

# Evaluation of Magnetic Resonance Imaging Findings of COVID-19-Related Rhino-Orbito-Cerebral Mucormycosis

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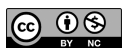
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## Abstract

**Objective:** Rhino-orbito-cerebral mucormycosis is an angioinvasive, opportunistic infection in coronavirus disease 2019 patients. The aim of this study is to evaluate the spread and complications of coronavirus disease 2019-related rhino-orbito-cerebral mucormycosis with magnetic resonance imaging findings.

**Methods:** The study included 14 patients with head and neck magnetic resonance imaging, positive severe acute respiratory failure syndrome Coronavirus 2 (SARS-CoV-2) reverse transcriptase polymerase chain reaction test, and pathologically proven mucormycosis. Paranasal sinus, orbital and intracranial involvement features were examined in detail and complications were evaluated.

**Results:** Diabetes mellitus was the most common comorbidity in all patients except one (92%). Systemic steroid treatment was provided to 10 patients (74%) and oxygen support was provided to 8 patients (57%). In our study, the mortality rate was found to be 35%. Rhinosinusitis was the most common radiological finding present in all patients at the time of diagnosis. Orbital involvement was detected in 10 patients (71%) and intracranial involvement in 9 patients (64%).

**Conclusion:** Magnetic resonance imaging has an important role in diagnosing and determining complications and managing the disease in patients with coronavirus disease 2019-associated rhino-orbito-cerebral mucormycosis.

**Keywords:** COVID-19, mucormycosis, rhino-orbito-cerebral, MRI

## INTRODUCTION

Mucormycosis is an infectious disease caused by fungi of the Mucorales group, showing an aggressive course with high morbidity and mortality rates and can be found commensal in the nasal cavity.<sup>1,2</sup>

The novel coronavirus disease 2019 (COVID-19) may present with a broad clinical spectrum, ranging from mild symptoms to life-threatening pneumonia. In addition, the incidence of mucormycosis, which accompanies viral symptoms worldwide due to the COVID-19 pandemic, especially with the second wave, has attracted attention.<sup>3,4</sup> Mucormycosis is a fungal infection that can be extremely mortal, particularly if it affects someone who has diabetes, uses steroids, or has a compromised immune system.<sup>5,6</sup> In COVID-19-related cases, the pathophysiology has not been fully elucidated, but a marked decrease in CD4+T and CD8+T cell counts, uncontrolled diabetes, steroid therapy, and prolonged hospitalization are among possible risk factors.<sup>7</sup>

Mucormycosis can be colonized in the nasal mucosa and can lead to invasive infection in immunocompetent patients, and spreads directly to adjacent areas via the superior orbital fissure and cribriform plate, while vascular invasion occurs through the ophthalmic vessels, and intracranial involvement is in the carotid artery or perineural invasion.<sup>8,9</sup> Rhino-orbito-cerebral mucormycosis (ROCM) is the most common mucormycosis involving the maxillofacial and orbital regions. It can spread intracranially in later stages and has a high mortality rate.<sup>10</sup> The incidence of ROCM is increasing in the COVID-19 pandemic worldwide, especially in India, and this situation is met with concern by the authorities.<sup>11,12</sup> The most common clinical findings are nasal congestion, rhinorrhea, facial swelling, facial and/or orbital pain, headache, proptosis, sudden vision loss, facial paresthesia and paralysis, sudden ptosis, diplopia, fever, and focal seizures.<sup>13</sup> Rhino-orbito-cerebral mucormycosis is a fatal disease with a progressive course, delay in diagnosis or treatment can have devastating effects on patient survival.<sup>14</sup> Early detection and treatment of mucormycosis can save lives, 1 week delay in treatment increases mortality from 35% to 66%.<sup>15</sup> Both computed tomography (CT) and magnetic resonance imaging (MRI) play an important role in diagnosing ROCM. Magnetic resonance imaging is superior to CT in detecting complications such as acute cerebral ischemia, cerebritis, abscess, and vessel wall invasion.<sup>16,17</sup>

This study aims to describe COVID-19-related ROCM imaging findings, cerebrovascular complications, and spread with imaging modalities.

## METHODS

This study was conducted by retrospectively scanning the preoperative imaging findings of 14 patients who developed COVID-19-associated ROCM between September 2021 and February 2022 in Çukurova University Faculty of Medicine Hospital After the approval of the ethics committee dated December 2, 2022 and numbered 128. Patients with positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test within 2 months were included in the study. All patients have pathological diagnosis and MR imaging.

Patients with primary malignancy, immunodeficiency, chemotherapy or radiotherapy were excluded from the study. Demographic data, comorbidities, all history and laboratory information regarding COVID-19 infection were collected. Two devices were used for MR examinations; 1.5 Tesla General Electric HDI ECHOSPEED (GE Healthcare, Milwaukee, USA) using an 8-channel head-neck coil, and Philips IntelliSpace Portal, Version 5.0, with a 16-channel head-neck coil (Philips Healthcare, Amsterdam, Netherlands). In addition to conventional MR sequences, diffusion-weighted imaging (DWI), axial and coronal fat-sat and mDIXON, time of flight (TOF) MR angiography, and post contrast 3DT1 were obtained for all patients. Post-contrast T1W images were acquired at 30 seconds after an injection of 0.1-mmol/kg gadobutrol (Gadovist; Bayer Schering Pharma AG, Germany). Radiological images were independently evaluated by 2 radiologists.

Paranasal sinus contents were evaluated by comparing with gray matter. The patients were evaluated in terms of orbital, retroantral region, masticator space, premaxillary/preseptal region involvement. Contrast-enhanced T1W and diffusion images were examined for infarction, black turbinate sign, dural contrast, cerebritis, intracranial abscess, perineural invasion, and orbital and intracranial spread pathways of infection. Vascular invasion/occlusion was evaluated with MR angiography sequences.

## RESULTS

The gender distribution of the 14 patients included in the study consisted of an equal number of men and women. The mean age was 58.7 (15-82). The median time from RT-PCR test positivity at the time of diagnosis was 17 days (min: 1-max: 59). Diabetes mellitus (DM) was the most common comorbid 13 (92%) comorbid diseases, and the mean HbA1c was found to be 8.4%. All of the patients were followed up with hospitalization; Systemic steroid therapy was provided to 10 patients (74%), and oxygen support was provided to 8 patients (57%). 5 patients (35%) died during follow-up.

Rhinosinusitis was present at the time of diagnosis in all patients and was the most common radiological finding. Maxillary and ethmoid sinuses were the most frequently involved paranasal sinuses. Orbital involvement was the second most common finding, seen in 10 patients (71%). Post-contrast images showed a loss of contrast enhancement

**Table 1.** Radiologic Imaging Findings in Patients Who Developed COVID-19-Associated Rhino-Orbito-Cerebral Mucormycosis

Imaging Findings	Number (%)
Paranasal sinus involvement	14 (100)
Orbital involvement	10 (71)
Cavernous sinus involvement	6 (42)
Pterygopalatine fossa involvement	8 (57)
Perineural spread	4 (28)
Pachymeningeal enhancement/involvement	8 (57)
Subdural abscess	4 (28)
Cerebritis	2 (14)
Unilateral ICA occlusion	4 (28)
Acute cerebral infarction	3 (21)

COVID-19, coronavirus disease 2019.

in the nasal mucosa defined as 'black turbinate' in 9 patients (64%). Cavernous sinus involvement in 6 patients (42%), pterygopalatine fossa involvement and pachymeningeal enhancement in 8 patients (57%), perineural spread in 4 patients (28%) (3 patient with 5th cranial nerve and one patient with 7th cranial nerve involvement), subdural abscess and unilateral internal carotid artery (ICA) occlusion in 4 patients (28%), cerebral infarction in 3 patients (21%), and cerebritis in 2 patients (14%) were detected. Mandibular osteomyelitis developed in one patient due to temporomandibular joint involvement, and osteomyelitis of the frontal bone developed in another patient. Table 1 shows radiological involvement areas.

## DISCUSSION

Rhino-orbito-cerebral mucormycosis is the most common variant of mucormycosis infection.<sup>18</sup> Rhino-orbito-cerebral mucormycosis has a fulminant course and shows a similarly high mortality in our study as stated in the literature.<sup>19</sup> Limited sinonasal disease is a broad term denoting rhino-orbital disease and/or rhino-orbital-cerebral disease. The disease is mainly manifested by facial swelling, headache, decreased vision, and fever.

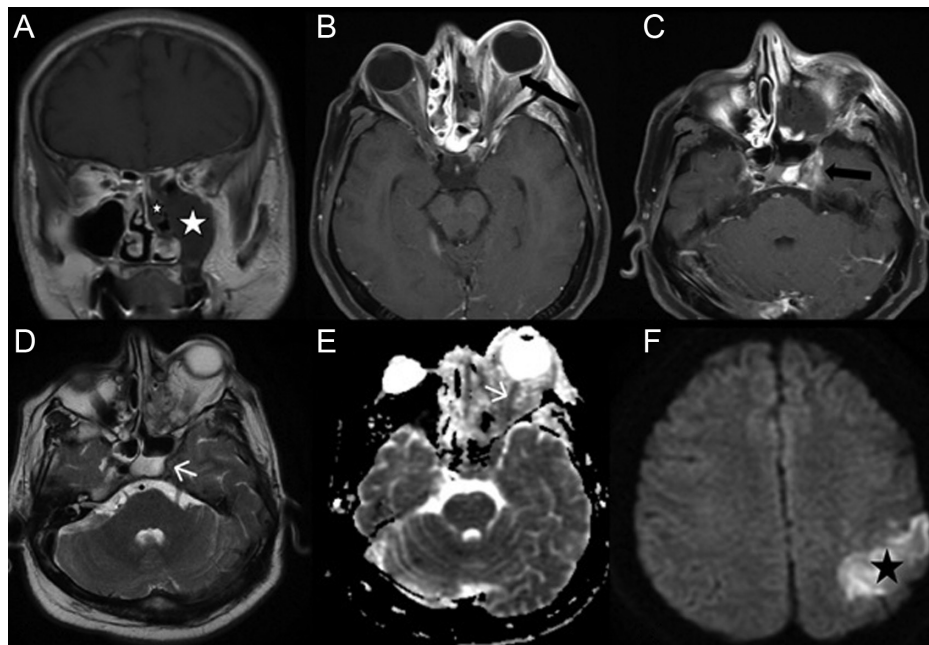
Due to the immune dysregulation that develops in COVID-19, patients become more prone to develop secondary infections.<sup>20</sup> In line with the results we obtained from our research, the most common comorbidity encountered in the development of mucormycosis infection is diabetes mellitus.<sup>21</sup> In addition, high-dose corticosteroids, which are widely used in the treatment of COVID-19, cause immunosuppression by inhibiting the sequestration of CD4+T lymphocytes and the transcription of cytokines in the reticuloendothelial system.<sup>22</sup>

Sino-nasal involvement was the most common finding in all patients at the time of diagnosis. 'Black turbinate' represents post-contrast signal loss due to microvascular angioinvasion of the nasal mucosa and consequent necrosis (Figure 1). Orbital involvement presents as intense inflammation in the pre- and/or post-septal distance, effacement in adipose tissue planes, proptosis, increased signal in extraocular muscles, and enhancement. Diffusion restriction in the optic nerve develops as a result of ophthalmic artery invasion and causes permanent vision loss (Figure 1 and 2). The 'Guitar Pick' sign is used to define the conical deformation of the eyeball as a result of increased intraorbital pressure (Figure 1).

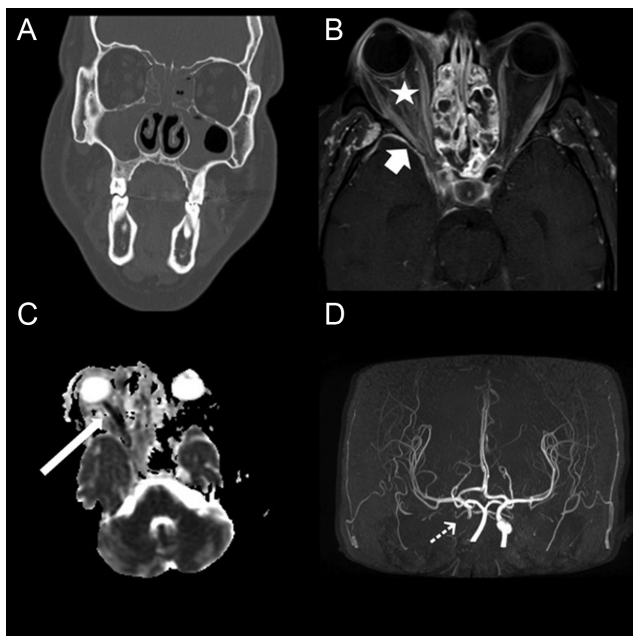
Intracranial involvement is the most dangerous and mortality-related complication. Although intracranial spread can occur in several ways, the majority of cases are the primary entry localization of the

## MAIN POINTS

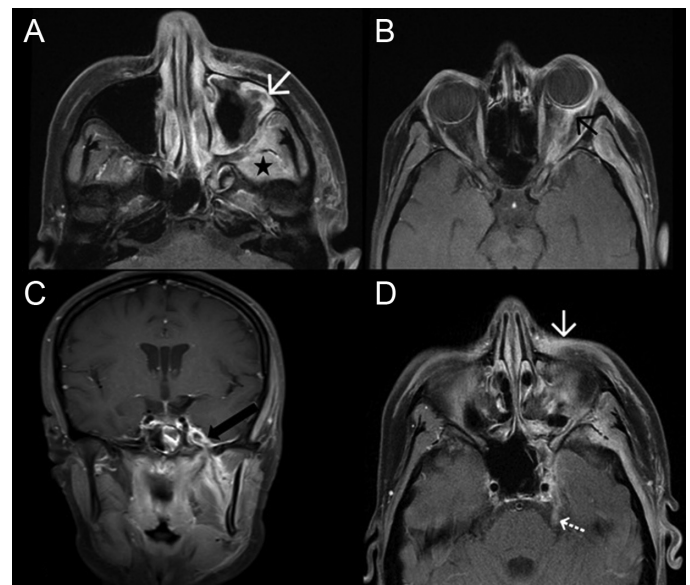
- Rhino-orbito-cerebral mucormycosis is an angioinvasive and opportunistic infection.
- Its frequency and aggressiveness increase with SARS-CoV-2.
- Magnetic resonance imaging has an important role in diagnosing and determining complications and managing the disease.



**Figure 1.** A 33-year-old male presented with swelling and pain in the left eye on the 13th day post-COVID. Coronal post-contrast T1W image (A) show the 'black turbinate sign' of the left middle nasal concha without contrast and the mucosa of the left maxillary sinus (white stars). Axial post-contrast T1W (B, C) images show 'guitar pick sign' and orbital fat tissue involvement due to conical posterior ocular deformation on the left, abnormal contrast enhancement in the left cavernous sinus wall and adjacent dura, absence of contrast enhancement due to occlusion in the left ICA (thick black arrow). Flow void detected due to occlusion in the left ICA on axial T2W image (D) (white arrow). ADC images (E) show hypointensity (white arrow) due to left optic nerve infarction. Diffusion-weighted imaging image (F) show diffusion restriction due to infarction in the left parietal lobe (black star).

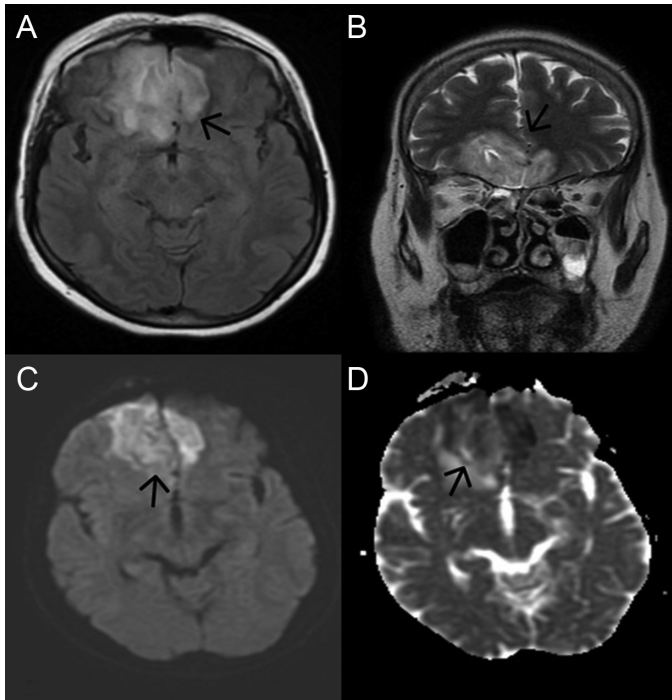


**Figure 2.** A 50-year-old man applied for vision loss and swelling in the right eye on the 9th day of COVID positivity. Coronal bone window CT image (A) shows intense opacification in the paranasal sinuses. Axial post-contrast T1W image (B) shows contrast enhancement (star) secondary to involvement in the right orbital fat tissue, proptosis, and anterior temporal dural enhancement (short arrow). ADC image (C) shows signal loss secondary to right optic nerve infarction (long arrow) and MR angiography (D) shows terminal blunt termination due to right ICA occlusion (dashed arrow). Although the patient had right ICA occlusion, no infarct finding was observed because the communicating arteries were patent.



**Figure 3.** A 15-year-old girl with type 1 diabetes and celiac disease received steroid treatment on the 14th day of COVID positivity and applied to the hospital with a complaint of swelling in the left eye. Axial post-contrast T1W images (A, B, D) show thickening and contrast enhancement in the left maxillary sinus mucosa and periantral soft tissue (white arrow). Contrast enhancement and proptosis (black arrow) secondary to involvement in the left retroorbital fat tissue and optic nerve, thickening and enhancement (dashed arrow) representing perineural invasion in the left trigeminal nerve ganglion are observed. Coronal T1W post-contrast image (C) show contrast enhancement due to inflammation in the left masticator space, intense inflammation extending to the cavernous sinus through the foramen ovale, and a subdural abscess adjacent to the cavernous sinus (thick black arrow).





**Figure 4.** A 61-year-old woman applied with a complaint of limitation in right eye movements on the 20th day of COVID positivity. In axial T2 FLAIR (A) and coronal T2W (B) images, there is intense signal increase in the right wider bifrontal basal areas and right middle frontal part. Diffusion-weighted imaging (C) and ADC (D) images show diffusion restriction secondary to cerebritis (arrows).

pterygopalatine fossa. In our study, the most common form of intracranial involvement was cavernous sinus involvement (Figure 1 and 3). Occlusion (Figure 1 and 2), perineural invasion (Figure 3), subdural abscess (Figure 3) and cerebritis (Figure 4) as a result of internal carotid artery (ICA) angioinvasion are other intracranial complications developed in our patient population. Vascular involvement, characterized by thrombosis and tissue necrosis, is the pathological hallmark of mucormycosis.<sup>23</sup> The presence of high amounts of free iron in tissues and blood is believed to play an important role in the pathogenesis of vascular invasion. Mucormycosis may form a mucorthrombus in the form of vasculitis or directly in the vessel lumen.<sup>24</sup> Four of our patients had unilateral ICA occlusion, but none of them developed pseudo-aneurysm formation.

The majority of case reports, series, and original articles in the literature have been based on data from the Indian patient population. In this respect, our study presents the most comprehensive study in Turkey in terms of the number of patients it includes. In addition, we have not come across any single-center study from Europe with such a large number of cases in the literature.

Mucormycosis infection should be kept in mind especially in cases such as concomitant diabetes, immunosuppression and prolonged hospitalization. Some studies suggest that patients with COVID-19 disease and at risk should be followed closely from the 10th day to the 6th week, when they are most vulnerable to mucor infection, and that screening imaging should be performed.

The limitations of the study include the small sample size, the fact that it is a single-center retrospective study, and the inability to demonstrate

radiological and clinical differences between mucor infection developing in patients with COVID-19 and unrelated COVID-19 mucor infection.

As a conclusion, radiologists should be aware of the diagnosis and complication imaging findings due to the high incidence of rhino-orbito-cerebral mucormycosis in the COVID-19 pandemic. Mucor infection, which is rare but mortal, should be kept in mind in patients with active or recovering COVID-19, especially those with concomitant diabetes and those receiving long-term steroid therapy, and MR imaging should be performed without delay, especially in determining intracranial complications and the spread of the disease.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Çukurova University (Date: December 2, 2022, Number: 128).

**Informed Consent:** Written informed consent was not obtained from the patients whose MRI images were included in this study, since the study was performed with radiological images only.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – Ö.K., Y.K.B.; Design – Ö.K., B.A.; Supervision – Ö.K., F.B., Y.K.B.; Resources – B.A., B.K.; Materials – B.A., B.K., Ö.K.; Data Collection and/or Processing – B.A., Ö.K.; Analysis and/or Interpretation – B.A., Ö.K.; Literature Search – B.A., A.Ç.A., N.N.K.; Writing Manuscript – B.A., Ö.K.; Critical Review – Ö.K.

**Declaration of Interests:** The authors declare that they have no competing interest.

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