DOI: 10.7860/JCDR/2023/59617.17471

Review Article

Ear, Nose and Throat Section

Post COVID Mucormycosis- A Narrative Review

SAKSHI DINESH FIRKE[1], PRASAD DESHMUKH[2]

ABSTRACT

Mucormycosis is an Acute Invasive Fungal Rhinosinusitis (AIFR). Omnipresent fungi and their interaction with humans are both boon and a bane. Fungal rhinosinusitis is now becoming an alarming situation in today's world, especially in India. It can be classified further into invasive or non invasive and acute or chronic. Categorisation helps us with its diagnosis and management. The invasion of the hyphae portrays mucormycosis into sinus tissue within less than four weeks. It comes with various predisposing factors such as underlying systemic disease, drug therapy, transplantation, and local lesion. Clinical manifestations such as headache, sinonasal congestion, black lesions on the nasal bridge, and facial inflammation associated with pain are prevalent in immunocompromised patients. Crucial steps such as early identification, definite treatment with a multidisciplinary integrated approach of various departments such as ENT, medicine, and radiology should be made. Intraorbital and intracranial complications can be prevented by treating disease process in the early stage.

Keywords: Coronavirus disease-2019, Diabetes, Nose, Paranasal sinuses, Sinusitis

INTRODUCTION

Fungi have complicated interactions with all flora, fauna, and people due to their ubiquitous occurrence in the earth's environment [1]. Human-fungal interaction can be beneficial (symbiotic) or harmful (infection). A rough estimation of 200 out of 625 fungal species are human related among vertebrates [2]. In one of his books, Nicholas Money said, *"Time for panic attack: their spores are everywhere and, depending upon your location, you may have inhaled hundreds of them since beginning to read this chapter"* [1]. Mucormycosis is an uncommon astute fungal contamination caused by order mucorales of class zygomycetes, known for their angioinvasive nature [3,4]. Sexual (oospore, zygospore), as well as asexual (sporangiospores) spores, are formed by all fungi of order mucorales [5]. Mucorales cultivated on routine laboratory media without chlorhexidine shows pronounced growth in 12-18 hours of plating [4]. On histology, broad-based, non septate hyphae are seen at right angles to each other [6]. Three commonly associated species with Mucormycosis are *Rhizopus* (most common), *Mucor*, and *Rhizomucor*; other species include *Abisida, Cunninghamella*, and *Syncephalastrum* [4,6].

MUCORMYCOSIS IN COVID-19

Fungal rhinosinusitis once thought of as a rare disease, now being the biggest concern in the Indian subcontinent as it accounts for noteworthy cases of mucormycosis within the world. Having a 12.9 case yearly incidence between 1990 and 1999 to frequency of 22 instances annually in postCOVID-19 (Coronavirus Disease) era. The statistics show that India's reported prevalence of mucormycosis is about 70 substantially larger than the estimated worldwide prevalence of 0.02-9.5 cases (with a median of 0.2 cases) per lac people [7]. Fungi detection, evaluation of host immune status, and integrated approaches using biopsies, radiographic, microbiological, histopathological, and medical management with prompt surgical procedure help in a positive outcome [1]. All these components in near future will help researcher to incorporate new methodologies and ideologies to decrease mortality and morbidity indicators. Although this condition was reported rarely in preCOVID-19 era but upsurge following COVID-19 pandemic with incidence of 22 cases yearly and median prevalence of 14 cases per lac people; associated anxiety among suffers and healthcare workers was increased [7]. So, necessity to revisit the entity to explore its novelties prevails. In this narrative review, we retrieved the literature on fungal rhinosinusitis mucormycosis from PubMed, ScienceDirect, and Medicine Databases. While searching the various database, the advanced search option MeSH terms of words like fungal, rhinosinusitis, mucormycosis, paranasal sinuses, and nose was considered.

Classification

In the last 20 years, mucormycosis has surged gradually in countries like France, India, Belgium, and Switzerland [8]. Also, *Mucor* is native to the Middle East and India. Modes of infection include inhalation or assemblage of spores in buccal, sinonasal or conjunctival mucosa [9]. Based on pathological demonstration of tissue invasion by fungal components, the most widely accepted method developed by a consensus workshop divides fungal sinusitis into invasive and non invasive diseases [1]. Mucormycosis was the old name for AIFR [10]. Unlike non invasive fungal rhinosinusitis, AIFR principally shows invasion into neurological and vascular tissues [10]. The proposed definition of AIFR includes the existence of fungal hyphae within the sinonasal mucosa, musculature, or a bone in the setting of sinusitis symptoms lasting one month or fewer [11]. Initial phase of AIFR confined to sinonasal area have significantly lower fatality, whereas fatality rate doubles on progressive extension to intra cranial region [12]. It is a fatal form of fungal sinusitis linked to a 50-80% death rate [10].

Predisposing/Risk Factors

Immunocompromised patients are more susceptible to mucormycosis AIFR [13]. It is rapidly progressive, with a clinical course spanning from a few days to less than 4 weeks [1]. Risk factors for mucormycosis include diabetic ketoacidosis, patients with haematolymphoid malignancy, haematopoietic stem cell and organ transplant recipients, patients on deferoxamine therapy, voriconazole administration, iron overload states, burn, and trauma patients. Long-term lymphopaenia in patients with severe COVID-19 may also influence their propensity to mucormycosis. Above mentioned different types of predisposing factors, result in the indistinct development of mucormycosis these risk factors can be further segregated into categories like underlying systemic disease, drug therapy, transplantation, and local lesion [Table/Fig-1] [3,14].

Underlying systemic disease	Drug therapy	Transplantation	Local lesions
Leukaemia	Corticosteroids	Solid-organ	Burns
Lymphoma	Deferoxamine	Bone marrow	Trauma
Neutropenia	Voriconazole	Peripheral stem cell	-
Diabetes with or without ketoacidosis	-	-	-
COVID-19	-	-	-

[Table/Fig-1]: Predisposing/risk factors for mucormycosis [3,14].

Causative Agents

They belong to order mucorales of class zygomycetes [4]. Three commonly associated species with Mucormycosis are *Rhizopus* (common), *Lichtheimia*, *Apophysomyces*, and *Rhizomucor*; other species include Mucor, *Abisida, Cunninghamella*, and *Syncephalastrum* [4,6,7]. Rhizopus subspecies such as *R.arrhizus, R.microsporus,* and *R.homothallicus* are commonly found in Indian soil. Among these, *R.arrhizhus* is very common, followed by other two showing frequent rise these years. Following Rhizopus, 60% of inflicted cases show *Apophysomyces variabilis* spp., securing second among India. *Lichtheimia* species accounts for 0.5% to 13% of cases from India, among them *L. ramosa* manifest as cutaneous mucormycosis [7].

Pathogenesis

There is significance of numerous predisposing aspects in mucormycosis pathogenesis. Pathogenic mechanism in particular predisposing factors such as diabetes mellitus with or without ketoacidosis, corticosteroids, and COVID-19 patients are elaborated below.

Role of diabetes mellitus with or without ketoacidosis: Ketoacidosis has a profound effect on mucormycosis, as basic physiology of cell which is carried out by iron is hampered [15]. Due to the apparent occurrence of hyperglycaemia in diabetes, the innate immune system is compromised, resulting in inhibition of neutrophil relocation, chemotaxis, and reduced phagocytosis. By blocking the iron seclusion by transferrin and ferritin, the ketone bodies can result in enhanced accessibility of free iron. In susceptible hosts, elevated pH and enhanced accessibility of free iron encourage fungal proliferation [16]. Acidic pH ranging between 7.3-6.88 and elevated free serum iron facilitates *Rhizopus* proliferation and activity [15,16]. Under provided acidic condition, iron binding capacity is decreased, which implies that acidosis (elevated H^+), impairs iron and transferrin interaction via proton H^+ mediated displacement of ferric ion from transferrin. *Aspergillus fumigatus and Candida albicans* cannot assimilate 8-fold and 40-fold more iron than *Rhizopus* can, according to in-vitro studies of radiolabelled iron uptake from deferoxamine in serum, respectively [15]. Hyperglycaemia plays a role not only by blocking the activity of iron sequestering proteins, hindering neutrophil phagocytosis and chemotaxis but also by affecting the oxidative and non oxidative pathways and modulating GRP78, CotH3 (fungal protein) [17].

Role of corticosteroids: They precipitate hyperglycaemia [16]. Mucormycosis infection is more prevalent in diabetic patients who have been treated for COVID-19 and have taken corticosteroids throughout their treatment [18]. Corticosteroids proclivity for impairing migration, ingestion, and phagolysosome fusion in macrophages possibly explain the patient's reduced immunity [16]. Angioinvasive mucormycosis is triggered by a long-term high dose of corticosteroids [19].

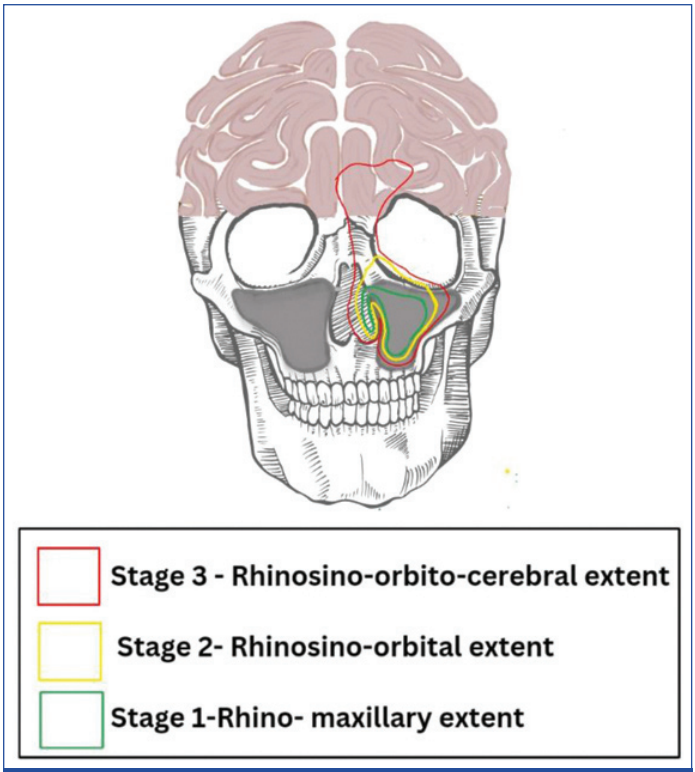
Progression to angioinvasion in COVID patients: Vascular endothelial damage, vessel thrombosis, and tissue necrosis are a cascade of events following angioinvasion of mucormycosis [20]. Angioinvasiveness results from SARS-CoV-2 facilitated endothelins and modulation of CotH3, GRP78. SARS-CoV-2 facilitated endotheliitis commences due to increased ferritin release in the bloodstream as a response to inflammation; this results in increased free iron. Reactive oxygen species cause oxidative stress and cell membrane lipoperoxidation due to the Fenton reaction of free iron. Free iron and ferritin catalyse endothelial disruption induced by free radicals, spreading endothelial inflammation and promoting endotheliitis [16]. Modulation of GRP78, CotH3 (fungal protein) occurs when extracellular grid laminin protein situated on the basement membrane is stimulated by an invasion of an organism in skin or mucosa [21]. Thus, the *Mucor* attaches to endothelial cells with receptor GRP78, found on the host endothelium working with contagious endocytosis [16]. The parasitic ligand, which helps in linking the GRP78 during the early intrusion of *Mucor,* has a place with a spore covering protein family (CotH3) [22]. GRP78 is a heat shock protein generated by endothelial cells' endoplasmic reticulum in response to stress [23]. The viral spike-glycoprotein provokes Endoplasmic Reticulum Stress (ERS) and increases GRP78 production during SARS-CoV-2 infection [24]. In a prospective case-control research, serum GRP78 was observed to be 5 times more significant in COVID-19 cases than in the test group [16]. Additionally, investigations have shown that the SARS-CoV-2 virus utilises GRP78 to internalise into host tissue [24]. In the same manner that the virus upregulates GRP78 for its entrance into tissues, it also enhances fungal endocytosis. While GRP78 is a stress-related protein, it is amplified whenever it interacts with ketone bodies on endothelium and high blood glucose [16]. The most common form of mucormycosis is a rhino-orbital-cerebral infection, which arises when the fungus infection spreads to orbit and brain parenchyma from paranasal sinuses [25]. There are three types of intracranial lesions that emerge as a consequence of rhinocerebral Mucormycosis-a) related to direct venous incursion and necrosis, which includes meningitis, brain abscess, and cranial nerve palsies; b) resulting from vascular injuries, e.g., thrombosis and aneurysm of the cavernous sinus or internal carotid artery, carotid-cavernous fistula, tissue infarction, haemorrhage in subdural space, and brain parenchyma; c) Obstructive hydrocephalus and behavioural changes are afflictions of a space-occupying lesion [26]. Orbital Apex syndrome is an unusual thing evidenced by ophthalmoplegia and rapid vision loss involving nerves that directly emerge from the brain: 2nd to 6th, which is deadly [25].

Clinical Features

Mucormycosis can present as an abrupt fulminant or gradual, lethargic intrusive infection. When the cause of immunocompromise is severe, the rate of progression is rapid, whereas when the source of immunocompromise is little or non existent, lethargic intrusive clinical signs appear [4]. The disease's first symptoms are non specific and similar to acute bacterial sinusitis [1]. The most prevalent symptoms include rhinorrhea (often explicit), nasal congestion, headache, fever with spikes, face paint and diplopia [1,11]. Thus, clinical features can be divided on basis on stage of disease into: early and late stage features.

In early stage: In the early stages, ischaemic pallor and colour changes appear in the nasal cavity [11]. Necrotic eschar or ulcer on nasal septum can be painless. Impairment in vision, diplopia, growth of scar tissue on the bony hard palate, hyperesthesia, and anaesthesia in the oral cavity are seen as the disease progresses with granulation tissue and necrosis of mucosa of the nasal cavity [1]. These symptoms are generally determined by the invasion into local anatomical architecture [10]. Sinus involvement includes ethmoidal group followed by maxillary, then sphenoidal and frontal [27].

In late stage: The pale or oedematous mucosa (early stage) becomes more vascular, darker, and finally black and necrotic (late-stage) as a result of neurovascular invasion in due course of time. Resulting in ulceration and peeling off the mucosa, leaving crust or a thick eschar [10]. Tissue ischaemia due to angiocentric invasion is indicated by white staining of the mucosa, whereas tissue necrosis is shown by black discolouration [28]. Clinical staging based on progression and extent are: Stage 1: Rhinomaxillary; Stage 2: Rhino-orbital; Stage 3: Rhino-orbito-cerebral. [Table/Fig-2]: Clinical staging based on progression and extent [1].



[Table/Fig-2]: Clinical staging based on progression and extent [1].

Diagnostic Methods

The problem is that the initial prodrome may be harmless and non specific [10]. The intrusive symptoms that follow might develop quickly and increase in a matter of hours, adding upto the difficulties of getting a timely diagnosis [10]. To tackle with this situation, awareness about early signs and symptoms, effective history taking, using highly specific and sensitive laboratory investigations, improvising healthcare facilities can be taken as measure. Investigations consist of blood, histopathological, microbiological, biochemical, and radiological parameters.

Blood investigations: Blood tests are to be done if there is a suspicion of AIFR. The gamut of blood investigations comprises whole blood count, which gives an image of neutropenia or malignancy of blood components, kidney function test, blood glucose ketones, serum iron level, and HIV screening [11]. In generalised view, it benefits in knowing about basic blood profile, markers of acute infections, and organ involvement. Disadvantage may include low specificity and sensitivity, not able to know progression of disease, and early involvement of adjacent structures. Blood investigations may not be suitable for diagnosis; therefore, we need further investigations for evaluation for disease.

Histopathological and microbiological: Disease confined to the nasal cavity signals an early stage in the pathophysiology of AIFR; if detected early enough, it is more receptive to total surgical resection by an endoscope, which may improve patient survival [28]. Imaging investigations and nasal endoscopy with potential biopsy should be part of an appropriate diagnostic work-up so treatment can begin as soon as possible. *The middle turbinates are a cogent site (sensitive+specific) for biopsy* [1].

A preliminary diagnosis of mucormycosis based on histological evidence shows broad-based aseptate hyphae [1,4]. Even though tissue specimen may not differentiate between hyphae of species such as aspergillus and mucorlaes but helps in identification of contaminant present [29]. Fungal hyphae is highlighted with Toluidine Blue, Haematoxylin and Eosin (H&E), and Gomori Methenamine Stain (GMS) [1,4]. Mucorale hyphae can be seen as non or pauciseptate, branched with bifurcation usually at 90 degree, irregular, and ribbon like [29].

Biochemical: Using fast and in-situ hybridisation for ribosomal RNA aims to identify fungal species that may be a beneficial strategy for identification, which includes Serology, Enzyme-Linked Immunosorbent Assays (ELISA), immunoblots, and immunodiffusion, and sometimes Mucorales specific T cells detection via an enzyme-linked immunospot (ELISpot) assay [1,29]. Above noted, all assays can be used either for detection or identification of Mucorales but most molecular assays target either the Internal Transcribed Spacer (ITS) or the 18S rRNA genes followed by some newer kids in the block, which includes 25 Sribosomal DNA, cytochrome b, PCR coupled to electrospray ionisation mass spectrometry [29-31].

Radiological: On nasal endoscopy, there will be alterations in the nasal mucosa, granulation tissue, ulcer, and tissue necrosis according to the degree of invasion [1,3]. In all cases of fungal rhinosinusitis, radiography and CT imaging of the nose and paranasal sinuses are performed to determine the openness of the osteomeatal complex, engagement of paranasal sinuses, and attrition of the sinus cavity's bone borders [32]. Plain radiographs show variation from apparently normal to appreciative bony erosion depending on the early and late stages of the disease, respectively [28]. Extent of involvement is explicitly exhibited by MRI, which further effectually helps in debridement of devitalised tissue [33]. With progressive invasion, a characteristic finding of early-stage rhinosinusitis appears, but it is hard to specify whether the radiograph is of bacterial sinusitis or viral sinusitis [4]. CT PNS is favoured over plain radiograph [28]. The imaging modality of preference is CT imaging of the sinuses and orbits; however, in the primordial stage of AIFR, 12% of patients show modest alteration, which may or may not be visible due to its fulminant nature [1]. The most reliable but non specific imaging feature is hypoattenuating dense mucosa with incomplete or total opacification of solitary one-sided nasal sinus or cavity [1]. The occurrence of hyper attenuation patches within opacified sinuses in immunocompromised individuals shows potential danger for elemental fungal aetiology [13]. With disease progression, the vascular spread is likely to happen, and also the spread beyond sinuses even though intact bony walls are seen [1]. The compartments close to the maxillary sinuses, such as the premaxillary, retro-antral fat, and pterygopalatine fossa, must be painstakingly investigated to study soft tissue infiltration [34]. The areas of coagulation necrosis correspond to the absence of contrast enhancement and the presence of a high fungal load [35]. Contrast-enhanced MRI is extensively used, and it has been demonstrated to be more efficient than CT at recognising AIFR [11]. While CT is perfect for detecting bony alterations, MRI is better for analysing retro-orbital or intracranial extension [1]. AIFR has defined different contrast enhancement patterns, such as gadolinium enhanced magnetic resonance imaging [10,27]. Follow-up for scans is essential, particularly in the case of orbital pathologic extension [6].

Treatment

A three-pronged approach to AIFR consists of reversal of risk factors, surgical debridement, and antifungal therapy [10]. Controlling the underlying aetiologic immune suppression state is critical to the therapy's success [1].

Reversal of risk factors: Reversal of diabetic acidosis, hyperglycaemia, iron overload states, electrolyte imbalance, and neutropenia; improvement of circulatory volume and tissue perfusion; cessation of steroid medication; constant removal of ketones from serum and urine seeks to improve immunological status while inhibiting disease progression [1].

Patients with diabetes benefit from aggressive insulin regimens for reversing diabetic Ketoacidosis [1]. Iron chelators, such as deferasirox, impede the potential of fungi to reproduce and prevent their spread. As neutrophils play a significant role in antifungal immunity, therapy of

granulocyte infusion and granulocyte-macrophage colony-stimulating factor offers great potential in reversing neutropenia [1].

Surgical debridement: Debridement of dead necrotic tissue is to be executed as soon as a normal metabolic state is established [10]. Proactive surgical interceding is required for both identifying biopsies and therapeutic debridement, both of which are well recognised as vital parts of management [1]. It is necessary to perform extensive surgical debridement with the goal of completely removing necrotic tissue with edges penetrating healthy bleeding tissue [1]. This may entail clearing a large amount of nasal mucosa, turbinates and executing extended sinonasal access procedures to clear the sinuses [10]. Endoscopic debridement has upgraded from Caldwell-Luc operations and ethmoidectomies, which serves as an advantage and is connected with appealing outcomes because it is minimally invasive, has enhanced visualisation and has reduced operating morbidity [4]. For advanced AIFR patients with orbit or intracranial issues, surgical decisions, including maxillectomy and orbital exenteration, which have disfiguring results, can be lifesaving [1,10]. Repeat sessions are frequently required to remove any necrotic tissue that is progressively accumulating [10]. Frozen section evaluation during surgery can facilitate the diagnosis and improve prognosis. In the circumstances such as the unavailability of frozen sections along with the risk of acute invasive fungal infection, the clinician should be notified about it straight away without postponing the usual process to be done and report the results to the physician in charge [1].

Antifungal medication: Should indeed be initiated soon after the onset of acute invasive fungal pathology to minimise fatality rates [1]. Amphotericin B is efficient on both mucorales and aspergillus species; a dosage of 1-1.5 mg/kg daily intravenous Amphotericin B deoxycholate was given previously [1]. Liposomal Amphotericin B (LAB) has become the preliminary medication of choice for management due to its improved tolerance and reduced nephrotoxicity. Unfortunately, the limitation to its long-term utilisation is due to its heavy price. Posaconazole and isavuconazole, two potential novel azoles, have been approved by the FDA as the second line of treatment for mucormycosis [1,8]. They can be taken orally and have a low incidence of side-effects, making them ideal for long outpatient regimens [1]. Caspofungin, a new antifungal medication and the first member of the echinocandin family, has demonstrated no effectiveness against mucormycosis in seclusion and exhibits collaborative activity with Amphotericin B [1]. Due to its action of liberating oxygen free radicals, oxygen under high pressure directly kills fungi and is thus utilised as a supplementary to management. This adjunct therapy is favourable in diabetic ketoacidosis induced AIFR [1,10].

Constellation of practical reasons such as omnipresent spores of mucorales, mammoth of susceptible hosts particularly diabetic, disregards regular health check-ups, lead to high prevalence [8]. People with oblivious diabetic status, tuberculosis, and chronic kidney disease are at risk. Mortality is linked with delays in medical assistants and severity due to evolved forms. The majority of lacunae in treatment are due to delays in diagnosis, limited medicines, and lesser management alternatives [8].

Prevention: Mucormycosis and its related morbidity and mortality rates necessitate its prevention. Especially in COVID-19, the levels of prevention which can be considered are:

a) Primary level includes vaccination of COVID-19, hygiene and cleanliness, avoiding damp atmosphere, awareness of signs and symptoms planning of outbreaks.

b) Secondary level includes early diagnosis of co-morbidities and its adequate treatment, quarantine and isolation measures. Specific things were observed, which were preventable with judicial use during this era were 21 days of oxygen therapy, steroid usage, prompt treatment of co-morbid conditions.

c) Tertiary level consists of disability limitation and rehabilitation. It is an intervention implemented in already established disease. It helps in better clinical outcome and prevents associated sequalae. When disease progresses into adjacent structures it will worsen the prognosis. As for example, intracranial extension can lead to brain abscess, thrombotic event, intraorbital extension can lead to ophthalmoplegia, and rapid loss of vision as mentioned in above context. Thus, block at such level prevents further disability [36-38].

CONCLUSION(S)

Fungal rhinosinusitis (Mucormycosis), caused by mucorales, has a rapid onset and progression. *Rhizopus.arrhizhus, Apophysomyces variabilis* spp. are the leading causative agents for this surge of cases. It is commonly seen in immunocompromised patients, the earliest sign being loss of sensation (anaesthesia) in an area. Prevention of mucormycosis is at three levels. To prevent fatal outcomes, early diagnosis with frozen biopsy, microscopy using fungal stains, nasal endoscopy; guide us for the type of treatment needed. Reversal of risk factors, aggressive surgical debridement, and antifungal therapy are the three gems of treatment.

REFERENCES

[1] Singh V. Fungal rhinosinusitis: Unravelling the disease spectrum. J Maxillofac Oral Surg. 2019;18(2):164-79.
[2] Fisher MC, Gurr SJ, Cuomo CA, Blehert DS, Jin H, Stukenbrock EH, et al. Threats posed by the fungal kingdom to humans, wildlife, and agriculture. mBio. 2020;11(3):e00449-20.
[3] Mignogna MD, Fortuna G, Leuci S, Adamo D, Ruoppo E, Siano M, et al. Mucormycosis in immunocompetent patients: A case-series of patients with maxillary sinus involvement and a critical review of the literature. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2011;15(8):e533-40.
[4] Ferguson BJ. Mucormycosis of the nose and paranasal sinuses. Otolaryngol Clin North Am. 2000;33(2):349-65.
[5] Ananthanarayan and Paniker's Textbook of Microbiology 10th Edition. General Aspects of Medical Mycology. 2017.
[6] Celis-Aguilar E, Burgos-Páez A, Villanueva-Ramos N, Solórzano-Barrón J, De La Mora-Fernández A, Manjarrez-Velázquez J, et al. An emergent entity: Indolent mucormycosis of the paranasal sinuses. A multicenter study. Int Arch Otorhinolaryngol. 2019;23(1):92-100.
[7] Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. Microorganisms. 2021;9(3):523.
[8] Sharma A, Goel A. Mucormycosis: Risk factors, diagnosis, treatments, and challenges during COVID-19 pandemic. Folia Microbiol (Praha). 2022;67(3):363-87.
[9] Deek AJ, Boukovalas S, Rathfoot CJ, Gotcher JE. Rhinocerebral mucormycosis as a sequelae of COVID-19 treatment: A case report & literature review. J Oral Maxillofac Surg. 2022;80(2):333-40.
[10] Deutsch PG, Whittaker J, Prasad S. Invasive and non invasive fungal rhinosinusitis-a review and update of the evidence. Medicina (Mex). 2019;55(7):319.
[11] Craig JR. Updates in management of acute invasive fungal rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2019;27(1):29-36.
[12] Slonimsky G, McGinn JD, Goyal N, Crist H, Hennessy M, Gagnon E, et al. A model for classification of invasive fungal rhinosinusitis by computed tomography. Sci Rep. 2020;10(1):12591.
[13] Raz E, Win W, Hagiwara M, Lui YW, Cohen B, Fatterpekar GM. Fungal sinusitis. neuroimaging. Clin N Am. 2015;25(4):569-76.
[14] Kulkarni AP, Siddiqui SS. Systemic Fungal Infections. API Textbook of Medicine 11th Edition. Volume 1. 2019.
[15] Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2012;54 Suppl 1:S16-22.
[16] Jose A, Singh S, Roychoudhury A, Kholakiya Y, Arya S, Roychoudhury S. Current understanding in the pathophysiology of SARS-CoV-2-associated rhino-orbito-cerebral mucormycosis: A comprehensive review. J Maxillofac Oral Surg. 2021;20(3):373-80.
[17] Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2012;54 Suppl 1:S23-34.
[18] Moorthy A, Gaikwad R, Krishna S, Hegde R, Tripathi KK, Kale PG, et al. SARS-CoV-2, uncontrolled diabetes and corticosteroids-an unholy trinity in invasive fungal infections of the maxillofacial region? A retrospective, multi-centric analysis. J Maxillofac Oral Surg. 2021;20(3):418-25.
[19] Kontoyiannis DP, Lewis RE. How I treat mucormycosis. Blood. 2011;118(5):1216-24.
[20] Shumilov E, Bacher U, Perske C, Mohr A, Eiffert H, Hasenkamp J, et al. In situ validation of the endothelial cell receptor GRP78 in a case of rhinocerebral mucormycosis. Antimicrob Agents Chemother. 2018;62(5):e00172-18.

[21] Chandley P, Subba P, Rohatgi S. COVID-19-associated mucormycosis: A matter of concern amid the SARS-CoV-2 pandemic. Vaccines. 2022;10(8):1266.
[22] Gebremariam T, Liu M, Luo G, Bruno V, Phan QT, Waring AJ, et al. CotH3 mediates fungal invasion of host cells during mucormycosis. J Clin Invest. 2014;124(1):237-50.
[23] Ibrahim IM, Abdelmalek DH, Elfiky AA. GRP78: A cell's response to stress. Life Sci. 2019;226:156-63.
[24] Ibrahim IM, Abdelmalek DH, Elshahat ME, Elfiky AA. COVID-19 spike-host cell receptor GRP78 binding site prediction. J Infect. 2020;80(5):554-62.
[25] Saldanha M, Reddy R, Vincent MJ. Title of the article: Paranasal mucormycosis in COVID-19 patient. Indian J Otolaryngol Head Neck Surg. 2022;74(Suppl 2):3407-10.
[26] Bhandari J, Thada PK, Nagalli S. Rhinocerebral Mucormycosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2022 Nov 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK559288/.
[27] Sharma S, Grover M, Bhargava S, Samdani S, Kataria T. Post coronavirus disease mucormycosis: A deadly addition to the pandemic spectrum. J Laryngol Otol. 2021;135(5):442-47.
[28] Mundra RK, Gupta Y. Mucormycosis of nose and paranasal sinuses with orbital complication in young diabetic. Indian J Otolaryngol Head Neck Surg. 2008;60(4):360-64.
[29] Skiada A, Lass-Floerl C, Klimko N, Ibrahim A, Roilides E, Petrikkos G. Challenges in the diagnosis and treatment of mucormycosis. Med Mycol. 2018;56(suppl_1):93-101.
[30] Mudgal S, Rao S, Pai M. Mucormycosis: A comparative update between conventional and molecular diagnosis strategies. Curr Med Mycol. 2022;8:44-53.
[31] Liu J, Yu Y, Cai Z, Bartlam M, Wang Y. Comparison of ITS and 18S rDNA for estimating fungal diversity using PCR-DGGE. World J Microbiol Biotechnol. 2015;31(9):1387-95.
[32] Suresh S, Arumugam D, Zacharias G, Palaninathan S, Vishwanathan R, Venkatraman V. Prevalence and clinical profile of fungal rhinosinusitis. Allergy Rhinol. 2016;7(2):e115-20.
[33] Sundaram N, Bhende T, Yashwant R, Jadhav S, Jain A. Mucormycosis in COVID-19 patients. Indian J Ophthalmol. 2021;69(12):3728-33.
[34] Deshmukh YA, Vaid S, Chandorkar A, Atre A, Patil S. Imaging spectrum of rhino-orbital-cerebral mucormycosis secondary to COVID-19 infection: A reporting checklist. Pol J Radiol. 2022;87:e333-47.
[35] Choi YR, Kim JH, Min HS, Won JK, Kim HJ, Yoo RE, et al. Acute invasive fungal rhinosinusitis: MR imaging features and their impact on prognosis. Neuroradiology. 2018;60(7):715-23.
[36] Ish P, Ish S. Prevention of mucormycosis in COVID-19-the need of the hour. Indian J Ophthalmol. 2021;69(7):1969.
[37] Mucormycosis infographics [Internet]. [cited 2022 Nov 2]. Available from: https://www.who.int/southeastasia/outbreaks-and-emergencies/covid-19/What-can-we-do-to-keep-safe/mucormycosis.
[38] Kisling LA, Das JM. Prevention strategies. InStatPearls [Internet] 2021 May 9. StatPearls Publishing.

PARTICULARS OF CONTRIBUTORS:
1. Student, Department of Ear, Nose and Throat, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, Maharashtra, India.
2. Professor and Head, Department of Ear, Nose and Throat, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Sakshi Dinesh Firke,
4, Shanti Nagar, Yawal Road, Bhusawal, Maharashtra, India.
E-mail: hemakshiddf@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 22, 2022
- Manual Googling: Oct 26, 2022
- iThenticate Software: Nov 28, 2022 (6%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Aug 11, 2022**
Date of Peer Review: **Oct 15, 2022**
Date of Acceptance: **Nov 10, 2022**
Date of Publishing: **Feb 01, 2023**