Print ISSN: 2321-6379
Online ISSN: 2321-595X

Case Report

A Case Series on Mucormycosis as Post - Coronavirus Disease 2019 Sequelae in Two Diabetic Patients

Neela Sunuwar[1], Anu Radha Twayana[2], Santosh Katuwal[1], Sudeep Yadav[3], Sagar Ghimire[4], Suraj Shrestha[5], Bibek Man Shrestha[5], Sansar Babu Tiwari[6]

[1]MBBS Graduate, BP Koirala Institute of Health Sciences, Dharan, Nepal, [2]MBBS Graduate, Kathmandu University School of Medical Sciences, Dhulikhel, Nepal, [3]Research coordinator, Division of Infectious Disease, University of Louisville, Kentucky, United States, [4]MBBS Graduate, Nepal Medical College Teaching Hospital, Kathmandu, Nepal, [5]Intern, Maharajgunj Medical Campus, Institute of Medicine, Kathmandu, Nepal, [6]MD, Department of Pathology, Maharajgunj Medical Campus, Institute of Medicine, Kathmandu, Nepal

Abstract

Background: Mucormycosis is a potentially deadly consequence of coronavirus disease 2019 (COVID-19) pneumonia. The most common contributory factors have been identified as uncontrolled diabetes and utilization of steroids. The inflammatory phenomena of severe COVID-19 necessitate the use of high-dose corticosteroids for treatment which instead even further lowers the immunity and increases the risk of various opportunistic infections. Mold enters the respiratory system through the nose and sinuses, then spreading to the orbital and cerebral tissues.

Case Report: A 44-year-old man known diabetic presented with features suggestive of COVID-19 and tested positive on oro-nasopharyngeal swab Reverse transcription polymerase chain reaction along with *Rhizopus* species isolation. A diagnosis of right rhino-orbital mucormycosis with COVID-19 pneumonia with diabetes was made. A multi-disciplinary approach of treatment was employed along with endoscopic debridement which significantly improved the patient's condition.

Conclusion: Clinicians should monitor patients with COVID-19 infection for mucormycosis. To avoid the risk of deadly mucormycosis, it is recommended that patients with COVID-19, especially those with diabetes, utilize corticosteroids sparingly and maintain optimum hyperglycemia.

Key words: Coronavirus disease associated mucormycosis, Long coronavirus disease, Rhino-orbital mucormycosis, *Rhizopus* species

INTRODUCTION

The usage of steroids in the treatment of coronavirus disease 2019 (COVID-19) can be a double-edged sword. While steroid treatment is widely regarded for its anti-inflammatory effect in combating cytokine storm against COVID-19-induced endothelium damage, it also poses a significant risk of *Rhizopus* invasion in patients with immunosuppression, particularly diabetics with uncontrolled diabetes.[1] *Rhizopus oryzae* is the most common fungus in humans, accounting for roughly 60% of mucormycosis cases and 90% of Rhino-orbital-cerebral infections.[2] Invasive fungal infections (IFIs) are caused by saprophytic environmental fungi–*Rhizopus* (most prevalent). Mucormycosis (formerly called Zygomycosis) can manifest itself in a variety of ways, including rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous manifestations.[3]

Mucormycosis in COVID has been demonstrated in numerous studies to be a dangerous combo. The findings are ground-breaking and have enormous public health implications, especially given the high mortality rate associated with mucormycosis. Mucormycosis intracranial involvement, in particular, increases the death rate to as high as 90%. Furthermore, the pace with which mucormycosis spreads is an exceptional phenomenon, and even a 12-h delay in diagnosis can be lethal, which is why 50 percent of

Access this article online

www.ijss-sn.com

Month of Submission : 06-2021
Month of Peer Review : 07-2021
Month of Acceptance : 07-2021
Month of Publishing : 08-2021

Corresponding Author: Neela Sunuwar, BP Koirala Institute of Health Sciences, Dharan, Nepal.

cases of mucormycosis have traditionally been diagnosed only in post-mortem autopsy series.[2]

Herein we present 2 cases of mucormycosis (rhino-orbital and orbital) who presented with eye swelling and pain while being treated for COVID pneumonia. A long history of diabetes combined with COVID-19 pneumonia and steroid use in both of the patients probably predisposed them to opportunistic infection by *Rhizopus* species. The primary goal of this case series is to highlight the need for judicious use of steroids especially in diabetics and the need for medical vigilance for early diagnosis and timely instigation of treatment which would aid in combating fatal consequences of COVID associated mucormycosis.

CASE REPORT

Case 1

A 58-year old man with a longstanding history of uncontrolled diabetes came to the emergency for sudden onset of diminution of vision along with a history of right-sided eye pain and swelling. He was recovering from COVID when he suddenly developed an impairment of vision. An immediate potassium hydroxide (KOH) mount was prepared which showed broad, hyaline aseptate hyphae with wide-angle branching [Figure 1]. Furthermore, radiological evaluation with computed tomography and magnetic resonance imaging (MRI) was ordered which revealed features suggestive of fungal invasion. MRI revealed T1 low and T2 high intensity over bilateral nasal cavity, bilateral maxillary, ethmoid and sphenoid cavity as well as a mucosal thickening in the bilateral frontal sinus. The enhancement in retro-orbital fat and soft tissue of right orbit and right lateral rectus muscle suggestive of post-septal cellulitis due to contiguous spread of fungal infection to the right orbit [Figure 2].

Case 2

A 44-year-old man with long-standing diabetes mellitus, hypertension, and acute coronary syndrome presented with 7 days of fever, dry cough, and progressive breathlessness. He was diagnosed with type 2 diabetes mellitus 10 years ago and has been taking oral hypoglycemic drugs irregularly and Amload 5 mg once daily at night before a meal for the last 5 years. The patient is an occasional smoker and consumes alcohol socially.

On admission, the respiratory rate was 26 breaths/min, blood pressure 150/90 mmHg, and heart rate of 82 beats/min. The oxygen saturation was 84% at room air and improved to 95% with a nasal cannula. Examination revealed bilateral crepitations on auscultation. Blood

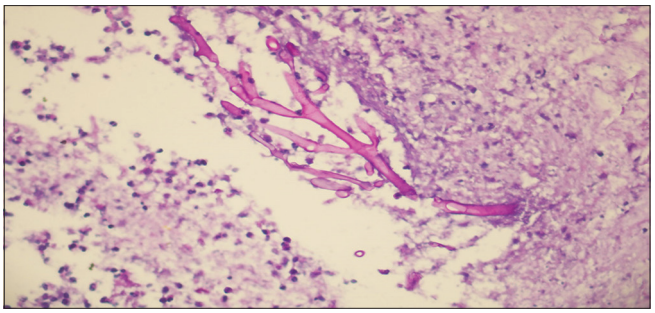

Figure 1: Broad, hyaline aseptate hyphae with branching on KOH mount

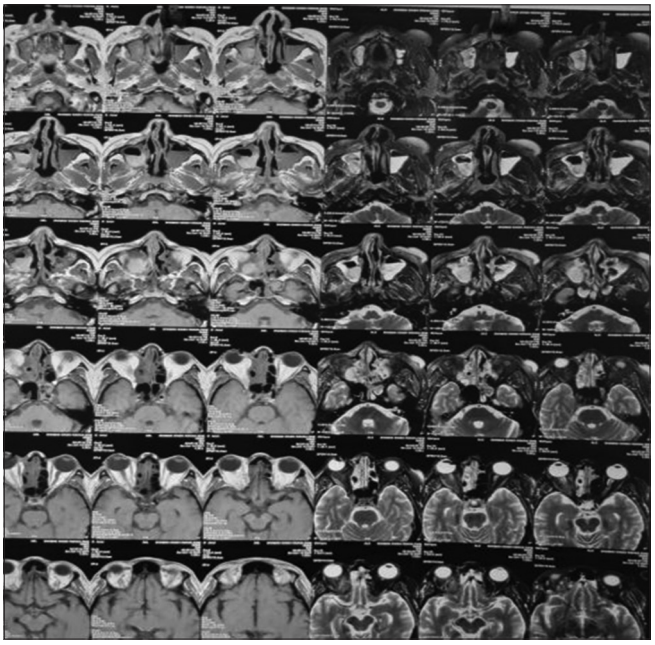

Figure 2: Radiological evidence of hyperintensity over bilateral nasal cavity, bilateral maxillary sinus, ethmoid and sphenoid with spread to the retro-orbital fat and right orbital area

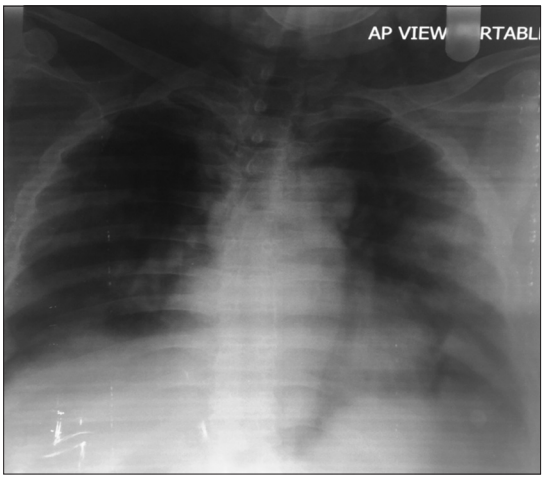

Figure 3: Chest X-ray showing bilateral infiltrates suggestive of pneumonia

investigations and Chest radiograph were ordered which showed bilateral diffuse interstitial opacities [Figure 3].

An oro-nasopharyngeal swab was positive for severe acute respiratory syndrome coronavirus 2 by Reverse transcription polymerase chain reaction (RT-PCR). He was also started on intravenous Dexona (6 mg once a day for the next 14 days) and redmdesivir (200 mg state and 100 mg for the next 5 days). Supportive care, including oxygen supplementation, thromboprophylaxis for venous thrombosis were given. His random blood glucose at admission was 120 mg/dL and increased to a maximum of 250 mg/dL and hence a sliding scale regular insulin was administered as per protocol. After 7 days he showed a significant clinical improvement, decreased oxygen requirement, and radiological resolution.

14 days later, the patient reported swelling in the right eye along with retro-orbital pain. A repeat oro-nasopharyngeal swab was taken for RT-PCR which showed positive results and *Rhizopus* species were isolated. A broad hyaline aseptate hypha with branching was identified on a wet KOH mount [Figure 4]. Therefore a diagnosis of right rhino-orbital mucormycosis post-COVID-19 infection with Diabetes was made.

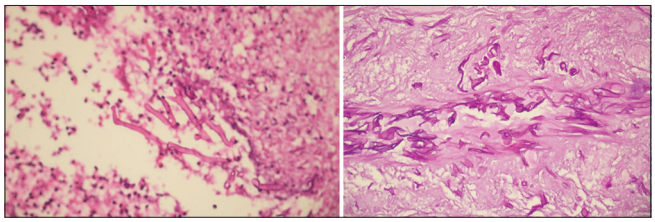

Figure 4: Histopathology of the patient showing aseptate hyphae with branching

A multimodal treatment approach was made with a referral to the Department of Ophthalmology and the Department of Head and Neck Surgery besides the usual COVID as per hospital protocol. Subsequently, an MRI was done which revealed a high-intensity lesion in the paranasal sinuses with extension to the orbital area and nasal cavity, as well as central non-enhancing areas suggestive of necrotic tissues, were evident. The right eyeball was slightly protruded with features suggestive of sinusitis and deviated nasal septum [Figure 5]. Features suspicious of invasive fungal sinusitis were present which included inflammatory changes in the orbital apex, inferior and medial rectus muscle with retro-orbital fat, and right infra-temporal fossa. Hence an endoscopic debridement via modified Denkler's approach was done which showed significant improvement in both of the cases. The patients were then discharged to home isolation and advised to follow up when needed.

DISCUSSION

Mucormycosis, also known as zygomycosis, is a rare and dangerous fungal infection that has a low incidence rate, ranging from 0.005 to 1.7 per million people. However, on the ongoing coronavirus pandemic, there has been a rise in many cases.[4] A study conducted by White *et al.* on 135 adults with COVID-19 infection reported an incidence of 26.7% for IFIs.[5] Subsequently, mucormycosis is a highly fatal condition surmounting to a global case fatality rate of 46%.[6] We reckon a combination of COVID-19 pneumonia with highly fatal mucormycosis will even add deadlier consequences.

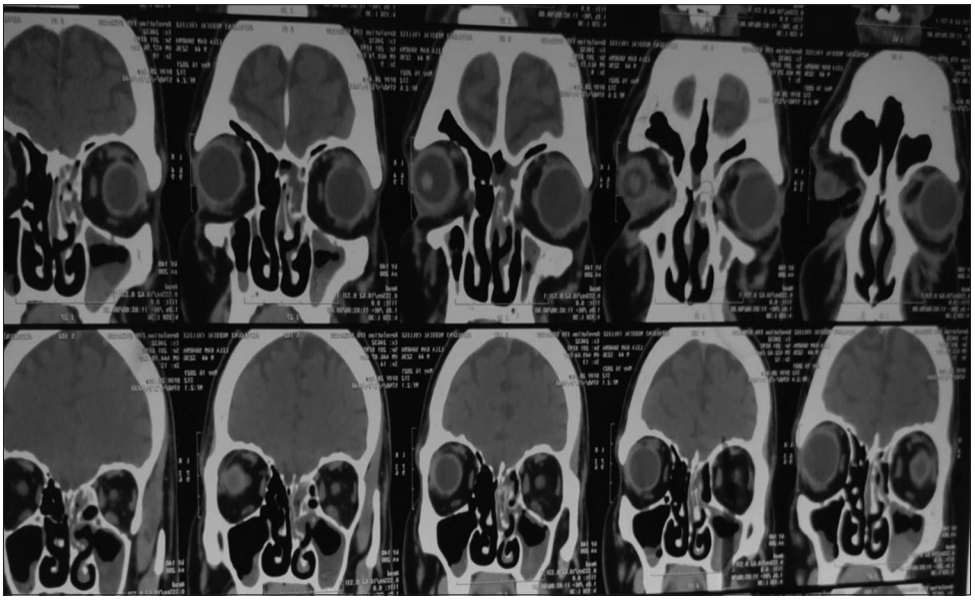

Figure 5: Heterogeneous T2/FLAIR high signal intensity with peripheral enhancement and central non-enhancing low signal intensity areas with patchy restriction in right maxillary and ethmoidal sinus. Axial, magnetic resonance imaging scans showing intra-orbital extension of mucormycosis

Mucormycosis is suspected if there is unilateral facial pain or swelling, orbital swelling, or proptosis. Tissue necrosis, a late sign, unfortunately, is the hallmark of mucormycosis, resulting from angioinvasion and vascular thrombosis.[7] In many situations, such as ours with COVID and diabetes, the steroid is started without regard for long-term implications, as it is deemed more important to address the life-threatening COVID-19-induced inflammation than the amount of immunosuppression. Furthermore, glucocorticoids are inexpensive, widely available, and have been shown to reduce mortality in hypoxemic patients with COVID-19. Multiple risk factors or concomitant conditions, particularly diabetes, in severe COVID-19 patients, raise the net state of immune suppression, predisposing them to invasive mold infections. In a recent review, 8% of coronavirus-positive or recovered patients had secondary bacterial or fungal infections during hospital admission, with the widespread use of broad-spectrum antibiotics and steroids.[8] Thus the development of mucormycosis can probably be attributed to the use of glucocorticoids.

Studies have shown a firm association between COVID-19 and increased fungal infections. There are various possible reasons for this association, including the immunosuppression caused by COVID-19 infection and disease process, or the extensive use of steroids and broad-spectrum antibiotics in the management of COVID-19. It is important to note that Diabetes Mellitus has been recognized as an important co-factor with COVID-19 in inducing mucormycosis infections. Despite a clear recommendation of steroid use for cases that require ventilators or supplemental oxygen by The National Institute of Health, according to the Randomised Evaluation of COVID-19 Therapy ("RECOVERY") Collaborative Group, the steroid is used rampantly even for milder cases.[1]

Mucormycosis is diagnosed primarily using histopathology, direct microscopy, and culture from clinical specimens. Preventing morbidity in this often fatal illness requires clinical suspicion and early surgical debridement.[7] However, the patient we present came to our department late in the disease as controlling COVID-induced life-threatening symptoms were being prioritized over glycemic control. A delay of even 6 days is associated with a doubling of 30-day mortality from 35% to 66% and hence early diagnosis and prompt management are usually advised.[6] On the contrary to the above statement, despite early diagnosis and aggressive combined surgical and medical therapy, the prognosis for recovery from mucormycosis is poor which makes the long COVID syndrome even more dangerous.[4]

Owing to the clinical suspicion and his COVID status a diagnosis of rhino-orbital mucormycosis post-COVID with diabetes was made after confirmation with an MRI and endoscopic tissue biopsy. Therefore he was managed according to the Song *et al.* management algorithm for COVID-19 associated with invasive fungal sinusitis which recommends surgical treatment whenever possible, as well as primary prophylaxis with posaconazole, and first-line treatment with liposomal Amphotericin B and oral posaconazole.[9] The patient was immediately commenced on Liposomal Amphotericin B (5 mg/kg/day) and Voriconazole (200 mg twice daily orally). In addition, glycemic control was achieved on time with sliding scale insulin thus helping in the early recovery of the patient. The favorable outcome in the current case was probably because of the better glycemic control in-hospital, and the timely initiation of liposomal amphotericin B. Studies have shown that amphotericin B is generally well-tolerated and can be safely administered in subjects.[10] Moreover, a study conducted on amphotericin use also reported delayed amphotericin B–based therapy (i.e., initiating treatment ≥6 days after diagnosis) can result in a 2-fold increase in mortality rate at 12 weeks after diagnosis, compared with early treatment (82.9% vs. 48.6%) which highlights the importance of early diagnosis and prompt treatment.[6] Once the diagnosis is considered and empiric antifungal treatment is started, a prompt surgical opinion should also be sought for better resolution and prevention of recurrence.[4] Similarly, a study was done in 2019 by the European Confederation of Medical Mycology (ECMM and Mycoses Study Group Education and Research Consortium strongly supports an early complete surgical treatment for mucormycosis whenever possible, in addition to systemic antifungal treatment.[11] The patient in our case also underwent endoscopic debridement twice with a significant improvement. Hence we can speculate mucormycosis has a good prognosis post-surgery when timely management is initiated.

CONCLUSION

Hyperglycemia control, early treatment with liposomal amphotericin B, and surgery are all necessary for successful mucormycosis care. Glucocorticoids should be avoided in mild COVID-19 cases (without hypoxemia) or at higher doses, with only judicious usage in severe and critical COVID cases.

REFERENCES

1. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post Coronavirus disease mucormycosis: A deadly addition to the pandemic spectrum. J Laryngol Otol 2021;135:442-7.
2. 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.

3. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, *et al*. Epidemiology and outcome of zygomycosis: A review of 929 reported cases. Clin Infect Dis 2005;41:634-53.
4. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. Am J Emerg Med 2021;42:264.e5-8.
5. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, *et al*. A national strategy to diagnose Coronavirus disease 2019-associated invasive fungal disease in the intensive care unit. Clin Infect Dis 2020:ciaa1298. Doi:10.1093/cid/ciaa1298.
6. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis 2008;47:503-9.
7. Spellberg B, Edwards J, Ibrahim A. Novel perspectives on mucormycosis: Pathophysiology, presentation, and management. Clin Microbiol Rev 2005;18:556-69.
8. Rawson TM, Moore LS, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, *et al*. Bacterial and fungal co-infection in individuals with Coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 2020;71:2459-68.
9. Song G, Liang G, Liu W. Fungal co-infections associated with global COVID-19 pandemic: A clinical and diagnostic perspective from China. Mycopathologia 2020;185:599-606.
10. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, *et al*. Coronavirus disease (COVID-19) associated mucormycosis (CAM): Case report and systematic review of literature. Mycopathologia 2021;186:289-98.
11. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SC, Dannaoui E, Hochhegger B, *et al*. Global guideline for the diagnosis and management of mucormycosis: An initiative of the European confederation of medical mycology in cooperation with the mycoses study group education and research consortium. Lancet Infect Dis 2019;19:e405-21.

How to cite this article: Sunuwar N, Twayana AR, Katuwal S, Yadav S, Ghimire S, Shrestha S, Shrestha PM, Tiwari SB. A Case Series on Mucormycosis as Post - Coronavirus Disease 2019 Sequelae in Two Diabetic Patients. Int J Sci Stud 2021;9(5):7-11.

Source of Support: Nil, **Conflicts of Interest:** None declared.