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Case Report

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A Rare Case of Rhino Orbito Cerebral Mucor Mycosis Associated with COVID 19 Infection

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Abstract

Background: Severe Acute Respiratory Syndrome Coronavirus disease 2019 (COVID-19) infections is known to be associated with a wide range of bacterial and fungal secondary infections. This is report of a patient with uncontrolled blood sugar and COVID-19 infection, who developed rhino-orbito cerebral mucormycosis.

Design/results: A 50-year-old female, newly detected Type 2 diabetes mellitus, and RT-PCR positive for acute respiratory syndrome coronavirus 2 (SARS-CoV-2), developed left eye pain with decreased vision during the hospital course. She was on intravenous steroids and antibiotics for 8 days. Magnetic resonance imaging of brain, orbits with paranasal sinuses, showed pansinusitis, cavernous sinus thrombosis and orbital involvement with extensive cerebral infarcts involving the ACA and PCA territories. Broad aseptate filamentous fungal hyphae conforming to the morphology of mucormycosis were detected in the nasal swabs and culture-confirmed.

Conclusions: Extensive use of steroids, broad-spectrum antibiotics, antifungals and other immunosuppressive drugs, in the presence of uncontrolled diabetes, may lead to the development or exacerbation of an underlying fungal disease. Even in the absence of facial swelling and cellulitis, a high index of suspicion is necessary to detect secondary invasive fungal or bacterial infections in patients with COVID-19 disease.

Keywords

Mucormycosis, COVID-19 infection, Orbital, Rhinocerebral

Introduction

Mucormycosis is an opportunistic infection which is caused by fungi of the order of Mucoromycetes, class Mucorales and the most common agents are Rhizopus spp., Mucor spp. and Lichtheimia (formerly Absidia and Mycocladus) [1]. It is commonly seen in immunosuppressed patients.

Mucormycosis infection presents as six types: rhino-orbito-cerebral (ROC), pulmonary, cutaneous, gastrointestinal, disseminated and other unusual presentations [2], with ROC seen in 40% of the cases [3]. The fungus causes devastating illness in immunocompromised patients and in patients with

poorly controlled diabetes mellitus. Rarely it may occur in immunocompetent patients as well [4].

Patient Description

A 50-year- old female, house wife from middle class family, newly detected to have Type 2 diabetes mellitus, was admitted to a primary care center with history of generalized malaise and mild fever. She had no associated cough, headache or breathing difficulty. She underwent dental extraction of left upper premolar tooth, 10-days back. A reverse-transcriptase polymerase chain reaction (RT-PCR) from the nasopharyngeal swab was positive for SARS-CoV-2 virus. She was managed with intravenous steroids (dexamethasone 4 mg IV thrice daily), broad spectrum antibiotics (ceftriaxone 1 gm IV bd) and other supportive measure including antihistamines and nebulization. Her blood glucose levels were high (> 400 mg/dl) during hospital stay. On the 2nd day of admission, blackish discharge from the nose was noted. This was followed by severe pain over left eye and maxillary region and associated with paraesthesia of left side of the face. After 4-days, she developed visual loss involving left eye. She could only perceive hand movements. They managed with IV antibiotics and steroids.

The peripheral center referred the patients to our tertiary care hospital after 8-days of illness, for further evaluation. On examination, her pulse rate was 108 /minute, and blood pressure was 130/70 mmHg. She was afebrile on admission with a respiratory rate of 18 /minute and oxygen saturation (SpO2) of 99% on room air. Physical examination revealed bilateral crackles at the lung bases with a normal cardiovascular status. On neurological examination she was drowsy, but arousable, and obeying to commands. She was cachexic, with a body-weight of 26 kilograms. Her previous body weight was 38 kg one year back. Cranial nerve examination showed ptosis of left eye, dilated and fixed left pupil with restricted extraocular movements. Her vision of left eye was diminished with appreciation of hand movements at 1 meter distance. Sensory loss over left side of the face over ophthalmic and maxillary division of trigeminal nerve was evident. She had left 2nd, 3rd, 4th, 5th and 6th cranial nerve involvement. Although she had neck stiffness, there were no other focal neurological deficits. Neurological examination was localizing to left cavernous sinus and orbital apex involvement based on optic nerve involvement. She had black eschars on her palate.

Her blood sugar levels were high 420 mg/dl and with HbA1c of 13.1%. Routine baseline investigations revealed a low hemoglobin level of 10.40 gm/dl (normal 12-15 gm/dl), neutrophilic leukocytosis with a total lymphocyte count of 29840 cells/mm^3 with 87% neutrophils). Platelet count was 4.75 lakhs (1.5-4.5 lakhs/cu mm). C-reactive protein (CRP) was 125.95 mg/l (normal < 5.0), procalcitonin was 0.34 ng/ml (normal < 0.5), with a D-dimer assay of 0.69 microgram/ml (normal < 0.50microgram/ml). Renal function test was normal. Her viral markers were negative (HIV, HCV and HBsAg). Computed tomogram (CT) of chest showed nodular lesions with ground glass opacities suggestive of infective etiology (Figure 1). The CT chest severity index was 8/25. In view of multiple cranial nerve involvement with alteration in sensorium, CT brain with Paranasal Sinus was taken (Figure 1), which showed pan-sinusitis involving bilateral maxillary, ethmoid, frontal and sphenoid sinus with multiple infarcts in the cerebral parenchyma. Steroids were stopped and she was added on liposomal amphotericin B at a dose of 10 mg/kg/day. Ceftriaxone was added at anti-meningitic dose of 2 gm intravenously, twice daily. Her blood glucose was adequately controlled with insulin.

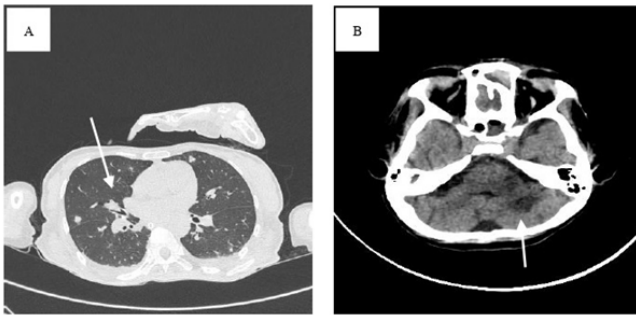

Figure 1: A-CT Chest showing ground glass opacities and pulmonary nodules. B-CT Brain showing left cerebellar infarct.

Magnetic resonance imaging (MRI) of the brain, orbits and paranasal sinuses, showed acute pan-sinusitis within all paranasal sinuses with evidence of cavernous sinus thrombosis on left side with non-enhancing optic nerve and extraocular muscles in orbital apex (Figure 2). Superior ophthalmic vein in left side showed reduced lumen and signal (Figure 2). There were multiple acute/subacute infarcts involving left anterior cerebral artery (ACA), left middle cerebral artery (MCA) and left anterior inferior cerebellar artery (AICA) territory (Figure 3). Magnetic resonance angiogram was normal.

Nasal swabs sent for smear and culture showed growth of Rhizopus (Figure 4). Option of biopsy and debridement

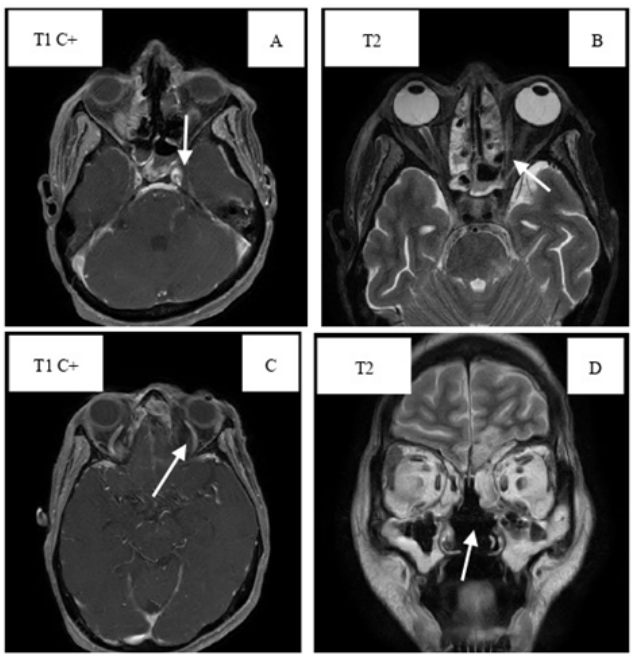

Figure 2: A- T1 C axial view showing cavernous sinus thrombosis. B-T2 axial image showing mucor involving left orbital apex soft tissue. C- T1 C axial image showing thrombosis of left superior ophthalmic vein. D- T2 coronal view of black turbinate sign.

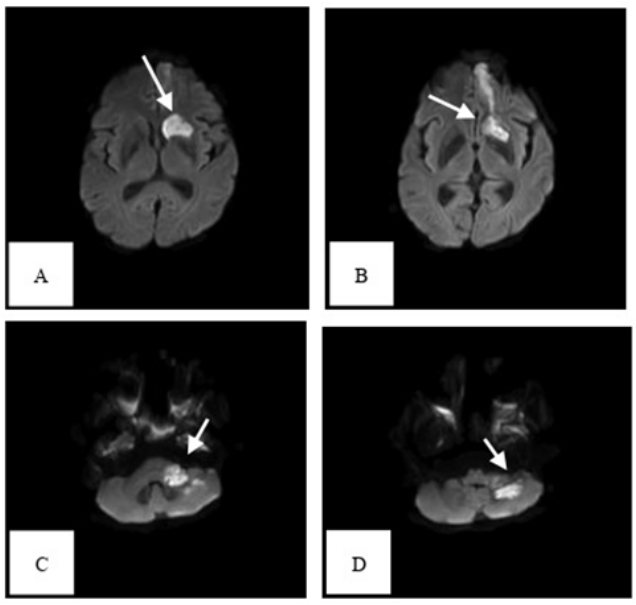

Figure 3: A- DW image showing infarct involving left caudate nucleus. B- DW image showing infarct involving left inferior frontal gyrus. C, D- DW image showing infarct involving left middle cerebellar peduncle and left cerebellar hemisphere.

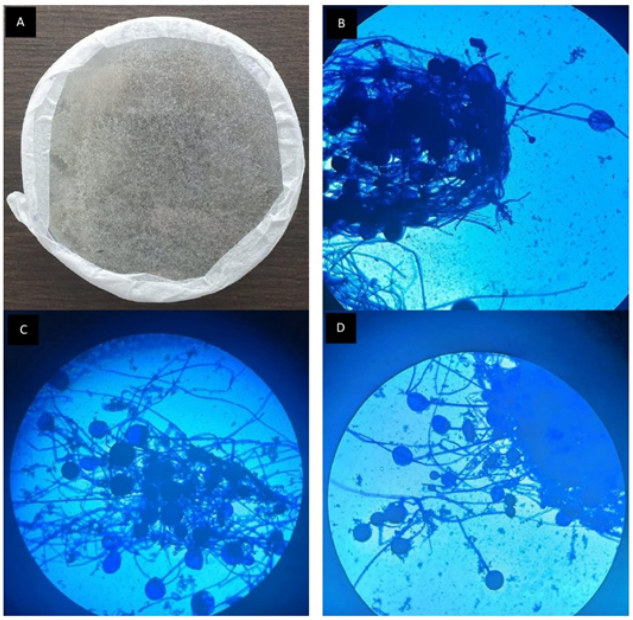

Figure 4: A-Showing rapidly growing mycelial colonies with hairy appearance described as cotton candy growth. B- Showing non septate hyphae with wide angle branching suggestive of Rhizoids. C, D- Showing sporangiophores which are long with dark sporangium.

was explained to relatives under high risk in view of CNS involvement. However, relatives opted for conservative treatment. Packed RBC transfusion was given due to drop in hemoglobin levels. On 4th day of admission her sensorium dropped, Glasgow coma scale (GCS) score was 6/15 (E2V1M3). In spite of medical and supportive management, she expired on 12th day of her illness.

Discussion

Rhinocerebral mucormycosis commonly presents with acute onset of sinusitis or periorbital cellulitis [5]. Facial pain and unilateral facial swelling are important clinical features with variable grade of fever [6]. Blackened necrotic eschars of the nasal mucosa or palate [7] is a disease specific finding in mucor. The disease may then progress to include unilateral ophthalmoplegia representing involvement of the orbital apex either by infection or vascular compromise [8]. Central nervous system involvement may present as thrombosis of cavernous sinus and encasement of internal carotid artery leading to cerebral infraction [9]. Cavernous sinus involvement often manifest as ipsilateral ophthalmoplegia. Patient may develop confusion and disorientation due to the neurological involvement [5]. Our patient never had facial swelling or feature of orbital cellulitis which was against the common presentation. Retrospectively her earliest symptom might have been dental pain and loosening of tooth, albeit inoculation following dental extractions have also been described [10].

Impaired innate immune response and increased availability of serum iron are two underlying conditions in most of the patients with mucormycosis [5]. Diabetic ketoacidosis has been proven to impair chemotaxis and phagocytic activity of neutrophils as well as to increase free serum iron [11]. The same pathogenesis can be explained in our patient in view of uncontrolled diabetic status.

Prolonged broad spectrum antibiotic therapy has also been implicated in its pathogenesis [12]. Antifungals such as voriconazole which are used in the treatment of other potentially invasive fungal species like Aspergillus fumigatus are also known to cause breakthrough mucormycosis in severely immunosuppressed patients like transplant recipients [13].

High incidence of fungal infections was noticed in Pakistan (23/147, 15.6%) and Italy (30/108, 27.7%), among covid cases and it was seen that invasive fungal infections can alter the natural history of the disease [14, 15]. Hosseini et al reported that mucormycosis in pterygopalatine fossa can spread to adjacent structures including the retroorbital space and infratemporal fossa [16]. It is also postulated that angioinvasion by the fungi is responsible for tissue necrosis and dissemination [15].

Current guidelines in India for the management of COVID-19 infection, recommend intravenous methylprednisolone in a dose of 0.5-1 mg/kg/day for three days and 1-2 mg/kg/day for moderate and severe cases of Covid-19 infection respectively [17]. The guidelines also mention the risk of developing a secondary infection like fungal and bacterial infections in view of steroid therapy [18].

Early diagnosis and prompt treatment of mucormycosis before the onset of CNS involvement, is vital for a good outcome [16]. Histopathological examination of specimens can confirm the clinical diagnosis with the visualization of typical right-branching aseptate hyphae of mucor species, and evidence of angio-invasion and tissue necrosis [19]. Fungal cultures can provide further confirmation [20], however histopathological confirmation should not delay initiation of antifungal therapy.

CT scans may be used to evaluate the progression of disease [21], however not the investigation of choice. MRI scans will help in accurately evaluating the extent of disease due to fungal invasion of soft tissues [18]. Diseased tissue which may turn necrosed and devitalized, may fail to take up contrast in MRI imaging showing "the black turbinate sign", a feature that can help in early detection of the disease [22].

The cornerstones of treatment of rhinocerebral mucormycosis are: reversal of underlying predisposing conditions, early initiation of antifungal therapy and appropriate and timely surgical intervention [16]. Euglycemia should be restored rapidly and any immunosuppressive conditions should be reversed if possible [21].

Amphotericin B deoxycholate (AMP) is the antifungal agent of choice for mucormycosis, though lipid formulations of amphotericin B are considered a safe and efficient alternative [23]. Recommended dose for the lipid formulation of amphotericin is 5-7.5 mg/kg/day with higher dosages (up to 10 mg/kg/day) in case of CNS involvement [21].

Iron chelation therapy and Posaconazole may be considered in refractory infection or Amphotericin B intolerance [21]. Reed et al supports an "aggressive-conservative" approach with frozen section guided surgical exploration, while Nithyanandam et al opted for a more aggressive early excision of infected structures [16, 24].

Conclusion

Rhino-orbito-cerebral mucormycosis should be suspected in patients with COVID -19 infection when associated with an immunosuppressed status such as uncontrolled Diabetes mellitus. High index of suspicion is necessary even in the absence of facial swelling or cellulitis for early diagnosis. Prompt treatment will help in improving the outcome of this devastating illness.

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

MG: Study design, concept, data acquisition, literature search, manuscript drafting, and critical review and will act as guarantor of the article. NB: Design, concept, data collection, literature search, manuscript editing and critical review. NT: Concept, manuscript editing, design, data collection and critical review. SJ: Data acquisition, concept, study design and literature search. SKR-Concept, design and critical review. VVT- Data acquisition, concept, study design.

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