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A case of breakthrough mucormycosis in a patient with COVID-19-Associated Pulmonary Aspergillosis (CAPA)

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Abstract

We report a case of a critically ill patient with COVID-19-Associated Pulmonary Aspergillosis (CAPA) who developed a breakthrough proven rhino-orbital mucormycosis, while receiving treatment with isavuconazole and who had no prior history of immunosuppression. So far, breakthrough invasive mold infections have been described only in patients with hematologic malignancies or hematopoietic stem cell transplantation receiving antifungal prophylaxis. Furthermore, combination therapy with liposomal amphotericin B with posaconazole failed and antagonistic effects between the two antifungals was demonstrated in vitro. Severe COVID-19 disease is possibly associated with severe immunosuppression and increased vigilance for breakthrough mixed mold infections is required in this group of patients.

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Case description

A 79-year old male (89 kg, Body Mass Index 31.5 kg/m^2) with a medical history of depression under no medication was admitted to the Emergency Department with respiratory failure following five days of low-grade fever and non-productive cough. He had bilateral patchy infiltrates on chest x-ray, PaO_2 of 36.9 mmHg, $PaCO_2$ of 17.8 mmHg and pH=7.41. Nasopharyngeal swab real-time Polymerase Chain Reaction (PCR) was positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Laboratory results revealed elevated markers of inflammation: CRP was 12.4 mg/dL, procalcitonin was 32.67 ng/mL, WBCs' were 16.4 K/μL. The patient was intubated and transferred to the Intensive Care Unit (ICU). He was treated with intravenous dexamethasone, piperacillin-tazobactam and levofloxacin for 8 days and subcutaneous low molecular weight heparin. Notably, he developed new onset diabetes mellitus necessitating high doses of intravenous insulin.

On ICU day 9, COVID-19-Associated Pulmonary Aspergillosis (CAPA) was suspected due to worsening hypoxemia associated with abundant bronchial secretions and new infiltrates on chest radiography. Broncho-Alveolar Lavage (BAL) galactomannan and *Aspergillus fumigatus* PCR assays were both positive. The patient was treated with intravenous voriconazole (400 mg/12 hr) from day 9 to day 15, when voriconazole was replaced by

intravenous isavuconazole (200 mg/8 h for the first 48 h and then 200 mg/24 h). A week later, the patient developed a necrotic skin lesion on the nasal bridge. Subsequent skin biopsy revealed morphological findings consistent with mucormycosis (Figure 1). At the same time, the patient presented mild leukocytosis (WBCs'=14.7 K/μL neutrophils predominant), anemia (Hb=9 g/dL), high blood glucose values (~180 mg/dL) despite insulin treatment, low serum albumin (2.8 g/dL) and acidemia (pH in the range of 7.25-7.28) because of respiratory and metabolic acidosis. Lactate values were normal (<10 mg/dL). On day 30, isavuconazole was substituted by a combined regimen of intravenous liposomal amphotericin B (10 mg/kg/24 h) and posaconazole administered via nasogastric tube (400 mg/12 h). Rapid expansion of the lesion was noted over the next 24 hours, including both ocular bulbs. The patient rapidly developed multiple organ failure and he eventually died on day 33.

Mycological workup

Culture results yielded a Mucorales species, which was subjected to molecular identification by sequencing the ITS1-5.8S-ITS2 region using the ITS1 (5-TCCGTAGGTGAACCTGCGG-3) and ITS4 (5-TCCTCCGCTTATTGATATGC-3) primers. High sequence alignment (100%) was found in Genbank Blast analysis with *Rhizophus arrhizus* (GenBank Accession No OQ458708). In vitro antifungal susceptibility was determined following the EUCAST E.DEF 9.4 broth microdilution reference methodology [1]. The 24 h EUCAST Minimum Inhibitory Concentrations (MICs; complete visual growth inhibition) were 4 mg/L for voriconazole, 1 mg/L for isavuconazole, 0.5 mg/L for posaconazole and ≤0.06 mg/L for amphotericin B. There are nor epidemiological neither clinical breakpoints for Rhizopus spp for interpretation of MIC values. Based on previous MIC data, the isolate belongs to the wild-type population for all drugs. However, based on clinical breakpoints for *Aspergillus fumigatus*, the isolate will be deemed susceptible to isavuconazole and amphotericin B and resistant to voriconazole and posaconazole.

In vitro interaction between amphotericin B and posaconazole was retrospectively determined with the gradient concentration strip method. In particular, the combination testing was performed by placing the MIC test strips (Liofilchem®, Roseto degli Abruzzi, Italy) in a cross formation, with the strips intersecting at the respective MICs of each drug in a 90° angle. Amphotericin B and posaconazole MICs were recorded as the lowest drug concentration at which the border of the elliptical zone of 100% and 80% growth inhibition, respectively, intersected the scale on the strip after 24 h of incubation. Synergy, additivity and antagonism were defined when the Fractional Inhibitory Concentration (FIC) index value was <1, 1-1.25 and >1.25, respectively, since these cut-offs were previously found to be more sensitive in detecting *in vitro* and in vivo significant pharmacodynamic interactions [2]. The combination was antagonistic with a FIC index of 2.35, increasing the MIC of amphotericin B from 0.094 to 0.19 mg/L and decreasing the MIC of posaconazole from 0.38 to 0.125 mg/L. Antagonism (FIC index 3.16) was also found when the strips were crossed at the steady-state free maximum serum concentrations, namely 1 mg/L for the liposomal amphotericin B dose of 10 mg/kg and 0.017 mg/L for the posaconazole dose of 400 mg, as the MIC of amphotericin B was increased to 0.25 mg/L and the MIC of posaconazole was decreased to 0.19 mg/L.

Discussion

The novel SARS-CoV-2, is accompanied by a relatively high incidence of ICU admissions resulting in a substantial mortality among infected persons worldwide. Mucormycosis and aspergillosis are relatively rare but serious opportunistic fungal infections associated with high morbidity and mortality. An increasing number of case reports and observational studies have shown that the clinical course of COVID-19 can be complicated by Invasive Mold Infections (IMIs), especially in critically ill patients [3].

The estimated incidence of CAPA is 13.5% while the prevalence of COVID-19-Associated Mucormycosis (CAM) has been reported to range between 0.3% and 0.8% [4]. In the largest observational study including 2826 cases of CAM, rhino-orbital involvement represented 74.1% of all cases, while 25.9% of cases exhibited CNS involvement [5]. Contrasting the results of the above studies which are based on clinical, imaging and laboratory criteria, autopsy proven invasive fungal infections, including CAPA, are uncommon (2% of decedents) highlighting the difficulties in diagnosing these infections antemortem [6].

Classical risk factors associated with myeloid cell dysfunction and development of IMIs have been implicated in CAPA, including chronic glucocorticoid therapy, prolonged neutropenia in patients with hematological diseases, stem cell or solid organ transplantation, immunosuppressive treatment and treatment with IL-6 inhibitors [7].

Importantly, distinct risk factors, including acidosis, iron overload syndromes and metabolic abnormalities, are associated with development of mucormycosis. Contributing factors for CAM appearance in critically ill patients include diabetes mellitus, obesity, use of corticosteroids, and the development of cytokine storm [8]. Diabetes, acidosis, obesity and corticosteroid use are the risk factors applying to our patient. Why COVID-19 disease predisposes to CAM is currently unknown. Whether immunometabolic defects in macrophages and other myeloid cell subsets result in loss of crucial antifungal effectors against Mucorales species requires further investigation.

The coexistence of aspergillosis and mucormycosis in patients with COVID-19 is rare and, so far, 10 cases have been reported in the literature. Only three patients survived despite antifungal therapy [3]. Table 1 summartizes the risk factors, isolated strains, infection site, treatment and outcome in COVID-19 patients with mixed mold infections reported so far, including our patient.

So far, breakthrough IMIs have been observed only in patients with hematologic malignancies or hematopoietic stem cell transplantation receiving antifungal prophylaxis. Among 103 patients who developed breakthrough mucormycosis while being on mold-active antifungals, only a few (16/103) were receiving Mucorales-active antifungals (9 isavuconazole, 6 posaconazole, 1 amphotericin B), while most (87/103) were on other mold-active agents (52 voriconazole, 22 echinocandins, 8 itraconazole, 5 echinocandin and voriconazole) [9]. The former group exhibited poorer outcome.

Isavuconazole was initially used for the treatment of invasive aspergillosis and candidiasis and later for mucormycosis. This agent possesses only modest in vitro activity against most Mucorales, with 50% MIC values of 1-4 mg/L and 90% MIC values of 4-16 mg/L against the five most common Mucorales genera [10]. However, the isolate in our patient had a relatively low MIC which would be considered susceptible using *A. fumigatus* breakpoints. A possible explanation of breakthrough infection

Table 1: Risk factors for mixed mold infections in COVID-19 patients.

	Age	Sex	Immunodeficiency	Species	Site	Concomitant isolation	Treatment	Outcome
Johnson 2021 [11]	79	M	Corticosteroids Diabetes	*A. fumigatus* *Rhizopus arrhizus*	Lung	*Aspergillus* first	VCZ→ AMB	Survival
Bellanger 2021 [12]	55	M	Lymphoma Neutropenia	*A. fumigatus* *Rhizopus microsporus*	Lung	Yes	AMB	Death
Lai 2022 [13]	70	M	Corticosteroids Tocilizumab	*A. terreus* *Cunninghamell abertholletiae*	Lung	*Aspergillus* first	VCZ+ADF→ AMB+ICZ	Death
Saltini 2021 [14]	72	M	Corticosteroids Diabetes MDS	*A. fumigatus* *Mucor circinelloides*	Lung Sinus	*Aspergillus* first	VCZ+ADF→ AMB+CPG	Death
Kim JH 2022 [15]	69	M	Corticosteroids	*A. fumigatus* *N/A*	Lung	*Aspergillus* first	VCZAMB	Death
Benhadid-Brahmi 2022 [3]	74	M	Corticosteroids	*A. welwitschiae Rhizopus delemar*		*Aspergillus* first	VCZ→AMB	Death
Bretagne 2021 [16]	73	M	Corticosteroids	*A. fumigatus* *Rhizopus microsporus*	Lung	Yes	AMB	Survival
Buil 2021 [17]	50s	M	Corticosteroids	*A. fumigatus* *Lichtheimia ramosa*	Lung	*Aspergillus* first	VCZ→AMB+PCZ	Died
Buil 2021 [17]	60s	M	Corticosteroids Hematological malignancy	*A. fumigatus* *Rhizopus microsporus*	Lung	*Aspergillus* first	VCZ+MCF→ ICZ →AMB	Died
Moorthy 2021 [18]	45	M	Corticosteroids	N/A	Sinus Eye	N/A	AMB	Survival
Our case	79	M	Corticosteroids Diabetes	*A. fumigatus* *Rhizophus arrhizus*	Nose Eye	*Aspergillus* first	VCZ+ICZ→PCZ+AMB	Died

M: Male; N/A: Not available; AMB: liposomal amphotericin B; VCZ: Voriconazole; ADF: Anidulafungin; ICZ: Isavuconazol; CPG: Caspofungin; PCZ: Posaconazole; MCF: Micafungin

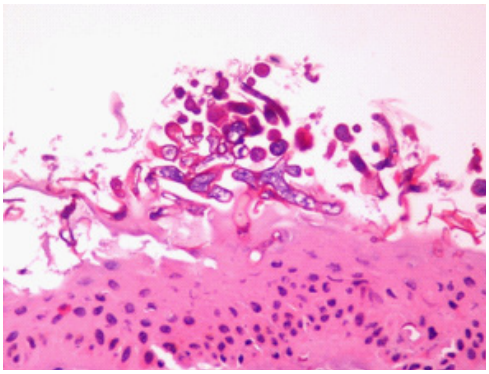

Figure 1: Irregular broad (empty-looking) nonseptate hyphae with wide-angle branching, consistent with mucor.

could be the subtherapeutic levels (<1 mg/L) observed in 5% of hospitalized patients. In addition, due to long half-life of isavuconazole steady state may be reached after 2 weeks of therapy.

Based on international guidelines, liposomal amphotericin B remains the recommended first-line treatment for mucormycosis. Nevertheless, in case of poor clinical condition, as in our patient, the co-administration of posaconazole can be considered. However it was administered for only 3 days prior to patient death. The general approach for successful management of mucormycosis involves surgical debridement of affected tissues whenever feasible in parallel to immediate systemic antifungal therapy. Notably, there are still no definitive data to support the use of polyenes with azoles combination therapy as the existing literature (mainly case reports) provides contradictory results. In fact, the reported discrepancies may be due to the different types of mucormycosis infections as well as the various Mucorales species involved and their corresponding responses to antifungal drugs, making it difficult to assess the true impact of this particular combination on outcome. In vitro combination testing with gradient concentration strips showed an increase of MIC of AMB when combined with posaconazole indicating some antagonistic effects. Previous studies have rarely found antagonism although in most of the conservative FIC index cut-off of 4 was used.

Our case is unique for three reasons. Firstly, we describe a critically ill COVID-19 patient, who sequentially developed two distinct mold infections, CAPA and CAM, without previous evidence of co-morbidities, immunosuppressive factors or other predisposing conditions, illustrating that severe COVID-19 is probably associated with severe immunoparalysis. Secondly, it represents the first documented case of a breakthrough proven rhino-orbital mucormycosis during isavuconazole treatment for CAPA. Thirdly, combination therapy with liposomal amphotericin B with posaconazole failed and antagonistic effects were observed in vitro.

Early diagnosis of IMIs and prompt reversal of underlying immunosuppressive conditions are associated with improved patient outcome. This case report underlines the increased vigilance healthcare professionals should have for breakthrough mixed mold infections, in critically-ill COVID-19 patients, even without a prior history of severe immunosuppression. Prospec-

tive studies evaluating the actual incidence of mixed CAPA and CAM infections and their susceptibility to antifungals are needed. Furthermore, the pathophysiologic link between COVID-19 disease and mold infections, especially CAM, deserves further investigation.

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