ORIGINAL RESEARCH

Clinical findings and treatment of rhino-orbital mucormycosis

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Received: 19 July, 2023 Accepted: 22 August, 2023

ABSTRACT

Background: Mucormycosis presents with a range of clinical symptoms with isolated involvement of many systems. Rhino-orbital cerebral and pulmonary disorders are the most prevalent and deadly symptoms. After the COVID-19 second wave, there was an increase in incidents, and because of the severe clinical presentation and scarcity of available treatments, there was cause for immediate worry. **Objective:** To evaluate the clinical manifestations and therapeutic results of rhino-orbital-cerebral mucormycosis patients who come to a central Indian tertiary care facility. **Methods:** This is a longitudinal clinical study. We observed 28 instances of steroid-dependent hyperglycemia, and COVID-19 associated mucormycosis patients. We collected and analyzed their medical histories, surgical procedures, microbiological and radiological findings, clinical symptoms, underlying systemic diseases, and demographic information. Outcomes were noted after 1 month Amphotericin B treatment (intravenously at a dose of 1 mg/kg each day). **Results:** There were a total of 28 patients, with a mean age of 52.3 years. Thirteen patients had type 2 diabetes mellitus, 15 patients (53.6%) were on anti-hypertensive therapy,3 patients were HIV infected and getting antiretroviral medication and 19 patients were COVID-19-related mucormycosis. These patients showed ophthalmoplegia, proptosis, orbital cellulitis, vision loss, central retinal artery blockage, and optic atrophy and 3 individuals had cerebral involvement. Every single one of the 28 patients (100%) had primary surgery of endoscopic debridement of sinuses. Effect of treatment on visual acuity and functional improvement was not so favourable. **Conclusion:** A multimodal approach of early identification, blood sugar management, immediate systemic antifungal medication, and sinus debridement surgery can be lifesaving in deadly condition known as invasive rhino-orbital-cerebral mucormycosis.

Keywords: Mucormycosis, Rhino-orbital cerebral Mucormycosis, COVID-19, Diabetes Mellitus, Ophthalmoplegia

INTRODUCTION

Although indolent illness has been reported in rare cases, mucormycosis refers to acute or subacute fast progressive infections caused by angioinvasive fungus of the order Mucorales [1,2]. The fungus is unusual in that it can cause severe illness and typically results in considerable morbidity and death in individuals with immunocompromised patients and poorly managed diabetes mellitus. When Indian data is excluded, the Leading International Fungal Education (LIFE) portal calculates the yearly prevalence of mucormycosis at around 10,000 cases worldwide. Adding Indian data makes the yearly total of cases 910,000 [3].

It has also been reported that people who appear to be immunocompetent occasionally develop mucormycosis. The Mucoraceae family of fungal hyphae are angioinvasive, causing necrotizing vasculitis, thrombosis, and invasion of blood arteries, which leads to widespread tissue infarcts and necrosis [4]. Although there are many other clinical syndromes associated with mucormycosis, including isolated involvement of the skin, kidney, gastrointestinal tract, and central nervous system, rhino-orbital cerebral and pulmonary syndromes are the most prevalent and deadly forms of the disease. Additionally, isolated cases of mucormycosis have been documented, mostly affecting the uterus, bladder, lymph nodes, heart and valves, mediastinum, middle ear, and parotid gland [5]. Rare cases of disseminated mucormycosis have been seen in preterm newborns and immunocompromised people. Rhino-orbital cerebral mucormycosis is the most prevalent clinical

symptom [6]. After inhaling fungal spores, the illness typically begins in the sinuses and nose. Via direct extension or a hematogenous pathway, it multiplies and spreads to the paranasal sinuses (sino-nasal mucormycosis), and subsequently to the orbit (sino-orbital mucormycosis). Additionally, it may migrate to the brain (mucicormycosis in the sino-orbital cortex). Despite the fact that the nose and paranasal sinuses are the major sites of infection, patients typically report with ocular signs and symptoms to ophthalmologists [7].Fungal spores that are breathed penetrate the nasal mucosa, causing a rhinoorbital infection. As the fungus progresses to the paranasal sinuses, sinusitis appears. When the infection spreads from the paranasal sinuses to the orbital wall, orbital involvement happens. Pain, chemosis, visual loss, ophthalmoplegia, and proptosis are possible symptoms. Infections of the muscles and orbital area or damage to the third, fourth, and sixth cranial nerves can result in ophthalmoplegia. Facial hypoesthesia and peripheral seventh cranial nerve paresis or paralysis are frequently seen [8].

Immunocompromised individuals nearly always have rhino-orbital cerebral mucormycosis; this includes those with uncontrolled diabetes mellitus, particularly when combined with acidosis or ketoacidosis, steroid therapy, recipients of solid organ or hematopoietic stem cell transplants, long-term oxygen therapy, chemotherapy, hematologic dyscrasias, retroviral illness, and malnourishment [9-11]. In the context of COVID 19, the incidence of mucormycosis has grown quickly and is now a serious issue. The cornerstone of therapy continues to be systemic amphotericin B combined with surgical sinus debridement and management of systemic diseases [12–14]. In this investigation, we examined the clinical features and therapeutic results of twenty-four instances with rhinoorbital-cerebral mucormycosis.

MATERIALS AND METHODS

Twenty-eight instances of rhino-orbital-cerebral mucormycosis that presented to a tertiary care hospital in central India throughout the previous three years were the subject of a longitudinal research. An analysis was conducted on their suspected sources of infection, clinical presentations, laboratory tests, and received treatments. A thorough workup was performed at the time of presentation, which included a thorough history of any pre-existing conditions, COVID treatment, a thorough examination of the eyes (including measurements of visual acuity, posterior and anterior segment evaluations, and movements of the eyes), an otorhinolaryngological examination, and a neurological examination to gauge the severity of the condition. Patients with COVID-19 were divided into three categories based on their CT severity score (CTSS): mild (CTSS < 8), moderate (CTSS - 8 - 15), and severe (CTSS > 15).

The paranasal sinuses, orbit, and brain were all imaged using CT scans and magnetic resonance imaging (MRI), fungal hyphae were demonstrated on KOH preparations, lactophenol cotton blue staining, and PAS staining of materials from the nasal cavity and paranasal sinuses were used to make the diagnosis of mucormycosis. The identification of wide branching aseptate fungal hyphae on KOH mount direct microscopy and the use of fungal stains on histopathology specimens were used to diagnose mucormycosis in clinico-radiological suspicion. As soon as mucormycosis was diagnosed, all patients received intravenous amphotericin B at a dosage of 1 mg/kg/day. Renal processes were seen. Insulin treatment helped to manage the diabetes. All patients underwent trans-nasal endoscopic radical debridement of the affected sinuses, after which a specimen was taken and submitted for culture and histology. Depending on how much the orbit and sinuses were involved in the radiological results, endoscopic debridement of the sinuses, orbital decompression, and orbital exenteration were performed.

A month was spent monitoring the patients. At one month following surgery, the visual, functional, radiological, and mortality outcomes of the treatment were assessed. A patient's visual result was assessed based on whether their visual acuity had improved, remained stable, or declined from the time of presentation. Ocular movements that were either unaltered, better, or worsened from the time of presentation were used to assess the functional result. The evaluation of the radiological result was based on whether there was any remaining illness or not.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

There were a total of 28 patients, with a mean age of 52.3 years (range: 20 to 64 years), including 16 male and 12 female patients. There was a 3–13 day lag between the start of symptoms and presentation. Thirteen patients (46.4%) had type 2 diabetes mellitus; six of these patients (47%), who had been diagnosed with the disease lately, and seven of the patients were known cases with a period of diabetes ranging from three to twelve years, three of whom were taking irregular medicines. Fifteen patients (53.6%) were on anti-hypertensive therapy and had a confirmed diagnosis of systemic hypertension. Three patients were getting antiretroviral medication after testing positive for the human immunodeficiency virus (HIV). COVID-19-related mucormycosis was found in 19 patients (67.9%). Nine of the 19 patients (47.37%) received systemic steroid therapy in order to manage COVID-19. For a duration of five to fifteen days, these patients were administered injectable intravenous methylprednisolone orally administered prednisolone. As part of their COVID-19 treatment, 11 patients (57.89%) received oxygen therapy while they were in the hospital. Thirteen patients (68.42%) received injection remdesivir as part of the COVID-19 treatment plan. Six mild cases, seven intermediate cases, and six severe cases of COVID-19 infection

were identified based on the CT severity score. 18 cases (64.3%) of ophthalmoplegia, 15 cases (53.6%) of proptosis, 6 cases (21.43%) of orbital cellulitis, 13 cases (46.43%) of vision loss, 4 cases (14.29%) of central retinal artery blockage, and 3 cases (10.71%) of optic atrophy were common ocular presenting characteristics. Three individuals had cerebral involvement [Table 1].

Table 1: Demographic features, causes of infection and clinical presentation

Baseline Characteristics	N	%
Male	16	57.14
Female	12	42.86
Age (years) Mean (range)	52.3 (20-64)	
Tentative causes of Mucormycosis		
Diabetes	13	46.43
Hypertension	15	53.57
HIV infecetion	3	10.71
COVID-19	19	67.86
Systemic corticosteroid for COVID-19	9	47.37
Oxygen therapy for COVID-19	11	57.89
Remdesivir Inj. for COVID-19	13	68.42
Mild COVID-19 (CTSS <8)	6	31.58
Moderate COVID-19 (CTSS 8-15)	7	36.84
Severe COVID-19 (CTSS >15)	6	31.58
Clinical Presentation		
Ophthalmoplegia	18	64.29
Proptosis	15	53.57
Diminution of vision	13	46.43
Orbital cellulitis	6	21.43
Central retinal arterial occlusion	4	14.29
Optic atrophy	3	10.71
Cerebral involvement	3	10.71

MANAGEMENT OF MUCORMYCOSIS

Amphotericin B was administered intravenously to each patient at a dose of 1 mg/kg each day. Every single one of the 28 patients (100%) had primary surgery. Seven patients, or 36.8%, underwent secondary surgery. Depending on the severity of the disease, three surgeries were performed: endoscopic debridement of the sinuses, endoscopic debridement with maxillectomy and orbital decompression, and endoscopic debridement with orbital exenteration [Table 2].

Table 2: Management of mucormycosis

Surgeries Performed	N	%
Endoscopic debridement of sinuses	9	32.14
Endoscopic debridement of sinuses with maxillectomy with orbital decompression	11	39.29
Endoscopic debridement of sinuses with maxillectomy with orbital exenteration	8	28.57

TREATMENT OUTCOMES OF MUCORMYCOSIS

When comparing visual acuity at one month following surgery to that at presentation, it was discovered that 13 patients (46.4%) had the same level of visual acuity, 9 patients (32.1%) had improved, and 7 patients (25%) had worsened. Ocular movements after one month after surgery were compared to those at presentation to assess the functional result. It was discovered that in 15 patients (53.6%), ocular motions were the same as at presentation, in 7 patients (25%) and in 6 patients (21.4%), ocular movements had worsened. When the radiological result was assessed one month following surgery for the presence or absence of residual disease, it was discovered that 12 patients (44.4%) had no residual disease and 15 patients (55.6%) had residual disease. One patient's death was discovered one month following the procedure.

Table 3: Treatment Outcome

	Unchanged		Improved		Deteriorated	
	N	%	N	%	N	%
Visual Outcome	13	48.15	8	29.63	7	25.93
Functional Outcome	15	55.56	6	22.22	6	22.22
Radiological Outcome	No residual disease = 15 (55.6%)		Residual disease present = 12 (44.4%)			

DISCUSSION

Potentially fatal, opportunistic, angioinvasive fungal infection, mucormycosis is exacerbated by uncontrolled diabetic mellitus, corticosteroids, immunosuppressive medications, and primary or secondary immunodeficiency. The nose, sinus orbit, gastrointestinal tract, lung, skin, jaw bones, heart, kidney, and mediastinum can all be impacted. Rhino-orbital-cerebral mucormycosis is the most prevalent manifestation of them. Uncontrolled use of steroids, chronic metabolic diseases like diabetes and hypertension, certain COVID-19 pathophysiological traits may make a person more vulnerable to developing secondary fungal infections, mucormycosis. With the second wave of the COVID-19 pandemic, rhino-orbital-cerebral mucormycosis incidence has sharply increased. The COVID-19 pandemic and poorly managed blood sugar levels (caused by either diabetes mellitus or steroid-induced hyperglycemia) appear to be intersecting crises. Because the fungus is so invasive and immediately aggressive, mucormycosis is regarded as an emergency. It is important to identify and treat the condition early on. It is essential for physicians to acknowledge the potential for invasive secondary fungal infections in patients who already have pre-existing risk factors. This will allow for early identification and treatment, which will ultimately reduce morbidity and death.

The cornerstone of care for rhino-orbital-cerebral mucormycosis has been microbiological identification, stabilization of the underlying systemic illness, and antibiotic therapy with debridement of necrotic tissue over time.The illness starts when spores are inhaled into the nasal and oral cavities. Because macrophages phagocytose fungal spores, infections in individuals with healthy immune systems are uncommon. However, because of their weakened immune systems, people with uncontrolled diabetes mellitus and immunocompromised state are more susceptible to infection. From here, the infection travels to the orbit and paranasal sinuses through the nasolacrimal duct, ethmoid, and maxillary sinuses, and ultimately results in orbital cellulitis. It is possible for the infection to spread posteriorly to the orbital apex, resulting in orbital apex syndrome and significant visual loss.

Histology, direct microscopy, and culture from clinical specimens are the three primary techniques used to diagnose mucormycosis [15, 16]. The paranasal sinuses, orbit, and brain CT scan and MRI, the detection of fungal hyphae on KOH preparations, the lactophenol cotton blue staining, and the PAS staining of specimens taken from the nasal cavity and paranasal sinuses were used to make the diagnosis of mucormycosis. Amphotericin B, a systemic antifungal, was administered to all patients along with blood sugar management and other necessary treatments. For each of the 38 patients, primary surgery was done. For certain individuals, follow-up surgery was necessary. Depending on the level of involvement seen by an MRI or CT scan, procedures that were done included orbital decompression, endoscopic sinus debridement, and orbital exenteration. We found that the most frequent risk factor was elevated blood sugar, which might be brought on by diabetes mellitus or steroids-induced hyperglycemia. The mainstay of treatment for rhino-orbital-cerebral mucormycosis remained surgical debridement of sinuses along with orbital decompression, orbital exenteration when required, systemic antifungals, and treatment of systemic diseases. Liposomal amphotericin B is the advised first-line medication for mucormycosis. Antifungal treatment is a proven life-saving intervention in this condition.

The deadly condition known as invasive rhino-orbital-cerebral mucormycosis necessitates a multimodal approach. The principal clinical results in our investigation were proptosis, ophthalmoplegia, and reduced vision. Since mucormycosis is an acute and severe disease, it is imperative to reduce mortality by obtaining a rapid diagnosis, starting antifungal medication very once, and performing surgical sinus debridement.

REFERENCES

1. Harrill WC, Stewart MG, Lee AG, Cernoch P. Chronic rhinocerebral mucormycosis. Laryngoscope. 1996 Oct;106(10):1292-7.
2. Xia ZK, Wang WL, Yang RY. Slowly progressive cutaneous, rhinofacial, and pulmonary mucormycosis caused by Mucor irregularis in an immunocompetent woman. Clin Infect Dis. 2013 Apr;56(7):993-5.
3. Prakash H, Chakrabarti A. Global Epidemiology of Mucormycosis. J Fungi (Basel). 2019; 21;5(1).
4. Kohn R, Hepler R. Management of limited rhino-orbital mucormycosis without exenteration. Ophthalmology 1985;92(10):1440-1444.
5. Xia ZK, Wang WL, Yang RY. Slowly progressive cutaneous, rhinofacial, and pulmonary mucormycosis caused by Mucor irregularis in an immunocompetent woman. Clin Infect Dis. 2013 Apr;56(7):993-5.
6. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomycosis: a review

of 929 reported cases. Clin Infect Dis. 2005 Sep 01;41(5):634-53.
7. Ferry AP, Abedi S. Diagnosis and management of rhinoorbitocerebral mucormycosis (phycomycosis). A report of 16 personally observed cases. Ophthalmology 1983;90(9):1096-1104.
8. Cd
9. Mehta S, Pandey A. Rhino-orbital mucormycosis associated with COVID-19. Cureus 2020;12(9):e10726.
10. Singh AK, Singh R, Joshi SR, et al. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021;15(4):102146.
11. Skiada A, Lass-Floerl C, Klimko N, et al. Challenges in the diagnosis and treatment of mucormycosis. Med Mycol 2018;56(suppl 1):93-101.
12. 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.
13. Pilmis B, Alanio A, Lortholary O, et al. Recent advances in the understanding and management of mucormycosis. F1000Res 2018;7:F1000.
14. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomicosis: a review of 929 reported cases. Clin Infect Dis. 2005;41:634–653.
15. Werthman-Ehrenreich A. Mucormycosis with orbital compartment syndrome in a patient with COVID-19. Am J Emerg Med 2021;42:264.e5-264.e8.
16. Mekonnen ZK, Ashraf DC, Jankowski T, et al. Acute Invasive rhino-orbital mucormycosis in a patient with covid-19-associated acute respiratory distress syndrome. Ophthalmic Plast Reconstr Surg 2021;37(2):e40-e80.