Rhino-Orbito-Cerebral Mucormycosis—The Bane of the 'Black Fungus'

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Abstract

Rhino-orbito-cerebral mucormycosis (ROCM) is an infection of the nasal passages and orbit caused by ubiquitous fungi of the order Mucorales. These fungi are known to affect patients with phagocyte and neutrophil dysfunction. Patients with uncontrolled diabetes, solid-organ, haematological malignancies and organ transplant recipients on immunosuppressive therapy are especially susceptible. The disease is being seen with alarming frequency in patients with COVID-19 infection or those who have recently recovered from it. Poor glycaemic control due to the indiscriminate use of steroids has been strongly implicated. Patients present with periocular pain, oedema, numbness or skin discoloration along with symptoms of the nasal blockade. Direct microscopy of a deep nasal swab taken from the involved mucosa reveals broad aseptate or pauci-septate fungal hyphae, clinching the diagnosis. CT scan of the paranasal sinuses and orbit would reveal a hyperdense lesion involving the nasal turbinates and sinuses with extension into the orbit. Lack of contrast enhancement indicates necrosis of the tissues. The treatment involves administration of systemic antifungals (Amphotericin B, Posaconazole and isavuconazole) and aggressive surgical debridement of involved tissues. In spite of all measures, the mortality rate is about 46% in these patients. Strict diabetic control and judicious prescription and monitoring of systemic steroids in the setting of COVID-19 infection, keeping a high index of suspicion with early detection of the disease can go a long way in improving the prognosis.

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Keywords

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11.1 Introduction

Mucormycosis is one of the most fulminant and devastating infections affecting the nasal cavity, sinuses and orbit. Colloquially called the 'Black fungus', this name aptly hints at the nature of the disease. It is a fungal infection caused by several species belonging to the order Mucorales. It is known to affect the nasal mucosa, paranasal sinuses, orbit, lungs and skin. In rare cases, involvement of the gastrointestinal tract, intracranial structures or disseminated infection may be seen. The recent steep rise in the number of patients affected has mirrored the rise of the second wave of COVID-19 infections in India (Sharma et al. 2021). This chapter aims at giving a comprehensive overview of rhino-orbito-cerebral mucormycosis (ROCM).

11.2 Cause and Pathogenesis

Fungi of the order Mucorales are the causative organisms. Species belonging to several genera including *Mucor, Rhizopus, Absidia* and *Cunninghamella* have been isolated. The most frequently reported pathogens in mucormycosis are Rhizopus spp., Mucor spp. and Lichtheimia spp. (formerly of the genera Absidia and Mycocladus), followed by Rhizomucor spp., Cunninghamella spp., Apophysomyces spp. and Saksenaea spp. (Roden et al. 2005; Skiada et al. 2011). *Rhizopus oryzae* is the most common organism and responsible for nearly 60% of mucormycosis cases in humans and also accounts for 90% of the Rhino-orbital-cerebral (ROCM) form (Sugar 2000). These fungi are ubiquitous and are very commonly found in moist, decaying matter. They release spores in the environment and are commonly found colonising the oral cavity, throat, nasal cavity and paranasal sinuses. However, infection in immunocompetent individuals is rare owing to the robust phagocytic elimination of these organisms.

The spores of these organisms are free to grow in immunocompromised individuals and develop into aseptate hyphae. These hyphae have a tendency to progressively invade surrounding tissues including the blood vessels and nerves, along with the destruction of the surrounding bones. This appears to be mediated through extracellular matrix laminin, type IV collagen (Bouchara et al. 1996) and glucose-regulated protein (GRP78) (Liu et al. 2010). This facilitates the spread into adjacent compartments. The angio-invasive property of the fungus leads to thrombosis of the involved blood vessels. Thrombosis leads to tissue infarction and resultant necrosis. The perineural invasion of the fungus results in loss of sensation,

pain, decreased vision and paraesthesias. The angio-invasiveness of the organism explains the haematogenous dissemination to other distant organs.

11.3 Risk Factors

1. Diabetes and mucor: Uncontrolled diabetes and ketoacidosis are the most important predisposing factors contributing to mucormycosis (Roden et al. 2005; Corzo-Leon et al. 2018). In the presence of hyperglycaemia and low pH, which is found in patients with diabetic ketoacidosis (DKA), phagocytes are dysfunctional and have impaired chemotaxis and defective intracellular killing by both oxidative and nonoxidative mechanisms (Chinn and Diamond 1982). The acidic serum helps to promote the growth of the mucor, decreases the iron-binding capacity of serum transferrin, thus increasing the free iron, promoting the reproduction of the mucor. Mucor has ketoreductase that helps it utilise the host's ketones to promote its growth (Ma et al. 2015; Mondal et al. 2012).
2. Neutropenia: Neutrophil and phagocyte dysfunction have been strongly implicated in the pathogenesis of mucormycosis (Ibrahim et al. 2012). Due to this reason, patients with haematological and solid organ malignancy patients receiving chemotherapy, solid organ transplant patients on immunosuppression and hematopoietic stem cell transplant patients are particularly susceptible to mucormycosis. Interestingly, patients with AIDS (lymphocyte dysfunction) did not seem to have an increased risk of mucormycosis (Sugar 2005).
3. Iron overload states like hemochromatosis, deferoxamine therapy, multiple blood transfusions provide an excellent setting for mucormycosis as it allows for the growth of the fungus and increases susceptibility (Ibrahim et al. 2012).
4. Mucormycosis has also been reported in chronic kidney disease, liver cirrhosis and malnutrition patients (Prakash et al. 2019).
5. Long-term systemic voriconazole (especially given in ICUs for prophylaxis) has also been implicated (Gupta et al. 2017).

ROCM is frequently observed in association with uncontrolled diabetes and DKA. Pulmonary involvement is commoner in patients having neutropenia, bone marrow and organ transplant and haematological malignancies. Gastrointestinal involvement is seen in malnourished individuals (Singh et al. 2021).

11.4 COVID-19 and Mucormycosis

The surge in COVID-19 cases in the second wave has brought with it aftermath of increased mucormycosis cases. Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000) in India compared to developed countries, in a recent estimate of the year 2019–2020 (Singh et al. 2021). As of May 2021, 101 cases of mucormycosis have been reported in patients with COVID-19, 82 of which are

from India. Most cases presented with concomitant COVID-19 infection or within 2–3 weeks of recovery.

Singh et al. (Singh et al. 2021) in their review discussed the reasons for the increased susceptibility of these patients to mucormycosis:

1. Diabetes Mellitus (DM) is often associated with increased severity of COVID-19 infection, as well as increased risk of contracting mucormycosis.
2. Uncontrolled hyperglycaemia and precipitation of DKA are often seen secondary to corticosteroid intake. Widespread indiscriminate use of steroids has been seen in several COVID-19 patients.
3. Like all viral infections, COVID-19 infection affects both innate and adaptive immunity and predisposes to secondary infections. COVID-19 is known to cause endotheliitis with damage, thrombosis, lymphopenia and reduction in CD4+ and CD8+ levels, predisposing to secondary fungal infections.
4. Transferrin and ferritin undergo glycosylation in hyperglycaemic states, releasing and allowing for increased free iron. An increase in cytokines (especially IL-6) and concomitant acidosis in these patients increases ferritin levels thus increasing free iron availability.
5. High glucose, low pH, free iron and ketones enhance the expression of fungal ligand spore coating homolog (CotH) protein and glucose-regulator protein 78 (GRP-78) of endothelial cells, facilitating angioinvasion, tissue necrosis and haematogenous dissemination.

Diabetes was present in 80% of cases, while corticosteroid treatment was given for COVID-19 in 76.3% of cases according to this study (Singh et al. 2021). Widespread indiscriminate use of steroids has led to systemic hyperglycaemia, which is especially worse in diabetics, but is not restricted to known diabetics. Other factors implicated are the use of Tocilizumab and prolonged mechanical ventilation through unclean oxygen humidifiers.

11.5 Clinical Features of Rhino-Orbito-Cerebral-Mucormycosis

Clinical features correlate with the structures involved. The nasal mucosa and turbinates are the first to be colonised by the pathogens. The patients will first experience nasal symptoms such as nasal discharge and stuffiness. At later stages, dark eschar may be visible in the vestibule of the nose with blood-tinged or dark coloured nasal discharge (Honavar 2021; Deutsch et al. 2019). As the sinuses are progressively involved, sinus headaches may be experienced accompanied by cheek oedema and erythema. Fungal invasion into the surrounding vessels results in vascular occlusion and resultant necrosis of the tissues. Externally it may manifest as reddish or dark discoloration of the skin, which eventually breaks down to form a dark eschar. Palatal involvement as an ulcer or eschar may also be seen.

Orbital involvement is secondary to invasion from the sinuses through intact bone, or with bone destruction. Medial and inferior orbit are commonly involved

Table 11.1 Clinical features of ROCM

Nasal involvement	Sinus involvement	Orbital involvement	Cerebral involvement
• Nasal stuffiness • Discharge • Foul smell • Epistaxis • Nasal eschar	• Facial edema • Facial pain • Dental pain • Sinus tenderness • Sinus headache • Sinus discharge • Malaise • Fever	• Eye pain, decreased vision • Proptosis • Ptosis • Diplopia • Conjunctival congestion and chemosis • Infraorbital nerve anaesthesia • Central retinal artery occlusion • Superior ophthalmic vein thrombosis • V1, V2, 3rd, 4th, 6th cranial nerve palsy	• Altered consciousness • Seizures • Hemi-cranial headache • Bilateral signs and symptoms • Hemiparesis

first, followed by spread to the rest of the orbit (Honavar 2021). Patients may complain of periocular pain, swelling with vision loss or diplopia. Lid oedema, erythema, limitation of ocular movements, proptosis, pupillary involvement (afferent pupillary defect), conjunctival congestion and chemosis may be seen to varying degrees. Extreme proptosis with corneal exposure may lead to epithelial defects or eventually corneal ulceration. Posterior segment involvement in the form of retinal vascular occlusions (commonly central retinal artery occlusion) due to direct invasion into the retinal vessels and embolization, may be seen, especially with apical involvement. Optic disc oedema or pallor resulting from optic nerve compression due to orbital inflammation may be observed. Isolated involvement of the orbital apex by invasion through the adjacent sinus is also seen. In such cases, severe vision loss, pupillary involvement, III, IV and VI cranial nerve palsies are much more marked as compared to proptosis and signs of ocular inflammation.

Intracranial extension of the disease may occur through the cribriform plate, direct extension from the sphenoid and frontal sinuses, throughout the orbital apex, cavernous sinus or through haematological routes (Ma et al. 2015). The manifestation of bilateral vision loss, III, IV and VI cranial nerve palsies or orbital congestion may point towards the intracranial spread. Patients usually present with severe headaches, seizures, hemiparesis, focal neurological disorders or altered sensorium (Ma et al. 2015). The common clinical features of ROCM are summarised in Table 11.1.

11.6 Imaging

Computed tomography (CT) and Magnetic resonance imaging (MRI) are both useful modalities to characterise the extent of involvement of the disease. Nasal cavity involvement is seen as nonspecific inflammatory turbinate hypertrophy and inflammatory fluid in the nasal cavity. CT scan of the paranasal sinuses (PNS) accurately

shows the bony details of the sinuses. Hence it is the preferred choice of imaging by the ENT surgeons, Involvement of the sinuses is seen as a heterogeneous hyperdense opacity within the sinus cavity. In more advanced cases, bone destruction with invasion into the orbit and intracranial cavity may be seen. One study found the ethmoid sinus was the most common paranasal sinus involved (86%) (Therakathu et al. 2018). In the majority of patients (79%) multiple sinuses were involved. The combination of maxillary, ethmoid and sphenoid (49%) was most frequently seen. Unilateral sinus involvement was more common (79.1%) than bilateral (20.9%) (Therakathu et al. 2018). Bone involvement in the form of bone rarefaction, erosions and permeative destruction was seen in 40% cases.

Orbital involvement begins adjacent to the involved sinus in the form of periosteal thickening and adjacent fat stranding. This progresses to involve the medial rectus, inferior rectus, optic nerve and adjacent fat (Fig. 11.1) (Honavar 2021). Further spread of the infection is indicated by diffuse heterogeneous lesion within the orbit and in the area of the orbital apex. Resultant proptosis with optic nerve stretch and tenting of the globe may be seen in extreme cases. Oculoplastic surgeons consider MRI as a better modality to judge the orbital inflammation and invasion and Intra-cranial spread (Mnif et al. 2005). On MRI the lesions are mildly hypointense on T1 weighted images and have variable intensity on T2 weighted images. Early cases may show low intensity on T2 weighted images. An abscess can be identified as lesions with peripheral enhancement and central non-enhancing portion. Intracranial involvement is seen on brain CT as irregular low-density areas within the cerebral parenchyma (Ma et al. 2015). MRI shows low T1-weighted imaging signals and high T2-weighted imaging signals. Contrast-enhanced MRI may show annularly enhancing lesions. Although CT and MRI can both diagnose intracranial inflammation and brain abscess, MRI shows better tissue details and is therefore preferred (Ma et al. 2015).

Although MRI has a greater advantage in delineating the disease extent, often the patients are too unstable to undergo this lengthy scan. In such cases, a CT scan with contrast may be obtained, as it is often quicker and more readily available.

The use of contrast greatly increases the information gained from the scan. Patchy contrast enhancement is seen in the initial stages in the nasal mucosa, paranasal sinus mucosa and orbit. In areas with complete occlusion of the feeder arteries, no contrast uptake is seen in the involved mucosae, turbinates (called the 'black turbinate sign') (Safder et al. 2010), sinuses and orbital tissues. Non-contrast-enhancing areas indicate portions with necrotic tissues and a high fungal load (Choi et al. 2018). This helps in planning the management of the patient. All the devitalised tissues seen as the portions not enhancing with contrast, have to be debrided during surgery. The presence of contrast uptake indicates that the tissues can possibly be salvaged. Therefore, more conservative approaches may be tried. MR angiography is especially being explored for assessing tissue perfusion and identifying vascular occlusions and viable tissue.

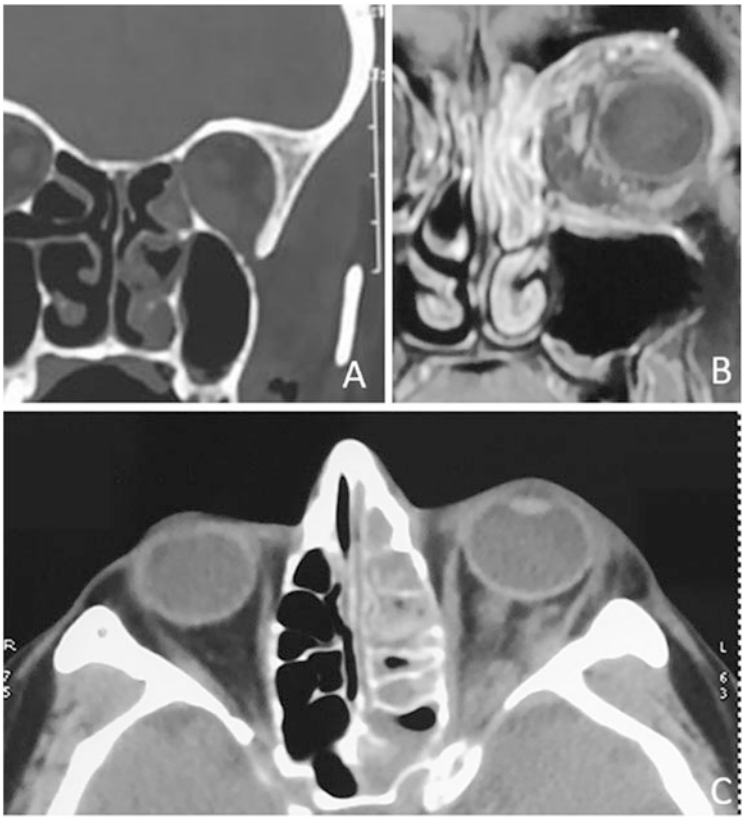

Fig. 11.1 Radiological features of rhino-orbital mucormycosis: (**A**) shows the CT scan of a patient showing a patchy hyperdensity involving the left ethmoid sinus and nasal cavity (turbinates), with adjacent edema of the left medial and inferior recti. (**B**) shows the CEMRI orbit and paranasal sinuses of another patient. This T1 weighted image shows patchy enhancement of the ethmoid sinus and adjacent infero-medial orbital involvement. The enlargement of inflamed nasal turbinates is also noted. (**C**) shows a heterogenous opacity involving the entire left ethmoid sinus. There is predominant left orbital apex involvement seen as a heterogenous hyderdensity at the apex, involving the medial rectus, the optic nerve sheath and surrounding fat

11.7 Microbiological Investigations

The most convenient and fastest modality of confirming the diagnosis is through direct microscopy as a KOH or calcofluor white mount. The sample is obtained from the nasal cavity or paranasal sinus preferably under endoscopic guidance, from the orbital tissue, or from the edge of the eschar to increase the yield. Another sample is also simultaneously taken for histopathology. Direct microscopy with fluorescent brighteners shows aseptate or pauci-septate hyphae, with a wide branching angle ($\geq$45–90°) and greater hyphal width (6–16μm). Histopathological sections may be

stained with haematoxylin-eosin (HE), periodic acid-Schiff stain (PAS), or Grocott-Gomori's methenamine-silver or both. Lesions show infiltration of the tissues by fungal hyphae, haemorrhagic infarction, coagulation necrosis, angioinvasion, infiltration by neutrophils (in non-neutropenic hosts) and perineural invasion (Frater et al. 2001). Often confusion arises while differentiating mucor from aspergillosis. They can be differentiated by molecular diagnostic techniques or PCR. The application of immunohistochemistry with commercially available monoclonal antibodies can also help (Jensen et al. 1997; Jung et al. 2015).

Culture of specimens in brain heart infusion agar, potato dextrose agar or Sabouraud dextrose agar with gentamicin or chloramphenicol and polymyxin-B, without cycloheximide, is strongly recommended for genus and species identification, and for antifungal susceptibility testing. Incubation at 30 °C and 37 °C separately will show rapid growth of fluffy white, grey or brown cotton candy-like colonies with coarse hyphae and interspersed brown or black sporangia (Honavar 2021).

Serological tests for antigen and antibody,1,3-β-D-Glucan and Galactomannan can aid diagnosis in suspected cases (Song et al. 2020).

Polymerase chain reaction (PCR) based molecular identification is also available. DNA sequencing based on bar codes 18s, ITS, 28s, rDNA, MALDI-TOF have limited availability, but can detect fungal DNA in paraffin-embedded tissues and serum. PCR is also a rapid and accurate test (Song et al. 2020).

11.8 Management

Patients presenting with classical signs and symptoms suggestive of mucormycosis with a history of uncontrolled diabetes, immunocompromised status, history or concurrent COVID-19 infection especially with steroid administration need further investigations. They may be classified for practical purposes into the following categories probable, possible and proven cases of mucormycosis (Honavar 2021) (Fig. 11.2).

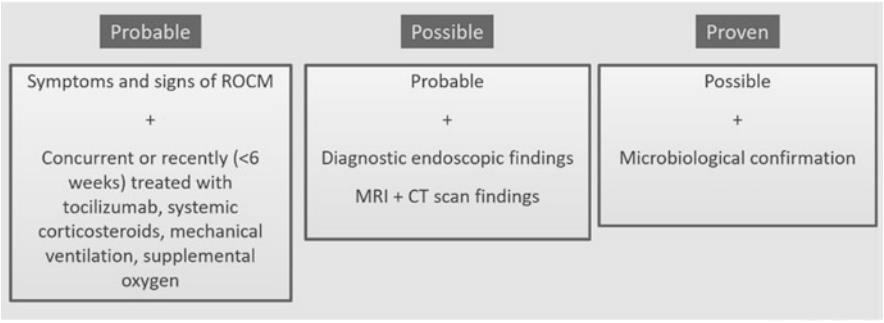

Fig. 11.2 Clinical categorisation of patients

All probable mucormycosis patient's nasal swab samples must be taken for microbiology and histopathology. A contrast-enhanced CT scan of the paranasal sinuses must be done. In cases where the orbital or intracranial spread is suspected, a CEMRI orbit with MR angiography may be preferred. A detailed and comprehensive evaluation of the nose and PNS is a must. Ocular evaluation with documentation of vision, intraocular pressure, pupillary reactions, extraocular movements, anterior segment evaluation, evaluation of retinal perfusion and the disc is essential.

Possible and confirmed cases of mucormycosis must undergo haematological investigations such as random blood sugar, serum electrolytes, renal function tests complete blood count and arterial blood gas (to rule out acidosis) (Craig 2019). Detailed iron studies may be required if iron overload is suspected. Testing for COVID-19 by RT-PCR is preferred. Once confirmed, the patient must be admitted for further management.

11.8.1 Medical Management

The global guidelines for diagnosis and management of mucormycosis were given in 2019 by the European Confederation of Medical Mycology ECMM and Mycoses Study Group Education and Research Consortium (MSGERC). Antifungal treatment with a thorough surgical debridement of involved tissues form the mainstay of the management (Cornely et al. 2019). Systemic antifungals have to be instituted at the earliest.

Amphotericin B is the drug of choice. It acts by binding with ergosterol, a component of fungal cell membranes, forming pores that cause rapid leakage of monovalent ions (K+, Na+, H+ and Cl−) and subsequent fungal cell death. It is available in the liposomal (LAmB), lipid complex (ABLC) and in deoxycholate (C-AmB) forms. The former two are preferred due to their established efficacy and lower renal toxicity. The commonly available forms are:

1. Liposomal amphotericin B: It is administered at the dose of 5 mg/kg/day (7.5–10 mg/kg/day in cerebral mucormycosis) over 4–6 h.
2. Amphotericin B Deoxycholate: 1–1.5 mg/kg/day is administered over 4–6 h. It is generally not preferred due to higher nephrotoxicity.

Dose adjustments are required in case of renal impairment. This treatment is continued for 2–4 weeks. This is followed by step-down treatment with azole antifungals. These act by interfering with the synthesis and permeability of fungal cell membranes, by inhibiting cytochrome P450-dependent 14-alpha-sterol demethylase. Isavuconazole and Posaconazole are approved for use either in combination with Amphotericin B (first line- in severe infections) or as a step-down treatment after initial treatment with Amphotericin B or as an alternative first-line treatment, in case of toxicity or non-availability of Amphotericin B (Rawson et al. 2020). The high cost of these medications and limited availability may be a deterrent.

1. Isavuconazole is administered at the dose of 200 mg thrice a day for the first 2 days, followed by 200 mg daily.
2. Posaconazole is given as 300 mg twice a day for 1 day followed by 300 mg daily.

Treatment is continued for 3–6 months or until 6 weeks after the radiological and clinical resolution or stabilisation (Honavar 2021). In case of renal toxicity or drug resistance, a combination with caspofungins and echinocandins has been explored due to the observed synergistic effect.

Retrobulbar amphotericin B is being explored as an option to increase globe salvage rates in cases of limited retrobulbar disease with viable tissues and preserved vision (Hirabayashi et al. 2017; Safi et al. 2020). Three to five 1 mL injections (3.5 mg/mL) given every consecutive or every alternate day has shown promising results.

11.8.2 Surgical Management

Any necrotic and infiltrated tissue is not viable and cannot be effectively treated with systemic antifungals alone due to lack of penetration. Therefore, thorough debridement is the only option. In case of limited sinus disease, FESS with clearance of the necrotic mucosa might give beneficial results (Nithyanandam et al. 2003). In case of extensive bony involvement and orbital involvement, a maxillectomy (total or partial), zygoma debridement or orbital exenteration may be necessary. During surgery, all visible necrotic tissues must be removed. The extent of debridement needed may also be determined by the non-perfused portion as seen on a CEMRI scan. Post-operative serial dressings and sinus irrigation with amphotericin B may be performed.

Orbital exenteration may be required in case of the presence of extensive necrotic tissue (Lee et al. 2020). Orbital exenteration when needed, maybe preferably performed through a lid sparing anterior approach. There have however been several reports of patients surviving despite withholding orbital exenteration. There are debatable indications for this procedure in mucormycosis management (Hargrove et al. 2006). Some reports have also found exenteration to worsen the outcomes of the patients. Post-operative socket related complications are also known to occur.

Intracranial involvement is mainly managed medically. If there is abscess formation, it may need the expertise of a skull base surgeon or a neurosurgeon for removal of the devitalised tissue (Ma et al. 2015).

11.8.3 Systemic Management

Reversal of the underlying predisposing factor is equally important. Control of blood sugars with the help of insulin injections and constant monitoring is essential (Corzo-Leon et al. 2018). Diabetic ketoacidosis has to be reversed along with adequate hydration and serum electrolyte correction. In patients on

immunosuppressive drugs, the doses may have to be decreased. Neutropenia in hematologic malignancies should be reversed, if possible, with the use of colony-stimulating factors and the withdrawal of cytotoxic chemotherapy. Deferoxamine therapy should be stopped and hydroxypyridine chelating agents should be used as a substitute (Yohai et al. 1994).

11.9 Disease Burden and Prognosis

Mucormycosis is known to have a high mortality rate. The rates are highest with disseminated, gastrointestinal and pulmonary disease (up to 90%) (Deutsch et al. 2019). ROCM form has a mortality rate of about 46% among people with sinus infections. The rate jumps to 76% for pulmonary infections and 96% for disseminated mucormycosis (Roden et al. 2005). The cutaneous disease carries the lowest mortality rate (15%). The factors related to a lower survival rate include delayed diagnosis and treatment, bilateral sinus involvement, hemiparesis or hemiplegia, leukemia, renal disease and treatment with deferoxamine (Yohai et al. 1994). A more recent meta-analysis (Vaughan et al. 2018) revealed that the survival rates in patients with chronic renal disease had improved from 19% to 52% and in patients with leukaemia from 13% to 50% compared to the analysis by Yohai et al. (Yohai et al. 1994) Facial necrosis and hemiplegia are poor prognostic indicators (33% and 39% survival rates, respectively). Early commencement of medical treatment led to better survival outcomes (61% if commenced within the first 12 days of presentation, compared to 33% if after 13 days) (Vaughan et al. 2018).

Even after recovery, the possible sequelae include the partial loss of neurological function, blindness and clotting of intracranial, orbital or pulmonary vessels. Additional poor healing in the surgical field predisposes to post-exenteration socket complications.

11.10 Prevention

Knowing the lengthy treatment process and the dismal prognosis, prevention and early recognition of the disease gives the best chance to the patient. In the COVID-19 era, judicious and supervised use of systemic steroids and tocilizumab must be stressed upon. Aggressive monitoring and control of diabetes mellitus is a must. In patients requiring supplemental oxygen, strict aseptic precautions must be followed (Honavar 2021).

Personal and environmental hygiene must be reiterated to patients. Betadine mouth gargles are advocated by some. Masks used for covering the nose and mouth should not be reused. Some centres are leaning towards the use of Posaconazole prophylactically in high-risk patients.

11.11 Conclusion

ROCM is a disease with high mortality despite all treatment. A high index of suspicion is necessary, especially in the setting of uncontrolled diabetes and recent COVID-19 infection. These patients present with orbital cellulitis like the picture, but with considerably fewer inflammatory signs. Early diagnosis, through appropriate diagnostic techniques and aggressive treatment is the key. Prevention, by limiting and controlling the use of immune-compromising drugs (especially steroids) goes a long way in the management of these patients. Awareness of this disease entity among the physicians and ophthalmologists, specifically in patients with predisposing factors, early diagnosis and treatment, monitoring of therapeutic agents would go a long way in reducing morbidity and mortality.

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