Coronavirus Disease 2019-Associated Mucormycosis in France: A Rare but Deadly Complication

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BRIEF REPORT

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We studied COVID-19 associated mucormycosis based on 17 cases reported nationwide and assessed the differences with India. They differed by frequencies of diabetes mellitus (47% in France versus up to 95% in India), hematological malignancies (35% versus 1%), anatomical sites (12% versus >80% rhino-orbito-cerebral) and prognosis (88% mortality versus <50%).

Keywords. CAM; CAPA; COVID-19; mucormycosis.

Coronavirus disease 2019 (COVID-19) has a wide spectrum of severity. Fungal superinfections, notably aspergillosis, can complicate the course of severe COVID-19 with a high mortality [1]. Emerging reports, mainly from India, recently described COVID-19-associated mucormycosis (CAM). In this country, more than 28 000 cases have already been reported and mucormycosis is now a notifiable disease [2]. Outside India, only a few case reports have been published [3, 4]. The aim of our study was to describe cases of CAM in France and analyze host factors, presentation, and outcome.

METHODS

We conducted a retrospective nationwide study on CAM. Our network of 59 French mycology laboratories, which covers most of the French territory, was requested to report CAM cases diagnosed from March 2020 to June 10, 2021 to the French National Reference Center for Invasive Mycosis and Antifungals (NRCMA) as part of its surveillance missions. Only cases occurring within the 3 months after COVID-19 diagnosis confirmed by a positive polymerase chain reaction (PCR) for severe acute respiratory syndrome coronavirus 2 were included. Clinical data were recorded anonymously on a standardized case report form. Cases were classified as proven or probable according to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) criteria [5], with the addition of diabetes mellitus (DM) and dexamethasone prescribed for COVID-19 as host factor and positive *Mucorales* PCR in serum, blood, or plasma as mycological evidence. Date of mucormycosis diagnosis was defined by the first positive sample for mucormycosis.

Patient Consent Statement

This report is part of the NRCMA official duties approved by the Institut Pasteur Internal Review Board (2009-34/IRB) in accordance with French Law. This investigation was considered to be a public health response and the necessity of written informed consent was waived. One case has already been published [6].

RESULTS

From March 2020 to June 10, 2021, 17 patients from 11 centers developed CAM (Table 1). Sixteen (94%) patients were male and the median age was 64 (range 25–79). The median body mass index was 28 (range 19–37). During the same period, 473 353 patients have been hospitalized for COVID-19 in France [7].

Underlying Risk Factors Before Coronavirus Disease 2019

Among the 17 patients, 7 (41%) had classic EORTC/MSGERC host factors for invasive mold infections before COVID-19,

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Table 1. Characteristics and Outcome of the Patients With COVID-19-Associated Mucormycosis

Patient	Sex	Age	Underlying Disease	EORTC/MSGERC Criteria	COVID-19 Therapy	ICU	CAM Location	Diagnosis	Species	Other Fungal Infection	CAM First-Line Therapy	Outcome Month 3
1	F	68	Dexa-DM, lung carcinoma	No	Corticosteroids	Yes, HFNC, IMV	Pulmonary	Probable	*Rhizomucor pusillus*	No	L-AmB	Death
2	M	65	HM, dexa-DM	Yes	Corticosteroids	Yes, IMV	Pulmonary	Probable	*Rhizomucor miehei*	No	No	Death
3	M	25	HM, allo-HSCT, neutropenia	Yes	Corticosteroids	Yes, HFNC, IMV	Pulmonary	Probable	*Rhizomucor* spp	No	No	Death
4	M	41	SOT, agammaglobulinemia	Yes	Corticosteroids, tocilizumab	No	ROC	Proven	*Rhizopus oryzae*	No	IVZ	Death
5	M	55	HM, auto-HSCT, neutropenia	Yes	No	Yes, HFNC, IMV	Pulmonary	Probable	*Rhizopus microsporus*	CAPA	L-AmB	Death
6	M	64	No	No	No	Yes, IMV	Digestive	Proven	*R microsporus*	No	IVZ	Alive
7	M	74	No	No	Corticosteroids	Yes, HFNC, IMV	Pulmonary	Probable	*Rhizopus delemar*	CAPA	L-AmB	Death
8	M	56	Pre-existing DM	No	Corticosteroids, tocilizumab	Yes, HFNC, IMV	ROC	Proven	*R delemar*	CAPA	L-AmB	Death
9	M	53	HM, neutropenia	Yes	No	Yes, HFNC, IMV	Disseminated	Probable	*Rhizomucor* spp	No	L-AmB	Death
10	M	66	Pre-existing DM	No	Corticosteroids	Yes	Pulmonary	Probable	NA	No	L-AmB	Alive
11	M	79	Dialysis	No	Corticosteroids	Yes, HFNC, IMV	Pulmonary	Probable	*R microsporus*	No	L-AmB	Death
12	M	65	COPD, dexa-DM	No	Corticosteroids	Yes, HFNC	Pulmonary	Probable	NA	No	No	Death
13	M	60	HM, pre-existing DM	Yes	Corticosteroids	Yes, HFNC, IMV	Disseminated	Probable	NA	CAPA	L-AmB	Death
14	M	60	No	No	No	Yes, HFNC, IMV	Digestive	Proven	*Lichteimia* spp	IC	L-AmB	Death
15	M	66	No	No	Corticosteroids	Yes, HFNC, IMV	Digestive	Proven	*R microsporus*	CAPA	No	Death
16	M	57	HM, neutropenia, dexa-DM	Yes	Corticosteroids	Yes, HNFC	Disseminated	Probable	*R microsporus*	No	No	Death
17	M	67	Underlying DM	No	Corticosteroids	Yes, IMV	Pulmonary	Probable	*R microsporus*	No	L-AmB	Death

Abbreviations: allo-HSCT, allogeneic hematological stem cell transplantation; auto-HSCT, autologous hematological stem cell transplantation; CAM, coronavirus disease 2019-associated mucormycosis; CAPA, coronavirus disease 2019-associated aspergillosis; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; dexa-DM, diabetes mellitus induced by dexamethasone; EORTC/MSGERC, European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium; F, female; HM, hematological malignancy; HSCT, hematological stem cell transplantation; HNFC, high-flow nasal cannula; IC, invasive candidiasis; ICU, intensive care unit; IMV, invasive mechanical ventilation; IVZ, isavuconazole; L-AmB, liposomal-amphotericin B; M, male; NA, not applicable; ROC, rhino-orbito-cerebral; SOT, solid organ transplant.

including 1 with solid organ transplantation and 6 (35%) with hematological malignancies (HM) [5]. Overall, 4 (24%) patients had pre-existing DM. Three (18%) patients received immunosuppressive drugs, 2 (12%) received long-term corticosteroids, and 2 (12%) were currently having antineoplastic chemotherapy. Seven (41%) patients had no classic risk factors for mucormycosis before COVID-19.

Coronavirus Disease 2019

Sixteen (94%) patients had severe COVID-19 requiring intensive care unit (ICU) care. Median time between first COVID-19 symptoms and ICU transfer was 7 days (range 0–86). Management of COVID-19 required corticosteroids for 13 (76%) patients, mainly dexamethasone, and tocilizumab for 2 (12%). Twelve (71%) patients had high-flow nasal cannula oxygen therapy, and 13 (76%) had invasive mechanical ventilation.

Four (24%) patients developed DM induced by dexamethasone for COVID-19, meaning that overall 8 patients (47%) had DM. Four (24%) patients had diabetic ketoacidosis. Eleven (65%) patients had renal failure, 8 (47%) requiring dialysis.

Mucormycosis

Coronavirus disease 2019-associated mucormycosis was diagnosed a median of 24 days (range 8–90) after COVID-19 first symptoms, 12.5 days (range 1–49) after ICU hospitalization, and 16 days (range 1–49) after corticosteroid prescription. Coronavirus disease 2019-associated mucormycosis location was mainly pulmonary (n = 9; 53%), but it was also digestive (n = 3; 18%), rhino-orbito-cerebral (n = 2; 12%), or disseminated (n = 3; 18%). Twelve patients with a pulmonary location had a chest computed tomography scan evidencing a reversed halo sign in 1 patient (8%) with HM and neutropenia, consolidation in 10 (83%) patients, including 4 (33%) with a cavitation, and 1 with nodules.

Mycology

Coronavirus disease 2019-associated mucormycosis was classified as proven in 5 (29%) patients and probable in 12 (71%). The culture grew *Mucorales* in samples from 11 (65%) patients (bronchoalveolar lavage [{BAL} n = 5] and tracheal aspirate and biopsy [n = 3, each]). *Mucorales* PCR assay (adapted from [8] in 7 centers, from [9] in 1 center, and from MycoGENIE [Ademtech, France] in 1 center) was found positive in 15 (88%) patients (serum [n = 14], BAL [n = 7], tissues [n = 3], peritoneal fluid [n = 1]). Ten patients had more than 1 positive sample (on different site). Polymerase chain reaction was the only means of diagnosis for 4 patients including 2 with positive serum and BAL samples. Histology identified hyphae compatible with *Mucorales* in biopsies from 5 patients.

Mucorales was identified to the genera or species level by culture or species-specific PCR in 14 (82%) patients, mainly (n = 9, 64%) with *Rhizopus* (*Rhizopus microsporus* [n = 6; 43%], *Rhizopus delamar* [n = 2; 14%], and *Rhizopus arrhizus* [n = 1; 7%]), secondary (n = 4, 29%) with *Rhizomucor* (*Rhizomucor pusillus*, *Rhizomucor miehei* [1 each, 7%]), and with *Lichtheimia* spp in only 1 case (7%). All species identified from both culture and PCR were concordant. The cases of *Rhizomucor* occurred in 3 patients with HM and in 1 patient with pulmonary carcinoma.

Other Fungal Infections

Five (29%) patients developed COVID-19-associated aspergillosis (CAPA), a median of 2 days (−28 to 0) before CAM. All patients with CAPA and CAM died before week 12 of mucormycosis.

Treatment and Outcome

Five (29%) patients died before the diagnosis was made and did not receive any specific treatment. Twelve (71%) patients were prescribed liposomal amphotericin B (n = 10, 59%) or isavuconazole (n = 2, 12%). Three (18%) patients had surgery; 2 for rhino-orbito-cerebral mucormycosis and 1 for colonic perforation.

Global mortality was 76% (13 of 17) at week 6 and 88% (15 of 17) at week 12. Death occurred after a median of 34 days (15–124) after the first symptoms of COVID-19 and after a median of 7 days (0–86) after the first positive sample for CAM. All 7 patients with EORTC/MSGERC criteria died within 3 weeks after the diagnosis of CAM. Twelve-week survival curves in the whole population and according to the host factors are presented in a Supplementary Figure.

DISCUSSION

In this study, we reported 17 cases of CAM in France, the largest series from 1 country outside India [4, 10]. We observed a large spectrum of clinical presentations and host factors, and we showed evidence of high mortality (88%) by 12 weeks. These findings differ from our historical (2005–2007) series of 101 mucormycoses in France (RetroZygo) and from CAM reported in India [4, 10, 11].

We compared this study with series of CAM and mucormycosis without COVID-19 from India and from the French RetroZygo study (Table 2). The frequency of underlying DM was lower in this cohort than that recorded in CAM in India (60%–95%) [4, 9]. By contrast, the frequency of hematological malignancy in CAM was higher compared with India (35% vs 1%) [10]. Clinical spectrum was different, with more frequent pulmonary (53% vs 28%) and less frequent rhino-orbito-cerebral locations (12% vs 25%) in the current series versus the historical RetroZygo Study. The presentation clearly differed from India, where CAM mainly presents with rhino-orbito-cerebral locations (>80%) [10]. This difference could be explained by higher prevalence of DM in Indian patients.

Culture and/or histology were positive in 76% of patients, whereas diagnosis of CAM was based only on a positive *Mucorales* PCR in 4 patients (24%). The broad use of *Mucorales*

Table 2. Comparison of Studies of Mucormycosis With COVID-19 (CAM) and Without COVID-19 (non-CAM) From France and India

Patient Characteristics	CAM France Present Study n (%)	CAM India Patel [10] n (%)	Non-CAM India Patel [10] n (%)	Non-CAM France Lanternier [11] n (%)
Number of patients	17	187	100	101
Age, years, mean (SD)	60 (12.5)	57 (12.5)	47 (16.4)	51 (19.9)
Sex, male, n	16 (94)	150 (80)	64 (64)	59 (58)
Underlying Diseases				
Hematological malignancy, n	6 (35)	2 (1)	2 (2)	50 (50)
Neutropenia, n	4 (24)	NA	NA	41 (41)
HSCT, n	2 (12)	NA	NA	12 (12)
Solid tumor, n	1 (6)	NA	NA	2 (2)
Solid organ transplantation, n	1 (6)	3 (2)	0	3 (3)
Diabetes mellitus, n	8 (47)	113 (60)	67 (67)	32 (32)
Trauma	0 (0)	3 (2)	9 (9)	18 (18)
Corticosteroids, n	13 (76)	146 (78)	6 (6)	NA
ICU admission, n	16 (94)	58 (31)	9 (9)	NA
CAM Location				
Pulmonary, n	9 (53)	16 (9)	6 (6)	28 (28)
ROC, n	2 (12)	161 (86)	74 (74)	25 (25)
Other, n	3 (18)	6 (3)	10 (10)	30 (30)
Disseminated, n	3 (18)	4 (2)	0	18 (18)
Diagnosis				
Culture growing *Mucorales*	11 (65)	100 (53)	38 (38)	68 (67)
Positive PCR	15 (88)	0	0	0
Histology of mucormycosis	5 (29)	143 (76)	37 (37)	NA
First-Line Therapy[a]				
Liposomal amphotericin B, n	10 (59)	136 (73)	84 (84)	68 (67)
Amphotericin B deoxycholate, n	0	31 (17)	5 (5)	6 (6)
Isavuconazole, n	2 (12)	19 (10)	2 (2)	0
Posaconazole	0	73 (39)	14 (14)	33 (33)
Surgery, n	3 (18)	131 (70)	73 (73)	(59)
Death week 12	15 (88)	75/170 (44)	42/86 (49)	43 (43)

Abbreviations: CAM, coronavirus disease 2019-associated mucormycosis; COVID-19, coronavirus disease 2019; HSCT, hematological stem cell transplantation; ICU, intensive care unit; NA, not applicable; PCR, polymerase chain reaction; ROC, rhino-orbito-cerebral; SD, standard deviation.

[a]First-line therapy includes combined antifungal therapy.

PCR could partly explain the higher frequency of CAM in France compared with other European countries [3, 8] and of some locations, mainly pulmonary or digestive, compared with the previous French Retrozygo studies, in which PCR was not used [11]. *Rhizopus microsporus* was the most frequent species in this small series. It is likely that although *Mucorales* is present in the environment, the species recovered are influenced by the geographic area, as well as the anatomic site, and the underlying risk factors, explaining the differences in species distribution among studies independently of COVID [4].

Twelve-week mortality was very high (88%) in our current CAM study, compared with the RetroZygo Study (44%), and with CAM in India (40%–50%) [4, 10, 11]. It is also higher than that reported for CAPA [1, 12]. This major difference might be partly explained by the higher frequency of pulmonary or disseminated presentations, which are classically associated with a poorer prognosis compared with rhino-orbito-cerebral locations. The severity of COVID-19 itself and the high proportion of patients hospitalized in the ICU might also account for these differences.

The differences in frequencies, comorbidities, anatomical location, and prognosis between our current series and CAM in India might be explained in part by a higher frequency of patients with DM in India [13]. Historically, there is a higher burden of mucormycosis in India. In addition to DM, we hypothesized that environmental and possibly genetic conditions might play a role in the occurrence of mucormycosis in this country independently of COVID-19. The addition of the COVID-19 pandemic, the broad use of dexamethasone, and the high frequency of DM lead to the so-called "black fungus threat" in India, which does not seem to be the case in France and other countries outside India.

Despite the multicenter design, the limitations of our study are the small number of cases and the retrospective design.

However, epidemiological surveillance in France is based on a reliable and sustained collaboration between French mycologists and the NRCMA, which limits the risk of reporting bias.

CONCLUSIONS

Coronavirus disease 2019-associated mucormycosis has a high mortality in this study. Better knowledge, identification, and earlier treatments of CAM might help to improve the prognosis. International studies are warranted to better understand and assess CAM.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. F. D. declares personal fees from Gilead outside the submitted work. F. L. declares personal fees from Gilead and F2G outside the submitted work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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