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General review

COVID-19-associated mucormycosis in India: Why such an outbreak?

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ABSTRACT

An unprecedented mucormycosis outbreak occurred in India during the second COVID-19 wave in spring 2021. COVID-19-associated mucormycosis (CAM) was observed, mainly rhino-orbito-cerebral mucormycosis (ROCM), in patients with poorly controlled diabetes and treated with inappropriate doses of glucocorticoids. The aim of this mini-review was to compare the characteristics of the CAM epidemic in India with (i) mucormycosis cases before the COVID-19 pandemic and (ii) CAM in the rest of the world (particularly in France) in order to identify the reasons for this outbreak. In India, the major mucormycosis epidemiologic change during the COVID-19 pandemic was an increase in the percentage of patients treated with corticosteroids who developed CAM. Compared with the rest of the world, India reported a higher mucormycosis incidence even before the COVID-19 pandemic. Moreover, in India, patients with CAM were more likely to have diabetes mellitus and ROCM; conversely, mortality rates were lower. The reasons for such a localized epidemic in India have remained unclear, but some hypotheses can be put forward, particularly the combination of high prevalence of uncontrolled diabetes mellitus and frequent indiscriminate corticosteroid utilization in a country that already had a high mucormycosis burden before the COVID-19 pandemic.

Introduction

Mucormycosis is a rare opportunistic infection caused by a filamentous fungus belonging to the Mucorales order. It mainly affects patients with compromised immune system (notably individuals with solid organ or allogenic stem-cell transplantation, hemopathy) or with uncontrolled diabetes, but rare cases have been described in immunocompetent patients (burns, traumatic wounds). The main clinical forms are pulmonary, rhino-orbito-cerebral, cutaneous and disseminated. The diagnosis is difficult and consequently it is often delayed, resulting in high lethality despite appropriate antifungal and surgical treatment [1].

India was particularly hurt by the coronavirus disease 2019 (COVID-19) pandemic: 44,587,307 cases including 528,629 deaths according to the World Health Organization on January 17, 2023 [2]. Surprisingly, in India, the COVID-19 pandemic, especially the second wave, led to an upsurge in mucormycosis cases among patients with COVID-19 (COVID-19-associated mucormycosis, CAM). Indian media, based on statements by members of the Indian government, reported 11,717 CAM cases on May 25 [3], 28,252 CAM cases on June 7 [4], 45,274 CAM cases (including 4332 deaths) on July 20 [5], and 51,775 CAM cases on November 29, 2021 [6]. These precise data were available because on May 20, 2021, mucormycosis became a notifiable disease under the Epidemic Diseases Act 1897 [7]. Before this epidemic, mucormycosis was considered a rare opportunistic infection. For example, in 2014, the reported incidence was 1.2 cases of mucormycosis per million of inhabitants in France [8], which corresponded to 79 cases per year. Moreover, very few CAM cases were reported outside India [9]. In Europe, fungal infections associated with COVID-19 were mainly COVID-19-associated pulmonary aspergillosis (CAPA), whereas CAM was rarer [10]. A multicentric prospective study in France [11] reported 76 proven/probable CAPA cases and 6 proven/probable CAM cases among 509 COVID-19 patients on mechanical ventilation. Conversely, in India, few CAPA cases were reported compared with the CAM cases [10].

Such epidemiological disparities could raise questions about the conditions that led to this CAM epidemic in India. The aim of this mini-review was to compare the characteristics of the CAM epidemic in India (i.e. incidence, diagnosis, distribution of Mucorales species, underlying diseases, clinical forms, prognosis) with (i) CAM cases in the rest of the world (with a particular focus on France) and (ii) mucormycosis cases before COVID-19 (non-CAM) to try to understand the reasons for such an epidemic.

Abbreviations: CAM, COVID-19-associated mucormycosis; CAPA, COVID-19-associated pulmonary aspergillosis; ROCM, rhino-orbito-cerebral mucormycosis

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Comparison of mucormycosis characteristics before/after the COVID-19 pandemic in India and in the rest of the world

Before the COVID-19 pandemic, **the reported incidence** of mucormycosis per million of inhabitants was 0.43 in Spain [12], 0.6 in Australia [13], 0.9 in France [14], 3 in the USA [15], and up to 140 in India [16]. Its incidence was estimated to be 70 times higher in India than in the rest of the world [17]. A computational model estimated that in India, the mean (± standard deviation) mucormycosis burden per year was 171,504 (±12,365.6) cases with a mortality of 65,500 (38.2%) [16].

During the COVID-19 pandemic, in India, CAM incidence ranged from 0.27% (28/10,517) [18] to 1.8% (47/2557) in hospitalized patients [19] and from 0% (0/1027) [20] to 1.6% (25/1579) among patients in intensive care units (ICU) [18]. The authors of the study without any CAM case in ICU [20] emphasized the strict glycemic control and the low glucocorticoid doses used at their center. The other study in ICU [18] reported a 2.1-fold increase of mucormycosis cases in September-December 2020 (COVID-19 pandemic) compared with the same period before the pandemic (September-December 2019). Outside India, CAM cases were described in at least 17 countries [21], mainly in cases reports. Some studies evaluated CAM incidence. For example, a French prospective study reported a CAM incidence of 1.2% (6/509) among patients with COVID-19 on mechanical ventilation in ICU [11].

CAM diagnosis is often delayed, because it is difficult to establish or because often it occurs late after COVID-19 confirmation. The median time between COVID-19 diagnosis and CAM diagnosis was 18 days (IQR, 11–27) [18]. Another study reported a mean time between COVID-19 onset and mucormycosis symptoms of 18.9 ± 9.1 days [22]. The mycological diagnosis is based on specimen culture and direct observation of non-septate hyphae. Of note, in a French retrospective study [23], a specific PCR test was the only mean of microbiological diagnosis in 4 of the 17 patients with CAM under study.

The **distribution of Mucorales species** causing mucormycosis is country-dependent [24]. Like in France, the *Rhizopus* genus was the most frequently isolated in India before and during COVID-19. It was identified in 49% of the Mucorales isolates in a French study before COVID-19 [25]. In India, it was isolated in 56–81% of specimens before COVID-19 [26] and in 83% of specimens from patients with CAM [9]. The second most frequently isolated genus was *Lichtheimia* in France (29%) [25] and *Apophysomyces* in India (8–26%) [26]. Of note, the *Lichtheimia* genus was the most frequently isolated in Spain before COVID-19 [27].

Concerning underlying diseases associated with mucormycosis in India (Table 1), before the COVID-19 pandemic, diabetes mellitus ranked first (54–76% of patients with mucormycosis among whom 8–22% had diabetic ketoacidosis), followed by traumatisms (7.5–22%), solid organ transplantation (2.6–11%) and hemopathy (1–9%) [26]. Similarly, in patients with CAM, diabetes mellitus was also the most frequently reported comorbidity, ranging from 60% (113/187) [18] to 92.1% (140/152) [22]. In a large Indian retrospective study on COVID-19-associated rhino-orbito-cerebral mucormycosis (ROCM) [28], 78% (2194/2825) of patients had diabetes mellitus, among whom 41% (893/2194) had uncontrolled diabetes and 3.6% (79/2194) diabetic ketoacidosis [28]. Moreover, 87% (2073/2371) of them were treated with corticosteroids [28]. Comparison of patients with and without CAM showed a significantly higher glucocorticoid use in the CAM group: 78.1% (146/187) vs 6% (6/100), p = 0.0001 [18]. As previously reported for patients with non-CAM [1], diabetes mellitus, diabetic ketoacidosis, and cumulative dose of glucocorticoids were risk factors of CAM in Indian case-control studies[22,29].

In France, before COVID-19, the most frequent underlying diseases were hematologic malignancies (50%; 50/101), followed by diabetes mellitus (23%, 23/101, among whom 35%, 8/23, had diabetic ketoacidosis), and traumatisms (18%; 18/101) [25]. In patients with CAM, data were scarce, but a study reported diabetes mellitus (47%; 8/17) and hematologic malignancies (35%; 6/17) as underlying diseases [23]. Glucocorticoid use was more frequent in patients with CAM (78%; 13/17) [23] than with non-CAM (26%; 13/50) [25]. Overall, diabetes mellitus was more common in Indian patients with CAM [21] whereas hematological malignancies [0.9% (2/233) vs 9.5% (4/42), p<0.006] and solid organ transplantation [2.1% (5/233) vs 9.5% (4/42), p = 0.03] were more frequent in patients with CAM from the rest of the world [9].

Before the COVID-19 pandemic, in India, **the clinical forms of mucormycosis** (Table 1) were mainly ROCM (45–74%), followed by cutaneous (10–31%), pulmonary (3–22%), disseminated (0.5–9%) and gastrointestinal (2–8%) mucormycosis [26]. Similarly, in patients

Table 1
Comparison of the characteristics of patients with mucormycosis before the COVID-19 pandemic and with COVID-19-associated mucormycosis in France and India. The denominator is only specified when it is different from the total number of patients included in the study of interest. *In this study, the use of corticosteroids was only indicated for patients with hematological malignancies (n = 50).

	Before the COVID-19 pandemic		During the COVID-19 pandemic	
	France *Lanternier & al, 2012*	India *Prakash & al, 2021*	France *Danion & al, 2022*	India *Muthu & al, 2023*
Study duration	3 years	From 21 months to 15 years	15 months	6 months
Patients	101	1566 (9 studies)	17	1733
Sex ratio (male/female)	1.38	2–2.8	16	2.9
Age (mean ± standard deviation), years	50.7 ± 19.9	–	60 ± 12.5	52,6 ± 12,5
ICU admission n (%)	–	–	16 (94)	331/1616 (20,5)
Underlying diseases n (%)				
Diabetes mellitus among whom with	23 (23)	54–76%	8 (47)	1402 (80.9)
diabetes ketoacidosis	8/23 (35)	8–22%		73/1402 (5.2)
Hematological malignancy	50 (50)	1–9%	6 (35)	6 (0.3)
Solid organ transplant	3 (3)	2.6–11%	–	31 (1.8)
Traumatism	18 (18)	7.5–22%	–	–
Corticosteroid treatment	13/50 (26)*	3.7–22%	13 (76)	1200/1604 (74.8)
Clinical forms n (%)				
ROCM	25 (25)	45–74%	2 (12)	1526 (88.1)
Pulmonary	28 (28)	3–22%	9 (53)	122 (7.0)
Disseminated	18 (18)	0.5–9%	3 (18)	–
Cutaneous	20 (20)	10–31%	–	5 (0.3)
Gastrointestinal	4 (4)	2–8%	3 (18)	2 (0.1)
Mortality n (%)	44% *(day 90)*	28–52%	15 (88) *(week 12)*	473/1471 (32.2) *(week 12)*

with CAM, ROCM was the most reported clinical form, ranging from 86% (161/1856) [18] to 97% (148/152) [22]. The main clinical presentation of ROCM includes orbital/facial pain and edema, vision loss, ptosis and nasal block [28]. Comparison of patients with CAM and non-CAM found no difference in terms of clinical presentation [18].

In France, before the COVID-19 pandemic, the main clinical presentations were: pulmonary (28%; 28/101), rhino-orbito-cerebral (25%; 25/101), cutaneous (20%; 20/101) and disseminated (18%; 18/101) [25]. In patients with CAM, the main forms were pulmonary (53%; 9/17) and disseminated (18%; 3/17) [23]. ROCM represented only 12% (2/17) of CAM cases [23]. Compared with the rest of the world [9], ROCM was more frequent in India [88% (206/233) vs 64% (27/42), $p<0.001$], whereas the pulmonary form was less frequent [7.3% (17/233) vs 21.4% (9/42), $p = 0.004$].

Before the COVID-19 pandemic, **mortality** (Table 1) at day 90 post-diagnosis ranged from 28 to 52% in India [26]. Similarly, in patients with CAM, mortality at week 12 ranged from 32.2% (473/1471) [29] to 44% (75/170) [18]. No difference in terms of mortality at week 12 was reported between CAM and non-CAM [44.1% (75/170) vs 48.8% (42/86), $p = 0.51$] among hospitalized Indian patients [18]. Mortality mainly depends on the infection site and treatment. Indeed, the rhino-orbital with cerebral involvement [21] and pulmonary forms have been associated with higher mortality rates than the rhino-orbital form [18]. In two Indian studies, a sequential antifungal treatment (amphotericin B followed by posaconazole or isavuconazole) was associated with reduced mortality in patients with CAM compared to treatment with a single antifungal agent [9,18]. This finding needs to be confirmed by double blind randomized trials. Moreover, as previously demonstrated for non-CAM [30], combined medical and surgical treatments are associated with lower mortality at week 12 (odds ratio 0.2, 0.14–0.27; $p = 0.0001$) [29].

Before the COVID-19 pandemic, in France, mortality at day 90 was 44% [25]. In a small retrospective cohort, mortality at week 12 in patients with CAM was 88% (15/17). Compared to the rest of the world, the mortality rate in Indian patients with CAM was lower [36.5% (85/233) in India vs 61% (26/42) in the rest of the world, $p = 0.002$] [9]. This may partly be explained by the lower mortality of ROCM that predominated in India during the COVID-pandemic compared with pulmonary and disseminated mucormycosis.

Possible reasons for the CAM outbreak in India

Different reasons could be hypothesized to explain the CAM outbreak in India.

(i) SARS-COV-2 infection results in pathophysiological changes that might increase the risk of mucormycosis. COVID-19-linked inflammation promotes iron overload and hyperferritinemia, endothelial damage, and glucose-regulated protein 78 (GRP78) overexpression. Hyperferritinemia leads to intracellular iron overload that generates reactive oxygen species, releasing free iron into the systemic circulation [31]. Free iron is a critical growth and virulence factor for Mucorales [32]. Patients who died from COVID-19 had diffuse alveolar damage and severe endothelial injuries [33]. These alterations may facilitate the Mucorales angioinvasion capacity [34]. COVID-19 infection also induces an increase in serum GRP78 concentration [35]. GRP78 has been identified as a receptor for the Mucorales spore coat protein homologs 2 and 3 (CotH2 and CotH3), enabling host cell invasion [36]. Thus, various elements linked to COVID-19 infection may interact to promote mucormycosis. However, COVID-19 was not limited to India, unlike the CAM epidemic, and other explanations must be found.

(ii) COVID-19 treatment may have indirectly contributed to this outbreak. Since the RECOVERY trial showing that corticosteroids reduce mortality in patients with moderate to severe COVID-19 [37], corticosteroids are recommended for these patients. However, long-term and high-dose treatments with corticosteroids (≥0.3 mg/kg for ≥3 weeks) have immunosuppressive effects and are a risk factor for invasive fungal infections [38], including mucormycosis. Polypharmacy is common in India [39] and corticosteroids are easily available over the counter in Indian pharmacies. Therefore, in the frightening context of COVID-19 pandemic, inappropriate (excessive dose/duration) use of corticosteroids was frequent, notably in home-care settings [40]. Immunomodulatory therapies (e.g. tocilizumab) also were widely used in patients with COVID-19 and they may be another CAM risk factor [41]. However, a recent large Indian case-control study found no difference in the rate of tocilizumab treatment between patients with COVID-19 and with/without CAM [2.4% (37/1536) vs 2.0% (72/3631), $p = 0.41$] [29]. It has been suspected that zinc therapy in COVID-19 patients could trigger the development of mucormycosis. Zinc is an essential micronutrient needed for the growth and the virulence of pathogenic fungi, including Mucorales [42]. However, the results of Indian case-control studies appear to be contradictory. One concluded that zinc supplementation was a protective factor [zinc supplementation: 5.8% (78/152) of patients in the CAM group vs 79.9% (151/200) of patients with COVID-19 without CAM; $p<0.001$] [22], whereas another study reported that it was a risk factor of CAM [zinc supplementation: 47.9% (741/1546) of patients in the CAM group vs 41.3% (1502/3633) of patients with COVID-19 without CAM; $p = 0.0001$] [29].

(iii) Diabetes mellitus is a risk factor for both severe COVID-19 [43] and mucormycosis [1], particularly uncontrolled diabetes and diabetic ketoacidosis [24]. A pathophysiological explanation could be that hyperglycemia induces overexpression of GRP78 to which the CotH proteins of Mucorales bind, facilitating their angioinvasion [36]. Moreover, severe COVID-19 increases insulin resistance [44] and damages pancreatic islet beta cells that express angiotensin converting enzyme 2 (ACE2), the entry receptor for SARS-CoV-2 [45]. COVID-19 also induces hyperglycemia indirectly through corticosteroid treatment. In 2021, India had the second more important population living with diabetes mellitus after China (74.2 million and 140.9 million diabetic adults, respectively) [46]. Moreover, a survey reported that only 52.5% of Indian people with diabetes are aware of their disease, 40.5% are treated, and 24.8% achieve glycemic control with treatment [47].

(iv) Mucorales are ubiquitous fungi in the environment, including soil, decaying matter and hospital wards, especially during renovation work [9]. Previously described sources of Mucorales community or hospital-acquired outbreaks were contaminated medical devices (Elastoplast bandages, linen, wooden tongue depressors) and air (ventilation, construction) [48]. Moreover, the Indian tropical and subtropical climate with high humidity and temperature may facilitate the growth and proliferation of Mucorales [49]. This humid weather, combined with poorly maintained air conditioning systems and ventilation and not properly sterilized reusable instruments, may explain the high CAM burden in Indian hospitals [41]. Moreover, one study found that the prolonged use of surgical (>6 h) or cloth masks (>4 h) is a CAM risk factor compared with no mask use [22]. Cloth mask reuse and lack of mask cleaning may facilitate moisture retention, thus increasing the risk of respiratory tract infections [50]. However, another study found that only 1.7% of 172 cloth masks were contaminated with Mucorales, suggesting that their use was unlikely to be a major source of contamination [49]. In India, mucormycetes spores have been detected in outdoor and hospital air samples [17,49], but at a low level. Although the presence of Mucorales spores in hospital air samples is worrying, these studies do not support the hypothesis that the airborne load of

Mucorales was the cause of the CAM outbreak. Molecular studies correlating environmental sample and patients isolates are needed to establish causality.

(v) The healthcare facility saturation during the second COVID-19 wave may have resulted in massive self-medication, including oxygen administration without proper hygienic standards [51]. Notably, nebulizers and humidifiers are prone to be colonized by fungi and need to be disinfected regularly [52]. Moreover, the stocks of liposomal amphotericin B, the gold standard treatment for Mucorales, were significantly decreased, and financial constraints have made it unaffordable for many Indians [26]. Finally, pre-exposure to voriconazole can lead to breakthrough mucormycosis in patients with COVID-19 [53]. Voriconazole over-the-counter availability and improper use may increase CAM risk [41].

Conclusions

An unprecedented CAM outbreak hit India during the second COVID-19 wave in spring-summer 2021. Indian patients with CAM were predominantly individuals with poorly controlled diabetes treated with inappropriate doses of systemic glucocorticoids. ROCM was the predominant clinical form in this context. The reasons for such localized outbreak in India remain unclear, but some hypotheses can be advanced. The high prevalence of uncontrolled diabetes mellitus in India combined with frequent indiscriminate steroid utilization in the context of the COVID-19 pandemic added to a pre-COVID-19 high incidence of mucormycosis could be the main reasons.

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Declaration of Competing Interest

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