Mucormycosis: An Epidemic Complicating the Covid-19 Pandemic

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Received: 22 June 2021

Accepted: 24 November 2021

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DOI 10.5001/omj.2023.16

Abstract

The novel Coronavirus disease 2019 (COVID-19) infection is a relatively new disease whose complete pathogenesis and complications have still not been elucidated. Apart from the morbidity and mortality caused by the virus itself, it is being noted that patients affected with this virus have higher susceptibility to bacterial and fungal co-infections. Mucormycosis is a rare and life-threatening fungal infection generally associated with uncontrolled diabetes mellitus and immunosuppression. It tends to rapid disease progression and poor prognosis if not diagnosed and managed promptly. There has been a sudden increase in the number of mucormycosis cases in patients with moderate to severe COVID-19 infection in the past few months. Herein, we present a series of ten mucormycosis cases diagnosed over one week.

Keywords: Mucormycosis, COVID-19, fungal infection, corticosteroids

Introduction

The outbreak of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the later part of 2019 has rapidly turned into a catastrophe of global proportion and has burdened the healthcare system around the world. The novel SARS-CoV-2 is associated with a wide spectrum of disease patterns, ranging from mild disease to life-threatening conditions[1]. The complete pathogenesis and complications of this disease have still not been completely elucidated. Apart from the morbidity and mortality caused by the virus itself, it is being noted that patients affected with this virus have higher susceptibility to bacterial and fungal co-infections[2]. Secondary infections are known to occur in various viral illnesses, and SARS-CoV-2 is also associated with varied bacterial and fungal co-infections[3]. A magnitude of research has been conducted on SARS-CoV-2 and its management to curb the infections and manage the patients judiciously. Rampant use of drugs like corticosteroids, although helpful in restraining the disease progression and improve patient survival, have contributed to a surge in secondary bacterial and fungal infections[3].

There is increasing evidence pointing towards these secondary fungal infections in COVID-19 patients, especially those who are or were severely ill, patients with pre-existing comorbidities like diabetes mellitus (DM), previous parenchymal lung damage and immunocompromised states[4]. Of these secondary infections, there has been a sudden surge in the cases of mucormycosis in the past few months which has risen to the proportion of an epidemic in itself and is associated with an aggressive disease course with a poor prognosis. Mucormycosis is a rare, life-threatening fungal infection that has an established association with uncontrolled diabetes mellitus and immunosuppression[1]. Many emerging articles in the literature have established an association between mucormycosis and COVID-19, however, the research is yet to pinpoint whether this increased co-infection should be attributed to

infection per se or the management modalities like steroid usage and mechanical ventilation, implemented for its treatment [1-5].

A similar escalation of suspected mucormycosis cases was observed and herein, we present a series of ten cases of mucormycosis diagnosed over one week.

Cases

Herein, we compile ten suspected cases of mucormycosis from the head and neck region received in the department of Pathology for evaluation. The patients presented with one or more of the following symptoms: facial/ periorbital swelling, diminution of vision, ptosis, ophthalmoplegia, headache. All the cases were either presently COVID-19 positive or were recovered cases of COVID-19 (diagnosed on Reverse Transcription Polymerase Chain Reaction (RT-PCR)). We looked for a detailed clinical history, history of co-morbidities, medications received, steroid administration and oxygen requirement during the COVID-19 treatment. Routine blood investigations and level of inflammatory markers were noted. All the cases underwent computerized tomographic (CT) scan and three cases underwent additional magnetic resonance imaging (MRI) of the paranasal sinuses and/or brain.

Sample received for histopathological examination included simple surgical debridement, maxillectomy and orbital exenteration specimens. A thorough sampling of the specimens was done and was examined with Haematoxylin and eosin (H&E) and special stains: Grocott-Gomori's methenamine-silver stain (GMS) and periodic acid-Schiff (PAS).

Results

We received ten specimens with suspected mucormycosis in a week. Out of these, five cases were of rhino-orbital mucormycosis and five cases involved the paranasal sinuses. The age group ranged from 25 years to 70 years and included nine males and one female. Among the ten cases, six patients were COVID-19 positive on admission and four patients presented with

symptoms of mucormycosis after recovery from COVID-19. Of the ten patients, six were known diabetics and four did not have DM. Five patients had received steroids for management of their COVID-19 infection and four of the patients required oxygen support. C-reactive protein (CRP) levels were raised in all the patients, with five patients showing a marked increase in CRP. (Table 1)

Table 1: Details of the patients of mucormycosis with their clinicopathologic parameters

No	**Age**	**Gender**	**COVID status**	**Co-morbidities**	**Steroid administration**	**Oxygen**	**CRP (mg/L)**	**IL-6 (pg/mL)**	**Serum ferritin (ng/mL)**	**D-Dimer (µg/mL)**
1.	25	Male	Previously positive	No	No	No	20.00	NA	NA	NA
2.	51	Male	Positive	DM	Not known	Not known	182.4	32	1234	>20
3.	60	Male	Positive	DM	Not known	Not known	185.7	NA	NA	NA
4.	31	Male	Previously positive	DM	Yes	Yes	32	NA	NA	NA
5.	38	Male	Positive	No	Yes	Yes	135.9	115.9	560.6	1.06
6.	60	Female	Positive	No	Not known	No	198.3	495.4	1472	2.17
7.	42	Male	Previously positive	DM	Yes	No	11.43	NA	NA	NA
8.	70	Male	Positive	No	Not known	Not known	163.7	3.1	742	2.63
9.	40	Male	Positive	DM, IHD, Thyroid disorder	Yes	Yes	14.2	18.6	641.6	2.97
10.	35	Male	Previously positive	DM	Yes	Yes	86.41	26.1	439.4	1.31

(CRP: C-Reactive protein, DM: Diabetes mellitus, IHD: Ischaemic heart disease, NA-not available)

Histopathological examination of all the cases revealed broad, non-septate fungal hyphae with right-angled branching in extensive areas of infarction along with angioinvasion which is the hallmark finding of mucormycosis. Four cases also showed evidence of intraneural invasion, while five cases demonstrated perineural invasion by *Mucor*. The fungal load was high in the areas of necrosis. Fungal profiles were well-appreciated with PAS and GMS stains. Necrotizing granulomatous inflammation with formation of epithelioid cell granulomas, foreign-body type of giant cell histiocytes and lymphocytes surrounding the fungal balls were noted in seven of the cases. Few cases demonstrated bony invasion, with the presence of fungal hyphae in the inter-trabecular spaces. Infiltration of the muscle by the fungus was also identified in two cases. (Figure 1, 2)

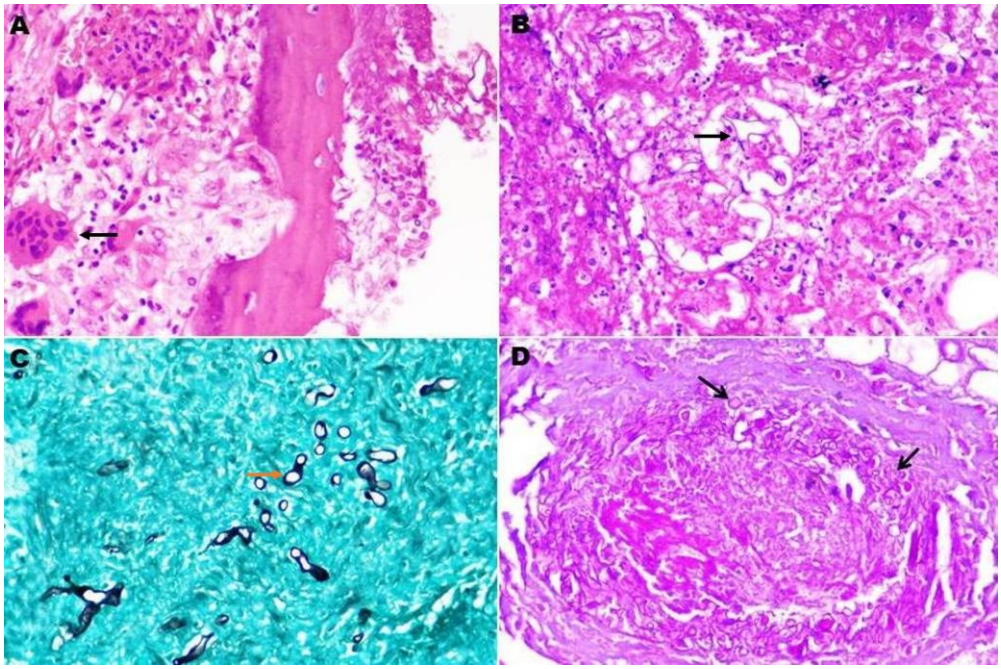

Figure 1: (A)Section showing epithelioid cell granuloma and foreign body giant cell reaction (black arrow) along with fungal hyphae (H&E, ×400). (B)Areas of necrosis along with broad fungal hyphae (black arrow) (H&E, ×400). (C)Necrotic soft tissue showing scattered fungal hyphae of *Mucor* (red arrow) (GMS, ×400). (D)Angioinvasion by fungal hyphae highlighted by special stain (black arrows) (PAS, ×400).

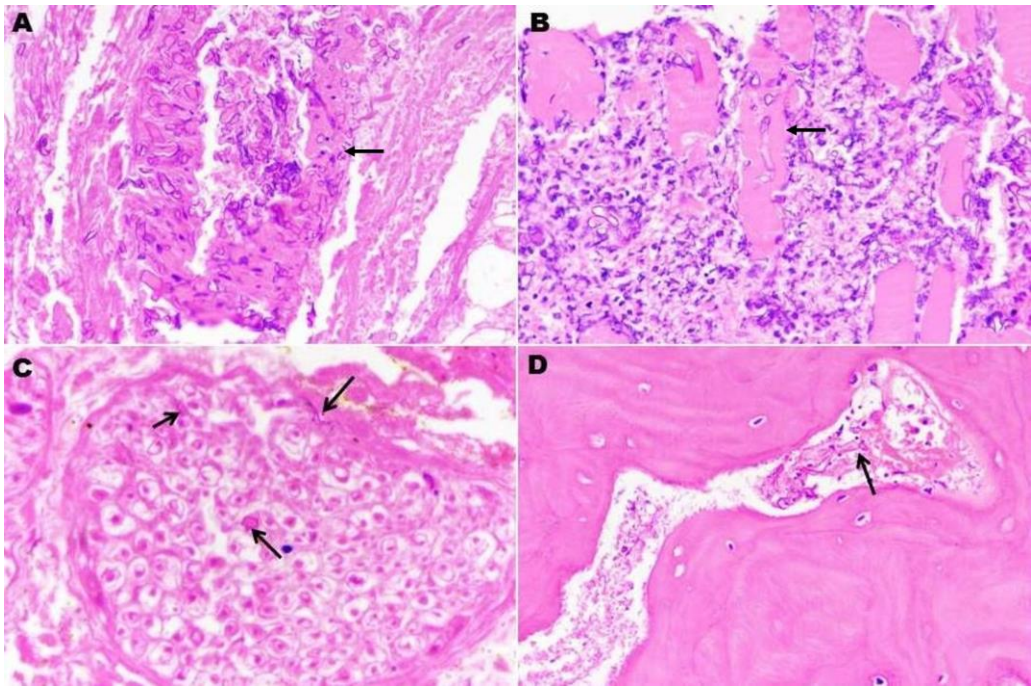

Figure 2: (A)Section showing angioinvasion by broad, aseptate fungal hyphae of *Mucor* species (black arrow) (H&E, ×400). (B)Infiltration of muscle by the fungal hyphae (black arrow) (H&E, ×400). (C)Segment of nerve showing intraneural invasion by broad, aseptate fungal hyphae (black arrows) consistent with *Mucor* species (H&E, oil immersion). (D)Bone invasion with presence of fungal hyphae in inter-trabecular space (H&E, ×400)

Discussion

Mucormycosis is a fungal infection caused by saprophytic fungi Mucoraceae, found in the decaying matter in soil, air and manure[5]. Mucormycosis has an incidence of 0.005 to 1.7 per million population with a global fatality rate of around 46%[2]. The most common presentation of mucormycosis is rhino-orbital-cerebral infection (44-49%)[6]. The entry of fungi is via inhalation into the nasal cavity and paranasal sinuses that can further invade into the orbit and brain via blood vessels and nerves. Other forms include cutaneous (10-19%), pulmonary (10-11%), disseminated (6-11%) and gastrointestinal (2-11%) mucormycosis[6]. Common risk

factors associated with the development of mucormycosis include uncontrolled diabetes mellitus, diabetic ketoacidosis, HIV/AIDS, iron overload and immunosuppressive therapies[5].

Usual presenting symptoms are fever, facial pain, headache, periorbital swelling, ophthalmoplegia and ptosis[6].

Diagnosis of mucormycosis requires a detailed history, physical examination and radiological imaging. A CT scan and MRI are essential diagnostic tools to identify involvement of sinuses, orbit, and brain invasion. Histopathological examination and microbiological cultures are gold standard for confirmation of mucor[6]. Histopathologically, these are seen as nonseptate, ribbon-like hyphae of variable width (6 to 50µm) with right-angle branching. The hallmark of mucormycosis on histopathology is the extensive tissue necrosis and infarction caused by angioinvasion and consequent thrombosis[9].

The treatment of choice accepted for mucormycosis is intravenous amphotericin B and surgical debridement[5]. Some other approved anti-fungal drugs include Posaconazole and Isavuconazole[9]. Isavuconazole being an extended-spectrum anti-fungal is used in the treatment of invasive mucormycosis.

Although an increased spurt of bacterial and fungal infections associated with COVID-19 have been reported across the globe, *Mucor*, in particular, has recently emerged as the most vicious of them all, infecting a large number of recovered and active COVID-19 patients in India. Patients are getting infected more in the later phase of COVID-19 infection[2]. These infections are more frequently seen in patients with severe symptoms of COVID-19 infection, those requiring admission to intensive care unit and mechanical ventilation. The mortality rate is also higher in COVID-19 cases with invasive fungal infection[2].

Many authors have pointed out that the increased association of mucormycosis with COVID-19 is attributed to various factors like immune suppression, steroid usage, and comorbidities.

There is also increasing evidence which points out the pathogenesis of COVID-19 infection which causes immune modulation and is playing a conducive role in the development of fungal infection[7].

Steroids are known immune-suppressive drugs and have beneficial effects in overcoming the hyper-inflammation and the subsequent cytokine storm associated with COVID-19 infections[4]. Current guidelines for COVID-19 in India recommend intravenous methylprednisolone 0.5-1 mg/kg/day for three days in moderate cases and 1-2 mg/kg/day in severe cases[3]. Severely ill patients who are on oxygen supplementation or ventilation are recommended the use of dexamethasone (6 mg per day for a maximum of 10 days)[3]. However, the risk of developing secondary infections due to the immunosuppressive nature of glucocorticoids has been specifically indicated with the guidelines.

COVID-19 infection has a propensity to cause immune dysregulation leading to a reduced number of both CD4+T and CD8+T lymphocytes and there can be a marked rise in the level of inflammatory cytokines like interleukin 2 (IL-2), IL-6 and tumour necrosis factor-alpha[1].

Mucormycosis is known to cause angioinvasion and endothelial damage which constitutes the main mechanism of its pathogenesis leading to extensive infarction. COVID-19 infection also causes thrombotic microangiopathies. The immunosuppressing effects of steroids along with immune dysregulation caused by COVID-19 infection and the possible microthrombotic complications of COVID-19 can form a fertile ground for increased mucormycosis infection[6,10].

Mucormycosis is associated with poor prognosis with a mortality rate ranging between 33.3% to 80%[6]. This makes the early diagnosis of this infection important, as delay in diagnosis even for a few days might result in worsening of prognosis. Even after early diagnosis,

together with systemic antifungals and aggressive surgical interventions; the prognosis for recovery from mucormycosis is still poor.

Though steroid usage and the presence of comorbidities are associated with an increased rate of mucormycosis in COVID-19 patients, an alarming observation that we found was some of the patients were infected with mucor despite the absence of these risk factors. It is not inappropriate to state that weakened immunity post-COVID-19 infection is even responsible for the susceptibility of mucormycosis, irrespective of steroid intake or DM. The compromised immune system may not be able to fight the mucor infection upon invasion in post-COVID-19 patients.

The situation exploded in India, and the acute rise in the number of cases led to *an epidemic within the pandemic*. The exact cause of the sudden surge in mucormycosis as a post-COVID-19 sequela is yet to be established. However, identifying the at-risk patients and looking out for warning signs can help in early recognition and prevention of this deadly infection.

Disclosure: The authors declared no conflicts of interest. Informed consent was taken from all the patients.

References

1. Silvino E, Eduardo M, Ribeiro IB, et al. Rare and Fatal Gastrointestinal Mucormycosis (Zygomycosis) in a COVID-19 Patient : A Case Report. *Clin Endosc*. 2020;53:746-749.

2. Sen M, Lahane S, Lahane TP, Parekh R HS. Mucor in a Viral Land: A Tale of Two Pathogens. *Indian J Ophthalmol*. 2021;69(2):244-252. doi:10.4103/ijo.IJO

3. Mehta S, Pandey A. Rhino-Orbital Mucormycosis Associated With COVID-19.

Cureus. 2020;12(9):10-14. doi:10.7759/cureus.10726

4. Ahmadikia K, Hashemi SJ, Khodavaisy S, et al. The double-edged sword of systemic corticosteroid therapy in viral pneumonia: A case report and comparative review of influenza-associated mucormycosis versus COVID-19 associated mucormycosis. *Mycoses*. 2021;(February):1-11. doi:10.1111/myc.13256

5. Maini A, Tomar G, Khanna D, Kini Y, Mehta H, Bhagyasree V. Sino-orbital mucormycosis in a COVID-19 patient: A case report. *Int J Surg Case Rep* . 2021;82(May):105957. doi:10.1016/j.ijscr.2021.105957

6. Moorthy A, Gaikwad R, Krishna S, et al. SARS-CoV-2, Uncontrolled Diabetes and Corticosteroids—An Unholy Trinity in Invasive Fungal Infections of the Maxillofacial Region? A Retrospective, Multi-centric Analysis. *J Maxillofac Oral Surg*. 2021;Mar 6:1-8. doi:10.1007/s12663-021-01532-1

7. Saldanha M, Reddy R, Vincent MJ. Title of the Article: Paranasal Mucormycosis in COVID-19 Patient. *Indian J Otolaryngol Head Neck Surg*. 2021:1-4. doi:10.1007/s12070-021-02574-0

8. Sravani T, Uppin SG, Uppin MS SC. Rhinocerebral mucormycosis: Pathology revisited with emphasis on perineural spread. *Neurol India*. 2014;62:383-386.

9. Alekseyev K, Didenko L, Chaudhry B. Rhinocerebral Mucormycosis and COVID-19 Pneumonia. *J Med Cases*. 2021;12(3):85-89. doi:10.14740/jmc3637

10. Vasquez-Bonilla WO, Orozco R, Argueta V et al. A review of the main histopathological fi ndings in coronavirus disease 2019 *. *Hum Pathol*. 2020;105:74-83. doi:10.1016/j.humpath.2020.07.023