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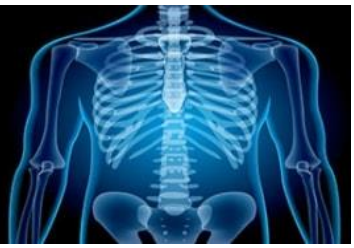

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Spectrum of invasive Rhino-orbito-cerebral mucormycosis in patients with COVID 19 infection: A new challenge

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Abstract
Introduction: COVID-19 is known to be associated with superimposed viral, fungal, and bacterial co-infections. However Sinonasal mucormycosis is an uncommon entity but there is significant rise in the incidence in patients with COVID-19 pneumonia mainly due to prolonged hospital stay and immunocompromised status of the patients. These infections are highly invasive nature and tend to be locally aggressive in nature involving orbits and/or intracranial structures.
Case Series: We describe the imaging findings in 5 cases of rhino/sino-orbital mucormycosis in patients with history of COVID-19. All cases had varying involvement of paranasal sinuses extending into the orbital compartment and some demonstrating intracranial extension of infection.
Conclusions: Rhino/Sino-orbital mucormycosis can have aggressive necrosis of the involved paranasal sinuses and orbits with or without cerebral extension. Hence, the correct imaging diagnosis is imperative as prompt antifungal drugs and surgical debridement can significantly reduce mortality and morbidity.

Keywords: COVID-19 infection, coronavirus 2(SARS-CoV-2), Rhino-orbital-cerebral mucormycosis, MRI scan paranasal sinuses, fungal sinusitis

Introduction

The novel 2019 corona virus disease is a viral infection caused by severe acute respiratory coronavirus 2(SARS-CoV-2) [1]. The current outbreak was officially recognized as a pandemic by World Health Organization on March 2020 and since then there have been over 515 million confirmed cases globally. COVID-19 infection primarily affects respiratory system manifested in the form of mild to severe pneumonia [2]. Several less virulent variants of the virus are still emerging.

Corona virus associated mucormycosis is a well-established due to sharp upsurge in number of cases of mucormycosis in survivors of COVID-19 infections in most part of the world, many of who were treated with systemic steroids. Early diagnosis and treatment can be lifesaving as the disease has shown extensive rhino/ sino-orbital involvement and poor prognosis if left untreated.

Magnetic resonance imaging remains the corner stone for management in patient with RCOM (Rhino-orbital-cerebral mucormycosis).

Mucormycosis is a severe opportunistic fungal infection resulting from a fungus of the order Mucorales [3]. India is currently facing a huge surge in the number of Coronavirus disease (COVID-19)-associated mucormycosis [4]. This fungal infection rapidly progress in individuals who are immunologically or metabolically compromised such as patients who have developed COVID-19 infection [5]. Early suspicion, rapid diagnosis, and initiation of treatment are the most important factors that determine prognosis in the management of mucormycosis.

The infection is centered in the paranasal sinuses and may extend into the orbits and cerebral parenchyma [6]. Uncontrolled diabetes mellitus and the use of corticosteroids for the treatment of respiratory symptoms are possible etiological factors. Mucormycosis can be life threatening as it has a high mortality rate of over 50% [7].

Imaging forms the cornerstone of management in patients with rhino-orbital-cerebral mucormycosis (ROCM). In patients where biopsy is planned, imaging can be used to help guide the site for biopsy to ensure maximum diagnostic yield.

This case series discusses the utility of MRI imaging in ROCM with an emphasis on classical imaging features of ROCM, the pathways of spread of infection, MRI for prognostication, MRI.

We present the imaging findings in 4 cases of rhino-orbital mucormycosis co-infections in COVID-19 patients. Contrast-enhanced MRI (CE-MRI) protocol of the paranasal sinuses, brain, and orbits included axial T1, T2, T2 FLAIR, GRE, DWI, T2 FS, T1 FS post-contrast (3 mm thickness), sagittal T2, T1 FS post-contrast (3 mm thickness), coronal T2, and T1 FS post-contrast (3 mm thickness) sequences. High-resolution CT thorax (HRCT thorax) of all the cases were done using 16 slice multidetector CT machine using thin sections (1 mm slice thickness). Histopathological evaluation of nasal discharge of all 4 cases was done on potassium hydroxide (KOH) wet mount and further confirmed on culture using lactophenol cotton blue (LPCB) stain. Final diagnosis of mucormycosis was made based on clinical details, imaging findings, and histopathology.

Case Series

Case 1

A 30 years old male patient presented with severe respiratory distress, fever and non-productive cough for duration 5 days. COVID-19 RT-PCR test done on nasopharyngeal swab was positive.

HRCT thorax was requested to access the severity and revealed multiple peripherally located ground glass opacities with superimposed interlobular septal thickening in bilateral predominantly involving lower lung fields CORADS 6 with CT severity score of 16/25.

After a week of hospitalization and following medial management patient showed features of recovery from COVID-19 clinical symptoms. However in due course, the patient developed nasal obstruction, swelling and complained of pain over the left maxillary region and left orbital region. He also complained aphasia, hemiparesis of left upper and lower limbs.

CE-MRI of paranasal sinuses, orbits and brain revealed soft tissue intensity area opacifying and causing expansion of the left maxillary sinus cavity, eliciting non-homogenous moderately high signal intensity on T2 and isointensity signal on T1 weighted images. In post contrast images there heterogeneous enhancement and patchy area of diffusion restriction is visualized with circumferential mucosal thickening with dependent fluid level in the left maxillary sinus.

The soft tissue component is causing expansion of the walls of the left maxillary sinus, eroding parts of the anterior and posterior lateral wall and associated lytic changes in the bone through which the lesion is extending to the deep facial planes. Superiorly it is extending to the left nasal cavity through maxillary ostium and in to the left ethmoid and frontal sinuses.

Mucosa overlying the left maxillary sinus is devascularised. Superiorly soft tissue is extending to the left orbit and periorbital area and orbital apex and infiltrating intraconal and muscular space infiltrating ocular muscles. Infiltration and occlusion of left ophthalmic vein is visualized.

Multifocal subtle ill-defined areas of T2 and T2 FLAIR hyper intensity are seen involving white matter of left medial temporal lobe, high parietal, occipital, centrum semi-ovale and frontal lobe with diffusion restriction and low ADC values and is consistent with multifocal acute infarcts.

Parasulcal space in the left high parietal lobe is prominent and focal dural thickening and minimal enhancement accompanied with surrounding edema and diffusion restriction and might suggest meningitis.

Histopathological evaluation of nasal discharge revealed broad aseptate ribbon-like fungal hyphae on KOH wet mount. Lactophenol cotton blue satin on sabouraud dextrose agar revealed broad aseptate ribbon like hyphae with sporangium

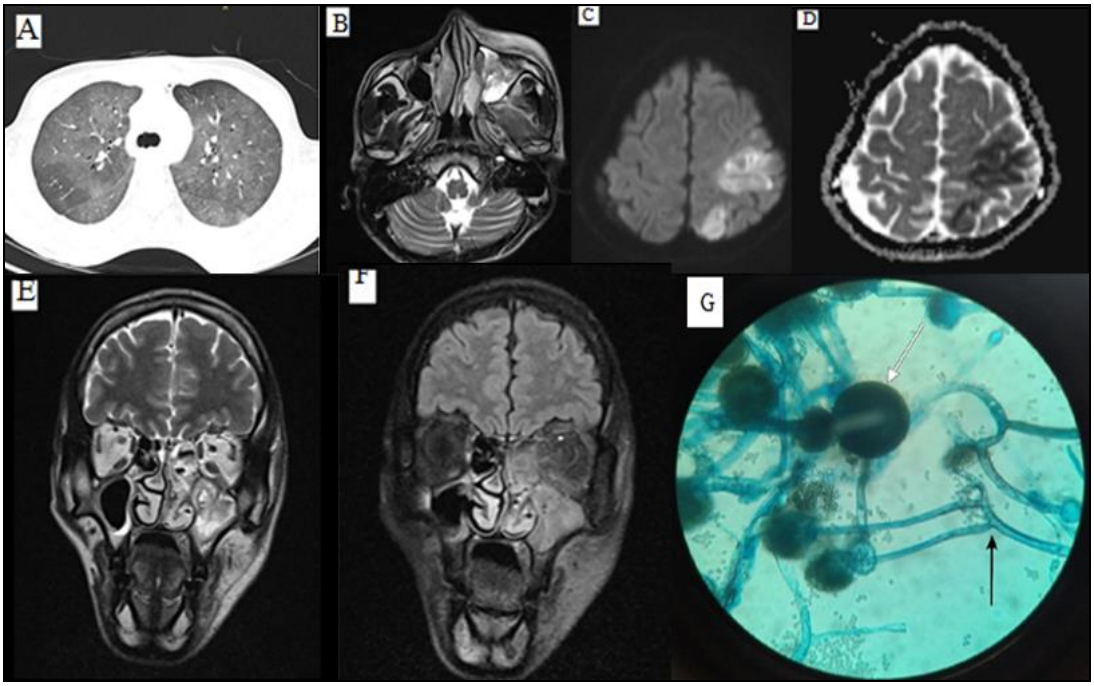

Fig 1: 30 years old male patient presented with severe respiratory distress. (A) Computed tomography of chest axial section shows ground glass attenuation in bilateral lung fields. (B&E) Axial and coronal T2 at the level of PNS shows gross mucosal thickening with intermediate signal intensity lesion in the left maxillary sinus with intraorbital and soft tissue (C & D) Axial diffusion weighted and corresponding ADC images suggest acute infarct in left high parietal lobe. (E) Post contrast T1 coronal images locally aggressive mild to moderate enhancing lesion in left maxillary sinus. (G) Lactophenol cotton blue (LCB) mount showed nonseptate hyphae.

Case 2

A 29 years old male patient presented with fever, right sided nasal obstruction and intermittent cough for 1 week. COVID-19 RT-PCR test using nasopharyngeal swab showed positive result.

HRCT thorax was requested and revealed multiple areas of ground glass opacities with superimposed interlobular septal thickening in bilateral predominantly involving lower lung fields and multiple thin walled cavitatory lesions CORADS 6 with CT severity score of 11/25.

CE-MRI of paranasal sinuses and orbits and brain revealed a lobulated soft tissue lesion demonstrating low signal intensity in the right ethmoid sinus. On T2 Weighted images the lesion appears iso intense and showing insignificant contrast enhancement. This lesion is causing mild expansion of the right posterior ethmoid sinus and causing lateral bulging of the medial wall of right orbit. However there is no obvious intraorbital extension. Mucosal thickening of bilateral sphenoid sinuses is visualized.

Histopathological evaluation of nasal discharge revealed broad aseptate ribbon-like fungal hyphae on KOH wet mount. Lactophenol cotton blue satin on sabouraud dextrose agar revealed broad aseptate ribbon like hyphae with sporangium.

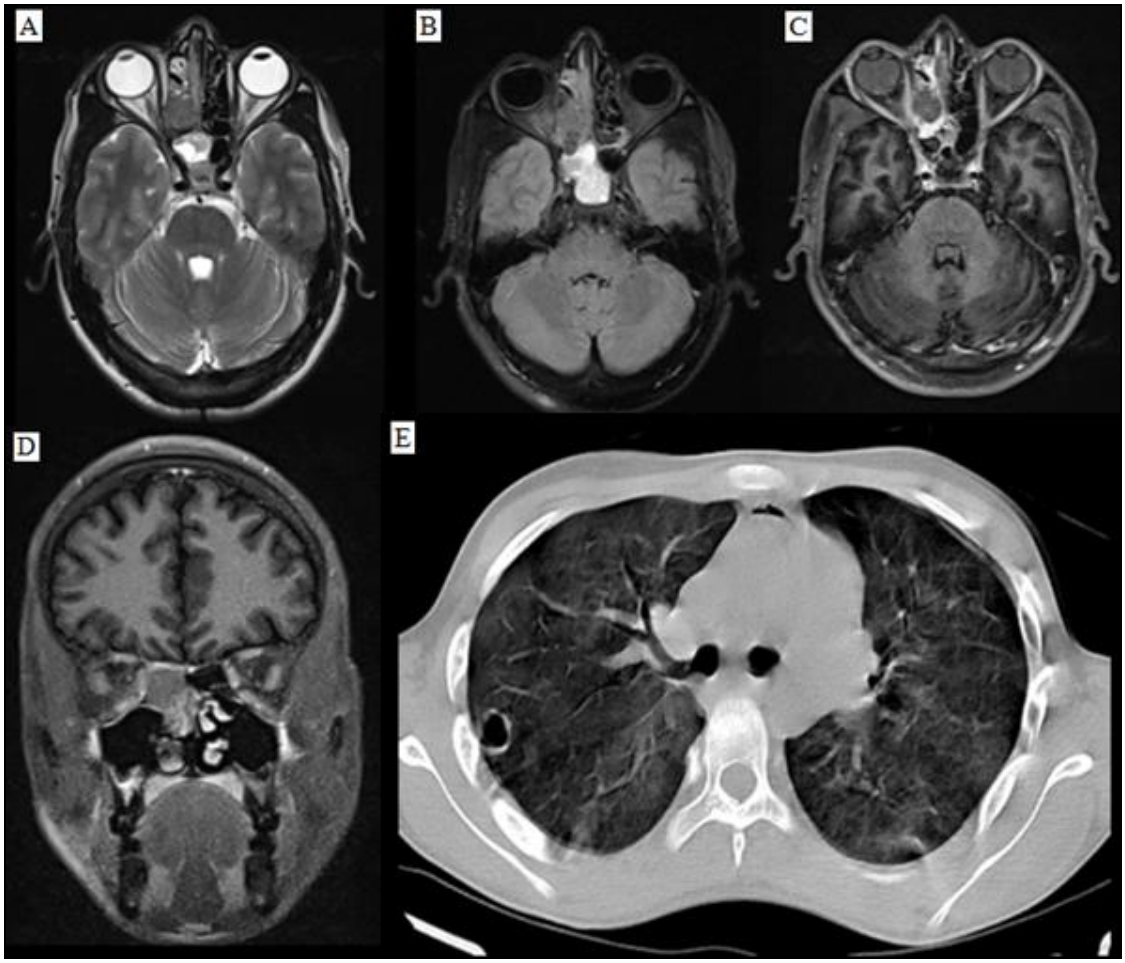

Fig 2: A 29 years old male patient presented with fever, right sided nasal obstruction (A&B) T2WI and STIR images shows heterogeneously isointense soft tissue lesion demonstrating in the right ethmoid sinus and sphenoid sinus with mucosal thickening with expansion of right posterior ethmoid sinus which bulges into the medial wall of right orbit without obvious intraorbital extension. (C&E) Axial and coronal T1 post contrast images shows minimal enhancement of the lesion. (E) HRCT thorax shows multiple areas of ground glass opacities with superimposed interlobular septal thickening predominantly involving lower lung fields bilaterally with multiple thin walled cavitatory lesions.

Case 3

30 years old male, RT-PCR proven case of COVID-19 complained of nasal discharge and fever since 4 days.

HRCT chest was requested and it revealed multiple peripherally located areas of ground glass opacities with CT severity score of 11/25.

CE MRI of paranasal sinuses and orbits was requested and shows thick lobulated moderately enhancing mucosa of the left maxillary sinus with air fluid level in the sinus cavity. Histopathological evaluation of nasal mucosa was consistent with fungal etiology.

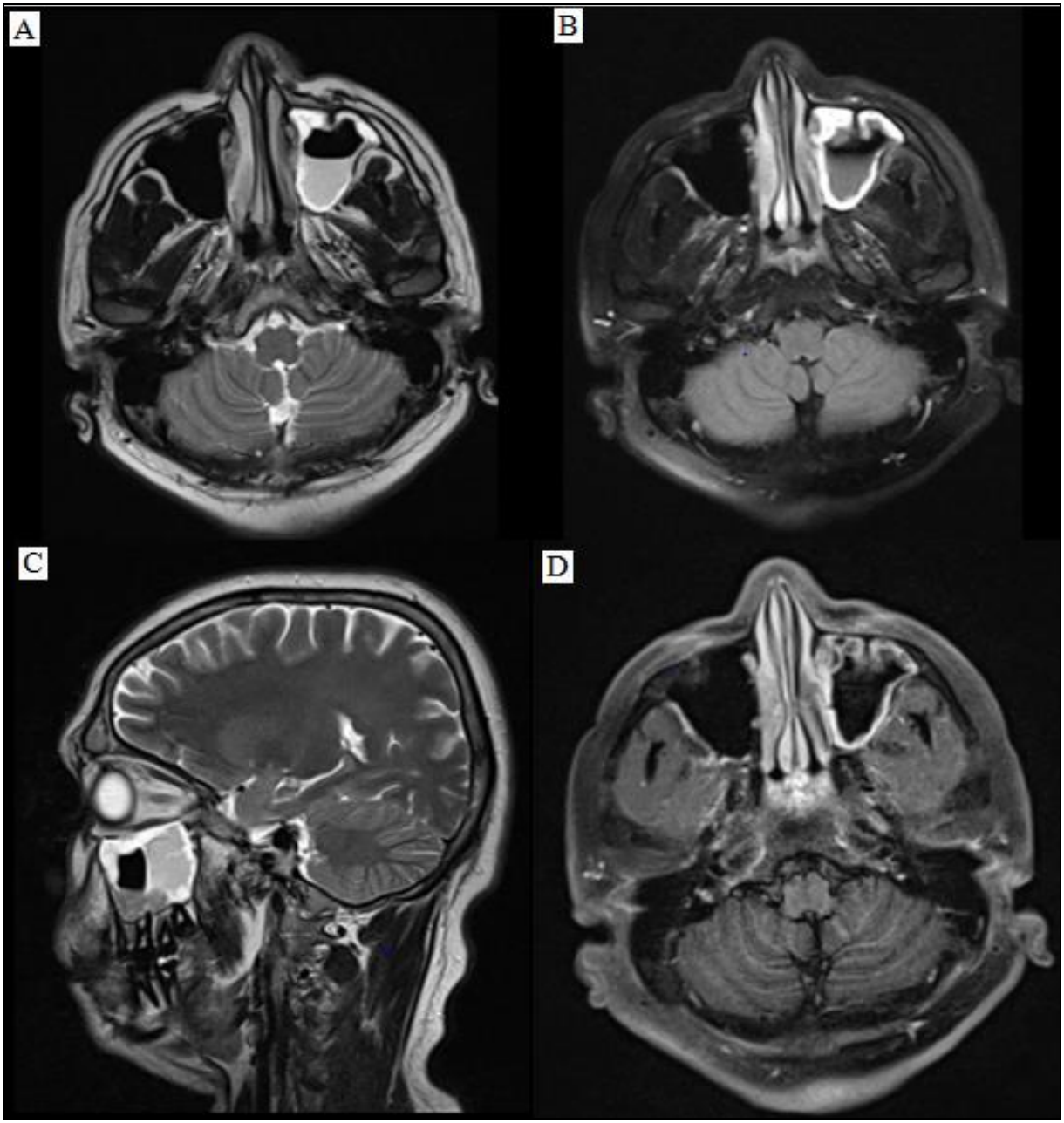

Fig 3: (A, B &C) Axial T2, STIR and Sagittal T2weighted images shows lobulated mucosal thickening with air dependent air fluid level in left maxillary sinus. (D) Axial post contrast T1 fat suppressed image shows thick enhancing mucosa of left maxillary sinus.

Case 4

A 40 years known male patient newly diagnosed RTPCR proven COVID-19 positive patient with CT severity score of 4/25 and lungs showing COVID-19 pneumonia. He was on medication and complained of right sided face pain, nasal discharge and headache since 1 week. CE MRI of paranasal sinuses and orbits was requested and shows right complex maxillary sinusitis suggestive of fungal etiology which was further reconfirmed by KOH mount and histopathological examination of the mucosa.

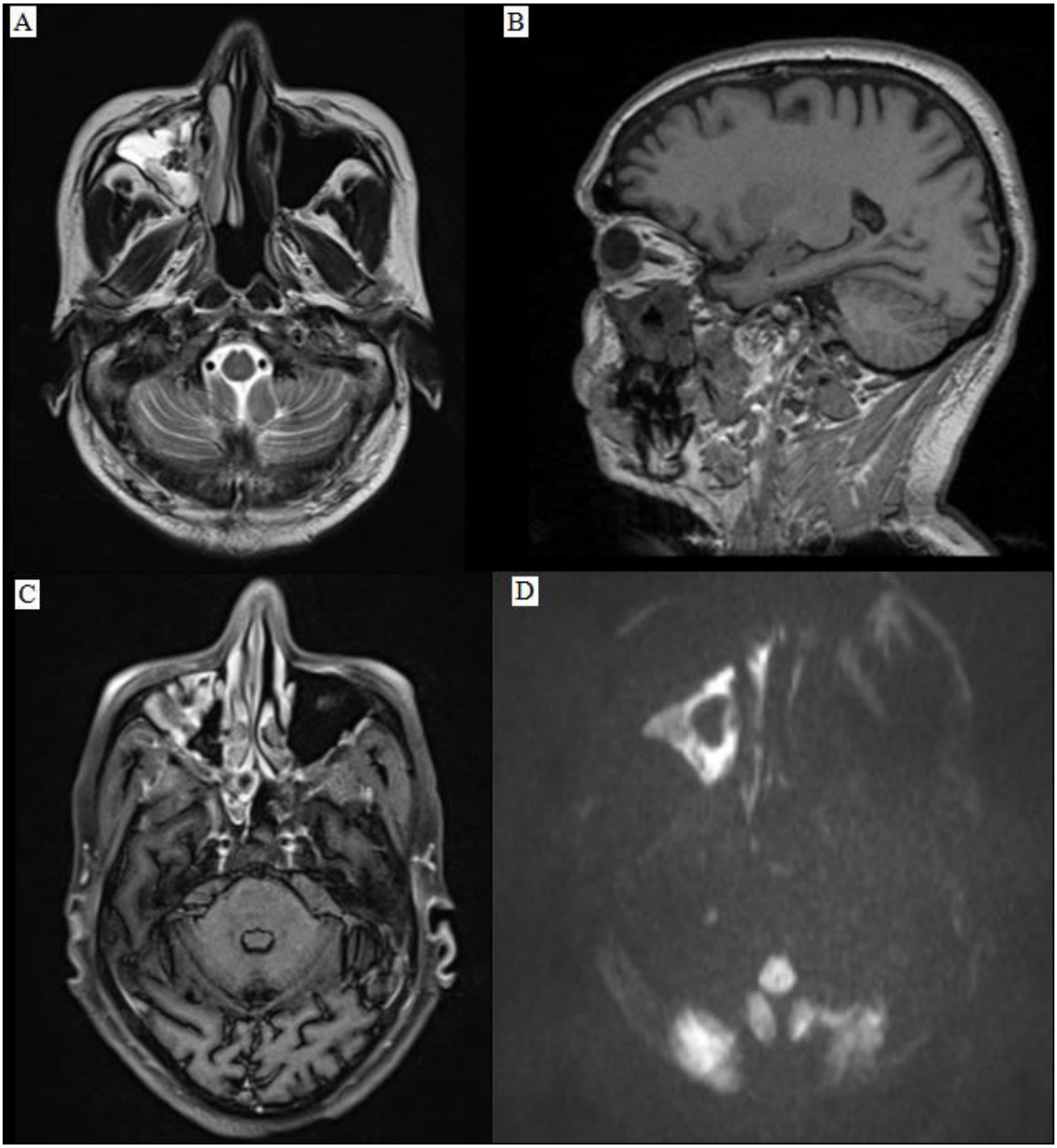

Fig 4. 30 years old male with headache, nasal discharge and nasal obstruction. (A) Axial T2 weighted images shows lobulated thickening of mucosa of right maxillary sinus which demonstrated heterogenously hyperintense signal.
(B) On T1 parasagittal image mucosal thickening appears hypointense and demonstrated thick nodular enhancement on post contrast images (C).

Case 5

50 years old male patient diagnosed as COVID-19 positive using RTPCR test done a week earlier presented with complains of headache and nasal obstruction. CE MRI of PNS and brain was requested and shows heterogeneous opacification and enhancement of the bilateral ethmoid and sphenoid sinuses. Histopathological evaluation of nasal mucosa was consistent with fungal etiology.

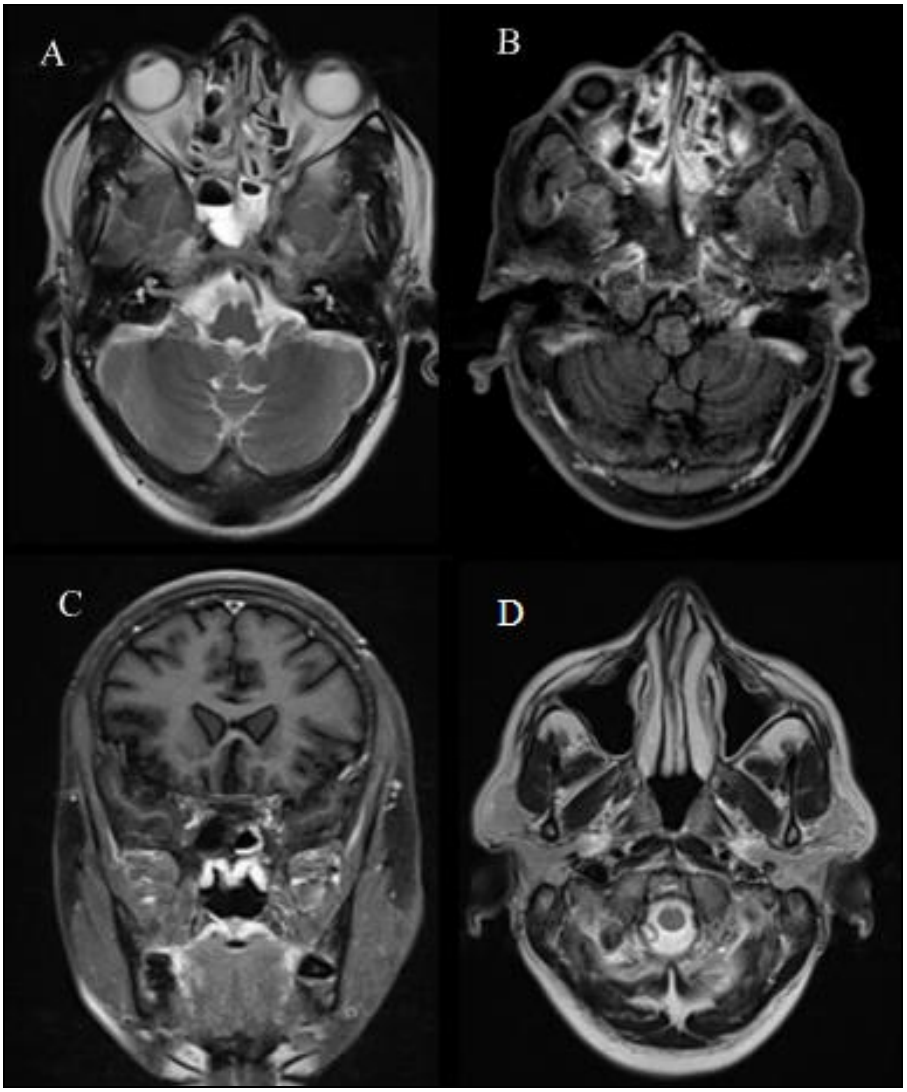

Fig 5: (A, B & C) Heterogeneous opacification and enhancement of the bilateral ethmoid and sinuses and showing mild peripheral enhancement and central hypo-enhancing areas in the sphenoid sinuses extension of abnormal signal intensity from the right sphenoid sinus. (D) Mild mucosal thickening of the bilateral maxillary and left frontal sinuses.

Discussion

There is complex interplay of factors, including a wide spectrum of preexisting diseases such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease or previous respiratory conditions, immunosuppressive therapy in cases of organ transplant or cancer patients, hospital-acquired infections, and systemic immune alterations of COVID-19 infection can lead to secondary infections which directly impact on the morbidity and mortality[8]. Due to abuse of broad-spectrum antibiotics and self-medication culture in India most of the causative organism are already resistant to broad spectrum antibiotics.

Indian guidelines recommend intravenous methylprednisolone 0.5-1 mg/kg/day for three days in moderate cases and 1-2 mg/kg/day in severe cases. The National Institute of Health recommends the use of dexamethasone (6 mg per day for a maximum of 10 days) in patients who are ventilated or require supplemental oxygen n but not in milder cases. The guidelines specifically mention the risk of developing a secondary infection.

The pathophysiologic features of COVID-19 has propensity to cause extensive pulmonary disease and increases the risk of invasive fungal infections due to immune dysregulation associated with COVID-19, with reduced numbers of T lymphocytes, CD4+T, and CD8+T cells, may alter innate immunity.

It is postulated that the SARS-CoV-2 infection affects CD4+ and CD8+ T cells, causes significant reduction in number of lymphocytes and T cells and creates a temporary state of compromised immunity.

Orbital involvement results from the spread through the medial orbital wall and nasolacrimal duct as in our case. The fungi invade the adjacent blood vessels causing thrombosis and infarction, as well as dissemination to the brain parenchyma.

MRI has proved to be very useful in detection of complications like orbital cellulitis, cavernous sinus thrombosis, and internal carotid artery thrombosis The MRI of the sinuses and orbits in rhino-orbital mucormycosis is documented to show three patterns with a majority of the cases showing iso- to hypointense appearance on T2, which is due to presence of iron and manganese in the fungal elements.

Another important radiological finding that has been widely mentioned in literature as relatively specific for the disease is the “Black turbinate sign” which is due to the devitalization of sinonasal mucosa and appears as non-enhancing mucosa on post contrast study.

In one cluster from New Delhi, India, 15 admitted patients with COVID-19 infection developed bloodstream candida infections. Of these, 10 had a Candida auris infection, of whom six died (60%) [9].

White *et al*. screened 135 adults with COVID-19 infection and reported an incidence of invasive fungal infections of 26.7% (commonly aspergillosis (14.1%), or yeast, usually candida (12·6%)). Patients with invasive fungal diseases had higher mortality (53% with vs 31% without), which was significantly reduced by appropriate therapy. Corticosteroid therapy and a past history of chronic pulmonary disease were associated with a higher risk of invasive fungal disease [10].

Similarly, high incidences have been seen in Pakistan (23/147, 15.6%) and Italy (30/108, 27.7%), with the authors suggesting that the development of invasive fungal infections alters the natural history of the disease [11-12].

Song *et al*. have suggested an algorithm for the early diagnosis and management of common invasive fungal infections (aspergillus, candidiasis, cryptococcosis, and mucormycosis) [13].

Conclusion

COVID-19 is associated with a significant incidence of secondary infections, both bacterial and fungal probably due to immune dysregulation. Additionally, the widespread use of steroids/monoclonal antibodies/broad-spectrum antibiotics as part of the armamentarium against COVID-19 may lead to the development/exacerbation of preexisting fungal diseases. The importance of keeping an eye out for the subtle but critical early imaging findings suggestive of invasive fungal sinusitis in a known COVID-19 case with symptoms of sinusitis is imperative. Physicians should be aware of the possibility of invasive secondary fungal infections in patients with COVID-19 infection especially in patients with preexisting risk factors and should enable early diagnosis and treatment with the subsequent reduction of mortality and morbidity. The use of therapeutic agents should be monitored to achieve a therapeutic effect at the lowest dose and shortest durations. The use of broad-spectrum antibiotics, especially in the absence of infection, should be re-evaluated.

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Informed consent: A written informed consent form was obtained from the patient to publish these data and images.

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