Original Research Paper

Volume - 12 | Issue - 05 | May - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Radio-Diagnosis

SPECTRUM OF IMAGING FEATURES (MAGNETIC RESONANCE IMAGING) IN RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS (ROCM) IN COVID-19 TREATED PATIENTS: CASE SERIES OF 15 PATIENTS

Dr. Balakrishna	Department Of Radiodiagnosis.
Dr. Rambhir Singh	Department Of Radiodiagnosis.
Dr. Rajendra Kumar Chowdhary*	Department Of Radiodiagnosis. *Corresponding Author
Dr. Manvika Chandel	Department Of Obstetrics & Gynecology.

ABSTRACT Rhino-orbital-cerebral mucormycosis is a potentially fatal fungal infection that commonly affects diabetic and immunocompromised patients but in recent time during the second wave of COVID- 19 infection in India a sudden rise of mucormycosis patients in post-covid patients were observed . We have come across 15 such patients. On retrospective analysis of the patient's medical records, we found that the majority have received steroid and other immunosuppressive medications like toclizumab for COVID-19 infection treatment. Rhino-orbital-cerebral mucormycosis is an angioinvasive disease associated with high mortality, hence early diagnosis can be life saving. Magnetic Resonance Imaging remains the main corner stone of management for patients with ROCM. The aim of the study was to characterization of imaging findings (Magnetic Resonance Imaging) and its utility in post-covid patients with rhino-orbital-cerebral mucormycosis for early diagnosis of the disease, extension of the disease and postoperative evaluation for taking a decision regarding second surgical or medical management as well as to familiarize every member of the multidisciplinary team involved in management of these patients to be able to interpret the finding on MRI in ROCM.

KEYWORDS : Post covid 19, Diabetes, Rhino-orbital-cerebral mucormycosis, ROCM, MRI characterization.

1.INTRODUCTION

Zygomycetes comprises of mucorales and entomothorales. The former order causes life-threatening fungal infection, mucormycosis mainly in immuno-compromised hosts, while the latter order causes superficial and mucocutaneous infections in immunocompetent hosts. Among *Mucoraceae*, *Rhizopus oryzae* is the most common cause of infection. It almost habitually affects diabetics with ketoacidosis, immunocompromised and organ transplant recipients on steroid or cytotoxic therapy, in patients with leukaemia and other blood dyscrasias and those metastatic cancer [1]. Phagocytes are the major host defense mechanism against mucormycosis. Additionally, corticosteroid treatment affects the ability of macrophages to prevent the germination of the spores of these fungi. A hallmark of mucormycosis infection is the presence of extensive angioinvasion with resultant vessel thrombosis and tissue necrosis[7]. In the current time there is a pandemic due to COVID- 19. It is a nonsegmented negative sense RNA virus which causes profound lymphopenia. In the later stages of infection, when viral replication accelerates, epithelial-endothelial barrier integrity is compromised and the inflammatory response and triggering an influx of monocytes and neutrophils is accentuated. Collectively, endothelial barrier disruption, dysfunctional alveolar-capillary oxygen transmission, and impaired oxygen diffusion capacity are characteristic features of COVID-19. Recently, we have noticed that there is an increase in the incidence of invasive mucormycosis infections in COVID-19 disease. We have come across 15 such cases and all cases were found to have some similarities. Here we present to you a case series of 15 cases. Uncontrolled diabetes is the most common predisposing factor as Ketoacidosis in diabetes enhances susceptibility to ROCM.[1,2]

Clinically, the presenting symptoms are nonspecific, including headache, nasal block, low-grade fever, facial swelling, orbital or paranasal sinus syndrome, impairment of eye vision, eye pain, and cranial nerve palsy . After infection of the nasal cavity and paranasal sinuses, the fungi cause a necrotizing vasculitis that extends rapidly into deep face, orbits, cranial cavity, and brain through skull base partitions and foramina[3,18].Rhino-orbito-cerebral mucor mycosis has a association with high morbidity and mortality[5,6] .Early diagnosis and timely intervention is key to successful treatment[1,4] We present a case series of ROCM to emphasize utility of magnetic resonance imaging (MRI) in diagnosis of this potentially fatal form of mucormycosis, however definitive diagnosis relies on direct microscopy, histopathology, and culture of tissue samples. Deep tissue biopsy of the involved site is commonly cumbersome because the patients are often too unstable to undergo invasive procedures. [9,10]

2. MATERIALS AND METHODS

Our study design is descriptive observational type of case series with the analysis of 15 patients who have been treated with covid 19 and now suspicions of ROCM were selected. All suspected ROCM cases were clinically diagnosed and sent for MRI assessment. The relevant demographic data, clinical, ophthalmic, and neurologic manifestations, underlying conditions, and medical treatments were recorded **[Table 5]**. In all 15 cases, they were subjected to MR imaging with a 1.5-T system. Protocol: MRI of paranasal sinuses, orbit, and brain were performed in all patients using T1W(pre-contrast and postcontrast), T2W, T2W fat suppressed , DWI, GRE and FLAIR sequences in the axial, coronal and sagittal planes. Postcontrast T1-weighted sequences were performed after intravenous injection of gadopentetate dimeglumineto. MRI imaging was performed using a superconducting 1.5 T MR machine (Achiva version 1.3; Philips Medical system, Best, Netherland) and a standard head coils. Magnetic Resonance Imaging (MRI) images were retrieved from the Picture Archiving and Communication System (PACS) in DICOM format and analyzed. Statistical analysis was performed using descriptive statistics with consensus by three staff radiologists to look for sites and extent of involvement , signal characteristics, and complications,

2.1. Image interpretation:

Images were evaluated for density, signal intensity, and contrast enhancement characteristics.The sinuses showing opacification on MRI were recorded in each case. The appearance on plain T1 and T2 images were documented.On post-contrast MRI, the type of contrast enhancement and involvement of any extra sinus structures including orbit, face,pterygopalatine fossa, masticator space, brain and cavernous sinus were noted. Presence of bone involvement was evaluated. Any complication like arterial thrombosis or perineural spread were noted on MRI **[Table 3]**. Fat stranding and soft tissue extension similar in appearance to the intrasinus soft tissue was taken as evidence of orbital, retro-antral,masticator, and pterygopalatine involvement. Orbital cellulitis was seen as stranding in the retrobulbar fat, without overt abscess formation.Cavernous sinus and internal carotid artery involvement was seen as thickening and nonenhancement on post-contrast scans with presence of abnormal surrounding soft tissue. Patients with intracranial extension were evaluated for dural enhancement, presence of extradural collections, infarcts, cerebritis, and intracerebral abscess. Neural involvements were evaluated for oedema, neuritis, and infarcts.

As patients presented to us at various stages of the disease, the patients in the study were divided into three groups based on the extent of regional involvement according to classification suggested by Rupaet al[4]. **[Table2].**

3. RESULTS AND DISCUSSION

A total of 15 patients of RT-PCR confirmed cases of covid 19 infection with post-infective status with suspected rhinocerebral mucormycosis having preoperative pre-and post-contrast MRI imaging were identified. Out of the 15 patients who had MRI, only 9 underwent contrast imaging with gadolinium,primarily because of the inability to use contrast in those patients with impaired renal function.

3.1. Demographic and clinical findings

Our study group comprised of 13 males and 2 females with ages ranging from 18 to 60 years (mean=39.2 years).Ten patients (66.6%) had a history of uncontrolled diabetes, with 9 patients (60%) having type 2 diabetes mellitus and 1 patient with type 1 diabetes mellitus. Three patients (20 %) had a predisposing immunosuppressive condition (CLD and CKD), one patient each with acute lymphoblastic leukemia .The clinical symptoms reported in our series were headache (7, 46.6%), facial and eye swelling (5, 33.3% patients),facial pain (7, 46.6%), decreased vision (2, 13.3%), and hemiparesis (2 , 13.3%) as described in **[Table 1].**

Table 1 Demographic and clinical details 0f patients with mucormycosis associated with COVID- 19

Case Number	Age/ sex	Comorbidities	Radiologic evidence	Signs&symptoms
1	40/M	CLD, Diabetic	Yes	Pain & swelling in the right jaw & eye
2	56/F	Diabetic	Yes	Right side facial pain & Headache
3	20/F	Leukaemia	Yes	Left eye swelling
4	21/F	Nil	Yes	Right sided weakness
5	60/M	Diabetic	Yes	Vision loss in both eyes
6	36/M	Hypertension, CLD	Yes	Pain & swelling , Pus formation in the right jaw
7	18/M	Diabetic	Yes	Headache
8	40/M	Diabetic	Yes	Left sided neck pain, Operated for nasal septal mucor mycosis
9	26/M	CKD	Yes	Left side facial pain & Headache
10	60/M	Diabetic	Yes	Right side facial pain &
11	43/M	Diabetic	Yes	Headache
12	32/M	Hypertension, CKD	Yes	Headache
13	43/M	Diabetic	Yes	Headache & swelling in the left orbit & face
14	38/M	Diabetic	Yes	Headache
15	56/M	Diabetic	Yes	B/L vision loss & left sided weakness

3.2. Imaging findings

Anatomical involvement

A pattern of anatomic involvement affecting the nasal cavity, maxillary sinus, orbit, and ethmoid cells was consistently observed. Additionally, there was variable involvement of the sphenoid sinus, cavernous sinus, carotid artery, skull base, floor, and intracranial structures as described in **[Table2]**

Table2 Extent of regional involvement

Stage	Areas involved	Number
Stage 1	Nose & paranasal sinuses alone	**0**
Stage 2	Paranasal sinuses with immediate adjacent area which are surgically resectable with minimal morbidity. Ex: -Orbits (extra conal), palate, oral cavity	**6(40%)**
Stage 3	Intracranial extension (extradural/intracerebral) or Partially resectable with extension of pterygopalatine fossa, cavernous sinus, cheek, and periorbital region	**9(60%)**

Various spectra & vivid combinations of paranasal sinuses involvement were seen **[Table 3].**

Table 3 Sinuses involved in mucormycosis infection

Sinuses involved	Numbers
Maxillary	12(80%)
Ethmoid	13(86%)
Sphenoid	9(60%)
Frontal	9(60%)
Maxillary+ethmoid	9(60%)
Ethmoid+sphenoid	7(46%)
Ethmoid+ Frontal	6(40%)
Maxillary+ethmoid+sphenoid	7(46%)
Maxillary+ Ethmoid+ Frontal	7(46%)
Pansinusitis	7(46%)

MR imaging of 15 patients showed predominant involvement of the ethmoid (13, 86%) and maxillary (12, 80%),Sphenoid (9,60%),frontal sinus (9,60%) sinuses.Maxillary+ethmoid9(60%) Ethmoid+ sphenoid7(46%), Ethmoid+ Frontal 6(40%), Maxillary+ ethmoid+ sphenoid7(46%),Maxillary+ Ethmoid+ Frontal7 (46%), Pansinusitis 7(46%). Paranasal sinuses showed mild mucosal enhancing thickening with complete blockade of the osteometal complex &showed bony erosion with extra sinus extensions.

Extension to the adjacent paranasal structures showed varied involvement, which has been graded into three stages with regional involvement **[Table 2]**. Out of 15 patients, there were 6 cases showing spread to immediate adjacent areas like palate, oral cavity & orbits, i.e, Stage II. Rest of all 9 cases had an intracranial extension or extension to the pterygopalatine fossa, cavernous sinus, cheek, and periorbital region which is stage III according to Rupa et al.[4]. There were no cases which showed stage I findings.

Extension to the orbit (9, 60%), orbital apex 4(26.6%), face (4, 26%),vascular invasion2(13.3%), and preceding involvement of the deep skull base (5, 33.3%) and brain (5, 33.3%)**[Table 4].**

Table 4

Extra Sinus Structures Involved	Number
Face	4(26.6%)
Orbit	9(60%)
Orbital apex	4(26.6%)
Pterygo-palatine fossa	2(13.3%)
Skull base	5(33.3%)
Cavernous sinus	2(13.3%)
ICA	2(13.3%)
Brain	5(33.3%)
Nasal septum perforation	1(6.6 %)

Extension to the adjacent structures indicates the invasive nature of the fungus which was seen as hyperintense, heterogenous, and hypointense areas on postcontrast with heterogenous/ hypointense areas suggesting non-vital tissue**[Table5,Figure1 and 2].**

After the administration of gadolinium, the lesions had variable enhancement patterns ranging from homogeneous to heterogenous or nonenhancing at all. Intense homogenous enhancement was seen in 5(55%), Heterogenous enhancement 3(33.3%), Central non-enhancement with rim enhancement 5(55%), and Peripheral enhancement 2(22.2%). **[Table 5].**

Table 5 Contrast was administered in 9 patients

MR features	Numbers
T1 W	
Isointense	7(46%)
Hypo intense	2(13.3%)
T2 WI	
Iso/hypointense	6(40%)
Hyperintense	7(46%)
Heterogenous	2(13.3%)
Post contrast enhancement pattern	
Intense homogenous enhancement	5(55%)
Heterogenous enhancement	3(33.3%)
Central non-enhancement with	5(55%)
Rim enhancement	0
Peripheral enhancement	2(22.2%)
FLAIR Hyperintensity	3(33.3%)
DWI showing restriction	7(77.7%)

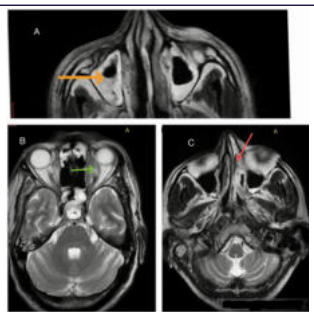

Fig.1. Different T2 patterns in RCOM A. Hyper intensity of the bilateral maxillary sinuses (Saffron arrow) B. Iso intense enhancement of the left orbit muscle (Green arrow) C. Heterogenous intensity, left ethmoid sinus (Red arrow)

Extension of the disease helps in management protocol and treatment decisions for the clinician.

Most of the patients (6 out of 15) had isointense lesions relative to brain in T1-weighted images. The signal intensity in T2-weighted images was more variable **[Figure 1],** with only a few patients(7 out of 15)showing hyperintensity and a few patients showing hypo-intensity within the T2 hyperintense area(2 out of 15) suggesting non-vital tissue.

The disease usually starts in the nasal mucosa, turbinate, or palate and spreads to the paranasal sinuses; it spreads to the retro-orbital region via the ethmoid sinus. Kulkarni et al. [13] proposed that the fungi enter the anterior ethmoidal sinus, which could not have any presentation until they spread to the orbit. Additionally, the cribriform plate and the roof of the orbit are very thin and could be the portal of entry to the intracerebral area. The disease may also progress through the retro-orbital region or cause sphenoid sinus involvement. Sadr-Hosseini et al. [14] reported that although the intracranial spread of fungi can occur via several routes, the pterygopalatine space is the main portal of entry in the majority of cases. The authors determined that the disease spread to the orbit and soft facial tissue from the pterygopalatine space, and then through the inferior orbital fissure, extending to the retro-global area of the orbit, resulting in ophthalmic manifestations. Pterygopalatine involvement was also reported in other studies [15–17].

MRI signal characteristics and imaging appearance of RCOM

Nonspecific:

Mucosal thickening and opacification of the sinus with secretions showing single intensity of the mucosa and secretion isointense on T1W and hyperintense on T2W sequence. Homogeneous enhancement pattern of mucosal thickening.

Specific (strong predictor):

MRI signal intensity of mucosal thickening and secretion isointense to hyperintense on T1Wt sequence and hypointense on T2Wt sequence with restriction on diffusion and susceptibility to gradient sequence(representing fungal hyphae). Heterogeneous enhancement with lack of enhancement within the mucosa appearing hypointense on post-contrast T1W sequence to suggest necrosis [**Figure 2].**

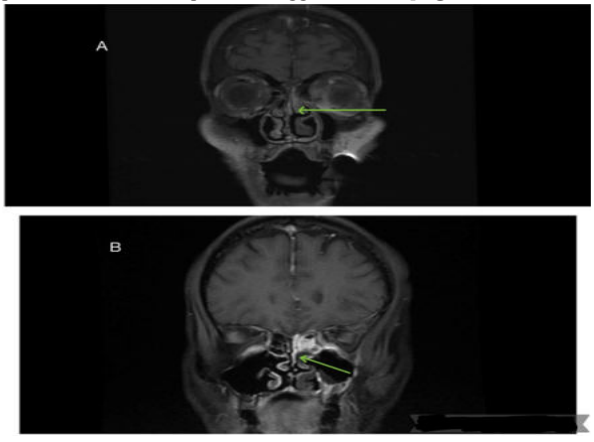

Fig.2. **A.** Pre-contrast image in a Post-COvid patient shows a hypointense area in the left middle & inferior turbinates. **B.** Post-contrast image in a Post-COvid patient shows a hypointense non-enhancing area in the left middle & inferior turbinates suggestive of non-vitaltissue/necrosis i.e, "Black turbinate sign" ROCM in nasal septum. Contrast-enhanced T1-weighted images are helpful in delineating the intracranial spread when meningeal enhancement is present as well as in identifying invasion of the cavernous portion of the internal carotid artery by the disease. Extensive angioinvasion is considered as the main cause leading to vascular thrombosis and tissue necrosis [20]

Intracranial extension was seen in 5 patients, Dural enhancement was observed in two patients, and mixed leptomeningeal and pachymeningeal enhancement was present in the rest of the patient, another 2 cases showing angioinvasion.

An aggressive sinonasal and orbital inflammatory process [11] with progressive and rapid involvement of the cavernous sinus, vascular structures, and intracranial contents is the usual evolution of rhino-cerebral mucormycosis.[12]

Extension of the disease helps in management protocol and treatment decisions for the clinician. gadolinium, and the les showed stage I findings.

Post contrast non-enhancing hypointensity on T1W imaging suggesting non-vital tissue or necrosis of nasal turbinate < black turbinate sign> and nasal septum <septal perforation> findings are highly specific. Changes in the adjacent structure like soft tissue , bone involvement in the form of rarefaction, erosion and permeative destruction, and intracranial extension , perineural spread, and vascular involvement were noted **[Figures 3]**.

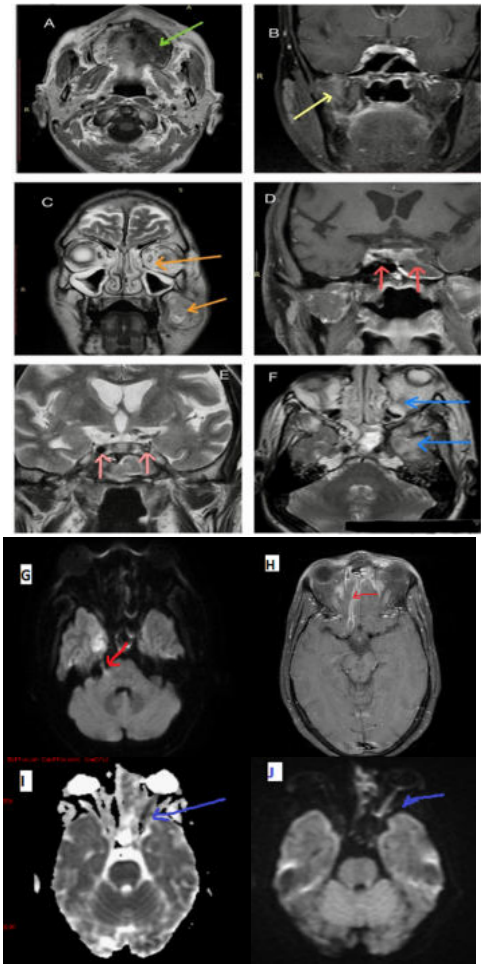

Fig.3.**Involvement of adjacent regional structures A**.

Hypo intensity of the left side Of hard palate (Green arrow**) B**. Hyperintense enhancement of the right masticatory muscles (yellow arrow**) C**. Hyper intensity left orbit& left side face (saffron doublearrow) **D**. Signal void in the right cavernous sinus & Non-

enhancing filling defect in the left cavernous sinus suggestive of thrombus (Pink double arrow) **E**. Non-enhancing filling Defect in the left internal carotid artery.(Pink double arrow) **F**. Abscess formation in the left Temporal lobe &ill-defined hyperintense soft tissue in the left orbit (blue arrows), **G**.Diffusion restriction along the right trigeminal nerve in Meckal's cave suggesting infarct or neuritis (Red arrow) **H**. There is significant post-contrast enhancement along the right olfactory tract (Red arrow) suggesting perineural spread of mucormycosis **I & J.** There is diffusion restriction of the left optic nerve (Blue arrow) suggesting infarct or neuritis.

Imaging helps in assessing the extent of the disease, identification of complications like ICA thrombosis and is indispensable for surgical planning [7,19]. However, imaging techniques including MRI show only nonspecific Features during the early stage of the disease like mucosal thickening which may delay diagnosis. Hence, a high clinical suspicion is mandatory for early pick-up of this condition. A, B, Mnif et al. and Herrera et al. have previously shown that the disease causes aggressive sinonasal and orbital changes on imaging [6,8]. Mohindra et al. have shown that MRI can detect cavernous sinus invasion and vascular complications such as thrombosis and ischemia [11].

As described in previous literature, MRI proved to be very useful in the detection of complications like orbital cellulitis, cavernous sinus thrombosis, and ICA thrombosis [15,16]. The retrospective nature of our study led to some variation in the imaging protocol used for evaluation of suspected mucormycosis cases.

4. CONCLUSION:

Based on our study, imaging of rhinocerebral mucormycosis showed heterogeneous variable T2W signal intensity, different enhancement patterns, and involvement of different sinuses with extrasinus extension. In our study group, patients tended to chiefly present in the advanced stages of the disease when there is extensive extrasinus involvement. MRI is an invaluable tool which is complementary to clinical evaluation in assessing the extent of disease and diagnosis of complications as well as diagnosis at an early stage which can be life saving.

A total of 15 patients with rhinocerebral mucormycosis having preoperative suspicion were identified. All 15 patients underwent MRI,out of which 9 patients were administered IV contrast. Different patterns of intensity and enhancement can be seen, to say hypointense, isointense, hyperintense compared to grey-white matter as described.

REFERENCES :

1. Volume: 114 issue: 6, page(s): 830-832 Issue published: June 1, 1996 Nelson C. Goldman, Clinical Photographs Editor, MD1, 2, ErezBendet, MD12, Yoav P. Talmi, MD1, 2, JonaKronenberg, MD1, 2Tel-Hashomer, IsraelDepartment of Otolaryngology–Head and Neck Surgery, The Chaim Sheba Medical Center
2. Prabhu RM, Patel R. Mucormycosis, and entomoph-thoramycosis: a review of the clinical manifestations, diagnosis, and treatment. Clin Microbiol Infect. 2004;10(Suppl 1):31–47.
3. Diego A, Herrera ABD. Imaging findings of rhinocerebral mucormycosis. Skull Base J North Am Skull Base Soc 2009;19:117–25. http://dx.doi.org/10.1055/s- 0028-1096209.
4. Rupa V, Maheswaran S, Ebenezer J, Mathews SS. Current therapeutic protocols for chronic granulomatous fungal sinusitis. Rhinology 2015;53:181–6. http://dx.doi. org/10.4193/Rhin14.183.
5. Chakrabarti A, Das A, Sharma A, Panda N, Das S, Gupta KL, et al. Ten years' experience in zygomycosis at a tertiary care centre in India. J Infect. 2001;42(4):261–6.
6. Gamaletsou MN, Sipsas NV, Roilides E. Rhino-orbital-cerebral mucormycosis. Curr Infect Dis Rep. 2012;14(4):423–34.
7. Middlebrooks EH, Frost CJ, Jesus ROD, Massini TC, Schmalfuss IM, Mancuso AA. Acute invasive fungal rhinosinusitis: a comprehensive update of CT findings and design of an effective diagnostic imaging model. Am J Neuroradiol2015;36:1529–35. http://dx.doi.org/10.3174/ajnr.A4298.
8. West BC, Oberie AD, Know-Chung KJ. Mucormycosis caused by Rhizopus microspores var microspores: cellulitis in the keg of a diabetic patient cured by amputation. J Clin Microbiol. 1995;33(12):3341–4.
9. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46(12):1813–21.
10. Walsh TJ, Gamaletsou MN, McGinnis MR, Hayden RT, Kontoyiannis DP. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis) Clin infected Dis. 2012;54(Suppl 1):S55–60.
11. Mohindra S, Mohindra S, Gupta R. Rhinocerebralmucormycosis: the disease spectrum in 27 patients. Mycoses. 2007;50:290–296.
12. Mnif N, Hmaied E, Oueslati S. Imaging of rhinocerebralmucormycosis. J Radiol. 2005;86:1017–1020.
13. Kulkarni NS, Bhide AR, Wadia RS. Rhinocerebralmucormycosis: an analysis of the probable mode of spread and its implications in early diagnosis and treatment. Indian J Otolaryngol Head Neck Surg. 2005; 57(2):121-4.
14. Hosseini SM, Borghei P. Rhinocerebralmucormycosis: pathways of spread. Eur Arch Otorhinolaryngol. 2005; 262(11):932-8.
15. Alleyne CH Jr, Vishteh AG, Spetzler RF, Detwiler PW. Long term survival of a patient with invasive cranial base rhinocerebralmucormycosis with combined endovascular, surgical and medical therapies: case report. Neurosurgery. 1999; 45(6):1461-3.
16. Pelton RW, Peterson EA, Patel BC, Davis K. Successful treatment of rhino-orbital mucormycosis without exentration: the use of multiple treatment modalities. OphthalplastRconstr Surg. 2001; 17(1):62-6.
17. Harrill WC, Sewart MG, Lee AG, Cernomg P. Chronic rhinocerebralmucormycosis. Laringoscope. 1996; 106(10):1292-7.
18. Parsi K, Itgampalli RK, Vittal R, Kumar A. Perineural spread of rhino-orbitocerebralmucormycosis caused by Apophysomyceselegans. Annals of Indian Academy of Neurology. 2013 Jul;16(3):414
19. Lone PA, Wani NA, Jehangir M. Rhino-orbito-cerebral mucormycosis: Magnetic resonance imaging. Indian Journal of Otology. 2015 Jul 1;21(3):215 , (DOI: 10.4103/0971-7749.159700)
20. Gamaletsou MN, Sipsas NV, Roilides E, Walsh TJ. Rhino-orbital-cerebral mucormycosis. Current infectious disease reports. 2012 Aug 1;14(4):423-34
21. Mehta S, Pandey A. Rhino-Orbital Mucormycosis Associated With COVID-19. Cureus. 2020 Sep;12(9)