Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 and mucormycosis in Latin America – An emerging concern

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During the Coronavirus Disease 2019 (COVID-19) pandemic, the improper use of corticosteroids and the presence of diabetes mellitus in patients marked the beginning of an increased incidence of fungal infections such as aspergillosis and mucormycosis in patients with this emerging viral infection [1–3].

Mucormycosis is a common angioinvasive infection with significant morbidity and mortality now complicating the course of, especially severe, COVID-19. The disease spectrum comprises rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal and disseminated mucormycosis [4–6].

Although corticosteroids are the first-line treatment for a wide range of inflammatory diseases, in COVID-19, their use is only recommended in critically ill patients [7]. In addition, before the COVID-19 pandemic, its use has been identified as a critical risk factor for mucormycosis. In one study, 46% of patients were administered corticosteroids one month before their diagnosis of mucormycosis [8]. However, the adverse effects at high or prolonged doses of corticosteroids cause hyperglycemia and immunosuppression [9]. Furthermore, although its use in patients with severe or critical COVID-19 has benefits [10], it is also associated with opportunistic infections [11]. As a result, its misuse could be an important factor in triggering aggressive mucormycosis in COVID-19 patients, as now observed worldwide.

In general terms, diabetes mellitus predisposes patients to invasive fungal infections, mainly when this metabolic condition is not controlled. Recently, there has been an increase in cases of mucormycosis with COVID-19, especially in patients with diabetes. The main risk factors for this fungal disease are diabetes, neutropenia, iron overload, malignancies, and organ transplantation [5].

In Latin America, more than two hundred cases have been reported in the literature across the region from Mexico to Argentina. Most cases have been described from Brazil. The number of cases has been increasing in the last decades, before COVID-19, and apparently, the mortality rate was decreasing. In a study from Brazil [11], the mean age of patients was 39.3 years, 61.5% being males, and the most frequent underlying conditions were diabetes mellitus (42%), burns or penetrating trauma (20.3%), immunosuppression (45.5%) due to malignancy (mainly haematological) (11.2%), solid organ transplantation (12.6%) and use of corticosteroids (6.3%), among others [11]. In that report, the case fatality rate (CFR) was 44% in men and 24% in women, while, due to underlying conditions, mortality was 45% in patients with diabetes mellitus; 37.9% in patients with burns or penetrating trauma; 58.5% in patients with immunosuppression, and 55.6% in patients who used corticosteroids. The most common clinical presentation was rhino-sinus-orbital-cerebral (44.8%), followed by skin and soft tissue infection (23.8%) and, in third place, pulmonary mucormycosis (11.9%). Infection with *Rhizopus* spp. was observed in 26.6% of the cases. Treatment exclusively using antifungals was reported in 30.1% of the cases, in 49.7% antifungals and surgery, and no antifungal treatment was described in 20.3%. Amphotericin B alone deoxycholate was used in 58.0% (with a mortality of 43.4%) and lipid formulation in 10.5% (with a CFR of 13.3%). Other drugs used were ketoconazole and posaconazole. It was concluded that the increasing use of antifungals and surgery has dramatically improved the prognosis of mucormycosis; however, CFR remains high [11].

Some recent reviews have identified an increase in the publication of case reports/case series of COVID-19 associated mucormycosis. Most of the cases are from India, and the most common comorbidity is diabetes mellitus. The median time interval between the diagnosis of COVID-19 and the first evidence of mucormycosis infection was 15 days. Corticosteroids use was reported in 85% of cases. The most common presentations of mucormycosis were rhino-orbital (42%), rhino-orbito-cerebral (24%) and pulmonary (10%). The mortality rate was 34%. Complementary surgery was performed in 81% of the patients and was associated with better clinical results [1].

A study reported that 101 cases of COVID-19-associated mucormycosis (CAM) had been reported worldwide, of which 82 are from India. Mucormycosis was observed predominantly in men (78.9%), both in people with the disease (59.4%) and recovered (40.6%) from COVID-19.

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Likewise, the presence of diabetes mellitus was reported in 80% of cases, while corticosteroid treatment for COVID-19 was administered in 76.3%. Mucormycosis affecting the nose and sinuses (88.9%) was the most common, followed by rhino-orbital (56.7%). Mortality was observed in 30.7% of the cases. Thus, a triad of diabetes mellitus, inappropriate use of corticosteroids and COVID-19 seems to increase mucormycosis cases. Therefore, every effort should be made to maintain optimal glucose and only the judicious use of corticosteroids in patients with COVID-19 [12].

In recent months, cases of mucormycosis associated with COVID-19 have been reported in other Latin American countries in addition to Brazil. In Peru, four cases of patients with mucormycosis after COVID-19 infection were reported. All of them had decompensated diabetes. In the first case, a 45-year-old male patient had high blood pressure as comorbidity. The clinical presentation was rhino-orbito-cerebral and, given a presumption of diagnosis, treatment with amphotericin B and then isavuconazole was started. However, the patient requested voluntary withdrawal. The second, a 51-year-old male patient who had rhino-orbital-cerebral mucormycosis. After receiving amphotericin B and isavuconazole, she had a favourable evolution and was discharged with oral isavuconazole treatment. The third, 45-year-old male patient also had rhino-orbital-cerebral mucormycosis, underwent surgery on three occasions and received amphotericin B and then isavuconazole. The fourth 48-year-old female patient with a rhino-orbital presentation, confirmed after biopsy, received amphotericin B treatment and surgical cleansing [13].

In Brazil, a report described a case of primary gastric mucormycosis in an 86-year-old male patient with a history of arterial hypertension who presented COVID-19 infection. The patient was in the Intensive Care Unit (ICU) for acute respiratory failure and hemodynamic instability due to the COVID-19 infection. He received ceftriaxone, azithromycin, oseltamivir and hydrocortisone, in addition to vasopressors and mechanical ventilation. At five days, the patient presented severe anaemia and melena accompanied by abdominal pain. It was decided to perform an esophagogastroduodenoscopy which revealed two giant gastric ulcers with dirty debris and a deep hemorrhagic base without bleeding. The pathological examination confirmed the diagnosis of mucormycosis. The patient died a week later [14].

Another report described a case of a 60-year-old patient whose comorbidity was uncontrolled diabetes, with a painful lesion on the hard palate. She was diagnosed with COVID-19 eight days before admission. After the diagnosis of mucormycosis, she was referred to hospitalization. She was treated with intravenous amphotericin B associated with hydrocortisone, and after a month and a half, the patient was discharged [15].

Also, in Brazil, a case of a 56-year-old male patient with insulin-dependent diabetes mellitus was reported. He arrives at the emergency room with an alteration in blood glucose and an infection in his right eye. He was diagnosed with fatal rhino-orbital mucormycosis, and treatment was with amphotericin B. Unfortunately, on the fourth day of hospitalization, the patient died [16].

Even in Latin America, in countries like Chile, cases of fungal coinfection have been published in patients with COVID-19. A group of 16 patients with COVID-19-associated invasive mould infection (CAIMI) was recently reported. It is said that no patient was immunocompromised and that all received antimicrobial therapy. Case 14 was of a previously healthy 62-year-old male patient (without comorbidities) treated with corticosteroids at a total dose equivalent to 115.5 mg of prednisone. He developed CAIMI 10 and 15 days after admission to the ICU and the start of invasive mechanical ventilation, respectively. In imaging studies, consolidations, pulmonary embolism, and pleural effusion were identified. The tracheal aspirate identified *Aspergillus niger* and *Rhizopus stolonifer*, diagnosing coinfection between aspergillosis and mucormycosis. He did not receive any antifungal therapy, and at the end of the follow-up, he survived. Case 15 was a 55-year-old male patient with uncontrolled diabetes (glycated haemoglobin 8.8%), hypertension and atrial fibrillation, who was treated with corticosteroids at a dose equivalent to 812 mg of prednisone. He developed CAIMI five days after admission to the ICU and five days after the start of invasive mechanical ventilation. Imaging studies revealed consolidations, nodules, and a cavitated nodule was identified in bronchoalveolar lavage *Rhizopus microsporus*. Disseminated mucormycosis with brain involvement and airway and skin infection, manifested as an acute thoracic skin lesion, was confirmed. He was treated with liposomal amphotericin B and died during follow-up [17].

In Mexico, a 24-year-old female patient with obesity and diabetes mellitus developed severe new-onset diabetic ketoacidosis, severe metabolic acidosis, severe COVID-19, and rhino-orbital mucormycosis (initially suspected and later confirmed through direct examination) was described. Due to the severity of the infection, imipenem, linezolid and amphotericin B were used as treatment. Despite severe diabetic ketoacidosis and mechanical ventilation treatment, the patient worsened to disseminated intravascular coagulopathy and died due to multi-organ dysfunction. As observed in this case, severe immunosuppression due to naive diabetic ketoacidosis predisposed to severe COVID-19 and mucormycosis [18].

Also, in that country, a case was reported of a 35-year-old male patient with glycemia in pathological intervals (without confirmed diabetes mellitus) with a presumptive diagnosis of COVID-19 and treated with dexamethasone 8 mg every 6 hours for approximately 15 days. After corticosteroid treatment, a dermatosis located in the infraorbital region and left maxillary region appeared, irregularly, accompanied by a maxillary abscess. Mucormycosis was diagnosed through histopathology. Treatment was liposomal amphotericin B, and three surgical debrides to the maxilla and fatty tissue on the orbital floor. In the beginning, the treatment was with amphotericin deoxycholate, but it was suspended due to the appearance of nephrotoxicity [19].

In Central America, specifically in Honduras, recently, a 55-year-old male patient was described developing a CAM. He was diagnosed with COVID-19 and treated in the ICU for two weeks, including corticosteroids. Two days after discharge, she developed a loss of sensation lining the malar area with periorbital pain and nasal congestion, as well as white crusts on the right hard palate on oral examination. Mucormycosis was diagnosed by KOH (direct examination), histopathology and fungal culture. Treatment was conservative with liposomal amphotericin B, later surgical debridement, as well as the use of isavuconazole [20].

Risk factors, such as diabetes, are widely prevalent in Latin America. In this region, around 32 million patients live with diabetes. Moreover, the prevalence of this disease has constantly increased throughout the time, with geographical variations: with higher prevalence in Ecuador (27%), Mexico (13.7%), Haiti (14.1% in women and 8.2% in men) and Puerto Rico (12.5–12.7% in the population aged 18 $\geq$ years and 26.8% in the population aged $\geq$45 years), and lower in Colombia (3.0% in the population aged 18 $\geq$ years, but 11.2% in the group aged $\geq$60 years), the Dominican Republic (3.5%), Peru (3.7%) and Uruguay (5.5–6.0%) [21]. In 2019, the number of people with diabetes in Latin America was estimated to be 31.6 million [22]. Furthermore, it is projected that by 2030, the number will increase to 40.2 million and 49.1 million by 2045 [23]. Furthermore, in the last decade, diabetes mellitus has been recognized as one of the leading causes of death in some Latin American countries and a significant risk factor for cardiovascular diseases, the leading cause of death in Latin America [24,25].

From 2005 to 2020, the prevalence of diabetes mellitus in Latin America was assessed in individual countries and through multinational studies [26,27], ranging from 3% to 36.3%. In addition, multiple studies reported a higher prevalence of diabetes among women and with increasing age, significantly above 60 years [15]. The prevalence of undiagnosed diabetes was higher in Guatemala (48.8%), Uruguay (48.7%), Puerto Rico (37.7–50%), Honduras (range 31.9–53.7%), Mexico (range 29.9–50%) and Nicaragua (43.3%) and lower in Colombia (Bogotá) (23.5%), the southernmost countries of South America (20.2%), and Costa Rica (10.3–28.4%) [28].

Additionally to diabetes, Latin America has been one of the regions with the highest prevalence of drug misuse, including ivermectin, chlorine dioxide, and corticosteroids used without indication and even in patients with mild or asymptomatic COVID-19. During the COVID-19 pandemic, frequent self-medication has been observed as prevention or symptomatic treatment. In this observed change in behaviour, self-medication with anti-inflammatory drugs was increased compared to the period before the onset of the pandemic [29]. The use of corticosteroids during the confinement of the first outbreak in Peru was one of the least used drug groups for self-medication [30]. However, inadequate use of corticosteroids was observed in patients who did not require oxygen therapy or during the first phase of the disease [31]. That was accompanied by a significant increase in the price of drugs used in COVID-19 [32].

In a study of hospitalized patients with a diagnosis of COVID-19 (confirmed or suspected) at the Cayetano Heredia Hospital in Lima, Peru, of a total of 132 hospitalized patients, 106 patients (80.3%) used drugs before hospital admission; of which 36 (33.9%) self-medicated. Thus, 58 patients (54.7%) used corticosteroids before their hospitalization and 18 of them (17.0%) without a prescription [33]. Furthermore, an analytical study in Health Sciences students even reported that 51.3% had self-medicated, of which 15.6% self-medicated with prednisone, dexamethasone or methylprednisolone [34]. Currently, concern about inappropriate steroid use in COVID-19 is associated with the development of mucormycosis (CAM) and its possible fatal outcomes [35]. The situation observed in Peru is a reflection of what is also seen in other Latin American countries. As reported in media, soon in other countries we will observe more reported cases [36].

Faced with this situation, the reports of mucormycosis associated with COVID-19 in India, but also in other countries on other continents, have generated significant concern, and in the case of Latin America, according to a recent epidemiological alert from the Pan American Health Organization (PAHO) [37], have been reported in seven countries, Brazil, Chile, USA, Honduras, Mexico, Paraguay, and Uruguay, a total of 16 cases, of which eight were women, eight men, with a median age of 52 years (IQR 43–63, min 24-max 74) [36]. In this group, 69% had diabetes, 13% overweight, 13% obesity, among other risk factors. In these patients, 56% presented rhino-orbital, 25% rhino-orbital-cerebral, and 19% pulmonary. Unfortunately, 56% of them died. As observed here, but in previous reports in COVID-19 patients [38], diabetes is a crucial risk factor.

In this issue of *Travel Medicine and Infectious Diseases*, a fatal case report and review from Turkey is published, describing a patient receiving high doses of systemic steroids with an unfortunate post-mortem diagnosis of CAM [39]. As concluded by the authors of that article, CAM is a is a growing challenge, where clinical guidelines should be implanted for appropriate management of COVID-19 cases. Particularly, the inappropriate use of steroids generates a concern regarding the risk of developing associated mucormycosis (CAM). Despite pharmacological and surgical treatment, mortality rate is high [39]. Then, as has been called, enhance surveillance, and clinical suspicion in the region should be kept achieving correct and prompt diagnosis, which may allow early treatment, especially in a condition that may lead to fatal outcomes in a significant proportion of patients.

Declaration of competing interest

Dr Rodriguez-Morales, report being a medical advisor of Abbott Diagnostics for Latin America, outside the submitted work. The rest of the authors declare no conflict of interest.

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