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Case Report

Successful Treatment of Acute Invasive Rhino-orbital Cerebral Mucormycosis Associated With COVID-19: Case Report and Literature Review

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ABSTRACT

Background and Aim: Mortality associated with post-coronavirus disease 2019 (COVID-19) rhino-orbital cerebral mucormycosis (ROCM) is an evolving concern. Association of COVID-19, corticosteroid therapy, and uncontrolled diabetes mellitus (DM) are considered predisposing factors for ROCM. We present two cases of successful treatment leading to patient survival for post-COVID-19, stage 4c-ROCM.

Case Presentation: Two middle-aged men with poorly controlled DM were referred to our hospital for post-COVID-19 ROCM. They had received intravenous antivirals and dexamethasone as treatment in a primary center. Both patients had unilateral oculofacial pain and swelling followed by acute visual loss, unilateral proptosis, facial palsy, and trigeminal hypoesthesia. A computed tomography scan revealed opacity and bony erosion of paranasal sinuses (PNS). Obtained specimens confirmed mucormycosis agent on histopathological examination. After the failure of conservative treatments, retrobulbar injections of liposomal-amphotericin B, PNS debridement, and orbital exenteration, both patients developed blurred consciousness owing to the extension of the infection into the intracranial cavity. Brain magnetic resonance imaging revealed a right frontal lobe abscess in case 1 and a left frontal sinus abscess and involvement in case 2. Both underwent transcranial debridement and resection of necrotic tissue and drainage of the abscess. At follow-up, the patients were in good condition, and the fungal cultures were negative for mucormycosis agents.

Conclusion: ROCM may be a complication of COVID-19 in high-risk patients. Control of the patient's underlying systemic condition and prompt treatment with antifungal agents, along with timely aggressive resection of cerebral abscess and necrotic paranasal tissues, are the mainstays of management for ROCM.

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Highlights

• Patients with poorly controlled diabetes mellites (DM) and under corticosteroid therapy are predisposed to COVID-19 associated with rhino-orbital cerebral mucormycosis (ROCM).

• Involvement of the brain lobes in ROCM is rare. Thus, clinicians should be aware that blurred consciousness can be a sign of extension of the infection into the intracranial cavity.

• The collaboration of a multidisciplinary team for providing prompt treatment with antifungal agents along with timely aggressive resection are the mainstays of management for ROCM and could provide patient survival.

Plain Language Summary

Black fungus is amongst the mortal complications in COVID-19 diabetic cases. During the treatment of COVID-19 patients, controlling blood sugar and restricting the use of synthetic steroids could prevent this complication. In case of signs of black fungi, such as facial pain and swelling, and visual loss, the patients should be referred to a multidisciplinary corona team. Antifungal medication and wide excision of the necrotic tissue could improve the survival of these patients. We, as neurosurgeons in the team, performed timely and sufficient brain debridement and incubated the site with betadine for 15 minutes. Despite high mortality, both of our patients survived the cerebral mucormycosis episode.

1. Background and Importance

The Coronavirus disease 2019 (COVID-19) devastatingly swept the world and has become a pandemic. By the fifth wave of COVID-19 (delta variant) in Iran, a great surge of post-COVID-19 mucormycosis is being referred to, and its high mortality has become a grave consequence [1, 2]. Currently, the triad of COVID-19, corticosteroid therapy, and uncontrolled diabetes mellitus (DM) are considered predisposing for mucormycosis [3].

The clinical system for staging rhino-orbital cerebral mucormycosis (ROCM) has been designed based on anatomical progression and severity and consists of four stages. The fourth stage includes the involvement of the central nervous system (CNS) [4]. A multi-centric study in India showed that, of the 2669 patients with post-COVID-19 ROCM, 21.4% (573) were at stage 4. In the CNS, cavernous sinus was most commonly involved (53%), followed by internal carotid artery (ICA) stenosis/occlusion (18%), temporal lobe abscess (12%), frontal lobe abscess (2.8%), skull base osteomyelitis (7.1%) [5], cerebral infarct [6, 7] and pachymeningitis [8], with a high mortality rate (59.1%) [9].

Our report aims to discuss clinical features, contributing factors, and outcomes of two diabetic patients with COVID-19 associated with ROCM. A multidisciplinary team consisting of an infectious disease specialist, otorhinolaryngologist, ophthalmologist, and neurosurgeons with timely aggressive debridement could provide patient survival.

2. Case Presentation

Case 1

A 50-year-old man was admitted for the second time to the hospital with complaints of recurrent right ocular pain and swelling accompanied by acute visual loss (light perception). On examination, he had severe proptosis, ptosis, and ophthalmoplegia. Right-sided facial nerve palsy (House-Brackmann facial nerve grade 4) and V2-V3 severe hypoesthesia were detected. The treatments he had received during primary admission for COVID-19 were O_2 with mask, interferon, dexamethasone, and remdesivir (200 mg on day 1 followed by 100 mg on days 2–5, in single daily infusions). He had been discharged with metformin and hydrochlorothiazide for type 2 DM and hypertension; on the fourth-day post-discharge, he was admitted.

Investigation revealed leukocytosis (21000 per mm^3), lymphopenia (11%), and moderate rise in C-reactive protein (CRP) (41 mg/L), while erythrocyte sedimentation rate (ESR) was 45 mm/h. Serum glucose was 388 mg/dL, and HbA1C was 10.8%, with no clinical evidence of ketoacidosis. A spiral chest computed tomography (CT) scan revealed bilateral patchy ground-glass opacities and consolidation, suggesting COVID-19 pneumonia (Figure 1A).

Endoscopic sinus biopsy and debridement were performed. Multiple different staining (Figure 2 parts A-C) of invaded tissues showed the spores, hyphae (broad, aseptate or pauci-septate, wide-angled with branching at 90°) with angioinvasion, in association with tissue damage and acute suppurative inflammation, confirming mucormycosis.

During his stay, he was treated with IV liposomal-amphotericin B (L-AmB) (CAS No. 1397-89-3) (AmBisome-Gilead Co., USA) (5 mg/kg, daily for 6 weeks), oral posaconazole (5 mL every 6 hours for 2 weeks), and additional IV caspofungin (70 mg/stat and 50 mg/d) for 2 weeks.

Definitive debridement consisted of maxillectomy, ethmoidectomy, sphenoidectomy, right-sided turbinectomy, and infratemporal fossa lesion resection and orbital apex decompression, which was done two days later. On repeat ophthalmological consult, right orbital exenteration was performed.

Later, he became drowsy and agitated with a decreased Glasgow coma scale (GCS) 13. A second contrast-enhanced magnetic resonance imaging (MRI) revealed a right frontal abscess, enlarged skull base lesions, midline shift, and frontal horn collapse (Figure 1B). He became a candidate for transcranial surgery. Right frontotemporal incision and pterional craniotomy were performed for debridement and resection of necrotic tissue and frontal lobe abscess. Then the orbital roof was debrided in an extradural manner. After entering the orbit, all necrotic tissues were removed, and the cavity was irrigated with H_2O_2 solution and packed with povidone-iodine (PVP-I) mesh. The patient had an uneventful postoperative course, and medical treatment was continued with IV infusion of L-AmB and oral suspension of posaconazole. At the 6-month follow-up, the patient was in good condition, and the fungal culture was negative for mucormycosis (Figure 1C, 1D).

Case 2

A 44-year-old male with known poorly controlled type I- DM since 4 years ago receiving insulin was infected with COVID-19 40 days prior to referral to our hospital. He had received IV-antiviral and dexamethasone as treatment in the primary center. He was admitted with a complaint of pain and swelling of the left eye

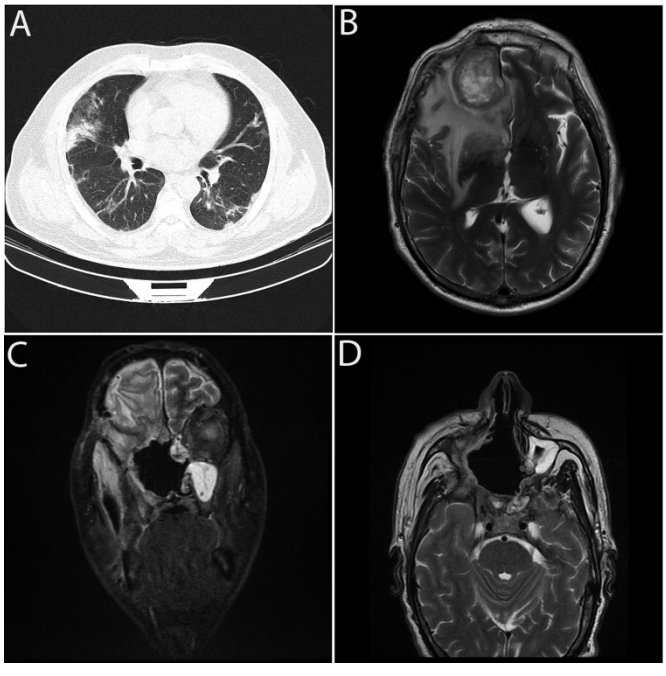

Figure 1. Chest CT Scan (parenchymal window) showing bilateral patchy ground-glass opacities and consolidation changes in both lungs, suggesting COVID-19 along with pneumonia

A) Pre-operative T2 weighted MR study with multiplanar images with different pulse sequences showed a heterogeneous signal lesion with severe peripheral edema in the right frontal lobe. Also, right cavernous sinus thrombosis with V3 involvement and dural invasion is present. Right optic nerve involvement and extension up to chiasma are visible; B) Postoperative coronal; C) and axial; D) images revealed total lesion removal.

Evidence of previous surgery as right maxillectomy, turbinectomy, ethmoidectomy, sphenoidectomy, nasal septal resection, and right orbital exenteration without significant enhancement is noted.

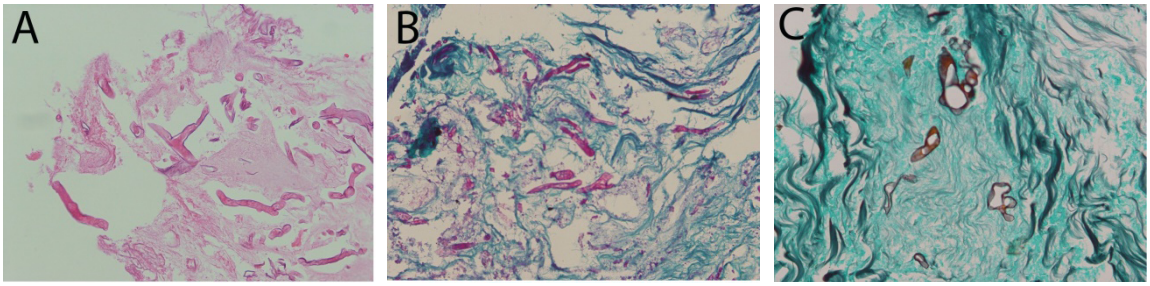

Figure 2. Histological view of broad and separate hyphae in case 1

A) Hematoxylin & eosin (H&E) staining ×400 magnification.

B) Periodic acid-schiff (PAS) staining ×400

C) Grocott's methenamine silver (GMS) staining ×400, show broad a broad and separate hyphae branching at 90°.

and face, followed by acute visual loss. On physical examination, he had severe proptosis of the left eye, ptosis, conjunctival chemosis, ophthalmoplegia, left periorbital and maxillary tenderness, left facial palsy (House-Brackmann facial nerve grade 4), and V1-V2-V3 hypoesthesia. Laboratory data revealed leukocytosis, lymphopenia (7.5%), elevated CRP (161 mg/L), and ESR (73 mm/h). His serum glucose was 304 mg/dL, and his HbA1C was 11.4%. Chest CT scan showed bilateral peripheral patchy ground glass opacities in favor of COVID-19 and pneumonia (Figure 3A).

A Spiral CT scan of paranasal sinuses (PNS) without contrast revealed left maxillary, ethmoid, and sphenoid sinuses opacification with bony erosion. An endoscopic endonasal evaluation was in favor of mucormycosis, and biopsies were obtained.

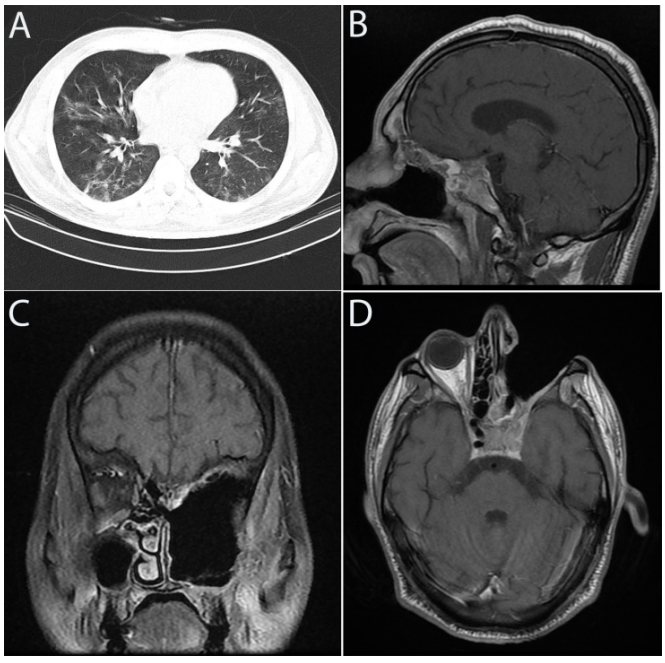

Figure 3. Spiral chest CT scan (parenchymal window) showing bilateral peripheral patchy ground-glass opacities, in favor of COVID-19

A) Pre-operative T1 weighted MR study with multiplanar images with different pulse sequences showing left frontal and sphenoid sinus abscess and cribriform plate involvement with gadolinium enhancement; B). Postoperative coronal; C) and axial; D) images revealed total lesion removal.
Evidence of previous surgery as left medial wall maxillectomy, turbinectomy, ethmoidectomy, and left orbital exenteration, are noted.

According to clinical and imaging findings, L-AmB was begun intravenously, and 6 times retrobulbar injections were performed, along with the administration of IV posaconazole. Definitive endoscopic sinus debridement was repeated twice within 3 weeks, along with turbinectomy, removal of the medial wall of the maxillary sinus, and left orbital exenteration.

During the hospital stay, he developed headaches and drowsiness with a GCS of 14. A second contrast-enhanced MRI revealed cavernous sinus thrombosis, cellulitis, and abscess formation spreading within the skull base (Figure 3B). Craniotomy was planned for anterior skull base debridement and abscess drainage. A bicoronal incision in the supine position anterior wall of the frontal sinus was removed on the left side, as well as the necrotic mucocele within the sinus, and thorough debridement was performed. The floor of the sinus cavity was removed associated with ethmoidectomy to expose the cribriform plate. Then the orbital necrotic tissue was debrided, maxillary sinus was unroofed, and total debridement and curettage of the maxillary sinus were performed. The resultant cavity was irrigated with H_2O_2 solution and packed with PVP-I mesh, and the patient was put on intravenous L-AmB ; after discharge, he was continued on oral suspension of posaconazole. At a 6-month follow-up after discharge, the patient was symptom-free without abnormal radiological findings (Figure 3C, 3D).

3. Discussion

The increasing incidence of ROCM in the setting of COVID-19 was a matter of immediate concern in India, Iran, and elsewhere. CNS involvement has been documented in 37% of the cases of post-COVID-19 ROCM [9]. Although most cases with post-COVID-19 stage 4-ROCM have been reported from India [5, 7, 8], reports from Egypt [10], USA [6], Turkey [11], and Iran [12] are on the surge.

The multidisciplinary ROCM care team must know the warning symptoms and signs of CNS involvement. V1 and V2 trigeminal hypoesthesia, ptosis, and features of the third, fourth, and sixth nerve palsy indicate cavernous sinus involvement. Bilaterality of these signs associated with contralateral orbital edema indicates cavernous sinus thrombosis. Hemiparesis, altered consciousness, and focal seizures indicate brain invasion and infarction [4]. Our cases with stage 4c (involvement beyond the cavernous sinus/skull base, ICA occlusion, and frontal sinus or lobe abscess) imply the involvement of the PNS, orbits, and CNS.

The concomitant use of steroids (>3 weeks), monoclonal antibodies such as tocilizumab, and broad-spectrum antibiotics for the management of COVID-19 can increase the chances of new-onset fungal infection [13]. According to the published literature, 76% of the patients with COVID-19-associated ROCM gave a history of prolonged high-dose systemic corticosteroids [14]. Both of our patients had a history of prolonged IV dexamethasone without tocilizumab and or azithromycin.

Other major risk factors for mucormycosis include uncontrolled DM, hematological or solid organ malignancies, chronic kidney or liver disease, immunological disorders, prior history of chronic sinusitis, iron overload, deferoxamine therapy and trauma [1], and use of mechanical ventilation or supplemental oxygen >3 weeks. Both of our patients had a history of poor-controlled DM. Nevertheless, DM may be induced de novo by COVID-19 infection; hence it might not only be a risk factor for a severe form of COVID-19 disease but also that infection could induce new-onset diabetes. Potential β-cell damage caused by the virus leading to insulin deficiency has been proposed by some studies [15]. Prophylactic oral posaconazole could be considered high-risk COVID-19 patients for ROCM [4].

In terms of therapeutic interventions, patients with CNS involvement alone seem to cope better than when PNS debridement and orbital exenteration are included in their management, which had been done for our patients [5]. In addition, the standard antifungal drug used in the studies was L-AmB, with or without posaconazole, as in our patients who received both drugs [6-8, 12].

PVP-I is considered to have the broadest spectrum of antimicrobial action compared with other common antiseptics, showing efficacy against bacteria, fungi, protozoa, and several viruses. PVP-I exposure damages the cell wall in fungi, such as Candida and Mucor species [16]. Previous studies have suggested that 0.5% PVP-I drop or irrigation solution or soaked mesh pieces packed in each nostril before and after operation in patients with PNS mucormycosis and COVID-19 is safe and protective, while betadine mouth gargle should be given to prevent ROCM in high-risk patients [4, 17]. Therefore, the intracranial abscess cavity was washed, and the nasal cavity was packed with PVP-I mesh. Using betadine 0.5% is safe and cost-effective in the deadly conditions of COVID-19 and may reduce the viral and fungal load in the PNS cavity perioperatively.

Because anterior ethmoidal air cells and frontal sinuses are not easily available during classic endonasal endoscopic approaches, the fronto-ethmoidal approach may be recommended as a solution for cases with extensive anterior skull base involvements.

Mortality in patients with ROCM with CNS involvement has been reported to be significantly higher (59.1%) compared with those without signs of progression to the CNS (24.3%) [9]. Nevertheless, both of our patients were alive after 6 months of follow-up.

Study Limitations

The approval of the predisposing effect of COVID-19 associated with corticosteroid therapy or DM for ROCM needs a sufficient number of cases for statistical evaluation which makes it a limitation of our study.

4. Conclusion

Clinicians should be aware that ROCM may be a complication of COVID-19 in high-risk patients. Therefore, control of the patient's underlying systemic condition, upper airway hygiene for mucormycosis, educating physicians about the early diagnosis, and prompt treatment with antifungals along with aggressive resection of cerebral abscess and necrotic tissues are the mainstays of management for ROCM.

Ethical Considerations

Compliance with ethical guidelines

We obtained written informed consent from the patient, as recommended by the Ethical Review Board of Tehran University of Medical.

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Authors' contributions

Conception and design: Hooshang Saberi; Data collection: Pedram Sdaghat, Ehsan Jaberansary, Nazi Derakhshanrad, Asghar Hajipour, Pouyan Aminishakib; Data analysis and interpretation: Nazi Derakhshanrad; Drafting the article: Hooshang Saberi, Nazi Derakhshanrad; Critically revising the article: Hooshang Saberi and Asghar Hajipour; Reviewing the submitted manuscript and final version approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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