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Rhinocerebral Mucormycosis as a Sequelae of COVID-19 Treatment: A Case Report & Literature Review



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A large volume of reports detailing a marked increase in Mucormycosis infections in India has filtered its way into world news articles. These patients frequently have 2 risk factors: recent treatment of COVID-19 with high dose steroids, and uncontrolled diabetes. Recently, at the University of Tennessee Medical Center in Knoxville, we successfully treated an uncontrolled diabetic patient with rhinocerebral Mucormycosis as a sequela of his COVID-19 treatment.

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Introduction

Several reports, primarily from India, describe cerebrofacial mucormycosis (Black Fungus) afflicting a number of patients with active SARS-CoV-2 infection or shortly after treatment for COVID-19. As dexamethasone has become a standard of care for treatment of COVID-19, affected patients with underlying immunosuppression are left susceptible to secondary infections. It has been reported that an increasing number of diabetic patients in India have been afflicted with Mucor infections of the head and neck.¹ India has the highest burden of Mucor worldwide and the second-largest number of diabetic patients aged 20 to 79.² These factors, in addition to the recent rise in COVID-19 infections, has led to a rapid increase in Mucor cases.

Mucormycosis is a rare fungal infection contracted via inhalation of Mucor and Rhizopus spores in the atmosphere. While healthy individuals are rarely affected by these fungi, immunocompromised patients are susceptible to develop severe infection. Symptoms vary depending on the involved anatomic area; however, poorly-controlled diabetic patients most commonly present with rhinocerebral infection.³ As mucormycosis is a rare disease, relevant literature is limited to case reports and series. The authors present this case report aiming to bring this disease to the attention of oral-maxillofacial surgeons, as its prevalence may increase due to the COVID-19 pandemic and our specialty participates in the treatment of head and neck infections.

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Case Description

Patient RM is a 75-year-old male with a past medical history significant for poorly controlled Type II diabetes mellitus (DM) (HbA1c of 14.2% on presentation), coronary artery disease with remote history of myocardial infarction (MI), and atrial fibrillation that presented to a community hospital in East Tennessee on 28 January, 2021 with altered mental status. He was also found to be in atrial fibrillation with rapid ventricular response (RVR) and diabetic ketoacidosis upon further workup. He was subsequently transferred to a larger outside hospital within the area for intensive care unit (ICU) admission. At the time of presentation to this outside hospital, a rapid COVID-19 PCR test was performed and found to be negative. Physical exam showed an older gentleman in mild distress. Left eye conjunctivitis with yellow crusting was also noted. Chest radiography demonstrated bilateral pneumonia, further warranting admission to the ICU at the outlying hospital. At this time, an oropharyngeal COVID-19 test was performed and resulted as positive. The patient was started on 6mg dexamethasone daily and received 1 unit of convalescent plasma treatment. After receiving 6 days of treatment, the patient's respiratory symptoms had resolved, he had no oxygen requirements, his leukocytosis had resolved, and he felt subjectively well. Therefore, he was subsequently discharged.

However, 5 days later, patient RM returned to the same outside hospital with worsening left sided facial swelling, subjective fever, and decreased visual acuity of the left eye. His conjunctivitis that was previously



FIGURE 1. Coronal view of the initial CT maxillofacial scan showing left facial abscess and emphysema, as well as maxillary osteomyelitis with multiple foci of intraosseous gas.

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noticed on his initial presentation had also worsened. The patient was transferred to our institution with concerns of left facial abscess, presumed to be odontogenic in origin, as well as atrial fibrillation with RVR, COVID-19 pneumonia (resolving), and poorly controlled DM. A maxillofacial CT demonstrated severe soft tissue emphysema throughout the left cheek extending from the inferior aspect of left maxilla superiorly to the level of the left orbit, anteriorly to the base of the nose, and posteriorly to the left masseter muscle. There was also evidence of left eye proptosis with associated preseptal cellulitis/fluid/conjunctivitis causing external compression on the left orbit, as well as left maxillary osteomyelitis with multiple foci of intraosseous gas. (Figs. 1 and 2) Laboratory workup was significant for a white blood cell count (WBC) of 13.4K, hemoglobin A1c (HbA1c) of 14.2%, hemoglobin (Hb) of 11.2 and hematocrit (Hct) of 33.2. Physical exam demonstrated nonreactive left pupil with decreased visual acuity of the left eye, as well as significant left facial cellulitis with crepitus. The patient was admitted to the oral-maxillofacial service and was taken emergently to the operating room for incision and drainage, extraction of nonrestorable teeth #5, 6, and 11, and debridement of the left face. As the patient was not fit to consent for the procedure, his daughter was contacted and agreed to treatment. Intraoperatively, a left maxillary vestibular incision was made and necrotic appearing maxillary and zygomatic bone were encountered. These areas were debrided and sent for pathologic analysis and cultures. The patient was empirically started on ceftriaxone, vancomycin, and metronidazole.

Following this first surgical procedure, primary care was transferred to the hospitalist service for medical management and optimization. Additional consults to

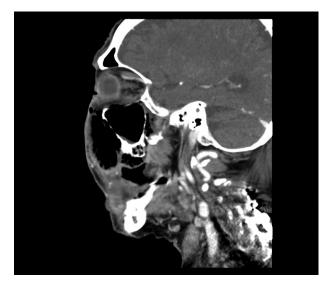


FIGURE 2. Sagittal view of initial maxillofacial CT scan. Deek et al. Rbinocerebral Mucormycosis. J Oral Maxillofac Surg 2022.

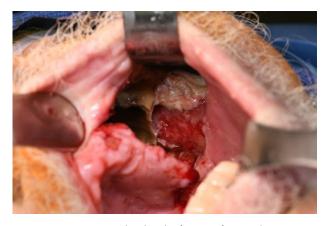


FIGURE 3. Necrotic hard and soft tissue after initial incision. Deek et al. Rbinocerebral Mucormycosis. J Oral Maxillofac Surg 2022.

infectious disease and ophthalmology were placed. Cultures taken intraoperatively from the facial abscesses grew Enterococcus faecalis, multiple drug resistant Escherichia coli, and Prevotella; targeted antibiotic therapy with piperacillin/tazobactam was begun. Two days later, the patient was brought back to the operating room by oral-maxillofacial surgery for further debridement of necrotic tissue and drainage of new abscesses of the left inferior temporal space and masseteric space. Intraoperatively, significant soft tissue necrosis of the buccinator and masseter were noted (Figs. 3 and 4). Washout and debridement was performed and fungal cultures were taken. Bone pathology returned showing extensive necrosis of the left maxilla and zygoma with "infiltrates by fungi and bacteria, specifically broad nonseptate hyphae with variable branching patterns" concerning for Mucor. The patient was started on amphotericin B empirically at this time. At that point, the patient's leukocytosis and fever had resolved, and repeat maxillofacial CT had shown resolving pre- and postseptal cellulitis. Eventually, fungal cultures resulted showing Mucor.



FIGURE 4. Necrotic turbinate bone excised during surgery. Deek et al. Rhinocerebral Mucormycosis. J Oral Maxillofac Surg 2022.

The following week, the patient returned to the operating room for multiple washout and debridement procedures. In the interim, the wound was packed with iodoform gauze. Evolving necrosis was observed from the lateral orbital wall through the zygoma, maxilla and hard palate and involved soft tissue including buccinator, masseter and buccal mucosa. The patient was started on savuconazonium in addition to liposomal amphotericin B. Fungal invasion into the ethmoid and sphenoid sinuses were noted during a washout and debridement. Due to the extent of the affected tissue and the evolving tissue necrosis, consultation to otolaryngology was placed with plan for a left orbital exenteration. Clinically, patient's mental status had deteriorated with inability to follow commands and complete left sided ophthalmoplegia was noted. An MRI of the head was ordered to rule out intracranial spread of the infection, but the patient could not follow commands and the exam was aborted due to excess motion.

The patient was taken to the operating room in conjunction with the otolaryngology team for left orbital exenteration, debridement of the midface and anterior skull base. Due to the extent of the disease, the patient was deemed to be a poor candidate for a lid sparing procedure. The orbit was removed at the apex and a diamond bur was used to remove surrounding bone until healthy bleeding cortex was noted (Figs. 5-7). The middle cranial fossa and dura matter were exposed and all remaining tissues appeared to be healthy and viable. A foam surgical



FIGURE 5. Preoperative surgical markings of left orbital exenteration. Deek et al. Rbinocerebral Mucormycosis. J Oral Maxillofac Surg 2022.



FIGURE 6. Intraoperative view following left orbital exenteration. Deek et al. Rbinocerebral Mucormycosis. J Oral Maxillofac Surg 2022.

scrub brush was saturated with nystatin cream and Mupirocin ointment, wrapped in xeroform gauze and secured with silk sutures in the surgical site with an eye patch over top.

The oral-maxillofacial surgery team continued to perform frequent washouts and packing replacements for the patient while the patient remained on antibiotics and antifungal medication. Since the patient was stable and no further debridement was indicated, a plastic and reconstructive surgery consultation was placed for reconstruction of the defect.



FIGURE 7. Patient's left orbit following exenteration. Deek et al. Rbinocerebral Mucormycosis. J Oral Maxillofac Surg 2022.



FIGURE 8. Intraoperative image demonstrating the final defect prior to reconstruction.

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Due to the extent of the wound and involvement of the frontal, maxillary and sphenoid sinuses, reconstruction with a free chimeric anterolateral thigh myocutaneous flap was planned. The otolaryngolotgy team performed chemical ablation of the sphenoid sinuses and created communication between the left and right frontal sinuses to avoid mucocele formation in the future. During final reconstruction, the fasciocutaneous component of the flap was used to cover the external skin defect, vastus lateralis muscle was used to obliterate the dead space and exposed sinuses and the palatal defect was closed using vastus lateralis and a full thickness skin graft (Figs. 8-13). Infectious



FIGURE 9. Bird's eye view demonstrating final defect. Deek et al. Rbinocerebral Mucormycosis. J Oral Maxillofac Surg 2022.



FIGURE 10. Intraoperative image demonstrating surgical markings.

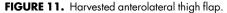
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disease recommended continuation of isavuconazonium for 3 months following the completion of his 6week course via PICC line. Eventually, after 109 days at University of Tennessee Medical Center, patient was transferred to a skilled nursing facility. The patient followed up with the plastic and reconstructive surgery team 2 months postoperatively and he had fully recovered, with no postoperative complications, healthy weight and baseline mental status. Figures 14 and 15 demonstrate postoperative images from his most recent office visit. Cosmetic revisions will be offered to the patient after 3-6 months postoperatively as needed.

Discussion

Mucor is an opportunist organism, native to the Middle East and India, commonly found in fruit, soil and feces.⁴ It is acquired by inhalation or establishment of spores in the oral, nasal or conjunctival





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mucosa through encounters with these everyday items.⁵ Most interactions do not lead to infection, although the immunosuppressed can become colonized and infected.⁶ Mucor infections can be broken down into subcategories based on areas of involvement: rhinocerebral, cutaneous, gastrointestinal, pulmonary or disseminated.⁵ Rhinocerebral is the most common, and most fatal form of Mucor infection.⁷

Patients with diabetes mellitus are at increased risk of rare infections and poor wound healing. The chronic hyperglycemic state of diabetes leads to alteration of the cell-mediated immune system via impaired chemotaxis, phagocytosis, and cytokine secretion of macrophages.⁸ In the presence of hyperglycemia and low pH, common in patients with diabetic ketoacidosis (DKA), further phagocyte dysfunction occurs related to impaired intracellular killing by both oxidative and nonoxidative mechanisms.⁹ The invasion of Rhizopus in DKA patients is facilitated by 3 factors: elevated levels of free serum iron contributing to growth, ketoreductase enzyme utilizing ketone bodies for energy, and impaired neutrophilic host response to fungi.^{10,11}

COVID-19 infection leads to immune dysregulation via decreasing T lymphocytes, CD4+ T cells, and CD8 + T cells.¹² Glucocorticoids have become standard treatment for COVID-19 due to their anti-inflammatory and immunosuppressive properties, although increased insulin resistance is a known side effect. This occurs secondary to interference with the GLUT4 transporter critical to glucose uptake into muscle cells.¹³ Their use has been shown to trigger DKA in patients with pre-existing DM.¹³ COVID-19's proinflammatory cytokine storm leads to microthrombosis causing vascular damage.¹⁴ Diabetic hyperosmolar stress dysregulates vascular regeneration.¹⁵ Together, these 2 pathologic states place patients at increased risk for invasive fungal infection. It is no surprise then that co-infection with aspergillosis, candida, and Mucor has been well documented. Recent studies have shown 8 to 27% of COVID-19 patients acquiring bacterial or fungal co-infection.¹⁶ Clinical symptoms of Mucor generally develop within 10 to 14 days of hospitalization for COVID-19.¹⁷

Mucor's angioinvasive nature leads to vasculitis and thrombosis progressing to tissue infarct and necrosis.¹⁸ The classic presentation of rhinocerebral mucormycosis includes a black eschar in the nasal cavity (black turbinates) or over the hard palate, although it is not always seen.⁶ Heightened suspicion on clinical exam of diabetic patients can include cranial nerve palsy, diplopia, mid-facial pain, proptosis, periorbital edema, orbital apex syndrome, and palatine ulcer.⁵ Ophthalmoplegia and diminished vision will commonly be the presenting symptoms.¹⁸ The clinical picture can be obscured due to neuropathic facial



FIGURE 12. Postoperative image after completion of the reconstruction. Deek et al. Rbinocerebral Mucormycosis. J Oral Maxillofac Surg 2022.

pain in the diabetic patient. It should be noted that neuropathic pain will present without swelling, facial asymmetry and other clinical signs of infection making Mucor infection a less likely diagnosis in these cases.²

Patients presenting with suspected infectious process should be evaluated with imaging for appreciation of the extent of the disease process. A cranial CT scan will show bony destruction, and MRI with its added sensitivity can show involvement of brain, sinuses, and orbit.¹⁹ In a recent study, ethmoid sinus involvement was seen in 100% of CT scans with 43% of patients having orbital involvement.⁶ Intracranial extension occurs in late disease with 8.69% of patients in this study having this finding.⁶ Histopathological examination on KOH mount will show broad aseptate hyphae with right-angled branching fungus, pathognomonic for Mucor.¹⁸ Even without microscopic diagnosis, clinicians should have high suspicion of Mucor infection in the uncontrolled diabetic



FIGURE 13. Intraoral immediate postoperative photo following completion of reconstruction. *Deek et al. Rbinocerebral Mucormycosis. J Oral Maxillofac Surg 2022.*



FIGURE 14. Postoperative image at 2 months after surgery.

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who presents with recent or current COVID-19 infection and rhino-orbital symptoms.²

Optimal treatment of mucormycosis requires a multi-disciplinary approach utilizing IV antifungals, surgical debridement, and treatment of underlying disease processes that made the patient susceptible.¹⁹ Liposomal amphotericin B is the first line of medical treatment and should be initiated as soon as clinical signs and symptoms of mucormycosis occur.²⁰ It has been described that amphotericin B can also be utilized via retrobulbar injection as an adjuvant therapy.²⁰ However, antifungals alone cannot adequately treat mucormycosis. Aggressive and repeated



FIGURE 15. Intraoral postoperative image at 2 months after surgery.

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debridement of the infected tissue is critical due to extensive thrombosis and ischemic necrosis preventing adequate penetration of antifungals. Worse outcomes were noted with delayed diagnosis or treatment, bilateral sinus involvement, and hemiparesis or hemiplegia.⁸ Delay in treatment of just 6 days has been shown to double the mortality rate.²¹ Even with aggressive treatment, reported mortality ranges from 33.3-80% in recent studies.⁶

Oral-maxillofacial surgeons (OMSs) should be aware of this rare disease, especially as COVID-19 patients are becoming more likely to survive their initial illness and develop sequelae of this disease and its treatment. Interestingly, there has been a report in Iran of a previously treated COVID-19 patient presenting to a dental office with facial swelling and tooth pain who was prescribed PO metronidazole, penicillin V and naproxen. The patient eventually made their way to a tertiary care hospital where she was treated for mucormycosis and recovered.⁷ This example shows that there will be a role for the dental community, especially OMSs, to identify these cases before significant morbidity or mortality occurs.

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