



Rhino-orbito-cerebral mucormycosis during the COVID-19 third wave in 2021: an Egyptian preliminary report from a single tertiary hospital

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Abstract

COVID-19 is a pandemic disease which predominantly affects the respiratory system with high critical care mortality and morbidity; however, it also causes multi-organ dysfunction in a subset of patients. Although causality between COVID-19 and mucormycosis remains unclear, many factors including glucocorticoids, worsening of blood glucose control, and viral-induced lymphopenia have been attributed to cause mucormycosis in patients with COVID-19. In COVID-19 patients, especially those who need oxygen support, inflammatory and cytokine storm or usage of steroids make the immune system weak. This may pave the way for opportunistic infections including mucormycosis. We report fourteen cases of COVID-19 infection, who developed rhino-orbito-cerebral mucormycosis, during treatment. Early recognition of this life-threatening infection is the key to allow for optimal treatment and improved outcomes.

Keyword Rhino-orbito-cerebral mucormycosis · COVID-19 · Uncontrolled diabetes mellitus · Invasive fungal infection

Abbreviations

ROCM Rhino-orbito-cerebral
CT Cerebral computed tomography

MRI Magnetic resonance imaging
DM Diabetes mellitus
DKA Diabetic ketoacidosis
HTN Hypertension
FESS Functional endoscopic sinus surgery
AIFR Acute invasive fungal rhinosinusitis
AIDS Acquired immunodeficiency syndrome
IL-6 Interleukin-6

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Introduction

Mucormycosis is a rare but life-threatening, fungal infection caused by various species of the order *Mucorales* affecting immunocompromised patients [1]. A high rate of mortality (up to 50%) was reported in patients infected with *Mucorales* species of fungus [2]. Mucormycosis most commonly occurs in patients with underlying weak immunity, although sporadically, immunocompetent personnel may be affected [1, 3, 4]. In the pre-COVID-19 era, hematological disorders especially malignancies were found to be the commonest worldwide diseases associated with mucormycosis infection followed by diabetes mellitus [5–9]. Mucormycosis may infect patients treated with steroids, those with impaired immunity secondary to human immunodeficiency virus, on peritoneal dialysis, having iron overload, receiving

deferoxamine therapy, on illicit drug infusion, and/or voriconazole therapy [10–13]. Mucormycosis spores are commonly found in organic matter particularly food, soil, and plants which require humidity to grow [11, 14]. It could be transmitted through hospital bed linen, unsterilized oxygen lines, and ventilators [14]. The inhaled spore forms hyphae that invade the paranasal sinuses, extending further through anatomical sites or through blood circulation within the skull causing rhino-orbital or rhino-cerebral infection [5].

The COVID-19 infection caused by the novel severe acute respiratory syndrome coronavirus may be associated with a wide range of disease patterns, ranging from mild to life-threatening pneumonia. A wide range of bacterial and fungal co-infections may exist and may be associated with preexisting morbidity (diabetes mellitus (DM), lung disease) or may develop as a hospital-nosocomial infection such as ventilator-associated pneumonia [15].

COVID-19-associated mucormycosis is a term globally used to describe several cases of mucormycosis associated with COVID-19 infection [16–23]. Many reasons describe the ability of *Mucorales* spores to germinate in people with COVID-19. These reasons include hypoxia, hyperglycemia, acidosis, high iron levels, and decreased phagocytic activity of white blood cells due to immunosuppression (SARS-CoV-2-mediated, steroid-mediated, or background comorbidities) [24, 25].

COVID-19-associated mucormycosis clinically classified as rhino-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, or others, which includes uncommon rare forms, such as endocarditis, osteomyelitis, and peritonitis. Rhino-orbito-cerebral (ROCM) form is the commonest variety seen in clinical practice worldwide [13, 26]. ROCM being a rapidly progressive disease, even a slight delay in the diagnosis or appropriate management, can have devastating implications on patient survival [27]. In this case series, fourteen patients of ROCM associated with COVID-19 infection are presented with a highlight on etiology, pathogenesis, clinical, histopathological, radiological findings, and treatment.

Materials and methods

This is a retrospective case series analysis of patients with COVID-19, who were diagnosed as ROCM during treatment presenting to a single tertiary center in Ain Shams University hospitals, Cairo, Egypt, during May to June 2021. Diagnosis of ROCM was based on the global guideline for the diagnosis and management of mucormycosis, which includes (1) recent manifestations of sinusitis, facial pain or swelling, proptosis, and decreased or loss of vision; (2) radiological evidence of bone destruction and orbit/brain infiltration by coronal, axial, and sagittal cerebral computed tomography

(CT) scans, magnetic resonance imaging (MRI), or both for sino-nasal region and brain; and (3) histopathological assessment of nasal biopsies and fungal culture for identification of fungal species [27]. This study received approval from faculty of medicine, Ain Shams university ethical committee. Written informed consents obtained from patients (or next of kin in case of patient's death).

Results

Over 2 months, fourteen cases with ROCM were identified; eight of them were male. The demographic and clinical data of the cases are detailed in Table 1. The age range (49–82) years, and the mean (SD) age was 64.7 ± 10 years. All cases had a positive history of recent COVID-19 infection at the time of diagnosis with ROCM. According to Egyptian national guidelines, moderate to severe COVID-19 patients were treated with steroids; oral (prednisolone) in 9 and parenteral (methylprednisolone/ dexamethasone) in four cases [28]. All patients are treated with oxygen mask; no one needs an invasive respiratory device.

All patients had DM except one had liver transplant and two patients had DKA at the time of occurrence of ROCM. Six cases (42.8%) had hypertension, two cases (14.2%) had chronic kidney disease, and one case (7.1%) had ischemic heart disease.

The range of time interval between COVID-19 diagnosis and evidence of ROCM infection or diagnosis was 7–30 days, and median were 12.5 days.

Staging of ROCM patients and their clinical features are presented in Table 2 [29]. The initial presenting signs of the cases were ptosis (92.8%), conjunctival chemosis and edema (92.8%), proptosis (92.8%), loss of vision (85.7%), and total ophthalmoplegia (85.7%). Nasal discharge was present in (85.7%), nasal crusts (21.4%), epistaxis (14.2%), and nasal ulcer (14.2%). Facial pain was the commonest first symptom of ROCM patients (85.7%), facial swelling (21.4%), periorbital edema (71.4%), facial discoloration (21.4%), and soft tissue necrosis and gangrene of lids of eye (14.2%). Palate perforation was detected in 64.2% of cases. Headache was the commonest neurological symptom in these cases (100%), followed by hemiplegia (42.8%) and altered consciousness (35.7%).

On radiological assessment Table 3, thirteen cases developed orbital infiltration (92.8%) with one case (7.1%) having bilateral involvement. Six cases had recent cerebral infarcts (42.8%), three cases (21.4%) developed cavernous sinus infiltration, two cases (14.2%) developed internal carotid artery infiltration, and one case (7.1%) had cerebritis (Figs. 1,2,3,4,5,6,7, and 8).

Functional endoscopic sinus surgery (FESS) debridement was performed to nine cases (64.2%). Direct microscopy of

Table 1 Demographic Profile and Risk Factors for ROCM

Parameter	Number of cases (14)	Percentage of cases
Age (years)	49–82	
•Range	64.7 ± 10	
•Mean ± SD		
Gender	9	64.2%
•Male	5	35.7%
•Female		
Diabetes Mellitus	13	14.3%
•Diabetic ketoacidosis	2	
•Duration of diabetes; range (years)	3–18	
Steroid administration	1	7.1%
•None	9	64.2%
•Oral	4	28.5%
•Parenteral		
Time interval between COVID-19 diagnosis and evidence of ROCM infection or diagnosis (days)	12.5 (7–30)	
Median (range)		
Other Comorbid conditions	6	42.8%
•Hypertension	1	7.1%
•Coronary artery disease	2	14.2%
•Chronic kidney disease	1	7.1%
•Liver transplant		

the diagnostic nasal endoscopy swab of the cases, showed non-/pauciseptate, irregular, broad, ribbon-like hyphae with wide angle non-dichotomous branching in 9 cases (64.2%). Eleven patients (78.5%) recovered and discharged from the hospital, while three patients (21.4%) died.

Discussion

We retrospectively analyzed fourteen cases of rhino-orbito-cerebral mucormycosis with COVID-19 infection. The patients were diagnosed upon a combination of clinical, radiological, and histopathological findings.

Patients with COVID-19 are at increased risk of fungal infection due to associated multiple risk factors, including pre-existing diabetes (DM, liver transplant), use of immunosuppressive drugs (steroids), hospital-acquired infections (ventilator acquired), and systemic immune alterations by COVID-19 itself [5–8, 14, 30].

Neutrophils are crucial for inhibiting fungal spores' proliferation. Both mononuclear and polymorphonuclear phagocytes of a normal host kill *Mucorales* by generating reactive oxygen species and cationic peptides, namely defensins [31, 32]. In case of neutropenia or impaired phagocytic function, the patient will be at higher risk of black fungus infection [33]. In contrast, patients with acquired immunodeficiency syndrome (AIDS) do not seem to be at increased risk for suffering from black fungus infection. This explains why

neutrophils play a key role in the inhibition of fungal spore proliferation, but not necessarily T lymphocytes.

In patients with hyperglycemia and diabetic ketoacidosis (DKA), phagocytes are impaired and have defect in chemotaxis and defective intracellular killing by both oxidative and non-oxidative mechanisms [34]. In this case series, all the patients had a history of DM, except one (92.8%), and were treated with steroid for COVID-19 infection (92.8%). It is expected that COVID-19 might have further worsened the glucose profile of the patients with DM, thereby further predisposing them to mucormycosis. The worsening of dysglycemia in patients with COVID-19 occurs due to damage of β -cell as SARS-CoV-2 can infect and replicate in the human islet cells [35–37]. Also impairing the phosphorylation of insulin receptor and insulin receptor substrate by interleukin-6 (IL-6) can lead to insulin resistance [37–39]. Lastly, many drugs used in the management of COVID-19, namely glucocorticoids, lopinavir-ritonavir, and remdesivir, can impair glucose control and predispose to mucormycosis [37].

Undoubtedly, the rush use of glucocorticoids in patients with COVID-19 has contributed to the outbreaks of COVID-19-associated mucormycosis [6, 40]. Glucocorticoid-induced immunosuppression, hyperglycemia, and lymphopenia predispose to the pathogenesis of mucormycosis [33]. Moreover, steroid reduces the phagocytic activity of white blood cells (both first-line and second-line defense mechanism) and causes impairment of bronchoalveolar macrophage migration, ingestion, and phagolysosome fusion,

Table 2 Staging and clinical features of ROCM patients

Parameter	Number of cases (14)	Percentage of cases
ROCM staging	14	100%
I. Involvement of nasal mucosa	14	100%
II. Involvement of paranasal sinuses	13	92.8%
III. Involvement of the orbit	9	64.2%
IV. Involvement of central nervous system		
Laterality of ocular disease at presentation	9	64.2%
• Right	4	28.5%
• Left	1	7.1%
• Bilateral		
Ocular signs and symptoms related to Mucormycosis at presentation	13	92.8%
• Ptosis	13	92.8%
• Conjunctival chemosis and edema	2	14.2%
• Proptosis	12	85.7%
• Diminution of vision	12	85.7%
• Complete loss of vision		
• Total ophthalmoplegia		
Nasal signs and symptoms at presentation	3	21.4%
• Crusting	2	14.2%
• Epistaxis	11	78.5%
• Discharge	2	14.2%
• Nasal ulcer		
Facial signs and symptoms at presentation	12	85.7%
• Facial pain	3	21.4%
• Facial swelling	10	71.4%
• Periorbital edema	3	21.4%
• Facial discoloration	2	14.2%
• Soft tissue necrosis and gangrene of eyelids		
Involvement of oral cavity at presentation	9	64.2%
• Palate perforation		
Central nervous system signs and symptoms at presentation	5	35.7%
• Altered sensorium	6	42.8%
• Hemiplegia	14	100%
• Headache		

making a diabetic patient exceptionally vulnerable to mucormycosis [25].

Also, free unbound iron in serum plays a role in the etiology of mucormycosis. One of the essential elements for cell growth and development is iron. Therefore, pathogens, bacteria, virus, and even fungus especially *Mucorales* cannot grow in normal serum iron. It uses some processes for obtaining iron from the host [41]. Hyperglycemia causes glycosylation of transferrin and ferritin and reduces iron binding allowing increased free iron [42, 43]. Moreover, increase in cytokines in patients with COVID-19 especially IL-6 increases free iron by increasing ferritin levels due to increased synthesis and decreased iron transport [44]. Also, the ability of transferrin to chelate iron is reduced by acidosis which increases free iron that promotes fungal multiplication [4, 25, 45].

COVID-19 often causes lymphopenia, reduction in CD4⁺ and CD8⁺ T-cell level, thrombosis, endotheliitis, and endothelial damage and thus predisposes to secondary or opportunistic fungal infection [31]. Endothelial adhesion and penetration are critical early steps in the pathogenesis of mucormycosis. Widespread endothelial damage might promote adhesion and penetration of *Mucorales* to the endothelium [25, 40].

Water used in oxygen humidifiers helps in dissemination of fungal spores. This is another indirect association between the concomitant surge in COVID-19 and mucormycosis [46]. Transmission of mucormycosis via water in oxygen humidifiers could be a potential reason for the disproportionate increase in the number of mucormycosis cases in a developing country [15]. Also, the unhygienic delivery of oxygen or low-quality tubing system to these patients at the hospital, the oxygen cylinders with unclean masks, or using contaminated/tap water in humidifiers and prolonged usage of same mask for more than two patients [24].

The disease usually starts in the nasal mucosa, turbinate, or palate and spreads to the paranasal sinuses; it spreads to the retro-orbital region via the ethmoid sinus [5]. The disease may also progress through the inferior orbital fissure, extend to the retro-global area of the orbit, resulting in ophthalmic manifestations [47]. When entering posteriorly to the optic foramen, these fungi cause edema, inflammation, necrosis, and damage to the ophthalmic artery and optic nerves. The orbital apex syndrome may therefore manifest by chemosis, ptosis, proptosis, loss of vision, and blindness [48]. Diplopia and ophthalmoplegia are the initial findings of the cavernous sinus involvement. Similarly, after invading the orbit, it can reach the central nervous system (CNS) tissue. Vascular invasion is a characteristic feature and eventually causes infarction, hemorrhage, and tissue necrosis [5].

In this study, headache, ptosis and ophthalmoplegia, diminished or lost vision, proptosis, and facial involvement symptoms and hemiplegia were the typical manifestations. In agreement with our findings, there are several reports on the most common manifestations of ROCM patients indicating headache, ptosis, proptosis, periorbital swelling, facial swelling, ophthalmoplegia, and diminished or lost vision and dysesthesia on the involved side and black necrotic area in the turbinate, palate, and other involved sites [1, 2, 5, 27, 49]. Also, early visual loss would favor the diagnosis of rhino-orbital-cerebral mucormycosis over bacterial cavernous sinus thrombosis in which blindness is a much later finding (12 out of 14 patients in this series) [50].

Imaging is very important and useful for assessing the extent of disease. Thickened mucosal lining, opacification of the paranasal sinuses, and obliteration of ostiomeatal complex are the principal radiographic findings concerning the sinuses during mucormycosis by CT scan (100% in the present series). Also, CT scanning may reveal fluid levels, bone

Table 3 Imaging, histopathology, and management data of mucormycosis

Parameter	Number of cases (14)	Percentage of cases
Mucormycosis with extension on CT PNS or MRI findings	14	100%
•Pan-sinusitis	13	92.8%
•Orbital invasion	6	42.8%
•Ischemic stroke	3	21.4%
•Cavernous sinus thrombosis and infiltration	2	14.2%
•Internal carotid artery infiltration	1	7.1%
•Cerebritis		
Histopathological and/or microbiological diagnosis	8	57.1%
•Mucormycosis	1	7.1%
•Mucormycosis and bacterial infection		
Anti-fungal treatment	5	35.7%
•Amphotericin B	5	35.7%
•Liposomal amphotericin B	1	7.1%
•Voriconazole	4	28.5%
•Posaconazole		
Type of surgery for the treatment of mucormycosis	5	35.7%
•Not performed	9	64.2%
•Functional endoscopic sinus surgery (FESS) debridement		
Outcome	11	78.5%
•Alive	3	21.4%
•Deceased		

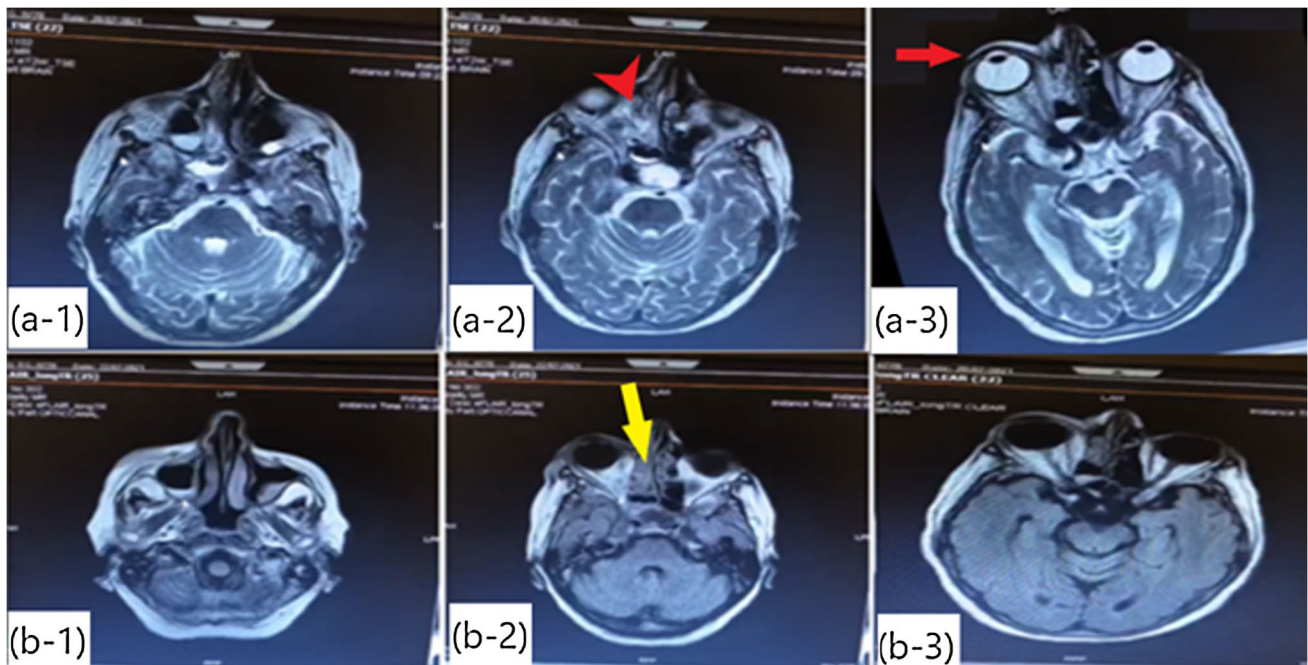


Fig. 1 Case 1, MRI brain axial T2 (a) and FLAIR (b): right retro-orbital inflammatory changes with smudging of the right intra/retro-orbital fat (read arrowhead), relatively bulky medial/superior rectus muscles. Mildly thickened right optic nerve associated with relative right exophthalmos with small preorbital edema (right arrow), involv-

ing the orbital apex as well as surrounding the cavernous segment of right internal carotid artery. Partially opacified right nasal cavity, total opacified right frontal and ethmoidal sinuses, and partially opacified sphenoid and left ethmoid sinuses (yellow arrow). Attenuated/obliterated ostiomeatal complex bilaterally, more on the right side

destruction, and osteomyelitis [27, 51]. However, radiological findings may be non-specific initially thus serial radiological investigations are required to assess progression and

extent [10]. Infection spread to the orbit, cavernous sinus, vascular structures, and intracranial contents can be evaluated by magnetic resonance imaging (MRI) [27, 49]. Similar

Fig. 2 Case 4, axial T2WIs (a) and (b) axial T2 FS (c) and (d) and coronal STIR (e) show left maxilla-ethmoidal and frontal sinusitis with edematous changes involving the pterygoid (short red arrows) and temporalis (long red arrows) muscles at the left side and minimal edematous changes involving the rectus muscle (yellow arrow) suggestive of sino-orbital mucormycosis

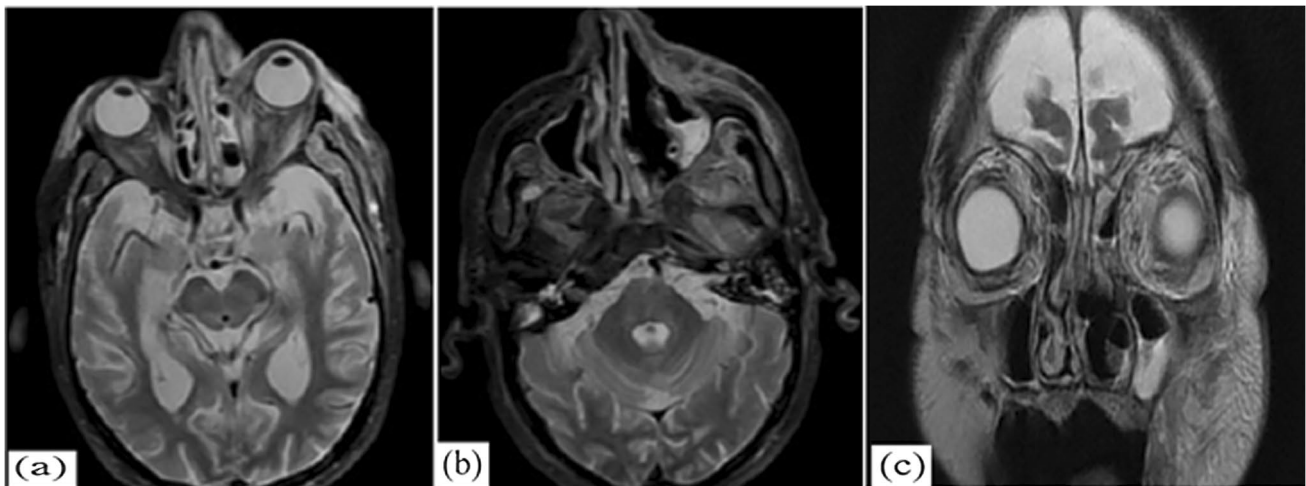
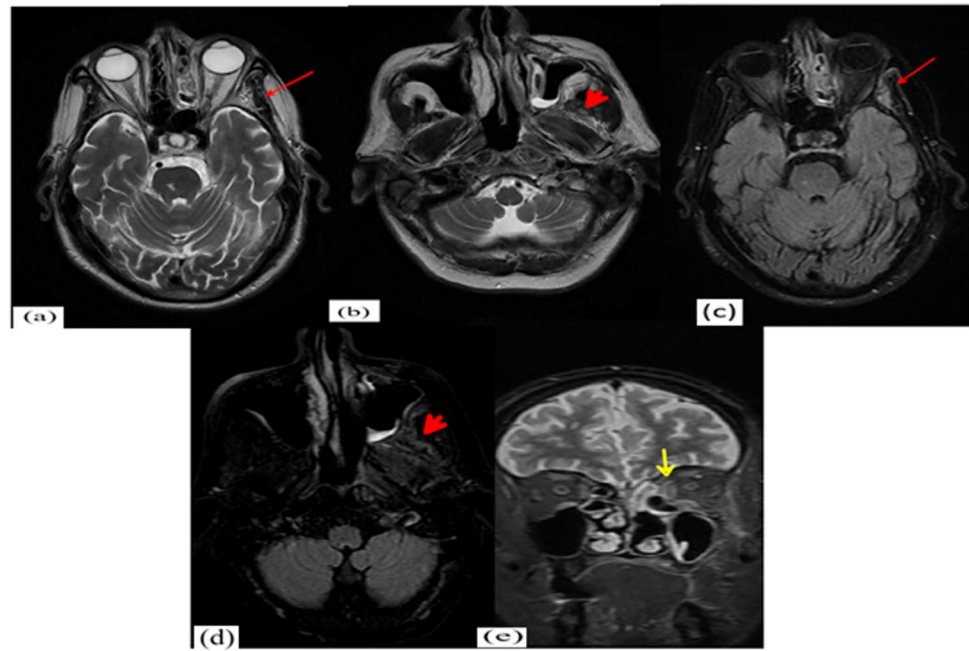


Fig. 3 Case 5, MRI axial STAIR (a) and (b) coronal T2WIs (c) show asymmetrical pan sinusitis with edematous changes involving the pterygoid and temporalis muscles, more at the left side and minimal

edematous changes involving the left orbital muscles and mild left side proposes suggestive of sino-orbital mucormycosis

radiological findings, recent cerebral infarction (42.8%), cavernous sinus thrombosis (21.4%), subarachnoid hemorrhage (14.2%), and cerebritis (one case), were reported in the present case series.

Definitive diagnosis is based on histopathological examination of biopsy specimens from the involved area. In the present study, a similar approach was used successfully in most of the patients (64.2%). Broad-based aseptate hyphae with irregular right-angled branching are characteristic microscopic features [52].

Pagano et al. [53] found the most frequent sites of infection were lungs (81%), CNS (27%), sinus (16%), liver (16%), orbital space (10%), and other sites. However, currently in the COVID-19 epidemic, ROCM form is the common site of infection followed by other organs [13, 26, 54]. As the area of involvement may differ due to underlying condition, ROCM is frequently observed in association with uncontrolled DM and DKA, whereas pulmonary involvement is often observed in patients having neutropenia, bone marrow and organ transplant, and hematological malignancies, while

Fig. 4 Case 5, CT coronal (a) and axial (b) cuts show asymmetrical pan sinusitis with edematous changes involving the pterygoid and temporalis muscles, more at the left side and minimal edematous changes involving the left orbital muscles suggestive of sino-orbital mucormycosis

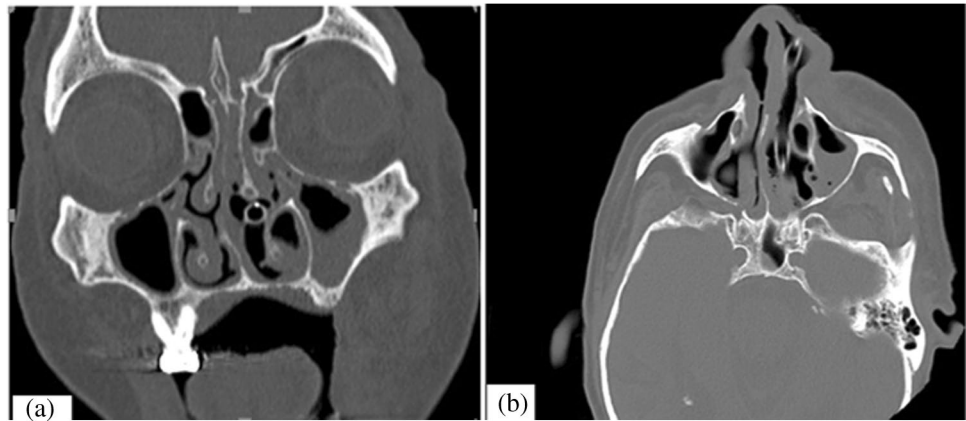


Fig. 5 Case 6, axial FLAIR (a), axial T2WIs (b), and coronal T2WI (c) show right side maxilloethmoidal sinusitis with early smudging of adjacent orbital fat tissue planes (arrows) associated with mild right-side proptosis suggestive of post COVID rhino-orbital mucormycosis

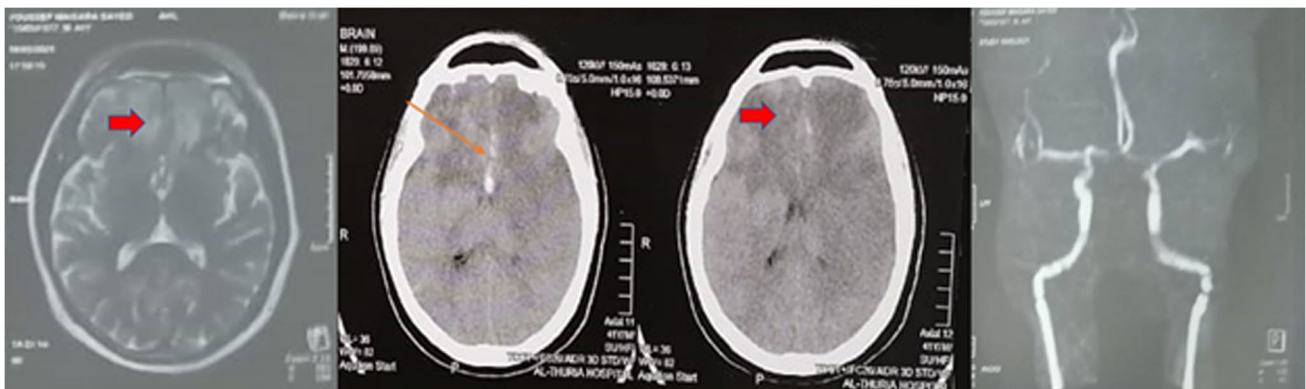
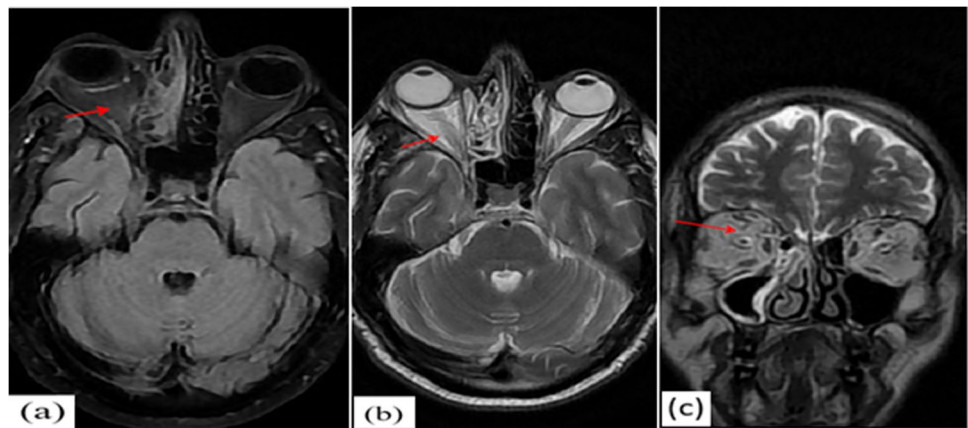


Fig. 6 Case 8, axial T2WIs, MRI brain axial CT brain, and MRA brain show bilateral basifrontal grey and white matter edema with high signal at T2WIs and hypodense at CT suggestive of cerebritis (short red arrows). Associated with adjacent extra axial hyperdense

hemorrhagic content at CT of associated subarachnoid hemorrhage (long red arrow). The MRA shows no obvious aneurysmal malformation or main branch occlusion

GIT gets involved more in malnourished individuals [25]. In the present series, all ROCM patients were diabetics.

In an interesting retrospective study conducted along a decade from 2007 to 2017 in children's cancer hospital 57,357 in Egypt, only 45 patients reported mucormycosis

[55]. Zaki et al. in 2010 reported 10 cases within 12-month duration analysis of admitted cases to Ain Shams specialized hospital with only 2 cases had a sinus mucormycosis and 8 cases had pulmonary mucormycosis [56], while in the current case series, 100% of the cases had a sinus infection.

Fig. 7 Case 13 CT coronal (a) and axial (b) show asymmetrical pansinusitis, more at right maxillary and right ethmoid air cells with early right orbital extension (yellow arrow) and edematous swollen right orbital muscles



Fig. 8 Case 13 MRI coronal T1 (a), coronal T2 (b), and axial DW (c) images shows post operative changes related to right antrostomy and ethmoidectomy with residual mucosal thickening and right frontal sinusitis. Right thalamic infarct is noted with restricted diffusion at DWI

In Egypt at the Department of Otorhinolaryngology, Mansoura University, El-Kholy et al. [57] reported a total of 36 patients with fungal rhinosinusitis (AIFR) in the last quarter of 2020 during the second wave of the pandemic. DM was the most common associated risk factor (27.8%). Analysis revealed infection with *Mucor* and *Aspergillus* species in 77.8% and 30.6% of patients, respectively. Sinonasal, orbital, cerebral, and palatine involvement was found in 100%, 80.6%, 27.8%, and 33.3% of patients, respectively.

Ebeid et al. [58] reported a dramatic increase in the rate of incidence of AIFR in patients with recent COVID-19 infection in comparison with pre-COVID-19 pandemic numbers. For 6-month period between July and December 2020, Tanta university hospitals (Egypt) admitted 28 AIFR patients. They found orbital affection with visual loss in 10 patients (50%), intracranial extension with disturbed conscious level in 4 patients (20%), and cavernous sinus thrombosis in 7 patients (35%). On the other hand, during a 3-year period between January 2017 and December 2019, only 20 AIFR patients were admitted in the same center.

Also, Fouad et al. [59] identified 12 patients with post COVID-19 ROCM presented to Ain Shams University Hospitals (Cairo, Egypt) during the second wave of the pandemic in Egypt (from March 25 till September 25, 2020). Orbital invasion noticed in all patients. 67% of them had cerebral invasion. The total number of cases diagnosed during this period of time is higher than the numbers reported in the prior 3 years during equivalent intervals (range, one to two cases).

Finally, Roushdy and Hamid [60] reported 4 cases of post COVID-19 mucormycosis that were presented to neurology department of Ain Shams University Specialized hospital (Cairo, Egypt) along the first few months of third wave of the pandemic 2021.

Thus, fourteen cases of ROCM in a 2-month duration encountered in a single hospital are considered relatively of significance for this disease when viewed in the context of literature reports. This is a preliminary report, and further studies are needed to corroborate the findings and explain possible underlying links, especially since we report the

experience of a single center due to the lack of a national registry.

This collected case series reported 21.4% mortality in 2 months, and this is considered low if compared to India publications as the mortality rate of ROCM range was (31–49%) [9, 61]. This emphasizes the importance of early diagnosis and management with a multidisciplinary team from otorhinolaryngologist, ophthalmologist, and pathologist. A delay of even 6 days in initiating treatment doubles the 30-day mortality from 35 to 66% [1].

Conclusion

COVID-19 is frequently associated with secondary infections, both bacterial and fungal possibly due to immune dysfunction. Besides this, the empirical use of broad-spectrum antibiotics, steroids, or monoclonal antibodies in the management of COVID-19 may lead to the development or exacerbation of pre-existing fungal diseases. The COVID-19 associated ROCM might be missed or misdiagnosed. COVID-19 patients, particularly those with DM, who are immunocompromised or severely ill, have a higher probability of suffering from invasive fungal infections. The clinician should be aware of the possibility of invasive fungal infections in such patients and should enable early diagnosis. Diagnosis should be suspected if there is unilateral orbital pseudotumor, orbital apex syndrome and/or cavernous sinus syndrome, ptosis, conjunctival chemosis, proptosis, facial pain or swelling, ophthalmoplegia, and diminution of vision. Good blood sugar control, restricted steroid use, early treatment, and intervention may reduce morbidity and mortality.

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