ABSTRACT There has been a rise in the variety of post-Covid complications with an increase in the number of cases with rhino-cerebro-orbital mucormycosis. We hereby report a series of 5 patients diagnosed with mucormycosis showing variable invasion to orbit, premaxillary soft tissue, masticator space, infratemporal fossa, and alveolar areas.

KEYWORDS mucormycosis, rhino-cerebro-orbital, Coronavirus disease 2019

Introduction
Coronavirus disease 2019 (COVID 19) is an infectious disease caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), affecting more than 10 million people worldwide. Severely ill, hospitalized COVID-19 patients have a higher chance to develop secondary infections, constituting about 10-30% of cases, of which Fungal infections have been found to be 10 times more common. Drugs like corticosteroids are believed to modulate the inflammatory responses, thereby reducing inflammation-mediated lung injury and progression of respiratory failure in COVID-19. There are many side effects noted, like increased secondary infections, immune modulation, a manifestation of latent diabetes mellitus, dizziness, weight gain, mood changes, insomnia, and muscle weakness [1]. Rhinocerebral mucormycosis is amongst the most fulminant form of zygomycosis caused by Mucorales species like Rhizopus, Mucor, Rhizomucor, Cunninghamella, and Absidia, which belong to the Phylum Zygomycota. It is an angioinvasive disease more often seen in immunocompromised individuals causing orbital and cerebral involvement, likely in Diabetic ketoacidosis with concomitant use of steroids, Leukemia, and Lymphoma[2]. The prevalence of Mucormycosis in the Indian population is 0.14 per 1000, about 80 times higher than in developed countries [2,3,4]. The fatality rate of Mucormycosis is 46% globally. However, intracranial orbital involvement secondary to irreversible immune suppression increases the fatality to as high as 50-80%. Hence a high level of suspicion must be maintained in immunocompromised patients[5]. The clinical presentation in the early stages is typical with fever, headache, facial pain, nasal discharge, nasal obstruction, and crusting. The disease progresses rapidly within a few hours to days leading to features of CNS involvement secondary to cranial nerve palsies. Early imaging is imperative in patients presenting with these features for timely diagnosis and assessing the extent of involvement which requires prompt and aggressive treatment.

Case report
Here we present a series of 5 cases that presented with typical symptoms in which Imaging was done, which revealed different stages of Mucormycosis.

Case 1:
A 52-year-old diabetic female presented with facial swelling associated with jaw pain on the right side. Clinical evaluation revealed that she had recovered from moderate COVID pneumonia and got treated with a mild steroid dosage. Present symptoms started after 20 days of recovery from COVID. There was no history of hospitalization.

MRI showed T2W hyperintensity along walls of the right maxillary and ethmoid sinuses with T2W hypointense areas in the right ethmoid sinus, causing occlusion of the right ostomeatal unit. On post-contrast gadolinium-enhanced T1W MRI, heterogeneous enhancement with non-enhancing areas (necrotic areas) was seen in the right maxillary sinus, extending into the right ethmoid sinus. In addition, heterogeneous
Figure 1: Coronal(A), Sagittal(B), T2, and coronal STIR(D) images are showing right maxillary and ethmoid sinusitis (black arrow) and T2 hypointense content (white arrow) in the right infundibulum and right middle turbinate. Post-contrast T1(C) showing non-enhancing areas in the right maxillary sinus and right middle turbinate (dotted arrow).

enhancement was noted in the retro-maxillary fat with the erosion of the lateral wall of the right maxillary sinus (Figure 1). Bilateral Orbits and their contents appeared normal. The patient was admitted for FESS (Functional endoscopic sinus surgery) with extensive surgical debridement and was placed on IV antifungals with good control of the sugar levels. The patient was discharged after 7 days with no complaints.

Case 2:
A 62-year-old diabetic female patient complained of nasal stuffiness on both sides with crusting and nasal discharge. Clinical evaluation revealed that she had recovered from mild COVID pneumonia and got treated with mild steroid dosage. Present symptoms started after 18 days of recovery from COVID. There was no history of hospitalization. Plain MRI showed mucosal thickening in bilateral maxillary and ethmoid sinuses with few T2W hypointense areas noted within ethmoid sinuses, causing occlusion of bilateral ostomeatal suggestive of sinusitis. Post-contrast T1W MRI images showed diffuse homogenous mucosal enhancement in bilateral ethmoid, maxillary and sphenoid sinuses with few unenhanced areas (necrotic) noted in the right ethmoid and sphenoid sinuses. (Figure 2) Bilateral orbits and their contents appeared normal with no areas of abnormal enhancement. The patient was admitted for surgery and expired on the next day with a sudden increase in facial swelling and proptosis.

Case 3:
A 43-year-old non-diabetic male came with complaints of diffuse facial puffiness, redness, and tenderness over the left premaxillary region and left the periorbital region, severe jaw pain, nasal stuffing, and nasal discharge. Clinical evaluation revealed that she had recovered from severe COVID pneumonia and got treated with oral steroids. Present symptoms started after 7 days of recovery from COVID. There was a history of hospitalization for 8 days. MRI showed sinusitis of left maxillary and ethmoid sinuses, causing occlusion of ostomeatal unit with heterogeneous T2W hypointense areas (fungal elements or necrotic tissue) within the left maxillary sinus. T2W hypointense areas in the left maxillary sinus were seen to cause erosion of the anterior wall and floor of the left maxillary sinus, thereby extending to the alveolar surface, further causing erosions along the posterolateral wall of the sinus.

STIR hyperintensities were seen in the soft tissues of the premaxillary region and infratemporal fossa with invasion into the masticator space. Erosion was seen on the roof of the left maxillary sinus with T2W hypointense areas noted in the floor of the left orbit, indicating spread to the orbit. Post-contrast images revealed non-enhancing hypointense areas in the left maxillary sinus and premaxillary soft tissues. (Figure 3) The patient underwent extensive surgical debridement with turbinectomy and was placed on antifungals for 10 days and discharged after that, with no recurrence of the complaints.

Case 4:
A 45-year-old female patient complained of severe pain and watering of the right eye, decreased movements / ophthalmoplegia and swelling. Nasal stuffiness with discharge and cheek pain was also present. Clinical evaluation revealed that she had recovered from moderate COVID pneumonia and got treated with oral steroids. Present symptoms started after 21 days of recovery from COVID. There was a history of hospitalization for 5 days. MRI showed bilateral maxillary, ethmoid, and sphenoid sinusitis with occlusion of the right ostomeatal unit. Erosion of the medial wall of the orbit was noted with STIR hyperintensities in the right orbit and infratemporal fossa, suggesting invasion with mild proptosis and preseptal soft tissue swelling. Post-contrast images showed non-enhancing areas of altered Sruthi Subramanian et al./ International Journal of Medical Reviews and Case Reports (2021) 5(14):1-4
A 53-year-old male diabetic patient came with complaints of severe headache. Nasal stuffiness with the discharge was also present. Clinical evaluation revealed he had recovered from severe COVID pneumonia and got treated with oral steroids. Present symptoms started after 18 days of recovery from COVID. There was a history of hospitalization for 8 days. MRI showed right ethmoid and sphenoid sinusitis with T2W hypointense foci and erosions in the left lateral wall of sphenoid with T2W intermediate signal lesion in the left temporal lobe associated with vasogenic oedema and a post-contrast image showing smooth peripheral enhancement suggestive of an abscess. (Figure 4) The patient was admitted, and surgical debridement with sinus irrigation was done. He was treated with IV antifungals and insulin to control his blood sugar levels during his hospital stay. He was discharged after 23 days of surgery with gradual improvement and no neurological deficits.

Discussion

Mucormycosis is a rare but rapidly spreading opportunistic fungal infection, mainly affecting elderly diabetic, immunocompromised individuals, which spreads rapidly, causing infarction and necrosis in host tissue. The nomenclature of mucormycosis is suggested by anatomic site localization rather than by mycological classification. For the head and neck region, they are classified into isolated nasal, Rhino-Orbital, or Rhino-Orbito-cerebral Mucormycosis. Fungi of genus Rhizopus accounts for the majority of clinical isolates[3,4,5,6]. Rhino-Orbito-cerebral is the most typical presentation wherein there is an invasion of infection from paranasal sinuses to the orbit and the brain. Orbital apex syndrome is a rare manifestation of invasive mucormycosis [4,7]. This condition is fatal and leads to a complete ophthalmoplegia with rapid vision loss, involving cranial nerves 2, 3, 4, and 6(5), which require immediate surgical debridement and treatment with antifungals.

Pathogenetic mechanisms involved in fungal aggressiveness include decreased phagocytic activity, accessible amounts of iron due to displacement of protons by transferrin in Diabetic Ketoacidosis, and Fungal Heme-oxygenase, which promotes iron absorption for its metabolism [7]. Therefore, it is hypothesized that SARS-CoV-2 infection may affect CD4+ and CD8+ T-cells and there is an absolute decrease in lymphocytes and T cells, which is associated with the worst outcomes[8]. The patients most commonly present with severe headache, facial puffiness and swelling, redness of the cheek, nasal stuffiness, nasal discharge, nasal crusting and jaw pain. Cases in which orbit was involved presented with ophthalmoplegia and loss of vision [9,10]. Focal regional deficits are observed when there is a spread to the brain. CT scan demonstrates nodular mucosal thickening with the absence of fluid levels and hyperdense contents leading to erosion of bony sinus walls. MRI provides a better evaluation of intracranial structures and the extent of soft tissue involvement, skull base invasion, perineural spread, and vascular obstruction[10,11]. MRI demonstrates variable signal intensity depending on the sinus contents due to the presence of Iron and Manganese in the fungal elements. MRI contrast study shows the invasion of orbital soft tissues, skull base infiltration, perineural spread, intracranial complications, and vascular obstruction involving the internal carotid artery. T2W slow flow can suggest Internal carotid artery invasion by the fungus.

In patients with no orbital and brain involvement, surgical debridement and medical treatment with antifungals, such as Amphotericin B (Fungostatic), are the mainstay of treatment. Liposomal Amphotericin B (LAmB) is less toxic than Amphotericin B and has improved CNS penetration. Itraconazole and Posaconazole have been shown in case reports to work suc-
cessfully and may be used as adjunctive therapy. Hyperbaric Oxygen Therapy and local treatment with Amphotericin B are adjunctive modalities. Surgery is an essential part of managing cases due to the massive amount of tissue necrosis during mucormycosis, which may not be prevented by killing the organism. In orbital involvement, a combination of cloxacillin and third-generation cephalosporin or fluoroquinolone is used as empirical management therapy. Surgical debridement of infective and necrotic tissue has to be performed as a matter of urgency. In rhino cerebral mucormycosis, early surgical excision of infected sinuses and appropriate debridement of retro-orbital space can prevent the spread from extending into the eye, thereby obviating the need for enucleation and resulting in extremely high cure rates (85%)[12,13] The patient’s prognosis depends on multiple factors, of which early initiation of treatment is an important element. Once the diagnosis is confirmed, conservative management is done. Orbital exenteration remains the most difficult decision in rhino-orbital extension due to concerns about disability and disfigurement. Although exenteration is a mutilating procedure and the last resort, it can be lifesaving.

Conclusion

Based on our study, imaging of rhino cerebral mucormycosis shows heterogeneous, variable T2W signal intensity, different enhancement patterns, and involvement of various sinuses. In the above cases, 2 patients presented early in the course of the disease while the other 3 presented in the advanced stages of the disease where there is Orbital or extra sinus involvement. Plain MRI and post-contrast MRI sequences are immensely valuable in diagnosis and assessing the spread of infection and its complications.

Funding

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

References

1. Wethman-Ehrenreich A (2020) Mucormycosis with Orbital compartment syndrome in a patient with Covid 19. Am J Emerg Med .ajem.2020.09.032
2. Chander J., Singla N., Kaur M., Punia R.S., Attri A., Alastruey-Izquierdo A., Stchigel A.M., Cano-Lira J.F., Guarro J. Saksenaea erythrospora, an emerging mucoralean fungus causing severe necrotizing skin and soft tissue infections—A study from a tertiary care hospital in north India. Infect. Dis. 2017;49:170–177.
3. Gamaletsou MN, Sipsas NV, Roilides E, Walsh TJ. Rhino-orbital-cerebral mucormycosis. Current infectious disease reports. 2012 Aug 1;14(4):423-34.
4. Aastha Maini, Gaurav Tomar, Deepak Khanna: Sino-Orbital mucormycosis in a Covid-19 patient.International Journal of surgical case reports:2021
5. Marina Saldanha, Rashmitha Reddy, Mark Jittu Vincent: Paranasal Mucormycosis in COVID-19 patient. Indian J Otolaryngol Head Neck Surg;2021
6. Quah WJ, Gunavathy M. Orbital apex syndrome: An unusual complication of invasive mucormycosis. Proceedings of Singapore Healthcare. 2018;27(4):287-289.
7. Amanda Wethman-Ehrenreich: Mucormycosis with orbital compartment syndrome in a patient with COVID-19:Emergency medicine;2020
8. Revannavar SM, Supriya PS, Samaga L, Vineeth VK. COVID-19 triggering mucormycosis in a susceptible patient: a new phenomenon in the developing world?. BMJ Case Reports CP. 2021 Apr 1;14(4):e241663.
9. Murthy, Somasheila Das, Sujata Deshpande, et al. Differential diagnosis of acute ocular pain, Indian Journal of Ophthalmology: July 2020 - Volume 68 - Issue 7 - p 1371-1379
10. Saifder S, Carpenter JS, Roberts TD, Bailey N. The “black turbinate” sign: an early MR imaging finding of nasal mucormycosis. American journal of neuroradiology. 2010 Apr 1;31(4):771-4
11. Ferguson BJ (2000) Mucormycosis of the Nose and Paranasal Sinuses.Otolaryngol Clin North Am 33(2):349-365
12. Ander UM, Taylor EJ, Martel JR (2015) Acute Orbital Apex Syndrome and Rhino-Orbito-Cerebral mucormycosis.Int Med Case Rep J 8:93-96
13. Salil Mehta, Abha Pandey: Rhino-Orbital Mucormycosis Associated with COVID-19:CUREUS;2020