

MR IMAGING IN COVID -19 RELATED RHINO-ORBITAL – CEREBRAL MUCORMYCOSIS

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Abstract

Background: Mucormycosis of the head and neck is divided into isolated nasal, rhino-orbital, rhino-orbito-cerebral mucormycosis (ROCM) according to the involved sites, indicating the course of the disease. We emphasize the importance of early detection with clinical, neuroimaging. **Aims:** This study aims to illustrate the MR imaging spectrum of ROCM head, neck and face region along with the usual sites such as nose, paranasal sinuses and orbits and also to evaluate the extension of disease in skull base, palate temporal bone. **Materials and Methods:** This is an observational cross sectional study was conducted in a cohort of 48 COVID-19 patients imaged who were confirmed by a positive RT –PCR (reverse transcriptase polymerase chain reaction) test. Clinically suspected mucormycosis patients and confirmed infection with COVID -19 within the previous 3 months are included in this study. **Result:** In our study we found all the MR imaging finding of mucormycosis including black turbinate sign (most commonly seen), obliteration of the nasopharyngeal planes, pre and retro antral fat infiltration, non-enhancing sino nasal mucosa, extra ocular muscles and fat and intracranial leptomeningeal enhancement and we concluded that MR imaging findings of mucormycosis features of post COVID -19 patients. In our study we found the extension of disease to maxillo facial soft tissues with bone invasion or bony invasion. That is stage 2a and stage 2b .No significant association of orbital and intracerebral extension with the posterior ethmoid and sphenoid sinuses. **Conclusion:** MRI based staging and classification had a significant relationship with patient mortality and explains the disease extent, determines the extent of the surgical debridement, and also plays a key role to assess the response to medical treatment and adequacy of surgical debridement.

INTRODUCTION

Mucormycosis has emerged as a formidable opportunistic secondary infection to post COVID- 19 patients particularly the rhino – orbital – cerebral-mucormycosis (ROCM) in critically ill and immunocompromised patients.^[1] Mid face and skull base invasive mucormycosis were seen in poorly controlled diabetes mellitus, immunocompromised individuals, hematological diseases following transplantation or chemotherapy. During the second wave of COVID-19, India has been in the midst of a rare angio- invasive fungal infection called mucormycosis, especially in COVID -19 diabetic patients treated with steroids, oxygen and or

prolonged intensive care admission developed rhino – orbital – cerebral mucormycosis. Vigorous usage of the steroids to suppress severe COVID -19 inflammatory syndromes in a ventilated diabetic patients has been incriminated the mucormycosis.^[2] Fulminant progression of the rhino – orbital – cerebral- mucormycosis is common and sometimes leads to death even in less than a week of the presentation.

Imaging plays an important role not only for early diagnosis, assessment of extent of the disease, but also to know the extent of the disease for pre surgical planning, follow up after surgery and for prognosis.^[3] Early diagnosis of mucormycosis is important to radiologist and the clinician for early institution of

antifungal treatment to limit the morbidity and mortality. Contrast enhanced Magnetic Resonance imaging (MRI) is the modality of choice to know the diagnosis, extent of the disease to early orbital involvement, early extension to the skull base, anterior and middle cranial fossa which can be asymptomatic in early stages.

Magnetic Resonance imaging (MRI) with or without intravenous gadolinium based contrast agent with or without computed tomography (CT) is used to know the diagnosis, as contrast enhanced MRI has superior contrast resolution for soft tissue and marrow abnormalities and CT to demonstrate bony erosion.^[4,5,6] Contrast enhanced MRI is useful to differentiate the viable tissue from a dead necrotic tissue in sinusitis, to differentiate abscess from phlegmon in its orbital and intracranial extension. This study aims to illustrate the MR imaging spectrum of ROCM head, neck and face region along with the usual sites such as nose, paranasal sinuses and orbits and also to evaluate the extension of disease in skull base, palate temporal bone.

MATERIALS AND METHODS

We described the common and uncommon radiological presentations of biopsy / fungal culture – proven rhino- cerebral mucormycosis in and this is an observational cross sectional study was conducted in a cohort of 48 COVID-19 patients imaged in the months of april to june 2021 who were referred to our Radiology department at Sri Venkateswara Medical College, Tirupathi. COVID -19 was confirmed by a positive RT –PCR (reverse transcriptase polymerase chain reaction) test. This study was permitted by our ethics committee. Written informed consent was acquired from all patients in our study. Clinically suspected mucormycosis patients and confirmed infection with COVID -19 within the previous 3 months are included in this study and the patients refused to surgical interference, absent pathological evaluation of the surgical specimen, patients previously had fungal infection or underwent prior sinus surgery and or mixed bacterial and fungal infections are excluded from the study.

MR Imaging Acquisition

All patients underwent paranasal MR examination using 1.5 Tesla MRI system (Achieva – class IIa, philips Medical Systems) with a standard head coil [Table 1].

Table 1: MR protocol

Plane	Sequences
Axial	T1,T2, T2FS, DWI, ADC, SWI
Coronal	T1, T2 fat saturation (T2FS)
Sagittal	T2FS
3D Bravo	T1 FS pre - contrast and T1FS post - contrast
Additional axial images of brain	T1,T2, FLAIR, DWI, ADC
Axial, coronal, sagittal	Post contrast T1WI –TSE (Turbo spin echo)

Statistical Analysis

The Shapiro – Wilk test was used to check and confirm the normal distribution of the data. When applicable, the data of the recruited patients were expressed as mean, standard deviation (SD), and range of number and percentage. The association between involvement of the posterior ethmoid and sphenoid sinuses, maxilla facial spaces and extra sinus extension to the orbits and the brain was determined using Pearson’ outcomes. Wiegthed kappa score (K- score) were employed to assess the diagnostic reliability of the proposed staging system. K- score of less than 0.20 represented poor agreement; 0.21-0.20 represented fair agreement; 0.41-0.60 represented moderate and 0.81-1 represented very good agreement. Stastistical analyses were accomplished using “SPSS 23”. The P- value was statistically significant if less than 0.05.

RESULTS

The primary site of inoculation of fungus is through nose and paranasal sinuses, clinical presentation in early disease is with pain, swelling over the face and or facial numbness, nasal stuffiness with black colored nasal discharge. Dental symptoms are predominantly seen in some of the patients as jaw pain or loosening of teeth. Disseminated disease include blurred vision, proptosis, ptosis, ophthalmoplegia, facial paresis, altered sensorium, and stroke. Many patients from remote areas landed late and require debilitating craniofacial resections and orbital exenteration.

The radiological features of COVID -19 associated with ROCM are similar to the historically identified Invasive fungal rhino-sinusitis (IFRS) in poorly controlled diabetes mellitus, immunocompromised individuals, hematological diseases following transplantation or chemotherapy in pre COVID era. Mucormycosis belongs to mucoraceae family, Angio- invasive nature of the fungal hyphae of mucormycosis are closely depicts on imaging features in which the invasion of hyphae in blood vessels resulting necrotising vasculitis and thrombosis leads to extensive tissue infarction [Table 2].

Table 2: MR imaging characteristics of ROCM

MR imaging characteristics of ROCM		Number of patients (percentage)
T1WI	Hypointense signal	48 (100%)
T2WI	Hyperintense signal	12 (25%)
	Heterogeneous enhancement	36 (75%)

Sinus enhancement	seen	16 (33.3%)
	Not seen	32 (66.7%)
	Homogeneous enhancement	4 (8.3%)
	Heterogeneous enhancement	22 (45.8%)
Affection to sinuses	Mucosal thickening of sinuses	20 (41.6%)
	Complete sinus opacification	10 (20.8%)
	Combined pattern	18 (37.5%)
Black turbinate sign	Seen	28 (58.3%)
	Not seen	20 (41.7%)

Maxillary and ethmoidal sinuses are the most commonly involved sinuses among all sinuses and middle turbinate is the most commonly involved turbinate among all turbinates, which filters the major volume of the nasal air flow explain the most common site of seeding of fungal infection. The classic imaging sign of the “black turbinate” (Fig – 1b) refers to lack of contrast enhancement of invaded mucosa of the middle turbinate secondary to small vessels occlusion.

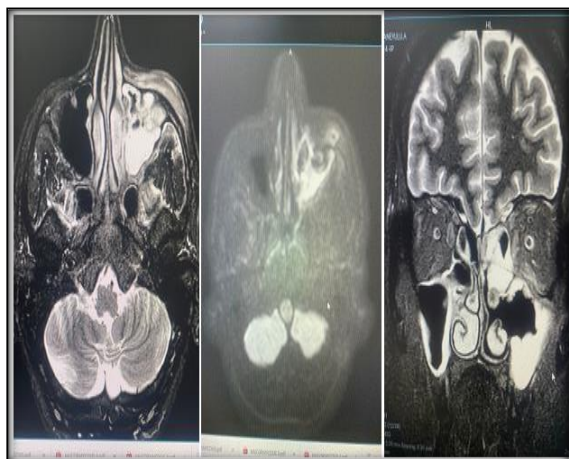


Figure 1a

[Figure -1a]. Axial T2 fat sat images shows heterogeneous mucosal thickening in left maxillary sinus without any bony erosions and diffusion restriction on DWI sequence. 1b. Black turbinate sign, in T2-STIR coronal image in left middle turbinate shows heterogeneously hypointense signal and heterogeneously non enhancing areas in left middle turbinate in post contrast T1WI in 67 year old male diabetic patient with left facial puffiness and nasal stiffness and the residual can be seen in fig 1b as post op defect of wall of the maxillary sinus appreciated.

Radiologist should cautious about reporting the black turbinate, in mucormycosis as in 30% of the patients without IFRS may show heterogeneous to non-enhancement of the posterior part of turbinate which is physiological, lack of contrast enhancement (loCE) lesion due to metallic artifacts of dental implants by susceptibility artifacts at the air – mucosa interface in non-contrast MRI. The hypointense signal on T2 sequence is due to presence of the paramagnetic iron and magnesium in fungal elements. High T2 signal intensity is seen in mucosa of the non-aggressive inflammatory sinusitis which enhances avidly and may co-exist with IFRS. In very early fungal sinusitis with superficial involvement can be easily missed to nonspecific or bacterial sinusitis. Air fluid levels are seen in bacterial sinusitis and air fluid levels are absent in fungal rhino sinusitis. The fungal hyphae shows hyperintense signal on Diffusion weighted images (DWI) images and hypointense signal on

apparent diffusion coefficient images (ADC) which characteristically differentiate fungal rhino sinusitis from bacterial sinusitis [Figure -1a]. T2-STIR (short tau inversion recovery), T1 without fat saturation and T1 contrast enhanced fat saturated sequences in the axial and coronal planes are particularly useful in evaluation of mucormycosis from other nonspecific inflammatory rhino sinus processes.

Predominant unilateral involvement is [Figure -1a] is specific for IFRS. Complete opacification with expansion of sinuses is most common imaging features of the bony involvement with thinning, erosion and remodeling of the sinuses and the walls of the paranasal sinuses may shows irregular bony destruction with adjacent mottled air foci. MRI is superior to CT as early bony invasion can be seen as marrow edema prior to the bony erosion [Figure -2].

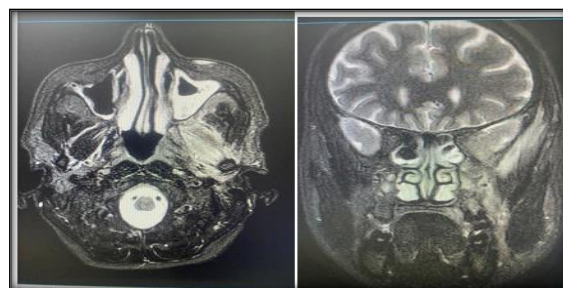


Figure 2:

[Figure 2]. axial T2-STIR image and coronal T2WI shows moderate mucosal thickening in left maxillary sinus and mild mucosal thickening in right maxillary sinus, spread of infection to left pterygopalatine fossa, infra temporal fossa and pterygoid muscles noted with interstitial edema.

Thinning, Periantral fat stranding is an early diagnostic sign of soft tissue invasion and extra sinus extension and is known to be the best predictor of IFRS on CT [Figure 2], however extension of mucormycosis beyond the sinus can be seen without bony destruction as it tends to spread along the vascular channels and nerves. The valveless ethmoidal veins and thin lamina papyracea are the two close proximity structures influence of the spread of mucormycosis from sinuses to the orbital fossa and the complex network of veins which directly drains

from nasal cavity and paranasal sinuses to orbit and cavernous sinuses. On imaging pre septal cellulitis which includes involvement of the soft tissues anterior to the orbital septum and postseptal cellulitis in which involvement of the soft tissues posterior to the orbital septum and contents of the orbit are commonly involved putting the optic nerve at risk. Varied degree of proptosis is seen in postseptal cellulitis. Radiologically, preseptal and retrobulbar edema, thickened, non-enhancing extra ocular muscles, optic nerve sheath enhancement and orbital apex soft tissue abnormality is seen. The extra ocular muscles shows lack of contrast enhancement and non-enhancing orbital apex soft tissues are seen in mucormycosis which are not seen in bacterial orbital cellulitis. Ipsilateral cavernous sinus involvement may shows asymmetric bulging contour indicated thrombophlebitis or prominent superior ophthalmic vein shows no enhancement on contrast MRI indicated thrombosis. Mucormycosis extends the skull base leading to skull base osteomyelitis (SBO) due to soft tissue infarction and necrosis, which appears as large non enhancing, profoundly hypointense signal, devitalised soft tissue areas in and around the central bony skull base and along the nasopharynx. Abscess formation is not seen in mucormycosis, which is commonly encountered in bacterial SBO, thus tissue infarction and necrosis are features of fungal SBO and abscess is a striking feature of bacterial SBO.

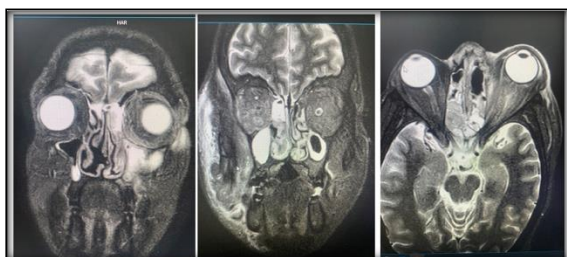


Figure 3:

[Figure 3a]. coronal T2WI showing interstitial edema involving extraconal compartment of medial aspect of the left orbit with mild thickening of the medial and inferior rectus muscle with moderate proptosis. B) Shows mild interstitial edema involving extraconal compartment of medial aspect of the right orbit with mild thickening of the medial and inferior rectus muscles. C) Optic nerve infarction is seen as heterogeneously hyperintense signal of the left optic nerve is seen in T2WI axial image showing diffusion restriction on DWI sequence.

In severe proptosis the tenting of the posterior globe is seen demonstrating the “guitar pick” sign. DWI plays a crucial role in describing the critical finding the optical nerve infarction [Figure 3] showing diffusion restriction in fungal orbital cellulitis as no diffusion restriction / abscess formation seen in bacterial orbital cellulites which is the striking feature of fungal sinusitis, thus DWI plays a crucial role

which can alter the management from medical to surgical.

The fungi invades the perineural connective tissue of the cranial nerves and their branches, perineural spread known along the trigeminal nerve is commonly encountered and rarely along the labyrinthine segment of the facial nerve and geniculate ganglion with retrograde extension into the internal auditory canal. The nerve microenvironment and neurotropic factors secreted in a gradient along the nerve may play a key role in pathogenesis of perineural invasion. On contrast enhanced MRI, the thick sheet of enhancing tissue along the involved cranial nerve or its branches is the earliest sign of perineural spread in addition to loss of normal fat pad adjacent to foramen.

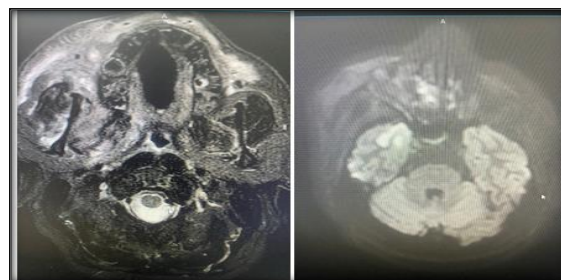


Figure 4:

[Figure 4a]. T2-STIR axial image shows increased T2 signal intensity with edema involving the floor of the right maxillary sinus, floor of the bony orbit with spread of infection to conal and extra conal compartments of the right orbit and extended to lamina papyracea and interstitial edema the axial DWI image shows Diffusion restriction in right medial temporal lobe in a 73 year old male diabetic post COVID-19 patient. Neuroparenchymal invasion of the mucormycosis occurs by invasion through superior orbital fissure, cribriform plate, perineural and angio - invasion which is the most devastating complication of mucormycosis. Hematogenous spread of the mucormycosis causes vasculitis and meningitis. Large vessel vasculitis is another distinct feature of cerebral mucormycosis seen as mural thickening and enhancement of the intracranial internal carotid artery (ICA), sometimes leads to ICA occlusion and cerebral infarction. Involvement of the brain parenchyma is suggestive of cerebritis, if untreated may lead to cerebral abscess formation. DWI sequence is more specific for fungal abscess, which shows diffusion restriction of the abscess wall and intracavitary projections while sparing the core of the lesion [Figure 4]. Postoperative MRI is obtained after surgical extirpation to revive any residual LoCE lesions [Figure 1b] which are associated with high mortality rates needs further debridement. When infarcted soft tissue cannot be completely eradicated by surgery due to poor access (pterygopalatine fossa) or possibility of complications (cavernous sinus), the prognosis is gloomy, however contrast enhancing lesions

including the orbit and brain may be conserved with antifungal medication [Table 3].

Table 3: Extra sinus extent of ROCM and MRI features

Extra sinus extension	No of patients (%)	MRI features
No extra sinus extension	6 (12.5%)	
Facial soft tissues		Infiltration of the soft tissue spaces with fat stranding are better manifested on T2 fat sat sequences
Pterygopalatine fossa	40 (83.3%)	
Pre antral soft tissue	36 (75%)	
Retroantral fat	32(66.6%)	
Infra – temporal fossa	22(45.8%)	
Preseptal space	20(41.6%)	
Buccal space	2(4.16%)	
Anterior maxillary and zygomatic bone	1 (2.0%)	Destruction of the involved facial bones with low T1WI and T2W images
Maxillary process of palatine bone	6 (12.5%)	
Orbit		Fat stranding of the retrobulbar fat on T2 fat sat Enhancement of the intraconal tissue
Intrarbital intra-conal fat	10 (20.8%)	
Intrarbital intra – conal soft tissue extension	6 (12.5%)	Thickening and decreased enhancement Stranding of infra orbital fat on T2 fat sat
Extra ocular muscles	4(8.3%)	
Infraorbital fat	4 (8.3%)	
Intracranial		Enhancement of the cavernous sinus Ectasia of cavernous portion of ICA Focal non vascular territorial based distribution of T2, FLAIR T2, FLAIR hyperintensity areas showing diffusion restriction
Cavernous sinus	1 (2.0%)	
Cavernous ICA ectasia	1 (2.0%)	
Focal cerebritis	1 (2.0%)	
Cerebral infarction	4 (8.3%)	

DISCUSSION

The current study demonstrated a systematic approach for the MR imaging in ROCM allowing thorough assessment of ROCM with regional involvement and potential sites of extension in head and neck region and also describing the different imaging spectra of the disease including localized sino-nasal and sino nasal mucormycosis with possible extensions to facial soft tissues, bone, orbital and intracranial extension. we demonstrated the diagnostic reliability In current study we focussed on the staging and classification of ROCM in post COVID- 19 patients and have found same results as Metwally et al.^[8] Rampage use of corticosteroids in COVID -19, especially in the presence of DM may result in hyperglycemia and acidosis which increases the risk of mucormycosis by eliciting phagocytosis dysfunction.^[9] according to two meta-analysis DM was the most common predisposing factor for mucormycosis accounting for 40 -64 % of cases. in our study DM was reported in 80 % of mucormycosis case and corticosteroid administration in 84.5%.

In our study we found all the MR imaging finding of mucormycosis including black turbinate sign (most commonly seen), obliteration of the nasopharyngeal planes, pre and retro antral fat infiltration, non enhancing sino nasal mucosa, extra ocular muscles and fat and intracranial leptomenigeal enhancement and we concluded that MR imaging findings of mucormycosis features of post COVID -19 patients are similar to previously documented fungal sinusitis except its intracranial leptomenigeal enhancement and cerebral infarction.

Son et al.^[10] reported that 93 % (13 cases) OF ROCM patients had sinus mucosal thickening and air fluid level with no cases with full sinus opacification, the current study demonstrated that 25% (12/48). 90%

of the cases shows heterogeneous post contrast enhancement with enhancing septae in the background of non-enhancing sinus giving a soap bubble appearance sign, this sign may explain the necrotizing nature of the fungal infection and it was previously documented in 68.8% - 70% of cases with chronic invasive fungal sinusitis and named septal enhancement with a sensitivity of 39.2 % - 42.4 % and specificity of 87.2 % - 91.5 %. The extra sinus fat infiltration is caused by either vascular congestion related edema of fungal infiltration and it can happened even before osteolysis as the fungal infection can spread primarily through perivascular channels.^[11]

In our study we found the extension of disease to maxillo facial soft tissues with bone invasion or bony invasion., that is stage 2a and stage 2b by Metwally et al.^[8] retroantral fat pad inflammation, osseous and orbital extension, according to Gorovoy et al.^[12] were specific but late and less prevalent characteristics of ROCM. however we reported the retroantral fat, facial bones and orbit in 66.6% (32/48), 14.5% (7/48), 20.8% (10/48) respectively. We found maxillo facial infiltration is seen early in our study which is contrary to Howells et al. study.^[13] this could be due to invasive fungal extension via trans vascular route rather than direct extension. Similarly, direct vascular invasion or embolic seeding causes fungal spread to the orbit and cerebral tissues.^[11] Mathur et al.^[14] found a association between posterior ethmoid and sphenoid sinuses affection and an increased risk of intracranial extension, contrary to the above study in our study did not found significant association of orbital and intracerebral extension with the posterior ethmoid and sphenoid sinuses. Finally we concluded that the MRI based staging and classification had a significant relationship with patient mortality and explains the disease extent, determines the extent of

the surgical debridement, and also plays a key role to assess the response to medical treatment and adequacy of surgical debridement.

we acknowledge that our study has some limitations as our study had a small sample size and we relied on patients short term follow up and we did not taken into account to the pulmonary mucormycosis patients which could effect the death rate at different stages.

CONCLUSION

In conclusion, in post COVID – 19 patients, as there is high mortality in patients with complications of mucormycosis, and imaging plays a vital role in assessing the involvement of paranasal sinuses, extent of orbital involvement as well as intracranial spread. MRI has high efficacy in early identification of disease process and extent of disease compared to CT, This study established systematic approach for appropriate MRI assessment of mucormycosis infection in head and neck region, as well as distinct imaging spectra of head and neck mucormycosis.

REFERENCES

1. Neofytos D, Horn D, Anaissie E, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. *Clin Infect Dis* 2009; 48:265–73.
2. Sanghvi D, Kale H. Imaging of COVID-19-associated craniofacial mucormycosis: a black and white review of the “black fungus”. *Clin Radiol* 2021; 76: 812-819.
3. Kumar J, Anbarasu A, Amarnath C, et al. Imaging in acute invasive fungal rhinosinusitis/mucormycosis. *IRIA-ICRI Guidelines and Recommendations*; 2021.
4. Groppo ER, El-Sayed IH, Aiken A, et al. Computed tomography and magnetic resonance imaging characteristics of acute invasive fungal sinusitis. *Arch Otolaryngol Head Neck Surg* 2011;137:1005e10.
5. Han Q, Escott EJ. The black turbinate sign, a potential diagnostic pitfall: evaluation of the normal enhancement patterns of the nasal turbinates. *AJNR Am J Neuroradiol* 2019;40:855e61.
6. Kim JH, Kang BC, Lee JH, et al. The prognostic value of gadolinium enhanced magnetic resonance imaging in acute invasive fungal rhinosinusitis. *J Infect* 2015;70:88e95.
7. Middlebrooks EH, Frost CJ, De Jesus RO, et al. Acute invasive fungal rhinosinusitis: a comprehensive update of CT findings and design of an effective diagnostic imaging model. *AJNR Am J Neuroradiol* 2015;36:1529e35.
8. Metwally M, Mobashir A, H Sweed. Post COVID-19 Head and Neck Mucormycosis: MR Imaging Spectrum and Staging: <https://doi.org/10.1016/j.acra.2021.12.007>
9. Corzo-Leon DE, Chora-Hernandez LD, Rodríguez-Zulueta AP, et al. Diabetes mellitus as the major risk factor for mucormycosis in Mexico: epidemiology, diagnosis, and outcomes of reported cases. *Med Mycol* 2018; 56:29–43.
10. Son JH, Lim HB, Lee SH, et al. Early differential diagnosis of rhino-orbitocerebral mucormycosis and bacterial orbital cellulitis: based on computed tomography findings. *PLoS ONE* 2016; 11:e0160897.
11. Gamba JL, Woodruff WW, Djang WT, et al. Craniofacial mucormycosis: assessment with CT. *Radiology* 1986; 160:207–212.
12. Gorovoy IR, Kazanjian M, Kersten RC, et al. Fungal rhinosinusitis and imaging modalities. *Saudi J of Ophthalmol* 2012; 26:419–426.
13. Howells RC, Ramadan HH. Usefulness of computed tomography and magnetic resonance in fulminant invasive fungal rhinosinusitis. *Am J Rhinol* 2001; 15:255–261
14. Mathur S, Karimi A, Mafee MF. Acute optic nerve infarction demonstrated by diffusion-weighted imaging in a case of rhinocerebral mucormycosis. *AJNR Am J Neuroradiol* 2007; 28:489–490.