Rhino-orbital-cerebral angioinvasive mucormycosis in two diabetic patients with COVID-19

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Abstract

Mucormycosis is a rare infection whose main risk factor is diabetes mellitus, and whose frequency has increased during the COVID-19 pandemic. Two cases of rhino-orbital-cerebral angioinvasive mucormycosis are described in adult male diabetic patients with COVID-19. Both cases had necrotic facial and orbital lesions, affecting the paranasal sinuses and involving the cavernous sinus and the internal carotid artery, which caused cerebral infarcts. They were diagnosed by finding mycotic structures in tissue from one of the patients and by directly examining secretions in the other. Both patients were treated with amphotericin B deoxycholate and one of them was taken to surgery; however, both cases had a fatal outcome. We emphasize the need for early diagnosis and immediate use of antifungal medications with proven efficacy. **(Acta Med Colomb 2023; 48. DOI: https://doi.org/10.36104/amc.2023.2732).**

Keywords: *mucormycosis, COVID-19, diabetes mellitus, mucorales, cerebral infarct.*

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Introduction

In December 2019, the pandemic caused by a new coronavirus (SARS-CoV-2), known as coronavirus 2019 disease (COVID-19) began in China (1). The inflammatory response seen in COVID-19 patients makes them susceptible to numerous infections, including mycoses. In addition, the routine use of corticosteroids in COVID-19 and associated diabetes mellitus foster the onset of mucormycosis (1).

Mucormycosis is a serious fungal infection caused by a group of molds classified in the phylum Glomeromycota, subphylum Mucoromycotina, order Mucorales; it includes several genera, and the *Rhizopus* species are the most significant (2).

Mucormycosis is a rare disease, but its incidence has increased during the pandemic, especially in India. Its most common clinical form is the rhino-orbital-cerebral form (3).

We present two cases of rhino-orbital-cerebral mucormycosis (ROCM) in two diabetic patients with COVID-19. Awareness of this emergent mycosis is of clinical interest due to the severity of the condition and its potentially fatal outcome.

Case 1

A 48-year-old man from Venezuela was referred due to a five-day history of pain, edema and redness on the left side of his face, palpebral ptosis and vision loss in the left eye. He had a history of a recent left upper tooth extraction, as well as type 2 diabetes mellitus treated with glibenclamide, and chronic sinusitis.

He was admitted on July 5, 2021, and the most important finding on physical exam was a blackish, necrotic lesion on the hard palate, along with palpebral ptosis and vision loss in the left eye with a dilated, nonreactive pupil. He was thought to have periorbital cellulitis and was treated with antibiotics and insulin. The lesion continued to worsen, and he developed left palpebral edema, proptosis, conjunctival discharge, chemosis, subconjunctival hemorrhages and corneal opacity. Subsequently, lower palpebral and left palate necrosis was found. On July 16, his left eyeball was eviscerated, and the necrotic matter was removed. On the 18th, he was found to have non-fluent aphasia and right flaccid hemiparesis with a positive Babinski sign. A computed tomography (CT) of the paranasal sinuses showed ethmoid, sphenoid and right maxillary sinusitis (Figure 1-A); a simple head CT revealed left temporal cerebral infarction. On July 19, he underwent an incisional biopsy of the gums and palate which reported non-septate hyphae (Figure 1-B) and, with a diagnosis of mucormycosis, treatment was begun with amphotericin B deoxycholate (1 mg/kg/day IV). On July 26, a PCR test was positive for SARS-CoV-2 (he had a negative antigen test

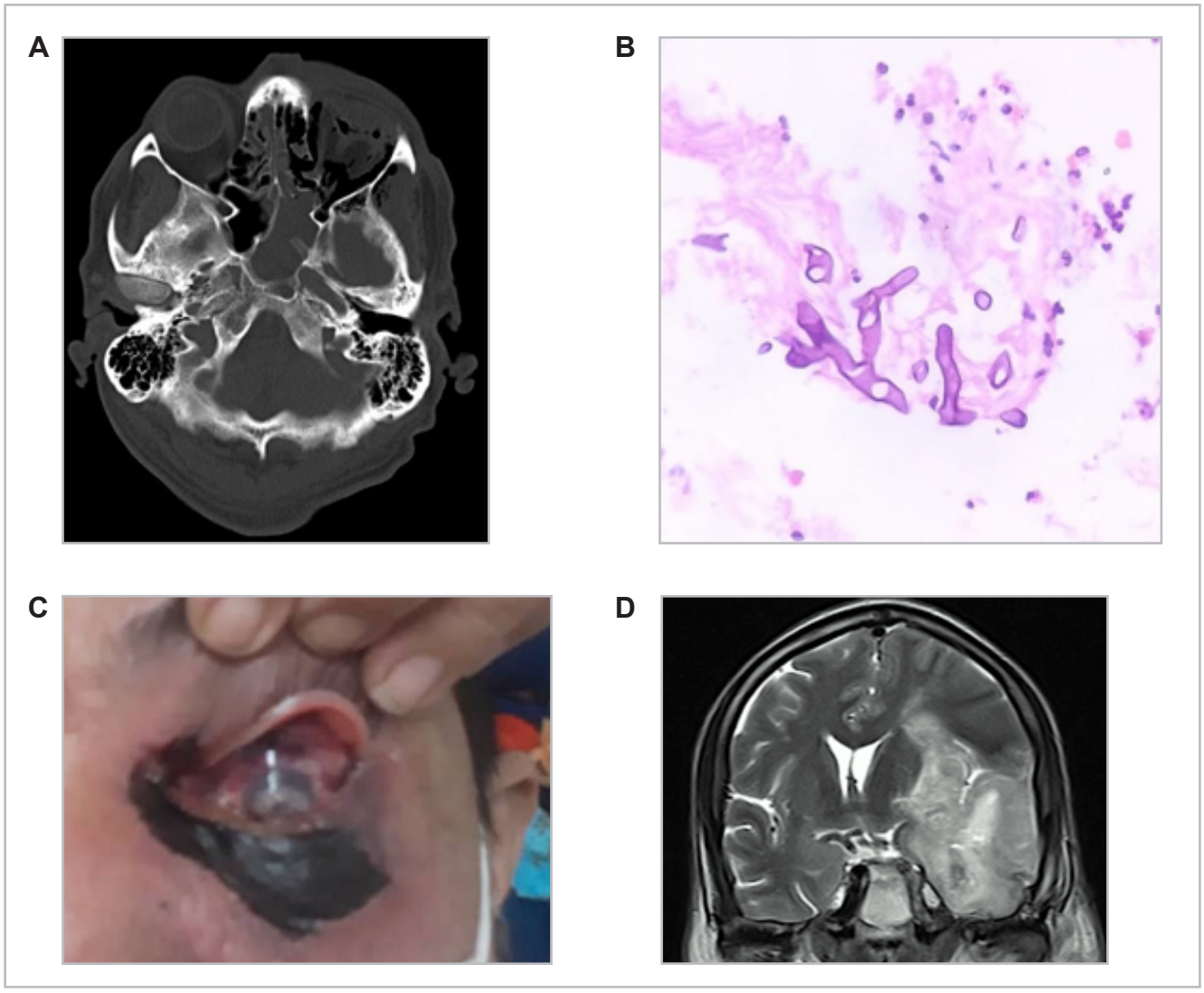

Figure 1. Patient 1. A*: Paranasal sinus CT: ethmoid-sphenoid sinus inflammation with postoperative changes following left ocular evisceration.* ***B:*** *biopsy of the necrotic palate tissue (HE 40x): nonseptate branching hyphae compatible with Mucorales,* ***C****: black necrotic lesion on the lower eyelid and left cheek. Residual necrotic changes in the orbital cavity.* ***D:*** *Coronal section (T2) of a simple brain MRI: thrombosis of the cavernous portion of the left internal carotid artery with an ipsilateral cortical-subcortical temporal-insular ischemic area as well as ischemia of the adjacent basal ganglia in the area supplied by the middle cerebral artery, with hemorrhagic transformation and mass effect.*

on admission); the patient had no respiratory symptoms, and the chest x-ray was normal. The necrotic left facial lesions persisted on July 27 (Figure 1-C). A direct exam and culture of the discharge from the lesions, performed after beginning antifungal treatment, were negative. The simple brain magnetic resonance imaging (MRI) (Figure 1-D) showed a thrombus in the cavernous portion of the left internal carotid artery, as well as an extensive frontal-temporal-parietal and left basal ganglia acute cerebral infarction with hemorrhagic transformation.

The patient underwent endoscopic ethmoidectomy and left orbital decompression, as well as necrotic wound cleansing. Despite surgical and antifungal treatment, the patient died on August 22, 2021.

Case 2

A 39-year-old man from Cúcuta was seen on August 19, 2021, due to a 12-day history of left facial inflammation and headache, treated with ceftriaxone, dexamethasone and diclofenac. He had a history of poorly controlled type 2 diabetes. On physical exam, he had an extensive black, necrotic lesion on the left side of his face and complete left ophthalmoplegia (Figure 2-A). Laboratory tests confirmed diabetic ketoacidosis. Initially, he was treated with intravenous fluids, insulin, antibiotics and acyclovir. On August 20, he had left palpebral ptosis along with a hyperpigmented lesion on the left hard and soft palates. Amphotericin B deoxycholate was added due to suspected mucormycosis. On August 22, his consciousness deteriorated and on the 24th,

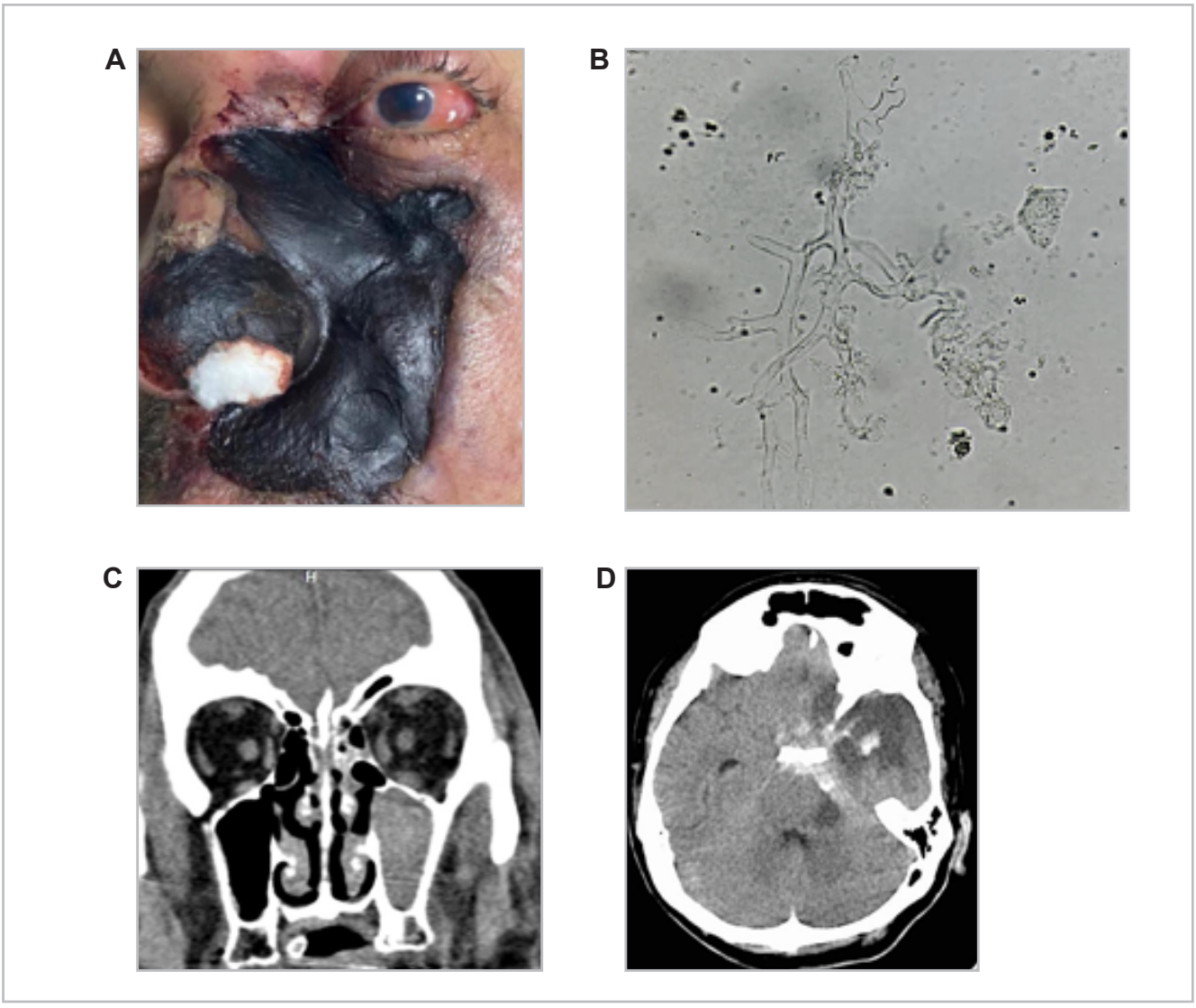

Figure 2. ***Patient 2. A:*** *black necrotic lesion involving the left nose, cheek and middle periorbital region, left ophthalmoplegia.* ***B****: direct exam with a nasal swab with KOH (40x): branching coenocytic hyphae, compatible with Mucorales.* ***C****: Paranasal sinus CT: predominantly left ethmoidal-maxillary sinus inflammation.* ***D****: Simple head CT: hemorrhagic transformation of acute left frontal-temporal ischemia in the area supplied by the middle cerebral artery, with subarachnoid hemorrhage in the basal cisterns and Sylvian fissure, on the left side.*

left ophthalmoplegia with exophthalmos, non-fluent aphasia, right flaccid hemiplegia with a positive Babinski sign and worsening facial lesions were confirmed. Direct examination of the discharge obtained by swabbing (Figure 2-B) showed branching non-septate hyphae; the culture was negative. A paranasal sinus CT (Figure 2-C) indicated paranasal and maxillary sinus inflammation. A simple brain CT on August 23 (Figure 2-D) showed left cavernous sinus inflammation, a left frontal-temporal-parietal cerebral infarction with hemorrhagic transformation and subarachnoid hemorrhage. A multiple PCR test (FilmArray®) of a respiratory tract sample identified SARS-CoV-2, and a chest CT showed right basal alveolar opacities. On August 24 he was transferred to the ICU where he worsened and died on September 3. He did not receive surgical treatment due to his critical condition.

Discussion

Mucormycosis was considered to be a rare mycosis. However, since the beginning of this century, it has emerged as a significant mycosis in hematological patients. The number of cases has increased during the COVID-19 pandemic, especially in India, attributed to the high prevalence of diabetes mellitus and environmental exposure to Mucorales spores produced by biomass burning (3).

COVID-19-associated mucormycosis is more prevalent in adult males and appears in all phases of the disease (3). Diabetes mellitus is the main risk factor (4). Other risk factors include prolonged neutropenia associated with hematological malignancies, steroid treatment, iron chelation therapy, chronic kidney disease and fungus inoculation through the skin due to wounds caused by natural disasters,

burns, surgical wounds and drug injection (4).

Central nervous system mucormycosis with no evidence of extracranial disease is known as isolated cerebral mucormycosis or, more commonly, ROCM. It may also originate in the lung and progress to the central nervous system (5). Rhino-orbital-cerebral mucormycosis initially affects the turbinates and paranasal sinuses, with the signs and symptoms of sinusitis (5). Necrotic scabs on the nasal mucosa or hard palate and bloody nasal discharge suggest the diagnosis. The disease generally progresses within a few days. Less than half of the patients have a fever. Orbital involvement is characterized by periorbital edema, proptosis and ophthalmoplegia. The cavernous sinus is often affected, and its thrombosis affects cranial nerves III, IV, V and VI. Cerebral infarction presents with altered consciousness and focal neurological signs like hemiparesis, aphasia or seizures (5).

Fungal invasion of the internal carotid leads to intra-arterial thrombosis (Figure 1-D) and, occasionally, to aneurysm formation and rupture (Figure 2-D). This invasive fungal carotiditis causes cerebral infarction and subarachnoid hemorrhage which can lead to death (6). In patients with mucormycosis and COVID-19, 11.8% have been found to have cerebrovascular effects and almost all have ROCM (6). Cerebral infarction is the most common presentation (91.8%), followed by brain hemorrhage (6.1%) and subarachnoid hemorrhage (2%) (6).

Diagnostic imaging, histopathology and microbiology tests are essential for diagnosing ROCM. On CT and MRI, sinus mucormycosis shows nonspecific nodular mucosal thickening (Figures 1-A and 2-C). Often, there is soft tissue infiltration and invasion of the temporal and infratemporal fossae. Lack of enhancement of the turbinate mucosa and inflamed paranasal sinuses on MRI, known as the "black turbinate" sign, is very suggestive of mycosis. There may also be destruction of the turbinates, paranasal sinus and orbital walls, base of the skull and hard palate. The differential diagnosis of ROCM includes other inflammatory diseases like thyroid orbitopathy, ocular Sweet's syndrome, idiopathic orbital inflammatory syndrome, and intraorbital masses like lymphoma, ocular leukemia, metastases and lacrimal gland tumors (1, 5). The most frequent findings of intracranial mucormycosis on diagnostic imaging are cavernous sinus thrombosis, internal carotid artery occlusion and cerebral infarction (5).

A microscopic exam is essential for early diagnosis of mucormycosis. It can be done on a fresh sample, with 10% potassium hydroxide (KOH) or with calcofluor-white. Wide (6-16 μm), branching (generally at 90º angles), nonseptate coenocytic hyphae are found. Mucorales grow rapidly on fungal culture media (2).

The fungi that most commonly cause mucormycosis are the *Rhizopus* species, especially *R. arrhizus* (also known as *R. oryzae*), which causes 90% of the ROCM cases (1, 6). *Mucor* spp. and *Lichtheimia* spp. have also been found, among others (1).

The diagnostic sensitivity of the different microbiological methods is as follows: direct microscopy of samples obtained from nasal swabs of deep tissues or endoscopy-guided paranasal sinus or orbital tissue swabs: 90%, histopathology: 80%, molecular tests: 75% and culture: 50% (7).

Treatment of ROCM is a medical emergency. The three treatment pillars are: surgery, antifungal medication and treatment of comorbidities (7). Surgery consists of extensive debridement of the necrotic remains, which often implies enucleation of the eyeball or extensive resection of bone tissue. The antifungal medication of choice is liposomal amphotericin B in the initial phase, followed by isavuconazole or posaconazole (3). In places where liposomal amphotericin is not available, amphotericin B deoxycholate may be used. Treatment of comorbidities, especially diabetic ketoacidosis and SARS-CoV-2 multilobar pneumonia, is essential to improve the prognosis (3). Mucormycosis is a rapidly progressive disease and, when the brain is involved, mortality is high (30-90%) (6).

Rhino-orbital-cerebral mucormycosis should be diagnosed promptly. Clinical suspicion in patients with risk factors should lead to a rapid microbiological diagnosis and initiation of treatment. The poor outcome in our patients highlights the lack of awareness of this serious disease and the treatment limitations in our healthcare institutions.

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