Section: Ophthalmology

Original Research Article

CORRELATION OF OCULAR AND RADIOLOGICAL FINDINGS IN RHINO-ORBITO-CEREBRAL MUCORMYCOSIS PATIENTS -A HOSPITAL BASED STUDY

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ABSTRACT

Background: Rhino-Orbito-cerebral mucormycosis (ROCM) is a life-threatening opportunistic fungal infection seen in immunocompromised patients. ROCM being a rapidly progressive, even a slight delay in diagnosis or appropriate management can have devastating effect on patient's survival. When the clinical features are supported by diagnostic nasal endoscopy findings, or contrast-enhanced MRI or CT Scan, the patient is considered as Probable ROCM. The objective was to describe the correlation of clinical ophthalmic findings with the imaging findings in patients with ROCM.

Materials and Methods: This retrospective study was conducted on 45 patients after obtaining approval from the Institutional Ethics Committee in the department of Ophthalmology and Radiology. Retrospectively the case records were reviewed for demographic, ocular manifestations and biopsy/culture proven data of invasive ROCM patients. CT and/or MRI images were obtained and correlated with stages of Mucormycosis.

Results: The cases categorized based on the staging system which follows the anatomical progression of ROCM from nasal mucosa to brain were, stage 1d (14), Stage 2d (12), stage 3b (8), and 3 each of stage 1c, 3c and 4b. Maxillary sinus was the most commonly affected sinus observed in 35 (77.8%), followed by Pansinusitis was detected in 17 (37.7%). Combination of maxillary, ethmoid and sphenoid sinus involvement was noted in 21 (46.7%), maxillary & ethmoid in 10 (22.2%) and Ethmoid & sphenoid in 4 (8.9%). Bone erosion was seen in 2 cases. Proptosis was noted in 5 cases and orbital decompression was performed in 1 case.

Conclusion: Study shows the presentation of patients in all the stages of the disease spectrum even with extensive extra sinus involvement. Imaging like CT and MRI shows a spectrum of findings in ROCM, is said plays a major role in assessing the extent of involvement and complications as "Early diagnosis can be lifesaving".

Keywords: COVID-19, diabetes mellitus, magnetic resonance imaging, mucormycosis, paranasal sinus.

INTRODUCTION

Rhino-Orbito-cerebral mucormycosis (ROCM) is an acute, fulminant and lethal opportunistic saprophytic fungi.[1] The exponential rise in the incidence of ROCM is due to certain predisposing factors like Diabetic ketoacidosis, solid organ transplantation, prolonged corticosteroid therapy, haemochromatosis, patients with Human Immunodeficiency Virus (HIV), neutropenia, malnutrition, and haematological malignancies.[2] This is owing to the fact that the normal phagocytic activity in immunocompetent hosts provide an adequate barrier against infection. This angioinvasive fungal infection primarily affects the paranasal sinuses presenting as fever, headache, facial pain, nasal discharge, nasal

obstruction and crusting progressing within hours to days to have orbito-facial and intracranial extension.[3]

A patient who has symptoms and signs of ROCM in the recently treated COVID-19 (> 6 weeks), diabetes mellitus, use of systemic corticosteroids and tocilizumab, mechanical ventilation, or supplemental oxygen is considered as Possible ROCM. Probable ROCM is when the clinical symptoms and signs are supported by diagnostic nasal endoscopy, or contrast-enhanced MRI or CT Scan findings. A Proven ROCM is when the Clinico-radiological features are coupled with microbiological confirmation on direct microscopy, culture, histopathology with special stains or molecular diagnostics.[4]

Early suspicion, rapid diagnosis and initiation of treatment determine the prognosis of mucormycosis that can have devastating implications on the patient survival.[5] As imaging forms the cornerstone of management by providing corroborative evidence of the disease the study intends to describe the stages based on the clinical and radiological findings that may be useful in empirical antifungal therapy even before the confirmation by microbiology or histopathology.

MATERIALS AND METHODS

This retrospective cohort study comprising of 45 positive Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) test and histopathologically or microbiologically diagnosed cases of acute Rhino-orbito-cerebral mucormycosis cases in the department of Ophthalmology, Otorhinilatyngology and Radiology was conducted after obtaining approval from the Institutional Ethics Committee (No.DMC/KLR/IEC/427/2021-22) the relevant clinical and imaging data from the medical records of patients with ROCM will be reviewed and analysed as below. Relevant patients' data including demography, clinical findings, blood investigations, endoscopic and imaging findings were assessed who presented to our tertiary care institution between April to September 2020. The analysis of the data was done from August to September 2023.

A staging system was proposed to grade the severity of ROCM depending on the severity of involvement and progression from nasal mucosa to the paranasal sinuses, orbit and brain.[4]

Table 1: Proposed staging of Rhino-Orbito-Cerebral Mucormycosis

Staging	Findings
Stage 1: Involvement of nasal mucosa	
Stage 1a	Limited to medial turbinate
Stage 1b	Involvement of inferior turbinate or ostium of the NLD
Stage 1c	Involvement of nasal septum
Stage 1d	Bilateral nasal mucosal involvement
Stage 2: Involvement of paranasal sinuses	
Stage 2a	One sinus
Stage 2b	Two ipsilateral sinuses
Stage 2c	> two ipsilateral sinuses
Stage 2d	Bilateral paranasal sinuses, zygoma or mandible involvement
Stage 3: Involvement of the orbit	
Stage 3a	Nasolacrimal duct, medial orbit, vision unaffected
Stage 3b	Diffuse orbital involvement
Stage 3c	CRAO or Ophthalmic artery occlusion, superior & inferior orbital fissure, orbital apex and loss of vision
Stage 3d	Bilateral orbital involvement
Stage 4: Involvement of the CNS	
Stage 4a	Focal or partial cavernous sinus involvement
Stage 4b	Diffuse cavernous sinus involvement
Stage 4c	Involvement beyond cavernous sinus
Stage 4d	Multifocal or diffuse CNS disease

Imaging findings: MRI has been performed using T1, T2, FLAIR and GRE weighted axial, coronal and sagittal sequences. Axial section of CT scan of paranasal sinuses was performed and sagittal and coronal section reformation was done to study the following and patients were segregated on the basis of the radiological staging of the disease.

- MRI features of paranasal sinus involvement
- Extent of regional involvement.
- Extra sinus extension

Statistical analysis

All clinical and radiological imaging data were tabulated and comparisons were done using Statistical Package for the Social Sciences (SPSS) software. All the quantitative measures is presented by mean, standard deviation and confidence interval and categorical data by frequency tables and percentages.

RESULTS

The study included 45 patients, with 36 (80%) males and 9 (20%) females, with a mean age of 48.8+10.3 SD years (range 29–75 years). Out of this Diabetes mellitus was the most commonly associated risk seen in 21 (46.7%) followed by history of RT-PCR positive COVID-19 in 20 patients (62.2%), steroid therapy in 21 (46.7%) and usage of oxygen mask in 18 (40%). [Table 2]

Table 2: Characteristics of COVID-19 associated mucormycosis.

Sl No	Factors		N	%
1	Mean age (range 29-75 years)		48.8+10.3	
2	Gender	Male	36	80
		Female	9	20
3	Laterality	Unilateral	27	60
		Bilateral	18	40
4	COVID -19 positive		28	62.2
5	Diabetes mellitus		33	73.3
6	Use of systemic steroid		21	46.7
7	Use of Oxygen mask		18	40

The most common symptoms were headache in 38 (84.4%), fever in 35 (77.8%), facial swelling and pain in 34 (75.6%) and periorbital oedema 33 (73.3%). And the commonest clinical findings were ptosis in 27 (60%), proptosis 20 in (44.4%), cranial nerve palsy in 13 (28.8%), Total Ophthalmoplegia in 10 (22.2%) and central retinal artery occlusion in 8 (17.8%) patients. [Table 3]

Table 3: Ocular signs in Rhino-Orbito-Cerebral Mucormycosis patients

Sl no	Clinical features		N	%
1	Symptoms	Headache	38	84.4
2		Fever	35	77.8
3		Facial swelling and pain	34	75.6
4		Periorbital edema	33	73.3
5		Decreased vision	17	37.8
6		Diplopia	13	28.9
7		Loss of Consciousness	2	4.4
8	Signs	Blepharoptosis	27	60
9		Proptosis	20	44.4
10		Cranial nerve palsy	13	28.8
11		Total Ophthalmoplegia	10	22.2
12		CRAO	8	17.8

Maxillary sinus was the most commonly affected sinus observed in 35 (77.8%), followed by Pansinusitis was detected in 17 (37.7%). Combination of maxillary, ethmoid and sphenoid sinus involvement was noted in 21 (46.7%), maxillary & ethmoid in 10 (22.2%) and Ethmoid & sphenoid in 4 (8.9%). [Table 4]

Table 4: Sinuses involved in Rhino-Orbito-Cerebral Mucormycosis

Sinuses involved	N	%
Maxillary	35	77.8
Frontal	1	2.2
Maxillary + ethmoid	10	22.2
Ethmoid + sphenoid	4	8.9
Maxillary + Ethmoid + Sphenoid	21	46.7
Pansinusitis	17	37.7

Based on the proposed staging system of ROCM 14 patients were in stage 2d (31.1%) followed by 13 (28.9%) patients in Stage 1d and Stage 3c each, 8 (17.8%) cases were in Stage 3d and extracranial extension noted in 3 (6.7%) patients. [Table 5]

Table 5: Extent of regional involvement of Rhino-Orbito-Cerebral Mucormycosis.

Stage	Areas Involved	N	%
Stage 1c	Involvement of Nasal septum	3	6.7
Stage 1d	Bilateral nasal mucosa	14	31.1
Stage 2d	Bilateral PNS or Zygoma	12	26.7
Stage 3b	Diffuse orbital Involvement	8	17.8
Stage 3c	Orbital apex, superior orbital fissure,	3	6.7
Stage 3d	CRAO, Ophthalmic artery occlusion	8	17.8
	Bilateral orbital involvement	1	2.2
Stage 4	Involvement of the CNS – Diffuse cavernous sinus involvement	3	6.7

CT and MRI confirmed the clinical findings of ROCM by revealing the involvement paranasal sinus, extent of regional involvement and extra sinus extension as shown in [Table 5].

Table 6: CT and MRI findings in Rhino-Orbito-Cerebral Mucormycosis

CT feature	N	%	MR I feature	N	%
Mucosal thickening in all sinuses	15	33.3	T1 hypointense and T2/FLAIR heterogenous signal intensity in all sinuses	18	40
Diffuse mucosal thickening in bilateral maxillary sinus with obliteration of left maxillary ostium	14	31.1	T1 hypointense and T2/FLAIR heterogeneously hyperintense signals in all sinuses with obliteration of left osteomeatal complex	11	24.4

Erosion of left lamina papyracea with with thickening and heterogenous enhancement of the nerve.	7	15.5	T2 / FLAIR hyperintense lesion in the left basitemporal region showing peripheral enhancement on post-contrast study –intracranial abscess with adjacent thickening & enhancement of meninges – suggestive of meningitis.	2	4.4
Mucosal thickening noted in all sinuses involving bilaterally with obliteration of bilateral maxillary ostia.	6	13.3	Orbit: Minimal T2 / FLAIR hyperintense signal noted in the preseptal space on the right side with mild proptosis. Heterogenous T2/FLAIR signal intensity of right medial rectus.	17	37.7
Diffuse mucosal thickening in bilateral maxillary sinus with obliteration of right osteo - meatal unit.	5	11.1	T2/FLAIR hyperintense signal intensities in the roof of right orbit, medial aspect of intraconal region and right orbital apex showing restricted diffusion - cellulitis.	5	11.1

DISCUSSION

Mucormycosis, an opportunistic potentially devastating angioinvasive fungal infection also known as zygomycosis and phycomycosis, was first described by Paulltauf in 1885.[6] It is caused by organisms of the family Mucoraceae (Mucor, Absidia, and Rhizopus).[7] These are ubiquitous fungi present in soil, air, skin, body orifices, manure, spoiled food and dust and inoculated by inhalation of spores that reach the nasal cavity and/or nasopharynx. But infection rarely occurs in a person with an intact immune system because macrophages phagocytize the spores. However, an immunocompromised individual is unable to mount an effective immune response against the inhaled spores resulting in germination and formation of hyphae in the sinuses and lungs. Subsequently the orbital invasion occurs through lamina papyracea, nasolacrimal duct, ethmoid foramina, and perforations of the medial orbital walls by vascular channels.[8]

Figure 1: Total ophthalmoplegia – Stage 3d

Figure 2: Stage 4 Mucormycosis case with ptosis

Figure 3: Stage 4 ROCM case with ptosis post orbital decompression

Figure 4: Stage 3c ROCM case involving left orbital apex

Certain risk factors like diabetes mellitus, corticosteroids and immunosuppressive drugs, primary or secondary immunodeficiency malignancies and haematological stem cell transplantation, solid organ transplantation, iron overload., etc predispose to this lethal infection.[2] Uncontrolled Diabetes mellites was the most common risk factor noted in 33 (73.3 %), COVID-19 positive status in 28 (62.2%) and oxygen usage in 21 (46.7%) compromising the host defense mechanism leading to opportunistic fungal infections.

As rhino-orbital-cerebral is the most common presentation of mucormycosis depending on the immune status of the individual, most patients in the study had non-specific signs such as sinus tenderness,

headache, fever and malaise and signs like ptosis 27 (60%), proptosis (44.4%) and Cranial nerve palsy 13 (28.8%) which was also observed in in other studies.[9-11] A very high index of suspicion is required in the vulnerable individuals because the fungus invades the blood vessels, causing mechanical and toxic damage to the intima leading to thrombosis which eventually results in emboli and vascular obstruction induced tissue necrosis.[12]

The ethmoid sinus is an important route of infection, since mucormycosis may invade through the thin lamina papyracea and gain access to the orbit and its contents. Several studies including present study found maxillary and ethmoid sinuses as the most commonly affected paranasal sinuses.[13-15] This was correlated with the CT & MRI findings as mucosal thickening in all sinuses and T1 hypointense and T2/FLAIR heterogenous signal intensity in all sinuses respectively.

Most of these images of ROCM show a rim of soft-tissue thickness along the paranasal sinuses, sinus opacification, air-fluid concentration and obliteration of the nasopharyngeal tissue planes. Variable intensity within the sinuses on T1- and T2-weighted images is usually seen as the Fungal elements themselves may cause a low signal intensity on T2 sequences in MRI.[16] The extra sinus spread such as diffuse orbital involvement in 7(15.6%), Orbital apex 13 (28.8%), CRAO in 8 (17.7%) and cavernous sinus in 3 (6.7%) observed were less than other studies.[13,18] Orbital extension showed intraconal, extraconal fat stranding of left orbit with poor delineation of the recti muscles in MRI.

Figure 5: Ct axial section brain widow showing soft tissue density noted in the bilateral maxillary sinuses with hyperdense area noted in the right maxillary sinus

This is due to the invasion of blood vessels by fungal hyphae that allows the perivascular spread of infection across the bony walls of sinuses.15 Also damage to the endothelium leads to clot formation which results in ischaemia and necrosis of the surrounding tissue that appears black necrotic eschar clinically20 and radiologically described as black turbinate which is a non-enhancement of turbinate on contrast-enhanced MRI.[16]

Figure 6: Ct axial section brain widow showing soft tissue density noted in the ethmoidal and sphenoid sinuses

Figure 7: Ct axial section showing erosion of the right lamina papyracea

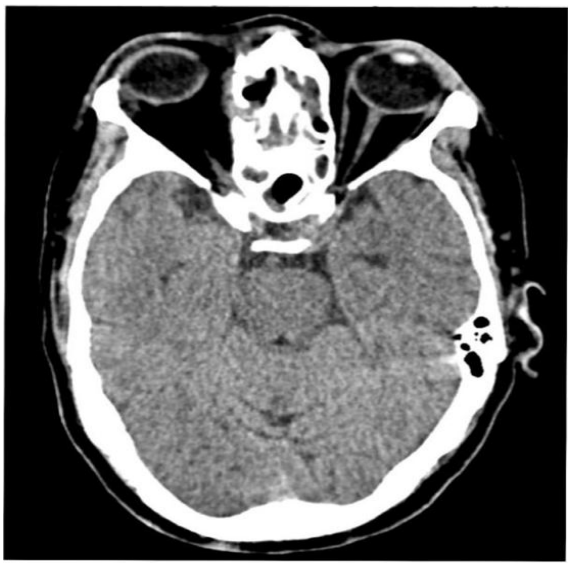

Figure 8: Ct axial section brain window showing the extension of the soft tissue density into the right orbit through the erosion of the lamina papyracea.

Figure 9: Ct axial section brain widow showing soft tissue density with hyperdense focii noted in the frontal sinus Also noted adjacent extension to frontal lobe with diffuse edema

Figure 10: Ct axial section brain window post contrast images showing oval lesion with smooth continuous peripheral ring of enhancement with significant surrounding oedema characteristic of an abscess

Ophthalmoplegia was associated with the extraocular muscle involvement was seen in 13 (28.8%) cases evidenced as fat stranding or soft tissue at the apex and Medial and inferior rectus muscles appeared thickened and showed heterogenous T2/FLAIR signal intensities.

Cavernous sinus thrombosis was common intracranial manifestations noted in 3 (6.7%) patients evident as abnormal enhancement on contrast-enhanced images and restriction on diffusion-weighted imaging, similar to observations of previous studies.[14,17,21] Fungal hyphae can traverse along the fibres to the cavernous sinus and spread to the brainstem or skull base.[22]

All the patients were immediately started with IV liposomal amphotericin infusions 5 mg/ml twice daily for 4 weeks with sinus irrigation and endoscopy guided debridement followed by oral antifungals posaconazole 300mg for 6 weeks – 3 months after evident clinical / radiological regression as patients treated with amphotericin B and wide debridement have an overall higher survival rate.23 Orbital decompression was performed in 2 cases.

Limitations

It is a retrospective study with a limited number of patients. Few of the clinical-radiologic correlations were limited as the ocular data were missing for the patients hospitalized in the ICU. Especially the duration of glycaemic status in diabetic patients. Also the correlations were not done for histopathological features and lastly and a prioritized Code-Mucor approach was not followed in most of the patients.

CONCLUSION

Study shows the presentation of patients in all the stages of the disease spectrum even with extensive extra sinus involvement. Although CT and MRI are complementary to evaluation they aid in clinically suspected cases to assessing the extent of disease progression and potential complications and initiation of empirical antifungal therapy instead of relying on the confirmation of diagnosis by microbiology or histopathology. Thus it is mandatory for every member of the multidisciplinary team to familiarize with the imaging in ROCM.

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