Introduction

In recent months, an increase in reports of cases of COVID-19 associated Mucormycosis (CAM) has been observed mainly in people with underlying diseases, such as diabetes mellitus (DM), diabetic ketoacidosis, or on steroids. In these patients, the most frequent clinical manifestation is rhino-orbital mucormycosis, followed by rhino-orbital-cerebral mucormycosis, which present as secondary infections and occur after SARS CoV-2 infection.1,2

Globally, the highest number of cases has been reported in India, where it is estimated that there are more than 4,000 people with CAM.3

In a retrospective multicenter study conducted in India4 between September to December 2020, it was found that among 287 patients with mucormycosis, 187 (65.2%) had CAM; with a prevalence of 0.27% among hospitalized patients with COVID-19. When comparing the period under study with the same period in 2019, a 2.1-fold increase in mucormycosis was observed.

Regarding the characteristics of the 187 patients with CAM, 80.2% were male, 32.6% had COVID-19 as the only underlying disease, 78.7% were treated with gluco-corticosteroids for COVID-19, 60.4% had diabetes mellitus, 62.6% had rhino-orbital mucormycosis, and 23.5% had rhino-orbital-cerebral mucormycosis.

Mucormycosis (previously called zygomycosis) is the term used to name invasive fungal infections (IFI) caused by saprophytic environmental fungi, belonging to the subphylum Mucoromycotina, order Mucorales. Among the most frequent genera are Rhizopus and Mucor; and less frequently Lichtheimia, Saksenaea, Rhizomucor, Apophysomyces, and Cunninghamella (Nucci M, Engelhardt M, Hamed K. Mucormycosis in South America: A review of 143 reported cases. Mycoses. 2019 Sep;62(9):730-738. doi: 10.1111/myc.12958. Epub 2019 Jul 11. PMID: 31192488; PMCID: PMC6852100).

The infection is acquired by the implantation of the spores of the fungus in the oral, nasal, and conjunctival mucosa, by inhalation, or by ingestion of contaminated food, since they quickly colonize foods rich in simple carbohydrates.

Mucormycosis is characterized by infarction and necrosis of the host's tissues, which results from the invasion of the vessels by the hyphae. The clinical presentations of mucormycosis can be: rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated.

Additionally, cases have been described in Brazil\textsuperscript{5}, Chile\textsuperscript{6}, Honduras\textsuperscript{7}, Mexico\textsuperscript{8,9}, Paraguay\textsuperscript{10}, the United States of America\textsuperscript{11,12,13}, Uruguay\textsuperscript{14}, Italy\textsuperscript{15} and United Kingdom\textsuperscript{16}.

**Cases reported in the Americas**

Below is a summary table of the cases reported in the Americas, for which information is available (Table 1).

As of 9 June 2021, 7 countries in the Region of the Americas have reported to PAHO/WHO or published the detection of CAM cases.

**Table 1. Description of cases of COVID-19 associated mucormycosis in the Americas (9 June 2021)**

<table>
<thead>
<tr>
<th>Age (year-olds)</th>
<th>Sex</th>
<th>Underlying diseases / Comorbidities</th>
<th>Clinical Presentation - Mucormycosis</th>
<th>Status*</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>Female</td>
<td>Diabetes mellitus, Rhinosinusitis, Severe diabetic ketoacidosis, Severe metabolic acidosis, Atypical pneumonia</td>
<td>Rhino-orbital</td>
<td>Deceased</td>
</tr>
<tr>
<td>35</td>
<td>Male</td>
<td>Uncontrolled type 2 diabetes mellitus</td>
<td>Rhino-orbito-cerebral</td>
<td>Deceased</td>
</tr>
<tr>
<td>52</td>
<td>Female</td>
<td>Overweight, Smoking</td>
<td>Rhino-orbital</td>
<td>On going</td>
</tr>
<tr>
<td>35</td>
<td>Male</td>
<td>Uncontrolled diabetes, obesity</td>
<td>Rhino-orbito-cerebral</td>
<td>On going</td>
</tr>
<tr>
<td>68</td>
<td>Male</td>
<td>Diabetes mellitus, Arterial hypertension, Dyslipidemia, Mycosis of the external auditory canal treated.</td>
<td>Rhino-orbital</td>
<td>On going</td>
</tr>
<tr>
<td>51</td>
<td>Female</td>
<td>Diabetes mellitus, Chronic renal insufficiency</td>
<td>Rhino-orbital</td>
<td>Deceased</td>
</tr>
<tr>
<td>67</td>
<td>Male</td>
<td>Diabetes mellitus</td>
<td>Pulmonary</td>
<td>On going</td>
</tr>
<tr>
<td>33</td>
<td>Female</td>
<td>Uncontrolled diabetes, Arterial hypertension, Asthma</td>
<td>Rhino-orbito-cerebral</td>
<td>Deceased</td>
</tr>
<tr>
<td>49</td>
<td>Male</td>
<td>Immune system compromise</td>
<td>Pulmonary</td>
<td>Deceased</td>
</tr>
<tr>
<td>60</td>
<td>Male</td>
<td>Uncontrolled diabetes, Arterial hypertension, Asthma</td>
<td>Rhino-orbital</td>
<td>Deceased</td>
</tr>
<tr>
<td>70</td>
<td>Male</td>
<td>Heart disease, Arterial hypertension</td>
<td>Rhino-orbito-cerebral</td>
<td>On going</td>
</tr>
<tr>
<td>61</td>
<td>Male</td>
<td>Heart disease, Lung transplantation, Lung transplantation</td>
<td>Pulmonary</td>
<td>Deceased</td>
</tr>
<tr>
<td>74</td>
<td>Female</td>
<td>Arterial hypertension, Diabetes mellitus</td>
<td>Rhino-orbital</td>
<td>Deceased</td>
</tr>
<tr>
<td>45</td>
<td>Female</td>
<td>Arterial hypertension, Diabetes mellitus</td>
<td>Rhino-orbital</td>
<td>On going</td>
</tr>
<tr>
<td>51</td>
<td>Female</td>
<td>Diabetic type 2 IR, poorly compensated, chronic hypertensive, obese (BMI over 30), severe COVID-19 pneumonia, severe acute respiratory failure, severe acute respiratory failure.</td>
<td>Rhino-orbital</td>
<td>Deceased</td>
</tr>
<tr>
<td>56</td>
<td>Male</td>
<td>Arterial hypertension, Asthma</td>
<td>Rhino-orbital</td>
<td>On going</td>
</tr>
</tbody>
</table>

* At the time of publication

**Source:** Data received from the International Health Regulations (IHR) National Focal Points of Brazil, Chile, Honduras, Paraguay, and Uruguay; information published by Mexico and the United States of America and reproduced by PAHO/WHO.
Guidance for national authorities

The Pan American Health Organization / World Health Organization (PAHO/WHO) recommends considering clinical suspicion of mucormycosis as a medical emergency.

Due to the progression and destructive nature of the infection, rapid diagnostic and therapeutic intervention is required. This intervention should be multidisciplinary, involving clinicians, surgeons, radiologists, and the microbiologists.

The Pan American Health Organization / World Health Organization (PAHO/WHO) urges Member States to prepare health services to increase clinical suspicion of mucormycosis in patients with COVID-19, especially those with diabetes mellitus, treatment with corticosteroids or other immunosuppressants, in order to perform a thorough clinical evaluation, originate an early diagnosis and initiate appropriate treatment of suspected cases of COVID-19-associated mucormycosis.

Diagnosis

The suspicion of mucormycosis is fundamental to proceed with the correct procedure and complementary examinations. Generally, mucormycosis should be suspected in patients with diabetes mellitus (DM), especially those with diabetic ketoacidosis, acquired immunodeficiency syndrome, iatrogenic immunosuppression, oncohemato-logical patients (mainly allogeneic bone marrow transplants) and solid organ transplant recipients. The current epidemiological situation incorporates patients with COVID-19 into this list.

Radiologic studies: magnetic resonance imaging of the paranasal sinuses, with cerebral contrast study, for rhino-orbito-cerebral mucormycosis (ROCM); simple computed tomography of the thorax, for pulmonary mucormycosis.

Histopathological diagnosis: biopsy of the affected tissues is the most critical form for diagnosis. To confirm the infection, tissue invasion of unseptated hyphae should be observed in tissue sections stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS) or Grocott-Gomori methenamine-silver (GMS), or both.

Microbiological diagnosis:

In the case of biopsy processing, biopsies should not be homogenized in a mortar. Unseptate or coenocytic filamentous fungi are very fragile and break easily, which makes microscopic visualization difficult and affects culture yield.

Microscopic examination: Microscopic examination is essential for an early diagnosis of mucormycosis. It can be performed fresh or calcofluor white (40x) and Giemsa staining (100x). Cenocitic (not septate), broad (6-16 µm), branched (usually at 90° angle) hyphae are observed.
Culture: Mucorales usually grow on culture media commonly used in mycology: Sabouraud glucose or honey agar and Brain and Heart Infusion agar (BHI); incubation at 28ºC and 35-37ºC. Unseptate fungi are fast developing (24-48h).

Other media that can be used to favor fructification are potato glucose agar and malt extract; and particularly Czapek agar, for Saksenaea and Aposthyssomyces.

General characteristics of colonies: cottony, white or grayish black.

Identification and antifungal susceptibility testing: identification to genus and species level improves the epidemiological understanding of mucormycosis. Identification can be performed by micro- and macromorphology, MALDI-TOF (depending on the database used) and molecular biology techniques (e.g., PCR + sequencing). Treatment guidance is based on direct microscopic examination and culture, regardless of identification to genus and species level. Antifungal sensitivity testing is not routinely performed and is clinically useful only in cases where treatment failure is observed, although therapeutic failure is multifactorial. The determination of MIC mainly allows establishing epidemiological knowledge and is usually performed in the national reference laboratory.

Detection of galactomannan and β-D-Glucan: both tests are negative.

Treatment

Treatment requires surgical debridement, antifungal treatment and, if possible, stabilization of risk factors.

First choice, induction phase, approximately 3 weeks: amphotericin B in lipid formulations 5 mg/kg or, in case of intolerance to amphotericin B, isavuconazole, loading dose 372 mg/iv or vo/d for 6 doses, followed by 372 mg/iv or vo/d.

Consolidation phase: isavuconazole, loading dose, 372 mg/iv or vo c/8 h for 6 doses, followed by 372 mg/iv or vo/d, until clinical improvement or posaconazole tablets, 300 mg/d. Serum level of > 1 μg/ml should be achieved (PAHO/WHO Treatment of Infectious Diseases 2020-2022 Eighth Edition, available at: https://bit.ly/3rdeWs).

It is recommended that the healthcare professional be informed and look for the advised of experts for detailed management regarding the complications and management of COVID-19.
References


3 Global Action Fund for Fungal Infections (GAFFI). Doctors around the world call for rapid response to deadly mucormycosis (the so-called “black fungus”) found in COVID patients in India. Available at https://bit.ly/352wj9F


5 Report by the Brazil International Health Regulations (IHR) National Focal Point (NFP), received by PAHO/WHO via email.

6 Report by the Chile International Health Regulations (IHR) National Focal Point (NFP), received by PAHO/WHO via email.

7 Report by the Honduras International Health Regulations (IHR) National Focal Point (NFP), received by PAHO/WHO via email.

8 Report by the Mexico International Health Regulations (IHR) National Focal Point (NFP), received by PAHO/WHO via email.


10 Report by the Paraguay International Health Regulations (IHR) National Focal Point (NFP), received by PAHO/WHO via email.


Report by the Uruguay International Health Regulations (IHR) National Focal Point (NFP), received by PAHO/WHO via email.
