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Aspergillosis and COVID-19 in an intensive care unit in Brazil: a series of cases

Aspergilose e COVID-19 em unidade de terapia intensiva brasileira: uma série de casos

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INFORMAÇÕES DO ARTIGO

ABSTRACT

COVID-19-Associated Pulmonary Aspergillosis (CAPA) is one of the main complications of severely ill patients with COVID-19. Thus, this study aimed to report cases of CAPA in patients hospitalized in an intensive care unit of a tertiary hospital. Method: Descriptive and retrospective study that included patients with CAPA admitted between March 2020 and December 2021 in the intensive care unit of a high complexity hospital. Results: Of the eight patients with CAPA described in this study, six were classified as possible cases and two as probable cases. Conclusion: Preventive actions and active investigation of invasive pulmonary aspergillosis in critical COVID-19 patients should be performed through appropriate screening and diagnostic protocols, considering the high risk of co-infection of these patients.

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RESUMO

A Aspergilose Pulmonar Associada à COVID-19 (APAC) é uma das principais complicações de pacientes com COVID-19 gravemente doentes. Dessa forma, esse estudo objetivou relatar casos de APAC em pacientes internados em unidade de terapia intensiva de um hospital terciário. Método: Estudo descritivo e retrospectivo que incluiu pacientes com APAC admitidos entre março de 2020 a dezembro de 2021 na unidade de terapia intensiva de um hospital de alta complexidade. Resultados: Do total de oito pacientes com APAC descritos nesse estudo, seis foram classificados como casos possíveis e dois como casos prováveis. Conclusão: Ações preventivas e investigação ativa de aspergilose pulmonar invasiva em pacientes com COVID-19 críticos devem ser realizadas por meio de protocolos de rastreamento e diagnóstico adequados, considerando o alto risco de coinfecção desses pacientes.

Palavras-chave:
COVID-19, SARS-CoV-2, Aspergilose, Cuidados Críticos, Micoses, Coronavirus

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Introduction

COVID-19 marked world history for the unprecedented damage generated in a pandemic that recorded more than 6.6 million deaths between March 2020 and November 2022 (*WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination*, 2022). The virus that causes COVID-19 was called SARS-CoV-2 due to is genetic similarity with the coronavirus of severe acute respiratory syndrome (SARS-CoV) (Zhu et al., 2020). This virus causes severe pneumonia with clinical symptoms different from known and rapidly evolving ones that have challenged health services worldwide (Castagnoli et al., 2020).

Since the beginning of the pandemic, bacterial and fungal coinfections have been reported in patients with COVID-19 and among the main genera of pathogens involved are *Acinetobacter, Klebisiella, Pseudomonas, Candida,* and *Aspergillus* (Musuuza et al., 2021). COVID-19-Associated Pulmonary Aspergillosis (CAPA) is one of the main complications of severely ill patients with COVID-19 (Calderón-Parra et al., 2022; Hashim et al., 2022), occurring in approximately 10% of patients admitted to the Intensive Care Unit (ICU) worldwide (Calderón-Parra et al., 2022; Hashim et al., 2022) and higher mortality rate compared with patients without CAPA (Bartoletti, 2020; Calderón-Parra et al., 2022; Chong et al., 2022). Recent reports from Netherlands, Brazil and Spain report invasive aspergillosis in 19%, 16% and 11% patients with severe COVID-19 pneumonia, respectively (Koehler et al., 2020; de Almeida Jr et al., 2022; Marta et al., 2022).

The diagnosis of CAPA is complex due to nonspecific symptoms, difficulty in performing biopsies and imaging tests that do not adequately differentiate lung damage caused by COVID-19 or invasive aspergillosis (Caggiano et al., 2022). Given the different definitions of CAPA used in research published at the beginning of the pandemic, the European Confederation of Medical Mycology/International Society for Human and Animal Mycoses (ECMM/ISHIM) proposed, based on validated tests, to classify the CAPA as proven, probable and possible. This classification allows researchers to homogeneously classify patients, conferring higher quality to studies and, to health professionals, adequate clinical management (Koelher, 2021). 2020 ECMM/ISHAM consensus definitions provide support for standardization of CAPA clinical research and surveillance studies based on conventional biomarkers and micrology of lower respiratory tract samples, such as microscopy and culture for fungi, in order to meet the microbiological diagnostic criteria (Permpalung et al., 2021).

The aim of this study was to report cases of COVID-19-associated pulmonary aspergillosis in patients admitted to the ICU of a tertiary hospital, from March 2020 to December 2021, with description of clinical characteristics, diagnosis, treatment and outcome.

Method

Design and ethical aspects of the study

This descriptive and retrospective study included patients with CAPA, adults (≥18 years), admitted between March 2020 and December 2021 in the ICU of a high complexity hospital, which has approximately 500 beds and is a reference in the southeastern region of Brazil.

The research was submitted and approved by the Human Research Ethics Committee, CAAE: 51805021.5.0000.5152.

Data collection and definitions

Patient data were collected in the electronic medical record including clinical and microbiological information, prescribed treatment and outcome. As there was no screening or screening protocol for CAPA in the period evaluated, the investigations occurred upon clinical suspicion.

The laboratory diagnosis of COVID-19 occurred by polymerase chain reaction with reverse transcriptase (RT-PCR). For the diagnosis of CAPA, the criteria of the 2020 ECMM/ISHAM consensus were used (Koelher, 2021), which classifies CAPA as proven, probable and possible: CAPA is proven by histopathological or direct microscopic detection, or both, of fungal elements that are morphologically consistent with *Aspergillus* sp, showing invasive growth into tissues with associated tissue damage, or (with or without) aspergillus recovered by culture or detected by microscopy, in histology studies or by a sterile aspiration or biopsy from a pulmonary site, showing an infectious disease. The diagnosis of probable and possible pulmonary PACA requires a pulmonary infiltrate combined with mycological evidence by culture of the respiratory tract obtained via non-bronchoscopic lavage or detection of biomarkers, being probable when the serum galactomannan index or bronchoscopic lavage is >0.5 and possible when galactomannan detected in non-bronchoscopic lavage, index >1,2.

The cases described in this report could not be proven due to the absence of samples obtained by biopsy or bronchoscopy. *Aspergillus* species were obtained in culture of tracheal secretion aspirate and serum galactomannan was obtained by enzyme immunosorbent assay (ELISA). The antimicrobial sensitivity profile of the isolated fungus species was not determined. The eight cases included in this study were described and relevant data were categorized.

Results

We identified 588 patients with COVID-19 admitted to the ICU during the study period, of which 170 had tracheal secretion cultures positive for bacteria or fungi. The consensus criteria followed included identification of *Aspergillus* sp in culture of tracheal secretion and serum

galactomannan >0.5, which allowed to classify eight cases of CAPA, six as possible CAPA and two as probable CAPA (Table 1).

Table1.
Characteristics of patients with COVID-19 Associated Pulmonary Aspergillosis (CAPA) in an Intensive Care Unit

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age	51 years	50 years	74 years	59 years	67 years	61 years	59 years	61 years
Sex	male	female	male	male	female	male	male	male
Comorbidities	Grade III obesity, DM, SAH	Grade III obesity	SAH, gastric ulcer	Grade II obesity, SAH	Grade II obesity, SAH	Grade I obesity; MD; SAH; CVD; CKD	Grade I obesity, DM, SAH	Grade I obesity, SAH
SAPS 3	66 points	34 points	not calculated	79 points	70 points	60 points	not calculated	76 points
Length of stay until identification of the fungus in culture	16 days	12 days	5 days	11 days	9 days	6 days	5 days	14 days
Time of mechanical ventilation until identification of the fungus in culture	11 days	10 days	4 days	8 days	9 days	3 days	3 days	12 days
Time between admission to the ICU and identification of the fungus in culture	11 days	10 days	5 days	9 days	9 days	5 days	5 days	11 days
Length of ICU stay/days	28 days	48 days	7 days	12 days	9 days	5 days	14 days	27 days
Hemodialysis	yes	no	yes	yes	no	yes	yes	yes
Length of hospital stay	33 days	50 days	7 days	14 days	9 days	6 days	14 days	30 days
Prone position	yes	yes	no	yes	yes	no	no	yes
Serum GM (positive: index >0.5)	Positive (0.8)	Negative*	not performed	Negative*	not performed	not performed	Positive*(1.25)	Negative*
Germ identified in Fungal Culture of Tracheal Aspirate	*Aspergillus sp.*	*Aspergillus sp.*	*Aspergillus fumigatus*	*Aspergillus sp.*	*Aspergillus fumigatus*	*Aspergillus fumigatus*	*Aspergillus fumigatus*	*Aspergillus fumigatus*
CAPA classification according to ECMM/ISHAM	Probable	Possible	Possible	Possible	Possible	Possible	Probable	Possible
Coinfection with other germs	no	*Klebsiella pneumoniae*	no	no	no	no	*Candida albicans*	*Acinetobacter baumanni*
Antifungal therapy	Empirical fluconazole and voriconazole replaced by liposomal amphotericin B after identification of *Aspergillus*	Voriconazole followed by Liposomal Amphotericin B	not started due to death	Liposomal amphotericin B	not started due to death	not started due to death	Liposomal amphotericin B	Liposomal amphotericin B

*Abbreviations: DM: diabetes mellitus; SAH: systemic arterial hypertension; CVD: cardiovascular disease; CKD: chronic kidney disease; SAPS 3: Simplified Acute Physiology Score 3; GM: galactomannan. Symbol: *: exam collected the day after the identification of Aspergillus in a culture of tracheal secretion aspirate.*

Common profile of the cases

The eight patients included in this report were admitted to the hospital due to symptoms of COVID-19 and then transferred to the ICU where they received invasive mechanical ventilation, used intravenous corticosteroid and had *Aspergillus* species identified in tracheal secretion culture. All patients underwent at least one chest computed tomography scan during hospitalization, indicating ground-glass pulmonary opacity. The eight patients progressed to death.

Presentation of the cases

Case 1

Male patient, 51 years old, with diabetes mellitus, systemic arterial hypertension and grade III obesity. Diagnosed with COVID-19 four days before admission. Chest tomography was performed on the day of admission with areas of ground glass with involvement of 20% of the pulmonary area. Due to worsening of the respiratory pattern was transferred to the ICU in D5 (fifth day of hospital stay), when it required mechanical ventilation and initiated renal replacement therapy. He presented persistent fever and infectious leukogram, even with broad-spectrum empirical antibiotic therapy and, in D9, fluconazole was also prescribed empirically. With a positive galactomannan test on D14, voriconazole was administered instead of fluconazole. In tracheal aspirate secretion collected on D16 was isolated *Aspergillus* sp and staggered treatment for liposomal amphotericin B. There was a worsening of the clinical picture and identification of *Acinetobacter baumannii* in aspirated tracheal secretion collected in D30. He died in D33.

Case 2

Female patient, 50 years old, grade III obesity, with a history of smoking for 40 years, abstaining for 10 years. Admitted due to diagnosis of COVID-19 the day before hospitalization and symptoms of dyspnea and cough five days before hospitalization. Chest tomography of the day of admission with bilateral ground glass opacities occupying more than 90% of the pulmonary parenchyma. It presented progressive worsening of the respiratory pattern, being transferred to the ICU with two days of hospitalization, D2, the day in which mechanical ventilation was installed. Due to persistent fever cultures were collected on D12, with identification of *Aspergillus* sp and *Klebisiella pneumoniae* in endotracheal aspirate secretion, instituted therapy with voriconazole on D16, maintained empirical meropenem started on D10 and associated inhaled gentamicin. After 15 days of treatment with voriconazole, this was replaced by liposomal amphotericin B in D31 due to alteration in hepatogram. In D35 was identified *Acinetobacter baumannii* in tracheal secretion culture. The patient presented worse ventilatory parameters and died in D50.

Case 3

Male patient, 74 years old, with systemic arterial hypertension. He went to the health service with cough and high digestive bleeding due to a gastric ulcer. On the day of admission, COVID-19 was confirmed and thorax tomography was performed with ground glass opacity occupying 40% of the total lung area, followed by transfer to ICU. On the second day of hospitalization, D2, presented worsening of the respiratory pattern, agitation and mental confusion, being installed mechanical ventilation. *Aspergillus fumigatus* isolate in endotracheal aspirate culture collected on D5 due to persistent fever. Renal replacement therapy initiated on D6. He presented hemodynamic instability and progressed to death in D7, the day on which the culture result was released, prior to the beginning of antifungal therapy.

Case 4

Male patient, 59 years old, with systemic arterial hypertension and grade II obesity. Admitted to the service the day he was diagnosed with COVID-19, with complaints of flu symptoms. He was transferred to the ICU the day after admission, D2 and, on the fourth day of hospitalization, D4, was intubated and installed mechanical ventilation, after presenting a progressive decrease in oxygen saturation, not responsive to other measures, and the imaging showed bilateral pulmonary opacity. In D9, renal replacement therapy was started. He presented persistent fever, leukocytosis and increased C-reactive protein, and broad-spectrum antibiotic therapy was started. In D11, *Aspergillus* sp was identified in endotracheal aspirate secretion concomitant to the worsening of the clinical picture. Started treatment with liposomal amphotericin B on D12, when the patient evolved to death.

Case 5

Female patient, 67 years old, with systemic arterial hypertension and grade II obesity. Diagnosed with COVID-19 five days before hospital admission. Admitted with major dyspnea, being intubated and referred to ICU on admission. Chest tomography performed at admission showed 40 to 60% of lung involvement. He presented persistent fever and, in D9, *Aspergillus fumigatus* was identified in endotracheal aspirate secretion and liposomal amphotericin B was prescribed. However, due to the worsening of the clinical picture the patient evolved to death before the beginning of treatment.

Case 6

Male patient, 61 years old, with diabetes mellitus, systemic arterial hypertension, grade I obesity, congestive heart failure and chronic kidney disease, undergoing conservative treatment until admission to the ICU, where the disease worsened and required renal

replacement therapy. Diagnosed with COVID-19 seven days before admission. He presented 25% of pulmonary involvement in chest tomography performed on the date of admission. Transferred to ICU in D2 and D4 mechanical ventilation was installed due to the worsening of the respiratory pattern. In D6, *Aspergillus fumigatus* was identified in endotracheal aspirate secretion, the day the patient died.

Case 7

Male patient, 59 years old, with diabetes mellitus, grade I obesity and hypertension. Prior to hospitalization, he received a dose of vaccine against COVID-19, whose date and manufacturer information were not recorded in the medical record. The diagnosis of COVID-19 occurred 11 days before hospitalization. Admission chest tomography showed 70% of lung involvement. He presented respiratory worsening and was transferred to ICU in D1. He needed mechanical ventilation in D2 and after three days renal replacement therapy was started due to alteration of renal function. Due to persistent fever and worsening of the clinical picture, in D5 cultures were collected with identification of *Aspergillus fumigatus* and *Candida albicans* in tracheal aspirate secretion and started treatment with liposomal amphotericin B. Collected serum galactomannan in D6, with index 1.25. The patient presented a worsening of the clinical picture with persistent fever, not responsive to the measures and prescribed broad-spectrum antibiotic therapy, evolving to death on D14.

Case 8

Male patient, 61 years old, with systemic arterial hypertension and grade I obesity, previous history of smoking, no record of time of cigarette use, and current history of alcoholism. Diagnosed with COVID-19 five days before admission. Submitted to orotracheal intubation and transferred to ICU in D4. Due to persistent fever and infectious leukogram, cultures and isolate *Aspergillus fumigatus* and *Acinetobacter baumannii* were collected in tracheal secretion within 15 days of hospitalization, when antifungal therapy was initiated with liposomal amphotericin B and replaced with empirical meropenem and teicoplanin by polymyxin and tigecycline. In D17, renal replacement therapy was started and, in the following days, there was a worsening of the clinical picture that culminated in the death of the patient in D30.

Discussion

Brazil is, along with the United States and India, among the countries with the highest number of cases and deaths from COVID-19 (Oliveira et al., 2022). CAPA has been of interest to scholars due to its ability to increase morbidity and mortality in critical patients and the need for better definitions regarding its clinical manifestations (Calderón-Parra et al., 2022;

Koehler et al., 2020). Studies indicate significantly higher mortality among patients with CAPA than in patients without CAPA (Borman et al., 2022; Hashim et al., 2022; Singh et al., 2021; Tio et al., 2021). In this report all patients evolved to death. However, it is worth mentioning the existence of comorbidities such as hypertension, obesity, diabetes and advanced age, in addition to the early clinical worsening by COVID-19 presented by the cases, given the high scores of Simplified Acute Physiology Score 3 (SAPS 3) obtained at the time of admission to the ICU. The SAPS 3 is a validated hospital mortality predictor system, which is based on variables of acute physiological disorders, conditions and health status prior to interventions occurred in hospitalization, since the calculation is performed with data from the first hour after the patient's admission to the ICU. This score can vary between zero and 120 and the higher the score, the higher the probability of death (Moreno et al., 2005).

Considering the greater possibility of poor outcomes in patients with COVID-19 coinfected by invasive pulmonary aspergillosis (Singh et al., 2021), it is relevant to mention the risk factors for the emergence of CAPA mentioned in the literature and also found in patients who composed the sample of this report, among which are the lung damage caused by COVID-19 itself, need for hospitalization in ICU, corticosteroid use, prolonged hospitalization, invasive mechanical ventilation, and advanced age (Arastehfar et al., 2020; Calderón-Parra et al., 2022; Er et al., 2022; Nasir et al., 2020), which is why routine screening is essential for early screening and decision-making (Caggiano et al., 2022; Gangneux & Dannaoui, 2022).

The diagnosis of aspergillosis in critical patients with COVID-19 is a topic widely discussed due to the difficulty in distinguishing between colonization by *Aspergillus* spp. or invasive infection, considering the frequent unavailability of histological findings and lack of clinical and radiological characteristics, which was observed in our cases and corroborated with other studies (Calderón-Parra et al., 2022; Koehler et al., 2020; Tio et al., 2021). Bronchoscopy to obtain samples free of contaminants is generally avoided due to the possibility of aerosol transmission during the procedure, and many patients were not clinically fit for a lung biopsy at the time of suspicion of CAPA. Likewise, imaging tests may not be feasible due to the clinical instability of patients or, when performed, they may not differentiate acute respiratory syndrome in COVID-19 and invasive pulmonary aspergillosis (Nasir et al., 2020).

In the cases reported here, five patients had serum galactomannan analysis in the period of identification of *Aspergillus* in tracheal secretion aspirate, where two had a positive result (index >0.5). Galactomannan, obtained in plasma or bronchoalveolar lavage fluid, is a biomarker that can assist in the diagnosis and prognosis of invasive pulmonary aspergillosis, being indicated its serum collection three times a week until discharge from the ICU, for CAPA screening in critical patients (Koelher, 2021; Patterson & Donnelly, 2019). Different authors defend its importance as a pre-test in situations of high probability, considering its high

specificity in non-neutropenic patients (de Almeida Jr et al., 2022; Ghazanfari et al., 2022; Koelher, 2021; Lim, Jin Lee et al., 2022). Galactomannan is detectable even before the onset of clinical symptoms and thus may be useful to guide early treatment (Caggiano et al., 2022). However, it is important to consider that, especially at the serum level, galactomannan has low sensitivity and may be positive even in case of colonization (Mitaka et al., 2020).

Given the rigorous criteria required by the ECMM/ISHAM to prove CAPA, many authors were concerned about the possibility of underestimation of its incidence(Bounhiol et al., 2022; Lim, Jin Lee et al., 2022; Nasir et al., 2020; Permpalung et al., 2021). Thus, the search for microbiological findings in tracheal aspirate, bronchoalveolar lavage or through nonbronchoscopic lavage is relevant in order to mitigate morbidity and mortality from this infection and, even cases classified as possible APAC, should receive antifungal therapy (Koelher, 2021; Machado et al., 2021; Marta et al., 2022; Nasir et al., 2020). On the other hand, some authors discuss the issue of early and prolonged treatment impacting increased costs, adverse reactions, drug interactions and antimicrobial resistance in patients already highly vulnerable in ICU, emphasizing the importance of applying and refining the diagnostic criteria of CAPA, which will provide realistic prevalence rates and appropriateness of therapy (Arastehfar et al., 2020; Egger et al., 2022). New studies may contribute to greater definitions of the benefits of using early antifungal treatment or prophylaxis for patients at high risk of invasive fungal infections (Gangneux & Dannaoui, 2022).

The CAPA treatment decision should consider all patient information and clinical data. Voriconazole is recommended as a first-line antifungal in the management of CAPA, even with the possible drug interactions with treatments commonly used in COVID-19, its narrow therapeutic window and toxicity that may aggravate the clinical picture of these patients admitted to the ICU (Koelher, 2021; Tio et al., 2021). One patient, among the cases presented in this report, required replacement of voriconazole by liposomal amphotericin B due to liver alteration, an adverse event most commonly presented by patients using voriconazole according to some authors (Eiden et al., 2007; Maertens et al., 2021). Liposomal amphotericin B is a viable option when the patient presents contraindication to triazoles due to its nephrotoxic potential and the renal alteration that commonly affects patients with severe COVID-19 (Maertens et al., 2021; Patterson et al., 2016; Ullman et al., 2018) observed in most of the patients in this report.

With clinical activity similar to voriconazole and fewer adverse effects are posaconazole and isavuconazole, safe options for the treatment of CAPA for patients who do not tolerate voriconazole or liposomal amphotericin B (Koelher, 2021; Maertens et al., 2021; Singh et al., 2021). Both drugs have a higher unit cost than voriconazole, which may justify their unavailability and non-use in some health services, although studies indicate a good cost-effectiveness of these alternative options (Floros et al., 2019; Greiner et al., 2010; Harrington et al., 2017).

This case report exemplifies the clinical difficulty in the diagnosis and management of patients with CAPA, even in large hospital centers. Among the several limitations of the study are the realization of the research in a single center, the small sample of CAPA cases, perhaps underestimated due to the lack of adequate screening and investigation, the lack of diagnostic tests that could prove CAPA and the absence of a control group without COVID-19, hospitalized in the same period, which would enable the analysis of the impact of COVID-19 on the development of invasive pulmonary aspergillosis. Thus, extensive studies that analyze risk factors, clinical manifestations, early diagnosis and therapy are necessary.

Conclusion

The high mortality, diagnostic and management complexity of patients with CAPA indicate the need for active investigation of invasive pulmonary aspergillosis in patients with COVID-19 in intensive care, through appropriate screening, diagnostic protocols, and preventive actions for patients with a high risk of co-infection.

Conflicts of interest

We declare that there are still no conflicts of interest in relation to this scientific text.

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