ORIGINAL RESEARCH PAPER

Radiology

SPECTRUM OF MAGNETIC RESONANCE IMAGING FINDINGS IN RHINO-ORBITO-CEREBRAL MUCORMYCOSIS PATIENTS DURING SECOND WAVE OF COVID-19 INFECTION IN A TERTIARY CARE HOSPITAL – A PROSPECTIVE STUDY.

KEY WORDS: Mucormycosis, sinonasal infection, invasive fungal infection, Magnetic Resonance Imaging

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ABSTRACT

Introduction- Mucormycosis is a lethal intrusive opportunistic fungal infection with increased morbidity and mortality. Its most common form is Rhino-Orbital-Cerebral Mucormycosis (ROCM). It has been described more in immunosuppressed people and currently in patients with recent history of/ concomitant Covid-19 infection. Magnetic Resonance Imaging (MRI) has been used to delineate extent of infection and spread and preoperative planning. MRI shows varied T1 and T2 signal intensity lesions with nonenhancement in necrosed tissues and extension of infection into adjacent structures. This prospective study aimed at delineating the spectrum of MRI findings in ROCM patients.

Methods and results- A prospective study of 31 patients with ROCM was done in Department of Radiology, Superspeciality hospital, Gajra Raja Medical College, Gwalior in May and June 2021 during second wave of COVID-19 pandemic. We found that 64.5% patients in study group had previously / recently diagnosed diabetes mellitus and 77.4% cases had recently treated or concomitant COVID-19 infection. All the patients had sinonasal involvement at the time of imaging. The other areas of involvement were orbit and its contents, some of adjacent soft tissues, cavernous sinus and cerebral parenchyma, hard palate and cavernous ICA in order of frequency.

Conclusion- ROCM is a grave infection which readily causes perivascular, perineural and soft tissue infiltration within a short span of time, hence most of the patients in this study had extension beyond the sinuses at the time of imaging. MRI is an essential tool for early identification of extrasinus extension of disease, detection of intracranial and vascular complications and presurgical planning.

INTRODUCTION-

Mucormycosis is a lethal intrusive opportunistic fungal infection with increased morbidity and mortality and can occur in any part of body[1]. Causative organisms are fungi of Mucoraceae family (of genera *Rhizopus, Lichtheimia and Mucor etc*)[2]. These develop in humid atmosphere, profoundly seen in soil, rotting vegetations and animal droppings[2]. It has been described in immunosuppressed people (e.g. patients with poorly controlled and previously unknown diabetes, diabetic ketoacidosis, long term corticosteroids, bone marrow transplant, hematological cancer, neutropenia, multiple blood transfusions, excessive trauma, burns etc.)[1,3,4] and currently in patients with recent Covid-19 infection (particularly those with diabetes, moderate to severe infection or receiving systemic corticosteroids)[5,6]. It has been reported that most common influencing factor for rhino-orbital-cerebral mucormycosis (ROCM) is uncontrolled diabetes (mostly with ketoacidosis)[7].

Roden et al. reported that paranasal sinuses were the most common site (39%) in 929 patients with mucormycosis together with 8% of Sino-orbital cases and 19% cases were not immunosuppresed[8]. *Rhizopus* species is described as the commonest cause of sinonasal-orbital mucormycosis[2,9]. Fungal spores are initially inhaled, enter into nasal mucosa but often are not phagocytosed owing to low immune response and then germinate to form hyphae that are angioinvasive[10,11].

Ethmoid sinuses are significant pathway for sinonasal infection to spread into orbital contents and optic nerve via lamina papyracea and nasolacrimal duct and then into posterior tissues into orbital apex, superior and inferior orbital fissure causing multiple cranial nerve palsies (involving cranial nerves III, IV, VI, and V1 and V2 branches), local invasion into blood vessels damaging intima causing thrombi, suppurative arteritis, affecting lymphatics and veins, causing necrosis of tissue and bony erosions, perineural invasion, further entering into cavernous sinus, intracranial vessels, infratemporal fossa, palate, deep face and cerebrum (causing brain infarction, hemorrhage, abscess)[6,10,12]. It progresses in three phases, first of which is sinonasal with minimal or no symptoms, then orbital involvement and later cerebral involvement[9]. Orbital apex syndrome can be seen in these patients with retro-orbital pain, weakness of one or more of eye muscles, and decreased vision[9].

Clinical symptoms of rhino-orbital mucormycosis include regional pain, nasal stuffiness, nasal discharge, epistaxis, redness of eye, periorbital swelling, focal discoloration, double vision, drooping of eyelid, proptosis, restriction of eye movements, decreased vision, headache, numbness of face, fever etc. and with brain involvement there may be seizures, paralysis and altered sensorium[1,12-14].

An important attribute of this infection is presence of black dead tissue in nasal turbinates or hard palate[6,15]. It has a very small duration between beginning of symptoms to extensive disease manifestation, necessitating early diagnosis and management[12,13].

Magnetic Resonance Imaging (MRI) has been used to delineate extent of infection and spread (involvement of orbits, brain etc.) and preoperative planning in mucormycosis[12,15]. All the patients who had clinical signs and symptoms of mucormycosis underwent MRI at our institute. MRI was done in Philips Ingenia 1.5T dstream scanner. For paranasal sinuses and orbits, T1-weighted imaging (T1W) and T2-weighted imaging (T2W) with fat-suppression was done in axial and coronal planes along with T2-weighted imaging with fat-suppression in sagittal plane, diffusion-weighted imaging (DWI) and Apparent diffusion coefficient (ADC) maps in axial plane were done in all cases and post-contrast T1-weighted images with fat-suppression (using gadolinium based contrast agents) in axial and coronal planes was done in patients in whom it was feasible. MRI of brain was done with routine sequences including T1-weighted imaging in axial plane, T2-weighted imaging in axial, sagittal and coronal planes, fluid-attenuated inversion recovery (FLAIR) image in axial plane, DWI, ADC map and T2* GRE images in axial plane.

MRI shows T1W isointense lesions (in comparison to brain) and T2W heterogeneous signal intensity lesions (likely owing

to occurrence of iron, manganese and calcium) in most cases[10]. Fungal components show hypointense signal on T2W images[10,12]. On post-contrast T1W imaging, there is nonenhancement in necrosed tissue[12] (known as black turbinate sign). There is usually absence of fluid levels in sinuses[10].

MRI also shows spread of sinonasal lesion into the orbits, orbital apex, superior orbital fissure, cavernous sinus, brain (causing infarct, abscess, edema, meningitis, dural enhancement), hard palate, vascular structures, adjacent soft tissue permeation of deep face, elimination of usual fat planes in periantral fat, pterygopalatine fossa, infratemporal fossa, pterygomaxillary fissure[9,10,12]. There may be invasion of vascular structures leading to thrombosis and vasculitis (in ICA, cavernous sinus, superior ophthalmic vein, ophthalmic artery, venous sinuses) showing loss of normal signal on T2W images with nonenhancement. The fungi being angioinvasive, bone erosions/ destruction/ infections occur later in sequence in sinonasal mucormycosis and are seen as absence of normal T1 hyperintense signal in marrow fat of skull base[10].

Computed Tomography (CT) imaging in sinonasal mucormycosis shows soft-tissue opacity containing hyperdense substance with mucosal thickening (in maxillary, ethmoid, frontal, and sphenoid sinuses in decreasing order of frequency) and adjacent border of soft tissue thickening[10].

Fungal hyphae are generally identified by KOH preparation, culture and histopathology of biopsy / scrapes/ other samples of infected tissues[1,3]. It is seen as characteristic aseptate, wide, uneven and right-angle branching fungal hyphae on special stains[14]. ROCM is a grave infection requiring early diagnosis and treatment with antifungal drugs, surgical drainage / debridement and controlling risk factors[6,7,15,16].

AIMS AND OBJECTIVES OF STUDY

This was a prospective study aimed to delineate the spectrum of MRI findings in Rhino-Orbital-Cerebral mucormycosis patients during COVID-19 pandemic, define the extension of disease into adjacent structures and for preoperative planning.

MATERIAL AND METHODS

A prospective study of 31 patients with ROCM was done in Department of Radiology, Superspeciality hospital, Gajra Raja Medical College, Gwalior in May and June 2021 during COVID-19 pandemic. All patients with clinical symptoms and signs of mucormycosis were evaluated with detailed history, clinical examination and laboratory tests at the time of presentation. All patients underwent MRI of paranasal sinuses, orbits and brain according to dedicated protocol. They were then confirmed with histopathological examination.

RESULTS AND DISCUSSION

This is a prospective study of 31 patients with ROCM. Mean age of the study group was 50.3 +/-12.9 (range 28-75) years. There were 19 males (61.3%) and 12 females (38.7%) in the study group with male to female ratio 1.6:1. Out of 31 patients, 24 patients (77.4%) had either recently treated (<6 weeks) or concomitant COVID-19 infection, similar to previous reports of mucormycosis affecting COVID-19 patients[4-6]. A total of 20 cases (64.5%) had diabetes mellitus, out of which 16 cases (51.6%) had known diabetes mellitus and 4 cases (12.9%) were previously unknown for diabetes mellitus, nearly similar to Dan M who had earlier reported that 70% of rhinocerebral mucormycosis occur in diabetic patients[16]. One patient (3.2%) had diabetic ketoacidosis at time of presentation. History of hypertension was found in 5 patients (16.1%). The average duration between COVID-19 diagnosis and onset of mucormycosis symptoms could be elicited in 11 cases and was estimated to be 13.3 days, close to Sen et al[6] who had reported it to be 15.6 days.

The most common presenting complaint in this study was orbital symptom as patients tend to overlook nonspecific sinonasal symptoms in early stage of disease. Most common symptom was periorbital swelling (77.4%) followed by eye/ facial pain (74.2%), headache (67.7 %), decreased vision (58.1%), nasal stuffiness (54.8%), facial/ nasal decreased sensation (32.3%), fever (25.8%), decreased movement of eye (22.6%), drooping of eyelid (22.6%), facial swelling/discoloration (16.1%), epistaxis/ foul nasal discharge (16.1%), weakness of limb (16.1%), ulcer/discoloration of palate (12.9%), watering and redness of eye (12.9%), bleeding from upper gum with spontaneous fall of tooth (3.2%), seizure (3.2%) and slurring of speech (3.2%).

All these patients diagnosed with possible ROCM based on clinical symptoms and signs were referred for MRI scan in our department. MRI was done as per dedicated protocol for paranasal sinuses, orbits and brain in all patients. Contrast enhanced T1W MRI was feasible in 2 patients (6.5%). We found in our study that there was mucosal thickening / opacification of one or more paranasal sinuses and mucosal thickening of nasal mucosa / turbinates appearing isointense on T1W images and heterogeneously hyperintense on T2W images, however these are not specific for ROCM as was shown by Therakathu et al[12]. Focal areas of T2W hypointensity were noted in paranasal sinuses in 7 (22.6%) patients (Fig.1) and focal DWI restriction in 21 (67.7%) patients (Fig. 2). Unilateral or bilateral involvement of ethmoid and maxillary sinuses and nasal cavity were found in all patients. Pansinusitis was seen in 9 patients (29%) of which 7 were diabetic. Contrast study could be done in 2 patients showing heterogeneous enhancement within the sinuses and nasal cavity with focal areas of nonenhancement (black turbinate sign) suggestive of tissue necrosis (Fig.3) and one of them showed mild dural contrast enhancement in frontotemporal region.

In our study, there was orbital involvement in MRI in 30 patients (96.7%) with ROCM, indicating that all these patients had local extension of disease at time of presentation. This happens because the initial non-specific symptoms of sinonasal fungal infection are usually ignored by the patients[9]. All of these cases had some areas of extraconal fat stranding (unilateral left side involvement seen in 56.7% cases and right side involvement in 43.3% cases). Among these patients, intraconal fat stranding was seen in 24 cases (80%), out of which 13 cases were on left side and 11 cases on right side. Periorbital edema was noted in 24 patients (80%), bilaterally in 10 cases and unilaterally in 14 cases (11 cases on left side and 3 cases on right side). Among the extraocular muscles, we found that medial rectus was most commonly involved (70%) showing mild thickening and/or altered T2W signal intensity and mild lateral displacement. Mild proptosis was seen in 26.7% cases.

Optic nerve showed altered T2W signal intensity in intraorbital part and /or adjacent fat stranding around it in 70% of patients with orbital involvement (11 cases on left side and 10 cases on right side). DWI restriction in intraorbital part of optic nerve was noted in 8 of these cases (Fig. 5). Posterior extension of the infection into superior orbital fissure was seen in 40% of these patients and in 43.3% cases orbital apex was involved in this study. Dilated superior ophthalmic vein (lumen diameter >3mm) was seen in 7 patients in our study.

We found in our study that there was unilateral or bilateral elimination of usual fat planes with edema/ swelling in adjacent soft tissues including periantral fat, pterygopalatine fossa and infratemporal fossa in 90.3%, 80.6% and 83.9% cases respectively. Two diabetic patients (6.4%) had unilateral focal large facial collections with erosion of anterior

wall of maxillary sinus. There was extension into cavernous sinus showing altered signal intensity in 38.7% cases and one patient (3.2%) had thrombosis of superior petrosal sinus on MR venography. In this study, 5 patients (16.1%) showed hard palate involvement (erosion/ abnormal signal intensity).

Cerebral involvement was seen in 12 cases (38.7 %) in our study, 10 of these patients had diabetes mellitus. 8 cases had cerebral infarction at time of imaging (of which 7 cases had diabetes mellitus), 2 patients had focal brain edema, 1 patient had abscess and 1 patient had both abscess and infarction. Cavernous ICA showed narrowing in 2 patients (6.4%) and abnormal T2 hyperintense signal in 1 case (3.2%) in our study.

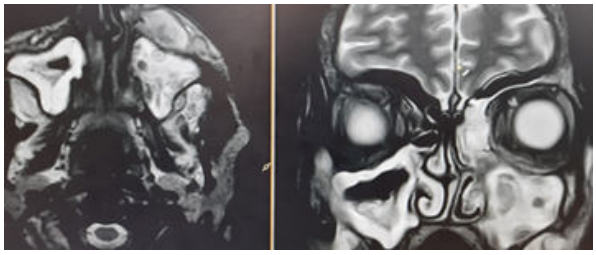
Most of the patients in this study had advanced stage of the disease with extrasinus involvement similar to Therakathu et al[12]. Most commonly there was orbital extension, followed by adjacent soft tissue infiltration, cavernous sinus and cerebral involvement, hard palate invasion and cavernous ICA involvement. Cerebral involvement was found to be more common in diabetic patients with most patients having focal brain infarction.

All these patients were diagnosed with probable ROCM based on clinical and imaging findings and underwent microbiological confirmation with direct microscopy/ culture/histopathology with special stains for ROCM.

CONCLUSION

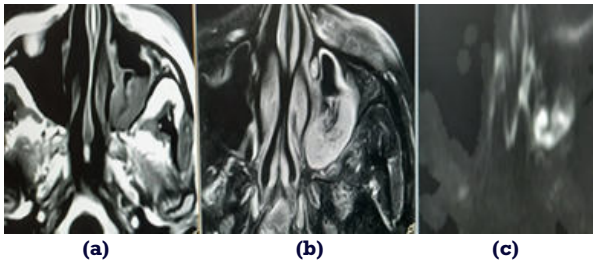
ROCM is a grave infection which readily causes perivascular, perineural and soft tissue infiltration within a short span of time, hence most of the patients in this study had extension beyond the sinuses at the time of imaging. MRI is an essential tool for early identification of extrasinus extension of disease, detection of intracranial and vascular complications and presurgical planning. High level of suspicion is required in patients with known risk factors and co-morbidities (particularly diabetes mellitus) to prevent extensive manifestation of disease and decrease morbidity and mortality.

Images



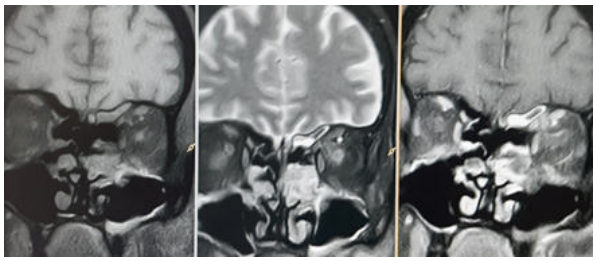
(a) (b)

Figure 1: Axial T2W fat suppressed (a) and coronal T2W fat suppressed (b) images of chronic diabetic patient with ROCM presenting with left periorbital pain and swelling and having T2W hyperintense thickening in both maxillary sinuses and left ethmoid sinuses with T2W hypointense areas in left maxillary sinus and focal extension into left periantral fat and bilateral infratemporal fossa.



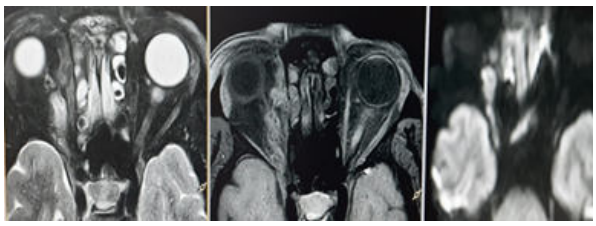
(a) (b) (c)

Figure 2: Axial T1W (a), axial T2W fat suppressed (b) and axial DWI (c) images of chronic diabetic and recently treated COVID-19 patient with ROCM complaining of left side eye pain with swelling, MRI showing T1W isointense and T2W hyperintense thickening in left maxillary sinus with T2W hypointense areas and focal diffusion restriction and altered fat in left pterygopalatine fossa and left periantral region.



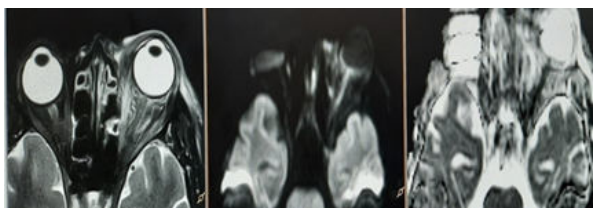
(a) (b) (c)

Figure 3: Coronal T1W fat suppressed (a), Coronal T2W fat suppressed (b) and post contrast (Gd-based) coronal T1W fat suppressed (c) images of chronic diabetic patient with ROCM presenting with left periorbital pain and swelling, decreased left sided vision, had blackening of left side of nasal septum on examination and MRI showing focal T1W isointensity and T2W hyperintensity in both anterior ethmoid sinuses, left maxillary sinus, left middle and inferior turbinates, showing heterogeneous contrast enhancement with nonenhancing areas (s/o focal tissue necrosis).



(a) (b) (c)

Figure 4: Axial T2W fat suppressed (a), axial T1W fat suppressed (b) and axial DWI (c) images of recently treated COVID-19 and chronic hypertensive patient with ROCM complaining of right eye pain and periorbital swelling, decreased right side vision, decreased right eye movement, decreased sensation in right side of face and ptosis. MRI showing T2W hyperintense and T1W isointense mild mucosal thickening in both ethmoid sinuses with focal extension into right medial orbital fat, right orbital apex and anterior part of right cavernous sinus, also showing diffusion restriction.



(a) (b) (c)

Figure 5: Axial T2W fat suppressed (a), axial DWI (b) and ADC map (c) images of chronic diabetic and recently treated COVID-19 patient with ROCM complaining of left side eye pain with swelling, ptosis, left side decreased vision and decreased eye movement. MRI showing fat stranding in left orbital intra- and extraconal fat, mild thickening with T2W hyperintensity in left medial rectus and diffusion restriction in intraorbital part of left optic nerve.

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