Rhino-Orbital-Cerebral Mucormycosis

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Rhino-orbital-cerebral mucormycosis (ROCM) is a life-threatening fungal infection caused by fungi of the order *Mucorales*. It commonly affects individuals with conditions like diabetes, immunosuppression, or COVID-19.

Epidemiology

The second COVID-19 wave in India has been associated with an unprecedented increase in cases of COVID-19 associated mucormycosis (CAM), mainly Rhino-orbito-cerebral mucormycosis (ROCM).

Rhino orbital cerebral mucormycosis rapidly became an epidemic following the COVID-19 pandemic [1)]

Gutiérrez-Delgado et al searched PubMed database from 1964 to 2014 for all available articles in the English language related to rhino-orbital-cerebral chronic infections caused by fungi of the order Mucorales and found 22 cases [2)].

Pathophysiology

- **Fungal Entry:** Spores are inhaled and lodge in the nasal mucosa or sinuses.
- **Tissue Invasion:** The fungi invade blood vessels, causing thrombosis, ischemia, and necrosis.
- **Spread:** The infection spreads from the sinuses to the orbit, cranial cavity, and brain.

Risk Factors

1. **Uncontrolled Diabetes Mellitus** (especially diabetic ketoacidosis).
2. **Immunosuppression:**
    1. Prolonged corticosteroid use.
    2. Chemotherapy or organ transplantation.
3. **COVID-19-Associated Factors:**
    1. Steroid-induced hyperglycemia.
    2. Hypoxia and acidosis.
4. **Trauma or Surgery** disrupting nasal mucosa.

Clinical Presentation

ROCM progresses through **three stages**:

1. Early Symptoms (Rhinosinusitis Stage)

- Nasal congestion and discharge (black or bloody).
- Sinus pain or pressure.
- Facial swelling or erythema.
- Black eschar on nasal mucosa or palate.

2. Orbital Symptoms

- Periorbital swelling and erythema.
- Proptosis (eye protrusion).
- Ophthalmoplegia (paralysis of extraocular muscles).
- Reduced or complete loss of vision.
- Severe orbital pain.

3. Cerebral Symptoms

- Headache.
- Altered mental status or confusion.
- Cranial nerve palsies (e.g., III, IV, VI, V).see cavernous sinus syndrome
- Seizures.
- Hemiparesis.

Diagnosis

1. **Clinical Suspicion:** Black necrotic lesions, rapid progression in high-risk patients.
2. **Imaging:**
    1. **MRI:** Preferred for soft tissue, orbital, and cerebral involvement.
    2. **CT Scan:** Useful for detecting bony destruction and sinus involvement.

3. **Microbiology:**
    1. Nasal swabs or sinus aspirates.
    2. Direct microscopy (KOH mount) showing broad, aseptate hyphae.
4. **Histopathology:** Evidence of angioinvasion by fungal elements.
5. **Fungal Culture:** Confirms diagnosis and identifies the species.

Treatment

Rhino-Orbital-Cerebral Mucormycosis Treatment.

Prognosis

Rhino-orbital-cerebral mucormycosis is usually associated with a poor prognosis and is almost exclusively seen in immunocompromised patients.

- **Mortality Rates:** 30–70%, depending on the site of infection and treatment timing.
- **Key Prognostic Factors:**
    1. Early diagnosis.
    2. Complete surgical debridement.
    3. Control of underlying conditions.

Complications: Arteritis which may thrombose the orbital veins and ICA or ACA. Produces proptosis, ocular palsy, and hemiplegia

Prevention

1. Monitor high-risk individuals (e.g., diabetics, immunosuppressed).
2. Educate healthcare providers and patients about early symptoms.
3. Avoid excessive corticosteroid use.
4. Maintain strict hospital infection control measures.

Key Takeaway: ROCM is a rapidly progressive fungal infection requiring prompt diagnosis, surgical intervention, and antifungal treatment to improve survival outcomes.

Prospective observational studies

Manchanda et al. propose a computed tomography (CT) severity index (CTSI) to describe the severity of rhino-orbital-cerebral involvement in symptomatic COVID-19 patients and hypothesize that higher CTSI correlates with disease severity and thus slow response/non-response to treatment.

Aim: To propose a scoring system using CECT to describe the severity of IFS and correlate it with clinical outcomes.

A prospective study on 66 COVID-19-positive patients with CECT PNS done for IFS was performed. Split-bolus single-phase CT technique was used. Based on the extent of involvement, a CTSI was designed. Disease in four major subsite areas was assessed. Each subsite involvement was given points according to this model and then summated. Based on the final summated CTSI, the disease was classified as mild, moderate, or severe. Two subsets were subsequently analyzed including survival and death; and responders and non-responders.

The study cohort was 66 COVID-19-positive patients with suspected IFS with a median age of 48.5 years. Mild disease was noted in 34 (51.52%), moderate in 28 (42.42%), and severe disease in 4 (6.06%) patients. There was a significant association of mortality and poor clinical response ($P = 0.02$) with disease bilaterality. Laterality and CTSI were significant predictors of response to treatment. The mean CTSI of responders was 6.3, of non-responders was 12.9 and the response to treatment was significantly associated with CTSI (t-test, $P < 0.001$). Receiver operating characteristic curve analysis (Liu method) to distinguish between responders and non-responders showed that the cut-off value for CTSI of 11 had a sensitivity of 78.26% and a specificity of 95.35% to predict response assessment.

CTSI can help in the quantification of the disease burden, mapping out disease extent, triaging patients, and response assessment; especially for patients with underlying comorbidities. A higher score would alert the clinician to initiate aggressive treatment, as severe disease correlates with slow response/non-response to the treatment [3)].

Case-control studies

A study examined post-COVID-19 ROCM patients' T regulatory cell (Treg), T helper 17 cells (Th17), and Myeloid-derived suppressor cell (MDSC) levels before and after three months of treatment. T-cell activation and MDSC profile were measured in peripheral blood from 20 post-COVID-19 mucormycosis patients and 20 age-matched controls.

Compared to controls, cases had significantly greater Th17 cells (CD4+IL-23R+) before and after treatment ($p < 0.05$), with no significant change between pre- and post-treatment. In pretreatment cases, Treg cells (CD4+CD25+FoxP3+) were lower than controls but dramatically increased ($p < 0.05$) following treatment. Further, these patients had significantly higher rates of monocytic (m) MDSCs (CD14+HLA-DRlow/-) compared to healthy persons ($p < 0.05$). Interestingly, after three months of treatment, mMDSC levels dropped to levels similar to healthy controls. Similarly, ROCM patients had higher levels of granulocytic (g) MDSCs (HLA-DRlow/-CD33+CD11b+CD66+) than healthy controls, although these levels normalized after three months. Patients had considerably greater expression levels of RORγt, TGF-β, and IL-10 mRNA before therapy compared to healthy controls. FoxP3 and Arg-1 mRNA expression were lower in pretreatment patients than in healthy people. After treatment, these individuals' IL-10, FoxP3, and Arg-1 mRNA expression increased.

Myeloid-derived suppressor cells may play a role in mucormycosis immunological dysregulation, suggesting that restoring balance may improve patient outcomes [4)].

Case series

59 patients were diagnosed with COVID-19 associated mucormycosis (CAM). The median duration from the first positive COVID-19 RT PCR test to the diagnosis of CAM was 17 (IQR: 12,22) days. 90% of

patients were diabetic with 89% having uncontrolled sugar level (HbA1c >7%). All patients were prescribed steroids during treatment for COVID-19. 56% of patients were prescribed steroids for non-hypoxemic, mild COVID-19 (irrational steroid therapy) while in 9%, steroids were prescribed in inappropriately high dose. Patients were treated with a combination of surgical debridement (94%), intravenous liposomal Amphotericin B (91%) and concomitant oral Posaconazole (95.4%). 74.6% of patients were discharged after clinical and radiologic recovery while 25.4% died. On Relative risk analysis, COVID-19 CT severity index ≥ 18 (p=0.017), presence of orbital symptoms (p=0.002), presence of diabetic ketoacidosis (p=0.011), and cerebral involvement (p=0.0004) were associated with increased risk of death.

CAM is a rapidly progressive, angio-invasive, opportunistic fungal infection that is fatal if left untreated. The combination of surgical debridement and antifungal therapy leads to clinical and radiologic improvement in the majority of cases [5].

Case reports

Three cases of rhino-cerebral mucormycosis in patients with acute myeloid leukemia: two females aged 35 and 29, and one male aged 42. Symptoms manifested during chemotherapy induction, with all patients experiencing symptoms suggestive of rhino, orbital, or cerebral infection in a background of severe neutropenia (ANC < 0.5). Nasal endoscopy revealed necrotic tissue in all cases, with contrast-enhanced computer tomography (CECT) confirming invasive fungal infection. Rhizopus species were isolated in cultures from the two female patients, and histopathological evidence of fungal invasion was noted in one. Prompt treatment with liposomal Amphotericin B combined with surgical debridement with functional endoscopic sinus surgery (FESS) and treatment of neutropenic sepsis resulted in the survival of two patients, though one succumbed during treatment.

This case series highlights the importance of early clinical suspicion and treatment of mucormycosis in hematological malignancies. Due to mild and atypical presentations and lack of confirmation by microbiological and histological methods, a multifaceted diagnostic approach combining clinical, laboratory, and imaging modalities is essential. A multidisciplinary treatment approach with the management of concomitant complications like neutropenic sepsis is crucial for better outcomes [6].

A 70-year-old woman with uncontrolled diabetes mellitus presented with bilious vomiting and persistent headache with ptosis, proptosis, absence of extraocular movement, pupillary light reflex, and light perception of the left eye. The radiographic investigation, KOH mount, and Biopsy showed mucormycosis in the sinus with intracranial extension leading to SIADH. Further investigation revealed hyponatremia and decreased plasma osmolality. Then, when diabetes was controlled and hydrocortisone and amphotericin were given along with Endoscopic sinus debridement, SIADH was well controlled. This case illustrates the potential of mucormycosis in paranasal sinuses can even lead to intracranial invasion and its treatment with the use of amphotericin B can improve the prognosis of the disease. Prompt diagnosis through clinical history, radiological investigation, and laboratory parameters is important and its treatment is crucial for a better prognosis [7].

2022

A 53-year-old male with diabetes presented with altered mental status. He had been recently discharged from admission for COVID-19 pneumonia treated with remdesivir and methylprednisolone. Imaging demonstrated a large left frontal mass with a 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. An autopsy revealed a cerebral mucormycosis infection.

Despite concern for a primary brain neoplasm the patient has 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.

In an era of high steroid usage to treat COVID-19, mucormycosis infection must be considered in high-risk patients demonstrating a disproportionate clinical decline [8)].

2015

A unique case of isolated intracranial mucormycosis of a slowly progressive nature in a healthy immunocompetent child. A 4-year-old girl with a clear medical and surgical history presented with complaints of right side facial asymmetry and unsteady gait for a period of 10 months. Clinical and radiographic investigations revealed right-sided lower motor neuron facial palsy caused by an infiltrative lesion on the right cerebellopontine angle. Initial surgical debulking was performed, a biopsy was sent for histopathological examination, and a course of prophylactic antibiotic and antifungal drugs was prescribed. The pathological report confirmed the mucormycosis fungal infection, and intravenous amphotericin B was administered for 3 weeks. One month after admission, the patient left the hospital with complete recovery. Follow-ups after 4, 8 and 12 weeks revealed no sensory or motor neurological deficits. In conclusion, this is a unique case of mucormycosis with regard to the nature and location of the infection, along with the host being a healthy child. Initial surgical exploration is a very critical step in the early diagnosis and treatment of such rare conditions [9)].

2014

A 42-year-old man who developed a cerebellar mucor abscess after undergoing hematopoietic stem cell transplant for the treatment of myelodysplastic syndrome. In the post-operative period he was admitted to the neurocritical care unit and received liposomal amphotericin B intravenously and through an external ventricular drain. This patient demonstrates that utilization of an external ventricular drain for intrathecal antifungal therapy in the post-operative period may warrant further study in patients with difficult to treat intracranial fungal abscesses [10)].

2013

A case of mucormycosis presenting with extensive necrosis of the maxilla with extension into the retrobulbar and infrabulbar region in an otherwise healthy patient. He underwent extensive debriding surgery followed by amphotericin B first and then oral antifungal therapy, but unfortunately, even after extensive surgery and medical treatment, he did not survive [11)].

2010

Yoon et al describe a case of Rhino-orbital-cerebral (ROC) mucormycosis with pericranial abscess occurring in a female patient with uncontrolled diabetes mellitus. The infection initially developed in the right-sided nasal sinus and later progressed through the paranasal sinuses with the invasion of the peri-orbital and frontotemporal region, due to the delayed diagnosis and treatment. Numerous non-septate hyphae of the zygomycetes were identified by a punch biopsy from the nasal cavity and by an open biopsy of the involved dura. The patient was treated successfully with extensive debridement of her necrotic skull and surrounding tissues, drainage of her pericranial abscess and antifungal therapy, including intravenous amphotericin B for 61 days and oral posaconazole for the following 26 days. She returned to a normal life and has had no recurrence since the end of her treatment 15 months ago [12].

2000

A 59-year-old immunocompetent white man sustained a high-pressure water jet injury to the right inner canthus while cleaning an air conditioner filter. He later had “orbital cellulitis” develop that did not respond to antibiotics and progressed to orbital infarction. Imaging studies and biopsy results led to a diagnosis of mucormycosis. Tissue culture grew Apophysomyces elegans, a new genus of the family Mucoraceae first isolated in 1979. Orbital exenteration and radical debridement of involved adjacent structures, combined with intravenous liposomal amphotericin, resulted in patient survival.

After orbital exenteration and debridement of involved adjacent structures along with intravenous liposomal amphotericin, our patient has remained free from relapse with long-term follow-up.

The agent causing this case of rhino-orbital-cerebral mucormycosis (Apophysomyces elegans) contrasts with the three genera most commonly responsible for mucormycosis (Rhizopus, Mucor, and Absidia) in that infections with this agent tend to occur in warm climates, by means of traumatic inoculation, and in immunocompetent patients. Rhino-orbital-cerebral mucormycosis should be considered in all patients with orbital inflammation associated with multiple cranial nerve palsies and retinal or orbital infarction, regardless of their immunologic status. A team approach to management is recommended for early, appropriate surgery and systemic antifungal agents [13].

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