A 40-Year-Old Woman With COVID-19 and Bilateral Vision Loss

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Abstract
Mucormycosis is a fast-spreading angioinvasive fungal infection with a very high mortality rate. It is associated with immunodeficiency, diabetes mellitus, iron overload, stem cell transplantation and the use of steroids. As cultures and histopathological biopsy may have low yield in invasive fungal infections, new generation sequencing of cfDNA (cell free deoxyribonucleic acid) has become a cornerstone for diagnosis. Over the past 18 months, increasing reports of COVID-19 associated Mucormycosis have emerged, most specifically in India and other nearby developing countries. Awareness and knowledge of this newly discovered association is of high importance and clinical relevance as the global COVID-19 pandemic continues. Herein, we present a case of a patient who was treated with steroids for COVID-19 in the outpatient setting and presented with unilateral periorbital pain and blurry vision. She progressively developed bilateral vision loss, fixed bilateral mydriasis, ophthalmoplegia and coma. Imaging findings included leptomeningeal, vascular, and subcortical enhancement accompanied with multifocal infarction. Subsequent biopsy of the paranasal sinuses revealed broad type fungal elements and cfDNA sequencing identified the pathogen as Rhizopus species. She was treated with intravenous amphotericin B, but succumbed to the infection.

Keywords
vision loss, basal ganglia necrosis, SARS-CoV2, COVID-19, Mucormycosis

A 40-year-old woman with a past medical history of alcoholic and hepatitis C cirrhosis, diabetes mellitus and subacute, moderate COVID-19 infection was admitted with progressive, painful, bilateral vision loss. Clinical history was significant for recent completion of a 10-day course of dexamethasone for COVID-19 and a four-day progressive history of left periorbital swelling, left orbital pain, holoccephalic headache, and blurry vision.

Physical examination was significant for left periorbital edema with surrounding erythema and left eye proptosis concerning for cellulitis. No appreciable external right eye pathology was noted. On neurological examination the patient was alert and oriented with normal cognitive and language function. Cranial nerve examination was significant for dilated and fixed pupils bilaterally (5 mm) with no light perception. Fundoscopic exam revealed extensive disc pallor on the left and normal findings on the right. Vertical and horizontal extraocular movements were intact bilaterally. Sensation to pinprick in the left V1 and V2 distributions was decreased. No other cranial nerve deficits were noted on exam. The sensori-motor examination of the extremities was normal and deep tendon reflexes were 2+ throughout. Over the subsequent 24 hours, her clinical course deteriorated with the development of complete left eye ophthalmoplegia and stupor, necessitating endotracheal intubation and ICU admission.

The presence of bilateral vision loss, fixed bilateral mydriasis, ophthalmoplegia, and trigeminal sensory loss

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potentially localize to both central and peripheral lesions. Progressive blindness specifically could include pre-chiasmatic lesions, bilateral intraocular pathology, or bilateral lesions of the primary visual cortex. Mydriasis can localize to discrete mesencephalic lesions, CN III nuclear-fascicular lesions, or peripheral 3rd nerve involvement. Ophthalmoparesis localization includes intraocular pathology, peripheral leptomeningeal nerve involvement or compression, and lesions in the mesoponine horizontal gaze centers. Isolated trigeminal impairment, specifically to V1 and V2 localizes to either peripheral leptomeningeal compression or central impairment of the caudal spinal trigeminal nucleus. Given the broad context of our patient’s neurological impairments (cranial nerves II, III, IV, V1, V2, and VI) in the setting of left eye ptosis, localization likely encompasses a peripheral cranial nerve compression, specifically within the cavernous sinus or orbital apex.

The abrupt decline in mental status 24 h after admission also warrants further localization as concurrent central neurology was likely. Acutely altered states of consciousness localize specifically to mesoponine cholinergic and monoaminergic nuclei, thalamocortical relay networks, and prefrontal and frontal processing domains. Etiologically, such factors are inhibited by both metabolic and structural lesions. In such case the likely presence of a diffuse metabolic or infectious cortical lesion is most likely given the absence of focal sensorimotor symptoms on examination. In context with the likely cavernous sinus pathology, infiltrative lesions were considered.

Given the collective findings of left orbital cellulitis, progressive bilateral vision loss, left orbital apex syndrome and cavernous sinus symptomatology and acute alteration in mental status, concern for a rapidly progressive lesion is warranted. Differential diagnosis in such case should include inflammatory, vascular, and infectious etiologies, such as rapidly progressive meningoencephalitis (bacterial, fungal, or viral), sarcoidosis, Tolosa-Hunt syndrome, systemic lupus erythematosus, microscopic polyangiitis, granulomatosis with polyangiitis, and primary CNS vasculitis. Neoplastic lesions in this case are less likely given the rapid progression; however, Foster-Kennedy syndrome remains a possible etiology.

The patient’s findings of rapidly progressive bilateral cranial neuropathies, orbital cellulitis, extensive disc pallor concerning for ophthalmic artery occlusion, and declining mental status is highly concerning for a fulminant infiltrative process. Such clinical presentations are usually caused by angioinvasive infections, including bacterial (eg, *Staphylococcus, Streptococcus*), fungal (eg, *Mucomycosis, Aspergillosis*), amoebic (eg, *Naegleria fowleri, Acanthamoeba*), and spirochetal infections (neuroborreliosis). Nonetheless, other less common infective etiologies should be considered, such as bacterial (*Neisseria meningitidis, Listeria*), viral (Herpes simplex virus type 1 (HSV-1), Varicella zoster virus (VZV), Enterovirus, Human Immunodeficiency Virus [HIV]) and fungal (*Cryptococcus, Coccidioidomycosis, Histoplasmosis*) sources.

To narrow the differential diagnosis and to identify the etiology further, extensive serum laboratory studies, cerebrospinal fluid (CSF) studies, digital subtraction angiography and a magnetic resonance imaging scan (MRI) of the brain with and without contrast were obtained. Hemoglobin A1c was 7.3% and serum glucose on admission ranged from 250-350 mg/dL. Blood cultures were negative, and urine cultures grew *Candida albicans*. Rapid plasma reagin (RPR) and treponema pallidum particle agglutination (TP-PA) were positive, consistent with history of untreated syphilis. HIV and Lyme disease serology were negative. Anti-nuclear antibody panel was not obtained given high suspicion for infectious etiology.

CSF analysis on day 4 of hospitalization revealed a white blood cell count of 740 per µL with 80% polymorphonuclear cells and no red blood cells. Protein in the CSF was elevated at 140 mg/dL. CSF fungal and bacterial cultures were negative, as were serologies for *Escherichia coli, Haemophilus influenza, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae, Cryptomegalovirus (CMV), Enterovirus (EV), HSV-1, Herpes simplex virus 2 (HSV-2), Human herpesvirus 6 (HHV-6), Human Pneumovirus (HPeV), VZV, and Cryptococcus neoformans/gattii*. VDRL (venerreal disease research lab) titers were 1:1. Digital subtraction angiography was obtained to ruled out carotid cavernous fistula. The study was significant for left ophthalmic artery occlusion and cavernous sinus thrombosis.

MRI brain with and without contrast were obtained on day 2 and 7 of hospitalization given persistent decline in exam and unclear etiology. The findings were consistent with progressive multifocal, inflammatory and necrotic changes with enhancement. *Figure 1* includes sections (A to F) of Brain MRI on day 7. Extensive leptomeningeal enhancement (Image A), basal cistern inflammation, and ventriculitis was evident. Progressive, multifocal inflammatory changes in paranasal sinuses (Image B) bilateral orbits, basal ganglia, thalamus, internal capsule, optic chiasm, optic nerves, and olfactory bulbs (Image C). Peri-arterial enhancement of supraclinoid internal carotid arteries, anterior cerebral arteries, and middle cerebral arteries were present (Image D). Left orbital tenting and proptosis was seen (Image E). Necrotic changes were seen in basal ganglia bilaterally (Image F).

While in the process of testing and work up, the patient was broadly treated with acyclovir, vancomycin, and ceftriaxone, but continued to decline clinically. Penicillin infusion was also initiated empirically given her history of untreated syphilis and weakly positive VDRL titers. The patient was treated with heparin drip for her cavernous sinus thrombosis. The patient remained intubated and comatose in the absence of sedation. Her diabetes was managed with insulin infusion, and cerebral edema was managed with hyperosmolar therapy. Despite all the measures taken, within
a few days, her neurological exam declined to only facial grimacing and extensor posturing to noxious stimuli, indicating severe brain injury. Fungal cultures in this case were obtained, though typically have low yield and require significant time for growth. However, given that our patient had little response to the broad-spectrum antibiotic therapy, a biopsy of the necrotic left middle turbinate was obtained and broad-spectrum antifungal therapy with voriconazole initiated. Biopsy revealed multiple fungal elements with evidence of arterial and boney invasion as shown in Figure 2 (Image A and B). A Karius Test™ identified Rhizopus delemar leading to disseminated Mucormycosis. A repeat brain MRI was also performed demonstrating diffuse, bilateral white matter hyperintensities, necrosis of the basal ganglia and orbitofrontal lobes, and multi-territory ischemic infarctions. The patient was then transitioned to definitive therapy with liposomal amphotericin B. Surgical debridement was not reasonable for our patient due to the presence of diffuse, deep, multifocal

![Figure 1](A - F). Axial magnetic resonance imaging (MRI) brain. Post-contrast fluid-attenuated inversion recovery (FLAIR) (images A, B, C, E, F) and post-contrast T1-weighted (image D) images show leptomeningeal enhancement (A), maxillary sinus enhancement (B), olfactory cortex enhancement (C), hypothalamus and periartrial enhancement (D), proptosis and left globe tenting (E), and bilateral basal ganglia enhancement and necrosis (F).

![Figure 2](A and B). Angioinvasion of fungus. Hematoxylin and eosin (H & E) stain (10x magnification) (A) and Periodic Acid-Schiff (PAS) for Fungus stain (20x magnification) (B) of a necrotic vessel. Vessel wall necrosis (black arrow) with numerous broad fungal hyphae (blue arrows).
lesions with devastating necrosis. Liposomal amphotericin B therapy was attempted for 2 days without clinical improvement. The patient was then transitioned to end-of-life care and ultimately died.

Discussion

Mucormycosis is a fast-spreading angioinvasive fungal infection with a very high mortality rate. It is associated with immunodeficiency, diabetes mellitus, iron overload, stem cell transplantation and the use of steroids. Awareness and knowledge of its presentation and treatment are of high importance—especially during the current pandemic—as COVID patients were being treated with steroids in several developing countries. Rhino-Orbital-Cerebral infection from Mucormycosis needs to be detected and treated early given its high mortality rate of 15-34%. Biopsies from affected tissues are proven to be the most useful, as yield of blood and CSF cultures is only 50%.

The most common agents of Mucormycosis are Rhizopus several species (spp.), Mucor spp., and Lichtheimia (formerly Absidia and Mycocladus) spp. Genera of other Mucorales, such as Rhizomucor, Sakseaee, Cunninghameilla, and Apophysomyces are less common.

The most common sites of invasive mucormycosis in human body are sinuses (39%), lungs (24%) and skin (19%). The most common clinical presentations of non-Covid-19 associated mucormycosis are rhino-orbito-cerebral followed by pulmonary, cutaneous, and disseminated disease. In patients with hematological malignancies, the main clinical form of the disease is pulmonary.

Among all the worldwide reported COVID-19 associated mucormycosis cases, majority of them were diagnosed in India alone. In this unique subset of patient population the common presentations were rhino-orbital (50%), followed by rhino-sinusal (17%), and rhino-orbito-cerebral (15%). The median time of diagnosis of mucormycosis was 5-20 days after diagnosis of Covid-19. This disease process was significantly associated with uncontrolled diabetes mellitus.

Recently, a study using bioinformatics and molecular modeling tools demonstrated that overexpression of GRP78 host cell surface receptors, which are a target of fungal coat proteins to bind to host cells, may be the rationale behind the increased vulnerability of SARS-CoV-2 patients to Rhizopus delemar infection.

Most cases of Mucormycosis resulted from inhalation of fungal sporangiospores that had been released in the air, or from direct inoculation of organisms into disrupted skin or gastrointestinal tract mucosa. The list of signs and symptoms that should be considered to be “red flags” includes cranial nerve palsy, diplopia, sinus pain, proptosis, peri-orbital swelling, orbital apex syndrome, and ulcers of the palate. Microscopy (direct and histopathology) and culture of various clinical specimens are the cornerstones of diagnosing Mucormycosis. New generation sequencing of the cell free DNA is a relatively new noninvasive diagnostic tool which successfully detects and identifies species of various infectious pathogens including Aspergillus and non-Aspergillus molds.

Patients with rhino-orbito-cerebral mucormycosis who are well enough for surgery often require orbital and maxillary sinus debridement. In one of the studies, survival rate was around 56% after being treated with surgical debridement and antibiotics. Although surgery has not shown to affect the outcomes in patients with CNS involvement but improved outcomes and lower mortality were seen in patients who underwent debridement surgery followed by antifungal treatment in the rhino-orbital disease (with no CNS involvement). Of the survivors, one third will suffer from near or total vision loss. ICU admission and proof of CNS involvement have also been found to be associated with higher mortality rate. The median survival time for patients with fatal outcome is around 26 days in rhino-orbital-cerebral disease.

These patients are also at increased risk for an ischemic stroke secondary to a mycotic thrombus, of which thrombus retrieval and carotid stenting may be performed in patients with acute large vessel occlusion. Cavernous sinus thrombosis from septic etiology is rare. The role of anticoagulation (AC) is controversial due to lack of large longitudinal studies and risk of hemorrhagic complications. Although AC is likely indicated in scenarios of underlying hypercoagulable state and lack of clinical improvement with antibiotics or surgery, data is limited. One retrospective study did not find any significant difference in the frequency of new intracerebral hemorrhage in patients who received AC in the setting of septic venous sinus thrombosis.

Intravenous (IV) liposomal amphotericin B is the drug of choice for initial therapy. Amphotericin is a polyene antifungal agent which acts by disruption of fungal cell wall synthesis. Posaconazole or Isavuconazole can also be used as step down or salvage therapy for patients who don’t respond to or cannot tolerate amphotericin B. Posaconazole and Isavuconazole are triazole antifungal agents which disturb the fungal cell wall formation process by inhibiting the enzyme lanosterol 14-alpha demethylase, decreasing the synthesis of ergosterol which is vital in fungal cell wall formation. Duration of treatment is not definite and should continue until resolution of the infection and improvement in radiographic and clinical signs. In some cases, therapy can continue for months to achieve eradication of infection or even be lifelong if the patients immunosuppression cannot be corrected.

Author Contributions

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References
1. Fairley C, Sullivan TJ, Bartley P, Allworth T, Lewandowski R. Survival after rhino-orbital-cerebral mucormycosis in an immunocompetent patient. *Ophthalmology*. 2000;107(3):555-558. doi:10.1016/s0161-6420(99)00142-6.
2. Walsh TJ, Gamaletsou MN, McGinnis MR, Hayden RT, Kontoyiannis DP. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). *Clin Infect Dis*. 2012;54(suppl 1):S55-S60. doi:10.1093/cid/cir866.
3. Petrikkos G, Skiada A, Lortholary O, et al. Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis*. 2012;54(suppl 1):S23-S34. doi:10.1093/cid/cir866.
4. Patel A, Agarwal R, Rudramurthy SM, et al. Multicenter epidemiologic study of coronavirus disease-associated mucormycosis, India. *Emerg Infect Dis*. 2021;27(9):2349-2359. doi:10.3201/eid2709.210934.
5. Dilek A, Ozaras R, Ozkaya S, Sunbul M, Sen EI, Leblebiciglu H. COVID-19-associated mucormycosis: Case report and systematic review. *Travel Med Infect Dis*. 2021;44:102148. doi:10.1016/j.tmaid.2021.102148.
6. Hoenigl M, Seidel D, Carvalho A, ECMM, ISHAM collaborators, et al. The emergence of COVID-19 associated mucormycosis: A review of cases from 18 countries. *Lancet Microbe*. 2022;25:e543-e552. doi:10.1016/S2666-5247(21)00237-8.
7. Elgohary AM, Elfiky AA, Barakat K. GRP78: A possible relationship of COVID-19 and the mucormycosis; in silico perspective. *Comput Biol Med*. 2021;139:104956. doi:10.1016/j.compbiomed.2021.104956.
8. Farmakiotis D, Kontoyiannis DP. Mucormycoses. *Infect Dis Clin North Am*. 2016;30(1):143-163. doi:10.1016/j.idc.2015.10.011.
9. Corzo-León DE, Chora-Hernández LD, Rodríguez-Zulueta AP, Walsh TJ. Diabetes mellitus as the major risk factor for mucormycosis in Mexico: Epidemiology, diagnosis, and outcomes of reported cases. *Med Mycol*. 2018;56(1):29-43. doi:10.1093/mycol/1000000000004742.
10. Lamotte G, Farzal Z, Zimmerman WD, et al. Clinical reasoning: Monocular vision loss, ophthalmoplegia, and strokes in a 61-year-old man with diabetes mellitus. *Neurology*. 2017;89(24):e276-e281. doi:10.1212/WMN.0000000000004742.
11. Alistruay-Izquierdo A, Castelli MV, Cuesta I, et al. Activity of posaconazole and other antifungal agents against Mucorales strains identified by sequencing of internal transcribed spacers. *Antimicrob Agents Chemother*. 2009;53(4):1686-1689. doi:10.1128/AAC.01467-08.
12. Hong DK, Blauwkamp TA, Kertesz M, et al. Liquid biopsy for infectious diseases: Sequencing of cell-free plasma to detect pathogen DNA in patients with invasive fungal disease. *Diagn Microbiol Infect Dis*. 2018;92(3):210-213. doi:10.1016/j.diagmicrobio.2018.06.009.
13. Arndt S, Aschendorff A, Echtermach M, Daemmrich TD, Maier W. Rhino-orbital-cerebral mucormycosis and aspergillosis: differential diagnosis and treatment. *Eur Arch Otorhinolar-*

yngol*. 2009;266(1):71-76. doi:10.1007/s00405-008-0692-y.
14. Scharf EL, Cloft HJ, Wijdicks E. Mucor thrombus. *Neurocrit Care*. 2016;24(2):268-272. doi:10.1007/s12028-015-0186-x.
15. Zuurbier SM, Coutinho JM, Stam J, et al. ISCVT investigators. clinical outcome of anticoagulant treatment in head or neck infection-associated cerebral venous thrombosis. *Stroke*. 2016;47(5):1271-1277. doi:10.1161/STROKEAHA.115.011875.
16. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis*. 2005;41(5):634-653. doi:10.1086/432579.
17. Skiada A, Lass-Floerl C, Klímko N, Ibrahim A, Roilides E, Petrikkos G. Challenges in the diagnosis and treatment of mucormycosis. *Med Mycol*. 2018(suppl 1):56:93-101. 10.1093/mmy/myx101.