Original Article

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Radiology Section

MRI Evaluation of Rhino-orbito-cerebral Mucormycosis in Post COVID-19 Patients: A Cross-sectional Study

SIDDAPPA RAMAPPA SHIRAHATTI[1], KS PRASHANTH[2], ERANNA PALLED[3], RC SUDHAKAR[4]

ABSTRACT

Introduction: Mucormycosis is the common cause of invasive fungal sinusitis in post Coronavirus Disease-2019 (COVID-19) patient. Mucormycosis is a life-threatening infection with a death rate of >50%. Early detection is critical for determining the amount of infection dissemination, as medical and surgical intervention can reduce death and morbidity.

Aim: To evaluate the Magnetic Resonance Imaging (MRI) findings of Rhino-Orbito-Cerebral Mucormycosis (ROCM) in the post COVID-19 patients to detect the extent of the disease and complications.

Materials and Methods: This was the retrospective cross-sectional analysis of medical records of 93 patients admitted from 1st June 2021 to 31st July 2021 in tertiary care centre with documented history of COVID-19 infection with clinically suspected and histopathologically confirmed ROCM retrieved for the study. Radiological findings such as involvement of Paranasal Sinus (PNS), intracranial extension, extrasinus extension, orbit, brain parenchyma, perineural extension in ROCM were recorded.

Results: Records of total 93 patients (65 males and 28 females; aged between 20-80 years) were studied. The MRI findings revealed, the most common sinus involved was ethmoid sinus (n=92, 98.92%) followed by maxillary (n=90, 96.77%), sphenoid (n=76, 81.72%) and frontal sinus (n=61, 65.59%). There was an involvement of infratemporal and pterygopalatine fossa (n=73, 78.49%), orbit (n=58, 62.36%), cavernous sinus (n=22, 23.65%), Internal Carotid Artery (ICA) (n=12, 12.90%), cranial nerves (n=6, 6.45%), brain parenchyma (n=22, 23.65%) and skull base (n=1, 1.07%). MRI showed T2 isointense to hypointense mucosal thickening and heterogeneous postcontrast enhancement as the most common finding. The mucosa was hypointense on T1W images in all cases (100%). Hypo to isointense components in thickened hyperintense mucosa on T2W images was seen in 77 cases (82.79%). Thickened hyperintense mucosa on T2W images was seen in rest of the 16 (17.20%) cases.

Conclusion: In clinically suspected post COVID-19 ROCM cases with typical imaging features (like mucosal thickening with hypointense components on T2W images, demonstration of spread beyond the sinus walls and presence of angioinvasion), even before microbiology or histopathology establish the diagnosis, empirical antifungal medication might be initiated. MRI plays important role in the evaluation of extent of the disease and planning treatment.

Keywords: Brain infarction, Cavernous sinus thrombosis, Coronavirus disease-2019, Hypointense areas, Internal carotid artery occlusion, Magnetic resonance imaging, Sinusitis

INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) causes COVID-19, with symptoms ranging from moderate to severe pneumonia [1,2]. The rhino-orbital mucormycosis co-infections in COVID-19 patients have increased in the second wave of the COVID-19 pandemic in India [3]. Mucormycosis is a fungal infection, caused by the pathogenic genera Absidia, Mucor, Rhizomucor, and Rhizopus of the family Mucoraceae [4,5]. It was initially debatable whether someone taking immunosuppressive drugs was more likely to contract COVID-19 or whether the immunosuppressive state caused more severe COVID-19 infection [6].

Severe COVID-19 disease is associated with an increase in pro-inflammatory markers, such as Interleukin (IL)-1, IL-6, and tumour necrosis alpha, decreased interferon gamma expression, cluster of differentiation (CD) 4 and CD8 cells; resulting in, increase in susceptibility to secondary bacterial and fungal infections [7]. Mucormycosis is an uncommon fungal infection that is often fatal. It is characterised by vascular invasion by fungal hyphae, resulting in thrombosis and necrosis [8,9]. The fungi infect the host by causing necrotising vasculitis of the nose and sinuses, and quickly spread into the orbits, deep face, meninges, and cranial cavity after being inhaled into the nasal cavity and PNS [9].

Early detection is critical for determining the amount of infection dissemination, as medical and surgical intervention can reduce death and morbidity [10]. Studies reported MRI is a better choice than Computed Tomography (CT) because of the coincident therapy with nephrotoxic drugs and possible compromised renal function may be made worse by potential nephrotoxicity of iodinated contrast use in CT [4,11-14]. MRI also provides better evaluation of intracranial and soft tissue involvement, skull base invasion, perineural spread, and vascular obstruction [15]. Further, it is important for all radiologist to be familiar with the imaging features of rhino-orbital mucormycosis. Hence, the present study aimed to describe the imaging findings in the post COVID-19 patients who were diagnosed with ROCM.

MATERIALS AND METHODS

The present retrospective cross-sectional analysis was conducted at Belagavi Institute of Medical Sciences (BIMS), Belagavi, Karnataka, India, a tertiary care referral centre during the period of 1st June 2021 to 31st July 2021. Medical records of all 93 patients referred within the specified period with documented history of COVID-19 infection with clinically suspected and histopathologically confirmed ROCM were retrieved. The bioethical approval was obtained from BIMS Belagavi for this study (BIMS-IEC/147/2020-21).

Inclusion criteria: Records of histopathologically confirmed mucormycosis cases irrespective of any age and sex who had undergone MRI examination were included.

Exclusion criteria: Patients with known head and neck malignancy, postchemoradiation, on chronic steroid or immunosuppressive drug therapy (pre COVID-19 infection) were excluded.

MRI images of ROCM cases were retrieved from the Picture Archiving and Communication System (PACS).

Procedure

All patients had MR imaging with a 1.5-T system. Both T1, T2-weighted images, diffusion-Weighted Imaging (DWI), Apparent Diffusion Coefficient (ADC) mapping were obtained as well as T1-weighted images after intravenous injection of gadopentetate dimeglumine (0.1 mmol/kg) were done in the patients. From the MRI images, detailed analysis was made on the signal character, anatomical site, extension, and complications of mucormycosis.

Outcomes: Demographic data, common areas involved, type of involvement were noted. Radiological findings such as involvement of PNS, intracranial extension, extrasinus extension, orbit, brain parenchyma, perineural extension in ROCM were recorded.

STATISTICAL ANALYSIS

All numerical variables were counted and percentages were calculated in Microsoft excel version 2013.

RESULTS

In the present study, there were 65 males and 28 females of varying age groups [Table/Fig-1]. Patient's age ranged from 20-80 years with predominant age group was 41-50 years [Table/Fig-1]. Most common sinus involved was ethmoid sinus (98.92%) followed by maxillary (96.77%), sphenoid (81.72%), and frontal sinus (65.59%) [Table/Fig-1]. Involvement of infratemporal and pterygopalatine fossa (n=73, 78.49%), orbit (n=58, 62.36%), cavernous sinus (n=22, 23.65%), ICA (n=12, 12.90%), cranial nerves (CN) (n=6, 6.45%), brain parenchyma (n=22, 23.65%) and skull base (n=1, 1.07%) was seen. In brain parenchyma, infarction (n=11, 11.83%), cerebritis (n=3, 3.22%), cerebellitis (n=2, 2.15%), brain abscess (n=6, 6.45%) were noted. Further details of sinus and extra sinus extension including the type of involvement are given in [Table/Fig-2,3].

Variables of all participants	Number of the patients	Percentages
Gender		
Male	65	69.89
Female	28	30.11
Age (Years)		
21-30	02	2.15
31-40	15	16.13
41-50	30	32.26
51-60	23	24.73
61-70	19	20.43
71-80	04	4.30
Area involved		
Maxillary sinus	90	96.77
Ethmoid sinus	92	98.92
Sphenoid sinus	76	81.72
Frontal sinus	61	65.59
Infratemporal fossa	73	78.49
Premaxillary soft tissue	70	75.27
Orbit	58	62.36
Cavernous sinus	22	23.65
Internal carotid artery (ICA)	12	12.90
Cranial nerves	06	6.45
Brain	22	23.65
Skull base	01	1.07

[Table/Fig-1]: Demographic details and anatomical site distribution in patients studied; Total N=93.

Anatomical site	MRI findings	Number of patients	Percentages
Thickened mucosa	Hypointense on T1W images	93	100
	Hypo to isointense components in hyperintense mucosa on T2W images	77	82.79
	Hyperintense mucosa on T2W images	16	17.20
Mucosal enhancement pattern	Enhancement with fungal balls appeared as non enhancing areas (heterogeneous)	77	82.79
	Homogenous enhancement	16	17.20

[Table/Fig-2]: Magnetic Resonance Imaging (MRI) findings in the Paranasal Sinuses (PNS); Total N=93.

Anatomical site	MRI findings noted for	Number of the patients	Percentages
Infratemporal fossa	Fat stranding	73	78.49
Premaxillary soft tissue	Fat stranding	70	75.27
Orbit	Fat stranding	58	62.36
Cavernous sinus	Thrombosis	22	23.65
Internal carotid artery	Narrowing	7	7.53
	Occlusion	5	5.38
Cranial nerves	Thickening and irregular with peripheral enhancement	6	6.45
Brain	Cerebritis	3	3.22
	Cerebellitis	2	2.15
	Abscess	6	6.45
	Infarction	11	11.83
Skull base	Marrow oedema erosions	1	1.07

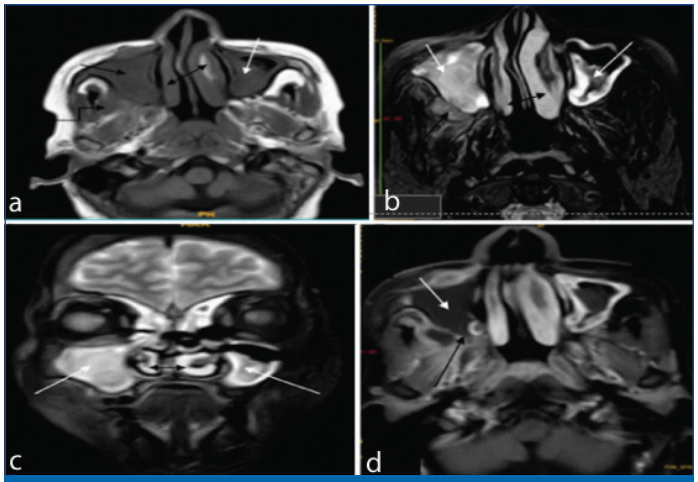
[Table/Fig-3]: Magnetic resonance imaging (MRI) findings in the Extra sinus involvement.

Paranasal Sinuses (PNS): PNS in cases of the present study were most common site of infection and showed mucosal thickening to compete opacification. The mucosa was hypointense on T1W images in all cases (100%). Hypo to isointense components in thickened hyperintense mucosa on T2W images was seen in 77 cases (82.79%) [Table/Fig-2]. Thickened hyperintense mucosa on T2W images was seen in rest of the 16 (17.20%) cases. These hypointense areas represent fungal ball and are hypointense due to its high iron and manganese content. On the postcontrast, mucosa showed heterogeneous enhancement with fungal balls appeared as non enhancing areas in 77 cases (82.79%). Mild homogenous enhancement noted in the rest of 16 cases (17.20%) [Table/Fig-2]. Mixed leptomeningeal, pachy meningeal enhancement with ring enhancing lesions were present in 22 patients (23.65%).

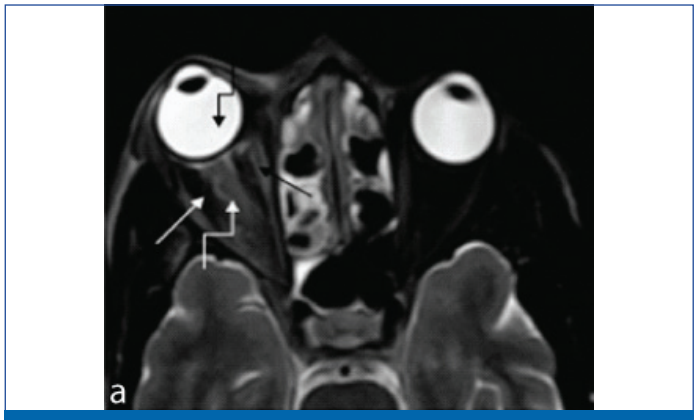
Extrasinus extension: Initially periantral fat was involved latter fungal infection was seen extending to premaxillary soft tissues in 70 cases (75.27%). The infection was seen extending to deeper planes involving infratemporal fossa and pterygopalatine fossa in 73 cases (78%). These areas were appeared as T2/FLAIR hyper intensities representing inflammation [Table/Fig-3,4].

Orbit: Infection was seen extending to the orbits in 58 cases (62.36%) through medial wall of ethmoid sinus. Thickening and lateral displacement of medial rectus was observed in cases of the present study. Intra and extraconal spaces were showed T2/STIR (Short Tau Inversion Recovery) hyper intensities with postcontrast enhancement representing cellulitis. Involved optic nerve was thickened with prominent perioptic space [Table/Fig-1,5].

Intracranial extension: From the PNS, mucor fungi often invade the orbit and progress posteriorly into the cavernous sinus. In 22 patients (23.65%), the cavernous sinus was distended and showed no elevation on postcontrast, indicating thrombosis. ICA narrowing was found in 7 (7.53%) of the individuals in the present study. Due to the sporadic blood supply in watershed territory, there were tiny infarcts

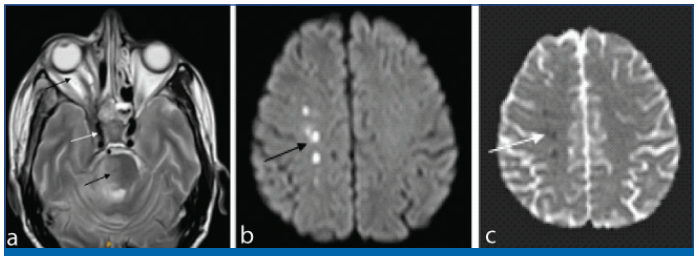


[Table/Fig-4]: a) T1weighted axial images showing hypointense complete opacification of right maxillary sinus (single black arrow) and hypointense mucosal thickening of left maxillary sinus (single white arrow). Bilateral turbinate are bulky and hypointense (double black arrow). Hypointense area noted in right infratemporal fossa (black bent arrow); b) T2weighted axial; c) T2 weighted coronal images respectively shows hypointense mucosal thickening in bilateral maxillary sinus (single white arrow). Bilateral inferior turbinate are bulky and hypointense (double black arrow). Hypointense area noted in right infratemporal fossa (single black arrow); d) T1 weighted axial postcontrast images show no enhancement of fungal elements in the bilateral maxillary sinus (single white arrow). There is a fungal element involving right infratemporal fossa with erosions walls of right maxillary sinus (single black arrow).



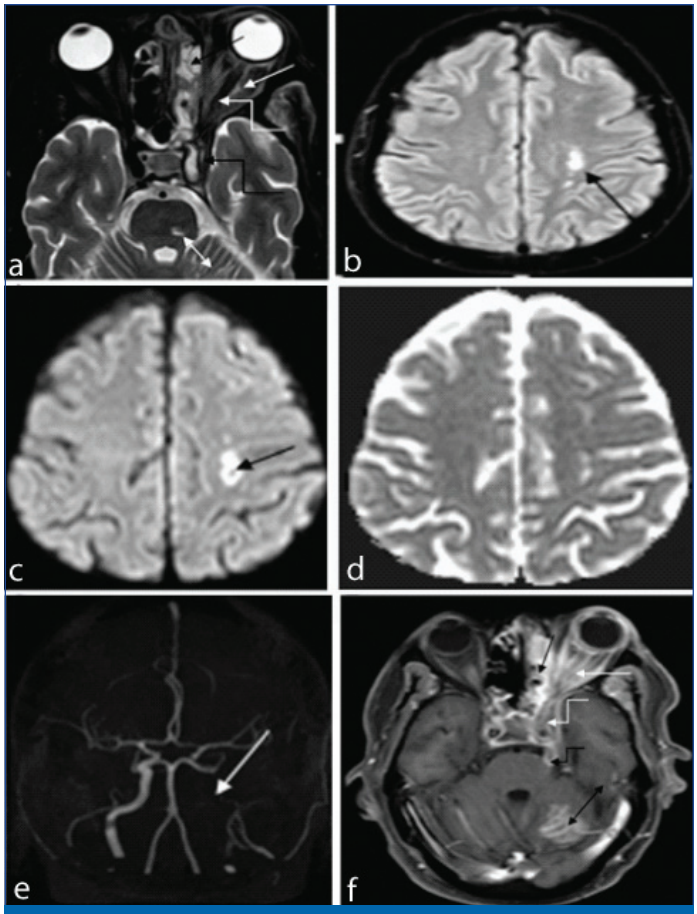
[Table/Fig-5]: T2/STIR (Short Tau Inversion Recovery) axial images show bulky intraocular muscles (single black arrow) with altered signal changes in the intra and extra conal space (single white arrow). There is thickened optic nerve (white bent arrow). Mild proptosis (black bent arrow).

in the watershed distribution with high parietal convexity. Absence of ICA flow voids was noted in the 5 (5.38%) cases indicating arterial occlusion secondary to invasion by fungus [Table/Fig-3,6,7].



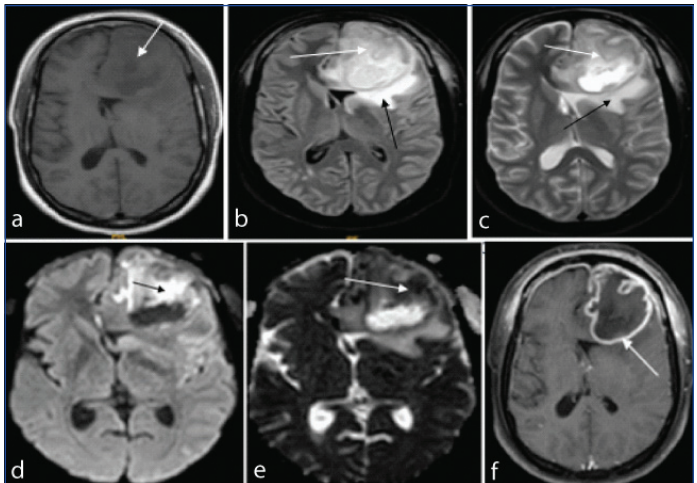
[Table/Fig-6]: a) T2 weighted axial image shows narrowing of right ICA (single white arrow) with hyperintense signal changes in the orbit and pons (single black arrow); b) DWI (single black arrow) & c) ADC (single white arrow) images at the level of the centrum semi ovale demonstrate reduced signal intensity on ADC (and corresponding increased signal intensity on DWI indicating small infarcts in the watershed distribution in parietal convexity due to the tenuous blood supply at watershed territory. (Due to narrowing of ICA in cavernous sinus).

Brain parenchyma: Spread to the brain may occur via the orbital apex, perineural and the cribriform. In the present study, direct extension to frontal lobe via cribriform was seen. We observed perineural extension from the cavernous sinus to the pons along the right trigeminal nerve. In this study, 3 (3.22%) cases of cerebritis and 2 (2.15%) cases of cerebellitis were noted. In 6 cases (6.45%), the authors noticed well-formed peripherally enhancing brain abscess [Table/Fig-3]. Intracranial extension may be in the form of distal

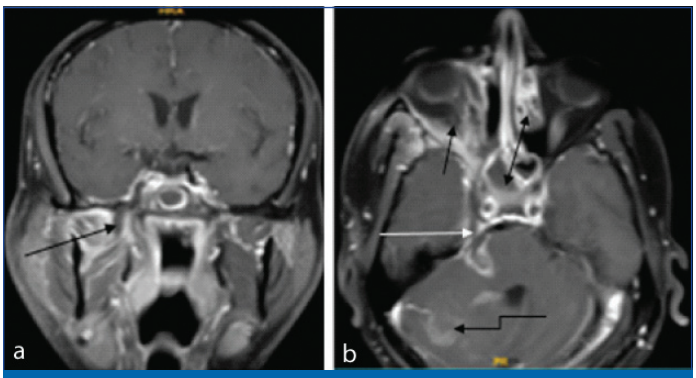


[Table/Fig-7]: a) T2weighted axial images demonstrating left ethmoid sinusitis (single black arrow), left orbital cellulitis (single white arrow) with thickening of optic nerve (white bent arrow), left cavernous thickened, absence of flow void in left Internal carotid artery (ICA) (black bent arrow)and hyperintense signals in the pons; b) Fluid-attenuated inversion recovery (FLAIR) axial image shows hyperintense area in the watershed distribution in left parietal convexity (single black arrow). c) Diffusion Weighted Imaging (DWI) & d) Apparent diffusion coefficient (ADC) axial images at the level of the centrum semiovale demonstrates pseudo normalisation on ADC and corresponding increased signal intensity on DWI (single black arrow), indicating Subacute infarct in the left parietal subcortical region; e) Time-of-flight Magnetic Resonance (MR) angiography shows occlusion of the left Internal Carotid Artery (ICA) (single white arrow); f) On postcontrast T1weighted images demonstrating left ethmoid fungal sinusitis (single black arrow), left orbital cellulitis (single white arrow) with thickening of optic nerve, left cavernous thrombosis (white bent arrow), non enhancing left ICA, thickened and enhancing left trigeminal nerve (black bent arrow) and left cerebellitis (double black arrow).

mycotic emboli were noted in cases of this study, without direct continuity of infection [Table/Fig-8].



[Table/Fig-8]: a) On T1 weighted image hypointense lesion noted in the left frontal region (single white arrow) with mass effect in the form of effacement of sulcal spaces and Ipsilateral ventricle and midline shift to right with subfalcine herniation; b & c) T2 & FLAIR axial MR images shows mixed intensity lesion in the left frontal region (single white arrow) with surrounding oedema (single black arrow). The lesion is causing significant mass effect in the form of effacement of sulcal spaces and ipsilateral ventricle and midline shift to right with subfalcine herniation; d & e) DWI (single black arrow) & ADC (single white arrow) images shows patchy areas of diffusion restriction; f) On postcontrast T1 weighted axial MR images shows peripheral enhacement (single white arrow)with central nonenhancing area.



[Table/Fig-9]: a) T1 weighted postcontrast coronal MRI images show thickened mandibular division of right trigeminal nerve (single black arrow) with widened foramen spinosum; b) On postcontrast T1weighted images demonstrating left ethmoid and sphenoidal sinus fungal sinusitis (double black arrow), right orbital cellulitis (single black arrow) with thickening of optic nerve, left cavernous thrombosis, non enhancing left ICA, thickened and enhancing right trigeminal nerve (single white arrow) and left cerebellitis (black bent arrow).

Perineural extension (Cranial Nerves): In total of 6 (6.45%) patients, there was thickened and enhancing maxillary division of the trigeminal nerve, thickened, and enhancing cavernous and cisternal portions of the trigeminal nerve [Table/Fig-3]. In few patients, the authors observed thickened, enhancing mandibular nerve and with widened foramen spinosum [Table/Fig-9].

Skull base involvement: The present study showed skull base involvement in 1 patient (1.07%).

DISCUSSION

Accurate and rapid diagnosis of fungal aetiology is the keystone of effective treatment [16,17]. Imaging aids in determining the extent of disease and detecting complications such as thrombosis, which are important for surgical planning [16,17]. The presence of angioinvasion and evidence of spread outside the sinus walls are the two most critical imaging characteristics that indicate a likely fungal aetiology. On contrast-enhanced MRI, the presence of necrosis in the affected structures can be clearly seen. It helps to see periantral and infratemporal fossa extension, orbital soft tissue involvement, and skull base invasion more clearly. Cavernous sinus involvement, vascular invasion, perineural dissemination, optic nerve infarction, and distinction of cerebral parenchymal invasion from infarction can all be detected using the extensive range of contrast mechanisms available on MRI [16,17]. In the present investigation, MRI of ROCM in post COVID-19 patients helped to visualise the disease's extent. In the present study, from the PNS fungal infection was seen extending to involve infratemporal and pterygopalatine fossa, orbit, cavernous sinus, ICA, cranial nerves, and brain parenchyma. Yousem DM et al., and McDevitt GR et al., concluded in their studies that MRI was highly useful in detection of complications like orbital cellulitis, cavernous sinus thrombosis and ICA thrombosis [11,18].

Most common sinus involved in the present study was ethmoid sinus followed by maxillary, sphenoid, and frontal sinus. Sharma RR et al., reported the involvement of the ethmoid sinus is the most commonly involved PNS (100%) among the included patients [4]. Another meta-analysis study found that the most prevalent symptom is PNS involvement, with the ethmoid sinus being the most commonly implicated sinus, trailed by the maxillary sinus.

The mucosa of PNS in all the cases was hypointense on T1W images. The mucosa was hypointense on T1W images in all cases and patchy hypointense areas in the hyperintense mucosa on the T2W images in most of cases. Rest of the cases mucosa was hyperintense on T2W images.T2W images showing the hypo to isointense components in thickened hyperintense mucosa in 77 cases (82.79%) represents the fungal infection. The variable signal intensity on the sinus contents was due to the iron and manganese contents in the fungal elements. In their investigation, Herrera DA et al., found that in T1-weighted imaging, the majority of the patients (80%) showed isointense lesions relative to the brain [12]. In T2-weighted images, signal intensity was more varied, with only 1 (1.07%) patient showing hyperintensity. The rest of the lesions were either hypointense or isointense in long retention time images. Shrestha DB et al., also described that mucosal thickening with hypointense components on T2W images was suspicious for fungal aetiology [16]. On the postcontrast mucosa showed heterogeneous enhancement and fungal balls were appeared as non enhancing areas in most of the cases. The observation was similar as in study by Taylor AM et al., and the enlarged mucosa and associated tissues are seen in Safder S et al., investigations describing postcontrast enhancement [19,20]. The "black turbinate sign" is defined as patches of non enhancing soft tissue within the afflicted turbinates and/or PNS [11,21].

Although, normal PNS are usually hypointense on all sequences, during the infection, mucor fungi often invade the orbit and progress posteriorly into the cavernous sinus from the PNS. Thrombosis of the cavernous sinus and cavernous carotid artery may then occur, and intracranial extension may be in the form of distal mycotic emboli or direct meningeal inflammation [13]. Extension beyond the sinuses is one of the most important indicators suggesting fungal aetiology. Orbit was the most common site of extrasinus involvement followed by the face [22]. Similarly, in this study, infection extended to the orbits in 62% cases through medial wall of ethmoid sinus. In a comparable study, Therakathu J et al., found that the orbit (76%) and face (57%) were the most prevalent sites of extrasinus involvement, followed by the orbital apex, masticator space, pterygopalatine fossa, bone, skull base, cavernous sinus, brain, and ICA [22]. Press GA et al., described from the PNS, mucor fungi often invade the orbit and progress posteriorly into the cavernous sinus [13]. Thrombosis of the cavernous sinus and cavernous carotid artery may then occur, and intracranial extension may be in the form of distal mycotic emboli or direct meningeal inflammation. According to Chan LL et al., in ROCM, thickening and lateral displacement of the medial rectus muscle are signs of orbital invasion from ethmoid sinus illness [14]. It's possible to notice a lack of elevation in the ICA, which is linked to vasculitis and thrombosis. Infarcts caused by arterial thrombosis, mycotic emboli, and frontal lobe abscesses are among the intracranial findings. Mc Lean FM et al., study showed that fungal hyphae tend to involve nerves and vessel wall leading to perineural spread and cavernous sinus invasion [23]. In patients of the present study, involvement of trigeminal nerve and perineural spread to the pons along trigeminal nerve were observed.

Skull base osteomyelitis and bony involvement is usually not present occurs last in the course of the disease [10,11]. This occurs due to the angioinvasiveness of the fungi and their susceptibility to extend into the soft tissues of the orbit and deep face and into the brain through vessels penetrating out of partitions in the skull base [14]. In the present study, skull base was involved in only in one case indicating the severity or later stage of the disease. In another similar study, five patients with acute mucormycosis developed chronic infection with bone involvement following the initial treatment [22].

Overall, the study states that MRI proved to be very useful in detection of extent of the disease and complications. However, the study has few potential limitations that need to be acknowledged. COVID-19 patients with high-risk features should be monitored carefully. Even with a slight suspicion of ROCM, clinicians should initiate early treatment with appropriate antifungal therapy need to be recommended. Diabetes and other any underlying risk factors should be treated at an earliest by clinicians to minimise patient's morbidity and mortality. Authors also recommend multi-centre studies with larger sample size to evaluate diagnostic potential of MRI.

Limitation(s)

First, it was a retrospective study with a limited number of patients and lacking control group. second, as the present analysis was retrospective, there were some differences in the imaging methodology utilised to evaluate suspected mucormycosis cases. The presence of metallic dental work and the presence of air within the sinuses alter the magnetic field, contributing to the artefacts in these areas. Finally, we needed follow-up data to evaluate whether the MRI anomalies were transient or not and their effects on visual acuity.

CONCLUSION(S)

In clinically suspected ROCM cases in post COVID-19 patients with typical imaging features like mucosal thickening with hypointense components on T2W images, demonstrating spread outside the sinus walls and the presence of angioinvasion, empirical antifungal medication can be initiated even before microbiology or histopathology confirms the causative organism which reduces patients morbidity and mortality. MRI helps to determine extent of the disease and complications. Finally, it guides the surgeon to decide about further line of management. Thus, MRI plays most important role in the management of patients with ROCM.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Radiodiagnosis, Belagavi Institute of Medical Sciences, Belagavi, Karanataka, India.
2. Senior Resident, Department of Radiodiagnosis, Belagavi Institute of Medical Sciences, Belagavi, Karanataka, India.
3. Professor and Head, Department of Radiodiagnosis, Belagavi Institute of Medical Sciences, Belagavi, Karanataka, India.
4. Senior Resident, Department of Radiodiagnosis, Belagavi Institute of Medical Sciences, Belagavi, Karanataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Siddappa Ramappa Shirahatti,
Assistant Professor, Department of Radiodiagnosis, Belagavi Institute of Medical Sciences, Belagavi, Karanataka, India.
E-mail: shirahattisiddu@gmail.com

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