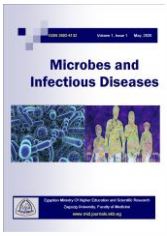
Microbes and Infectious Diseases 2024; Article-In-Press, **DOI:** 10.21608/mid.2024.271750.1812



Microbes and Infectious Diseases

Journal homepage: https://mid.journals.ekb.eg/

Review article

COVID-19 associated mucormycosis (CAM) and other fungal infections: A review

CT Swamy*

Department of Microbiology, Captain Srinivasa Murthy Central Ayurveda Research Institute, Chennai, India.

ARTICLE INFO

Article history:
Received 21 February 2024
Received in revised form 6 April 2024
Accepted 12 April 2024

Keywords:
Candidiasis
Aspergillosis
Glucocorticoids
Sinus mucormycosis
Pulmonary mucormycosis

ABSTRACT

Background: SARS-CoV-2 virus caused the COVID-19 epidemic, which eventually turned into a global pandemic. Immunomodulatory drugs used in COVID-19 treatment pave the way for opportunistic fungal infection and eventually lead to death in immunocompromised patients. Mucormycosis, candidiasis, aspergillosis, and fungal pneumonia are humans' most common fungal infections. Mucorales fungi like *Rhizopus, Rhizomucor, Mucor, Rhizopus oryzae*, and other fungi including *Aspergillus, Candida auris, Candida* sp., etc. induce COVID-19-associated mucormycosis (CAM) and also other fungal infections in immunocompromised patients. In addition, Mucorales produce a localized infection in the sinuses (paranasal sinuses), infection in orbit (sino-orbital), and infection in the orbit of the brain parenchyma (rhinocerebral infection). The angio-invasive fungus infects the pulmonary and dermal regions. Fever, headache, cough, shortness of breath, eyelid drooping, chest pain, periorbital and nasal oedema (swelling), and inflammation are major symptoms of CAM. Direct microscopic methods, fungal culture on medium, and molecular approaches are used to confirm the fungal strains at the species level. Antifungals such as amphotericin B, posaconazole, or isavuconazole are utilized to treat fungal infections and, in critical condition, surgically remove the debridement. However, antifungal-resistant fungal species appear harmful and discovering novel compounds to combat them is a top priority for the scientific community.

Introduction

In recent decades, new viruses and illnesses have become ubiquitous, posing a severe threat to the world's population. COVID-19 was discovered in Wuhan in December 2019 while treating patients with pneumonia-like symptoms. Initially known as the 2019 novel coronavirus (2019-NCOV), the virus was renamed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and designated a pandemic by the World Health Organization (WHO) [1]. Coronavirus belongs to the family Coronaviridae and the order Nidovirales and has a large RNA genome, i.e., positive-sense single-stranded RNA. Some portion of the viral genome folds into a stable structure, which regulates the virus's life cycle and prevents mRNA transcription and genome packaging into new virions from being disrupted [2]. Several medicines have been used to tackle COVID-19, but patients may experience mild to severe side effects [3]. Nelfinavir, emetine, and teicoplanin are reported to be effective against the SARS-CoV-2 virus during in-vitro evaluation [2]. COVID-19 infection leads to lung damage, which can be managed by administering glucocorticoids like dexamethasone for up to 10 days to modulate inflammation-mediated lung injury and thereby prevent respiratory collapse and death [4]. Mucormycosis infection has been observed in individuals recovering from COVID-19 infection

DOI: 10.21608/MID.2024.271750.1812
* *Corresponding author:* Swamy CT
E-mail address: swamyct23@gmail.com

who are severely immunocompromised, subjected to immunomodulatory agents/drugs. Mucormycosis is life-threatening in immunocompromised patients, along with other comorbidities like diabetic ketoacidosis, neutropenia, organ donation, and/or elevated iron levels in the bloodstream [5].

The fungi that cause mucormycosis belong to the order Mucorales [6]. Mucorales, a thermo-tolerant mould, were observed on bread, vegetable waste, agricultural trash, compost piles, animal excreta, and in the soil between growing seasons. However, scientific data refuted this generalization of their presence. Fungal spores are easily aerosolized and distributed in the environment due to their tiny size (3-11 μm) when get in contact with human surfaces such as mucosa of the lower and upper respiratory tract cause the infection [7].

Mucorales are now classified as members of the phylum Mucoromycota, comprising 55 genera and 260 species. In addition, 38 species belonging to 11 genera have been documented to cause mucormycosis infections in humans [8]. *Rhizopus, Rhizomucor, Mucor, Cunninghamella, Lichtheimia, Saksenaea*, and *Apophysomyces* are the most prevalent genera that cause mucormycosis in humans [6]. In low- and middle-income countries, diabetes mellitus is the most frequent underlying condition, and it leads to mucormycosis caused by *Rhizopus oryzae*, which accounts for about 70% of all CAM cases [5].

Antivirals and other medications like steroids used in COVID-19 control may lead to bacterial and fungal infections such as aspergillosis and mucormycosis in immunocompromised patients with comorbidity like diabetes [4,9].

The COVID-19 illness is commonly treated with systemic glucocorticoids, which have many adverse effects on the haematological and cardiovascular systems of patients. Antiviral medications like atazanavir had more side effects than other medications. Drugs used in the treatment had some common side effects [3]. Due to the widespread usage of steroids, broad-spectrum antibiotics, and monoclonal antibodies during the COVID-19 pandemic, few cases of preexisting fungal illnesses in COVID-19 patients have come to the limelight [10,11]. COVID-19 patients had a higher risk of mucormycosis death than non-COVID-19 patients [9]. Mucormycosis is caused by spores in the environment and significantly impacts immunocompromised persons; however, it is not communicable [12]. Even though it is not communicable, it infects immunocompromised persons quickly; therefore, improving personal hygiene and immunity can control secondary mucormycosis infection in COVID-19 patients. In this review, COVID-19-associated mucormycosis (CAM) and other fungal infections occurrence, causative agents, symptoms, precautions, microbiology, and treatments are focused. In the present study, the keywords COVID-19, mucormycosis, COVID-19 associated mucormycosis, and COVID-19 associated fungal infections were searched in Google Scholar, ScienceDirect, and Wiley Online Library sites. The studies of CAM were analyzed, and a review was prepared.

Types of mucormycosis

Based on the clinical manifestations, mucormycosis infection is classified as sinus mucormycosis, pulmonary mucormycosis, cutaneous mucormycosis, gastrointestinal mucormycosis, miscellaneous, and disseminated infection [13]. The CAM forms are mainly sinus mucormycosis (rhino-orbital and rhino-cerebral), pulmonary mucormycosis, cutaneous mucormycosis, and gastrointestinal mucormycosis.

i.Sinus mucormycosis

Sinus infections can be localized, affecting just the paranasal sinuses, or they can spread to the orbit (sino-orbital) or the orbit of the brain parenchyma (rhino-cerebral) [13]. The clinical manifestations of sinus mucormycosis are unilateral facial swelling, headaches, black lesions on the nasal bridge or upper inside of the mouth that rapidly worsen, nasal or sinus congestion, and fever have all been reported [12]. COVID-19 has been associated with several sinus mucormycosis cases reported worldwide. It continuously develops as a secondary infection after COVID-19 treatment. In most instances, *Rhizopus* spp. and *Rhizopus oryzae* are the causative agents of CAM [5,8,14–18]. A nasal sample analysis of a COVID-19 patient with diabetes treated with broad-spectrum antibiotics also exhibited rhino-orbital mucormycosis signs and filamentous fungal hyphae reported during culture on media. Using steroids, monoclonal antibodies, and broad-spectrum antibiotics are major risk factors for mucormycosis in patients [11].

Several cases of mucormycosis and COVID-19 infection have been reported frequently [11,19–21]. A Mucorales-type fungus causes a

rhino-orbital infection with a 50% mortality rate even after the existing treatment. It's an opportunistic infection characterized by the invasion of fungal hyphae into blood vessels, infarction, and necrosis of the host tissue [22].

The suspected rhino-cerebral mucormycosis in patients with type 1 diabetes mellitus is confirmed by CT and MRI (magnetic resonance imaging) scan. The scanning reports confirmed that the disease is spreading to the sinuses, and intracranial abscess in the infratemporal fossa is a chronic sinusitis condition. Later, cefepime with IV abelcet (amphotericin B complexed with two phospholipids) was used as a treatment combined with debridement of the infected tissues [23].

ii.Pulmonary mucormycosis

Pulmonary mucormycosis is a rare fungal disease that affects individuals with diabetes mellitus, haematological malignancies, COVID-19, and immunocompromised conditions. In the early stages of infection, pulmonary mucormycosis is challenging to diagnose [24]. Therefore, endobronchial or percutaneous tissue samples are used to identify fungal hyphae, and it is helpful to confirm mucormycosis and distinguish it from invasive pulmonary aspergillosis (IPA) [25].

Invasive pulmonary mucormycosis and aspergillosis infections were observed as secondary complications in critically ill COVID-19 patients. A bronchoalveolar lavage (BAL) biopsy sample of a COVID-19 patient fungal culture microscopic examination confirmed *Rhizopus arrhizus* and *Aspergillus fumigatus*, which are causative agents pulmonary mucormycosis and aspergillosis, respectively [26].

In another case report, an autopsy of a patient's lung tissue examined under a microscope revealed the presence of invasive non-pigmented fungal hyphae. The internal transcribed spacer (ITS) sequencing of the same lung tissue confirmed the *Rhizopus* microspores fungi, the causative agent of mucormycosis. However, no symptoms of dissemination of fungi were detected [18].

iii.Cutaneous mucormycosis

A fungus that causes cutaneous mucormycosis belongs to the phylum Glomeromycota and subphylum Mucormycotina. It is commonly seen in immunocompromised and diabetic patients. The cutaneous mucormycosis seen in immunocompromised and diabetic patients may also be acquired by direct inoculation after a traumatic event [27]]. A cutaneous mucormycosis case was reported with a heart-transplanted COVID-19 patient, along with upper respiratory and systemic symptoms [15].

iv.Gastrointestinal mucormycosis

The most challenging problem is antemortem diagnosis in gastrointestinal (GI) mucormycosis. It is typically seen in malnourished individuals, newborns with low birth weight, and peritoneal dialysis patients [17].

Though gastrointestinal mucormycosis is uncommon in COVID-19 patients, it has a significant death rate among them. In a case report, an 86-year-old patient with severe diarrhoea was admitted to the hospital; cough, fever, and dyspnea were observed for five days. The patient also had COVID-19, and melena was seen, necessitating the transfusion of three units of red blood cells. Additionally, an esophagogastroduodenoscopy revealed two massive gastric ulcers with necrotic debris and a deep hemorrhagic base without active bleeding, as well as biopsies confirming a rare and lethal gastrointestinal mucormycosis in that patient [28].

Mode of infection

Mucormycosis is caused by inhalation, ingestion, and inoculation of parasitic fungal spores from the environment, which can cause lung or sinus infection, as well as skin injuries such as cut burns, through which fungal spores can enter and cause disease [12]. Furthermore, medicine, uncontrolled hyperglycemia, and excessive steroids may exacerbate the condition in immunocompromised patients with preexisting comorbidities in COVID-19 patients, leading to co-fungal secondary infections [19,29].

Symptoms of CAM

i.Rhinocerebral mucormycosis (sinus and brain)

Patients showed acute sinusitis with fever, purulent nasal discharge, nasal congestion, headache, paresthesia, drooping of the eyelid, swelling at the periorbital and nasal region, headache, inflammation, proptosis, ophthalmoplegia (external and internal), loss of vision, and necrosis (black colour), and facial pain. Further, sinuses are involved and spread to the adjoining palate region and orbit, and the brain usually progresses rapidly. The spread of the disease on sinuses showed palatal eschars by palate tissue necrosis, turbinates destruction, and swelling of

perinasal and facial skin cyanosis overlying the involved sinuses [11,12,21,23,30,31].

ii.Pulmonary (lung) mucormycosis

Cough, fever, shortness of breath, chest pain, and firm lesions (hemorrhagic, hyperemic, or necrosis) were observed in lung tissues. Central lesions are found in a round shape when infarction is present in the lungs compared to peripheral lesions. Further, direct invasion of fungi to the lung's adjacent tissues, such as the chest wall, heart, mediastinum, and diaphragm, was observed [9,12,18,25].

iii.Cutaneous (skin) mucormycosis

The skin blisters or ulcers are observed, turning the infected region into black colour. In addition, other symptoms such as pain, extreme redness, or wound adjacent area swelling and warmth are also observed [12]. Further, a COVID-19 patient with cutaneous mucormycosis showed skin discolouration to purplish and fluctuant swelling at the right axilla was also noted [15].

Preventive measures

The preventive measures may not fully control the disease attack. However, avoid dusty areas, use N95 masks, clean the reusable masks frequently, reduce immunomodulatory drugs, and use antifungal agents [12].

Diagnosis and microbiology

While diagnosing mucormycosis, healthcare providers or doctors, based on the symptoms that determine the disease condition and severity, examine the infected tissue biopsy under the microscope or culture methods employed to delineate the fungi that caused the infection. Other scanning processes, such as CT/MRI scans of lungs and nearby infection parts, sinuses, and other suspected infection locations, also provide methods of confirmation of the fungal infection [32]. To diagnose invasive fungal infections, comprehensive diagnostic methods include histopathology, direct microscopic examination of a portion of a tissue biopsy, culture methods, (1,3) -b- D-glucan, galactomannan assay, and molecular/PCR-based assays are widely used [33].

i.Direct microscopic methods

The microscopic examination of infected clinical specimens or doubtful samples is mounted with the potassium hydroxide (KOH) method. It is one of the oldest and most commonly used dermatology procedures for rapidly detecting fungal elements. Briefly, 1-2 drops of 10% KOH are mixed with tissue or skin scrapings and covered with a coverslip; heating the slide to digest the tissue reaction and observe under the microscope (10X and 40X) for fungal morphology documentation. This method has pros such as cost-effectiveness, providing immediate results, being carried out in minimal infrastructure, routine, and higher sensitivity. In addition, cons include cloth fiber interference, lack of colour contrast, dissemination while sampling collection, etc. [34].

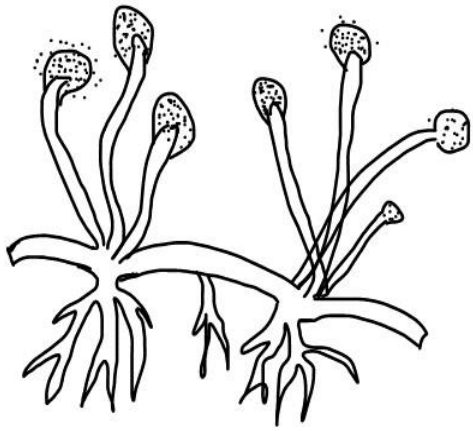
The direct microscopic observation of the infected tissue portion delineated the fungal species in rhinocerebral mucormycosis patients [30]. The KOH mount of CAM clinical specimens are examined under the microscope for hyphal morphology and then confirmed the fungal species. A broad, irregular, non-septate hyphae is a possible indicator of mucormycosis reported from pathological examination of the gastric border and base with necrotic fibrinoid debris [28]. Filamentous fungi were observed from a stained sputum sample of the patient in microscopic evaluation [14]. The KOH mount of the pathology specimen confirmed mucormycosis in direct microscopic examination of clinical samples [35]. Direct examinations using 10% KOH and histopathological examination using haematoxylin and eosin (H&E) staining showed non-septate, ribbon-like, broad hyphae with right-angle branching fungi suggestive of mucormycosis [36]. A histopathological examination of paranasal sinuses debrided necrotic tissues showed granulomatous inflammation, vasculitis, and irregular non-septate with branched eosinophilic filaments in H&E staining that were markedly angioinvasive and confirmed the mucormycosis [21]. A microscopic examination of the CAM patient's lung autopsy showed invasive non-pigmented fungal hyphae [18].

ii.Culture methods

Rhizopus spp. cultured from the patient's sputum, and the resected lung sample showed hyphae morphologically consistent with mucormycosis as the causative agent [37]. The patient's sputum culture on Sabouraud's dextrose agar (SDA) revealed the pauci-septate hyphae with unbranching sporangiophores and no prominent characteristic features of Mucorales [14]. In a study, out of 6 patients with COVID-19, 4 reported a fungal infection after the observation and culture of sinus debridement of necrotic tissue. However, a

deep nasal swab of three patients affected side culture study showed no growth [20]. Sometimes, the pretreatment (medication) effect inhibits the growth of fungi in culture methods [36]. Though sometimes sputum smear examination for fungi is observed to be negative, a sputum culture on a medium helps to grow the fungi. The culture of negative sputum smear reported a cottony greyish-white colony, and lactophenol cotton blue (LCB) mount suggesting *Rhizopus microsporus* [9]. A *Rhizopus* species was cultured from a tissue sample from a rhino-orbital mucormycosis patient with COVID-19-associated ARDS (acute respiratory distress syndrome) [31]. CAM patient's tissue samples culture and staining analysis were identified as *Rhizopus oryzae* [16]. The respiratory secretions collected by bronchoalveolar lavage (BAL) culture analysis and microscopic examination with the potassium hydroxide (KOH) preparation reported the *Rhizopus arrhizus* and *Aspergillus fumigatus* [26]. The middle turbinate region nasal biopsy revealed the presence of broad aseptate filamentous fungal hyphae, and it is confirmed on SDA medium culture, which is a potential causative agent of mucormycosis [11]. After the fungal culture on the medium, a microscopic depiction is shown in **(Figure 1)**.

Figure 1. Mucormycetes illustration.



iii.Molecular methods

The MALDI-TOF (Matrix-assisted laser desorption ionization time-of-flight) method confirmed the filamentous fungi isolated from the patient's sputum and pleural fluid as *Rhizopus* spp. The advanced D1/D2 ribosomal DNA regions internal transcribed spacer (ITS) analysis confirmed the *Rhizopus azygosporus* fungi from the pleural clinical sample of a patient [14].

DNA extracted from a fresh patient biopsy sample and PCR analysis reported the *Rhizopus oryzae* [36]. A MALDI-TOF technique is used to identify the fungal culture. The sputum culture showed a white cottony greyish fungal culture identified by MALDI-TOF [9]. The autopsy sample of the CAM patient showed fungal hyphae, and ITS analysis confirmed *Rhizopus microspores* cause pulmonary mucormycosis [18].

Treatment options

Mucormycosis is a severe infection and to treat it, antifungal medicines such as amphotericin B, posaconazole, or isavuconazole are administered intravenously or taken orally. Antifungal medications, including fluconazole, voriconazole, and echinocandins, are ineffective against mucormycosis. As a result, the mucormycosis-infected tissues were occasionally removed by surgery [20,30,38]. The liposomal amphotericin B 3 mg/kg/day is widely used as an antifungal drug in maximum mucormycosis cases [9,15,20,21,28,29,36]. In addition, dexamethasone is also used to treat CAM with or without amphotericin B [4,31].

Surgical methods

A nasal endoscopy is performed on a patient who suffered left facial pain, and the left eye complete ptosis revealed a deviated nasal septum to the right with a spur. The patient also suffered from COVID-19 and fungal sinusitis, so endoscopic surgery with or without debridement with maximum precautions was reported [35]. A functional endoscopic sinus surgery (FESS) is employed in mucormycosis or CAM patients for sinus debridement [20]. An endoscopic sinus surgery is used to remove the mucormycosis-infected nose and paranasal sinus portions [35].

COVID-19 associated with other fungal diseases

COVID-19 individuals who are very unwell or immunocompromised have an increased risk of developing invasive mycoses. Mainly in COVID-19-associated *Aspergillus* and *Candida* infections, early detection is better to ensure effective treatment options such as antifungal administration or surgery in severe infection conditions [33].

i.COVID-19-associated pulmonary aspergillosis

Aspergillus fumigatus is found ubiquitously in the environment that belongs to the *Aspergillus* genera and causes many human infections. The *Aspergillus*-associated infections are

as follows: *Aspergillus* bronchitis, allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis (CPA), and invasive pulmonary aspergillosis (IPA) [39–41]. An acute respiratory distress syndrome (ARDS) develops in the immunocompromised COVID-19 patient with *Aspergillus* co-infection. However, more cases are undiagnosed, mainly due to a lack of clinical awareness and diagnostic screening methods [42]. In COVID-19-associated pulmonary aspergillosis (CAPA) infection, a pattern release of danger-associated molecules responsible for epithelial damage and inflammatory disease finally leads to pulmonary aspergillosis. Furthermore, the side effects of host recognition pathways essential for antiviral immunity activation, perhaps, lead to a highly permissive inflammatory reaction that facilitates fungal infection. The principal method of diagnosing aspergillosis was galactomannan assays on blood and bronchoalveolar lavage (BAL) fluid bronchoscopy-guided biopsies during bronchial lesions present. However, due to hypoxia and ventilation conditions, computed tomography (CT) scanning is impractical for several patients [43]. The most sensitive diagnostic methods for aspergillosis include bronchoalveolar lavage fluid galactomannan testing and culture, which are complicated because bronchoscopies are rarely conducted in COVID-19 patients due to the risk of disease transmission, which makes the diagnosis of CAPA difficult. The treatment of CAPA is also difficult due to the interactions of broad-spectrum azoles, tissue damage by the virus, and renal tropism, which poses a severe challenge during the use of amphotericin B and the emergence of azole resistance [41].

Several antifungal drugs used to treat aspergillosis, such as voriconazole or isavuconazole [44], liposomal amphotericin B [45], and posaconazole or echinocandin [44,46]. The invasive aspergillosis with triazole-resistant *Aspergillus fumigatus* (TR34/L98H mutation) was reported from the respiratory specimen of a 56-year-old patient with COVID-19 [47]. Novel antifungal classes against fungal infection are under development, such as olorofim, fosmanogepix, ibrexafungerp, and rezafungin, which seem to follow treatment options [48].

An acute respiratory distress syndrome (ARDS) may be associated with *Aspergillus* sp. and other fungal co-infections due to immunological dysregulation. Several antibiotics are used to treat patients and address antibiotic-associated complications in intensive care units (ICU) Saccharomyces (probiotics) are widely used. Interestingly, these Saccharomyces are involved in invasive infection in immunocompromised patients after supplementation as probiotics [49].

ii.COVID-19-associated invasive candidiasis and *Candida auris* infection

Human mycobiome, such as *Candida* species, can cause invasive fungal infections, leading to high mortality in immunocompromised COVID-19 patients. Invasive yeast infections (IYIs) develop in COVID-19 patients due to prolonged ICU stays, broad-spectrum antibiotic use, and central venous catheters. The IYIs are treated with echinocandins and azoles [50]. The multidrug-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus*, multidrug-resistant Gram-negative bacteria, and finally *Candida glabrata*, lead to a fatal condition in COVID-19 patients with prior type-2 diabetes [51]. Unfortunately, COVID-19 patients could be complicated by either urinary tract infections and/or *Candida auris* bloodstream infections [52,53].

Conclusion and future study

Mucormycosis caused by opportunistic fungi and other fungal infections is common in immunocompromised patients. The medications used in COVID-19 treatment, comorbid conditions, ICU stays, etc., lead to fungal infections such as COVID-19-associated aspergillosis, candidiasis, mucormycosis, and other bacterial infections. Recently, drug-resistant fungal strains were reported from hospitalized ICU patients. The antibiotics widely used to control CAM and other fungal infections to reduce antibiotic stress use Saccharomyces, and they also cause infection in immunocompromised patients, which is a prime concern at present. Future studies mainly focus on preventing fungal infection in hospitalized (ICU) immunocompromised patients. The improper use of antibiotics leads to the development of drug-resistant fungal strains, so control over the use of drugs is essential. Focusing on alternative medicines for drug-resistant strains is our primary concern. Along with fungal infections, bacterial infections were also reported in COVID-19 patients, and it is alarming to develop comprehensive medication for all these problems.

Acknowledgements

I would like to thank the Central Council for Research in Ayurvedic Sciences (CCRAS) New Delhi and Captain Srinivasa Murthy Central Ayurveda Research Institute (CSMCARI) Chennai.

Conflict of interest

None.

Funding

None.

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