COVID-19-associated Aspergillosis in the ICU Setting

Eitor Letter

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Dear Editors

The The COVID-19 pandemic has led to worldwide interest from the scientific community in studying this disease in all its aspects and its immediate and future consequences.

Pulmonary Aspergillosis is one such complication related to SARS-COV2 infection. Incidence has been reported between 5 and 35%, varying according to the geographic location. Currently, there are no well-defined criteria for the diagnosis of COVID-19-associated pulmonary aspergillosis1 which contributes to the differences in incidence found in the literature. Establishing the diagnosis is crucial due to the significant impact on the prognosis of these patients.

Known risk factors for co-infection include corticosteroid therapy or immunosuppressive treatment with anti-IL-6 monoclonal antibodies.[1] Nonetheless, other studies have been developed to understand how SARS-COV2 infection itself may be a risk factor for Invasive Pulmonary Aspergillosis.[2]

Acute respiratory distress syndrome (ARDS) induced by viral infection and hypoxia compromise the host's innate imunnity.[3] Upregulation of Th2 cellular response and downregulation of Th1 response may be related to the negative regulation of macrophage action and increase the host's susceptibility to *Aspergillus* infection.

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Pulmonary Aspergillosis syndromes that complicate serious viral infections are different from classic Invasive Pulmonary Aspergillosis,[4] so its diagnosis has been a challenge and studies on this subject have been increasing.[5]

Pulmonary Aspergillosis related with SARS-COV2 infection usually develops within the first weeks of disease.

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) has proposed diagnostic criteria for COVID-19-associated pulmonary aspergillosis, based on host factors, clinical and microbiological evidence, and applied to immunocompromised patients.[1,4]

Influenza-Associated Pulmonary Aspergillosis (IAPA) has similarities with COVID-19-associated aspergillosis, namely the absence of defined host risk factors. The differences relate to the pathophysiology of the viruses.

The Invasive Pulmonary Aspergillosis In Intensive Care Unit Patients (AspICU) criteria were previously used for the diagnosis of pulmonary co-infection with influenza virus and Invasive Pulmonary Aspergillosis and include clinical and host factors, as well as lower respiratory tract cultures.[1] The latter include the determination of serum galactomannan and in bronchoalveolar lavage (BAL), with BAL culture and direct microscopy positive for *Aspergillus spp*.?

Systemic markers, such as serum galactomannan and BAL fluid, are suboptimal for the diagnosis of COVID-19-associated pulmonary aspergillosis, with a sensitivity of less than 50%. -d-glucan, although more sensitive, can be detected in several invasive fungal infections.[4]

	Sex	Age	Comorbidities	APACHE II score at ICU admission	Day of COVID-19 symptom when *AF* identified	How Many Day after admission to the ICU, was *AF* identified?	Renal Failure requiring renal replacement therapy	ARDS		
								PaO_2/FiO_2 at ICU admission	Prone Possition	ECMO
Patient 1	Masculine	57	Grade I obesity, dyslipidemia	4	9	13	Yes	78 mmHg	Yes	No
Patient 2	Masculine	79	Arterial hypertension, Type II diabetes mellitus stage 4 chronic kiney disease	23	10	16	Yes	96 mmHg	No	No
Patient 3	Masculine	65		15	6	15	Yes	45 mmHg	Yes	No
Patient 4	Femenine	45	Grade III obesity Arterial hypertension	10	16	5	No	96 mmHg	No	No

	Corticosteroid Therapy	Another Inmuno Suppressive treatment	Germens Identification before *AF*	Positive culture test for *AF*		Germens identification after *AF*
Patient 1	Dexamethasone 6mg 10 days, Methylprednisolone 16 days on taper	No	0	3 Samples	1	*Stenotrophomonas maltophilia, Klebsiella pneumoniae*
Patient 2	Dexamethasone 6mg 6 days	No	0	1 Sample	1	0
Patient 3	Dexamethasone 6mg 7 days, Methylprednisolone 3 days	No	0	1 Sample	1	0
Patient 4	Dexamethasone 6mg 10 days,	No	0	3 Samples	0	0

	Case Classification?	Antifungal treatment?	Days to death after *AF* identification?	Day of ICU discharge?
Patient 1	Probable	Voriconazole 4mg/kg 12/12hr, 7 days Amphotericin B, 0.5 mg/kg, 14 days	27 27	NA
Patient 2	Probable	Amphotericin B 0.5 mg/kg 4 days (until dead)	5	NA
Patient 3	Probable	Voriconazole 4mg/k 12/12h 3 days (until dead)	5	NA
Patient 4	Possible	Voriconazole 4mg/kg 12/12hr, 3 days	NA	19

TABLE 1: CHARACTERISTICS OF THESE PATIENTS. APACHE II- ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION SCORE II; ICU- INTENSIVE CARE UNIT; ARDS- ACUTE RESPIRATORY DISTRESS SYNDROME; ECMO- EXTRACORPOREAL MEMBRANE OXYGENATION; NA- NOT APPLICABLE; *AF- Aspergillus Fumigatus*

Philipp Koehler et al[1] proposed a case definition distinguishing them as proven, probable, or possible, considering microbiological isolations and imaging changes.

As COVID-19-associated aspergillosis is associated with worse prognosis and increased mortality, treatment is recommended in all cases where superinfection is proven, probable, or possible with a 6 to 12-week course of either voriconazole or isavuconazole.[2,4,6–8]

Given the persisting lack of knowledge about COVID-19-associated pulmonary aspergillosis[6] the authors describe the existing cases in their Intensive Care Unit (ICU).

Between December 2020 and July 2021, 294 patients with severe SARS-COV2 infection were admitted to the ICU, among which the authors identified four cases of possible or probable COVID-19-associated pulmonary aspergillosis (Table 1).

The four patients were admitted to the Intensive Care Unit with severe ARDS, with Horowitz indices less than or equal to 96 mmHg.

The diagnosis was established through positive sputum cultures for *Aspergillus fumigatus* Three patients also had positive BAL cultures. The diagnosis was made on the 13th, 16th, 15th, and 5th day of ICU stay, respectively.

All patients presented with peripheral infiltrates and septal thickening on chest computed tomography. Cases 1, 2 and 3 also presented with nodulariform consolidations (Figure 1).

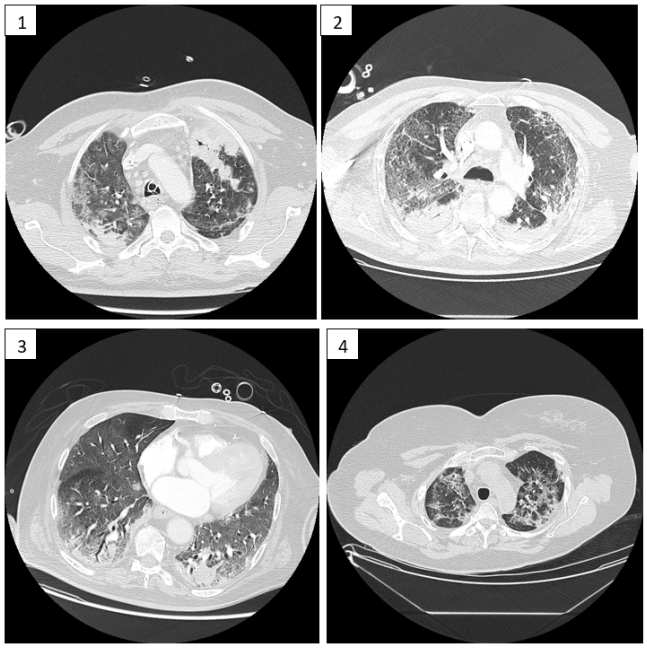

Figure 1: Patients´ Computed tomography Scans.

According to the classification proposed by Philipp Koehler et al[1] cases 1, 2 and 3 are probable, due to the temporal relationship with SARS-COV2 infection, imaging findings, and positive sputum and BAL culture. Case 4 is possible, due to the temporal relationship with SARS-COV2 infection, imaging findings, and positive sputum culture.

Although all patients were started on antifungal treatment immediately following positive microbiological isolation, three ended up dying 5 to 27 days after the identification of *Aspergillus fumigatus*.

The authors underscore the importance of timely diagnosis and early initiation of treatment, even in suspected cases. The data presented corroborate the association of COVID19-associated pulmonary aspergillosis and a worse prognosis. Attention to host factors, clinical risk, and radiological findings are essential for early identification and treatment.

Some authors highlight factors related to the ICU environment which may represent hitherto underestimated risk factors, such as isolation conditions, ventilation systems, and management of a large number of hospitalized patients4. Therefore, these must also be identified, monitored, and improved according to established safety standards.

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