validated for this type of sample.

Both patients were treated with voriconazole, and therapeutic drug monitoring was performed. The *Aspergillus* isolates from both patients were tested for antifungal resistance and found to be sensitive to voriconazole. Repeated cultures of tracheal secretions during antifungal therapy did not yield any growth. Patient 1 had a therapeutic BAL performed 14 days after initiation of antifungal therapy. The BAL sample was also without growth, but a GM test was strongly positive (index 8.2). Sadly, both patients had continuous severe respiratory failure despite supportive and antifungal therapy, and both had a fatal outcome.

In the same period 25 other patients—six on ECMO and 19 treated with invasive mechanical ventilation for COVID-19-associated ARDS at our centre—were screened for aspergillosis with tracheal secretion cultures and serum GM tests, but there were no positive findings.

* Corresponding author: Marie Helleberg, Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark.
E-mail address: marie.helleberg@regionh.dk (M. Helleberg).

https://doi.org/10.1016/j.cmi.2020.07.047

Table 1
Characteristics of two COVID-19 patients treated with ECMO (extracorporeal membrane oxygenation) and diagnosed with pulmonary aspergillosis

	Patient 1	Patient 2
Gender	Female	Female
Age (years)	63	53
Co-morbidity	Hypertension	Asthma
History of smoking	Prior smoker	Prior non-regular smoker
Neutrophil/lymphocyte count at time of hospital admission ($\times 10^9$/L)	3.3/0.8	5.3/1.1
Days with symptoms at time of hospital admission	8	6
Days hospitalized before transfer to ICU	3	4
Days intubated prior to ECMO	7	22
Days on invasive mechanical ventilation prior to diagnosis of aspergillosis[a]	5	1
Treatment with systemic corticosteroids during admission[b]	No	Yes, methylprednisolone 80 mg i.v. for 2 days followed by oral prednisolone 37.5 mg for 4 days
Experimental treatments for COVID-19 (i.e. IL-6 inhibitor, JAK inhibitor etc.)	None	None
Antibiotics during admission before diagnosis of aspergillosis	Piperacillin–tazobactam, meropenem	Piperacillin–tazobactam
Bacterial co-infections	None documented	None documented
Chest x-ray findings	Severe bilateral infiltrates	Severe bilateral infiltrates
Tracheal secretion cultures	*Aspergillus fumigatus* (++)	*Aspergillus fumigatus* (+) x 2
Aspergillus galactomannan antigen, index (days after first positive culture)	Serum[c]: positive,1.1 (2)	Tracheal secretion: positive, 2.2,
	BAL[d]: positive, 8.2 (15)	Serum: negative, 0.1
Antifungal therapy	Voriconazole	Voriconazole
Outcome	Died with multiorgan failure 41 days after hospital admission	Died of a large intracranial haemorrhage while on ECMO, 34 days after hospital admission

BAL, bronchoalveolar lavage; JAK, Janus kinase.
[a] Defined as date of collection of the first sample with growth of *Aspergillus fumigatus*.
[b] Before diagnosis of aspergillosis.
[c] The sample was collected 4 days after discontinuation of piperacillin–tazobactam.
[d] Therapeutic BAL was performed 15 days after first positive culture and 14 days after initiation of voriconazole to clear thick airway secretion; culture was without growth and a respiratory virus multiplex analysis yielded only negative results.

We conclude that invasive aspergillosis may complicate severe COVID-19 pneumonia and that ECMO patients may constitute a subpopulation at increased risk. We suggest that ICU patients who have progressive respiratory failure and do not respond to antibacterial therapy are examined for invasive aspergillosis with cultures and biomarkers.

Author contributions

All authors contributed to conceptualization, formal analysis, investigation and resources. MH wrote the original draft of the manuscript. All authors edited and reviewed the manuscript and approved the final version.

Transparency declaration

MH received funding from the Danish National Research Foundation (grant #126), MS and MCA declare no conflicts of interest with respect to the current work. Outside the current work, MH has, over the past 5 years, received speaker honoraria (personal fees) from Gilead, GSK and MSD, contract work from Gilead, and travel grants from GSK. MS has received speaker honoraria (personal fees) from Gilead and MSD. MCA has, over the past 5 years, received research grants/contract work (paid to the SSI) from Amplyx, Basilea, Cidara, F2G, Gilead, Novabiotics, Scynexis and T2Biosystems and speaker honoraria (personal fees) from Astellas, Gilead, Novartis, MSD, and SEGES. She is the current chairman of the EUCAST-AFST.

References

[1] Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 2018;6:782–92.
[2] Piñana JL, Gómez MD, Montoro J, Lorenzo I, Pérez A, Giménez E, et al. Incidence, risk factors, and outcome of pulmonary invasive fungal disease after respiratory virus infection in allogeneic hematopoietic stem cell transplantation recipients. Transpl Infect Dis 2019;21:e13158.
[3] Chen X, Yu Z, Qian Y, Dong D, Hao Y, Liu N, et al. Clinical features of fatal severe fever with thrombocytopenia syndrome that is complicated by invasive pulmonary aspergillosis. J Infect Chemother 2018;24:422–7.
[4] Martino R, Piñana JL, Parody R, Valcarcel D, Sureda A, Brunet S, et al. Lower respiratory tract respiratory virus infections increase the risk of invasive aspergillosis after a reduced-intensity allogeneic hematopoietic SCT. Bone Marrow Transplant 2009;44:749–56.
[5] Koehler P, Cornely OA, Böttiger BW, Dusse F, Eichenauer AD, Fuchs F, et al. COVID-19 associated pulmonary aspergillosis. Mycoses 2020;63:528–34.
[6] Blaize M, Mayaux J, Nabet C, Lampros A, Marcelin AG, Thellier M, et al. Fatal invasive aspergillosis and coronavirus disease in an immunocompetent patient. Emerg Infect Dis 2020:26.
[7] Blot SI, Taccone FS, van den Abeele AM, Meersseman W, Brusselaers N, Dimopoulos G, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med 2012;186:56–64.
[8] Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European organization for research and treatment of cancer and the mycoses study group education and research consortium [published online ahead of print, 2019 dec 5]. Clin Infect Dis 2019:ciz1008. https://doi.org/10.1093/cid/ciz1008.