sciendo

DOI: 10.2478/rjr-2022-0017

Romanian Journal of Rhinology, Volume 12, No. 47, July - September 2022

LITERATURE REVIEW

Mucormycosis in COVID-19 patients with uncontrolled diabetes – the lethal triangle

Mihaela Neagu[1], Carmen Badea[1], Ionut Tanase[1,2]

[1]ENT&HNS Department, "Sfanta Maria" Hospital, Bucharest, Romania

[2]CESITO Centre, "Sfanta Maria" Hospital, Bucharest, Romania

ABSTRACT

BACKGROUND. Coronavirus disease 2019 (COVID-19) is one of the main global health problems of the twenty-first century, with more than one-hundred million people infected and more than two million deaths. The immunosuppression caused by SARS-CoV-2 infection along with steroidal treatment, hyperglycaemia and elevated ferritin levels creates the perfect environment for opportunistic infections such as mucormycosis. COVID-19-associated mucormycosis carries a high mortality rate. Therefore, in addition to antifungal therapy and aggressive surgical debridement of necrotic tissue, strategies to improve glycaemic index is the key factor in order to obtain a favourable outcome.

MATERIAL AND METHODS. For the purpose of this article, the PubMed databases were searched using MeSH descriptors and the Boolean operator "AND" for the terms "rhinosinusal" and "mucormycosis" and "diabetes", between February 2019 – December 2021. Clinical characteristics, therapy and outcome data were gathered and compared to what has previously been reported in the literature. Also, we report the case of a 68-year-old patient with uncontrolled type 2 diabetes mellitus, who developed mucormycosis during post-COVID period, to underline the need of early detection of this potentially deadly fungal illness.

RESULTS. The clinical and imaging evaluation revealed no evidence of disease recurrence, at one- and two-months' follow-ups.

CONCLUSION. In this context, we would like to emphasize the importance of a high index of suspicion for mucormycosis in patients with COVID-19 infection, with pre-existing medical disorders, presenting with rhino-orbital or rhino-cerebral symptomatology.

KEYWORDS: mucormycosis, COVID-19, diabetes mellitus, Amphotericin B.

INTRODUCTION

Mucormycosis is a life-threatening disease caused by a ubiquitous fungus that, in immunocompromised patients, through its angio-invasive properties, determines tissue necrosis and can rapidly spread to adjacent regions and even to other regions of the body (brain, lungs, skin).

Rhino-orbital mucormycosis is caused by a fungus known as Mucorales, part of the Zygomycetes family, which contains more than 1050 species[1]. Commonly called "bread molds", it includes *Rhizopus, Mucor* and *Phycomyces*, has the ability to grow on a variety of substrates, and a few can act as human pathogens[2].

In recent years, it was observed a surge regarding the incidence of mucormycosis infection; extracted evidence from multiple published epidemiological studies revealed a pooled prevalence of Coronavirus disease 2019 (COVID-19)-associated mucormycosis 50 times higher than before the pandemic era[3-5].

The proposed mechanism of pathogenesis consists of inhalation of fungal spores from air that determine the colonization of respiratory mucosa at the level of the nasal cavity and paranasal sinuses and rapid spread to surrounding structures, facilitated by its angio-invasive properties.

Based on the anatomical region where mucormycosis has developed, it can be classified into rhino-orbito-cerebral (ROCM), gastrointestinal, pulmonary, renal, cutaneous, disseminated. Other rare sites include ear, parotid gland, heart, lymph nodes, bones[6,7].

In this paper we will focus on the rhinosinusal mucormycosis, with an emphasis on the association with COVID-19 infection and comorbidities that increase its aggressiveness, and therapeutic strategies that increase the rate of survival.

Corresponding author: Ionut Tanase, MD, PhD, ENT&HNS Department, "Sfanta Maria" Hospital, 37-39 Ion Mihalache Blvd.., District 1, Bucharest, Romania

ORCID: https://orcid.org/0000-0003-4475-7737

e-mail: ionut_tanase1987@yahoo.com

Received for publication: March 29, 2022 / **Accepted:** April 20, 2022

Table 1. Common risk factors, co-morbidities, affected area.

Author	No. of patients	Diabetes mellitus	Corticosteroids use	Involved area
Bayram et al.[14]	11	72.7%	100%	Sino-orbital involvement - 100% Cerebral involvement - 27%
Pal et al.[16]	99	85%	85%	Rhino-orbital - 42% Rhino-orbito-cerebral - 24%
Singh et al.[17]	101	80%	76.3%	Nose and sinuses - 88.9% Rhino-orbital - 56.7% Rhino-orbito-cerebral - 22.2%
Garg et al.[19]	10	100%	100%	Sinusitis - 70% Orbital involvement - 30%
Dilek et al.[20]	100	79%	90.5%	Rhino-orbital - 50% Rhino-sinusal - 17% Rhino-orbito-cerebral - 15%
Pippal et al.[21]	80	90%	83.75%	Intraorbital - 37.5% Intracranial involvement - 12.5% Palate - 42.5%
Mitra et al.[22]	32	100%	78.1%	Paranasal sinuses - 87.5% Orbit - 43.75% Orbital apex showing thrombosed ophthalmic artery - 68.75% Pterygopalatine fossa - 81.25% Vidian canal and pterygoid wedge - 50% Palate - 25% Cheek and eyelid soft tissues - 56.25%
Desai et al.[23]	50	82%	84%	Maxillary sinus - 52% Ethmoid - 38% Orbit - 70% Cavernous sinus - 36% Hard palate - 30% Skull base - 16% Intracranial involvement - 6%
Gupta et al.[24]	56	85%	66%	Maxillary sinuses - 94% Ethmoid sinus - 79% Frontal sinus - 67% Sphenoid sinus - 62% Orbital involvement - 33%. Palatal involvement - 14% Intracranial involvement - 7% Bilateral disease - 28%
Panwar et al.[25]	7	100%	42.8%	n/a

MATERIAL AND METHODS

For the purpose of this article, the PubMed databases were searched using MeSH descriptors and the Boolean operator "AND" for the terms "rhinosinusal" and "mucormycosis" and "diabetes" and "COVID-19", between February 2019 – December 2021, with a filter on "clinical trials" and "review". After all duplicates were excluded, out of 15 results only 10 articles were included in the study. The articles included needed to explore the relationship between diabetes, corticosteroid use and development of mucormycosis in patients with RT-PCR confirmed COVID-19 infection.

RISK FACTORS FOR COVID-19-ASSOCIATED MUCORMYCOSIS

Previous to the pandemic era, the occurrence rate for mucormycosis was between 0.5 - 1.5 per million[7], but with the surge of COVID-19, it has risen up to 26.7%[8], India being the most affected country[9,10].

According to Reid et al., the most frequently involved areas in the development of mucormycosis are the paranasal sinuses (39%), the lungs (24%), disseminated (23%), skin and soft tissue infection (19%)[11].

The predisposing factors for the development of mucormycosis infection were previously studied and it is well known that immunodeficiency, diabetes mellitus, corticosteroid use, malignant hematologic disorders are the main reasons why this ubiquitous fungus can induce, through its angio-invasive properties, necrosis of the invaded tissue[12].The major risk factor for developing rhino-orbito-cerebral mucormycosis (ROCM) in the context of COVID-19 infection are diabetes mellitus, corticosteroid use and the immunosuppression induced by the COVID-19 infection itself[11,13] (Tabel 1). Depending on the study, diabetes prevalence varies, but it is the risk factor most commonly encountered, between 73.4% and 100%[14,15]. A recent systematic review that included 99 patients confirmed with COVID-19 infection found that approximately 85% of patients that developed mucormycosis had diabetes mellitus and only 4 patients did not have any associated comorbidities[16]; this data is in accordance with the results from other studies that found a similar prevalence (80% of 101 patients)[17]. A study made by Roden et al. prior to the COVID-19 pandemic found that those patients who developed mucormycosis and had as a concurrent comorbidity diabetes mellitus had a mortality rate of 45% compared to those without diabetes that had a mortality rate of 35%[6].

Corticosteroids use was approved for the treatment of COVID-19 infection in patients with moderate to severe illness by the RECOVERY trial ("Randomised Evaluation of COVID-19 Therapy")[18] published in June 2020. The benefit was proven for low-dose administration of Dexamethasone for short periods of time. Careless administration of corticosteroid in high doses in patients that do not meet the criteria for moderate to severe illness exacerbates the potential for second bacterial and fungal infections, like mucormycosis.

Apart from host factors that leave the door open for the mucormycosis infection, Mucorales has its own virulence factors that facilitate the fungus to cause disease. One example is the capacity of acquiring iron from the host, this being an essential element involved in the cellular cycle, making patients with high iron serum level uniquely susceptible to the mucormycosis infection. Taking this into consideration, the iron supplements used in the treatment of COVID-19 infection also seem to be linked to the progression of the disease, helping the fungus metabolic process into further growing[12].

In order to counteract its rapid spread and high mortality rate, early recognition and prompt specific treatment must be established.

PATHOPHYSIOLOGY OF RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS

A complex interaction between a multitude of factors appears to act as the basis that triggers the activation of the mucormycosis infection.

Mucorales, also known as common molds, are generally found in soil, dust, decaying food. In people with competent immune system, the spores that reach the respiratory tract are eliminated by sneezing or swallowing. In case of an existing breach at the level of the mucosa, neutrophils phagocytose and neutralize the fungi. Therefore, patients with neutropenia or neutrophil dysfunction are the most susceptible to developing the disease. After the fungi evolve into hyphal forms inside the susceptible host, they are able to invade blood vessels, inducing an extensive angioinvasion, which materializes in thrombosis and tissue necrosis[26].

Table 2. Median time interval from the COVID-19 infection to the debut of mucormycosis infection.

Author	Median time interval	Number of patients	Symptomatology
Bayram et al.[14]	14.4 ± 4.3 days	11	Orbital apex syndrome - 63.6% Orbital cellulitis-36.4% Endophthalmitis - 54.5% Retinoschisis -18%
Garg et al.[19]	24.6 days (range 22–28 days)	11	Headache - 100% Vision impairment - 30% Other complaints: cheek oedema, nasal obstruction/discharge, localized pain
Mitra et al.[22]	18 (± 4) days	32	Blurring of vision - 87.5% Headache - 65.62% Cheek and eyelid swelling - 59.37% Proptosis -50% Ophthalmoplegia - 46.87% Ptosis - 40.62% Orbital pain - 25%
Pal et al.[16]	15 days	99	N/A

TIME RELATION BETWEEN RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS AND COVID-19 INFECTION

Based on the occurrence of ROCM in relation to the COVID-19 infection, the median time interval varies from 8 to 18 days. Most studies[15] found that ROCM infection was more commonly found after the first 14 days from the confirmation of COVID-19 infection, but it can develop as late as 90 days after the debut of COVID-19 infection[26] (Table 2).

CLINICAL FEATURES OF RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS

The clinical picture of a patient presenting with rhinosinusal mucormycosis varies depending on the extent of the disease. The most common symptoms are: headache, facial pain, loss of vision, proptosis, restricted eye movements, cheek and eyelid swelling (Table 2).

Taking into consideration the clinical picture of patients with mucormycosis, the treatment has to be instituted without any delay in order to avoid sepsis and multiorgan failure, that would only lead to prolonged hospitalization and higher mortality rates[27].

IMAGING STUDIES

Nasal endoscopy is the first investigation used for the evaluation of a patient suspected for rhinosinusal mucormycosis**.** Both computed tomography (CT) and magnetic resonance imaging (MRI) are essential in the diagnosis of ROCM, especially in establishing the extent of the pathology. While the CT scan may reveal mucosal thickening, bone erosions, fluid filling the paranasal sinuses, the MRI scan provides a better view of soft tissue and blood vessels, being useful in evaluating intraorbital or intracranial extension[28].

Due to its invasive nature, ROCM has a survival rate of 59.5%[29], being able to rapidly spread to critical surrounding structures. Understanding of the local anatomy and possible pathways through which the disease can spread helps the surgeon in focusing on specific areas in order to restrain further spread of the disease and verify if the debridement was completely done before finishing the procedure.

In order to accomplish these objectives, radiological imaging has a major impact in establishing the area of involvement and regions that need debridement. CT scans used in operated cases were found to be of great importance[28].

The most common sinuses found to be involved in the ROCM were the maxillary (92%) and ethmoid (88%) sinuses according to Patel et al.[28], the sphenoid and frontal sinus being affected in 75%, respectively 61% of cases. Imaging studies made by Dave et al. revealed paranasal sinus involvement (100%), orbital apex involvement (41%), cavernous sinus involvement (30%), and central nervous system (CNS) involvement (33%)[30]. Bayram N. et al. study showed that the ethmoid sinus was affected in 90.9% of cases, maxillary sinuses in 81.8%, sphenoid in 54.5% and frontal in 36.4%[14].

TREATMENT OF RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS

There are multiple staging systems and stage-related treatment strategies described in the literature (Honavar et al., Kapil Soni et al.), but there is still not a consensus regarding the treatment[31,32]. What is well established is that early diagnosis, together with appropriate treatment consisting of both surgical and medical treatment, is the key to improving survival rates[31,32].

Endoscopic sinus debridement with medial maxillectomy should be performed as proposed by K. Soni et al., with further tissue debridement in accordance with the extent of the disease[32].

A few bony landmarks need to be established before surgery in order to prevent intraoperative complications and to be certain that the surgical debridement is correctly and completely done.

Despite the fact that the treatment of mucormycosis is based on complete debridement of the affected tissue, there are limits of the endoscopic sinus surgery, that need to be respected in order to avoid fearsome complications. For instance, involvement of posterior and lateral sphenoid sinus walls makes preposterous the resection of bone at this level. Addressing the involved bony tissue of the skull base at the level of the ethmoid bone predisposes to secondary complications like CSF leak or even brain tissue herniation.

In order to have a better control of the disease, optimal glucose level should be maintained throughout the day, using oral antidiabetic drugs or injectable insulin when needed.

Corticosteroids should be rationally administered in the treatment of COVID-19 infection due to their influence onto the immune system and glucose level, that enables fungal growth, and iron supplements avoided.

The management of patients with rhinosinusal mucormycosis based solely on surgery has not been demonstrated to be curative. Current treatment recommendations, supported by the European Confederation of Medical Mycology (ECMM) and by Centers for Disease Control and Prevention, comprise surgical and antifungal treatment.

Traditionally, aggressive surgical debridement is recommended when addressing mucormycosis infection[33,34]. Recently, due to the large-scale implementation

Table 3. Mortality rate in rhino-orbital-cerebral mucormycosis.

Study	Mortality rate
Bayram et al.[14]	7/11 (63.6%)
Singh et al.[17]	31/101 (30.7%)
Gupta et al.[19]	9/56 (16%)
Dave et al.[30]	20/58 (34%)
Kapil et al.[32]	26/145 (18%)
Sekaran et al.[40]	5/30 (17%)

Figure 1. Right eye proptosis – preoperative aspect.

Figure 2. Preoperative nasal endoscopic aspect. – complete necrosis of the right middle and inferior turbinate, ethmoidal cells, medial maxillary wall with black eschar visible on the nasal mucosa and purulent discharge from the middle meatus and sphenoethmoidal recess.

of nasal endoscopic surgery, some authors published studies claiming similar results with frequent endoscopic debridement[35-38].

Topical administration of Amphotericin B was used by some researchers, in an attempt to reduce the adverse effects on the renal and hepatic functions[37,39]. Further controlled clinical studies need to be made in order to evaluate its efficiency.

MORTALITY RATE IN RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS

The mortality rate reaches up to 63.6% (Table 3) and it depends on the extent of the disease (central nervous system involvement at presentation representing the only mortality predictor factor) and other variables, such as cavernous sinus involvement, presence of comorbidities (uncontrolled diabetes) being associated with an unfavourable outcome[14,31].

OUR EXPERIENCE

Herein, we present the case of a 68-year-old male patient, who presented to the Emergency Department for right side hemicrania, right eye proptosis, ophthalmoplegia and vision loss. The symptomatology debuted 10 days prior to the presentation and had progressively worsen.

From his medical history we must mention that he had type 2 diabetes and recent COVID-19 infection, 3 weeks prior to the debut of his current symptomatology. During this period, his pancreatic function was altered, and he needed to switch from oral antidiabetics to injectable insulin medication in order to control the high values of serum glucose (>400 mg/dl).

On arrival, his vital signs were notable for hypertension and tachypnea. He was afebrile, but his SpO2 dropped down to 70% in the first few hours from admission. Upon inspection, the most notable was the right eye proptosis (Figure 1).

Five days prior to admission he had an ophthalmologic evaluation that revealed the absence of perception of light for the right eye.

Preoperative nasal endoscopy was suggestive for rhinosinusal mucormycosis (Figure 2).

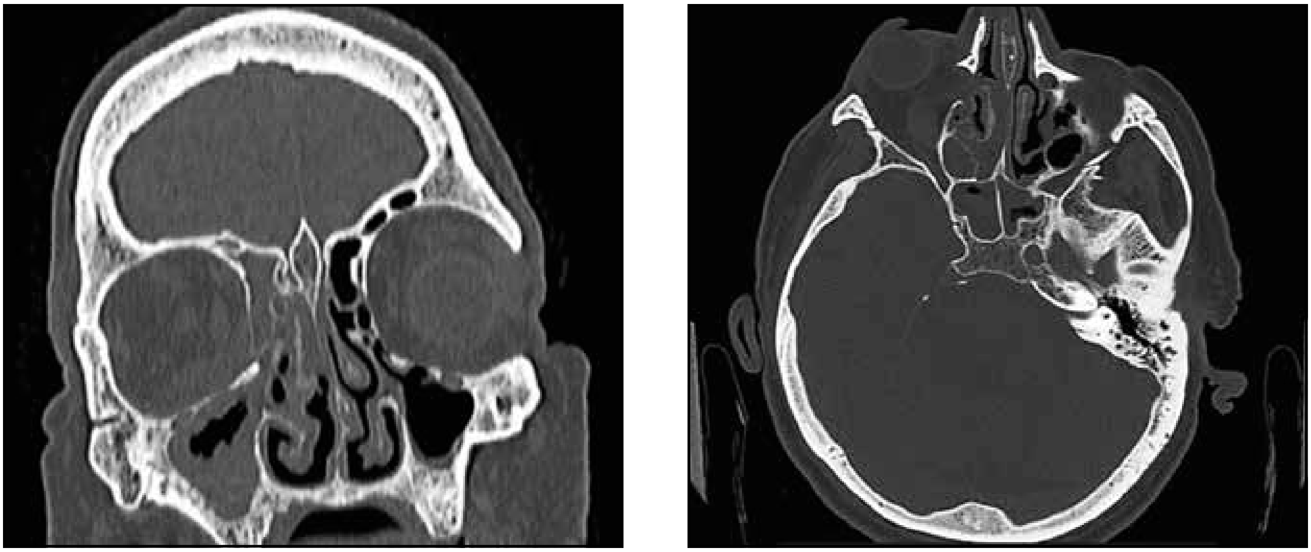

Figure 3. Coronal and axial view of preoperative CT scan – obliteration of right-side maxillary, frontal, ethmoid, sphenoid sinuses with bone erosions and extension of the disease into the retro-orbital space, with soft-tissue thickening at the level of the orbital apex.

The day before admission, he performed a sinonasal CT scan that revealed rhino-orbital extension of the disease (Figure 3).

At admission, the RT-PCR for SARS-COV-2 turned out positive, although specific symptomatology regarding the COVID-19 infection debuted 3 weeks prior and he tested positive at the time.

Blood works on admission were suggestive for marked inflammatory syndrome (ESR = 91 mm/h, CRP = 65.75 mg/L, fibrinogen = 792 mg/dL), serum glucose = 138 mg/dl, shift to the left of WBC count, normochromic normocytic anemia, hepatic cytolysis (AST = 151 U/L, ALT = 32 U/L). Due to high levels of AST, a gastroenterological consultation was requested, which stated that the hepatic cytolysis was in the context of the current infecto-inflammatory syndrome, and specific treatment was promptly started with a favourable evolution during the hospital stay.

Regular blood work was made, and acute kidney injury was noticed after 7 days of antifungal and antibiotic treatment, so supplemental liquid intake was provided.

Although the patient was in the recovery period after the COVID-19 infection, SpO2 levels started to drop and came as low as 70% in the first night of admission, so non-invasive O2 support was needed and maintained until the 10th day when he was able to maintain SpO2 over 95% without an oxygen mask.

Based on the extent of the disease, the treatment strategy consisted of endoscopic removal of the necrotic tissue seconded by antifungal therapy. After all the investigations were completed, surgical debridement was made by right

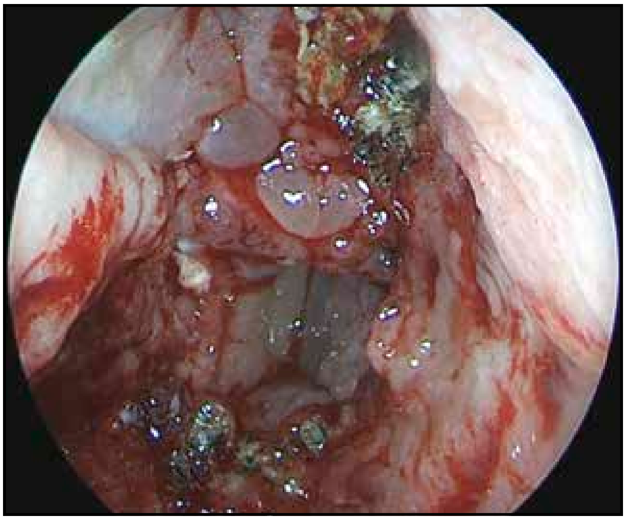

Figure 4. Intraoperative aspect after removal of the affected tissue.

Figure 5. Necrotic inferior turbinate.

medial maxillectomy with removal of the inferior and middle turbinate, ethmoidectomy, transnasal sphenoidotomy and orbital decompression by endoscopic removal of the lamina papyracea (Figure 4).

All the necrotic tissue removed (Figure 5) was sent for histopathologic exam that described ribbon-like hyphae invading blood vessels, suggestive of mucormycosis.

Postoperatively, daily aspiration of secretions was made, with monitoring of local and general evolution under parenteral treatment with antifungal therapy (Amphotericin B 5 mg/kg/day), antibiotic therapy (Gentamicin 240 mg/day, Metronidazole 500 mg/12h), steroidal anti-inflammatory drug (Dexamethasone 4mg/day), administration of rapid-acting and long-acting insulin (as prescribed by the diabetologist), anticoagulant therapy (0.8 ml/12), under which the evolution was favourable. Before discharge, the last endoscopic exam revealed free upper respiratory tract, nasal mucosa covered by hematic crusts that were present at the level of the lateral nasal wall and the roof of the nasal cavity, with permeable drainage pathway of the frontal and sphenoid sinus. Clinically, right eye proptosis was significantly reduced, but the loss of vision was permanent (Figure 6).

We must take into consideration monitoring the renal and hepatic functions while administering nephrotoxic and hepatotoxic medication like Amphotericin B, which was made by regular monitoring of the liver and renal functions.

After discharge, the patient continued the oral antifungal therapy with Posaconazole 300 mg/day for 21 days, saline irrigation and topical antibiotic and returned for follow-up once a week for the next 8 weeks. After completion of treatment, a control CT scan was performed that excluded the reoccurrence of the disease (Figure 7).

Figure 6. Postoperative aspect of right eye proptosis, 14 days after surgery.

Based on this review and our clinical experience regarding rhino-orbital mucormycosis, we suggest that practitioners should follow a minimal step-by-step approach in order to promptly diagnose this type of pathology. For this, we propose a guideline for the diagnosis and management of rhino-orbital mucormycosis (Figure 8).

CONCLUSIONS

In the current context of the COVID-19 pandemic, awareness should be risen when dealing with patients with multiple comorbidities (especially diabetes) with a recent SARS-COV-2 infection that develop clinical signs of infec-

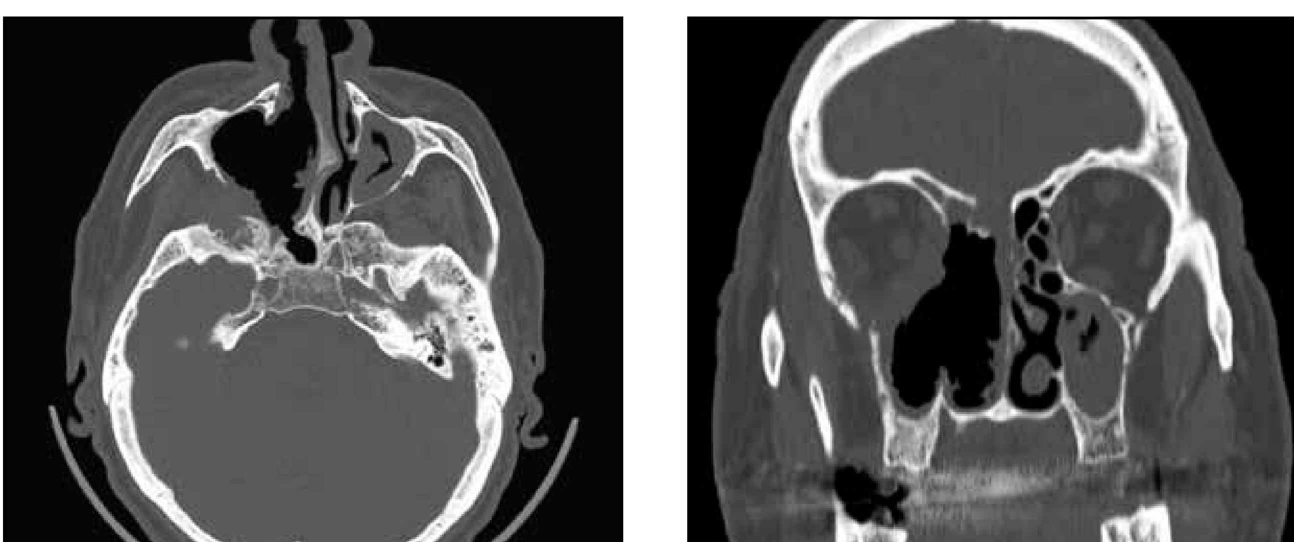

Figure 7. Axial and coronal view of postoperative CT scan – showing complete removal of the medial wall of the maxillary sinus, inferior and middle right turbinate, absence of the medial and inferior part of the lamina papyracea and the vertical plate of the palatine bone and no pathological process.

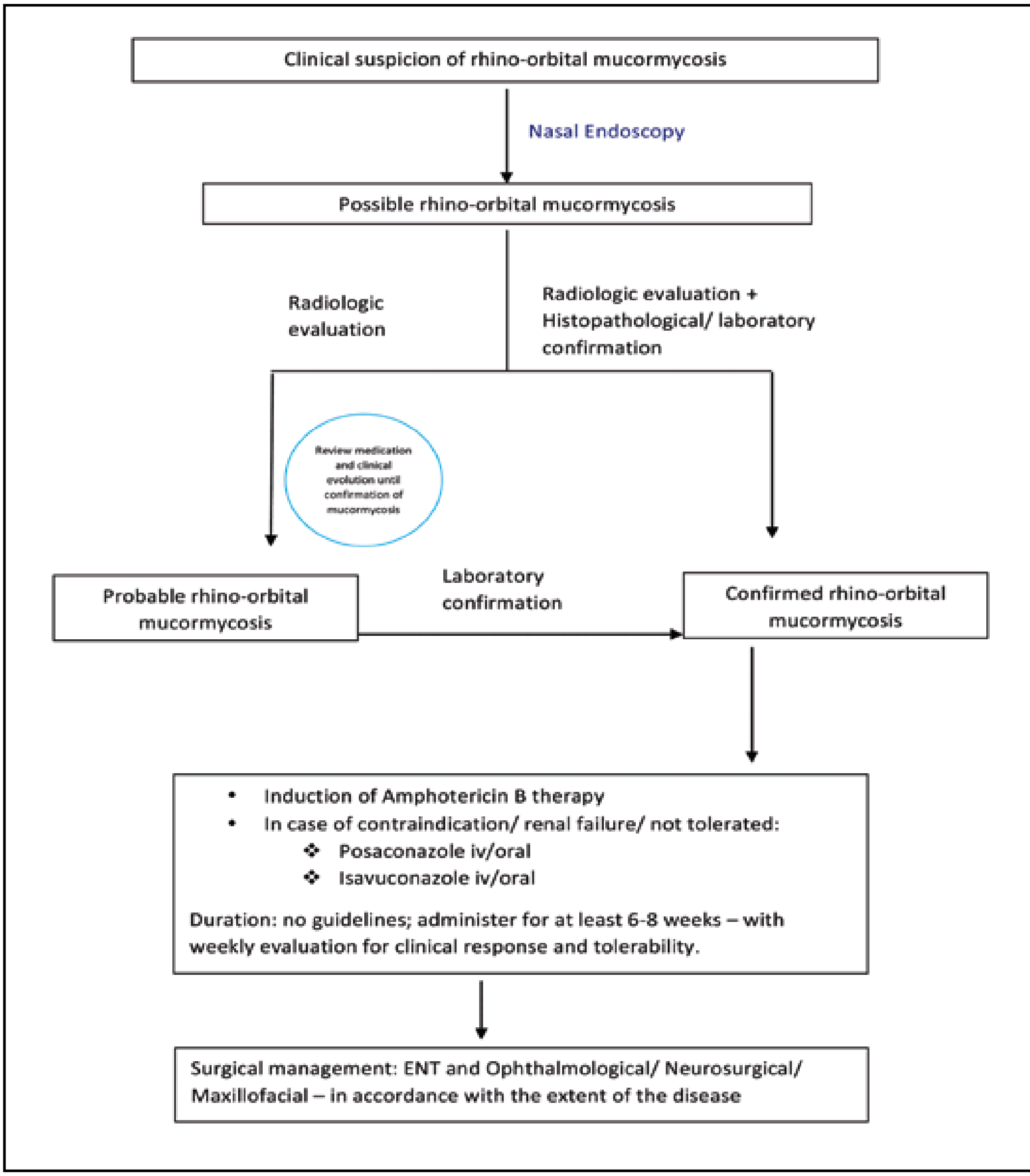

Figure 8. Guideline for the diagnosis and management of rhino-orbital mucormycosis.

tious rhino-orbital pathology, the mean duration between the onset of symptoms of mucormycosis and diagnosis of COVID-19 infection being 15 days.

Taking into consideration its aggressiveness, early diagnosis and specific treatment should be immediately started in order to have a better control of the disease, reduce morbidity and mortality.

Factors such as early diagnosis and involved areas (especially cranial involvement) determine the prognosis of the disease.

Conflict of interest: The authors have no conflict of interest to disclose.

Contribution of authors: All the authors have equally contributed to this work.

REFERENCES

1. Voigt K, Kirk PM. Classification of Zygomycetes: Reappraisal as coherent class based on a comparison between traditional versus molecular systematics. In: Batt CA, Tortorello ML (editors). Encyclopedia of Food Microbiology. Volume 2, Second Edition. Academic Press; 2014, p.54-67.
2. Volk TJ. Fungi. In: Levin SA (editor). Encyclopedia of Biodiversity, Volume 3. Academic Press; 2001, p.141-63.
3. Hussain S, Riad A, Singh A, Klugarová J, Antony B, Banna H, et al. Global prevalence of COVID-19-associated mucormycosis (CAM): Living systematic review and meta-analysis. J Fungi (Basel). 2021;7(11):985. DOI: 10.3390/jof7110985.
4. Ramaswami A, Sahu AK, Kumar A, Suresh S, Nair A, Gupta D, et al. COVID-19-associated mucormycosis presenting to the Emergency Department-an observational study of 70 patients. QJM. 2021;114(7):464-70. DOI:10.1093/qjmed/hcab190.
5. Mishra Y, Prashar M, Sharma D, Akash, Kumar VP, Tilak TVSVGK. Diabetes, COVID 19 and mucormycosis: Clinical spectrum and outcome in a tertiary care medical center in Western India. Diabetes Metab Syndr. 2021;15(4):102196. DOI: 10.1016/j.

dsx.2021.102196.
6. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41(5):634-53. DOI: 10.1086/432579.
7. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clin Microbiol Infect. 2019;25(1):26-34. DOI: 10.1016/j.cmi.2018.07.011.
8. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, et al. A national strategy to diagnose coronavirus disease 2019-associated invasive fungal disease in the Intensive Care Unit. Clin Infect Dis. 20201;73(7):e1634-44. DOI: 10.1093/cid/ciaa1298.
9. Raut A, Huy NT. Rising incidence of mucormycosis in patients with COVID-19: another challenge for India amidst the second wave? Lancet Respir Med. 2021;9(8):e77. DOI: 10.1016/S2213-2600(21)00265-4.
10. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019;19(12):e405-21. DOI: 10.1016/S1473-3099(19)30312-3.
11. Reid G, Lynch JP III, Fishbein MC, Clark NM. Mucormycosis. Semin Respir Crit Care Med. 2020;41(01):099-114. DOI: 10.1055/s-0039-3401992.
12. Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clin Infect Dis. 2012;54(Suppl 1):S16-S22. DOI: 10.1093/cid/cir865.
13. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13. DOI: 10.1016/S0140-6736(20)30211-7.
14. Bayram N, Ozsaygılı C, Sav H, Tekin Y, Gundogan M, Pangal E, et al. Susceptibility of severe COVID-19 patients to rhino-orbital mucormycosis fungal infection in different clinical manifestations. Jpn J Ophthalmol. 2021;65(4):515-25. DOI:10.1007/s10384-021-00845-5.
15. Dubey S, Mukherjee D, Sarkar P, Mukhopadhyay P, Barman D, Bandopadhyay M, et al. COVID-19 associated rhino-orbital-cerebral mucormycosis: An observational study from Eastern India, with special emphasis on neurological spectrum. Diabetes Metab Syndr. 2021;15(5):102267. DOI: 10.1016/j.dsx.2021.102267.
16. Pal R, Singh B, Bhadada SK, Banerjee M, Bhogal RS, Hage N, et al. COVID-19-associated mucormycosis: An updated systematic review of literature. Mycoses. 2021;64(12):1452-9. DOI: 10.1111/myc.13338.
17. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr. 2021;15(4):102146. DOI: 10.1016/j.dsx.2021.05.019.
18. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693-704. DOI: 10.1056/NEJMoa2021436.
19. Garg R, Bharangar S, Gupta S, Bhardwaj S. Post Covid-19 infection presenting as rhino-orbital mycosis. Indian J Otolaryngol Head Neck Surg. 2021;1-8. DOI: 10.1007/s12070-021-02722-6. [Epub ahead of print].
20. Dilek A, Ozaras R, Ozkaya S, Sunbul M, Sen EI, Leblebicioglu H. COVID-19-associated mucormycosis: Case report and systematic review. Travel Med Infect Dis. 2021;44:102148. DOI: 10.1016/j.tmaid.2021.102148.
21. Pippal SK, Kumar D, Ukawat L. Management challenge of rhino-orbito-cerebral mucormycosis in Covid 19 era: A prospective observational study. Indian J Otolaryngol Head Neck Surg. 2021;1-7. DOI: 10.1007/s12070-021-02947-5. [Epub ahead of print].
22. Mitra S, Janweja M, Sengupta A. Post-COVID-19 rhino-orbito-cerebral mucormycosis: a new addition to challenges in pandemic control. Eur Arch Otorhinolaryngol. 2021;279(5):2417-22. DOI: 10.1007/s00405-021-07010-1.
23. Desai SM, Gujarathi-Saraf A, Agarwal EA. Imaging findings using a combined MRI/CT protocol to identify the “entire iceberg” in post-COVID-19 mucormycosis presenting clinically as only “the tip”. Clin Radiol. 2021;76(10):784.e27-784.e33. DOI: 10.1016/j.crad.2021.07.002.
24. Gupta S, Ahuja P. Risk factors for procurence of mucormycosis and its manifestations post Covid-19: a single arm retrospective unicentric clinical study. Indian J Otolaryngol Head Neck Surg. 2021;1-8. DOI: 10.1007/s12070-021-02825-0. [Epub ahead of print].
25. Panwar P, Gupta A, Kumar A, Gupta B, Navriya SC. Mucormycosis in COVID diabetic patients: a horrifying triad! Indian J Crit Care Med. 2021;25(11):1314-7. DOI: 10.5005/jp-journals-10071-24025.
26. Hernández JL, Buckley CJ. Mucormycosis. In: StatPearls [Internet]. [Updated 2021 Jul 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544364/.
27. Ferry AP, Abedi S. Diagnosis and management of rhino-orbitocerebral mucormycosis (phycomycosis). A report of 16 personally observed cases. Ophthalmology. 1983;90(9):1096-104. DOI: 10.1016/s0161-6420(83)80052-9.
28. Patel DD, Adke S, Badhe PV, Lamture S, Marfatia H, Mhatre P. COVID-19 associated rhino-orbito-cerebral mucormycosis: imaging spectrum and clinico-radiological correlation- a single centre experience. Clin Imaging. 2022;82:172-8. DOI:10.1016/j.clinimag.2021.10.014.
29. Vaughan C, Bartolo A, Vallabh N, Leong SC. A meta-analysis of survival factors in rhino-orbital-cerebral mucormycosis-has anything changed in the past 20 years? Clin Otolaryngol. 2018;43(6):1454-64. DOI:10.1111/coa.13175.
30. Dave TV, Nair AG, Hegde R, Vithalani N, Desai S, Adulkar N, et al. Clinical presentations, management and outcomes of rhino-orbital-cerebral mucormycosis (ROCM) following COVID-19: A multi-centric study. Ophthalmic Plast Reconstr Surg. 2021;37(5):488-95. DOI: 10.1097/IOP.0000000000002030.
31. Honavar SG. Code Mucor: Guidelines for the diagnosis, staging and management of rhino-orbito-cerebral mucormycosis in the setting of COVID-19. Indian J Ophthalmol. 2021;69(6):1361-5. DOI: 10.4103/ijo.IJO_1165_21.
32. Soni K, Das A, Sharma V, Goyal A, Choudhury B, Chugh A, et al. Surgical & medical management of ROCM (Rhino-orbito-cerebral mucormycosis) epidemic in COVID-19 era and its outcomes - a tertiary care center experience. J Mycol Med. 2021;32(2):101238. DOI: 10.1016/j.mycmed.2021.101238.
33. Mohindra S, Mohindra S, Gupta R, Bakshi J, Gupta SK. Rhinocerebral mucormycosis: the disease spectrum in 27 patients. Mycoses. 2007;50(4):290-6. DOI: 10.1111/j.1439-0507.2007.01364.x.
34. Sugar AM. Mucormycosis. Clin Infect Dis. 1992;14 Suppl 1:S126-9. DOI: 10.1093/clinids/14.supplement_1.s126.
35. Ferguson BJ. Mucormycosis of the nose and paranasal sinuses. Otolaryngol Clin North Am. 2000;33(2):349-65. DOI: 10.1016/s0030-6665(00)80010-9.
36. Jiang RS, Hsu CY. Endoscopic sinus surgery for rhinocerebral mucormycosis. Am J Rhinol. 1999;13(2):105-9. DOI: 10.2500/105065899782106751.
37. Avet PP, Kline LB, Sillers MJ. Endoscopic sinus surgery in the management of mucormycosis. J Neuroophthalmol. 1999;19(1):56-61.
38. Songu M, Unlu HH, Gunhan K, Ilker SS, Nese N. Orbital exenteration: A dilemma in mucormycosis presented with orbital apex syndrome. Am J Rhinol. 2008;22(1):98-103. DOI: 10.2500/ajr.2008.22.3121.
39. Luna JD, Ponssa XS, Rodríguez SD, Luna NC, Juárez CP. Intraconal amphotericin B for the treatment of rhino-orbital mucormycosis. Ophthalmic Surg Lasers. 1996;27(8):706-8.
40. Sekaran A, Patil N, Sabhapandit S, Sistla SK, Reddy DN. Rhino-orbito-cerebral mucormycosis: an epidemic in a pandemic. IJID Regions. 2022;2:99-106. DOI: 10.1016/j.ijregi.2021.12.009.