

**Case Report**

# A Diabetic Man in the Era of COVID-19

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**Citation:** Georgousi K, Provi D, Nikitopoulos D, Bisia A, Lazarou A, et al (2023) A Diabetic Man in the Era of COVID-19. Ann Case Report. 8: 1177. DOI:10.29011/2574-7754.101177

**Received:** 13 February 2023, **Accepted:** 17 February 2023, **Published:** 20 February 2023

## Abstract

A 71-year-old man with medical history of uncontrolled diabetes mellitus, admitted to COVID-19 clinic with SARS-CoV-2 PCR test positive and dyspnea. After a few days of hospitalization he had an abrupt deterioration with decreased consciousness, facial edema with purple blue discoloration, ptosis, proptosis, facial palsy and necrotic eschars in the oral cavity. Brain MRI and necrotic tissue sample biopsy were conducted. Although MRI images were suspicious of Rhino-Orbito-Cerebral-Mucormycosis, the diagnosis was set from histopathology findings with dermis subcutaneous fat tissue infiltration of the filaments fungi “mucor”. The risk assessment of COVID-19 mucormycosis co-infection is a worrisome scenario for patients suffering from uncontrolled co-morbidities, such as diabetes mellitus.

**Keywords:** COVID-19; Mucormycosis; Central Nervous System Invasion **Case**

## Introduction

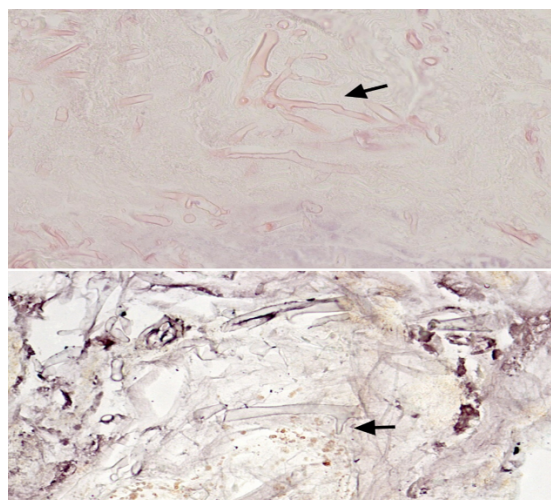
Mucormycosis is an opportunistic infection with rapid and lethal progression caused by filamentous fungi belonging in the order mucorales. These filamentous fungi exist anywhere in the environment affecting patients with diabetes mellitus (mainly with keto-acidosis), lymphoma, leukaemia, prolonged treatment with corticosteroids, organ or stem-cell transplantation, burns and malnutrition. In the era of COVID-19, patients either hospitalized with active infection caused by SARS-CoV-2 and needs of supplemental oxygen, antiviral and corticosteroid therapy either post-hospitalized are prone to secondary fungal infections such as Mucormycosis. The Rhino-Orbito-Cerebral form of mucormycosis which is the most prevalent type of this fungal infection is prescribed in the context of SARS-CoV-2 / Mucormycosis co-infection in a diabetic patient.

A 71-year-old man admitted to the COVID-19 clinic with polymerase chain reaction (PCR) test positive, referring shortness of breath when SARS-CoV-2 mutation BA.1 had begun to prevail in Greece. He had previously received two doses of SARS-CoV-2 vaccination. His medical history included uncontrolled diabetes mellitus, severe renal disease, amputation of his second toe of the right lower limb, percutaneous transluminal angioplasty, in the context of diabetic microangiopathy, and operated gastric cancer. On the clinical examination he was afebrile, hemodynamic stable with bilateral dry lung rhonchi and severe hypoxia (oxygen saturation in room air: 85%). His lung computed tomography (CT) showed peripheral infiltrates ground glass type of the lower lung lobes bilaterally. Immediately, he was started a therapeutic scheme of systemic corticosteroids and supplemental oxygen without intravenous remdesivir due to his pre-existing renal compromise. After a few days of hospitalization the patient had an abrupt clinical deterioration with decreased consciousness, right facial swelling with purple discoloration, right eyelid ptosis, proptosis and

anisocoria for the right eye. Results of the laboratory examination at that time showed leucocytosis (29,100 cells/ $\mu$ L), lymphopenia (1,290 %), reduced absolute count of lymphocytes (380 cells/ $\mu$ L), increased C-reactive protein of 20,9 mg/dl and serum ferritin of 727 ng/mL. Subsequently, the patient underwent a lumbar puncture examination with no findings (zero cells/ $\mu$ L). Despite the fact of apyrexia, broad spectrum of antibiotics (piperacillin / tazobactam and linezolid) were started while the patient's clinical condition continue to worse with bilateral eyelid and facial enema with blue discoloration (Figure 1). Neurological examination revealed altered consciousness, facial palsy indicative of VII nerve infiltration, weak reflexes and hypoaesthesia of the right arm, in the context of hemiparesis as a result of CNS involvement. Ophthalmological assessment demonstrated bilateral ptosis and proptosis and ocular motility restriction leading to total ophthalmoplegia as a result of III, IV, and VI nerve involvement. A brain magnetic resonance imaging (MRI) was conducted revealing bilateral nasal sinus mucosal thickening with fluid level in the sinus causing partial opacification, and on T2-weighted images bilateral hyperintense areas in temporal lobes mainly in the left temporal lobe, in the form of CNS ischemic damage. MRI images also revealed soft tissue swelling of malar with subcutaneous solid lesions growth, while the same lesions were shown in the right upper jaw along with mild heterogeneity of palate and oral cavity area. Maxillofacial surgery consultation was requested and revealed ischemic-necrotic eschars in the right infra orbital region and hard palate. Tissue samples of the necrotic lesions were sent for culture and histopathology. Due to increased suspicion of Rhino-Orbito-Cerebral-Mucormycosis, antifungal treatment (isavuconazole) was added in the previous antibiotic scheme. Although Amphotericin B is considered the treatment of choice in mucormycosis [1], the decision of antifungal monotherapy was made because of the patient's pre-existing renal compromise. Histopathologic analyses of necrotic eschar of the infra orbital region and hard palate revealed degeneration and necrosis of the subcutaneous fat tissue with infiltration by a septate or semi septate, irregular, ribbon-like hyphae. In positions, there was development of one hypha across another as a result of hyphal folding. Special stains used like Haematoxylin-Eosin and Grocott-Gomori's methenamine-silver which revealed the right broad-angle of branching (~90 degree) and wide hyphal width (Figure 2). In places, nerve infiltration and angioinvasion by the mentioned hyphae was noted. The conclusion of the histopathological examination was "image compatible with dermis-subcutaneous fat tissue infiltration of the filamentous fungi mucor". Surgical debridement of the infected tissues was abandoned as therapeutic protocol due to severe patient's condition and uncertain benefit. The patient died a couple of days later.



**Figure 1:** 71-year-old patient suffering from bilateral eyelid and facial purple-blue discoloration.



**Figure 2:** Histopathological findings of tissue sample (400 x magnification). Haematoxylin-Eosin stain, (up), shows a septate or semi-septate, irregular hyphae (arrow). Grocott-Gomori's methenamine-silver stain, (down), shows a ribbon-like hypha with right broad-angle of branching (~90 degree) and wide hyphal width (arrow) (Colour should be used for any figures in print).

## Discussion

Mucormycosis is a lethal fungal infection caused by the filamentous fungi classified under subphylum Mucoromycotina; Class Glomeromycetes; order mucorales (previously classified under class zygomycetes) [2]. Spores of these filamentous fungi are found in the air, dust, organic garbage and food. Inhalation of sporangiospores or invasion through an abrading skin, leads

to several forms of mucormycosis such as rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal and disseminated mucormycosis. Fungi of mucorales are well known about their angioinvasiveness causing tissue thrombosis and necrotic damage. In a recently systematic review contacted by Shah et al. [2], it is claimed that mucormycosis is an added burden to COVID-19 patients. COVID-19 - associated Mucormycosis (CAM) is becoming more common over the world, but it is most prevalent among diabetics in India and China [3]. Nevertheless, it is already known that patients at risk for mucormycosis infection are those with poorly controlled diabetes mellitus or who are immunosuppressed due to corticosteroids, malignancy or haematological cancer treatment and solid organ / hematopoietic stem cell transplantation. SARS-CoV-2 infection cause favourable conditions for CAM development such as i) endothelitis which promotes mucorale adhesion, (ii) phagocytes impairment leading to immunosuppression and fungi proliferation, and (iii) hyperferritinemia which acts as a promoter for establishment of mucormycosis [4]. During the COVID-19 era, the incidence of CAM in developed countries is almost 0,005-1,7% compared to 0,14% in developing countries like India, [5], with a mortality rate of about 50%.

The diagnostic methods of mucormycosis are direct microscopy with optical brighteners, fluorescence microscopy, histopathology, PCR based assays and culture of fresh tissue. The histopathological findings are crucial diagnostic features when compared to other filamentous fungi [6], rendering to histopathology using special stains major significance for diagnosing mucormycosis [7], as in our case. Nevertheless, the culture of the sent tissue was negative for mucorales identification. Reportedly, tissue culture is susceptible to damage from shear stress lowering the sensitivity of this method, with false negative results in up to 50% of mucormycosis patients [2]. Brain T2-weighted MRI image in Rhino-Orbito-Cerebral Mucormycosis, usually reveals CNS involvement which occurs most frequently (70%) due to contiguous spread from the paranasal sinuses and orbits [8]. In the rest 30% of the cases, mucorales either spread hematogenously either represent an isolated CNS damage, usually in drug injectors. Brain imaging shows signs of parenchymal involvement in the inferior parts of the frontal lobes, and lesions may be either hypo- or hyperintense on T2-weighted series, as in our case [1,9]. Generally, diagnosis of CNS mucormycosis is set indirectly by sinus tissue biopsy taken from Ear, Nose and Throat (ENT) surgeon via nasal endoscopy. According to the Code Mucor [10], our patient had symptoms and signs of Rhino-Orbito-Cerebral-Mucormycosis in the clinical setting of co-current treated COVID-19 with systemic corticosteroids and supplemental oxygen. Hence, as per Code Mucor, the diagnosis of

4d-stage Proven COVID-19-Associated-Rhino-Orbito-Cerebral-Mucormycosis could be set (CAROCM), due to ischemic damage of dermis, nasal sinus, orbits and bilateral temporal lobes.

In conclusion, the risk assessment of COVID-19/ mucormycosis co-infection is an important issue for patients suffering from uncontrolled co-morbidities such as diabetes mellitus and renal impairment with disappointing results, as in our case. We draw attention to this unusual and valuable learning case of mucormycosis in the era of COVID-19, so that clinicians be vigilant and cautious.

**Acknowledgements:** We thank Dr. Konstantinos Kokkinis, Director of Radiology Department of Peripheral General Hospital of Attica KAT for his assistance in manuscript writing regarding the detailed description of MRI findings. Unfortunately, MRI images weren't clear enough for disclosure.

**Conflict of Interest Statement:** There is no conflict of interest

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