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Two Adults with Rhinosinusitis Fungal Infection Post COVID-19 in A Lebanese Hospital: Case Report

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a newly-emerging viral illness, affecting primarily the respiratory tract, that has been linked to the occurrence of severe opportunistic fungal and bacterial infections. The incidence of fungal infection increases in patients infected with COVID-19 due to the use of corticosteroids and the accompanying uncontrolled hyperglycemia. We report two cases of acute invasive fungal rhinosinusitis (AIFR): Mucormycosis and Aspergillosis (cases 1 and 2 respectively), diagnosed radiologically and histopathologically. Both cases were treated by a combination of medical treatment and surgical debridement. The first patient improved and was discharged home, while there was a delay in the operation for the second patient who passed away. It is important to raise efforts to adjust hyperglycemia and limit the excessive systematic use of steroids during COVID pandemic to reduce fungal infections.

Keywords: *COVID-19, Mucormycosis, Aspergillosis, Fungal Infection*

Introduction

COVID-19, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus), is a viral illness affecting mainly the respiratory tract, which is now considered to be a global health issue. The infection is associated with several symptoms of varying degrees of severity ranging from mild (cough, fever, and myalgia), to severe (dyspnea, acute respiratory syndrome ARDS) and life-threatening pneumonia (Mohammadi *et al*., 2021; Mehta and Pandey, 2020). Furthermore, fungal infections of different types and severity are being increasingly reported in association with this virus. Candida spp. and Aspergillus spp. have been found to be the most common fungal pathogens associated with COVID-19 infection (Singh *et al*., 2021).

Mucormycosis is an angioinvasive fungal infection caused by mold fungi belonging to the genus Rhizopus, Mucor, Rhizomucor, Cunninghamella, and Absidia. Accounting for about 60% of mucormycosis cases as well as 90% of rhino-orbital-cerebral disease, the Rhizpus oryzae constitutes the most common

type (Singh *et al*., 2021). This uncommon fatal infection affects mainly immunocompromised and diabetic patients. The two most important clinical forms of this infection are rhino-orbital-cerebral and pulmonary infections (Nambiar *et al*., 2021). Aspergillosis is another kind of fungal infection which occurs in patients with severely impaired immune systems such as prolonged neutropenia, human immunodeficiency virus (HIV)/Acquired immunodeficiency syndrome (AIDS), bone marrow transplant (BMT) recipients, as well as solid organ transplant patients (Hoyek *et al*., 2022).

Reviewing the literature from Lebanon, we found one published case report of rhinocerebral mucormycosis, but no published articles concerning rhinosinusitis due to aspergillosis post COVID-19 infection.

Case Presentation

Case 1

A 45-year-old previously healthy male patient transferred to our hospital for swelling over the right eye with ophthalmoplegia and headache. His past medical history was relevant for COVID-19 infection for which he was treated in another hospital, where he received steroids and was reported to have persistently high glucose readings. One month after his discharge, the patient started having new-onset right-sided facial swelling, so he presented to a second hospital, where a computed tomography (CT) scan of the brain was ordered and revealed the presence of right-sided maxillary sinusitis. A biopsy of the right maxillary sinus was taken and was positive for mucormycosis, however a description of the type of species was not provided. The patient was then transferred to our hospital for treatment. Upon presentation to our hospital, the patient's vitals were within normal limits. Physical examination revealed swelling in the right periorbital area with redness. Initial laboratory investigations are shown in (Table 1). His HbA1C (hemoglobin A1c) was high (9.4%).

Table 1: Result of lab test done upon admission (Case 1).

	WBC	Neutro	lympho	Hb	Hct	PLTS	BUN	creat	CRP	HbA1C
Normal value	4-11 k/µL	40-65%	25-40%	13-16 g/dl	40-54%	140-440 k/µL	8-20 mg/dl	0.6-1.3 mg/dl	0-1 mg/dl	4.5-6.3%
Patient	9.6	80.60%	9.30%	12	35.1	257	6	0.4	9.1	9.4

WBC: white blood cell count; neutro: neutrophils percentage; lympho: lymphocytes percentage; hb: hemoglobin; hct: hematocrit; PLTS: platelet count; BUN: blood urea nitrogen; creat: creatinine level; CRP: C-reactive protein; HbA1C: hemoglobin A1c

Immediately upon admission, the patient was started on intravenous (IV) Liposomal Amphotericin B at a dose of 5mg/kg/day. The next day, a magnetic resonance imaging (MRI) of the brain was performed and revealed total opacification of the right ethmoid cells extending to the orbital floor and to the right maxillary sinus invading the right inferior rectus muscle (Fig. 1). On the third day of

admission, the patient underwent his first surgical intervention, where a right maxillectomy with right optic nerve decompression was done (Fig. 2). IV Caspofungin was added on the fourth day for synergistic effect, at a loading dose of 70 mg intravenously, followed by 50 mg IV once daily thereafter.

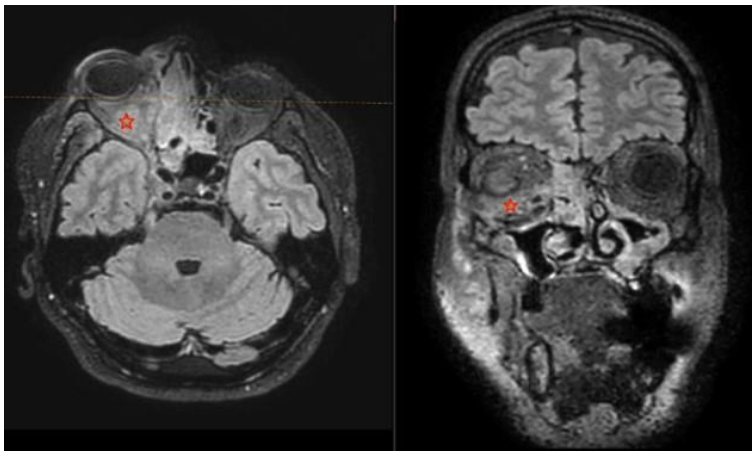

Figure 1: MRI brain for Case 1 (at presentation): The stars represent in the infection infiltrating the right orbital floor and the right inferior rectus muscle associated with air pockets (noted on the Coronal FLAIR image represented by the dark dots) and exophthalmos.

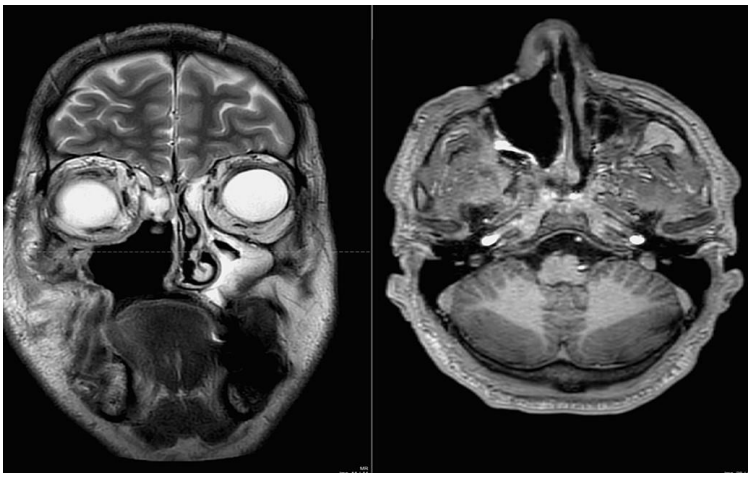

Figure 2: MRI brain for Case 1 (after surgical debridement).

The second surgery involved sinus and nerve debridement, and was performed on day 14. The third and last surgical procedure was performed on day 27, where a muscle and cutaneous flap were done. On day 30 of treatment, Liposomal Amphotericin B liposomal amphotericin B became unavailable in our hospital due to a nationwide shortage, so our patient was switched to Posaconazole at a dose of 300 mg orally twice daily for two doses, then 300 mg orally once daily. A follow-up MRI of the brain was performed towards the end of treatment course and showed total resolution of inflammatory findings. The patient was discharged after six weeks of antifungal treatment, and three surgical debridement procedures.

Case 2

A 74-year-old male patient presented to the emergency room for left-sided facial and orbital swelling, eye prominence, reduced vision in his left eye, headache and ophthalmoplegia. The patient was known to have type II Diabetes Mellitus, Hypertension, and heart failure on pace maker (PM). He was diagnosed with COVID-19 infection three weeks prior to presentation, and was treated by IV corticosteroids in another hospital. He also received treatment with acyclovir for the facial swelling, but had no improvement. Upon presentation to our Emergency Department, vitals showed a temperature of 36.9°C, a heart rate of 63 bpm, a blood pressure of 150/60 mmHg and an oxygen saturation of 95% on room air. Physical exam revealed edema in the left periorbital region with erythema and soft tissue necrosis. Initial laboratory investigations are showed in (Table 2). His HbA1C was 8.9%.

Table 2: Result of lab test done upon admission (Case 2).

	WBC	Neutro	lympho	Hb	Hct	PLTS	BUN	creat	CRP	HbA1C
Normal value	4-11 k/µL	40-65%	25-40%	13-16 g/dl	40-54%	140-440 k/µL	8-20 mg/dl	0.6-1.3 mg/dl	0-1 mg/dl	4.5-6.3%
Patient	10.3	89%	8.90%	13.1	39.7	190	8.7	0.61	4.8	8.9

WBC: white blood cell count; neutro: neutrophils percentage; lympho: lymphocytes percentage; hb: hemoglobin; hct: hematocrit; PLTS: platelet count; BUN: blood urea nitrogen; creat: creatinine level; CRP: C-reactive protein; HbA1C: hemoglobin A1c

CT scan of the brain was done and showed left retro-orbital inflammation, soft tissue edema, and left maxillary sinusitis with no masses nor abscesses. At this point, the patient was clinically suspected of having mucormycosis. Taking into consideration the probable delay in performing MRI due to the presence of a pacemaker, he was empirically started on IV Liposomal Amphotericin B (5 mg/kg/day), as to prevent any delay in treatment. After disabling the pacemaker, MRI of the brain was done (Fig. 3-4), demonstrating significant necrotic changes in the left ethmoid cells, sphenoid and maxillary sinuses, extending to left inferior frontal and the left temporal lobes, thus confirming the diagnosis of invasive fungal disease.

Alongside Liposomal Amphotericin B, Caspofungin at a loading dose of 70 mg IV followed by 50 mg IV once daily thereafter, was added to the treatment regimen, aiming for synergistic effect. Twelve days after admission, surgical debridement was done with left maxillectomy, orbital decompression, sinusotomy, left eye evacuation (Fig. 5).

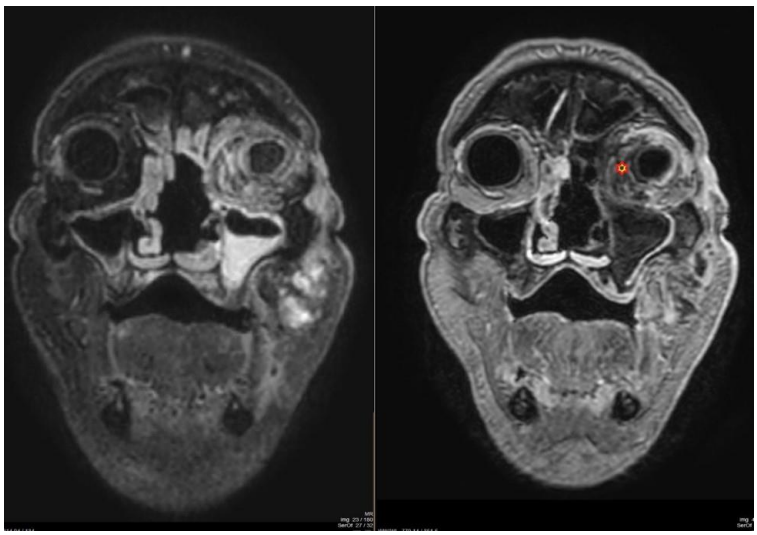

Figure 3: MRI brain for Case 2 (at presentation): The star indicates the left intra-orbital extension of the infection associated with exophthalmos.

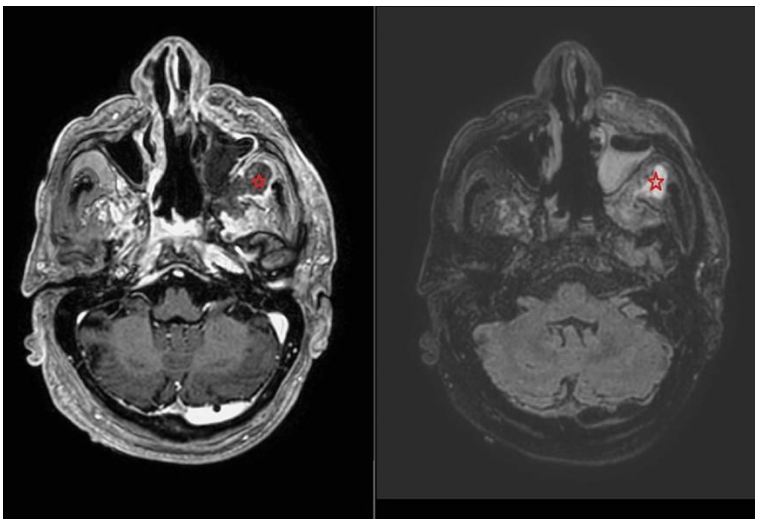

Figure 4: MRI brain for Case 2 (at presentation): The star represents a small collection deep to the left zygomatic arch.

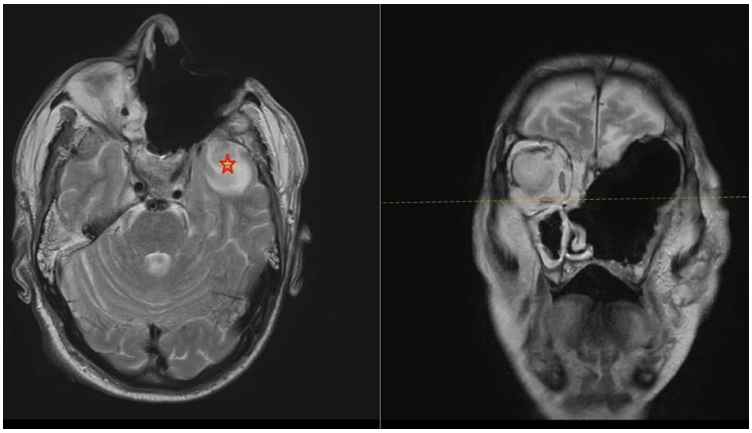

Figure 5: MRI brain of Case 2 (after debridement). The star indicates the increase in the size of the left temporal lesion.

An intraoperative biopsy was taken, which later demonstrated presence of Aspergillus fumigatus pathogen. Unfortunately, twelve days after initiating treatment, Liposomal Amphotericin B became unavailable, and the patient had to be switched to oral Posaconazole as an alternative. Voriconazole was also, unfortunately, not available. Our patient's clinical course was complicated by pleural effusions and respiratory distress, which necessitated the admission to an intensive care unit. Eventually, he was intubated, and passed away after few days.

Discussion

Mucormycosis is a fungal infection caused by ubiquitous molds (found in soil and vegetation) belonging to the Mucoraceae family such as Rhizomucor pusillus, Rhizopus arrhizus, Lichtheimia corymbifera, and Apophysomyces variabilis. Symptoms are variable depending on the affected site, and they range from headache, nasal congestion, facial edema, infarction and black eschar of the nose and palate (Roushdy and Hamid, 2021). Tissue culture, direct testing, radiological and histopathological identification of organism, by microscopic observation of hyphae, confirm the diagnosis of mucormycosis (Singh *et al*., 2021; Roushdy and Hamid, 2021). Treatment of this infection consists of a combination of surgical debridement and antifungal medication namely Liposomal Amphotericin B at a recommended dose of 5 mg/kg/day (Bhatia, 2022).

Aspergillosis is an opportunistic fungal infection caused by various Aspergillus species, such as Aspergillus niger, Aspergillus terreus, Aspergillus flavus, and Aspergillus fumigatus, the latter being the most frequently-encountered, in addition to being responsible for serious life-threatening infections. Rhino-sinusitis and pulmonary aspergillosis are the most commonly affected sites of invasive aspergillosis (Tabarsi *et al*., 2022; Jain and Taneja, 2021). Early diagnosis of invasive aspergillosis by imaging (CT or MRI) and histological examination, typically displaying hyphae that branch at 45 angle, can improve prognosis and decrease morbidity rate (Jain and Taneja, 2021). Combination of antifungal medication and surgical debridement is needed. Voriconazole is recommended as a first-line therapy for Invasive Aspergillosis as it was demonstrated to be superior to Liposomal Amphotericin B in this type of fungal infection (El-Kholy *et al*., 2021).

Acute invasive fungal rhinosinusitis (AIFRS), increasingly being reported post COVID-19 infection in various countries around the world including Iran, USA, Tunisia, India, Australia, Turkey, and the United Kingdom (Tabarsi *et al*., 2022; Ismaiel *et al*., 2021), has been notably associated with frequent use of steroids, DM, liver and renal failure, and immunosuppression (Ismaiel *et al*., 2021). This form of infection has been reported to have high morbidity and mortality rates (18-80%) (El-Kholy *et al*., 2021). Mucor and aspergillus are the two pathogens most commonly affecting patients (El-Kholy *et al*., 2021;

Ismaiel *et al*., 2021; Baghel *et al*., 2022). The most frequently encountered symptoms are facial pain, headache, ophthalmoplegia (Tabarsi *et al*., 2022; El-Kholy *et al*., 2021; Baghel *et al*., 2022). Uncontrolled diabetes and hyperglycemia caused by the use of corticosteroids during COVID-19 infection presents a predisposing factor for fungal infection (Garg *et al*., 2021).

Concerning COVID-19 associated mucormycosis (CAM), review of literature published till December 2021 shows that the most cases are found in India compared with the rest of world (Pal *et al*., 2021; Muthu *et al*., 2021), with a male predominance (Pal *et al*., 2021; Dilek *et al*., 2021). Rhino-orbital mucormycosis was the most documented clinical presentation followed by rhino-orbital-cerebral and pulmonary mucormycosis (Pal *et al*., 2021; Dilek *et al*., 2021). The mortality rate ranged between 30-40% (Pal *et al*., 2021; Dilek *et al*., 2021) and was as high as 49%, as reported in the case series review, which was attributed to patients diagnosed with having disseminated infection, cerebral involvement, or pulmonary mucormycosis (Hoenigl *et al*., 2022). An improvement in clinical outcome was observed when a combination of medical treatment and surgery was utilized (Pal *et al*., 2021).

In our reported cases, both of the patients were males. The patient in the second case was a known diabetic, nonetheless uncontrolled, whereas the patient in the first case was an undiagnosed diabetic, and the two of them were found to have an elevated HbA1c. Similarly, they both had a previous COVID-19 infection treated by steroids and presented with headache, ophthalmoplegia. Comparably, our cases were compatible with the available current literature. Concerning treatment, both patients received a combination of medical (Liposomal Amphotericin B) and surgical treatment, with delayed surgical debridement in patient 2 leading to death. This result is in line with what was reported in other studies showing the importance of a combination between medical and early surgical debridement in reducing mortality rate.

Conclusion

COVID-19 is associated with several bacterial and fungal infections that may be fatal, such as mucormycosis and Aspergillosis. This relationship is due to the widespread use of steroids without considering uncontrolled diabetes and the immunity status of these patients. Our cases highlight the importance to adjust hyperglycemia early in the course of Covid-19 treatment. They also raise the awareness of Clinicians on the potential for acute invasive fungal rhinosinusitis (AIFRS) and rhino-cerebral mucormycosis especially in diabetic patients and thus encourage the rationalization in the systematic use of steroids during COVID pandemic according to the recommended doses by World Health Organization (WHO). An early diagnosis and treatment will likely reduce morbidity and mortality.

References

Baghel SS, Keshri AK, Mishra P, Marak R, Manogaran RS, Verma PK, Srivastava AK, Kumar R, Mathialagan A, Bhuskute G, Dubey AK, Dhiman RK. The Spectrum of Invasive Fungal Sinusitis in COVID-19 Patients: Experience from a Tertiary Care Referral Center in Northern India. *J Fungi (Basel)* 2022; 8: 223.

Bhatia M. The rise of mucormycosis in Covid-19 patients in India. *Expert Rev Anti Infect Ther* 2022; 20: 137-138.

Dilek A, Ozaras R, Ozkaya S, Sunbul M, Sen EI, Leblebicioglu H. COVID-19-associated mucormycosis: Case report and systematic review. *Travel Med Infect Dis* 2021; 44: 102148.

El-Kholy NA, El-Fattah AMA, Khafagy YW. Invasive Fungal Sinusitis in Post COVID-19 Patients: A New Clinical Entity. *Laryngoscope* 2021; 131: 2652-2658.

Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, Puri GD, Chakrabarti A, Agarwal R. Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): Case Report and Systematic Review of Literature. *Mycopathologia* 2021; 186: 289-298.

Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, Nasir N, Bonifaz A, Araiza J, Klimko N, Serris A, Lagrou K, Meis JF, Cornely OA, Perfect JR, White PL, Chakrabarti A; ECMM and ISHAM collaborators. The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. *Lancet Microbe* 2022; 3: e543-e552.

Hoyek NE, Ghorayeb J, Daou I, Jamal D, Mahfoud N, Nawfal G. A post-COVID-19 Aspergillus fumigatus posterior mediastinitis: Case report. *SAGE Open Med Case Rep* 2022; 10: 2050313X221081386.

Ismaiel WF, Abdelazim MH, Eldsoky I, Ibrahim AA, Alsobky ME, Zafan E, Hasan A. The impact of COVID-19 outbreak on the incidence of acute invasive fungal rhinosinusitis. *Am J Otolaryngol* 2021; 42: 103080.

Jain A, Taneja S. Post-COVID fungal infections of maxillofacial region: a systematic review. *Oral Maxillofac Surg* 2021; pp. 1–7.

Mehta S, Pandey A. Rhino-Orbital Mucormycosis Associated With COVID-19. *Cureus* 2020; 12: e10726.

Mohammadi F, Badri M, Safari S, Hemmat N. A case report of rhino-facial mucormycosis in a non-diabetic patient with COVID-19: a systematic review of literature and current update. *BMC Infect Dis* 2021; 21: 906.

Muthu V, Rudramurthy SM, Chakrabarti A, Agarwal R. Epidemiology and Pathophysiology of COVID-19-Associated Mucormycosis: India Versus the Rest of the World. *Mycopathologia* 2021; 186: 739-754.

Nambiar M, Varma SR, Damdoum M. Post-Covid alliance-mucormycosis, a fatal sequel to the pandemic in India. *Saudi J Biol Sci* 2021; 28: 6461-6464.

Pal R, Singh B, Bhadada SK, Banerjee M, Bhogal RS, Hage N, Kumar A. COVID-19-associated mucormycosis: An updated systematic review of literature. *Mycoses* 2021; 64: 1452-1459

Roushdy T, Hamid E. A case series of post COVID-19 mucormycosis-a neurological prospective. Egypt J Neurol Psychiatr Neurosurg 2021; 57: 100.

Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr* 2021; 15: 102146.

Tabarsi P, Sharifynia S, Pourabdollah Toutkaboni M, Abtahian Z, Rahdar M, Mirahmadian AS, Hakamifard A. Coinfection by Aspergillus and Mucoraceae Species in Two Cases of Acute Rhinosinusitis as a Complication of COVID-19. *Case Rep Med* 2022; 2022: 8114388.