



Coronavirus disease (COVID-19) complicated by rhino-orbital-cerebral mucormycosis presenting with neurovascular thrombosis: a case report and review of literature

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Abstract

Among the ever-increasing literature of the coronavirus disease 2019 (COVID-19), there have been reports on several complications in association with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), such as secondary bacterial and fungal infections. We report a 61-year-old woman with a past history of diabetes mellitus who presented to our hospital suffering from COVID-19 infection. During the course of her hospitalization, the patient developed chemosis and proptosis in both eyes, ultimately leading to a diagnosis of invasive rhino-orbital-cerebral mucormycosis and cerebrovascular thrombosis. This study strengthens the possible association between the occurrence of COVID-19 and invasive mucormycosis infection, providing new impetus for further investigations to substantiate this correlation.

Keywords COVID-19 · SARS-CoV-2 · Mucormycosis · Thrombosis

Introduction

Acute invasive rhino-orbital-cerebral mucormycosis (ROCM) is an infrequent, fatal infection that predominantly affects individuals with an immunocompromised state, a possible result of conditions, such as hematologic malignancies, diabetes mellitus, or organ transplantation (Hirabayashi et al. 2019). A novel coronavirus (severe acute respiratory syndrome-coronavirus-2 [SARS-CoV-2]) emerged from China in December 2019. The disease has spread into other countries at a rapid rate and developed into a pandemic (Wang et al. 2020a). However, in regard to the relevant literature thus far,

fungal co-infection and secondary infection with SARS-CoV-2 virus are relatively overlooked. In fact, there have been comparatively few reports published in the literature concerning the association of coronavirus disease 2019 (COVID-19) with fungal infection (Wang et al. 2020b; Chen et al. 2020a; Yang et al. 2020). Critically ill COVID-19-infected individuals who need mechanical ventilation, or must stay in the hospital for 50 days or longer, or have an immunosuppressed health state are more vulnerable to contracting fungal co-infections (Yang et al. 2020). Several etiopathogenic mechanisms (e.g., a marked increment in some of the interleukins (IL) and cytokine storms, low levels of CD4 cells expressing interferon-gamma, and decrement in the total count of T-helper 1 and 2 cells) can contribute to the development of secondary invasive fungal infections in severely affected COVID-19 patients (Chen et al. 2020b). Herein, we report a case of rhino-orbital-cerebral mucormycosis (ROCM) in association with COVID-19 infection and discuss the demographic, clinical, and prognostic characteristics of the aforementioned cases of sinonasal mucormycosis in association with COVID-19 in order to improve the diagnostic and treatment approaches in patients severely affected by SARS-CoV-2 and *Rhizopus*.

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Case report

A 61-year-old woman presented to our emergency department complaining of body pain, malaise, headache, hemianopia, and hemiparesis. She had a history of fatigue, generalized body pain, and progressive headache for 10 days preceding the admission. One day prior to the admission, sudden onset left-sided hemianopia and hemiparesis were added to her previous symptoms. Her past medical history (PMH) was notable for diabetes mellitus and hypertension. On arrival at the hospital, she was awake and oriented and her vital signs were normal with oxygen saturation (SpO₂) of 90% on room air. Neurological examination revealed left-sided homonymous hemianopia, left-sided hemiparesis with Medical Research Council (MRC) scoring of 0/5 and 2/5 in the left upper and lower extremities, respectively. Otherwise, the neurologic examination was unremarkable. Initial laboratory test results were as follows: white cell ($17.4 \times 10^3/\mu\text{l}$, with lymphocyte count 17%, normal $4\text{--}10 \times 10^3/\mu\text{l}$), C-reactive protein (CRP) ($> 150 \text{ mg/l}$, normal $0\text{--}6 \text{ mg/l}$), erythrocyte sedimentation rate (ESR) (138 mm/h , normal $0\text{--}30 \text{ mm/h}$), blood sugar (410 , normal $80\text{--}140 \text{ mg/dl}$), hemoglobin A1c (12.8% , normal $< 6\%$), ferritin level (4144 ng/ml , normal $4\text{--}204 \text{ ng/ml}$), D-dimer (2700 ng/ml FEU , normal up to 500 ng/ml FEU), venous blood gas (VBG) (PH 7.56 , normal $7.35\text{--}7.45$; Hco₃ 19.2 mmol/l , normal $22\text{--}26 \text{ mmol/l}$), and negative serum ketone. Due to the flu-like symptoms and blood test results, real-time reverse-transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 using oropharyngeal/nasopharyngeal swabs (Roche, Penzberg, Germany) and lung high-resolution computed tomography scan (HRCT) were studied which were consistent with COVID-19 infection (Fig. 1A). Consequently, the patient was promptly treated with lopinavir/ritonavir $400/100 \text{ mg}$ per oral (P.O.) twice daily, and her hyperglycemia was initially treated using lantus 10 units S.C (subcutaneous) qhs and sliding-scale protocol. The brain computed tomography (CT) showed hypodensities in the right frontal and parietooccipital junction regions suggestive of acute watershed infarct (Fig. 1B). On the 3rd day of admission, her level of consciousness was decreased with a Glasgow Coma Scale (GCS) of 8 out of 15; as a result, she was intubated. Due to the patient's condition worsening and her level of consciousness dropping and since her hyperglycemia was uncontrolled, the insulin intake protocol was changed from a subcutaneous protocol to a regular insulin IV infusion 1 unit/h regimen to maintain a blood glucose level of $150\text{--}180 \text{ mg/dl}$. On the 5th day of admission, she developed a GCS score of 6 out of 15, with proptosis, chemosis, and negative doll's eye reflex in both eyes. Although the first brain CT scan showed no

evidence of inflammation of the mucosal lining of the paranasal sinuses, the third one demonstrated a mucosal thickening of the paranasal sinuses, erosion of the right lamina papyracea with extraconal fat stranding, as well as hypodensities in the adjacent parts of the both frontal lobes (Fig. 1C–E). Furthermore, the brain CT venography was performed which showed filling defects in the bilateral cavernous sinuses and superior ophthalmic veins, predominantly on the right side, suggestive of cavernous sinus thrombosis (Fig. 1F, G). Consequently, unfractionated heparin 1000 units/h as a continuous IV infusion and amphotericin liposomal 10 mg/kg IV once daily (Cornely et al. 2019) were added to the patient's previous treatment regimen. Subsequently, an otolaryngology consult was requested and the patient was scheduled for endoscopic sinus surgery. In the first step of the endoscopic sinus surgery, RT-PCR for SARS-CoV-2 was performed again from nasopharyngeal secretions using nasopharyngeal swab which was positive. Afterwards, ostium of all of the sinuses were opened, and necrotic tissues were debrided as much as possible. Pathologic examination of the necrotic tissue revealed broad and non-septated hyphae consistent with invasive mucormycosis (Fig. 1H). During the course of hospitalization, blood sugar was relatively controlled with regular insulin intravenous infusion and the patient had no evidence of metabolic acidosis. All of the vasculitis and hypercoagulable markers including protein C, protein S, factor V leiden, and antiphospholipid antibodies were within the normal limits. On the 11th day of the admission, she became hypotensive and hemodynamically unstable; therefore, levophed was prescribed but the treatment was ineffective and the patient expired on the 12th day of the admission.

Discussion

Several factors, such as diabetes mellitus, neutropenia, systemic use of corticosteroid/immunosuppressive drugs, and hematologic malignancies can play a role as a predisposing factor for mucormycosis (Serris et al. 2019). Literature concerning the association of SARS-CoV-2 and fungal infections is scant with the prevalence of fungal co-infection, including invasive pulmonary aspergillosis and candidiasis in the setting of critically ill COVID-19 patients varying from 5 to 33.3% in these reports (Chen et al. 2020a; Yang et al. 2020; Alanio et al. 2020; van Arkel et al. 2020; Koehler et al. 2020). The combination of severe alveolo-interstitial inflammatory changes and damage, alteration of the immune response by SARS-CoV-2 virus including cytokine storms (marked elevation of both pro-inflammatory (IL-1, IL-2, IL-6, tumor necrosis alpha) and anti-inflammatory (IL-4, IL-10)

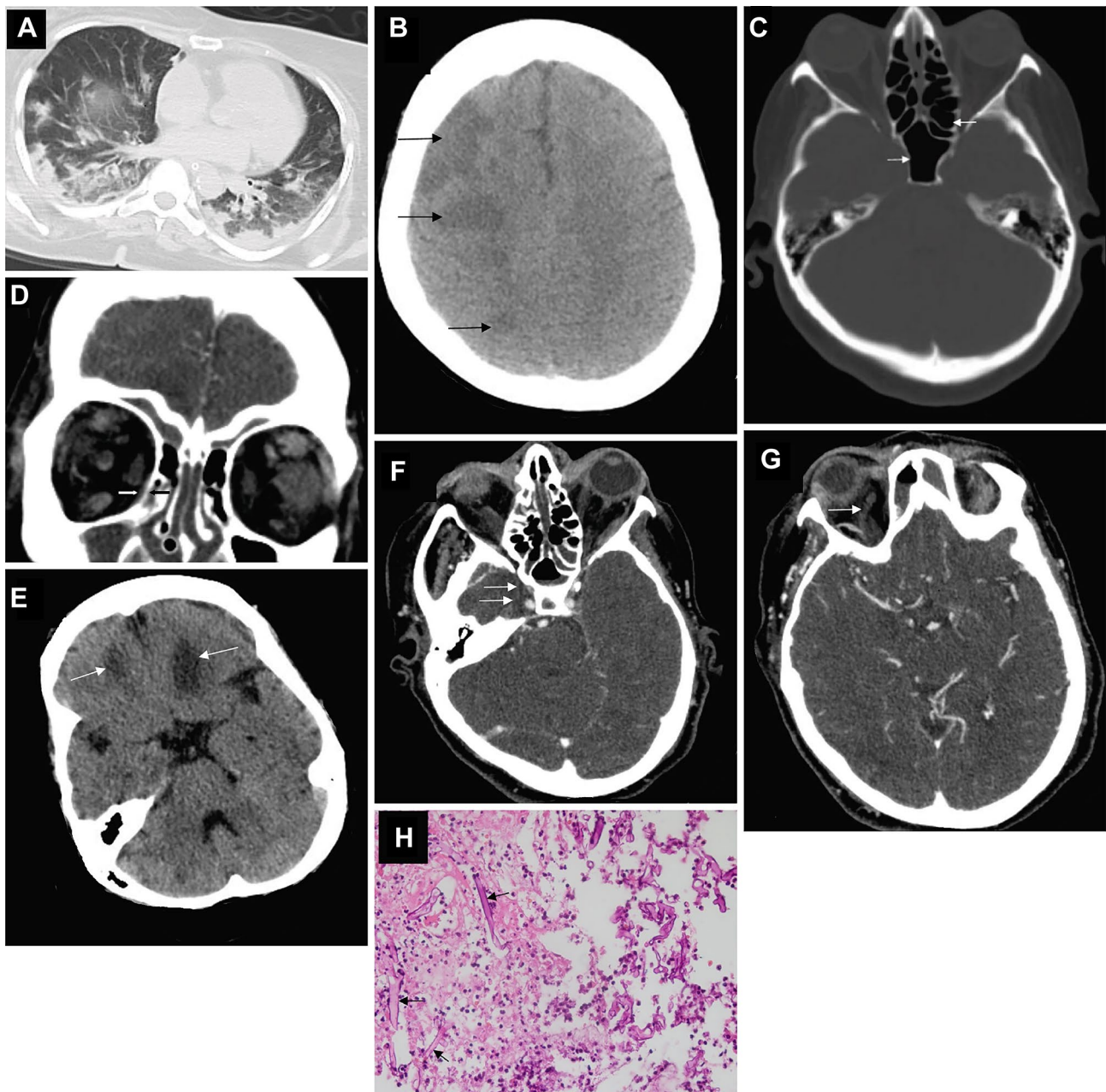


Fig. 1 **A** Lung high-resolution computed tomography (HRCT) shows several peripherally located patches of ground glass opacities in the lower lobes of both lungs highly suggestive of COVID-19. **B** Axial non-enhanced spiral brain CT scan shows hypodensities in the middle cerebral artery-posterior cerebral artery (MCA-PCA) and MCA-anterior cerebral artery (MCA-ACA) junctions suggestive of acute watershed infarct (black arrows). **C** Axial non-enhanced spiral brain CT bone window on admission shows normal air-filled paranasal (ethmoidal and sphenoidal) sinuses (white arrows). **D** Paranasal sinuses CT scan (PNS CT) on the 5th day of admission shows mucosal thickening of the ethmoidal sinus with right lamina papyracea bone

erosion (black thick arrow) associated with adjacent extraconal fat stranding (white thick arrow) suggestive of orbital involvement. **E** Axial non-enhanced spiral brain CT scan shows bilateral hypodensities in the base of both frontal lobes adjacent to the posterior ethmoidal sinuses (white arrows) indicative of intracranial extension of infection. **F, G** Brain CT venography (CTV) shows expansion of the right cavernous sinus (white arrows) as well as filling defects in the both cavernous sinuses and right superior ophthalmic vein (white arrow). **H** Microscopic section from sinonasal tissue shows necrotic background with many broad and non-septated mucormycosis hyphae (black arrows) (hematoxylin and eosin stain, $\times 400$)

cytokines), as well as reduced levels of both CD4 and CD8 T cells; hypoxia; the administration of immunomodulatory drugs such as systemic steroids, tocilizumab (anti-interleukin-6), and

anakinra (recombinant interleukin-1Ra); and widespread use of broad-spectrum antibiotics, may result in an increased risk of secondary fungal infection in severe cases of COVID-19

Table 1 Characteristics of reported case of invasive sinonasal mucormycosis i association with COVID-19

First author/ year	Case (first author)	Number of cases	Age (years)/ sex	History of DM/DKA on admission	BS (mg/dl) on admission/ HbA1C (%)	Mucormycosis clinical symptoms	History of mechanical ventilation before diagnosis of mucormycosis	Interval between COVID-19 and mucormycosis infection (days)	Steroid usage before mucormycosis infection	Thrombotic event	Treatment for COVID-19	Treatment for mucormycosis	Outcome
Werthman-Ehrenreich		1	33/F	+/+	649/NM	Proptosis, proptosis, ophthalmoplegia, fixed dilated pupil, and palatal necrosis	NM	0	–		NM	Amphotericin B (IV)+endoscopic surgical debridement+ lateral canthotomy	Dead
Mehta et al		1	60/M	+/-NM	NM/NM	Proptosis, fixed dilated pupil, facial edema and cellulitis	+	10	+		Oseltamivir, dexamethasone, tocilizumab	Amphotericin B (IV)	Dead
Mekonnen et al		1	60/M	+/-	105–143/14	Proptosis, chemosis,	+	8	–		Remdesivir, dexamethasone	Amphotericin B (IV)+ Caspofungin +retrobulbar local amphotericin injection	Dead
Sen et al		6	60 ± 12° /M	+ in all patients/+ in 3 patients	222 ± 144°/9 ± 3°	Proptosis, proptosis, loss of vision and ophthalmoplegia in all patients, chemosis in 4 patients, fixed dilated pupil in 2 patients, palatal necrosis in 2 patients and nasal sign in 3 patients	NM	15 ± 9°	+ in 5 patients	SOV thrombosis in 1 patient, cavernous sinus thrombosis and partial ICA thrombosis in 1 patient	NM except for systemic steroids that used in 5 patients	Amphotericin B (IV) followed by posaconazole (PO) in all +endoscopic surgical debridement in all + eye exenteration in two patients	All alive
Ostovan et al. (present case)		1	61/F	+/-	410/12.8	Proptosis, chemosis, and ophthalmoplegia	+	14	–	SOV, cavernous sinus and partial ICA thrombosis	Lopinavir/ritonavir	Amphotericin B (IV)+endoscopic surgical debridement	Dead

COVID-19 coronavirus disease 2019, DM diabetes mellitus, DKA diabetic ketoacidosis, BS blood sugar, CNS central nervous system, F female, M male, NM not mentioned, IV intra venous, PO per oral, SOV superior ophthalmic vein, ICA internal carotid artery

* Mean ± SD

(Chen et al. 2020a, b; Koehler et al. 2020; Rawson et al. 2020; Armstrong-James et al. 2020). These factors contribute to the development of invasive pulmonary fungal diseases, but it is still unclear whether sinonasal tissue as an upper respiratory tract is likewise susceptible to fungal infections in critically ill COVID-19 patients.

To the best knowledge of the authors of the present study, thus far, only a few cases of invasive sinonasal mucormycosis in association with the COVID-19 infection have been reported in the literature, of which the demographic data, clinical characteristics, and outcomes are shown in Table 1 (Werthman-Ehrenreich 2020; Mehta and Pandey 2020; Mekonnen et al. 2021; Sen et al. 2021). Given the interval between the occurrence of COVID-19 and that of mucormycosis in the previously reported cases and in our study (only 2 out of 10 cases happened concurrently), it seems that SARS-CoV-2 has a provocative effect on the development of ROCM in patients. However, the existence of diabetes mellitus as the most common predisposing factor for mucormycosis in all of the patients makes it difficult to identify the relationship between COVID-19 and mucormycosis with certainty. As shown in Table 1, 6 out of 10 cases had a history of systemic steroids administration before the emergence of the mucormycosis-associated symptoms. As a result, systemic steroids can be considered as a potential risk factor for the development of invasive mucormycosis in the setting of SARS-CoV-2 infection, particularly in patients with uncontrolled hyperglycemia. Although prescribing systemic steroids is advised by UK RECOVERY Collaborative Group in critically ill COVID-19 patients (RECOVERY Collaborative Group et al. 2021), these case reports may raise concern about the safety of using systemic steroids in the context of severe COVID-19 infections and diabetes mellitus. Therefore, further studies and clinical trials are warranted to elaborate on the risk–benefit ratio of steroids in patients suffering from both diabetes mellitus and severe COVID-19.

Considering the rapid progression of ROCM in cases of severe COVID-19 infections in the previously reported cases as well as our own, it appears that mucormycosis has a more aggressive and relentless course when occurring in patients already suffering from a severe COVID-19 infection. However, more cases are required in order to obtain a more accurate assessment of the case fatality rate and the pathogenesis of mucormycosis in co-occurrence with COVID-19. Besides, a detailed review of the clinical characteristics of the previously reported cases and ours shows that a history of mechanical ventilation before the appearance of mucormycosis-associated symptoms is the worst prognostic factor and that all patients who needed mechanical ventilation ultimately expired.

ROCM is an invasive fungal infection with a 30-day mortality rate of 35% which increases to 66% in case of

a 6-day delay in diagnosis and appropriate treatment initiation (Chamilos et al. 2008). Among the patients with invasive mucormycosis and COVID-19, 4 out of 10 were intubated or had decreased level of consciousness at the time of the mucormycosis diagnosis and they were not able to complain of mucormycosis-associated symptoms, which might have delayed a timely diagnosis and consequently increased the mortality rate. Additionally, if the patient is intubated, performing magnetic resonance imaging (MRI), as a gold standard imaging modality for the diagnosis of invasive sinonasal fungal disease, is not possible, which creates more difficulties for a correct diagnosis.

Systemic anti-fungal treatment and surgical debridement are the standard and accepted treatment for invasive rhino-orbital mucormycosis; however, in cases of reversible immunosuppression, good preoperative visual acuity, and low burden of orbital disease, local retrobulbar injection of liposomal amphotericin B as an adjunctive treatment can effectively halt the progression of the fungal infection and reduce the exigency of performing high-morbidity procedures such as orbital exenteration (Colon-Acevedo et al. 2015).

Although the exact role of COVID-19 in venous and arterial thrombosis is still being debated, 3 out of 10 patients displayed evidence of arterial or venous thrombosis of the central nervous system (Table 1), which might be due to the synergistic effects of SARS-CoV-2 and mucormycosis. SARS-CoV-2 can provoke a thrombotic cascade via various mechanisms, including the activation of the renin-angiotensin system, direct invasion of the endothelium, the activation of the complement system, and increasing the inflammatory biomarkers (IL-6 and IL-1 β) (Tal et al. 2020).

As we live in the era of the COVID-19 pandemic and due to the high mortality and morbidity rates of ROCM in the context of COVID-19, regularly checking for the appearance of facial edema, facial cellulites, nasal or palatal necrosis, proptosis, chemosis, or ophthalmoplegia (particularly in immunocompromised individuals with a severe SARS-CoV-2 infection) is crucial in order to improve outcomes and reduce morbidity and mortality.

As a major limitation, the patient in our study had diabetes mellitus as a main predisposing factor of mucormycosis; therefore, we can't identify the causal relation between COVID-19 and mucormycosis with certainty. Moreover, due to the patient intubation early in the hospital course, magnetic resonance imaging (MRI) could not be performed to measure the severity of encephalitis with accuracy.

In conclusion, this case report implies a possible association between COVID-19 and invasive sinonasal fungal diseases. Many more cases and studies must yet be published for this correlation to be substantiated.

Author contribution Material preparation and data collection were performed by VRO, SR, ZB, LH, RJ, MHA, and MR. The first draft of the manuscript was written by VRO, SR, ZB, LH, RJ, MHA, and MR and reviewed critically by VRO. All authors read and approved the final manuscript.

Declarations

Ethics approval and consent to participate The protocol of this study was approved by the ethics committee of Shiraz University of Medical Sciences (Approval No # IR.SUMS.MED.REC.1400.104). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from the patient's next of kin for the publication of her anonymized data in this case report.

Conflict of interest The authors declare no competing interests.

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