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Mucormicosis, COVID-19 and Diabetes Mellitus

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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 phyomycosis, 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 Sinuso Orbito Cerebral Mucormicosis [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 COVI-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, septicemia 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. Mucorals 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

and treatment. After the administration of corticosteroids, the predominant mechanism responsible for hyperglycemia consists of the reduction of glucose uptake due to hepatic and peripheral insulin resistance, but also due to inhibition of insulin secretion, which mainly provokes postprandial hyperglycemia. The pattern of corticosteroid-induced hyperglycemia varies widely, depending on the type of glucocorticoid used, as well as the dose and frequency of administration. Intermediate-acting corticosteroids (prednisone and methylprednisolone) have a peak of action at 4–8 hours and a duration of action of approximately 12–16 hours. In patients without diabetes, and in those with well-controlled diabetes, hyperglycemia. Induced by intermediate-acting glucocorticoids, in morning dose, is characterized by an absence or minimal elevation of fasting blood glucose. Basal blood glucose levels are normal or minimally elevated, but there is an exaggerated increase in postprandial blood glucose levels, resulting in hyperglycemia in the afternoon and evening. In these cases, we must select therapeutic measures with a preferential hypoglycemic effect in the afternoon and little or no effect in the early morning to avoid hypoglycemia. When these corticosteroids are used two or more times a day, hyperglycemia persists for 24 hours, but maintains a postprandial predominance. Long-acting glucocorticoids, such as dexamethasone, have a longer hyperglycemic effect. In healthy volunteers it has been quantified in around 20 hours, but in clinical practice it seems to be longer. In this case, the hyperglycemic profile usually lasts for more than 24 hours and is predominantly postprandial, with a slight decrease in blood glucose during the overnight fast. Although originally, the trend of affectation in the diabetic population predominates in older adults who are at greater risk of becoming seriously ill from COVID-19, more and more young patients are seen, in the same situation, mostly men. In the USA, hispanic and black patients appear to be disproportionately affected, which could be related to social determinants of health or differences in the type of work (essential workers), the structure of the household with extended family (making physical distancing more difficult), dependence on public transportation, and inferior quality of medical care. Hoenigl, M. et al [23] reviewed 80 cases of mucormycosis in COVID-19, mostly in patients from India (42 out of 80). The prevalence in patients admitted to the ICU ranged from 0.3% to 0.8%. Most of the patients (77.5%) were men, with a median age of 55 years (10 to 86 years). Two groups were distinguished; those with rhino sinuso orbito cerebral clinical forms and those with pulmonary forms. At the time of diagnosis, most of the patients (92.5%) were hospitalized for ongoing COVID-19. 95% had additional risk factors; diabetes was the most common pre-existing disease, especially type 2 diabetes (89.4% of cases, compared with 9.1% of patients with type 1 diabetes). Most of the patients had uncontrolled or poorly controlled diabetes, with ketoacidosis diabetes, hyperglycemia, elevated levels of glycated hemoglobin (HbA1c), or end-stage kidney disease. 75% of the patients received corticosteroids, and in 80% of these patients, treatment with corticosteroids had been started before the diagnosis of mucormycosis. Mucormycosis was diagnosed a median of 10 days after COVID-19 diagnosis (0 to 90 days). The diagnosis was confirmed by histology or culture. In 65.1% of the cases, radiological abnormalities were observed (sinusitis and necrosis in patients 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.

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