RESEARCH

IMAGING SPECTRUM OF INTRACRANIAL MANIFESTATIONS OF COVID-19 ASSOCIATED RHINO-ORBITO-CEREBRAL MUCORMYCOSIS: A STUDY OF 35 PATIENTS

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Abstract

Background: The study seeks to show the radiological characteristics of Cov-ROCM, show the typical pathways by which the disease spreads to the orbital and intracranial compartment, and look for a correlation between risk variables and radiological disease severity. **Materials and Methods:** 35 patients who had COVID-19 infection in the past 3 months and were diagnosed with ROCM underwent CECT PNS examinations which were assessed by two experienced radiologists. They were divided into three groups based on the intraorbital and intracranial involvement and were correlated with various risk factors. **Result:** The total number of patients in our study is 35 with 25 males and 10 females(M>F, male: female ratio 2.5:1. The mean age is 50 years with a range of 29y-65yrs. Diabetes was the most common risk factor in our patients(31/35,88.5%) with 23 out of 31 diabetic patients having uncontrolled hyperglycemia (65% of total patients) and 4 patients having diabetic ketoacidosis (11.4%). History of corticosteroids usage iv/oral for an average of 7-14 days for treatment of covid-19 pneumonia was the next most common risk factor (23/35,65.7%). Of the 35 Patients, 29 Patients (82.8%) had atleast one or more of the following neurological symptoms like headache is the most common symptom (54.2%) and GTCS is the least common (2.8%). Among the patients with complete occlusion entire ICA was occluded in 3 cases whereas segmental occlusion was seen in 6 patients. Bony erosions of any potential route of spread to orbit or brain like lamina papyracea, cribriform plate, floor/roof of orbit, perpendicular plate of ethmoid or sinus walls was present in 16 patients (45%) whereas rarefaction with irregular lytic changes was noted in 9 patients (25.7%) most commonly involving structures of anterior skull base (5 cases) followed by middle cranial fossa (3 cases) with involvement of both anterior and middle cranial fossa in one patient. **Conclusion:** Neuroimaging plays a major role in patients with acute invasive sinusitis for early diagnosis and treatment which will improve the outcome in ROCM patients.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in December 2019. Since its first discovery it presented new challenges across the world. India hadreported the highest number of mucormycosis infections associated with COVID-19. This association has been documented in varioustcase reports/case series and institutional experiences.[1,2,3,4]

A significant fraction of COVID-19 patients currently experience respiratory problems, and the majority of them receive long-term mechanical ventilation, antibiotics, and steroids as part of the care strategy. It has been demonstrated that glucocorticoids lower mortality in hypoxemic COVID-19 patients.[5] However, use of systemic glucocorticoids can increase the risk of secondary fungal and bacterial infections. The immune dysregulation caused by the virus with synchronous use of immunomodulatory drugs further increase the

risk of secondary infections in COVID-19 patients.[6,7]

MATERIALS AND METHODS

This single centre cross-sectional study It included 35 patients. Medical records of all patients admitted with the following.

Inclusion Criteria

Patients with ROC mucormycosis diagnosed on CT, a history of COVID-19 verified by a positive SARS-CoV-2 RT-PCR in the last three months, and typical hyphae on KOH mount or histopathologically demonstrated for filamentous fungus of the family Mucoraceae.

Exclusion Criteria

Patients who are unwilling to give informed consent, under the age of 18, or taking immunosuppressants for purposes other than COVID-19 infection-related

The patients' demographic information, underlying comorbidities, and entire COVID-19 infection history were gathered. There have been reports of the KOH mount or Mucormycosis-specific culture growth employing necrosed tissue samples.

There was a normal and contrast-enhanced CT scan of the paranasal sinuses. From the vertex of the skull to the hyoid bone, the area was covered. As the disease is angioinvasive and can affect areas far from the affected paranasal sinuses, the brain and orbit were covered to look for any intraorbital or intracranial extension. Two Head and Neck Radiology experts who were blinded to earlier pictures and clinical data independently assessed each scan. Disagreements between readers were discussed in order to come to a consensus. FESS (Functional Endoscopic Sinus Surgery) findings and imaging findings of the nasal cavity, paranasal sinuses, bones, and pathways of spread were supported by each other. Additionally, MRI brain/orbits were performed to validate any subtle or inconclusive findings in the orbit and intracranial cavities.

Each scan was examined for soft tissue involvement and abnormal mucosal thickness in the paranasal sinuses and nasal cavity. After ruling out the likelihood of a hemorrhage, the presence of hyperdense contents (HU > 60), which are relatively specific for the presence of fungal elements, was noticed. Bony erosions were identified as an area of focus for discontinuities. We searched for subcutaneous tissue/fat stranding involvement in the premaxillary and preseptal regions. Particularly in the retroantral fat pad, regional expansions and fat stranding were observed in the suprahyoid neck space. With a focus on the extraocular muscles and the involvement of the orbital apex, the extraconal and intraconal compartments of the extraorbital extension of the soft tissue/fat stranding were assessed. Optic neuritis was seen as abnormal enhancement of the optic nerve or fat stranding around the optic nerve. Pachymeningeal and leptomeningeal involvement, cavernous sinus thrombosis, internal carotid artery thrombosis, infarct, hematoma, or intraparenchymal abscess were among the intracranial consequences described. The precise paths by which the illness moved to the orbits and cerebral cavities were noted. The disease was categorized as spreading through angioinvasion in situations where there was no bone erosion or direct aberrant soft tissue extension into the intraorbital and cerebral compartments. The path with the greatest amount of soft tissue was taken into account when there were numerous possible spread routes. In the study, aggressive Cov-ROCM was labeled whenever the intraorbital or cerebral compartments were involved.

To highlight crucial elements, the raw data was gathered, categorized, and presented in a tabular format. There were descriptive statistics applied, such as frequency, proportion, mean, and standard deviation.

RESULTS

The total number of patients in our study is 35 with 25 males and 10 females(M>F, male: female ratio 2.5:1. The mean age is 50 years with a range of 29y-65yrs. The mean duration of presentation with symptoms of ROCM after diagnosis of covid 19 infection was 30.5 days.

Table 1: Main Risk Factors in Patients of present study

Main Risk Factors in Patients	Number of patients	Percentage
Diabetes	31	88.5
Steroids	23	65.7
HTN	12	34
CKD	1	2.8
CAD	1	2.8

Diabetes was the most common risk factor in our patients (31/35,88.5%) with 23 out of 31 diabetic patients having uncontrolled hyperglycemia (65% of total patients) and 4 patients having diabetic ketoacidosis (11.4%).History of corticosteroids usage iv/oral for an average of 7-14 days for treatment of covid-19 pneumonia was the next most common risk factor (23/35,65.7%). All 35 patients have either diabetes melllitus or corticosteroid usage as a risk factor with 12 patients having history of only diabetes,4 patients having history of only steroids usage and 19 patients having both as risk factor.

Hypertension was present in 12 patients with no associated significant history of CAD except for 1 patient. 1 patient has chronic kidney disease and on dialysis. History of immunomodulatory drugs for treatment of covid 19 pneumonia could not be obtained due to inconsistent patient records. None of our patients had known history of malignancy or HIV or in on chemotherapy.

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Table 2: Chief complaints of the patients in present study

Chief Complaints	Number of patients	Percentage
Neurological		
Headache	19	54.2
Hemiplegia	12	34.2
Visual Problems	10	28.5
Facial Pain	10	28.5
7th Cranial Nerve Palsy	3	8.5
Altered Sensorium	2	5.7
GTCS	1	2.8
Non-Specific		
Fever	8	22.8
Cough	7	20
Nasal Discharge	3	8.5
Toothache	2	5.7

Of the 35 Patients,29 Patients(82.8%) had atleast one or more of the following neurological symptoms like headache ,hemiplegia, altered sensorium, facial pain, visual problems ,deviation of mouth with slurring of speech, while 6patients(17.1%) had only non specific symptoms like fever, cough, shortness of breath or nasal discharge. Headache is the most common symptom (54.2%) and GTCS is the least common (2.8%).

Table 3: Major Cerebral Imaging Findings of study

Major Cerebral Imaging Findings	Number of patients	Percentage
Vascular Invasion	14	40
Abcess	13	37.1
Acute Infarcts	11	31.4
Cerebritis	8	22.8
CSVT	7	20
Pachymeningeal Enhancement	6	17.1
Perineural Trigeminal Enhancement	2	5.7
Empyema	1	2.8

Of the 14 patients with evidence of vascular invasion 5 had complete luminal occlusion (Right ICA =3 and Left ICA=2), 5 had luminal narrowing only (Left ICA =3, Right MCA=1, Bilateral ICA=1) and 4 patients had both complete occlusion as well as narrowing in different segments of the same artery (Right ICA=3 ,Left ICA=1).Among the patients with complete occlusion entire ICA was occluded in 3 cases whereas segmental occlusion was seen in 6 patients. However narrowing was only segmental in all patients with narrowing. Overall petrous (12) and cavernous (12) were the most common segments of ICA involved in our study followed by supraclinoid (9) and cervical (9). Overall right side was more commonly involved than the left side.

Among the 13 patients with abscess, Basi-frontal lobe was the most commonly involved followed by anterior temporal (frontal =8, temporal=5).12 patients had involvement of either frontal or temporal lobe but one patient had abscess in both frontal and temporal lobe. Subdural empyema was seen in one patient.

Among 11 patients with acute infarcts frontal lobe followed by parietal lobe were the most common regions involved (frontal lobe =8, parietal lobe=7, temporal=4, occipital=3, centrum semi-ovale=4, corona radiata=3).Left side was involved more commonly than right side (left=6,right=5). MCA was the most common territory involved. Infarct with haemorrhagic transformation was seen in 3 patients out of 11 patients with infarcts.

Among 8 patients with cerebritis frontal lobe was most commonly involved (frontal lobe=6 temporal=1). Bilateral involvement was more common (bilateral=3 right=2 left=2). CSVT in the form of cavernous sinus thrombosis was observed in 7 patients. Out of 7 patients with CVST, 6 patients had simultaneous involvement of ICA either in the form of narrowing or occlusion. Pachymeningeal enhancement was seen in 6 patients most commonly along anterior temporal convexity (anterior temporal (4)>frontal (1)>parasellar (1)). Unilateral perineural enhancement along trigeminal nerve was seen in 3 patients(right=1 left=1),bilaterally was seen in one patient. 2 patients had nonspecific involvement of posterior fossa in the form of chronic infarcts in cerebellum.

Orbital involvement is recorded as present when there is either bulky extraoccular musculature with/without fat stranding, bulky optic nerve with/without perineural enhancement, soft tissue opacity in extraconal/intraconal compartment/orbital apex, subperiosteal abscess along the orbital walls. Thus 27 out of 35 patients (77.1%) had orbital involvement. In our study group bulky extraoccular musculature was the most common orbital finding (18/35) with medial rectus (14) being the most common extraoccular muscle affected. Unilateral involvement seen in 19 patients (right=12 left=7) and bilateral involvement seen in 8 cases. Superior ophthalmic vein thrombosis was observed in 17 patients (48.5%) and optic nerve was involved in 9 patients. Features suggestive of orbital compartment syndrome was seen in 4 patients (11.4%).12 cases (34.2%) had infective collection within any one of the orbital compartment, medial extraconal (7 cases) being the most common followed by superior extraconal (5 cases) and inferior extraconal (3).

Bony erosions of any potential route of spread to orbit or brain like lamina papyracea, cribriform plate, floor/roof of orbit, perpendicular plate of ethmoid or sinus walls was present in 16 patients (45%) whereas rarefaction with irregular lytic changes was noted in 9 patients (25.7%) most commonly involving structures of anterior skull base (5 cases) followed by middle cranial fossa (3 cases) with involvement of both anterior and middle cranial fossa in one patient.

Associated Pulmonary mucormycosis in the form of cavities/fungal ball is observed in 4 of our patients. All the patients are treated with iv liposomal amphotericin B 200 ml or iv/oral posaconazole 200 mg/100 mg in patients with poor renal function.

FESS with debridement with or without orbital exenteration was performed in 12 patients,

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craniotomy with abscess evacuation was performed in 3 patients and 9 patients underwent both FESS and craniotomy with abscess evacuation with or without orbital exenteration based on severity of disease.

Images in present study

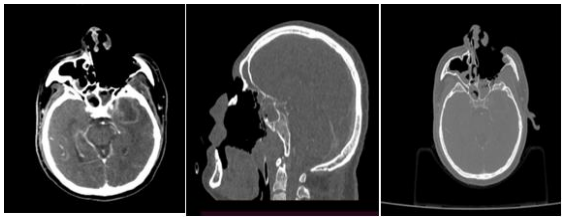

Figure 1: a) Abscess in Left Temporal Lobe B) Erosion of Superolateral Wall of Left Sphenoid Sinus C) Soft Tissue Opacification of Bilaeral Sphenoid and Right Maxillary Sinus

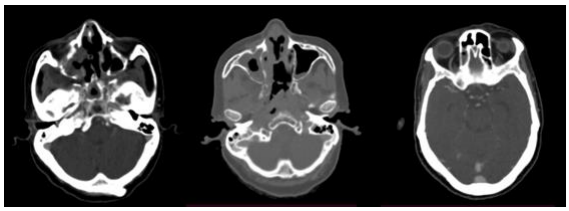

Figure 2: A) Non Opacification Of Right ICA B)Rarefaction And Erosions In MCF Structures C)Non opacification of Left SOV

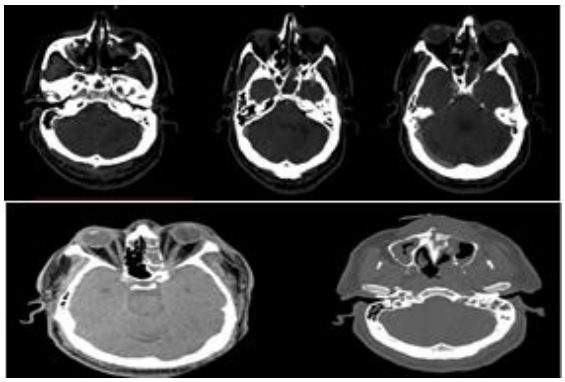

Figure 3: A) Narrowing Of Left Petrous, B) Cavernous ICA. C) Non opacification of Supraclinoid ICD, D)Bulky Left on With Perineural Dural Enhancement, E) Rarefaction And Lysis of Anterior Skull Base

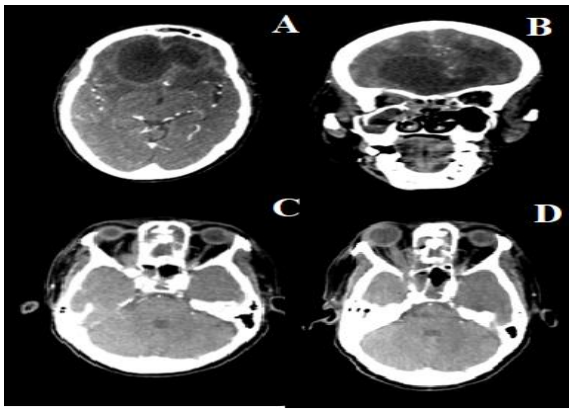

Figure 4: A,B)Bifrontal Abscess C)Right Subperiosteal Abscess, D)Axial Proptosis With Perineural Dural Enhancement

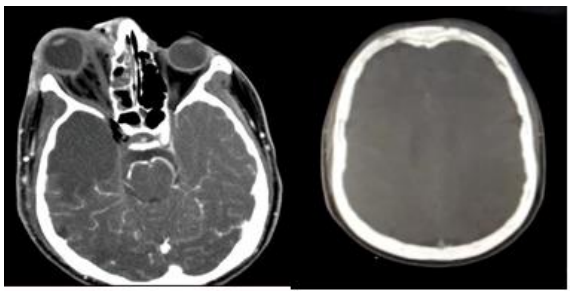

Figure 4: A, B) Subdural empyema with osteomyelitis of frontal bone

DISCUSSION

Fatality rate with mucormycosis is pretty high, especially with the intracranial involvement which can rise up to 90%.[8] Hence, early diagnosis is crucial especially considering the vast numbers of people effected. Our patients commonly presented with symptoms of headache, fever, facial pain with or without swelling, sinusitis, orbital cellulitis, decreased vision and cranial palsies. In general, visual loss with CSVT should prompt the diagnosis of rhinocerebral mucormycosis, as in bacterial cavernous sinus thrombosis visual loss is uncommon or late feature.[9]

Differential diagnosis to be considered when reporting cases of orbital cellulitis and sinusitis in patients with immunosuppression are other fungal infections, paranasal sinus malignancy, bacterial cellulitis, carotico-cavernous fistula and thrombosis, inflammatory pseudotumor and Graves' disease.[10] CT allowed to accurately define the extent of sinus involvement which is important to the surgeon since debridement is a crucial part of therapy. Mucor mycosis can spread via the posterolateral maxillary wall into the infratemporal fossa, pterygopalatine fossa, and pterygomaxillary fissure or may show intracranial extension through the cribriform plate into the frontal lobe via direct, perivascular and perineural channels or through the orbital apex into the cavernous sinus without radiologic evidence of bone destruction, thus it is important to view all these structures. Distal non-contiguous brain infarction or abscess formation signifies vascular fungal dissemination.

MR is superior where there is perineural infiltration involving skull base, cisterns, and brain stem.[11] MR is especially useful in patients with diabetic nephropathy undergoing treatment with nephrotoxic Amphotericin B in whom the use of CT contrast agents is relatively contraindicated.

Abscess and infarction were the two main intracranial manifestations of RCM in our patients both of which tended to occur only after extension into orbit or deep facial structures such as the infratemporal fossa, pterygopalatine fossa and pterygomaxillary fissure. Isolated CNS mucormycotic was not seen in any of our patients and is reported to occur more commonly in IV drug users.[12] Brain parenchyma at the base of the frontal and middle cranial fossae, ipsilateral to the

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initial diseased areas was involved with the frontal lobe being the most common site involved.

Intracerebral abscess was represented by masses with low attenuation values in a nonvascular distribution or a rim of spared cortex that may exhibit fluctuating peripheral enhancement and limited surrounding vasogenic edema. Mucormycosis need not have the characteristic well-defined ring enhancement seen with bacterial abscesses. This characteristic may be an indication of a host with a weak immune response to the fungi. Contrarily, infarcts without intracerebral abscess and without any indication of a spared cortex or vasogenic edema occurred in a vascular distribution. With CT, it was occasionally challenging to tell a bland infarct from an abscess. Only by carrying out successive CT scans to track the lesion's development could the difference between the two be distinguished. After a week, a growing mass impact that extends past a vascular Radiologically, the cavernous and petrous section of the internal carotid artery was where thrombosis and vascular invasion were most frequently found. In 2 instances, MRI showed a bulging of the cavernous sinus and a loss of the signal void of the cavernous ICA. These findings may indicate significant ICA stenosis or thrombophlebitis with blockage.

Despite internal carotid artery occlusion, there were no radiological symptoms of stroke in one of our instances. This might be accounted for by the circle of willis's efficient collateral blood supply.

The patient has a higher chance of developing an intracranial condition if the orbit and deep paranasal tissues are involved. This should provoke a thorough examination of the cerebellum, cavernous sinus, and brain's base. In some circumstances, thin CT sections and direct CT coronal scans may be helpful to further record the extent of the disease. The intervals between CT scans to track disease expansion and treatment response should be brief due to this disease's quick natural course.

In general, every patient should undergo an unenhanced CT scan with soft and bone algorithm reconstruction to determine the true extent of paranasal sinus inflammation, and every patient with a confirmed ROCM infection should undergo an MRI to more clearly define orbital invasion and intracranial infection.

A previously recognized CT-specific symptom for orbital apex involvement by mucormycosis is an enlargement of the superior ophthalmic vein with no clear contrast enhancement and the nonenhancement of the superior ophthalmic artery. It is possible that the ethmoid sinuses directly caused extraconal infection, subperiosteal abscess, and concurrent involvement of the orbital musculature. 4 of the 27 patients who had orbital involvement throughout the study's time frame subsequently underwent orbital exenteration. Similar imaging characteristics, presentation, and risk factors apply to angioinvasive aspergillosis.[13] Because of this, the only way to distinguish between the two is by histopathology, where the hyphae of Aspergillus display regular branching at acute angles and those of Mucor display irregular branching at angles of 90° or more. In general, delayed therapy, cerebral expansion, palatal, and orbital involvement are signs of poor prognosis in ROCM. Antifungal medications administered intravenously, such as amphotericin, anti-oedema measures, and surgical debridement of the necrotic tissue until normal perfused healthy tissue is visible are all part of the treatment for rhinocerebral mucormycosis.

CONCLUSION

Our study highlights the common imaging findings, life threatening cerebrovascular complications of COVID-19 associated ROCM during COVID-19 pandemic. Neuroimaging plays a major role in patients with acute invasive sinusitis for early diagnosis and treatment which will improve the outcome in ROCM patients.

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