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A CASE SERIES OF THE PIGGYBACK DISEASE CHARACTERIZED BY BLACK ESCHAR FOLLOWING COVID-19 RHINO-ORBITAL CEREBRAL MUCORMYCOSIS.

Souvagini Acharya[1], Sharmistha Behera[2], Alaska Sahu[3], Asmita Pradhan[2] Braja Behari Panda[4], Somy Purohit[2]*
[1]Department of Otolaryngology, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Sambalpur, Odisha, India.
[2]Department of Ophthalmology, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Sambalpur, Odisha, India.
[3]Department of Pathology, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Sambalpur, Odisha, India.
[4]Department of Radiodiagnosis, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Sambalpur, Odisha, India.

Abstract

Purpose

This case series focused on examining the clinical profile of individuals suspected of having Post post-COVID mucormycosis. These patients were admitted with the presence of black eschar on their face and eyes.

Methods

This case series includes six individuals who were suspected to have post-COVID Mucormycosis. They presented with black eschar. The cases were examined over six months, from May 2021 to October 2021, at the Ophthalmology Department of Veer Surendra Sai Institute of Medical Sciences and Research (VIMSAR), Burla.

Results

All the cases included in the case series exhibited symptoms of black eschar and were in the age group of over 40 years. All the cases had a history of Type II Diabetes mellitus (T2DM) in their medical records. Two individuals had undergone oxygen therapy and steroid therapy as part of their treatment for COVID-19. In addition, one case had a previous admission to the Intensive Care Unit (ICU). Upon admission, all patients underwent Diagnostic Nasal Endoscopy (DNE) and were subsequently administered liposomal amphotericin B (AMB) for 21 days, followed by oral Posaconazole. Two patients underwent skin grafts, while another patient required exenteration. Unfortunately, four patients did not survive, but there were positive outcomes for three patients who experienced improved visual activity. Additionally, two patients only had the disease affecting one eye.

Conclusion

The simultaneous occurrence of T2DM, a history of steroid use, and oxygen therapy were significant factors contributing to the development of post-COVID Mucormycosis. Despite implementing timely interventions, the mortality rate for post-COVID mucormycosis was significant, reaching approximately 50%. Indeed, a fungus in the realm of viruses caused widespread devastation.

***Keywords**: Amphotericin B, Black Eschar, Invasive Mucormycosis, Lid Exenteration, Post COVID-19, Uncontrolled Diabetes*
***Submitted: 2024-03-26** Accepted: 2024-03-28*
*Corresponding Author: Alaka Sahu**
Email: sahudralaka@gmail.com
Department of Pathology, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Sambalpur, Odisha, India

INTRODUCTION

Rhino-orbital-cerebral mucormycosis (ROCM) is a life-threatening infectious disease and the causative organism is a fungus belonging to the order Mucorales [1]. Mucormycosis is an opportunistic infection that has a predilection for affecting the immunocompromised, especially those with uncontrolled Type II Diabetes mellitus (T2DM). The hyperglycemic state creates a weak immune system which favors fungal invasion [2]. Fungal spores circulate within the environment and colonize in the nasal or sinus mucosa. The fungal hyphae via angioinvasion spread to the neighboring areas of the orbit, cavernous sinus, and brain, causing microvascular thrombosis and surrounding tissue necrosis [3]. The hallmark of this fungal invasion is dark necrotic patches of tissue, eschar, or blackish discharge from oral, nasal, or sinus cavities.

Previous statistics suggest that there were 41512 cases and 3554 deaths due to post-COVID-19 mucormycosis in India. Furthermore, around 80% of the cases with

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mucormycosis have been diagnosed with T2DM. Therefore, both COVID-19 and mucormycosis seemed to be 'twindemics' [4]. There is growing evidence of this fungal infection during the COVID-19 outbreak (Piggy Back Disease). This study includes the cases of post-COVID mucor with a black eschar at our hospital.

METHODS

Study design

This is a retrospective observational study that contains hospital records from patients who developed mucormycosis after being infected with COVID-19.

Study setting

The research was carried out over six months (May 2021-October 2021) by the Ophthalmology and Otorhinology Departments at the Veer Surendra Sai Institute of Medical Sciences and Research (VIMSAR), Burla.

Participants

The study includes six cases of suspected post-COVID mucormycosis with black eschar (Figure 1A and 1B).

Ethical considerations

The VIMSAR Institutional Research & Ethical Committee (VIREC) reviewed and approved the study protocol. The study was carried out following VIREC's ethical standards, as well as the norms of the Helsinki Declaration of 1975, as revised in 2000. Patients provided informed consent to allow identifying images to be archived.

Procedure

These are the following criteria used for diagnosing a patient with Post COVID-19 mucormycosis [5] - A) host factors B) criteria for diagnosis and C) mycological criteria. Also, the presence of other clinical features was taken into consideration including eyelid signs, periorbital or facial edema with blackish discoloration, vision loss, fever, facial palsy, nasal discharge, proptosis, conjunctival chemosis, ophthalmoplegia, palatal eschar.

A) Host Factors (one of the following)

®Recent (< 6 weeks) history of treatment for COVID-19
®Uncontrolled T2DM (HbA1C >7%)
®History of treatment for COVID-19 using steroids
®History of treatment for COVID-19 using immunomodulators

B) Criteria for Diagnosis

®Diagnostic nasal endoscopy (DNE) reveals eschar, blackish staining, and ulceration over the nasal mucosa of the middle turbinate, middle meatus, and septum (Figure 2A, 2B).

® Magnetic Resonance Imaging (MRI) of the orbit, paranasal sinuses, and brain using gadolinium contrast and fat saturation postcontrast sequences (Figure 3).

C) Mycological criteria

®Direct tissue examination was performed, and sinus debridement or biopsy from orbital tissue was stained with 10% potassium hydroxide (KOH). Inoculation in Sabaroud Growth Agar (SGA) medium and blood agar for up to 1 and 2 weeks at 37°C and 25°C, respectively. Mucormycosis was identified by the presence of quickly expanding grey fluffy colonies on culture media, as well as direct examination revealing fungal components.
®Histopathological examination (HPE) of mucormycosis - On tissue biopsy, the presence of aseptate fungal components, its hyphae branching at wide-angle with surrounding tissue necrosis on slides stained with Hematoxylin and Eosin, 10% KOH, and Gomori's methenamine silver stains.

Data analysis

The parameters that were documented included the age of the patients, their gender, glycemic control status in patients with a history of T2DM, oxygen dependency while on COVID-19 treatment, presence of any other comorbidities, history of treatment with corticosteroids and/or immunomodulators (tocilizumab) for COVID 19, HPE report (Table 1).

RESULTS

The patients were reviewed retrospectively following their treatment for ROCM infection at VIMSAR, Burla by the departments of Ophthalmology and Otolaryngology. The average age of the patients was determined to be 48±12 years, with an equal distribution of three males and three females. All of them arrived for treatment within 21 to 35 days after receiving medical care for COVID-19 at another facility. Out of the six patients, five had a previous diagnosis of type 2 diabetes mellitus, with four of them having uncontrolled blood sugar levels upon admission. The patient's clinical presentation upon admission exhibited a range of symptoms, including ocular pain, redness, peri-orbital swelling, chemosis, proptosis, facial pain, and nasal discharge.
The information obtained from the patient records consisted of radiological observations (Magnetic Resonance Imaging - MRI) indicating sinus mucosal thickening and the presence of bony erosion on the orbit, paranasal sinuses, and brain (Figure 3). There were indications of potential fungal evidence in four patients and confirmed fungal evidence in the remaining two patients, indicating a possible case of mucormycosis.
There was a history of steroid therapy during their COVID-19 management in three patients and five of them were on oxygen therapy during their COVID stay. All the patients were managed with DNE by

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Modified Denker's technique and treated with Intravenous Amphotericin B (AMB) (Liposomal) 5-10 mg/kg and followed up with Tablet Posaconazole on discharge. Only one of the patients underwent Exenteration. All of them had received Retrobulbar Transcutaneous AMB in the dose of 3.5mg/ml with sinus irrigation of 1mg/ml. Four out of six cases died despite all necessary measures.

Figure 1A – Patients presenting with black eschar over eyelid (right).

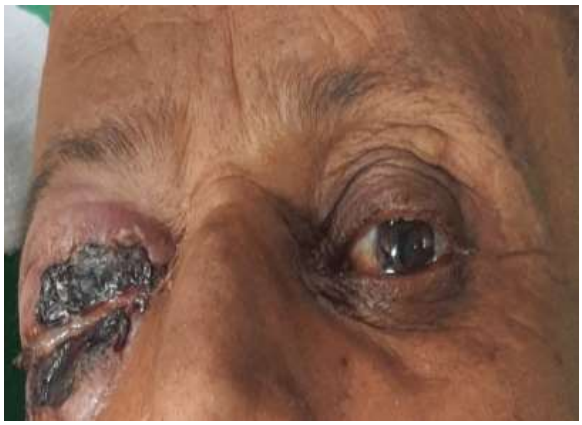

Figure 1B – Patients presenting with black eschar over the eyelid (right) and over the face (right).

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Figure 2A and B – DNE evidence showing black necrotic tissue observed over nasal and sinus mucosa.

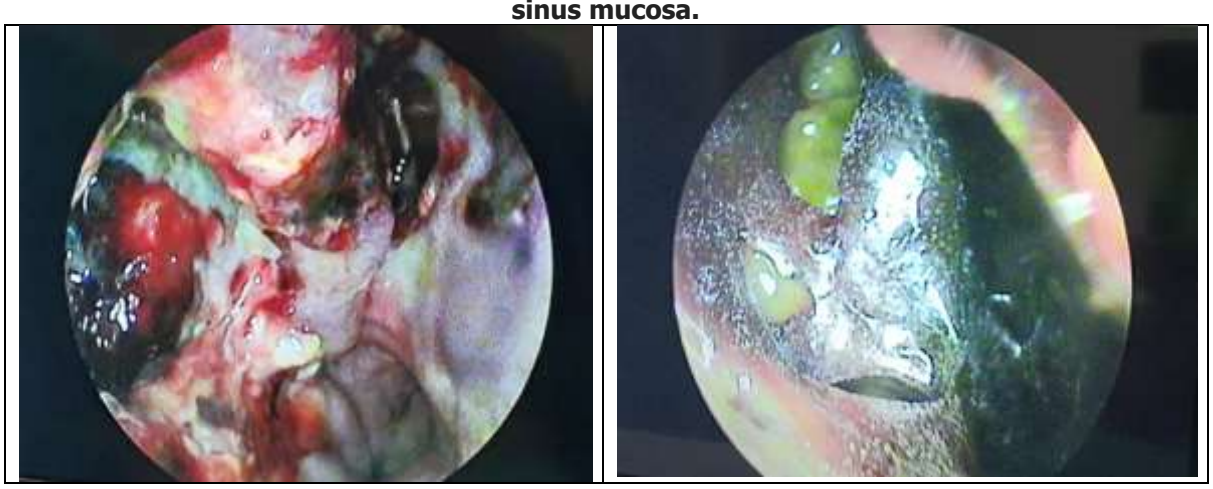

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Figure 3 – MRI picture of a patient showing the mucosal thickening

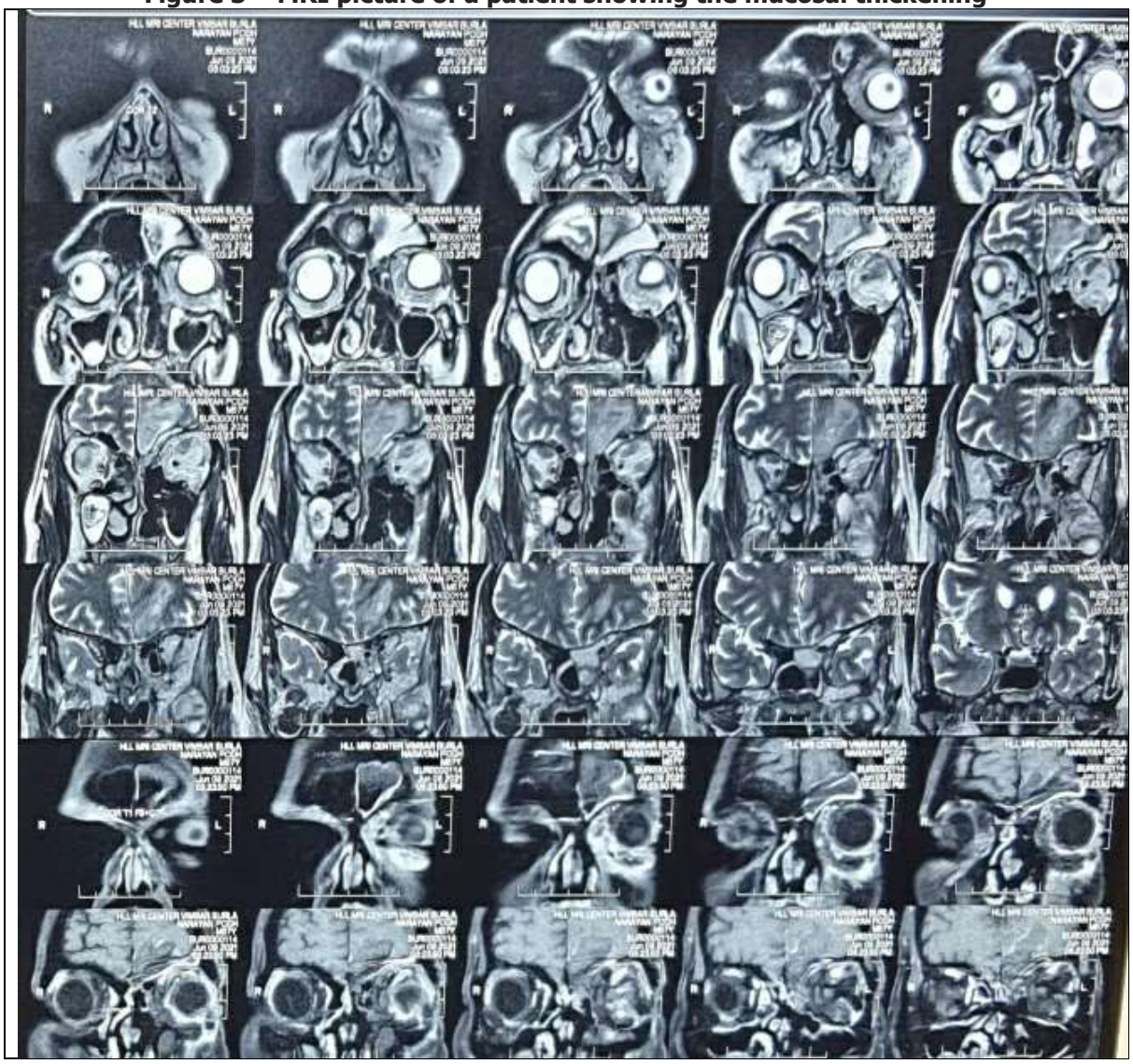

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Table 1 – Parameters documented for evaluation of the clinical profile, treatment given followed by their clinical outcome.

	Age	Comorbidities	Steroid therapy	Presentation	O2 Requirement	HPE and Fungal smear	Treatment	Outcome
1	55 year	Diabetes	Yes	Lid swelling, chemosis,	Yes	Yes	DNE + Inj AMB + Exenteration + Tablet Posaconazole	Improved
2	60 year	Diabetes	Yes	Lid swelling, chemosis	No	No	DNE + Inj AMB + Table Posaconazole	Improved
3	43 year	Diabetes	Yes	Periorbital swelling with diminution of vision	Yes	Yes	DNE + Inj AMB + Tablet Posaconazole	Death
4	53 year	Diabetes, Hypertension	No	Right-sided peri-orbital pain, chemosis	Yes	No	DNE + Inj AMB + TRAMB + Tablet Posaconazole	Death
5	59 year	Diabetes	No	Peri-orbital swelling, epistaxis	Yes	No	DNE + Inj AMB + TRAMB + Tablet Posaconazole	Death
6	48 year	Diabetes, Hypothyroid	No	Facial swelling, diminution of vision	Yes	No	DNE + Inj AMB + TRAMB + Tablet Posaconazole	Death

AMB- Amphotericin B, DNE-diagnostic nasal endoscopy, HPE- histopathological examination, INJ-injection, TRAMB- Transcutaneous retrobulbar amphotericin B

DISCUSSION

This case series depicts that ROCM is a well-known phenomenon in patients with a history of COVID-19 infection. Phagocytes, both mononuclear and polymorphonuclear, play a significant part in the pathogenesis of mucormycosis. The oxidative byproducts and defensins released by the phagocytes damage the fungal elements [6]. There is a deficiency of lymphocytes observed in COVID-19 while the increased proliferation of neutrophils and monocytes is an inflammatory response to viral replication. This imbalance in turn makes the patient more susceptible to systemic fungal infections [7]. There has been rampant use of steroids for the management of COVID-19 to reduce the dependency on invasive ventilation in hypoxic patients. Prolonged use of steroids has the propensity to predispose patients to various opportunistic infections like those of mucormycosis. Additionally, steroids also cause lymphopenia thus accelerating the progress of fungal infection [8]. Recent studies indicated that COVID-19 is a pro-coagulable state and is associated with poor outcomes particularly thrombotic events. This pro-coagulable state helps in easier angioinvasion of mucormycosis further leading to the spread of the disease [7].

In a study conducted by Song et al, the authors identified 99 patients with post-COVID-19 systemic fungal infections. It was found that 5% of the fungal infections were caused due to *Aspergillus* and 7% due to *Mucormycosis*. As per their findings impaired T-cell immunity coupled with an immunocompromised state is one of the underlying causes of mucormycosis in COVID-19 [9]. Furthermore, in a retrospective study conducted in Maharashtra, India Chavan et al also reported that T2DM, previous COVID-19 infection, steroid use, and history of

oxygen use were major risk factors for contracting mucormycosis [10].

This case series highlights the urgency of early recognition and management of Post post-COVID mucormycosis, particularly in patients with predisposing factors such as uncontrolled Type II Diabetes Mellitus, oxygen therapy, and steroid use during COVID-19 treatment. Despite prompt interventions, the significant mortality rate underscores the need for further research to enhance our understanding and management of this complication.

Future research should focus on identifying additional risk factors, exploring novel diagnostic modalities, evaluating adjunctive therapies, and assessing long-term outcomes. Addressing these gaps will inform clinical practice and optimize strategies for the prevention, diagnosis, and management of post-COVID-19 mucormycosis.

CONCLUSION

Post-COVID-19 mucormycosis has been associated with a very high rate of morbidity as well as mortality. Thus, it warrants us to have a very high degree of clinical suspicion. The presence of comorbidities like uncontrolled T2DM and the use of steroids has been a significant association with developing post-COVID-19 mucormycosis. A timely multi-disciplinary approach and an aggressive course of action can reduce overall morbidity and mortality.

Recommendation

Early recognition and aggressive management are crucial for Post post-COVID mucormycosis, given its high mortality rate. Suspect mucormycosis in patients with black eschar, especially those with uncontrolled diabetes, oxygen therapy, and steroid use during COVID-19 treatment. Prompt diagnostic nasal endoscopy and mycological examination are key for confirmation, followed by immediate antifungal therapy like liposomal amphotericin B and necessary surgeries. Multidisciplinary collaboration is vital for optimal outcomes. Further research is needed to identify additional risk factors and interventions for improved management.

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List of Abbreviations

ROCM: Rhino-orbital-cerebral mucormycosis
T2DM: Type II Diabetes Mellitus
ICU: Intensive Care Unit
DNE: Diagnostic Nasal Endoscopy
AMB: Amphotericin B
MRI: Magnetic Resonance Imaging
KOH: Potassium Hydroxide
SGA: Sabouraud Growth Agar
HPE: Histopathological Examination

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Conflict of interest

The authors declare no conflict of interest.

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