Annals of Clinical Case Reports

Research Article
Published: 07 Jun, 2022

Spectrum of Imaging Findings of Rhino-Orbital-Cerebral Mucormycosis during COVID-19 Pandemic: A Case Series Study

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Abstract

Purpose: Imaging study on Rhino-Orbital-Cerebral Mucormycosis (ROCM) in post COVID-19 patients with combined Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) studies.

Materials and Methods: A retrospective study of 17 patients who developed ROCM in post COVID-19 infection treated with steroids, Remdesivir or oxygen for the spectrum of imaging studies was conducted.

Several clinical parameters *viz*., RTPCR status, clinical history, diabetic and vaccination status and analysis by combined CT and MR imaging was carried to outline the fungal disease. ROCM was confirmed by either KOH mount or histopathological investigations followed by Amphotericin B and Functional Endoscopic Sinus Surgery (FESS).

Results: In a survey of 17 patients aged 35 to 65 years, men (76.47%) were more affected than women (23.53%). CT and MRI showed involvement of the bilateral paranasal sinuses in all patients (100%), and the major involvement of the ethmoid sinuses in 76.47% of patients and the maxillary sinuses in 94.11% of patents. The incidence of disease to orbit was 58.82%, with right and left involvement at 5.88% and 52.94%, respectively. Both orbital extensions were seen at 5.88% and optic nerve involvement at 23.529%. Cavernous sinus disease, meningeal association and brain parenchymal extension were observed in 11.764%, 58.823% and 5.882%, respectively.

Conclusion: Clinicians and practitioners should be aware of the possibility of ROCM after COVID-19 infection and the combined use of CT and MR imaging. Identifying the disease in the early stages through CT and MRI imaging plays an important role in effective treatment.

Keywords: Rhino-orbital-cerebral mucormycosis; COVID-19: Computed tomography: Magnetic resonance imaging

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Received Date: *05 May 2022*
Accepted Date: *24 May 2022*
Published Date: *07 Jun 2022*

Citation:
Byale M, Pattanshetti R. Spectrum of Imaging Findings of Rhino-Orbital-Cerebral Mucormycosis during COVID-19 Pandemic: A Case Series Study. Ann Clin Case Rep. 2022; 7: 2211.

ISSN: 2474-1655

Introduction

COVID-19 (Coronavirus Disease 2019) is an infectious disease that is caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) and leads to acute respiratory syndrome and was declared a pandemic by the World Health Organization (WHO) in March 2020 [1]. It has now spread all over the world and causes presentations of life-threatening diseases. The widespread use of steroids and antibiotics, especially in those with immunocompromised and diabetic states, has led to an increase in new or existing fungal diseases [2]. Rhino-Orbital-Cerebral Mucormycosis (ROCM) caused by angio-invasive saprophytic organisms, a class of phycomycetes, is additional threat as opportunistic fungi and the COVID-19 disease spectrum [3]. Early detection and intervention are necessary to prevent disease transmission and death. There are several reports on the role of magnetic resonance imaging in Coronavirus-2019 Associated Rhino-Orbital-Cerebral Mucormycosis (CA-ROCM) with different clinical backgrounds [4,5]. For successful treatment, early diagnosis and elucidation of key structures should be diligently investigated by combined Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) gadolinium contrast, which plays an important role in detecting nasal, orbital, and intracranial extension. In this study, we report the imaging findings of 17 patients with post-COVID-19 condition, who were treated with steroids, Remdesivir or oxygen, have been confirmed as ROCM with KOH mount or other histopathological investigations. Final observations are based on the total amount recovered after amphotericin B administration followed by FESS.

Materials and Methods

Patient population

In a prospective case study, a series of 17 patients with past history of COVID-19 and suspected to have ROCM underwent combined CT and contrast enhanced MRI and confirmed with KOH mount or histopathological investigations during March-May 2021. Patients with reduced Glomerular Filtration Rate (GFR), raised creatinine values (more than 2 mg/dL) and raised BUN (Blood urea nitrogen) levels (more than 30 mg/dL) and MRI incompatible metallic implants were not included in this study.

Data acquisition

All patients underwent CT imaging using a Siemens Emoticon 16 slice multi-detector scanner with image reconstruction in soft-tissue and bone windows. All patients underwent gadolinium contrast enhanced MR imaging using a Philips 1.5 T machine. Unenhanced axial and coronal T1, T2, Short Tau Inversion Recovery (STIR) as well as sagittal T2 images and Diffusion-Weighted Images (DWI) were obtained. Contrast enhanced sequences such as T1 multiplanar DIXON was obtained. Ethical and informed consents were not required as the images were anonymous.

Results

In this retrospective survey of 17 patients aged 35 to 65 years, 76.47% with men (n=13) were more affected than women (n=4) with 23.529%. Patients with diabetes (n=14) were 82.23% and those without diabetes (n=1) were 5.88%. Symptoms of ROCM after COVID19 illness ranged from 1 to 3 months. Steroids were given in 76.47% (n=13) of cases, and (n = 4) 23.529% were given Remdesivir. 64.705% of patients (n=11) required oxygen for their COVID-19 disease. CT and MRI of 17 patients observed bilateral paranasal sinus involvement (100%). The predominant involvement of the ethmoid sinuses was in 76.47% (n=13) and the maxillary sinuses 94.11% (n=16). CT Plain study shows hypodense diffuse mucosal thickening involving the paranasal sinuses and nasal cavities along the turbinate's with combined bony erosions involving the medial wall of the orbit, the ethmoid trabeculae and the bony nasal septum (Figure 1).

Disease extension into orbit was observed (n=10) with 58.82% of the right side (n=1) 5.88% and the left side (n=9) 52.94%. Bilateral orbital and optic nerve involvement were found in (n=1) 5.88% of patients and (n=4) 23.52% of patients, respectively.

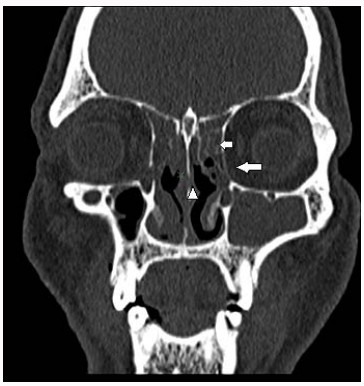

Figure 1: Coronal CT section in bone window shows lytic erosions of medial wall of left orbit (long arrow) with intra-orbital extension of contents. There were also erosions of ethmoid trabeculae (short arrow) and bony nasal septum (arrow head).

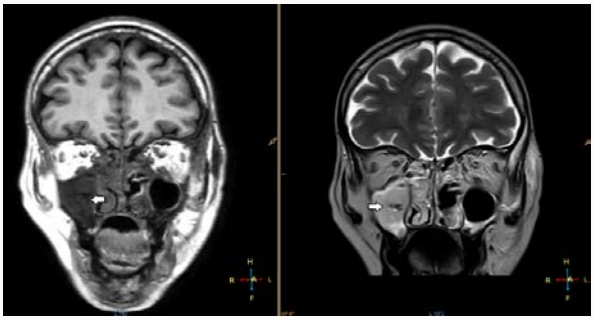

Figure 2: Coronal T1WI (on left) shows hypointense and T2WI (on right) hyperintense fungal elements in right maxillary sinus.

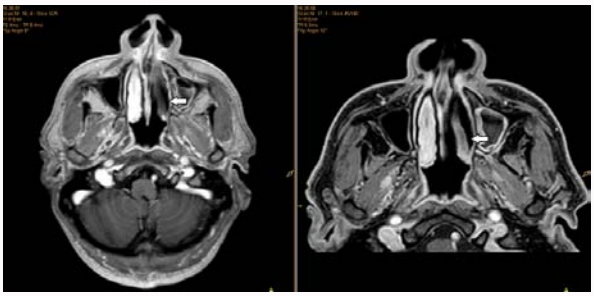

Figure 3: Axial T1 contrast (a) and T1 fat suppressed post contrast image (b) showing no significant enhancement of left inferior turbinate (arrow) giving the classical black turbinate appearance.

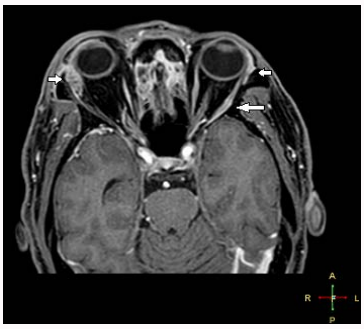

Figure 4: Axial T1 weighted Fat Suppressed Post Contrast image (FSPC) showing fungal elements within orbit (short arrows) and bulky left lateral rectus (long arrow).

Cavernous sinus disease (n=2) was observed in 11.764%, (n=10) meningeal involvement was observed in 58.823%, and (n=1) cerebral extension was observed in 5.882% of patients. No significant perineural disease was transmitted through the trigeminal nerve and other nerves.

CT showed bone erosions in (n=13), 76.47 % and adjacent soft tissue thickening with features of cellulitis as cardinal findings in most of the cases.

MRI showed T1 hypointense and T2 hyperintense signals with contiguous foci of non-enhancing necrotic mucosa giving the appearance of Black Turbinate sign in nasal cavity in many of the cases (n=6) 35.23%. MRI is the imaging of choice to assess intraorbital and parenchymal expansion of the brain. Mucosal involvement of the paranasal sinuses shows T1 hyperintense and T2 hyperintense signal intensity. This indicates the fungal elements as shown in Figure 2. The 'black turbinate' sign refers to the non-enhanced pattern of nasal

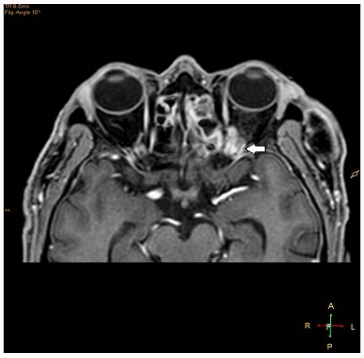

Figure 5: Axial T1 weighted (FSPC) image showing perineural enhancement of retro orbital and peri orbital segments of left optic nerve (arrow) with surrounding fat stranding and enhancing soft tissue causing crowding at orbital apex.

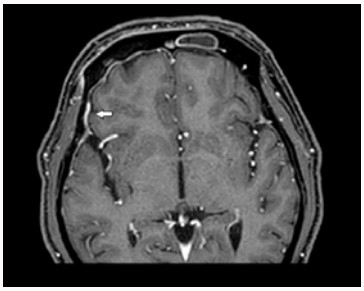

Figure 6: Axial T1 weighted (FSPC) image showing abnormal thickened meningeal enhancement in right fronto-temporal region (arrow).

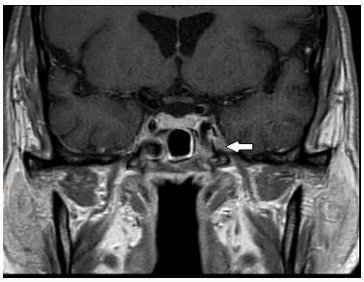

Figure 7: Axial T1 weighted (FSPC) image showing extension into left cavernous sinus (arrow).

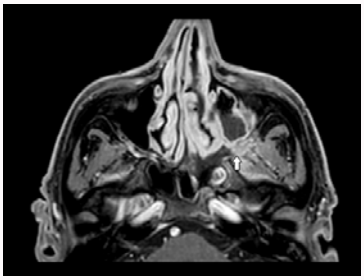

Figure 8: Axial T1 weighted (FSPC) image showing disease extension into left pterygopalatine fossa, sphenopalatine fossa and causing pterygomaxillary fissure widening.

turbinate's due to the combination of necrosis and fungal factors as shown in Figure 3.

The orbital involvement shows heterogeneously enhancing soft tissue within the medial wall, the floor, apex or roof based on the sinus

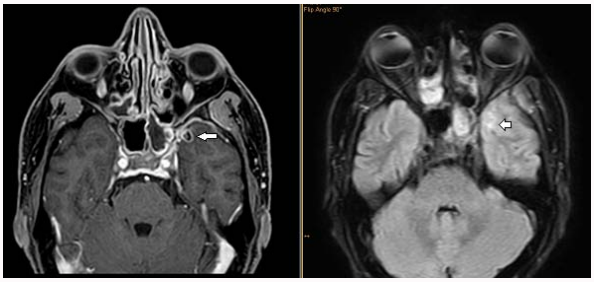

Figure 9: Axial T1 weighted (FSPC) image showing left infratemporal abscess formation (long arrow) (a) and surrounding edema appearing FLAIR hyperintense (short arrow) (b).

area involved (Figure 4) shows fungal elements and bulging lateral rectus muscle, while enhancement of the optic nerve sheath was also observed (Figure 5). Meningeal enhancement in the basi-frontal and frontotemporal regions is an indicator of the parenchymal expansion of the brain as illustrated in Figure 6. The asymmetric bulge may extend to the cavernous sinus, as shown in Figure 7. Extension to the pterygopalatine or sphenopalatine fossa occurs from the nasal cavity or orbits, as seen in Figure 8 as variable enhancing signals. As the disease progresses intracranially, it can lead to cerebritis and cerebral abscess formation, which appears as a ring enhancing lesion as shown in Figure 9.

Discussion

Fungi belong to mycology subgroup of microbiology. Morphologically fungi can be yeasts, moulds and dimorphic fungi that exist in both mould and yeast form. *Candida* and *Aspergillus* species are most commonly encountered fungal species in medical practice [3]. Fungi, which were rarely encountered with invasive potential, belong to Zygomycota order (*Mucor*, *Rhizopus*, *Apophysomyces*, *Rhizomucor* species [3]. Immunocompromised individuals are the most susceptible group for these fungi, for example Mucormycosis which belong to the group of moulds called Mucormycetes affecting mostly the sinuses or the lungs after inhaling fungal spores in air. Types include Rhinocerebral (sinus and brain) mucormycosis, Pulmonary (lung) mucormycosis, gastrointestinal mucormycosis, Cutaneous (skin) mucormycosis, and disseminated mucormycosis. There is a wide variety of spectrum of fungal Paranasal sinuses infections. Hora et al. [6] described two broad categories. These were invasive or non-invasive, based on potential of fungal hypha to invade the tissues through the epithelium (invasive) in comparison to the infection being limited to the superficial epithelium (non-invasive) [6-9]. Invasive fungal sinusitis is further divided into acute and chronic invasive Fungal Rhinosinusitis (FRS) and chronic granulomatous invasive fungal rhinosinusitis. Non-invasive fungal sinusitis was further divided into saprophytic fungal infestation, fungal ball and allergic fungal rhinosinusitis. Acute Invasive Fungal Rhinosinusitis (AIFR) is important as it shows aggressive course with high mortality rates (around 50% but can be as much as 80%) [10,11]. AIFR primarily invades neural and vascular structures (rather than mere mucosal colonization) in comparison to other non-invasive forms. Fungal spores after inhalation (due to poor immunological response) grows on the mucosal lining and invades adjacent neurovascular structures [12,13]. Further, it causes thrombosis with local or distant ischemia and necrosis. Commonly, it spreads outside the infected sinus cavity into surrounding tissues and bone. Causative organisms of AIFR include: *Aspergillus* species and Zygomycetes order. AIFR was most

commonly observed in immunocompromised patients, patients with hematological malignancies, those who have undergone bone marrow or solid organ transplantation, people with Diabetes Mellitus (DM) and in chemotherapy induced neutropenia [14,15].

India has highest prevalence rates of type 2 DM (8.9 % of adults). Poorly controlled diabetic patients were frequently associated with diabetic ketoacidosis. Zygomyecetes order was isolated in this subgroup of patients due to their affinity for acidotic environments with high glucose concentrations [12]. Although neutropenia, hematological malignancies, HIV/AIDS show strong association with AIFR, and most of them are associated with hematological malignancy [16,17]. *Aspergillus* species has been isolated in this subgroup and also having high iron levels, after receiving deferoxamine for iron chelation or in renal failure. The mechanism behind this was that some fungi (*Rhizopus*) can utilize deferoxamine for their growth [15]. AIFR in post COVID-19 patients appear to be multifactorial which includes uncontrolled DM (especially with diabetic ketoacidosis) [18], immunosuppressive therapy and immune alterations by COVID-19 infection [19]. Patients with COVID-19 infection have increased production of cytokines and cell mediated immunity with reduced cluster of differentiation (CD4+ T) and CD8+ T cell counts resulting in increased susceptibility to fungal infections [20,21]. Opportunistic fungal infections also occur with steroid overuse in treatment of COVID-19 which lowers overall immunity and increases blood sugar levels [22]. Patients with AIFR can present with paranasal sinusitis, facial edema and erythema, proptosis, headaches, double/loss of vision and other neurological deficit (brain parenchymal or meningeal involvement). Nerve deficits (CN III, IV and VI) can indicate the involvement of cavernous sinus [12]. Mehta and Pande et al. [23] reported a case study of a patient with COVID-19 infection, during the course of the treatment, developed rhino-orbital mucormycosis. Further, these authors 23 confirmed soft tissue swelling in the right preseptal, malar, and premaxillary and retrobulbar regions with paranasal sinusitis by MRI of brain, orbits and paranasal sinusitis. They confirmed mucormycosis by the presence of fungal hypha which lines with the present study. Blood stream Candida infections were reported amongst the COVID-19 patients in New Delhi, India [24]. White et al. [25] have reported invasive fungal infection that had the highest mortality rate amongst COVID-19 patients. Steroid therapy and chronic respiratory infections could be the reasons found for high risk of invasive fungal diseases [25]. Similar reports were also observed in Pakistan and Italy [26,27]. It was reported that an MRI of the brain was shown to contain multiple areas of infarction and ischemia in a case of invasive fungal disease in a female having diabetic ketosis with COVID-19 infection [28]. Mucor was identified from nasal biopsy. Early identification of fungal infections may reduce severity of the disease. Confirmative diagnosis carried by histopathological evidence of fungal elements. KOH of the soft tissue also aids in diagnosis.

Conclusion

The combined use of CT and MRI imaging illustrates unique findings, with bone erosions and mucosal thickening of the paranasal sinuses with invasion into the orbits, cavernous sinus and meningeal structures. Early diagnosis and identification of the disease can help in early interventions and a good prognosis plays an important role in the outcome.

Acknowledgement

The authors acknowledge S. Nijalingappa, Reasearch Institute, Bagalkot, and Karnataka, India for their support during this study.

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