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General review

COVID-19-associated mixed mold infection: A case report of aspergillosis and mucormycosis and a literature review

Yasmine Benhadid-Brahmia, Samia Hamanea, Benjamin Soyerb,c,d, Alexandre Mebazaab,c,d, Alexandre Alanioa,e, Benjamin Choustermanb,c,d, Stéphane Bretegnea,e, Sarah Dellièrea,e,*

ABSTRACT

COVID-19-associated mold infections have been increasingly reported, and the main entity is COVID-19-associated aspergillosis (CAPA). Similarly, COVID-19-associated mucormycosis has been reported in hematology, and its prevalence is high and has been increasing in the diabetic population in India during the third COVID-19 pandemic wave. Simultaneous infection with Mucorales and Aspergillus is rare and even rarer during COVID-19. Here, we report the case of a previously immunocompetent patient with severe SARS-CoV-2 infection complicated with probable CAPA and mucormycosis co-infection. Specific diagnostic tools for mucormycosis are lacking, and this case highlights the advantages of analyzing blood and respiratory samples using the quantitative polymerase chain reaction to detect these fungi. We further reviewed the literature on mixed Aspergillus/Mucorales invasive fungal diseases to provide an overview of patients presenting with both fungi and to identify characteristics of this rare infection.

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Introduction

There have been few studies on mixed mold diseases, and they are rarely reported in immunocompromised patients with neutropenia, malignant hemopathy [1,2], solid organ transplantation [3], or poorly controlled diabetes mellitus [4,5]. Viral infections, especially severe influenza and COVID-19, which cause acute respiratory distress syndrome (ARDS), increase the susceptibility to mold infection in previously immunocompetent patients [6,7]. COVID-19-associated pulmonary aspergillosis (CAPA) and COVID-19-associated mucormycosis (CAM) are associated with a higher mortality rate in this patient population [8,9]. CAPA and CAM prevalence rates vary widely between studies, which may be explained by different awareness and diagnostic strategies [8]. Our center screened every mechanically ventilated COVID-19 patient who clinically worsened despite adequate standard of care for CAPA. This case is a patient with Rhizopus/Aspergillus coinfection in a previously immunocompetent COVID-19 patient and a discussion about mixed mold infections.

CASE

A 74-year-old retired man with a history of hypertension that was being treated with calcium channel blockers presented in the emergency ward on October 21, 2020 with a cough and a fever that lasted 4 days (Figure 1). He had evocative chest computed tomography (CT) scan findings, and the COVID-19 diagnosis was confirmed using real-time reverse-transcriptase polymerase chain reaction (PCR) on a nasopharyngeal swab (RealStar® SARS-CoV-2 Kit, Altona Diagnostics). The patient had a history of gastric lymphoma that was treated surgically in 1975, and he has subsequently been in remission. Upon admission in the pneumology ward, the patient received ceftriaxone, azithromycin, and preventive anticoagulation by enoxaparin sodium (0.8 mL × two per 24 h subcutaneously). On October 23rd, 2020, the patient received dexamethasone 6 mg/day because of a persistent SpO2 of 85% on room air and a fever (38.6 °C). After multiple desaturation episodes despite increased oxygen support (up to 6 L/min), he received a bolus of 120 mg methylprednisolone and was controlled diabetes mellitus [4,5]. Viral infections, especially severe influenza and COVID-19, which cause acute respiratory distress syndrome (ARDS), increase the susceptibility to mold infection in previously immunocompetent patients [6,7]. COVID-19-associated pulmonary aspergillosis (CAPA) and COVID-19-associated mucormycosis (CAM) are associated with a higher mortality rate in this patient population [8,9]. CAPA and CAM prevalence rates vary widely between studies, which may be explained by different awareness and diagnostic strategies [8]. Our center screened every mechanically ventilated COVID-19 patient who clinically worsened despite adequate standard of care for CAPA. This case is a patient with Rhizopus/Aspergillus coinfection in a previously immunocompetent COVID-19 patient and a discussion about mixed mold infections.

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transferred to the intensive care unit (ICU) on October 26, 2020 (Day 1). The patient presented with polypleo (respiratory rate, 34 breaths/minute) with signs of respiratory distress such as abdominal breathing and SpO2 91% under 15 L/min of oxygen. His-white blood cell count was 10,000 cells per mm³ (normal range, 4000 to 10,000) with 90% neutrophils (9040, normal range 1700 to 7000 cells per mm³) and 3.8% lymphocytes (400, normal range 1500 to 4500 cells per mm³), and his C-reactive protein level was 194 mg/dL (normal value <5 mg/dL), procalcitonin was 1.49 µg/L (normal value <0.05 µg/L), fibrinogen was 7.77 g/L (normal range 2 to 4 g/L), and β-dimer was 2830 ng/mL (normal value <500 ng/mL). He had metabolic alkalosis with profound hypoxemia at 55 mmHg and lactatemia at 1.4 mmol/L. The simplified acute physiology score II (SAPSII) and Sepsis-related Organ Failure Assessment (SOFA) at 24 h were 32 and 4, respectively. A third BAL was performed on Day 24 due to symptom persistence (9.1%). In

| BAL Day 19 | Serum Day 19 | BAL Day 24 | Plasma Day 24 |
|------------|-------------|------------|--------------|
| DE Culture | Negative    | ND         | ND           | Aspergillus- and Mucorales-type mycelium ND |
| Aspergillus weitschiae | Candida parapsilosis | ND | ND | |
| GM Ag | Aspergillus > 4.63 | ND | GM Ag > 4.63 | Aspergillus weitschiae |
| BDG | ND | 30.7 pg/mL | GM Ag > 5.12 | ND |
| PCR Mucor / Rhizopus | negative | positive* (Cq 30.87) | ND | negative |
| PCR A. fumigatus | negative | positive (Cq 25.65) | ND | positive (Cq 24.62) |
| PCR: Polymerase chain reaction; *PCR added retrospectively. |

References for this review were identified by searching the PubMed database using a combination of title keywords that referred to mixed mold infection (mucormycosis AND [aspergilosis OR aspergilus], mixed fungal infection, mixed mold infection). Thirty-five cases reporting Aspergillus and Mucorales were analyzed (Table 2). These cases were described mostly in males (n = 21; 60%) with a median age of 51 (IQR, 34–65) years. These mixed infections were reported in patients with hematological malignancy (n = 12; 34%), diabetes (n = 10; 29%), trauma (n = 3; 9%), solid cancer (n = 1; 3%), solid organ transplantation (n = 1), Castleman disease (n = 1), and while receiving high-dose corticosteroids (n = 4). Most infections involved the lungs (n = 21; 60%) and CT scan showed cavitations (n = 13; 62%). Sinuses, brain, and skin were involved in 11 (31%), 4 (11%), and 2 (6%) cases, respectively. When identified to the species. The most frequently identified genera were Mucor (n = 11; 31%) and Rhizopus (n = 8; 23%) followed by Lichtheimia (n = 4; 11%), Cunninghamella (n = 3; 9%), and Rhizomucor (n = 2; 9.1%). In fifteen cases, Mucorales order members were only identified upon histopathological biopsy examination. In twelve (34%) cases, aspergilosis was diagnosed before mucormycosis and voriconazole was prescribed, and the patient was subsequently switched to amphotericin B. Thirteen of 35 (37%) patients died. Among these thirteen patients, most had European Organization for Research and Treatment of Cancer (EORTC) host factors (hematological malignancy, n = 5; high dose corticosteroids, n = 3; cancer under chemotherapy,
Table 2
Published cases of mixed mucormycosis and aspergillosis infection.

| Reference | Sex | Age | Underlying condition | Localization | Imaging | Aspergillus sp. | Mucorales sp. | Concomitant isolation | Classification* | Treatment | Outcome |
|-----------|-----|-----|----------------------|--------------|---------|----------------|---------------|----------------------|-----------------|-----------|---------|
| Bellanger (2021) [15] | M | 55 | COVID-19, Neutropenia; Hematological malignancy | Lung | Not contributive | Aspergillus fumigatus | Rhizopus microsporus | YES | Probable* | AMB | Died |
| Johnson (2021) [16] | M | 79 | COVID-19, Diabetes | Lung | Cavitation | Aspergillus fumigatus | Rhizopus oryzae | YES | Aspergillus first | Probable* | VCZ+AMB | NA |
| Brachinger (2021) [17] | M | 73 | COVID-19, Diabetes, Obesity | Lung | Not contributive | Aspergillus fumigatus | Rhizopus microsporus | YES | Aspergillus first | Probable* | VCZ+AMB+PCZ | Died |
| Buil (2021) [18] | M | Late 50 s | COVID-19, Hematological malignancy, Diabetes | Lung | CAVITIES, reversed halo-sign | Aspergillus fumigatus | Lichtheimia ramosa | Aspergillus fumigatus | Rhizopus microsporus | Aspergillus first | Proven | Died |
| Buil (2021) [18] | M | Late 60 s | COVID-19, Hematological malignancy, Diabetes, Obesity | Lung | Progression of pulmonary lesions, dissemination to the kidneys | Aspergillus fumigatus | Rhizopus delenae | First Probable* | VCZ-AMB | NA |
| Present case | M | 74 | COVID-19, High-dose corticosteroids | Lung | Cavitation | Aspergillus fumigatus | Rhizopus microsporus | YES | Putative | VCZ+AMB | Alive |
| Bergamini (2013) [19] | F | 58 | Hematological malignancy | Lung | Consolidation; Cavitation | Aspergillus sp. | Mucor sp. | YES | Proven* | AMB | Alive |
| Chemetetz (2016) [20] | M | 17 | Cerebral glioma; Chemotherapy | Brain, Sinus | Sinus opacification; Brain lesion | Aspergillus flavus | Rhizomucor sp. | YES | Proven* | AMB | Died |
| Davodi (2014) [21] | M | 24 | Hematological malignancy; Neutropenia | Lung | Opacities; Cavitation | Uncultured | Rhizomucor sp. | YES | Proven* | AMB+VCZ+CAS | Alive |
| Hu (2021) [22] | M | 51 | Hematological malignancy | Lung | Gastrointestinal | Massive high-density shadow in the right superior lobe, free abdominal gas under the diaphragm, and peritoneal fluid | Aspergillus flavus | Cunninghamella bertholletiae | YES | Proven* | VCZ→AMB+VCF →AMB+Posaconazole |
| Taha (2021) [23] | F | 38 | Hematological malignancy; HCT | Skin | NA | Aspergillus fumigatus | Rhizopus oryzae | YES | Probable* | AMB | Died |
| Kibbel (2008) [24] | F | 49 | Hematological malignancy; Neutropenia | Sinus | NA | Aspergillus fumigatus | Mucor sp. | YES | Probable* | AMB+CAS | Died |
| Lai (2021) [25] | M | 70 | COVID-19, High-dose corticosteroids | Lung | Infiltrations | Aspergillus terreus | Cunninghamella bertholletiae | Aspergillus first | Probable* | VCZ+ADP →AMB | Died |
| Lefrak-Vanacchi (2018) [26] | M | 44 | Trauma | Lung | Cavitation | Aspergillus fumigatus; Aspergillus flavus | Uncultured | Uncultured | Aspergillus first | Proven* | VCZ→AMB+VCZ | Alive |
| Liu (2019) [27] | M | 52 | Diabetes | Lung | Cavitary maxillary sinusitis, erosion of orbital bone, extension into right orbit | Aspergillus sp. | Mucor sp. | YES | Proven* | AMB | Died |
| Madan (2011) [28] | F | 27 | Diabetia | Lung | Consolidation; Cavitation | Aspergillus fumigatus | Mucor sp. | YES | Proven* | AMB+VCZ | Died |
| Maoro (2005) [29] | M | 66 | Castleman disease | Sinus | NA | Uncultured | Uncultured | YES | Proven* | AMB | Alive |
| Manero (2019) [30] | F | 55 | High dose corticosteroids; Dermatomyositis | Brain | Accees | Aspergillus sp. | Mucor sp. | YES | Aspergillus first | Proven* | VCZ→AMB | Died |
| Mclintock (2005) [31] | M | 19 | Hematological malignancy; Neutropenia | Lung | Cavitary | Aspergillus fumigatus | Lichtheimia corymbifera | YES | Proven* | AMB+ITZ+NA | Died |
| Moorthy (2021) [32] | M | 45 | COVID-19 | Sinus, eye | NA | Uncultured | Uncultured | NM | Proven* | AMB+VCZ | Alive |
| Ohradovic-Yamaev (2021) [33] | M | 28 | Trauma | Skin | NA | Uncultured | Uncultured | Yes | Proven* | AMB+VCZ | Alive |
| Point (2017) [34] | M | 61 | Diabetes | Lung; Sinus | Consolidation; Sinus opacification | Aspergillus fumigatus | Uncultured | Aspergillus first | Proven* | VCZ→AMB | Alive |
| Pouvaert (2019) [35] | F | 52 | Hematological malignancy; Iatrodose | Brain; Kidney | Acceess | Aspergillus fumigatus | Lichtheimia sp. | Aspergillus first | Proven* | VCZ→AMB | Alive |
| Radovicki (2011) [36] | M | 22 | Trauma | Lung | NA | Aspergillus fumigatus; Aspergillus flavus | Cunninghamella bertholletiae | YES | Proven* | AMB | Died |
| Ravindra (2021) [37] | M | 65 | Alcoholic | Lung | Ground-glass opacity, consolidation (reverse halo sign); cavitation consolidation | Uncultured | Uncultured | YES | Proven* | AMB | Alive |
| Ravindra (2021) [38] | M | 70 | None | Lung | Intra-cavitary mass, crescent of air, thick-walled cavity | Aspergillus sp. | Mucor sp. | YES | Proven* | AMB | Alive |
| Safai Nodeh (2019) [39] | F | 34 | Hematological malignancy; Neutropenia | Lung; Sinus | Sinus opacification; Bone lysis | Aspergillus sp. | Uncultured | Aspergillus first | Proven* | VCZ→AMB | Alive |
| Salini (2021) [40] | M | 72 | COVID-19, Hematological malignancy, Diabetes, High dose corticosteroids | Lung | Sinus | Aspergillus fumigatus | Mucor circinelloides | Aspergillus first | Probable* | VCZ+ADP →AMB+CPF | Died |
| Singh (2021) [41] | F | 50 | Diabetes | Sinus | NA | Aspergillus fumigatus | Mucor sp. | YES | Proven* | AMB→VCZ | Alive |

(continued on next page)
**Table 2 (Continued)**

| Reference | Sex | Age | Underlying condition | Localization | Imaging | Aspergillus sp. | Mucorales sp. | Concomittant feature* | Treatment | Outcome |
|-----------|-----|-----|----------------------|--------------|---------|----------------|---------------|----------------------|-----------|---------|
| Singh (2021)[57] | F   | 60  | Diabetes             | Rhino-ocular | NA      | Aspergillus fumigatus | Mucorales sp. | YES                  | Proven* AMB | Alive   |
| Singh (2021)[57] | M   | 35  | Diabetes             | Sino-nasal   | NA      | Aspergillus fumigatus | Mucorales sp. | YES                  | Proven* VCZ | Alive   |
| Weng (2012)[58] | M   | 10  | Hematological malignancy; Lung; Disseminated | Cavitation | NA      | Aspergillus fumigatus | Rhizopus sp. | Mucorales sp. | HSCT | Sinus opacity first Proven* AMB | Alive |

ADF: Anidulafungin; AMB: liposomal amphotericin B; CPF: caspofungin; EORTC/MSG: hematopoietic stem cell transplant; ICZ: isavuconazole; MCF: micafungin; NA: not assessed; NM: not mentioned; PCZ: posaconazole; SOT: solid organ transplant; VCZ: voriconazole. Classification used was °ECMM/ISHAM for COVID-19 patients[7], *EORTC/MSG Education and Research Consortium, Blot et al.[28] for patients in intensive care unit with EORTC/MSG host factor and proven infection.

**Discussion**

Here, we report the case of a patient with severe SARS-CoV-2 infection with the probable complications of CAPA and CAM.

One important aspect of our case is the co-infection with both A. *welwitschiae* and *R. delemar*. *Aspergillus* and *Rhizopus* are two fungal genera with an angioinvasive ability. This association has been rarely described in the immunocompromised subject with an often fatal outcome in pulmonary and brain localizations (Table 2). More cases are described in case series of mucormycosis with up to 44.4% of *Aspergillus* co-infection [12]. Furthermore, the VITAL trial that assessed the efficacy of isavuconazole for treatment of mucormycosis also reported six cases among 37 patients, suggesting that this co-infection may be underdiagnosed [13,14]. The triple association COVID-19/*Aspergillus*/Mucorales has been reported in severely immunocompromised patient after stem cell transplantation and in patients with diabetes mellitus [15,16]. In one other case, a mixed mold infection was reported in a patient receiving high-dose corticosteroids for dermatomyositis [17].

There have been several publications on the subject of COVID-19 and mold co-infection since the beginning of the first COVID-19 pandemic wave. The main co-infection that was studied was aspergillosis [7,18,19], and these studies highlighted several potential risk factors including mucormycosis and mechanical ventilation, high-dose corticosteroids [20,21], azithromycin for 3 days [22], tocilizumab [23,24], and immunological storm including high inflammatory cytokine levels [18]. CAM was reported less frequently especially in the first two COVID-19 pandemic waves, but it appears to be an increasing problem in India [25]. Although mucormycosis and mixed *Aspergillus*/Mucorales infection have been described less frequently, risk factors are expected to be similar [25,26]. Most cases of CAM are reported in patients with underlying conditions who are at a high risk of contracting these invasive infections (i.e. EORTC and the Mycoses Study Group Education and Research Consortium [EORTC/MSG] host factors or diabetes mellitus), and is it unclear whether COVID-19 infection is associated with a higher risk in this population or if there is a publication bias toward mucormycosis in patients with concomitant COVID-19 infection. Our patient was immunocompetent before contracting COVID-19. The risk factors for co-infection with mold disease were azithromycin administration for 7 days, high-dose corticosteroids, and the use of mechanical ventilation. This combination of factors probably led to the development of mixed invasive fungal disease.

Similar to any environmental mold that is isolated in respiratory specimens, there is always a discussion about colonization and infection. Because most COVID-19 patients have no classical host factors for invasive mold disease, other classifications besides the EORTC/MSG ERC classification [27] were developed and used to identify invasive fungal diseases. These classifications are AsplCU [28], an influenza-associated pulmonary aspergillosis classification developed by Verweij et al. [29], and most recently, a classification that was proposed by ECM/ISHAM [7]. Both aspergillosis and mucormycosis are consistent with putative or probable CAPA or CAM because both BAL direct examination and culture results were positive. Additionally, a CT-scan showed patterns that were compatible with invasive fungal disease. Furthermore, a highly positive galactomannan index in both blood and BAL and a positive Mucorales qPCR result in the blood.
strongly suggested an invasive disease. Therefore, the patient could have been classified as having a CAPA and CAM infection. However, careful investigation of our patient’s corticosteroids doses indicated that he met the EORTC criteria [27] because he received a prednisone equivalent dose >0.3 mg/kg/day for 3 weeks (0.08 mg/kg/day of dexamethasone for 8 Days [0.6 mg/kg/day prednisone equivalent], 0.3 mg/kg/day of dexamethasone for 20 Days [1.9 mg/kg/day prednisone equivalent], and a methylprednisolone bolus of 120 mg [150 mg prednisone equivalent]) [27,30]. Therefore, a careful evaluation of the cumulative dose is required before concluding that the patient has no known EORTC/MSGERC risk factor for invasive mold infection.

Aspergillus section Nigri is also worth discussing because it is rarely responsible for infection compared to Aspergillus fumigatus due to its physiological characteristics such as its large conidia, which makes it more difficult to reach alveoli, and its optimal germination temperature, which is approximately 30 °C [31]. Invasive aspergillosis due to A. section Nigri is mostly reported in severely immunocompromised patients [32]. One other case report describes a fatal CAPA infection due to A. section Nigri with a high galactomannan index at Day 10 after ICU admission [33]. The delay between hospitalization in the ICU and CAPA infection of 19 days was longer than the median time that was published in CAPA cohorts of approximately 6 days [29]. This could be explained because reaching a critical dose of corticosteroids was required for invasive disease to develop in a previously immunocompetent patient.

Molecular biology tools to diagnose invasive fungal infections (IFIs) have only recently been developed. Aspergillus qPCR have been included in international guidelines for invasive aspergillosis since 2020 [27], and they are included when making a CAPA diagnosis [7]. However, detection of circulating Mucorales DNA (cmDNA) is not recommended by default to diagnose mucormycosis [34] despite data showing a high sensitivity and its ability to predict a diagnosis and quantify the fungal burden [9]. The important angioinvasive ability of Mucorales makes it possible to detect the fungus in blood samples. Regular screening of at-risk patients such as severely burned patients suggests that cmDNA detection allows an earlier diagnosis of invasive mucormycosis in this population and earlier treatment initiation [35]. Unlike galactomannan detection for the diagnosis of aspergillosis, there are no tools that target the Mucorales antigens, which emphasizes the need to include cmDNA detection in the mucormycosis diagnosis standards. This could be considered to be a screening tool for COVID-19 patients who are clinically worsening despite an appropriate standard of care and who have additional risk factors such as uncontrolled diabetes or high-dose corticosteroids.

Finally, there are no guidelines or standard practice for IFI management in COVID-19 patients, and clinical effectiveness of antifungal administration in these cases has not been demonstrated [7]. The treatment that is being promoted for patients with CAPA is intravenous voriconazole or isavuconazole, the latter of which covers the Mucorales species and Aspergillus species, and is showing promise in
mixed mold infections [7,14]. In 34.2% of co-infections that were analyzed in this literature review, Aspergillus was identified and treated first with voriconazole suggesting that the mucormycosis may be a breakthrough IFI that could be avoided using isavuconazole as a first-line treatment. Our patient was treated with voriconazole, against which Rhizopus delemar has high a MIC, which was confirmed by our data [36]. He was later switched to liposomal amphotericin B after Mucorales-type mycelium was identified in the direct BAL examination. However, this antifungal modification may have occurred too late in the infection’s course considering that the serum PCR was retrospectively found to be positive 6 days before the antifungals were changed.

CONCLUSION

The SARS-CoV-2 virus has highlighted the existence of multiple fungal superinfections in patients who were not previously immunocompromised and who did not have common risk factors for invasive mold disease. However, the cumulative steroid dose for concomitant fungal superinfections in patients who were not previously immunocompromised as shown in the case of our patient, require adapting the management of these patients by screening respiratory and serum samples using biomarkers.

Declaration of Competing Interest

The authors have nothing to declare.

Acknowledgment

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