Article published online: 2022-12-16

COVID-Associated Sinonasal Mucormycosis: Radiological Pathological Correlation and Prognostic Value of MR Imaging

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Indian J Radiol Imaging 2023;33:46–52.

Abstract

Purpose Our aim was to assess the sinonasal magnetic resonance imaging (MRI) features of acute invasive fungal rhinosinusitis (AIFRS) in coronavirus disease (COVID)-associated mucormycosis (CAM) and to correlate these with histopathology and patient outcome in terms of duration of hospital stay and survival at 10 weeks.

Methods Twenty patients with histopathologically confirmed sinonasal CAM underwent MRI (including postcontrast T1-weighted and diffusion-weighted imaging). Histopathological findings (presence of coagulative necrosis, granulomatous reaction, and fungal burden) were recorded and all patients were followed up at 6 and 10 weeks. Statistical analysis was done using chi-square test and Fischer's exact test.

Results Enhancement patterns seen in our subjects included homogeneous, heterogeneous, and lack of contrast enhancement (LOC), with LOC being the most common (65%). Diffusion restriction was found in 90% patients. Statistically significant correlation was found between LOC pattern and presence of coagulative necrosis (p-value = 0.007), extent of fungal hyphae (p-value = 0.047), and duration of hospital stay (p-value = 0.004). Restricted diffusion was also seen to correlate with a high fungal load (p-value = 0.007).

Conclusion Our study describes the MRI findings of AIFRS in CAM and highlights the imaging features which may be surrogate markers for coagulative necrosis and fungal burden.

Keywords
- lack of contrast enhancement
- MRI
- diffusion restriction
- fungal load
- coagulative necrosis

Introduction

As the second wave of coronavirus disease 2019 (COVID-19) wreaked havoc in India beginning in April 2021, a potentially devastating fungal infection began to occur in its wake. While patients started to recover from COVID-19 pneumonia, a drastic surge was seen in the incidence of acute invasive fungal rhinosinusitis (also known as mucormycosis) among such patients contributing to added morbidity and mortality. The rapid rise in the incidence of COVID-associated mucormycosis (CAM) led to it being declared as a notifiable disease in many parts of India. Similar outbreaks of saprophytic fungal

article published online December 16, 2022

DOI https://doi.org/10.1055/s-0042-1759639.
ISSN 0971-3026.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

infections have been recorded in the past following natural disasters in India and other countries, the Indian Ocean tsunami in 2004 being noteworthy.[1]

The sudden deluge in the cases of CAM has been attributed to preexisting uncontrolled diabetes or diabetes worsened by COVID-19, indiscriminate use of steroids in the management of COVID-19, oxygen therapy, and high serum ferritin levels.[2] Clinical diagnosis is difficult as symptoms often overlap with those of nonspecific bacterial and viral rhinosinusitis. Imaging plays a crucial role in early diagnosis of this aggressive disease so that prompt treatment is initiated to reduce the associated morbidity and mortality.

Magnetic resonance imaging (MRI) has been considered a sensitive modality to detect mucormycosis; however, overall MRI appearance of the disease entity and its correlation with histopathological findings and disease outcome is poorly understood. The aim of our study is to assess the signal intensity on T1- (T1WI) and T2-weighted images (T2WI), enhancement pattern and diffusion characteristics in CAM and to correlate these with histopathological findings and disease outcome.

Materials and Methods

The institutional ethical committee of Maulana Azad Medical College approved this prospective study vide IEC number (F.1/IEC/MAMC/(84/02/2021/No.396). Twenty-eight consecutive patients with clinical suspicion of CAM underwent MRI in the institution between May and July 2021. As per the institutional policy, MRI was done only for patients who were reverse transcription polymerase chain reaction (RT-PCR) negative for COVID at the time of presentation. Of the 28 patients, 3 had undergone surgical debridement/functional endoscopic sinus surgery prior to imaging and were not included in the study. Three of the remaining 25 patients could not be administered gadolinium-based intravenous contrast due to impaired renal function (estimated glomerular filtration rate < 30 mL/min/1.73m^2) and were excluded. Two patients did not have any features of mucormycosis on MRI and their nasal endoscopic findings were also normal. These patients were not taken up for debridement and were also excluded. The remaining 20 patients formed the final study group. All 20 patients underwent debridement within 48 to 72 hours after MRI and the diagnosis was confirmed on histopathology. They were followed up at 6 weeks and again at 10 weeks from the diagnosis, and outcome was recorded in terms of duration of hospital stay (more than 6 weeks from confirmation of CAM) and patient survival.

Imaging Technique

MR examination was done on a 3T MR system (Magentom-Skyra; Siemens, Erlangen, Germany) in supine position using a dedicated 32-channel phased array head coil. A standardized imaging protocol was followed for all patients and included the following sequences in multiple planes:

- Spin-echo T1WIs (TR: 450–634 ms, TE: 7.1–9.4 ms) with an intersection gap of 1 to 2 mm, slice thickness of 3 mm, and matrix of 256×256.
- T2-weighted turbo spin-echo images (TR: 3200–5900 ms, TE: 75–103 ms) with an intersection gap of 1 to 2 mm, slice thickness of 3 mm, and matrix of 256×256.
- Fat-suppressed T2-weighted fast spin-echo images (TR: 4430–6610 ms, TE: 79 ms) with an intersection gap of 1 to 2 mm, slice thickness of 3 mm, and matrix of 256×256.
- Contrast-enhanced fat-suppressed T1WIs (TR: 450–1010 ms, TE: 7.1–11 ms) with an intersection gap of 1 to 2 mm, slice thickness of 3 mm, and matrix of 256×256 after intravenous administration of gadopentetate dimeglumine (Magnascan, Unijules Life Sciences Ltd, India) at a dose of 0.1 to 0.2 mmol/kg.
- Diffusion-weighted images were obtained using multishot echo planar RESOLVE (readout segmentation of long variable echo-trains) diffusion-weighted sequence in the axial plane at b values of 0 and 1000 s/mm^2 followed by generation of apparent diffusion coefficient (ADC) maps.

Analysis of Clinical and Imaging Data

Clinical data for patients was recorded with special emphasis on duration between diagnosis of COVID-19 and CAM and underlying risk factors including diabetes mellitus, steroid use, and oxygen therapy. Images were analyzed by two radiologists with 20 and 12 years of experience in head and neck radiology. Differences in opinion were resolved by consensus.

- Predominant signal characteristics of the involved region were analyzed on T1WI and T2WI and were categorized as hypointense, isointense, and hyperintense relative to cerebral gray matter.
- On postcontrast images, predominant enhancement pattern of the involved sinonasal region was classified as homogeneous, heterogeneous, or lack of contrast enhancement (LOC). LOC was defined as a nonenhancing lesion of minimum size 5×5 mm on contrast-enhanced T1-weighted fat-suppressed images with preservation of intervening bone/fat. When there was no LOC in the lesion, the lesion was categorized into homogeneous or heterogeneous enhancement pattern.
- Presence or absence of diffusion restriction in the region of the predominant enhancement pattern was noted. Lesions having a bright signal on diffusion-weighted images (b value $= 1000$ s/mm^2) and low signal on ADC maps were considered to have restricted diffusion.

Histopathological Correlation

Histopathological specimens were analyzed by a pathologist with 25 years of experience for the presence of mucosal, osseous, vascular, and neural invasion, presence of coagulative necrosis, granulomatous inflammatory reaction, and vascular granulation tissue. Type of fungal organism seen and extent of fungal hyphae were also noted, the latter being categorized as $+1$, $+2$, and $+3$ ($+1$: present in 1–2 fields, $+2$: visible easily, $+3$: large in number).

Statistical Analysis

The collected data was entered in MS Excel and analysis was done using SPSS version 21.0. Qualitative data was presented as percentages for categorical variables. Statistical

differences between the categorical variables for two comparable groups was measured using chi-square test, while for more than two groups, Fischer's exact test was employed. Predictive accuracy of each independent factor was measured using sensitivity, specificity, positive predictive value (PPV), negative predictive value, and accuracy. A *p*-value of less than 0.05 was considered significant.

Results

A total of 20 patients were included in the study of which 13 were men and 7 were women. The age of the subjects ranged from 35 to 76 years, with a mean age of 51.5 years. In 6 patients, bilateral involvement was seen and all but 2 patients showed extrasinonasal involvement.

Out of the 20 patients, 15 had RT-PCR-confirmed severe acute respiratory syndrome COVID-19 infection within the 4 weeks prior to testing positive for CAM. In the remaining 5 patients, there was a high degree of clinical suspicion for recent COVID-19 in view of history of typical symptoms (such as sore throat, cough, anosmia) or a prior chest radiograph showing bilateral ground-glass infiltrates. Prominent risk factors for CAM among patients included in the study group were diabetes (found in 16 of the 20 study subjects, i.e., 80%), history of oxygen support in the form of either invasive or noninvasive ventilation (in all subjects), and treatment with systemic corticosteroids for COVID-19 (in 10 patients, i.e., 50%). The most common steroid regimes followed were intravenous methylprednisolone 0.5 to 1 mg/kg or intravenous dexamethasone 0.1 to 0.2 mg/kg (moderate COVID) and intravenous methylprednisolone 1 to 2 mg/kg in two divided doses or intravenous dexamethasone 0.2 to 0.4 mg/kg (severe COVID) usually for a duration of 5 to 10 days.[2]

On T2-weighted MR images, signal pattern was found to be variable with lesions appearing hyperintense (45%), hypointense (30%), and isointense (25%) (►**Table 1**). Out of all 20 cases of CAM included in our study, 90% were hypointense on T1WIs and only 2 patients showed iso- to hyperintense signal.

The enhancement patterns on T1 fat-saturated postcontrast images are summarized in ►**Fig. 1**. The most common pattern of enhancement in the diseased area was found to be LOC, seen in 13 cases (65%). The most common sites depicting LOC were the maxillary and ethmoid sinuses, each being involved in 8 out of 13 patients (61.5%).

As shown in ►**Table 2**, out of the 20 cases analyzed, 18 showed diffusion restriction (90%). In addition, LOC was 100% predictive of restricted diffusion.

Of the 13 patients showing LOC, 12 showed presence of coagulative necrosis on histopathology (92.3%), whereas only one each of the homogeneously and heterogeneously enhancing lesions showed coagulative necrosis. This was found to be statistically significant (*p*-value = 0.007), as coagulative necrosis was not demonstrable in 71.4% of lesions showing enhancement patterns other than LOC (►**Fig. 2**).

No significant difference in the presence of granulomatous reaction was seen between lesions showing LOC, homogeneous, or heterogeneous enhancement. Six cases showed simultaneous presence of coagulative necrosis and granulomatous reaction, all of which showed LOC pattern of enhancement.

Table 1 Correlation of enhancement pattern with other imaging variables, histopathological findings, and patient outcome

Variables	LOC, *n* = 13 (%)	Non-LOC, *n* = 7 (%)	*p*-Value
Diffusion restriction			
Present	13 (100)	5 (71.4)	0.110
Absent	0 (0)	2 (28.6)	
T2 signal intensity			
Hyperintense	5 (38.5)	4 (57.1)	0.523
Hypointense	5 (38.5)	1 (14.3)	
Isointense	3 (23)	2 (28.6)	
Coagulative necrosis			
Present	12 (92.3)	2 (28.6)	0.007[a]
Absent	1 (7.7)	5 (71.4)	
Granulomatous reaction			
Present	7 (53.8)	5 (71.4)	0.392
Absent	6 (46.2)	2 (28.6)	
Extent of fungus			
+1/+2	3	5 (71.4)	0.047[a]
+3	10	2 (28.6)	
Outcome – Duration of hospital stay			
< 6 wk	4 (30.8)	7 (100)	0.004[a]
> 6 wk	9 (69.2)	0 (0)	
Outcome – Survival			
Survived	10 (76.9)	7 (100)	0.251
Deceased	3 (23.1)	0	

Abbreviation: LOC, lack of contrast enhancement.
[a]Statistically significant.

Of the 13 patients, 10 with LOC as the predominant enhancement pattern had +3 score for extent of fungal organism (76.9%), and presence of higher fungal load in lesions with LOC was statistically significant (*p*-value

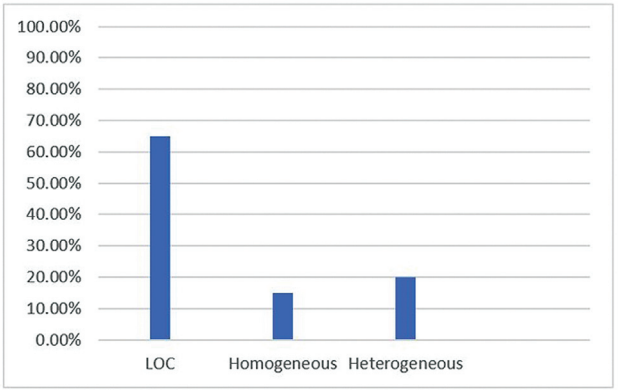

Fig. 1 Magnetic resonance (MR) enhancement patterns in coronavirus disease (COVID)-associated mucormycosis (CAM).

Table 2 Correlation of diffusion restriction with histopathological findings and patient outcome

Variables	Diffusion restriction + $n = 18$ (%)	Diffusion restriction – $n = 2$ (%)	*p*-Value
Coagulative necrosis			
Present	13 (72.2)	1 (50)	0.521
Absent	5 (27.8)	1 (50)	
Granulomatous reaction			
Present	10 (55.6)	1 (50)	0.710
Absent	8 (44.4)	1 (50)	
Extent of fungus			
+1	0 (0)	1 (50)	0.007[a]
+2	7 (38.9)	0 (0)	
+3	11 (61.1)	1 (50)	
Outcome – Duration of hospital stay			
< 6 wk	9 (50)	2 (100)	0.289
> 6 wk	9 (50)	0 (0)	
Outcome – Survival			
Survived	15 (83.3)	2 (100)	0.716
Deceased	3 (16.6)	0 (0)	

[a]Statistically significant.

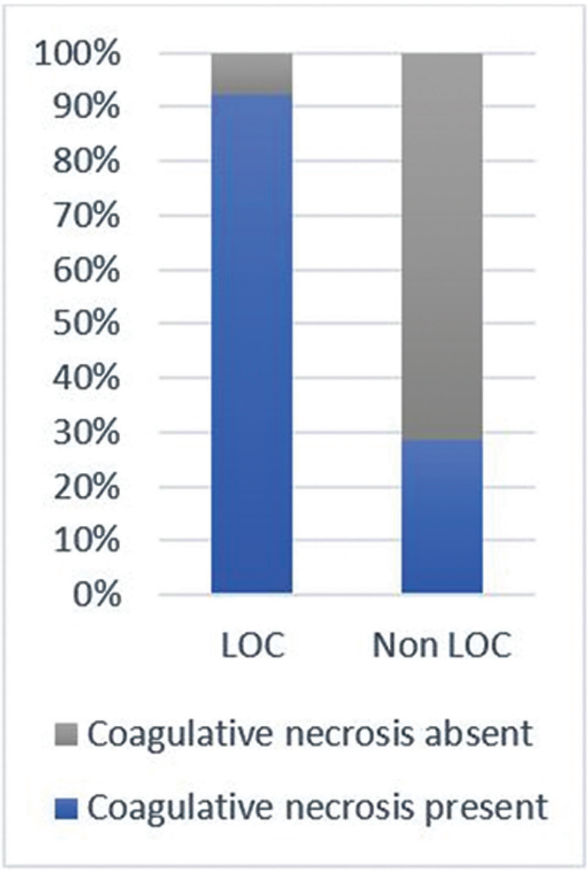

Fig. 2 Coagulative necrosis in lack of contrast enhancement (LOC) and non-LOC lesions.

= 0.047). All 18 patients with restricted diffusion had a histopathological fungal score of +2 (7/18, 38.9%) or +3 (11/18, 61.1%), whereas none of the restricting lesions had a score of +1. This was also found to be statistically significant (*p*-value = 0.007).

Coagulative necrosis was seen in 13 of the 18 patients showing diffusion restriction (►**Table 2**); however, no statistically significant relationship could be derived.

All 9 patients with prolonged hospital stay (> 6 weeks) showed LOC as the predominant enhancement pattern and 3 of these patients expired during follow-up. Patients with homogeneously or heterogeneously enhancing lesions had a hospital stay shorter than 6 weeks. No deaths were recorded in this group. The relationship between predominant enhancement pattern and duration of hospital stay was found to be statistically significant with *p*-value = 0.004.

Nine of the 18 patients with presence of restricted diffusion had a short duration of hospital stay and an equal number had prolonged stay. However, only 2 of the 20 patients showed absence of restricted diffusion and both had a short duration of hospital admission.

Discussion

Mucormycosis is an acute invasive fungal infection seen in immunocompromised individuals, caused by saprophytic organisms belonging to the class Zygomycetes and genera Rhizopus, Rhizomucor, Absidia, and Mucor.[3] Although many different sites of involvement have been seen, rhino-orbital-cerebral disease is the most common form. Clinical symptoms often include facial pain and swelling, blurring of vision, and bloody nasal discharge with crusting.[4]

Although the definitive diagnosis is histopathological,[5] MRI has been considered the imaging modality of choice for evaluation of mucormycosis.[3,6–8] It detects subtle changes in extrasinonasal soft tissues and has been found to be a good correlate with disease extent as seen on surgery.[9]

Postcontrast enhancement patterns on MRI in mucormycosis have been classified into three types, namely LOC, homogeneous enhancement, and heterogeneous enhancement[10] (►**Figs. 3–5**). In 2010, Safder et al[11] first described the devitalized nonenhancing sinonasal mucosa as the "Black Turbinate" sign on MRI in two cases of rhinocerebral mucormycosis, which was later reiterated by Taylor et al.[12] Seo et al[13] also concluded that the presence of cervicofacial tissue infarction resulting from angioinvasive nature of these fungi is seen as a region with LOC in the sinonasal tract or its vicinity. According to the study published by Choi et al[10] in 2018, LOC was found to be the most common pattern of enhancement (47.8%) in their study group of 23 subjects. Our findings were in concurrence with their study as 65% of our study subjects also demonstrated LOC.

In our study, the lesions showed variable signal intensity on T2WIs (9 hyperintense, 6 hypointense, and 5 isointense), whereas 18 out of 20 cases showed hypointense signal on T1WI. Available literature suggests that low signal intensity on T1WI and an even lower signal intensity on T2WI is usually seen in the involved areas.[14,15] In a study undertaken

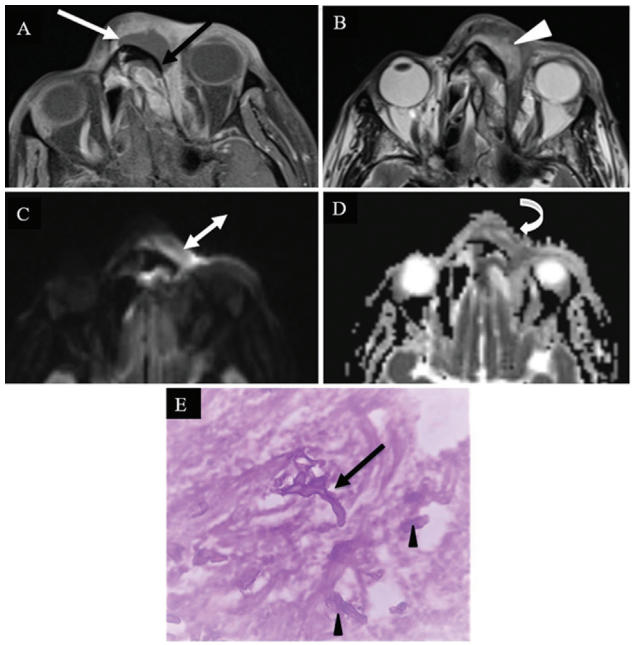

Fig. 3 (**A**–**E**) Lack of contrast enhancement. Axial contrast-enhanced fat-saturated T1-weighted image (**A**) shows lack of contrast enhancement (LOC) in the soft tissue involving the left nasolacrimal region and anterior ethmoid air cells (white arrow) with preserved in-between bone (black arrow). The area of LOC shows predominantly hyperintense signal on T2-weighted image (white arrowhead in **B**) and restricted diffusion on axial diffusion-weighted image (DWI) (double-headed arrow in **C**), and corresponding apparent diffusion coefficient (ADC) map (curved arrow in **D**). Histology shows coagulative necrotic background and broad aseptate hyphae with right angle branching of Mucor (black arrow in **E**). Small fragments of hyphae (black arrow heads) are also seen (hematoxylin and eosin ×600).

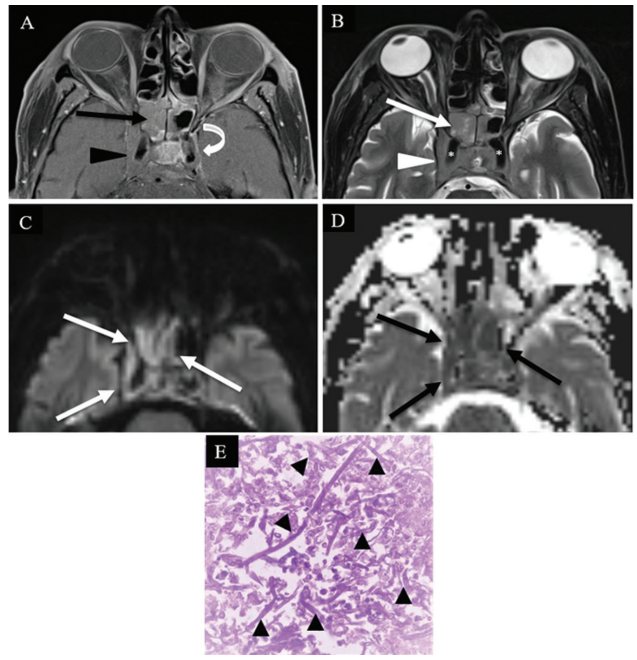

Fig. 4 (**A**–**E**) Homogeneous enhancement pattern. Axial contrast-enhanced fat-saturated T1-weighted image (**A**) shows homogeneous enhancement in the right sphenoid sinus (black arrow) and right cavernous sinus (black arrowhead). Left cavernous sinus is also bulky (white curved arrow). Isointense signal is seen in this region on T2-weighted image (white arrow and white arrowhead in **B**) with restricted diffusion on axial diffusion-weighted image (DWI) image (white arrows in **C**) and corresponding apparent diffusion coefficient (ADC) map (black arrows in **D**). Bilateral internal carotid artery (ICA) flow voids are maintained (* in **B**). Histology shows long ribbon-like septate hyphae with right angle branching (black arrowheads in **E**) (+3 fungal load) in the background of acute inflammatory reaction (hematoxylin and eosin ×400).

by Zinreich et al,[14] 6 patients with pathologically proven fungal sinusitis underwent MRI, all of whom demonstrated markedly hypointense signal on T2WI. Similarly, Choi et al[10] demonstrated that homogeneously and heterogeneously enhancing lesions showed exclusively low signal intensity on T2WI. Hypointensity on T1WI and T2WI in fungal disease has been attributed to the accumulation of hemosiderin and paramagnetic materials such as calcium, iron, magnesium, and manganese.[14,16] However, we did not see significant hypointensity on T2WI in our study, and no correlation of T2 signal was seen with enhancement pattern. Ilica et al[7] stated that differences in T2 signal may be found due to variable degree of inflammatory and fibrotic reaction, consistency of fluid present, fungal load, and mineral deposition in the involved areas. Hyperintensity on T2WI may also possibly be the result of a greater degree of necrosis, as described by Sreshta et al.[17]

Coagulative necrosis is the typical form of cell injury seen in ischemic/infarcted tissues. In our study, 12 of the 13 patients with LOC showed coagulative necrosis on histopathology whereas it was seen in only 2 of the 7 patients with other enhancement patterns. This was found to be statistically significant (Fisher's exact test p-value = 0.007), with LOC having a positive likelihood ratio of 5.14 and a PPV of 92.31% for the presence of coagulative necrosis. Of these 13 subjects, 10 also depicted a high fungal burden on histopathology with a subjective score of +3, thus establishing a significant relationship between the presence of LOC and fungal load (p-value = 0.047). Choi et al[10] also concluded that LOC lesions are associated with coagulative necrosis and a high fungal burden. This is also in agreement with the study performed by Safder et al,[11] who demonstrated that areas of nonenhancement in the sinonasal region contained angioinvasive fungal hyphae on pathological correlation.

Restricted diffusion was seen in all our patients with LOC. The presence of coagulative necrosis in restricting lesions was also prominent and seen in 13/18 patients (72.2%; p-value = 0.521). These findings point to a common underlying pathogenesis of LOC, restricted diffusion, and coagulative necrosis, although significant correlation between diffusion restriction and coagulative necrosis could not be established. This may be due to the small data set, and evaluation with further studies is warranted.

Our results indicate statistically significant correlation between presence of diffusion restriction and fungal hyphal burden. We used a subjective method for categorizing the extent of fungal hyphae visible on light microscopy and all lesions showing restricted diffusion had a high fungal load, that is, score of +2 or +3 (p-value = 0.007). To the best of our knowledge, no literature is available till date that correlates these two variables.

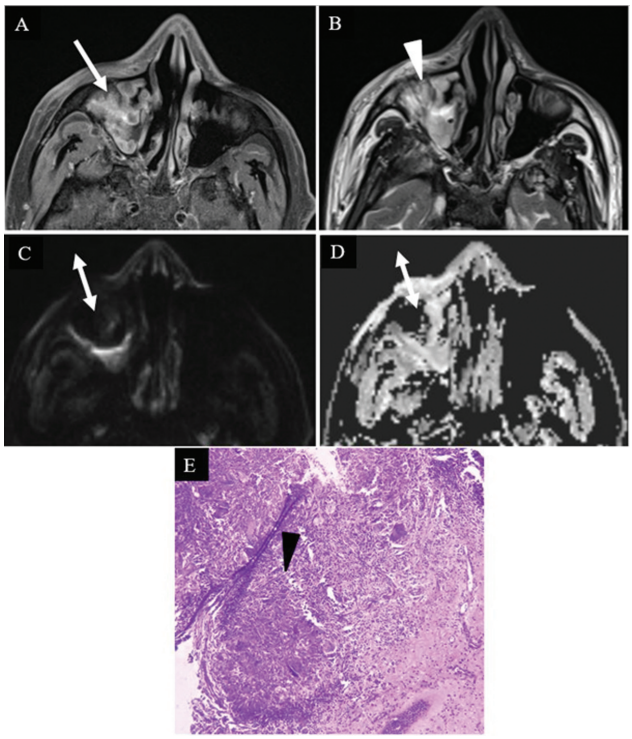

Fig. 5 (**A**–**E**) Heterogeneous enhancement pattern. Axial contrast-enhanced fat-saturated T1-weighted image (**A**) shows heterogeneous enhancement in the right maxillary sinus (white arrow) which shows predominantly hyperintense signal on T2-weighted image (white arrowhead in **B**). The region does not depict any focus of restricted diffusion on corresponding diffusion-weighted image (DWI) (**C**) and apparent diffusion coefficient (ADC) map (**D**). Histology depicts epithelioid cell granuloma (black arrowhead) admixed with multinucleate giant cells and few fungal hyphae (+1 fungal load) (hematoxylin and eosin ×400).

Most of the available literature regarding prognostic factors in mucormycosis deals with clinical and laboratory parameters with limited studies addressing the significance of imaging features in predicting morbidity and mortality. Underlying diseases, accompanying neutropenia, C-reactive protein levels, symptom duration, involvement of nasal septum, and the presence of facial swelling have been seen to influence the prognosis of mucormycosis.[18] We analyzed our study data for any probable association of imaging features with disease prognosis/outcome and found that enhancement pattern may act as a predictor for prolonged hospital stay (p-value = 0.004). All patients with hospital stay longer than 6 weeks showed LOC, whereas all patients with homogeneous or heterogeneous enhancement were discharged within 6 weeks. Although mortality was seen exclusively in the LOC group, this was not found to be statistically significant (p-value = 0.251). Enhancement pattern and diffusion restriction did not correlate with the final patient outcome in terms of survival; however, the role of imaging in predicting survival may have been downplayed by the overall low mortality in our study population. In the study by Choi et al,[10] LOC was found to be the sole independent prognostic factor for disease-specific mortality, probably due to a high fungal load and rapidly progressive coagulative necrosis. On analysis of pre- and postoperative enhanced MR images, Kim et al[19] concluded that extrasinonasal presence of non-enhancing lesions resulted in poor disease-specific survival as compared to individuals having only intrasinonasal involvement.

Limitations of our study included a small sample size with presence of concurrent diabetes as a risk factor in 80% of the subjects which may represent a significant bias. Second, we saw a relatively favorable prognosis in CAM patients (85% survival), which is better when compared with survival statistics of mucormycosis in the pre-COVID era.[20] This may have been either due to a better immune status of our patients who had no other significant cause of immunosuppression apart from recent COVID-19 infection or early intervention owing to a high index of suspicion during the pandemic. Third, duration of hospital stay may have additionally been affected by other complications secondary to COVID-19, complete assessment of which was not practically possible.

Conclusion

The importance of MRI as a tool for diagnosis of mucormycosis cannot be overstated. In our study, we have described the MRI findings in CAM, highlighting the imaging features which may act as surrogate markers for the presence of coagulative necrosis and fungal burden. We found that LOC was seen to correlate with presence of coagulative necrosis and high fungal load, while presence of diffusion restriction correlated with a high fungal burden. Although LOC also correlated with prolonged hospital stay, the case series is too limited to provide prediction of the patients' outcomes and it may act as a preliminary study upon which further studies can be based.

Funding
None.

Conflict of Interest
None declared.

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