An Instructive Case of Cerebral Mucormycosis

BELINDA SHAO, MD, MPH; MATTHEW J. HAGAN, BS; RAHUL A. SASTRY, MD; MICHAEL KRITSELIS, DO; JOHN E. DONAHUE, MD; STEVEN A. TOMS, MD

ABSTRACT

BACKGROUND: Mucormycosis can lead to fatal rhinocerebral infection.

CASE: A 53-year-old male with diabetes presented with altered mental status. He had been recently discharged from an admission for COVID-19 pneumonia treated with remdesivir and methylprednisolone. Imaging demonstrated a large left frontal mass with midline shift suspicious for a primary brain neoplasm. His neurologic exam rapidly declined and the patient was taken to the operating room for decompressive hemicraniectomy. Post-operatively, the patient remained comatose and failed to improve. Autopsy revealed a cerebral mucormycosis infection.

DISCUSSION: Despite concern for a primary brain neoplasm the patient was diagnosed postmortem with a mucormycosis infection. Other features supporting this diagnosis included nasal sinusitis on initial scans, his fulminant clinical decline, rapidly progressive imaging findings, and persistent hyperglycemia throughout his clinical course.

CONCLUSION: In an era of high steroid usage to treat COVID-19, mucormycosis infection must be considered in high-risk patients demonstrating disproportionate clinical decline.

KEYWORDS: mucormycosis, diabetic ketoacidosis, COVID-19, glioblastoma, immunosuppression, cerebral edema, decompressive hemicraniectomy

INTRODUCTION

Mucormycosis is a fungal infection that can cause a variety of clinical syndromes, particularly in patients with uncontrolled diabetes mellitus (DM) or underlying malignancy.[1] Patients who are immunocompromised secondary to steroid use are also at risk.[2] Most commonly, mucormycosis leads to rhino-orbital-cerebral (34%), cutaneous (22%), or pulmonary infection (20%).[1] There is a 50% mortality rate in those infected.[3] While rare, the prevalence of mucormycosis infection is increasing due to an increase in the immunocompromised population.[2] The current estimated incidence in the United States is three cases per million.[4] However, the prevalence of mucormycosis infection, and fungal infections in general, may be rising.[4-6]

Due to the rarity of the disease and the non-specific presentation of patients with mucormycosis, timely diagnosis is challenging. Frequently, by the time an accurate diagnosis has been made it may too late to effectuate meaningful treatment.[2] Here we present the case of a patient admitted to the hospital with non-specific neurologic symptoms who then experienced a rapid clinical decline with eventual postmortem diagnosis of mucormycosis.

CASE PRESENTATION

A 53-year-old male with a history of insulin dependent type II DM, lymphedema, compensated hepatitis C virus cirrhosis, hypertension, and recent COVID-19 infection presented to the emergency department following a transient episode of right upper extremity weakness and a ground level fall. The patient had been discharged four days prior to this visit after an admission for COVID-19 pneumonia, treated with remdesivir and methylprednisolone. Since discharge, he experienced progressive confusion, fatigue, and difficulty with ambulation.

On initial evaluation, the patient was alert and oriented to person and situation, but notably confused compared to his previous visit and was unable to report his address or his medical problems. His right upper extremity weakness had resolved and his motor, sensory, and language function had otherwise returned to baseline.

The patient's laboratory studies are reported in **Table 1** and notable for thrombocytopenia, which is his baseline, as well as hyperglycemia. Liver function tests were minimally elevated and at baseline. Computed tomography (CT) of the head demonstrated a left frontal mass-occupying lesion with midline shift as well as paranasal sinusitis (**Figure 1**).

Body imaging was negative for any potential primary malignancy. A chest x-ray revealed bilateral multifocal airspace disease consistent with his recently treated COVID-19 pneumonia. Subsequent magnetic resonance imaging (MRI) revealed an infiltrative and hemorrhagic left frontal mass extending across the corpus callosum, highly suspicious for a primary central nervous system (CNS) neoplasm (**Figure 2**). The patient was started on dexamethasone (6 mg every 6

Table 1. Patient laboratory results upon presentation.

Lab	Value
Complete blood count	
White blood cells (x109/L)	5.0
Red blood cells (x1012/L)	4.1
Hemoglobin (g/dL)	12.5
Hematocrit (%)	38.8
Platelets (x109/L)	41
Serum Chemistry	
Sodium (mEq/L)	134
Potassium (mEq/L)	4.7
Chloride (mEq/L)	103
Bicarbonate (mEq/L)	23
Blood urea nitrogen (mg/dL)	16
Creatinine (mg/dL)	0.79
Glucose (mg/dL)	244
Aspartate aminotransferase (iu/L)	65
Alanine aminotransferase (iu/L)	55
Alkaline phosphatase (iu/L)	111
Venous blood gas	
pH	7.42
pCO2 (mmHg)	38
pO2 (mmHg)	46
O2 saturation (%)	82

Figure 1. Head computed tomography (CT) upon presentation. Axial view revealing large region of hypodensity in the left frontal lobe, sulcal effacement, and extension across the corpus callosum toward the right frontal lobe (arrow). Visualization of left-to-right midline shift up to 6 mm anteriorly.

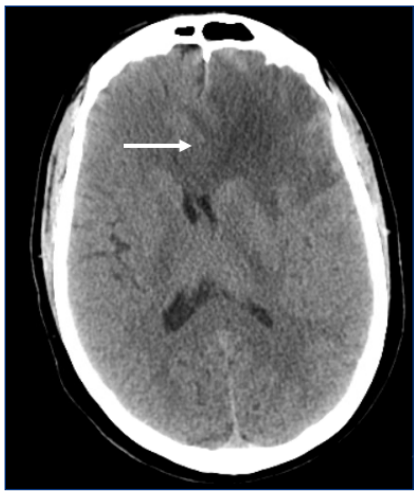


Figure 2. Initial brain magnetic resonance imaging (MRI). Axial T2 sequence revealing extensive high signal in the left frontal lobe extending across the corpus callosum with sulcal effacement and mass effect on the frontal horns (arrow). Demonstration of an irregular rim of enhancement consistent with hemorrhage (asterisks).

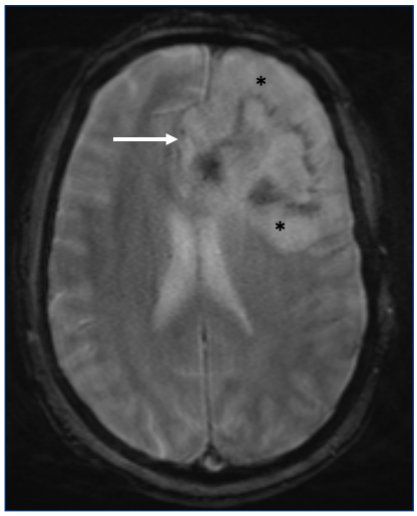
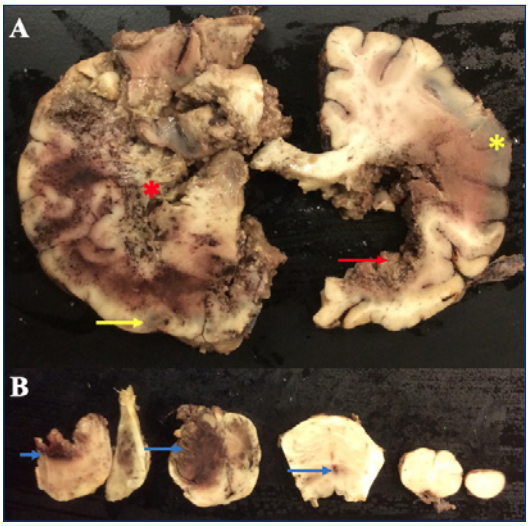


Figure 3. Gross pathology upon post-mortem autopsy.
(A) Cross section of the frontal lobes, demonstrating duskiness (yellow arrow/asterisk) bilaterally with central necrosis (red arrow/asterisk) involving the left frontal lobe. This extends posteriorly to involve the left parietal lobe and right posterior frontal lobe/temporal lobe.
(**B**) In the brainstem, there was a circular, well-circumscribed hemorrhage (blue arrows) that involved the right cerebral peduncle and surrounding midbrain at the level of the red nucleus and extends inferiorly to involve the pons at the level of the fifth cranial nerve.



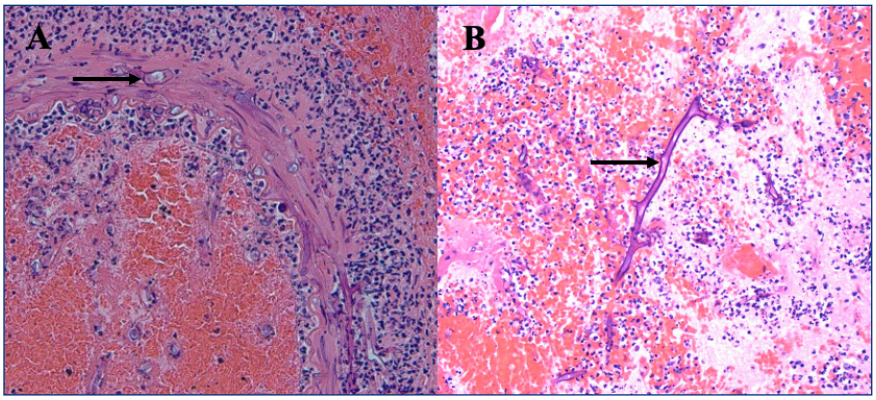
hours) for cerebral edema, and tentative plans for surgical biopsy and/or resection were made.

On hospital day one however, the patient's neurologic exam rapidly declined; he became disoriented and nonverbal, followed by extensor posturing. The patient was emergently intubated. Repeat CT brain studies that day revealed rapidly progressive cerebral edema and midline shift, and hypodense areas suspicious for lesion spread. Cerebral edema was treated with increasing doses of dexamethasone as well as mannitol and hypertonic saline. An insulin drip was initiated, as well. Given this fulminant decline and comatose state due to central herniation, the patient was taken emergently to the operating room for decompressive hemicraniectomy. Platelets were administered pre-operatively given his thrombocytopenia. Intraoperatively, immediately following bony decompression, the patient's brain swelled out of the calvarial defect, demonstrating severe cerebral edema. Given this as well as his thrombocytopenia, no intraoperative biopsy of the lesion was performed due to concern for intracerebral hematoma given the tissue's friability.

Post-operatively, the patient remained comatose. Given his disproportionate clinical decline, as well as new lesions and peripheral contrast enhancement on post-operative brain MRI, as well as a new leukocytosis of 15.0 x10^9/L and fever on post-operative day 1, an infection was suspected. The patient was started on empiric ampicillin, vancomycin, and meropenem. However, he continued to decline and on hospital day four he was transitioned to comfort measures only status.

Postmortem autopsy and neuropathology revealed a mass lesion with extensive hemorrhage and necrosis in the

Figure 4. Histologic slides upon post-mortem autopsy and neuropathology.
(**A**) High-power magnification photograph showcasing invasion of arteriolar lumen and tunica media by the fungal organisms (arrow). Hematoxylin and Eosin, 200X.
(**B**) High-magnification photograph highlighting the morphology of the fungal organisms. The organisms contain hyphae that are broad-based and non-septated with right-angle branching (arrow). Hematoxylin and eosin, 200X.



bilateral frontal and parietal lobes, corpus callosum, and deep gray matter structures, extending inferiorly into the brainstem through the left cerebral peduncle and into the pons (**Figure 3**). Microscopically, the mass was diagnosed as a hemorrhagic abscess with angioinvasion secondary to mucormycosis (**Figure 4**).

DISCUSSION

We present a patient with a left frontal brain lesion and fulminant neurological and radiographic decline in the setting of diabetes mellitus, recent steroid treatment for COVID-19 pneumonia, and possible underlying nasal sinusitis. Given the initial clinical picture, the patient's first suspected diagnosis was primary infiltrative CNS neoplasm; however, rapid and disproportionate clinical decline soon raised suspicion for other etiologies. The patient was ultimately diagnosed with a mucormycosis infection postmortem, with impressive hallmark gross and histological pathology findings featured in this vignette. While not necessary to make the diagnosis, other features supporting this diagnosis during the patient's clinical course included the contrast enhancement pattern of the lesions on MRI, nasal sinusitis on his initial CT, and marked hyperglycemia throughout his clinical course due to diabetes and both inpatient and pre-admission steroid usage.

Rhino-orbital-cerebral involvement is the most common manifestation of mucormycosis,[7] often presenting with fever (44%), nasal ulceration or necrosis (38%), impaired vision (30%), opthalmoplegia (29%), sinusitis (26%), and headache (25%).[8] Notably, the patient described did not report or demonstrate these symptoms on his initial presentation, although retrospectively his initial head CT imaging report did comment on nasal sinusitis.

The most common underlying disorder in those diagnosed with mucormycosis is diabetes, specifically type II DM.[9] Classically, mucormycosis infection is associated with diabetic ketoacidosis. While our patient was not ever clinically diagnosed with diabetic ketoacidosis and his blood gases and serum bicarbonate levels were normal throughout admission, his serum glucose values were elevated both before and during his hospitalization. This was likely due to his acute disease processes and steroid usage both during his discussed hospitalization as well as his prior hospitalization for COVID-19 pneumonia. Patients can be at risk for mucormycosis infection with blood sugar levels greater than 200 for more than seven days, even without ketoacidosis.[10] Furthermore, in about 9% of cases, patients have no predisposing risk factors for mucormycosis.[11] In sum, diagnosis of mucormycosis requires a high index of suspicion in at-risk patients presenting with fever, sinusitis, altered mental status, and necrosed tissue on the nose or palate. Diagnosis confirmation is ultimately made by histopathology and tissue culture showing broad aseptate hyphae.[12,13]

In the contemporary period of high COVID-19 prevalence, co-infection is expected to occur at some background rate. This is especially true given that the standard therapy for severe COVID-19 pneumonia is corticosteroids which could precipitate mucormycosis infection due to their immunosuppressive and hyperglycemic effects.[14,15] Concurrent COVID-19 and mucormycosis infection has been reported previously in case reports[15-18] as well as analyzed in a systematic literature review of 101 patients.[19] In the present clinical vignette, our patient had many medical comorbidities predisposing him to mucormycosis including poorly controlled insulin-dependent DM and cirrhosis.[20,21] This was likely exacerbated by his recent infection with COVID-19 given its immunosuppressive treatment with dexamethasone, ultimately leading to his rapidly progressive mucormycosis infection, neurological decline, and eventual demise. Notably, Elhamamsy et al. (2021)[18] reported a case series of three nondiabetic immunocompetent patients who presented with rhino-orbital cerebral mucormycosis in the setting of a COVID-19 infection. They were subsequently treated with corticosteroids at dosages higher than those recommended by the World Health Organization. The authors concluded that guidelines regarding corticosteroid dosages to treat COVID-19 should be adhered to. Similarly, the patient in the present case report was receiving dosages of dexamethasone higher (6mg every 6 hours) than recommended for COVID-19 therapy (6mg daily for 7-10 days).[22] Of course, the

indication for steroids in this case was cerebral edema and not COVID-19 infection, however. Lastly, the authors suggest that immune dysregulation caused by COVID-19 may contribute to an increased risk of mucormycosis infection.[18]

Due to the aggressive and invasive nature of the disease, timely initiation of treatment is tantamount. The primary medical treatment is the antifungal amphotericin B.[11] The liposomal formulation of amphotericin B is commonly used as it has a lower side effect profile.[23] The recommended starting dose for liposomal amphotericin B is 5mg/day[24-26] although some literature supports the use of doses closer to 10mg/day.[27] Aggressive early surgical debridement has been associated with improved outcomes.[28] Removal of the affected necrotic and infarcted tissue can be disfiguring and may necessitate removal of the orbit and palate. In patients with mucormycosis and COVID-19 coinfection, surgery appears to decrease mortality and disease progression.[26] When anatomically feasible, endoscopic interventions have also been employed successfully.[29] In addition to antifungal therapy and surgery, patients must be medically optimized to attenuate risk factors for disease progression and recurrence. These measures include treating underlying diabetes and metabolic acidosis as well as stopping any immunosuppressive therapies.[30]

CONCLUSION

In high-risk patients with contrast-enhancing cerebral masses that demonstrate disproportionate progression of neurologic decline, edema, and lesion spread, rhinocerebral mucormycosis must be considered and not missed. This illustrative vignette may be particularly useful in an era of high COVID-19 prevalence and its requisite management with steroids that can exacerbate hyperglycemia and immunosuppression in patients with diabetes and sinusitis.

References

1. Jeong W, Keighley C, Wolfe R, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. *Clinical Microbiology and Infection.* 2019;25(1):26-34.
2. Skiada A, Lass-Floerl C, Klimko N, Ibrahim A, Roilides E, Petrikkos G. Challenges in the diagnosis and treatment of mucormycosis. *Med Mycol.* 2018;56(suppl_1):93-101.
3. Palejwala SK, Zangeneh TT, Goldstein SA, Lemole GM. An aggressive multidisciplinary approach reduces mortality in rhinocerebral mucormycosis. *Surg Neurol Int.* 2016;7:61.
4. Prakash H, Chakrabarti A. Global Epidemiology of Mucormycosis. *J Fungi (Basel).* 2019;5(1).
5. Rees JR, Pinner RW, Hajjeh RA, Brandt ME, Reingold AL. The epidemiological features of invasive mycotic infections in the San Francisco Bay area, 1992-1993: results of population-based laboratory active surveillance. *Clin Infect Dis.* 1998;27(5):1138-1147.
6. Webb BJ, Ferraro JP, Rea S, Kaufusi S, Goodman BE, Spalding J. Epidemiology and Clinical Features of Invasive Fungal Infection in a US Health Care Network. *Open Forum Infect Dis.* 2018;5(8):ofy187.
7. Gupta S, Goyal R, Kaore NM. Rhino-Orbital-Cerebral Mucormycosis: Battle with the Deadly Enemy. *Indian J Otolaryngol Head Neck Surg.* 2020;72(1):104-111.
8. Yohai RA, Bullock JD, Aziz AA, Markert RJ. Survival factors in rhino-orbital-cerebral mucormycosis. *Surv Ophthalmol.* 1994;39(1):3-22.
9. 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.
10. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. *Clin Infect Dis.* 2000;30(6):851-856.
11. Bhandari J, Thada P, Nagalli S. Rhinocerebral Mucormycosis. [webpage]. 2021; https://www.ncbi.nlm.nih.gov/books/NBK559288/.
12. Balai E, Mummadi S, Jolly K, Darr A, Aldeerawi H. Rhinocerebral Mucormycosis: A Ten-Year Single Centre Case Series. *Cureus.* 2020;12(11):e11776.
13. Challa S. Mucormycosis: Pathogenesis and Pathology. *Current Fungal Infection Reports.* 2019;13(1):11-20.
14. Group TCST. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. *JAMA.* 2021;326(18):1807-1817.
15. Mehrabi Z, Salimi M, Niknam K, et al. Sinoorbital Mucormycosis Associated with Corticosteroid Therapy in COVID-19 Infection. *Case Reports in Ophthalmological Medicine.* 2021;2021:9745701.
16. Dilek A, Ozaras R, Ozkaya S, Sunbul M, Sen EI, Leblebicioglu H. COVID-19-associated mucormycosis: Case report and systematic review. *Travel Med Infect Dis.* 2021;44:102148.
17. 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.
18. Elhamamsy S, Bayer T, Al-Kaffas M, et al. Rhino-Orbital Cerebral Mucormycosis in Non-Diabetic Patients with COVID-19. *R I Med J (2013).* 2021;104(8):19-21.
19. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr.* 2021;15(4):102146.
20. Elsiesy H, Saad M, Shorman M, et al. Invasive mucormycosis in a patient with liver cirrhosis: case report and review of the literature. *Hepat Mon.* 2013;13(8):e10858.
21. Abbas Z, Jafri W, Rasool S, Abid S, Hameed I. Mucormycosis in patients with complicated cirrhosis. *Singapore Med J.* 2007;48(1):69-73.
22. Dexamethasone in Hospitalized Patients with Covid-19. *New England Journal of Medicine.* 2020;384(8):693-704.
23. Lemke A, Kiderlen AF, Kayser O. Amphotericin B. *Applied Microbiology and Biotechnology.* 2005;68(2):151-162.
24. Handzel O, Landau Z, Halperin D. Liposomal amphotericin B treatment for rhinocerebral mucormycosis: how much is enough? *Rhinology.* 2003;41(3):184-186.
25. Hussain S, Baxi H, Riad A, et al. COVID-19-Associated Mucormycosis (CAM): An Updated Evidence Mapping. *Int J Environ Res Public Health.* 2021;18(19).
26. Aranjani JM, Manuel A, Abdul Razack HI, Mathew ST. COVID-19–associated mucormycosis: Evidence-based critical review of an emerging infection burden during the pandemic's second wave in India. *PLOS Neglected Tropical Diseases.* 2021;15(11):e0009921.
27. Lanternier F, Poiree S, Elie C, et al. Prospective pilot study of high-dose (10 mg/kg/day) liposomal amphotericin B (L-AMB) for the initial treatment of mucormycosis. *Journal of Antimicrobial Chemotherapy.* 2015;70(11):3116-3123.

28. Di Carlo P, Pirrello R, Guadagnino G, et al. Multimodal Surgical and Medical Treatment for Extensive Rhinocerebral Mucormycosis in an Elderly Diabetic Patient: A Case Report and Literature Review. *Case Reports in Medicine.* 2014;2014:527062.
29. Saedi B, Sadeghi M, Seilani P. Endoscopic management of rhinocerebral mucormycosis with topical and intravenous amphotericin B. *J Laryngol Otol.* 2011;125(8):807-810.
30. Spellberg B, Ibrahim AS. Recent advances in the treatment of mucormycosis. *Curr Infect Dis Rep.* 2010;12(6):423-429.

Authors

Belinda Shao, MD, MPH, PGY-3, Department of Neurosurgery, Warren Alpert Medical School of Brown University, Providence, RI.

Matthew J. Hagan, BS, MS-3, Warren Alpert Medical School of Brown University, Providence, RI.

Rahul A. Sastry, MD, Department of Neurosurgery, Warren Alpert Medical School of Brown University, Providence, RI.

Michael Kritselis, DO, Department of Neuropathology, Warren Alpert Medical School of Brown University, Providence, RI.

John E. Donahue, MD, Department of Neuropathology, Warren Alpert Medical School of Brown University, Providence, RI.

Steven A. Toms, MD, Department of Neurosurgery, Warren Alpert Medical School of Brown University, Providence, RI.

Disclosures

The authors report no relevant disclosures pertaining to the present manuscript.

Correspondence

Matthew Hagan, BS
Warren Alpert Medical School of Brown University
222 Richmond Street
Providence, RI, 02903
matthew_hagan@brown.edu