Post covid-19 mucormycosis - New menace

Covid-19 has affected every country in the world, about 17 crore people are affected overall. India with its huge population of 1.3 billion is going through one of the most difficult health crisis due to covid-19. In India number of cases have crossed 2.5 crore. Health system and health care workers are under stress. Rate of recovery from covid is 98-99% and fatality rate is less than 2%. Large number of patients who have recovered from covid-19 are facing new problem in the form of mucormycosis loosely called as Black fungus by media and lay people.

Mucormycosis is not a new disease specific to post covid-19 state. Earlier it was commonly seen in immunocompromised patients, uncontrolled diabetes mellitus, patients with stem cell transplant or solid organ transplant and those who are on immunosuppressive therapy for various diseases[1]. Sudden increase in numbers of mucormycosis cases in post covid-19 patients in India has raised alarm bells among common public as well as administration. Disease which was seen in subset of patients has suddenly become rampant in post covid-19 patients.

Mucormycosis is a fungal infection caused by fungus (moulds) belonging to the order of Mucorales. Four varieties mucoracea are responsible for human and animal infection. They are Absidia, Mucor, Rhizomucor and Rhizopus. Mucorales are invasive in nature and invade blood vessels leading to tissue infarction and necrosis. Rhizopus accounts for 70% of the reported Rhino Orbito Cerebral Mucormycosis[2]. Before pandemic prevalence of mucormycosis was 14 cases per 100000 in India, higher compared to other countries. As on May 26th 2021, 11,717 cases of mucormycosis have been reported across India in second wave of covid-19, showing exponential increase in numbers[3]. Government of India has asked the states to declare it as a notifiable disease under the epidemic act 1897.

Why is mucor affecting covid-19 patients ?

1. Covid-19 causes immune suppression as well as hyperglycemic state.
2. Use of steroids in covid-19 patients as part of treatment protocol which are again immunosuppressive.
3. Use of broad spectrum antibiotics in patient admitted with ICU to prevent bacterial infection.
4. Poorly maintained oxygen humidifier bottles. (suspected cause)
5. Continuous use of same masks by public without proper washing. (suspected cause)

Warning signs of post covid-19 mucormycosis:

1. Pain - Facial pain, nasal pain, eye pain, worsening headache
2. Nasal discharge - bloody, foul smelling
3. Eyelid oedema/ facial oedema
4. Eyelid/periorbital/facial discoloration - Blackish or bluish
5. Proptosis/ptosis - change in visual acuity
6. Sudden loss of vision
7. Restricted eye movement, Diplopia
8. Fever, disorientation, seizures or paralysis

Any patient presenting with these symptoms either active covid-19 case or post recovery (less than 6 weeks) should be investigated to rule out mucormycosis[4].

Diagnostic tools for Rhino orbito cerebral mucormycosis (ROCM):

1. Diagnostic nasal endoscopy - change in color of nasal mucosa, blackish eschar and turbinates.
2. Contrast enhanced CT and MRI.
3. Microbiological confirmation
   - Direct microscopy - KOH mount of nasal swab from representative area
   - Culture of swab from nasal cavity, paranasal sinuses or orbital tissue. Genus and species identification is done on culture. Media used are brain heart infusion broth, Potato dextrose agar and Sabouraud dextrose agar with gentamycin and polyamine B but without cyclohexamide, incubated at 30-37^{o}C
4. Molecular diagnostics using quantitative polymerase chain reaction (PCR) have sensitivity of about 75%
5. Histopathology with Haematoxylin and Eosin (H&E) stain, Periodic acid Schiff (PAS) or Grocott Gomori Methanamine silver special stains are used to detect fungal elements, branching pattern and tissue invasion.

Proposed Staging of Rhino-Orbito-Cerebral Mucormycosis (ROCM)

Staging of Rhino-Orbito-Cerebral Mucormycosis	Symptoms	Signs	Primary Assessment	Confirmation of Diagnosis
Stage 1: Involvement of the nasal mucosa 1a: Limited to the middle turbinate 1b: Involvement of the inferior turbinate or ostium of the nasolacrimal duct 1c: Involvement of the nasal septum 1d: Bilateral nasal mucosal involvement	Nasal stuffiness, nasal discharge, foul smell, epistaxis	Foul-smelling sticky mucoid or black-tinged, or granular or haemorrhagic nasal discharge, nasal mucosal inflammation, erythema, violaceous or blue discoloration, pale ulcer, anaesthesia, ischemia, eschar	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT- scan	Deep nasal swab or endoscopy-guided nasal swab or nasal mucosal biopsy for direct microscopy, culture and molecular diagnostics; nasal mucosal biopsy for rapid histopathology with special stains
Stage 2: Involvement of paranasal sinuses 2a: One sinus 2b: Two ipsilateral sinuses 2c: > Two ipsilateral sinuses and/ or palate/oral cavity 2d: Bilateral paranasal sinus involvement or involvement of the zygoma or mandible	Symptoms in Stage 1 + facial pain, facial edema, dental pain, systemic symptoms (malaise, fever)	Signs in Stage 1 + unilateral or bilateral, localized or diffuse facial edema, edema localized over the sinuses, localized sinus tenderness	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT- scan	Same as Stage 1 + sinus biopsy for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 3: Involvement of the orbit 3a: Nasolacrimal duct, medial orbit, vision unaffected 3b: Diffuse orbital involvement (>1 quadrant or >2 structures), vision unaffected 3c: Central retinal artery or ophthalmic artery occlusion or superior ophthalmic vein thrombosis, involvement of the superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision 3d: Bilateral orbital involvement	Symptoms in Stage 1 and 2 + pain in the eye, proptosis, ptosis, diplopia, loss of infraorbital nfraorbital and facial V1 V2 nerve anesthesia	Signs in Stage 1 and 2 + conjunctival chemoses, isolated ocular motility restriction, ptosis, proptosis, infraorbital nerve anesthesia, central retinal artery occlusion, features of ophthalmic artery occlusion and superior ophthalmic vein thrombosis. V1 and V2 nerve anesthesia, and features of III, IV and VI nerve palsy indicating orbital apex/superior orbital fissure involvement.	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT- scan	Same as Stage 2 + orbital biopsy if indicated and if feasible (if the disease is predominantly orbital) for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 4: Involvement of the CNS 4a: Focal or partial cavernous sinus involvement and/or involvement of the cribriform plate 4b: Diffuse cavernous sinus involvement and/or cavernous sinus thrombosis 4c: Involvement beyond the cavernous sinus, involvement of the skull base, internal carotid artery occlusion, brain infarction 4d: Multifocal or diffuse CNS disease	Symptoms in Stage 1 to 3 + bilateral proptosis, paralysis, altered consciousness, focal seizures	Signs in Stage 1-3 (some features overlap with Stage 3) + V1 and V2 nerve anesthesia, ptosis, and features of III, IV and VI nerve palsy indicate cavernous sinus involvement. Bilaterality of these signs with contralateral orbital edema with no clinico-radiological evidence of paranasal sinus or orbital involvement on the contralateral side indicate cavernous sinus thrombosis. Hemiparesis, altered consciousness and focal seizures indicate brain invasion and infarction.	Diagnostic endoscopy, Contrast-enhanced CT Scan, MRI (preferred)	Same as Stage 3

Table-1 Proposed staging of ROCM

Management Approach for Possible, Probable or Proven Rhino-Orbito-Cerebral Mucormycosis (ROCM)

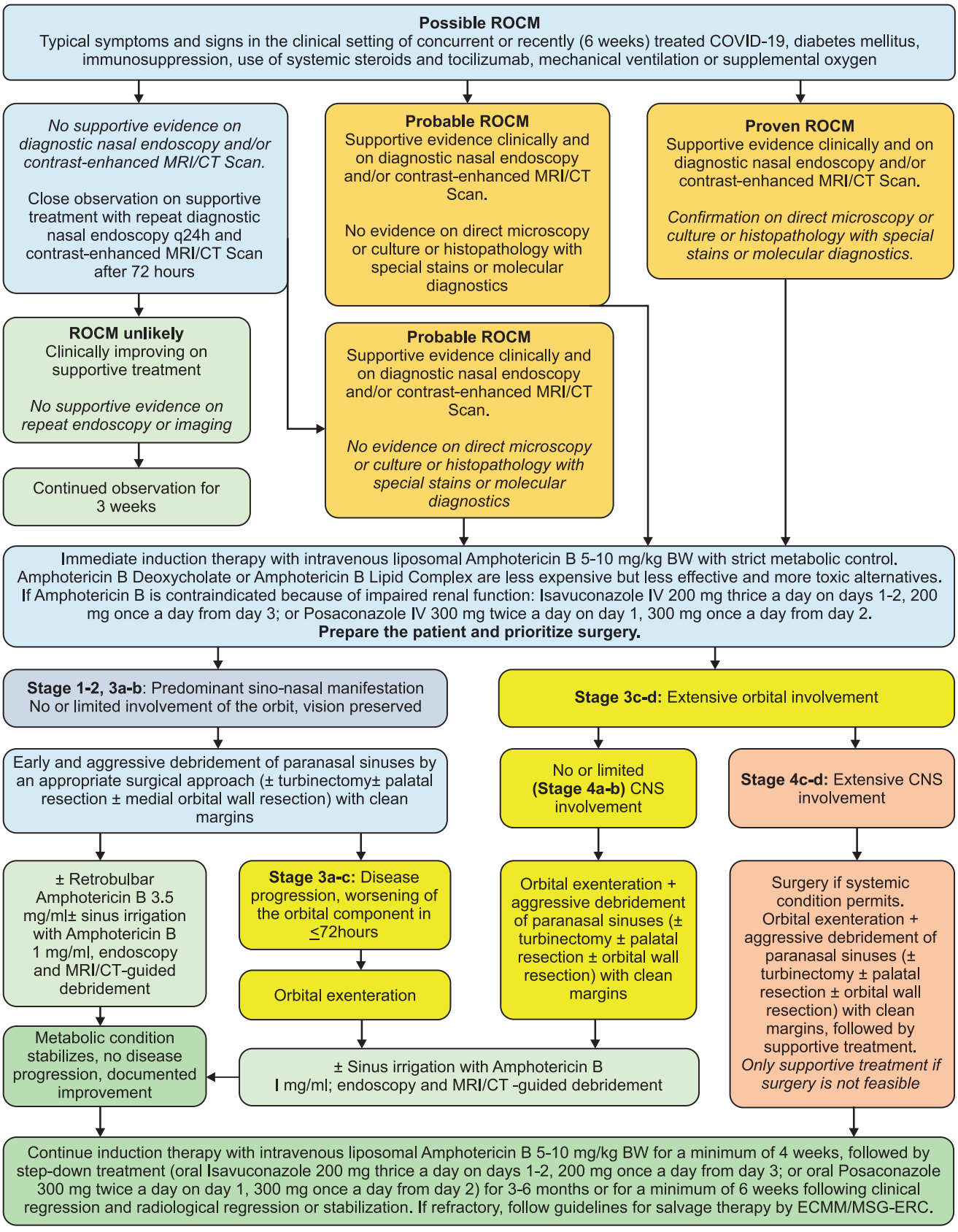

Fig -1. Logical management protocol for treating ROCM.

Management of ROCM:

It includes surgical debridement of necrotic tissue till the viable margins are reached with concomitant administration of IV Amphotericin-B in full dose with supportive therapy like control of hyperglycemic state. Early diagnosis and prompt management reduces morbidity and mortality due to mucormycosis. Staging of ROCM (table-1) and logical management protocol for ROCM (fig -1) is given[4,5].

Team managing these patients needs specialists from different specialties. Team should consist of Otolaryngologist, Ophthalmologist, Radiologist, Microbiologist, neurologist and neurosurgeon. European Confederation of Medical Mycology and Mycosis study group Education and Research Consortium on regular intervals issues comprehensive diagnostic as well as management guidelines for better management of these infections across the globe.[5]

Liposomal Amphotericin-B is preferred over other formulations like Amphotericin Deoxycholate or Amphotericin-B lipid complex or Amphotericin-B colloidal dispersion, because of dose limited toxicity and nephrotoxicity of amphotericin B deoxycholate. Patients on Amphotericin-B deoxycholate should be monitored for nephrotoxicity and electrolyte disturbances.

Surgical resection involves removal of dead and necrotic tissue until healthy tissue is reached. Extensive debridement along with exenteration of eyeball leaves behind ugly facial defects which can have lifelong psychological implications to the patient. This needs to be clearly discussed and conveyed to patient as well as relatives. In addition to this the cost of Liposomal Amphotericin-B, which is to be given for prolonged period (2 months) burdens economically weaker sections of society. Post operatively regular endoscopic surveillance of operative area and monitoring of inflammatory markers will help in detecting any lurking disease.

However with surgery and Amphotericin-B therapy survival rate is still 70%[6]. Thus prevention of mucormycosis is more important in covid -19 patients. Judicious use of steroids and tocilizumab, strict glycemic control, use of sterile water in humidifiers, aseptic precautions are few of the steps that can prevent development of this dangerous disease. Patients at risk should be asked to report immediately if they develop any warning signs.

References:

1. *Skied A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: An update. J Fungi(Basel)2020;6:265*
2. *Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Sahaufele RL etal. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005;41:634-53.*
3. *Sen M, Black fungus: These 5 states account for 65% of India's 11,717 mucormycosis cases. www.livemint.com 2021.*
4. *Honavar SG. Rhinoorbitocerebral mucormycosis- Guidelines for diagnosis,staging and management. Indian J Ophthalmol 2021;69:XX-XX.*
5. *Cornely OA,Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hocchegger B, et al. Global guidelines for the diagnosis and management of mucormycosis: An initiative of the European Confederation of Medical Mycology in cooperation with the Mycosis study Group Education and Research Consortium. Lancet Infect Dis 2019;19:e405-21*
6. *Wali Upender, Balkhair Abdulla, Al-Mujaini Abdulah. Cerbro-rhino-orbital mucormucosis: An update. Journal of infection and public health2012;5:116-26.*

Dr. Chandrashekharayya SH

Professor of ENT, S.N. Medical College,
Bagalkot, Karnataka, India