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Abstract

Objectives: The main objective of this study was to determine invasive pulmonary aspergillosis (IPA) incidence in the COVID-19 patients admitted to the intensive care unit (ICU), describe the patient characteristics associated with its occurrence and evaluate the impact on prognosis.

Methods: We conducted a retrospective cohort study including all successive COVID-19 patients hospitalized in four ICUs with secondary deterioration and ≥1 respiratory sample sent to the mycology department. A strengthened IPA testing strategy including seven mycological criteria was used. Patients were classified as probable IPA according to the EORTC/MSGERC classification if immunocompromised and to the recent COVID-19-associated IPA classification otherwise.

Results: Probable IPA was diagnosed in 21 out of the 366 COVID-19 patients (5.7%) admitted to the ICU and the 108 patients (19.4%) who underwent respiratory sampling for deterioration. No significant differences were observed between patients with and without IPA regarding age, gender, medical history and severity on admission and during hospitalization. Treatment with azithromycin for ≥3 days was associated with the diagnosis of probable IPA (odds ratio, 3.1; 95%-confidence interval, 1.1-8.5; p=0.02). A trend was observed with high dose dexamethasone and the occurrence of IPA. Overall mortality was higher in the IPA patients (15/21, 71.4% *vs*. 32/87, 36.8%; p<0.01).

Conclusion: IPA is a relatively frequent complication in severe COVID-19 patients responsible for increased mortality. Azithromycin, known to have immunomodulatory properties, may contribute to increase COVID-19 patient susceptibility to IPA.

Keywords : Aspergillus, COVID-19, azithromycin, SARS-CoV-2, Critical Care, Coronavirus, Corticosteroids

Introduction

Although pulmonary invasive fungal disease is typically described in the immunocompromised host, invasive pulmonary aspergillosis (IPA) has been increasingly reported in critically ill patients including patients without classical risk factors of immunosuppression [1]. In acute respiratory distress syndrome (ARDS) patients, ~12.5% of the patients had IPA as shown by random post-mortem histopathological examination of lung tissue [2]. Coronavirus disease 2019 (COVID-19)-associated pulmonary aspergillosis (CAPA) has been increasingly reported [3-5]. Whether the use of immunomodulatory therapies such as corticosteroids prescribed to dampen detrimental inflammatory response and antibiotics to treat and/or prevent bacterial superinfections is responsible for increased susceptibility of COVID-19 patients to pulmonary invasive fungal disease remains incompletely studied [6,7]. The aim of our study was to evaluate the incidence of IPA and the risk factors associated with IPA in severe COVID-19 patients admitted to the intensive care unit (ICU), and evaluate the impact of IPA on patient's outcome.

Method

We conducted a retrospective observational cohort study. All successive COVID-19 patients admitted to the four ICUs of our two university hospitals between March 15th and May 1st 2020 with a positive SARS-CoV-2 PCR (Cobas® SARS-CoV-2 Test, Roche) and ≥1 respiratory sample (bronchoalveolar lavage (BAL), tracheal aspirate, sputum) sent to the mycology department were included (Figure 1). Of note, the 27 first patients included were previously partially analyzed [3]. On respiratory sample, culture, galactomannan (GM) (BAL only) and *Aspergillus* quantitative polymerase chain reaction (qPCR) were systematically performed. In concomitantly received blood sample, GM, ß-D-glucan (BDG) and *Aspergillus* qPCR were performed on serum/plasma. Patients were classified as probable IPA according to European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group Education and Research Consortium (MSGERC) consensus criteria in immunocompromised patients [8] and according to the consensus case definition proposal for influenza/COVID-19-associated pulmonary aspergillosis (CAPA) in ICU patients otherwise (Table S1) [9]. An extensive list of clinical data was collected as part of the initial protocol (Table 1). The cumulative dose of corticosteroids, azithromycin and ß-lactams were determined as the total dose of drug received prior to the day of sampling. Prescription of azithromycin >1500mg and ß-lactams >3 days were predefined as exposure variables. Azithromycin was systematically prescribed before or on the day of admission to the ICU, except for 2 patients for whom it was introduced at day 4 and 5, respectively. If no fungal infection was diagnosed the latest sample was used. Corticosteroids doses were quantified as dexamethasone-equivalent [10].

Culture of respiratory specimens were performed, as previously described [11]. For *Aspergillus* qPCR, DNA was extracted from 1mL of plasma or from bead-beaten pellet of the respiratory sample and resuspended in 1000μL of DNA-free water using the Qiasymphony DSP virus/Pathogen Mini kit (Qiagen,) and a QIAsymphony apparatus (Qiagen). PCR assay was previously reported [12]. GM and BDG detection were performed using Platelia Bio-Rad kit (BioRad Laboratories) and Fungitell assay (Cape Cod Diagnostics) according to the manufacturer respectively.

Statistics

Data were reported in percentage, mean and standard deviation (SD) or median and interquartiles [Q1-Q3] as appropriate. Univariate analyses were performed to assess an association between clinical factors and IPA using Fisher's exact, Chi-2 and Wilcoxon tests as appropriate. Odds ratios (OR) with 95%-confidence intervals (IC95%) were calculated for each significant variable based on univariate logistic regression. All analyses were performed using R software, version 3.5.3 (http://www.r-project.org).

Ethical statements

Our institutional ethics committee approved the study (IDRCB, 2020-A00256-33; CPP, 11-20-20.02.04.68737).

Results

A total of 366 patients with positive SARS-CoV2 qPCR were admitted to the four intensive care units between March 15th and May 1st 2020 among which 246 were intubated and mechanically ventilated (Figure 1). The mycology department received 193 respiratory samples from 108 patients, whose conditions deteriorated despite appropriate initial care. Patient characteristics are described in Table S2. Male/female sex ratio was 4.4 and median age was 61 years.

Twenty-one patients developed probable IPA according to CAPA criteria *stricto sensu* (n=19) and EORTC/MSGERC definitions (n=2; one solid organ transplant recipient and one myeloma patient). Overall, incidence was 5.7% (21/366) in severe COVID-19 patients admitted to the ICU and 8.5% (21/246) in those mechanically ventilated. IPA incidence in patients whose conditions worsened despite appropriate care was 19.4% (21/108). The median times from symptom onset to IPA diagnosis and from ICU admission to IPA diagnosis were 16 days (10-23) and 6 days (1-15), respectively.

When comparing patients who developed probable IPA (n=21) or not (n=87), no significant differences were observed regarding general population characteristics and severity upon admission (Table 1). Prescription of hydroxychloroquine (n=34) did not differ between both groups. Administration of azithromycin for more than 3 days (cumulative dose ≥1500mg) was associated with probable IPA (OR, 3.1; IC95%, 1.1-8.5; p=0.025) (Figure S1). Of note, 34 patients received azithromycin, which was prematurely discontinued on day 1 or day 2 in 8 patients because of QT interval prolongation. Administration of high-dose corticosteroids was not significantly associated with IPA (11.5 *vs*. 28.6%; p=0.08), although the cumulative dose ≥100 mg tended to be higher among IPA patients (OR, 3.7; IC95%, 1.0-9.7). Details for the incidence of IPA among patients who received azithromycin and/or corticosteroids is available in Table S3. Mortality was significantly higher in the probable IPA group (15/21, 71.4% *vs*. 32/87, 36.8%; p<0.01). Further details on each IPA patients are available in Table S4.

Discussion

In our study, the incidence of IPA in COVID-19 patients was 5.7% in all ICU patients and 8.5% in those mechanically ventilated yet may be underestimated considering only patients with clinical worsening were tested.

A cumulative azithromycin dose ≥1500mg was associated with IPA. Azithromycin have *in vitro* antiviral effect and is a broad spectrum antibiotic with immunomodulatory properties which could have also both prevented bacterial superinfections and reduced inflammation [13]. A recent meta-analysis found an increased mortality when hydroxychloroquine is associated to azithromycin [14]. Azithromycin-related impact on the risk of secondary infections have been only incompletely studied. Azithromycin has been shown to decrease serum interleukin-6 and induce delayed down-regulation of neutrophil oxidative burst and increased apoptosis up to 28 days after 3 doses of azithromycin (*i.e.* 1500 mg) in humans [15]. Neutrophils and oxidative burst represent the first and most important immune system barrier against aspergillosis [16]. Furthermore, azithromycin may promote *Aspergillus* colonization by altering the lung microbiome [17].

Corticosteroids are known to increase susceptibility to invasive fungal disease due to complex quantitative and qualitative immune deregulation [10]. High dose corticosteroid, although not precisely defined, was previously found to be associated with CAPA [4,5]. Although not significantly associated to IPA in our study, probably because of insufficient statistical power, a trend was observed after a cumulative dose of ≥100 mg dexamethasone-equivalent (OR, 3.7; IC95, 1.0-9.7), Recent studies such as the RECOVERY trial and various meta-analyses showed that corticosteroid administration is beneficial in COVID-19 patients requiring hospitalization [18]. Interestingly, the cumulative dose of dexamethasone using the RECOVERY trial regimen does not exceed 60 mg.

Although no severity score or variables, including oxygenation parameters, were found to be associated to IPA occurrence, we cannot rule out the extension of the lesion to be an associated risk factor. Indeed, the extension of lung lesions quantified by computed tomography was a predictor of COVID-19 severity and early death [19].

Susceptibility to IPA in previously immunocompetent critically ill patients is most likely multifactorial. In ARDS patients, epithelial damage, impaired mucocilliary clearance and temporary immune deregulation, starting with excess release of danger-associated molecular patterns (DAMPs)

secondary to COVID-19 damages, may be initiating factors [20]. The addition of known or suspected risk factors, such as corticosteroid or azithromycin, further inhibiting neutrophils and innate immune response may tilt the balance in favor of IPA development. The risk of IPA associated with corticosteroids compellingly depends on its cumulative dose although cut-offs are not clearly defined and depends on the underlying host factor [8]. Our findings raise questions regarding the possible connection between azithromycin use and the observed increased susceptibility to IPA, which needs to be further explored.

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Conflict of interest

The authors declare no conflict of interest related to the content of the present study

Authors contribution

Writing-Original draft: SD and AA. *Writing-Review & Editing*: All. *Conceptualization*: SD, AA and SB. *Investigation*: SD, ED, SF, SV, MC. *Data curation*: SD, ED, SF, SV, MC, TFG. *Formal analysis*: PAO, MS. *Visualization*: SD, AA, BM, EA, AM. *Supervision*: AA, BM, EA, AM.

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251 **Table 1.** Comparison of severe COVID-19 patients with and without probable invasive pulmonary

252 aspergillosis

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	Total (n=108)	**Without IPA (n=87)**	**With IPA (n=21)**	***OR***	***CI95%***	***p*-value**
Male *n (%)*	88 (81.5)	72 (82.8)	16 (76.2)	0.7	0.2-2.1	-
Age *median [Q1-Q3]*	62 [56-68]	62 [56-68]	63 [56.75-68.25]	-	-	0.63∘
Mechanical ventilation *n (%)*	105 (97.2)	85 (97.7)	20 (95.2)	0.5	0.04-5.3	
COVID risk factors						
HTA *n (%)*	64 (59.3)	50 (57.5)	14 (66.7)	1.5	0.5-4.0	-
Diabetes *n (%)*	40 (37.0)	31 (35.6)	9 (42.9)	1.4	0.5-3.6	-
Obesity *n (%)*	35 (32.4)	31 (35.6)	4 (19.0)	0.4	0.1-1.3	-
Coronary disease *n (%)*	15 (13.9)	13 (14.9)	2 (9.5)	0.6	0.1-2.9	-
BMI *median [Q1-Q3]*	28 [25-31]	28 [26-32]	28 [25-29]	-	-	0.70∘
Other patient characteristics						
Asthma *n (%)*	5 (4.6)	3 (3.4)	2 (9.5)	2.9	0.5-18.9	-
COPD *n (%)*	2 (1.9)	2 (2.3)	0 (0.0)	0.8	0.04-17.2	-
Immunocompromised patient *n (%)*	10 (9.3)	8 (9.2)	2 (9.5)	0.6	0.1-2.9	-
Long term corticosteroids *n (%)*	11 (10.2)	8 (9.2)	3 (14.3)	1.6	0.4-6.8	-
Severity at admission						
PaO2/FiO2 *mean (SD)*	173.47 (123.19)	169.63 (125.85)	187.79 (114.74)	-	-	0.34∘
Vasopressors in first	65 (60.2)	52 (59.8)	13 (61.9)	1.1	0.4-2.9	

48H *n (%)*						
Creatininemia (mg/dL) *mean (SD)*	103.34 (74.01)	92.64 (47.19)	149.85 (132.96)	-	-	0.08◦
D-dimer *median [Q1-Q3]*	2395 [1193-4635]	2325 [1163-4563]	2515 [1610-10917]	-	-	0.63◦
LDH *mean (SD)*	755.11 (312.15)	759.49 (303.61)	740.20 (350.52)	-	-	0.80◦
SAPS2 *mean (SD)*	39.93 (14.40)	40.4 (14.6)	38.1 (13.8)	-	-	0.58◦
SOFA *mean (SD)*	6.02 (3.79)	5.8 (3.6)	7.1 (4.5)	-	-	0.28◦
Severity during hospitalization						
Nadir PaO2/FiO2 *mean (SD)*	79.75 (37.21)	81.54 (39.01)	72.50 (28.40)	-	-	0.50◦
ECMO *n (%)*	10 (9.3)	9 (10.3)	1 (4.8)	0.4	0.1-3.6	-
Renal replacement therapy *n (%)*	38 (35.2)	30 (34.5)	8 (38.1)	1.2	0.4-3.1	-
Vasopressors *n (%)*	89 (82.4)	70 (80.5)	19 (90.5)	2.3	0.5-10.9	-
Specific COVID therapy						
Lopinavir-ritonavir *n(%)*	16 (14.8)	10 (11.5)	6 (28.6)	3.1	0.9-9.8	
Hydroxychloroquine *n(%)*	34 (31.5)	27 (31.0)	7 (33.3)	1.1	0.4-3.1	
Azithromycin + Hydroxychloroquine *n(%)*	29 (26.9)	22 (25.3)	7 (33.3)	1.4	0.5-4.1	
Immunoglobulins *n(%)*	3 (2.8)	3 (3.4)	0 (0.0)	0.6	0.03-11.3	
Sarilumab *n(%)*	1 (0.9)	1 (1.1)	0 (0.0)	4.3	0.3-71.8	

Eculizumab *n(%)*	6 (5.6)	4 (4.6)	2 (9.5)	2.2	0.4-12.8	
Tocilizumab *n(%)*	4 (3.7)	2 (2.3)	2 (9.5)	4.5	0.6-33.8	
Therapy with cumulative dose before sampling						
Azithromycin >1500 mg total dose *n (%)*	26 (24.1)	17 (19.5)	9 (42.9)	**3.1**	**1.1-8.5**	
Dexamethasone >1000mg *n (%)*	16 (14.8)	10 (11.5)	6 (28.6)	3.1	1.0-9.8	
Any ß-lactam > 3 days *n (%)*	90 (83.3)	74 (85.1)	16 (76.2)	0.6	0.2-1.8	
Respiratory sample characteristics						
PaO2/FiO2 at sampling *mean (SD)*	173.69 (91.70)	173.18 (96.05)	175.66 (74.40)	-	-	0.612∘
% BAL macrophages *mean (SD)*	31.23 (21.94)	31.00 (22.76)	32.17 (20.21)	-	-	0.836∘
% BAL PMN *mean (SD)*	47.37 (30.92)	47.08 (31.99)	48.50 (28.89)	-	-	0.959∘
% BAL Lymphocytes *mean (SD)*	20.63 (18.94)	21.17 (19.10)	18.50 (19.92)	-	-	0.795∘
Outcome						
Mortality *n (%)*	47 (43.5)	32 (36.8)	15 (71.4)	**4.3**	**1.5-12.1**	<0.01◊
LOS days *mean (SD)*	24.33 (18.88)	25.13 (19.18)	21.05 (17.60)	-	-	0.313∘

BAL: Bronchoalveolar lavage; BMI: body mass index; CI95%: 95% confidence interval; IPA: invasive pulmonary aspergillosis; LOS: length of stay; OR: odd ratio; PMN: polymorphonuclear; SAPSII, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; ∘Wilcoxon test

Figure 1. Study flowchart.

Direct examination of respiratory samples were performed only on samples collected after the March 27th as initial data regarding the contamination risk of lab technicians were not available. *as recommended by the manufacturer. BAL: bronchoalveolar lavage; BDG: ß-D-glucans; GM: galactomannan; ICU: intensive care unit; qPCR: quantitative polymerase chain reaction.