Rhino-orbital Mucormycosis in a COVID-19 Patient: The First Case in Malaysia

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Abstract
Mucormycosis is an aggressive and potentially fatal fungal infection caused by fungi of the order Mucorales. There has been an increase in the number of cases of rhino-orbital mucormycosis in people with COVID-19, particularly in India. Rhino-orbital-cerebral mucormycosis is the most common manifestation of mucormycosis associated with COVID-19. We report the first case of rhino-orbital mucormycosis in a diabetic patient with SARS-CoV-2 infection in Malaysia. The diagnosis of mucormycosis was confirmed by histopathological examination, but the fungal culture and PCR results were negative. He was treated with antifungal therapy and had extensive debridement. Treatment of mucormycosis requires a multidisciplinary approach that includes addressing underlying risk factors, effective antifungal therapy, and surgical debridement.

Keywords
Coronavirus disease, COVID-19, mucormycosis

Introduction
There has been an increase in mucormycosis cases during the coronavirus disease 2019 (COVID-19) pandemic, with rhino-orbital-cerebral mucormycosis being the most common form. Early diagnosis and treatment of mucormycosis are critical for successful treatment outcomes. Hypoxia, hyperglycemia, and steroid use were all significant risk factors in patients infected with COVID-19.1,2 Treatment of mucormycosis focuses on reversing risk factors, antifungal therapy, and extensive surgical debridement. It is prudent to ensure adequate doses of antifungal are given and proper debridement is done to avoid devastating complication such as blindness, organ dysfunction, loss of specific organ tissue, or even death.

Case Report
A 42-year-old Bangladeshi man with type 2 diabetes complained of left facial swelling and pain, headache, cough, and nasal congestion for 1 month. A few days after the onset of symptoms, he was diagnosed with COVID-19 by rapid antigen testing and then underwent a 10-day home isolation without corticosteroid therapy. He sought medical attention at Hospital Selayang in Malaysia after his symptoms did not improve after two weeks. He worked in a supermarket and had spent the previous 7 years in Malaysia, with no recent travel history. On examination, he was afebrile with a blood pressure of 136/89 mmHg, and his pulse rate was 105 beats/min. His respiratory rate was 20 breaths/min, and the oxygen saturation was 92% while breathing ambient air. He had a periorbital swelling on the left side. There was no conjunctivitis, proptosis, or ophthalmoplegia, and bilateral visual acuity, color vision, and fundus examinations were normal. An oral examination revealed the presence of an ulcer with irregular margins and black eschar on the left palate (Figure 1). Auscultation of the lungs revealed bibasal crackles.

The initial laboratory tests were within normal ranges. Chest radiography showed lung infiltrates in the bilateral lower zones. During this admission, a nasopharyngeal swab was taken in which SARS-CoV-2 was detected using the RT-PCR method (Ct values: RDRP = 25.8, N = 22.5, E = 20.56). He was given dexamethasone 6 mg once daily and supplemental oxygen through a nasal cannula. The sputum culture was negative for fungal organisms. He responded well and was weaned off supplemental oxygen two days later. Glycemic control was optimized with insulin therapy. Because the presence of palatal eschar raised the possibility of mucormycosis, intravenous amphotericin B deoxycholate (1 mg/kg) was started.

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on the same day of admission. A CT scan of the paranasal sinuses revealed soft tissue densities with local invasion in the bilateral ethmoid, bilateral maxillary, bilateral sphenoid, and left frontal sinuses (Figure 2). The left lateral rectus, medial rectus, inferior rectus, and superior oblique muscles, as well as the left optic nerve were thickened with enhancement. The brain CT scan was normal, and the thoracic CT scan revealed patchy ground-glass opacities in both lung fields and consolidative changes in the dependent regions.

Rigid nasal endoscopy revealed crusts on the medial aspect of the left inferior turbinate with an intact nasal septum. The necrotic tissue was removed endoscopically, and tissue biopsy was performed in the same setting. Histopathological examination revealed fungal organisms with broad ribbon-like hyphae, few septations, and rare irregular branching, consistent with *Mucor* spp. (Figure 3). Sporangia were present, but there was no definite angioinvasion on examination. The periodic acid–Shiff and Grocott’s methenamine silver stains were both positive for the fungal organisms. The diagnosis of rhino-orbital mucormycosis was made, but fungal culture and PCR came back negative.

**Figure 1.** An ulcer with irregular margins and black eschar on the left palate.

**Figure 2.** CT showing soft tissue densities in (a) bilateral ethmoid and sphenoid sinuses and (b) bilateral maxillary sinuses (more severe on the left side).

**Figure 3.** Histopathological examination (a) broad ribbon-like hyphae (black arrow) (H&E stain, x400 magnification), (b) the hyphae showing irregular branching (green arrow) and occasional septation (red arrow) (PAS stain, x400 magnification), and (c) appearance of a sporangium (H&E stain, x400 magnification).
Endoscopic debridement of necrotic tissue and nasal toileting were performed on multiple occasions. He received intravenous amphotericin B for a total of 6 weeks at our hospital, which resulted in a significant improvement in his symptoms. He then returned to his home country to continue his treatment.

**Discussion**

Mucormycosis is a rare fungal infection caused by the fungi of order Mucorales. Mucorales species most frequently recovered from clinical specimens include Rhizopus (the most common genus associated with mucormycosis), Lichtheimia and Mucor, while species of other Zygomycetes genera, namely, Rhizomucor, Saksenaea, Cunninghamamella, and Apophysomyces, are relatively less common. Diabetes, with or without diabetic ketoacidosis, hematological, and solid organ malignancies, transplant recipients (hematopoietic stem cell and solid organ transplants), corticosteroid therapy, and neutropenia are all major risk factors for mucormycosis. There has been an increase in the number of cases of mucormycosis in patients with COVID-19 and a multicentre study in India found a 2.1-fold rise in mucormycosis during the COVID-19 pandemic compared to the previous year. Furthermore, COVID-19-associated mucormycosis was found in 187 of 287 (65%) mucormycosis patients. The main factors promoting Mucorales growth in COVID-19 appear to be hypoxia, which creates an ideal environment for the fungi; hyperglycemia, which could be due to underlying diabetes mellitus or steroid induced; elevated ferritin levels; and a weakened body immune system, which leads to impaired phagocytic activities of the leucocyte due to steroid use or a prolonged hospital stay.

Mucormycosis is divided into six types based on anatomic location: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and uncommon presentations (endocarditis, osteomyelitis, peritonitis, and pyelonephritis). In COVID-19 patients, rhino-orbital-cerebral mucormycosis (ROCM) is the most common presentation, followed by pulmonary mucormycosis. Mucormycosis was suspected in our case because the patient had facial swelling and pain, as well as nasal congestion and the presence of an upper palatal ulcer with eschar. Patients with mucormycosis may experience facial numbness or edema as a result of involvement of the maxillary, frontal, or ethmoidal paranasal sinuses. Mucormycosis with palatal involvement can cause an ulcer on the upper palate, toothache, maxillary tooth loosening, and restriction of jaw movement. Patients with suspected ROCM should be evaluated for blurred vision or diplopia, as well as orbital pain, proptosis, or paresthesia, as these may indicate orbital invasion. Revannavar et al. reported a case of orbital apex syndrome with brain infarction in a patient with non-ketotic diabetes and COVID-19. The patient presented with a brief history of left facial pain, which was similar to our patient’s. In addition, this patient had sudden onset complete left eye ptosis. This demonstrated that mucormycosis is a very aggressive disease, and early detection is critical to allow for early treatment to avoid further complications.

Mucormycosis is difficult to diagnose clinically and necessitates a high level of clinical suspicion. Early detection and treatment of mucormycosis are critical because they can improve patient outcomes. In this present case, COVID-19 was confirmed by RT-PCR detection of SARS-CoV-2. The presence of clinical and imaging findings consistent with mucormycosis led to the clinical diagnosis of COVID-19 associated mucormycosis. In our case, the definitive diagnosis of mucormycosis was established following the detection of Mucor spp. by histopathological examination of the nasal cavity tissue. The characteristic hyphae of Zygomycetes were seen in this case, which were broad, ribbon-like, and predominantly asperate with wide-angle branching.

Treatment of mucormycosis requires a multidisciplinary approach that includes reversing the underlying risk factors, effective antifungal therapy, and surgical debridement of the affected tissues. Amphotericin B, posaconazole, and isavuconazole are effective antifungals against mucormycosis. Early antifungal therapy with amphotericin B has been shown to improve survival. The duration of treatment for patients with mucormycosis should be individualized, and antifungal therapy should be continued until all clinical, laboratory, and imaging findings have resolved and immunosuppression has been reversed. As mentioned, surgical debridement is often necessary and adequate resection of the margins is of paramount importance. In view of resultant severe defects following debridement in some of the cases, reconstruction surgery is usually required to protect vital structures and to restore blood circulation in the diseased area allowing sufficient drug penetration of antifungal therapy through the blood supply. In a case series reported by Mette et al., four patients with rhinocerebral mucormycosis underwent aggressive wound debridement with combination of antifungal therapy and hyperbaric oxygen therapy followed by early reconstructive operation. The outcome was successful with no relapse of mucormycosis or flap failure.

**Conclusions**

We report, to the best of our knowledge, the first case of COVID-19 associated rhino-orbital mucormycosis in Malaysia. There is no doubt that mucormycosis cases are becoming more common in this COVID-19 era due to the widespread use of steroids in these patients. Clinicians should be vigilant in identifying mucormycosis in COVID-19 patients with compatible clinical presentations.

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**Author Contributions**

C.Y.C. and Y.L.G. collected data and drafted the manuscript. F.I.Z. performed histopathological examination and provided relevant images. A.P.R. critically reviewed the manuscript and prepared the final draft.

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Data Availability
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