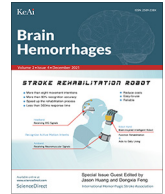




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Case Report

Orbital mucormycosis – Post SARS-CoV-2 sequelae

Hafsa Mobeen^{a,b}, Naveed Ullah Khan^{a,c,*}, Muhammad Hassan^{a,c}, Ijaz Ali^{a,c}, Zakir jan^{a,f}, Nadir Hussain^d, Mazhar Badshah^{a,e}

^aShaheed Zulfiqar Ali Bhutto Medical University (SZABMU), Islamabad, Pakistan

^bHouse Officer, Department of Neurology, SZABMU, Pakistan

^cResident Neurologist, Department of Neurology, SZABMU, Pakistan

^dDepartment of Neurology, Lahore General Hospital, Pakistan

^eProfessor, Department of Neurology, SZABMU, Pakistan

^fAssistant Professor, Department of Neurology, SZABMU, Pakistan

ARTICLE INFO

Article history:

Received 26 August 2021

Accepted 14 September 2021

Available online 27 September 2021

Keywords:

Mucormycosis

SARS-CoV-2

COVID-19

Sino-orbital disease

ABSTRACT

Multisystem involvement has not been uncommon in SARS-CoV-2 infection. There has been reports of devastating neurological complication both during and after the infection. Here we present a rare case of sino-orbital mucormycosis, diagnosis of which was confirmed on histopathology. Our patient presented with headache, 18 days after her recovery from SARS-CoV-2 infection and was extensively worked up for the cause. Initially she was treated as a severe sinusitis but failure to respond to antibiotics treatment warranted for further investigations and imaging. Our patient had to undergo right eye enucleation plus debridement under general anesthesia. She is currently on anti-fungal treatment as advised by infectious disease department.

© 2021 International Hemorrhagic Stroke Association. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

The rapidly spreading outbreak of SARS-COV-2 on global scale have turned all great efforts of accomplishing definitive treatment futile. Disease if treated in its early course its superinfections and co-infections are stills major havoc. Secondary infections have been commonly observed in severely ill and hospitalized SARS-COV-2 patients and fungal infections are 10 times more common. Mucormycosis is potentially life-threatening infection, caused by *Zygomycota Mucorales*, haunting particularly immunocompromised hosts, most commonly afflicting those with diabetes mellitus. The disease course of mucormycosis is mainly dependent on early diagnosis and aggressive management. According to one study, the mortality rate often double from 33% to 66% with the delay in diagnosis of one week.¹ The hallmark of mucormycosis, tissue necrosis, is often the late sign.

Globally, mucormycosis has case fatality rate of 45%, and it increases to 50% to 80% with inclusive factors like intracranial or

orbital involvement and immune suppression.¹ Often in SARS-COV-2 patients there have been such symptoms like cough, hypopnea, anosmia, fever, and body aches. Moreover, patients preexisting conditions such as diabetes mellitus, ischemic heart disease and hypertension have pivotal role in exacerbation of Covid pneumonia. Mucormycosis is unusual secondary infection more commonly associated with immunocompromised people.²

In extensive literature research, there have not been any case reported case of sino-orbital mucormycosis, however there have been one case of Post-Covid secondary pulmonary mucormycosis for which they considered immunocompromised state most likely cause.³ Here we present a case of a diabetic and hypertensive patient for 15 years with well-controlled blood sugar levels who developed sino-orbital mucormycosis as post SAR-COV-2 sequelae.

2. Case presentation

A 48-year-old female presented with high grade fever, shortness of breath and malaise. She is diabetic for 15 years, complaint and controlled on insulin for previous 6 months. She is hypertensive for past 10 years, taking antihypertensives, maintaining blood pressure of 140–120 mmHg systolic and 80–90 mmHg diastolic. We send nasopharyngeal swab for SARS-COV-2 RT-PCR which confirmed the Covid-19 diagnosis. She was subjected to intensive care

* Corresponding author at: Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), Islamabad, Pakistan.

E-mail addresses: hafsamobeen123@gmail.com (H. Mobeen), naveed733@yahoo.com (N.U. Khan), drhassaanshafqat2011@gmail.com (M. Hassan), drijazali@gmail.com (I. Ali), drzakirjan@gmail.com (Z. jan), nadirszmc@yahoo.com (N. Hussain), drmb43@gmail.com (M. Badshah).

unit for 5 days. We started on inj. remdesivir with the loading dose of 200 mg then continuing with 100 mg per day for 5 days. She also received dexamethasone 6 mg OD along with antibiotics and the rest of the supportive treatment. Inj. cefoperazone/sulbactam 2 g and moxifloxacin 400 mg. She was vitally stabilized and discharged on 5th hospital day when the symptoms resolved.

Following 18 days post Covid, when the infectivity period was over, she started developing complains of severe headache, right eye swelling, reduced vision in the right eye, weakness of right side of face, dysphagia, and dysarthria. On examination she had ophthalmoplegia, restriction of movement in all planes (involvement of III, IV and VI cranial nerves) of right eye. She had proptosis, orbital cellulitis, chemosis, right sided VII cranial nerve palsy. HRCT chest showed lung fibrosis that was consistent with the previous resolved infection (Fig. 1). CT venogram of the brain showed asymmetric hypo-enhancement of right cavernous sinus. There was asymmetric hypo-enhancement of the right superior ophthalmic vein concerning thrombosis. There was no CT evidence of any other dural venous or cortical venous thrombosis. CT brain (non-contrast) showed extensive opacification of the right frontal, ethmoid, and sphenoid sinuses. Moderate mucosal thickening is also seen in the left maxillary sinus with internal ill defined hyper density concerning for fungal sinusitis. There is partial opacification of posterior ethmoid sinus with minimal mucosal thickening involving left sphenoid sinuses. MRI brain with contrast suggested muco-inflammatory changes at bilateral maxillary, right ethmoid and frontal sinuses (Fig. 2). CT Paranasal sinus and orbits with contrast study performed on 2nd day of presentation was conclusive of sinusitis with right orbital cellulitis and moderate right proptosis. Though frank osseous erosions or any hyper density were not present on the above imaging, the possibility of fungal sinusitis could not be excluded. CT Paranasal sinus and orbit with contrast study performed on 14th day of presentation showed overall sinusitis with right orbital cellulitis and moderate right proptosis. Right ethmoid medial sinus walls were eroded along with extra-ocular muscles swelling and heterogeneous asymmetric enhancement including superior rectus/superior oblique as well of medial rectus and associated right cavernous sinus thrombosis. There was also slight prominence of the right superior ophthalmic vein.

We initiated our management on the line of right orbital cellulitis with extensive sinusitis and cavernous sinus thrombosis. Empirical antibiotics were started i-e. ceftriaxone, vancomycin, and amphotericin 1 mg/kg/day, while culture and sensitivity were awaited. Fungal growth came out to be negative on Indian ink Stain. For the optimum control of the disease, otolaryngologist, ophthalmologist, neurologist, and neurosurgeons were taken on board. After repetitive consultations with multidisciplinary board, lid sparing modified enucleation surgery was planned for right eye. Patient was prepared and under general anesthesia with IV sedation infective eye was enucleated. by using wire speculum operative field was freed, after undermining the posterior tenon's

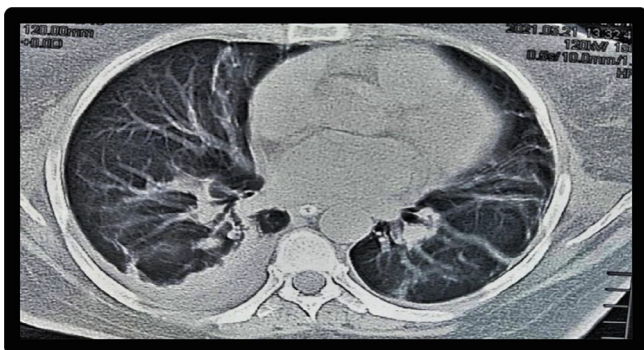


Fig. 1. HRCT CHEST shows bilateral lung fibrosis consistent with resolved infection.

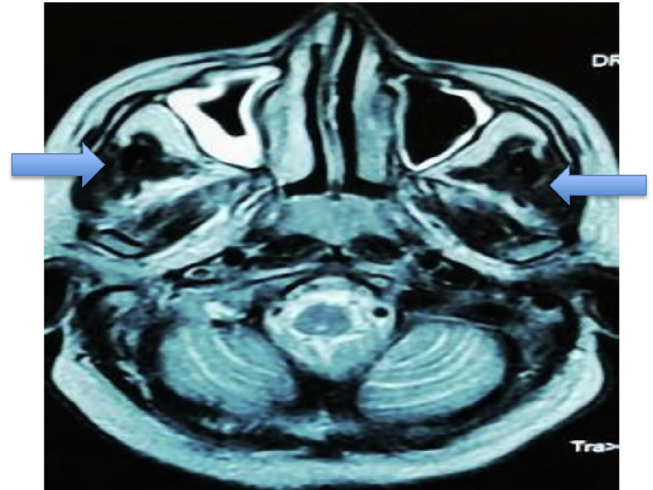


Fig. 2. MRI brain with contrast suggested muco-inflammatory changes at bilateral maxillary, right ethmoid and frontal sinuses (arrows).

fascia each rectus was double tagged and eventually transected (Fig. 3). The eyeball (Fig. 4) was prolapsed between the blades of speculum and optic nerve was divided little anterior to superior orbital fissure. Hemostasis was achieved. Right maxillary sinus was entered by eroded part of maxilla and drainage of purulent discharge was done. Fungal lavage of the orbit and maxillary sinus was done before closing. Histopathology report confirmed the presence of a fungal infection (Fig. 5).

3. Discussion

Mucormycosis is a serious fungal infection, if left untreated it can prove to be fatal. It is an angioinvasive infection that is distinguished by tissue infarction and gangrene.⁴ Mostly mucormycosis has sporadic occurrence however, outbreaks of mucormycosis are noticed. The paramount risk factors found in association with the disease are diabetes, especially with diabetic ketoacidosis, organ

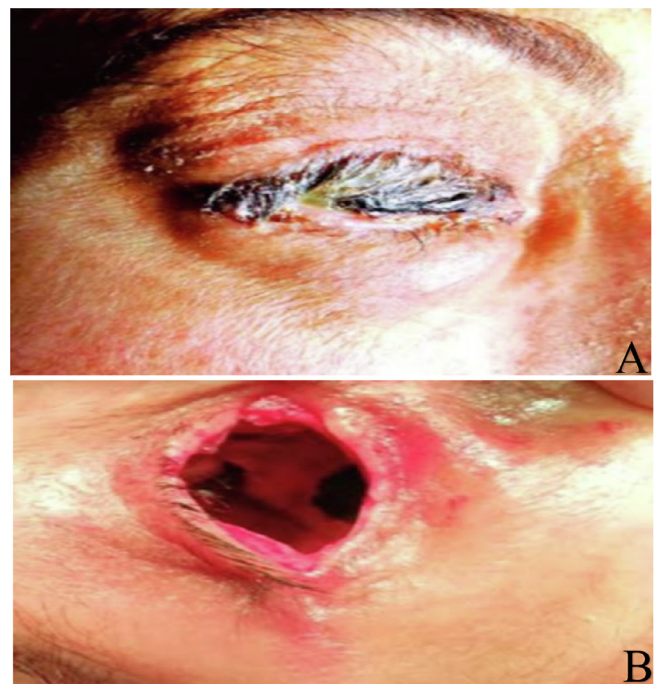


Fig. 3. A; showing eye fungal involvement, B; post Enucleation surgery.



Fig. 4. Orbital cavity post extensive enucleation surgery. Specimen for culture sensitivity and histopathologic studies were sent.

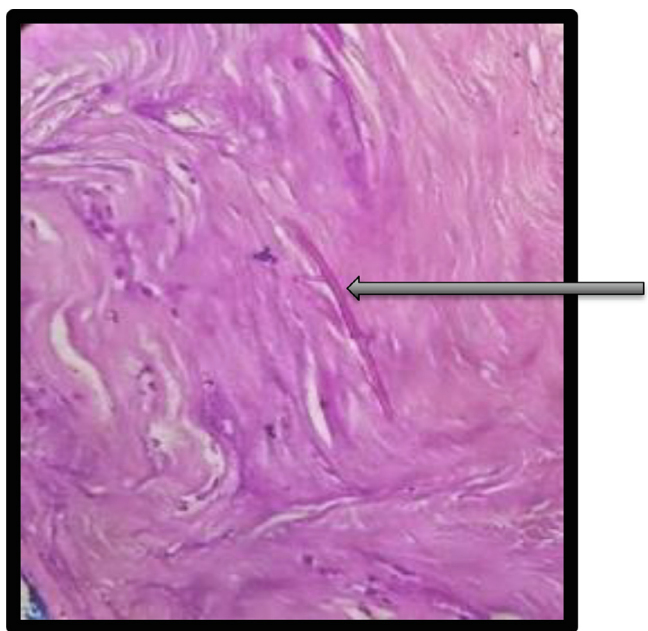


Fig. 5. Broad base non-septate hyphae branching at right angles (arrow), consistent with mucormycosis on H&E stain.

transplant, stem cell transplant, cancer, injection drug use, too much iron in the body (iron overload or hemochromatosis), long-term corticosteroid use, burns or wounds, skin injury due to surgery, prematurity, and low birth weight. Among others causes implicated in mucormycosis, healthcare associated outbreaks include negative pressure rooms, non-sterile medical instruments, poor air filtration, water leaks and wooden tongue depressors.⁵ Patients who have been on prolonged oxygen support are the most susceptible to being infected with this fungus. The fungus usually lodges in the nasal tract. The source of it mainly is the poor quality of water used, through which the piped oxygen in hospitals passes to make it hydrated oxygen before it reaches the patient's nostrils. The fungus can travel up to the eye and brain too. It has the potential to paralyze the nerves it travels through.

In one study carried out to explore association of invasive fungal infection and corona virus disease. There were 23 cases of SARS-COV-2 out of which 21 cases were diabetics and 12 cases had uncontrolled blood sugar levels.⁶ Moreover, all patients included in study had a history of steroid use in their treatment course for SARS-COV-2.⁶ Depending upon organ being involved

mucormycosis has several types. Amongst pulmonary, cutaneous, renal, gastrointestinal, rhino-cerebral, Sino-orbital and disseminated forms, rhino-orbital-cerebral mucormycosis type has the highest incidence in India. According to a research performed for epidemiology of disease in India the rhino-orbital-cerebral mucormycosis has the highest incidence (45–74%), followed by skin (10–31%), respiratory (3–22%), renal (0.5–9%), followed by gut (2–8%), and then disseminated infections (0.5–9%). Diabetes mellitus is a widespread predisposing component for the rhino-orbital-cerebral mucormycosis.⁴ A recent study from India figured out that 77% of cases of rhino-cerebral-orbital mucormycosis were in the diabetic population.⁴

Among the worst affected are those with diabetic people and people who have health problems or take medicines that lower the body's ability to fight germs and sickness. Steroids given in treatment for SARS-CoV-2 also have a role in lowering immunity and raising blood sugar levels which makes the patient more susceptible to infection by mucormycosis. The lowered immunity, breaches in hospital asepsis along with high fungal spore counts in the hospital environment creates the perfect setting for mold infections. Patients suffering from the fungal infection typically have symptoms of headache, stuffy and bleeding nose; swelling of and pain in the eye; drooping of eyelids; and blurred and finally, loss of vision in severe cases. There may also be blackening of the skin in patchy pattern around the nose. If the infection goes uncontrolled it can also lead to the death of the patient.

Regarding diagnosis of mucormycosis blood test have very preliminary value, it mostly relies upon histopathological evidence. Even in disseminated disease blood cultures are negative. In histological evidence Mucorales have quite distinct appearance. It has irregular non-septate hyphae that branch at right angles.⁷ The rhino-orbital-cerebral type of mucormycosis needs emergent and aggressive management. Surgical debridement under the cover of Amphotericin-B is considered ideal line of management. In one study carried inn India, patients observed under combination therapy of Amphotericin-B with surgical debridement of necrotic tissue indicated mortality rate of 19–44% in comparison with high rising mortality rate of 50–61% in monotherapy with amphotericin-B.⁴

Distilled water should only be used for oxygen hydration, but sadly, in our hospitals, common tap water or water from any other available source is used due to negligence or downright ignorance, by the para medical staff. There should be no leakage from the humidifier and hygiene should be maintained. Failure to strictly follow these protocols may later present with post covid sequelae which unfortunately is the case in may centers here in our country. If the patient notices any of these symptoms post Covid, they should immediately see a medical doctor who can advise scans and refer them to ENT specialists. After the initial debridement procedure, and sending the biopsy, once the Mucormycosis is confirmed, patient can be started on Anti-fungal medications and in some cases, patient may also require surgery.

4. Conclusion

It is extremely important to keep such complications in mind as a physician in the times of SARS-CoV-2 pandemic. Patients with similar symptoms as above should always be investigated for the possibility of grave fungal infections. Timely diagnosis and management of such cases may prevent serious complication like our patient had.

Declaration

Consent for publication

Available.

Availability of data and material

Yes.

Competing interests

Nil.

Funding

Nil.

Ethics approval and consent

The protocol for the research project has been approved by a suitably constituted research ethics committee of the institution within which the work was undertaken. All participants gave informed consent for the research, and that their anonymity was preserved.

CRedit authorship contribution statement

Hafsa Mobeen:,Naveed Ullah Khan:,Muhammad Hassan:,Ijaz Ali:,Zakir jan:,Nadir Hussain:,Mazhar Badshah:.

Acknowledgements

Nil.

References

1. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. *Am J Emerg Med.* 2021;42:264.e5.
2. Garg D, Muthu V, Sehgal IS, et al. Coronavirus disease (Covid-19) associated mucormycosis (CAM): case report and systematic review of literature. *Mycopathologia.* 2021;186(2):289–298.
3. Rajeshwari A, Gangadhara S. Rhinocerebral mucormycosis: an unusual presentation. *Am J Med Sci.* 2012;2(1):16–19.
4. Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. *Microorganisms.* 2021;9(3):523.
5. Neblett Fanfair R, Benedict K, Bos J, et al. Necrotizing cutaneous mucormycosis after a tornado in Joplin, Missouri, in 2011. *N Engl J Med.* 2012;367(23):2214–2225.
6. 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(5):442–447.
7. Reid G, Lynch JP, Fishbein MC, Clark NM. Mucormycosis. *Semin Respir Crit Care Med.* 2020;41(01):99–114.