**Microbiology & Infectious Diseases**

**Mucormicosis, COVID-19 and Diabetes Mellitus**

Hector Carvallo¹, Roberto Hirsch², Marcelo Corti³ and Mabel Carrera⁴

¹Former Director, Ezeiza Hospital, Argentina.
²Chief, Dept. of Infectology, Muñiz Hospital, Argentina.
³Professor of Infectology, Buenos Aires Medical School, Argentina.
⁴President XXI International Congress of Nutrition, Buenos Aires, Argentina.

Correspondence: Hector Carvallo, Former Director, Ezeiza Hospital, Argentina.

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**ABSTRACT**

Mucormycosis is an opportunistic fungal infection that is associated with states of immunosuppression, among which uncontrolled diabetes mellitus (ketoacidosis) and the use of corticosteroids stand out. Both conditions are interwoven between the comorbidities and the treatments most used in patients with COVID-19. That is why its presence must be taken into account as a complication to be ruled out, and highlights the need to incorporate the Diabetologist into the Multidisciplinary Team for COVID management.

**Keywords**

Mucormycosis, COVID-19, Diabetes mellitus, Corticosteroids.

**Introduction**

Mucormycosis, also called zygomycosis or phymycosis, is an infection caused by various fungi of the Mucorales order (class Zygomycetes, genera Rhizopus, Rhizomucor and Mucor) the most involved in human infections [1-3]. It was first described in 1729 by P. A. Micheli, who found that the conidial head of this fungus resembled aspergillum [1].

Due to its pathogenic behavior, it is included in the group of opportunistic mycoses. Mucormycosis is caused by common fungi that are normally found in soil and on decaying fruits and vegetables. Its spores pass into the air and are frequently inhaled. Most people are exposed to these fungi, but they only behave as serious pathogens in those with compromised immune systems [4-7].

The conditions most commonly associated with mucormycosis include: insulin-dependent diabetes (poorly controlled / ketoacidosis), prolonged or high-dose use of corticosteroids, extensive burns, metabolic acidosis, organ transplantation, leukaemia’s and lymphomas, severe malnutrition, HIV / AIDS disease.

**Clinical Features**

The target organs define the clinical presentation forms of mucormycosis. These include:

- Rhino sinuso orbito cerebral mucormycosis
- Pulmonary mucormycosis
- Gastrointestinal mucormycosis
- Cutaneous mucormycosis

**Rhino Sinus Orbital Cerebral Mucormycosis [8,9]**

It appears in an acute form and is usually associated with poorly controlled diabetes mellitus, in which patients develop ketoacidosis. In decompensated diabetics, the extreme dryness of the mucous membranes makes it easier for spores to adhere to the tissue.

The infection begins in the nasal mucosa or paranasal sinuses and evolves into unilateral, rapid-course and necrotizing pansinusitis. Necrotic eschar can be seen on the nasal and palatal mucosa and on the skin of the face (“black fungus”). Without treatment, the infection progresses to the orbit where it causes orbital cellulitis...
with pain, swelling of the corresponding area, proptosis, loss of vision, and ophthalmoplegia. Progression by contiguity can cause cavernous sinus thrombosis (favored by the hypercoagulable state present in patients with COVID-19) and, eventually, frontal lobe abscess. Infectious arteritis due to the invasion of the fungus into the vascular endothelium produces ischemic brain necrosis. This picture is accompanied by headache, seizures, and impaired level of consciousness. Brain involvement does not occur in all cases; chronologically, it is the last to appear and can be avoided by early and correct diagnosis and adequate treatment consisting of the removal of necrotic tissues and administration of amphotericin B intravenously, in its classic formulation or some variant in liposomal vehicle.

**Pulmonary Mucormicosis [10-19]**

The pulmonary location is second in frequency after the rhino sinuso orbito cerebral one. The pulmonary variety of mucormycosis also occurs in patients with leukemia or prolonged overdose of corticosteroids. In them, alveolar macrophages do not eliminate sporangiospores that reach the lower respiratory tract. The evolution is acute, although slower than the rhino sinuso orbito cerebral form; however, patients without adequate treatment die in about 30 days, generally due to invasion of the mediastinal vessels. It is characterized by a productive cough, and in some cases hemoptysis, hyperthermia, progressive dyspnea, and pleuritic pain. It can cause pneumonia with a tendency to cavitation and sometimes intracavitary fungal balls. In some cases, the radiological image is similar and indistinguishable from that of acute invasive pulmonary aspergillosis, with the sign of the “inverted halo”.

**Gastrointestinal Mucormicosis [19]**

It occurs in severely malnourished children or adults, who usually have a poor, carbohydrate-based diet. Patients with these degrees of malnutrition frequently present co-existing intestinal parasites that can enhance the invasion of the fungus in the tissues of the digestive tract and from there affect other organs of the abdominal cavity. It is produced by the ingestion of contaminated food and the lesions can compromise the stomach or colon with necrosis, perforation, sepsis, and peritonitis with high mortality. The diagnosis is generally made by the histopathological study of the surgical piece.

**Skin Mucormicosis [19]**

It can be acquired by patients with normal immunity. The main predisposing factor is inadequately-managed extensive burns or abrasions of the skin. Mucorales present in the environment can develop on the surface of the lesion, forming superficial colonies. Infection is also caused by contaminated bandages or adhesive fabrics.

Another very different group of patients is made up of those who have a disease that compromises the immune response (diabetes mellitus, AIDS, etc.). These patients can develop more serious complications from the skin infection that may even make amputation or hyperbaric oxygen therapy necessary.

**Mucormicosis, COVID-19 and Diabetes Mellitus**

The first death registered by mucormycosis in COVID-19 ("black fungus") in Argentina happened on June 18, 2021. It was a 35-year-old man with uncontrolled diabetes, who was admitted to a hospital in Lomas de Zamora (Buenos Aires Province).

Obesity and diabetes mellitus are the most common - and most worrying - comorbidities in patients with coronavirus infections. Various reports, including those from the US Center for Disease Control and Prevention (CDC), indicate that patients with DM2 and metabolic syndrome could have up to a ten-fold higher risk of death when they contract COVID-19. Emerging evidence demonstrates an important direct endocrine and metabolic link to the viral disease process. The relationship between COVID-19 and DM could be two-way directed. ACE2 (angiotensin converting enzyme 2) receptors have been found to be present in a large number of tissues, including the pancreas, where their expression is very high. Medical Doctors must ensure early and complete metabolic control for all patients affected by COVID-19. However, in the context of severe cases, it is difficult to determine whether the presence of pancreatitis is due to direct damage to pancreatic tissue by SARS-CoV-2 or whether it is the result of the dysregulated inflammatory response, which is part of COVID-19 disease. Regardless of the cause, pancreatic injury is an important risk factor for the future development of DM or prediabetes, as well as an obstacle to correctly treat patients with previous DM. There is sufficient evidence supporting the concept of pancreatic injury and pancreatitis in COVID-19.

Based on the authors' studies [20,21] and, after the publication of the RECOVERY trial [22], it is indisputably considered that corticosteroid therapy reduces mortality in patients with COVID-19. However, this treatment (in combination with other pre-existing or simultaneous-onset clinical and immunological factors) could increase the risk of secondary fungal infection. This is valid for aspergillosis, candidiasis, fusariosis and mucormycosis [19].

Diabetes plays a decisive role, since it considerably complicates the management of patients with COVID-19. The use of dexamethasone in treatment increases the risk of invasive fungal infections because hyperglycaemia (which can also be seen in patients with undiagnosed or uncontrolled diabetes). Diabetic patients present an inflammatory state, involved in the recruitment and activation of cells that participate in the immune response (macrophages and neutrophils), which release significant amounts of pro-inflammatory cytokines that contribute to the persistence of the inflammatory state. Uncontrolled diabetes can cause inflammation that affects the immune system. In patients with COVID-19, activation of the antiviral immune system accentuates the inflammatory phenotype and predisposes to secondary infections. Regardless of the current pandemic, corticosteroid-induced hyperglycemia is a common problem, usually disregarded both in terms of diagnosis
In 65.1% of the cases, radiological abnormalities were observed 90 days). The diagnosis was confirmed by histology or culture. Diagnosed a median of 10 days after COVID-19 diagnosis (0 to 86 years). Two groups were distinguished; those with rhino sinuso orbito cerebral mucormycosis, and nodules and cavities in patients with pulmonary mucormycosis.

In any case, the diagnosis of mucormycosis is often-sometimes-difficult, since the radiological signs of pulmonary and disseminated mucormycosis can overlap with those of COVID-19. The diagnosis is based on clinical evaluation, in which the doctor - as a first premise - must bear this probability in mind, and it is confirmed with histopathological examinations: tissue samples looking for wide non-septate, tape-like hyphae. The hyphae are large, with irregular diameters and right-angle branching patterns [19]. The evaluation must be thorough, because much of the necrotic debris does not contain microorganisms. Before the finding, the culture should be carried out, but also start with the treatment pending confirmation.

Treatment consists of intravenous amphotericin B. A high-dose amphotericin B lipid formulation (7.5 to 10 mg / kg intravenously once daily) is recommended as initial therapy. Posaconazole can also be effective, but it has not been studied as a primary therapy. Even with aggressive treatment, mortality rates are high [19]. It should be noted that 69.2 million people suffer from diabetes in India, making it the country with the highest incidence of this disease. In comparison, 29 million people in the United States (9.3 percent) have diabetes. In our country (Argentina), it is estimated that 1 in 10 Argentines aged 18 years or older has diabetes and as they remain without symptoms for several years, approximately 4 out of 10 people who suffer from it do not know their diagnosis. According to a 2019 survey in Peru, 3.9 cases of diabetes mellitus are registered for every 100 individuals over 15 years of age [23,24].

Conclusions
For all the above-mentioned details, and taking into account the high rate of infections during the current pandemic, the greater severity of clinical cases in patients with comorbidities (especially DM and obesity), the frequent and growing need for the use of corticosteroids as part of the scheme. therapeutic, the ability of corticosteroids to trigger hyperglycemia and/or DM by mechanisms that are intrinsic and unavoidable, the immunocytopenia that both corticosteroids and DM- produce in the individual, the greater probability of the appearance of opportunistic mycoses in these situations, and the importance of correct metabolic management of these patients during viral infection, the need to include the Diabetologist in the health team that treats patients with COVID-19 becomes a very reasonable move.

References
1. Murray HW. Pulmonary mucormycosis: One hundred years later. Chest. 1977; 72: 1-2.
2. Sobonya ER. Fungal disease, including allergic bronchopulmonary aspergillosis. Pathology of the lung. New York: Thieme. 1995: 324.
3. Chandler FW, Watts JC. Fungal infections. Pulmonary pathology. New York: Springer-Verlag. 1995; 392-395.
4. Mc Adams HP, Rosado de Christenson M, Strollo DC, et al. Pulmonary mucormycosis: Radiologic findings in 32 cases. AJR. 1997; 168: 1541-1548.
5. Hoenigl M, Strenger V, Buzina W, et al. European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) host factors and invasive fungal infections in patients with haematological malignancies. J Antimicrob Chemother. 2012; 67: 2029-2033.
6. Perusquia-Ortiz AM, Vázquez-González D, Bonifiz A. Opportunistic filamentous mycoses: aspergillosis, mucormycosis, phaeohyphomycosis and hyalohyphomycosis. J Dtsch Dermatol Ges. 2012; 10: 611-621.
7. Warnock DW. Trends in the epidemiology of invasive fungal infections. Japanese J Med Mycol. 2007; 48: 1-12.
8. Moreno A, Cervera C, Fortú J, et al. The OL -HIV-FIPSE Cohort Investigators. Epidemiology and Outcome of Infections in Human Immunodeficiency Virus/Hepatitis C Virus-Co-infected Liver Transplant Recipients: A FIPSE/GESIDA Prospective Cohort Study. Liver Transplant. 2012; 18: 70-82.
9. Brown J. Zygomycosis: An emerging fungal infection. Am J Health Syst Pharm. 2005; 62: 2593-2596.
10. Freifeld A, Iwen P. Zygomycosis. Seminar Respir Crit Care Med. 2004; 25: 221-231.
11. Karanth M, Taniere P, Barraclough J, et al. A rare presentation of zygomycosis (mucormycosis) and review of the literature. J ClinPathol. 2005; 58: 879-881.
12. Talmi YP, Goldschmied-Reouven A, Bakon M, et al. Rhinorhino-orbital and rhino-orbito-cerebral mucormycosis. Otolaryngol Head Neck Surg. 2002; 127: 22-31.
13. Fan KT, Whitman GI, Chew FS. Pulmonary zygomycosis. Am J Radiol. 1996; 167: 946.
14. Tedder M, Spratt JA, Anstadt MP, et al. Pulmonary mucormycosis: Results of medical and surgical therapy. Ann Thorac Surg. 1994; 57: 1044-1050.
15. Rubin SA, Chaljub G, Winer-Muram HT, et al. Pulmonary zygomycosis: A radiographic and clinical spectrum. J Thorac Imaging. 1992; 7: 85-90.
16. Del Real-Mora O, Quezada-Zamora J, Abud-Mendoza C, et al. Mucormycosis Informe de 14 casos. Rev Invest Clin. 1983; 35: 237-240.
17. Matsushima T, Soejima R, Nakashima T. Solitary pulmonary nodule caused by phycomycosis in a patient without obvious predisposing factors. Thorax. 1980; 35: 877-878.
18. Bigby TD, Serota ML, Tierney LM, et al. Clinical spectrum of pulmonary mucormycosis. Chest. 1986; 89: 435-439.
19. Negroni R. Mucormycosis. Compendio de Infectología. Ed. Atlante. 1ª edición. 2014; 269-271.
20. Hirsch R, Carvallo H. SARS COV2, Emerging, Reemerging and Potentially Emerging Diseases in Argentina. J Virol Infect Dis. 2021; 2: 13-17.
21. Carvallo H, Matozza F, Hirsch R. COVID-19 and Repurposed drugs: How much is a human life? Clin Immunol Res. 2021; 5: 1-11.
22. RECOVERY Trial. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021; 25: 693-704.
23. Hoenigl M, Danila S, Carvalho A, et al. The Emergence of COVID-19-associated Mucormycosis: Analysis of cases from 18 countries. Lancet. 2021: 1-33.
24. Singh AK, Singh R, Joshi SR, et al. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 2021; 15: 102-146.