

COVID-19 Related Rhino-Orbital-Cerebral Mucormycosis: Neurological Manifestation And Related Risk Factors In Two Cases

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Abstract

Mucormycosis is an opportunistic infection that has become a serious concern as a result of the immunosuppressive drugs used during COVID-19. In this report, we describe two cases of rhino-orbital-cerebral mucormycosis with neurological presentation and ophthalmologic problems accompanied by a history of COVID-19 and diabetes.

COVID-19 Related Rhino-Orbital-Cerebral Mucormycosis: Neurological Manifestation And Related Risk Factors In Two Cases

Running Title: Neurological Manifestation Of ROCM

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Abstract Mucormycosis is an opportunistic infection that has become a serious concern as a result of the immunosuppressive drugs used during COVID-19. In this report, we describe two cases of rhino-orbital-cerebral mucormycosis with neurological presentation and ophthalmologic problems accompanied by a history of COVID-19 and diabetes. **Keywords :** ROCM, seizure, COVID-19, diabetes mellitus

Introduction

Mucormycosis is an opportunistic infection caused by organisms belonging to the order Mucorales affecting between 0.4 and 1.7 cases per 10,000 of the world's population as reported in 2012 [1, 2]. Due to COVID-19 mucormycosis has become far more common and is now considered a major health threat [1, 3]. Rhino-orbital-cerebral-mucormycosis (ROCM) is the common type of mucormycosis mostly associated with diabetes mellitus (DM, particularly uncontrolled DM) and less commonly other immunosuppressive conditions such as malignancies, organ transplants, HIV, and long-term broad-spectrum antibiotics or immunosuppressive treatment like steroids which is the conventional treatment for COVID-19 [4].

Despite recent case reports and systematic reviews, we still do not have a strong grasp of mucormycosis, including the possibility of brain invasion, abscess formation, and neurological symptoms. Unfortunately, Bhattacharyya et al. reported a high mortality rate of mucormycosis related to COVID-19 (33-80%)[1]. In this article, we will discuss two cases of ROCM with brain abscesses, unusual neurological presentations, and possible effective management.

Cases

Case 1

40 Y/O man came to the emergency room with a seizure, reduced level of consciousness (LOC), and headache. In the last five days, she experienced fever and malaise. On examination, there was mild ptosis with restricted movement toward the right in the right eye suggesting right abducens nerve damage accompanied by impaired visual acuity and color vision. There wasn't any sign of palate necrosis or nasal discharge. Kernig sign was negative however specimen from lumbar puncture evidenced meningitis.

Patients declared a history of diabetes with regular insulin usage and Covid-19 infection in the past two months. A Chest CT scan denoting an ongoing COVID-19 infection was obtained (figure 1). The patient had experienced uncontrolled blood sugar (Blood Sugar = 548 mg/dL) during the usage of broad-spectrum antibiotics along with corticosteroids at the time of the COVID-19 infection. We also recorded a rise in creatinine (highest blood creatinine = 3.3 mg/dL) during treatment.

Imaging evaluation revealed CNS findings as depicted in figure 1. Suggesting mucormycosis or other bacterial infection mimicking low-grade glioma therefore we started broad-spectrum antibiotics accompanied by liposomal amphotericin B (5 mg/kg) followed by definitive surgery.

There were no sinonasal symptoms but due to the origin of the lesion that was seen from below, we chose the Endoscopic transnasal corridor. After ethmoidectomy, we encountered frank puss and granulation tissue as white creamy material. The grand and basal lamellae were destroyed. We entered the cranial cavity; a Frontal basal abscess was drained and copious irrigation was implemented. We took advantage of the absence of arachnoid bridge and CSF leakage and let the skull base be opened to the nasal cavity for further abscess drainage.

Despite our expectations for suppurative bacterial infection pathological findings were:

Section of brain tissue shows well-formed and occasionally coalescing granulomas composed of epithelioid histiocytic multinucleated giant cells, lymphocytes, and central neutrophilic microabscesses with an area of

necrosis containing fragmented broad fungal hyphae with right-angle branching and no septation, perivascular inflammation, astrogliosis, and edema are noted which is diagnosed as necrotizing granulomatous encephalitis consistent with mucormycosis without any evidence of malignancy.

In the course of treatment, the patient's headache and drowsiness worsened. New imaging revealed aggravation of cerebral edema and persistent frontal mass effect. Hence, unilateral frontal craniotomy and removal of necrotic tissues were performed, and it was attempted to close the base defect with fascia lata and decompress the frontal lobe.

After the surgery, three sessions of retrobulbar amphotericin B (5mg/kg) were injected by ophthalmologists due to orbital apex syndrome (OAS). Nasal endoscopy was normal before discharge. finally, the patient was discharged after two months without any visual deficit or headache. He was prescribed to use posaconazole (300 milligrams) and antibiotics. After 3 months of follow up patient has not experienced any significant neurological signs and symptoms including headache, altered LOC, and visual defects along with any recurrence manifestation.

Fig. 1. *The parenchymal lesion in left frontal base with mild enhancement paranasal sinus involvement in T1 with D, E: Chest CT scan illustrating COVID-19 involvement F: hypodensity in left frontal base.*

Case 2

Our second case is a 50Y/O man who presented with seizures (2 times), headache, obtundation, left mild proptosis, and orbital pain since 2 weeks ago; 3 weeks after recovery from COVID-19 infection. At the physical examination, we didn't find further remarkable neurological signs.

The patient had a history of diabetes mellitus. COVID-19 was confirmed by PCR and corticosteroid usage was noted in this treatment regimen. Based on the probability of mucormycosis, we started liposomal IV amphotericin B (5 mg/kg) and broad-spectrum antibiotics followed by the surgery.

Although MRI defined intracranial mass and edema, because of the involvement of ethmoid sinus and continuation of epidural collection to sinonasal space we had a preliminary diagnosis of purulent complicated sinusitis with epidural empyema and chose the intranasal endoscopic path to open affected sinuses and brain epidural puss and irrigation. We found black debris and puss characteristics of sinonasal mucormycosis. Ethmoidectomy and entrance to epidural space ensued.

Despite the specimen and puss was not confronting a classic fungal mucormycosis infection, the pathology was: Left periorbital soft tissue debridement is necrotic and inflamed fibro adipose tissue with non-septate right-angle branching hyphae which is morphologically consistent with mucormycosis fragments of inflamed and necrotic respiratory mucosa present Middle turbinate and bilateral ethmoidal sinus debridement, focally necrotic respiratory mucosa with non-necrotizing granulomatous inflammation no fungal element identified in this sample.

A week after surgery, sinus endoscopy revealed septum necrosis so we resected the crust, and the sinuses were washed. patient's diabetes was controlled by our endocrinologist during the treatment course and finally after the one-month patient was discharged from the hospital without visual defect or headache. During the last three months of follow-up, there is no evidence of significant neurological problems as well as any recurrence of the infection.

Fig. 2 A, B, C: hypointense lesion in T1 with ring enhancement in left anterior skull base and frontal base which spreads to the medial part of left orbit D: ethmoidal erosion in bone window CT scan

Discussion

Rhinocerebral mucormycosis is an aggressive infection and failure to diagnose or treat can lead to high mortality. [1]. Mucormycosis has five different spread sites: rhinocerebral, gastrointestinal, cutaneous, respiratory, and disseminated. ROCM is the predominant manifestation of the infection which can progress to the orbital and deeper sites of the brain through paranasal sinuses[1, 5] and could result in uncommon

presentations such as seizures, reduced LOC, or ophthalmic involvement. Mucormycosis infects the nervous system in 20% of hematological cases and brain abscess occurs rarely in 2 of 43 patients with mucormycosis[5, 6]. Unfortunately, It has been observed that mucormycosis has been rising since the COVID-19 pandemic began, and recently it has become an issue of concern for our health care system[1]. The condition could be a consequence of a dysregulated immune system due to a reduction in T cell count, altered CD4/CD8 ratio, and overuse of immunosuppresses like corticosteroids following the COVID-19 which is exacerbated by uncontrolled blood sugar in people with undetermined diabetes cases[1]. Sharma *et al* . in their prospective study believe diabetes is the most common risk factor for the ROCM after COVID-19 which 57% of the cases presenting with uncontrolled diabetes (HBA1c > 6.5 mg/dl)[7].

Diagnosis of ROCM is based on the clinical finding including headache, nasal or sinus congestion, and blackish discoloration within the nose or palate. Radiological findings such as CT or MRI and pathological investigations are crucial for confirmation of the diagnosis. Involvement of the paranasal sinuses and at the top of them ethmoid sinus is the highly common form. However, it could progress to the other sinuses and infect the orbit, extraocular muscles, and finally the brain[8].

Rhinorage and the blackish plate were the most common presentation of mucormycosis in our center during the COVID-19, however, the common presentation was absent in our recent cases. Instead, these two patients suffered from neurological problems such as seizures, low LOC, and OAS which means we should be concerned more about mucormycosis in immunosuppressed patients especially in tumor mimicking masses and always keep it in our differential diagnosis.

visual defects were reported in mucormycosis cases, this may be caused by infarctions in blood vessels supplying the retina or optic nerve, in addition to the compression of the nerve through the cavernous sinus, as well as infection and necrosis[8].

Amphotericin B plus posaconazole was the regimen commonly used in previous studies [1]. consistent with our cases, other studies found intraorbital and retrobulbar injection of amphotericin B useful[1, 9]. However surgical debridement is the final and crucial approach for these patients.

Conclusion

we believe the incidence of this opportunistic infection is increasing due to the higher incidence of the mentioned risk factors and the key solution was early detection since mucormycosis has broad manifestation and correct intervention to reduce mortality and morbidity.

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