Invasive fungal sinusitis-A neglected but important association with COVID 19 infection and a ticking bomb

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ABSTRACT

A retrospective analysis of severe acute respiratory syndrome (SARS) and influenza data worldwide has concluded that fungal coinfections associated with global SARS-coronavirus 2 (CoV-2) are likely to be missed or misdiagnosed. The coronavirus disease-2019 (COVID-19) patients, especially those who are severely ill or immunocompromised, are more likely to suffer from invasive mycoses which require early detection and treatment. We report two such cases, one of which is a case of aspergillosis of unilateral orbit and maxilla and another case is of mucormycosis infection of the paranasal sinuses and bilateral orbits.

Keywords: Aspergillosis, COVID-19 infection, influenza, orbit, paranasal sinuses, rhizomucormycosis, RT-PCR (reverse transcriptase-polymerase chain reaction), SARS (severe acute respiratory syndrome), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been declared an emergency global public health event.[¹] The virus not only causes diffuse alveolar damage in the lungs but also leads to immunosuppression with decreased CD4 and CD8 T cell count.[²] These patients can develop fungal infections during the middle and later stages of the illness, especially those who have associated comorbidities.[³] Moreover, critically ill patients, admitted to the intensive care unit (ICU), requiring mechanical ventilation, or longer duration of hospital stay, and/or accompanied immunocompromised state are also vulnerable to developing fungal coinfections.[⁴,⁵]

In a developing country such as India, chronic illnesses such as diabetes mellitus often go unnoticed or neglected until emergencies arise. The emergence of the COVID-19 pandemic also brought a surge of opportunistic infections, such as invasive fungal infections. It is, hence, important that family practitioners are aware of the early signs of invasive fungal infections and have a high level of suspicion, especially elderly patients with comorbidities, such as diabetes mellitus, suffering from COVID-19 infection.

We report two such cases, one of which is a case of aspergillosis of unilateral orbit and maxilla and another case is of mucormycosis infection of the paranasal sinuses and bilateral orbits.

Case Report

Case 1: A 52-year-old male patient presented to the emergency center with complaints of left eye swelling and proptosis which were associated with severe left eye pain and left eye vision loss.
loss for 10–15 days [Figure 1]. The patient was concurrently suffering from the COVID-19 infection, which was confirmed on RT-PCR (reverse transcriptase-polymerase chain reaction). His comorbidities included long-standing diabetes mellitus and hypertension. On examination, crusting was found on the left middle turbinate, and the second pass of nasal endoscopic examination, the crusting was detected on the middle turbinate with pus formation at the superior and inferior turbinates. On ophthalmic examination, there was proptosis of the left eye with upper and lower lid edema, the conjunctiva showed ecchymosis, blackening, and necrosis. The eye movements were restricted. To release intraorbital pressure of the left eye, an emergency lateral canthotomy was performed.

Skin scraping from the left upper eyelid was sent for fungus culture and sensitivity. Intravenous liposomal amphotericin-B was initiated. The culture report showed growth of a few gram-negative septate fungal hyphae.

A computed tomography (CT) scan of paranasal sinuses showed soft-tissue attenuation without contrast enhancement along all walls of the left maxillary sinus, left anterior ethmoidal, and left frontal sinuses. A hyperdense focus was seen in the left maxillary sinus. There was a subtle erosion of the left lamina papyracea. There was also a soft-tissue thickening and enhancement in the left pre-septal space, left medial canthus, and premaxillary subcutaneous fat. Left ophthalmic artery was thrombosed on contrast enhanced CT scan (CECT) [Figure 2]. The left optic globe was smaller than the right.

The magnetic resonance imaging (MRI) scan of the paranasal sinuses showed proptosis and changes of endophthalmitis in the left eye with disease infiltration into retrobulbar fat, occlusion of the left superior ophthalmic vein as well as a left ophthalmic artery. The optic nerve on the left side showed a loss of the perineural fluid signal suggesting involvement up to the optic canal [Figure 3]. There was disease extension along the left inferior orbital fissure and retromaxillary fat. Soft tissue and subcutaneous fat were involved in the left periorbital and malar region. The findings were suggestive of a chronic invasive infective disease, possibly of invasive fungal disease to be ruled out.

A subsequent biopsy from the left nostril showed branching septate hyphae and spores in the nostril favoring aspergillosis.

After 3 days, the extended functional endoscopic sinus surgery with the left orbital exenteration was performed under general anesthesia. The biopsy of the tissue specimen showed the presence of fungal infection in the nasal biopsy, upper and lower eyelid margin, extraocular muscle from the superior and inferior margin, and periorcular fat from all margins. However, the optic nerve cut end and eyeball (pupil to optic nerve) were free from fungal infection.

The patient recovered and was discharged after 1.5 months of hospital stay.

Case 2
A 45-year-old male patient presented with complaints of blood-tinged discharge from the nose for the past 1 week. The patient also had complaints of reduced sensations over the face and left upper eyelid swelling for the past 2 weeks. This patient too was concurrently suffering from the COVID-19 infection. The patient was diagnosed to have associated diabetes mellitus. On examination, the right upper eyelid swelling was present with restricted right eye dextro-elevation and dextro-depression suggesting a possibility of the right orbital apical syndrome. A nasal swab was sent for culture which showed the growth of rhizomucormycosis. He was treated with oral clotrimazole and functional endoscopic sinus surgery was done.

The MRI showed polypoidal mucosal thickening in all paranasal sinuses [Figure 4]. There was bone erosion/dehiscence seen in the right cribriform plate and right lamina papyracea. There was also abnormal residual ill-defined enhancing soft tissue in the bilateral orbits in the superomedial extraconal space, suggestive of intraorbital extension. An abnormal T2 hyperintense signal with minimal postcontrast enhancement was seen along the right optic nerve sheath, suggestive of right optic neuritis. The patient was then medically managed with a long hospital stay. The vision though reserved, was, however, compromised.

Discussion
The most commonly associated fungal pathogens in severe COVID-19 patients are aspergillus and candida, mucor, and Cryptococcus. Several studies have suggested that patients with a COVID-19 infection and associated coinfection with invasive fungal diseases had higher mortality (53% with vs. 31% without), which was significantly reduced by appropriate therapy.

Our literature search indicated paucity in the reports of infection with aspergillosis or candida in the paranasal sinuses and orbit in COVID-19 patients in India. Mehta et al. reported a case of a 60-year-old male, a long-standing diabetic with SARS-CoV-2 concurrent infection and invasive fungal mucormycosis who developed signs of orbital cellulitis, and the MRI suggested the involvement of the right preseptal, malar, premaxillary, and retrobulbar regions, as well as paranasal sinuses. This patient succumbed without any operative intervention.

Sen et al. in her case series of six patients found that all patients with RT-PCR-positive reports and uncontrolled diabetes mellitus had developed rhino-orbital mucormycosis as late as 30–42 days after the diagnosis of COVID-19. All of their patients had compromised vision and only two cases had to undergo orbital exenteration, however, all of them survived.

Both our patients were diabetics and one was morbidly obese which made them vulnerable to developing an associated fungal infection. However, timely surgical intervention in one saved the eye, but in the other, delayed presentation lead to enucleation. Both our patients survived.
The nasal cavity acts as a primary target for opportunistic fungi through inhalation from where they gain access to paranasal sinuses. The orbit due to its adjacent location and various access routes via the infratemporal fossa, inferior orbital fissure, orbital apex, and through thin lamina papyracea of the ethmoid bone becomes a potential target by these opportunistic microbes. The brain too can be involved through potential gateways via the cribriform plate of the ethmoid, supraorbital fissure, and perineural invasion. Imaging plays a significant role in the early diagnosis aiding in prompt management and tailored surgical intervention which would help in reducing morbidity. It effectively identifies the extent of orbital involvement and intracerebral complications like cavernous sinus thrombosis, sagittal sinus thrombosis, carotid occlusion, cerebral infarction, intracranial aneurysm/hemorrhage, and cerebral abscesses.

It is very important to have a high index of clinical suspicion if patients present with symptoms of headache, periorbital pain, redness, periocular swelling, and diminution of vision.

CT features like hyper attenuation or soft-tissue attenuation associated with subtle to aggressive bone destruction of the sinus walls should raise the suspicion of a fungal disease in appropriate clinical scenarios. The extension beyond the sinuses may occur with intact bony walls as the fungi may extend along the blood vessels and nerves. Obliteration of the periantral fat is a subtle sign [Figure 5a and 5b] and must be sought for in all the patients at risk for acute invasive fungal sinusitis. MR is best in evaluating the intracranial and intraorbital extension of the disease. Heterogenous appearance and fat stranding along the orbital fat [Figure 6b] and extraocular muscles [Figure 7] with resultant proptosis [Figure 7a] are the early signs of an orbital invasion.

The cerebral extension of the disease is suggested on MRI when there is a leptomeningeal enhancement, adjacent cerebritis, nodular or ring-enhancing lesions suggesting granulomas, and/or cerebral abscess. More extensive changes such as retroantral fat pad inflammation, bone erosion, and orbital or intracranial invasion are more specific, but late, infrequent features.[9,10]

One of our cases showed features like infiltration of the retrobulbar fat with occlusion of the left superior ophthalmic vein and artery, involvement of optic canal as well as extension along the left inferior orbital fissure and retro maxillary fat, which suggested orbital extension [Figure 6b]. While in the other case, there was abnormal soft tissue in the right medial extraconal space which was abutting the right medial rectus muscle and levator palpebrae superioris muscle with changes of optic neuritis [Figure 7].

Multiple tests like direct microscopy, histopathology, culture, and molecular identification are available to diagnose fungal infection
Polymerase chain reaction (PCR) and deoxyribonucleic acid (DNA) sequencing can also be done but are available in limited laboratories but offer the advantage that they can detect fungal DNA in the serum and paraffin-embedded tissues. PCR is also a rapid test as compared to histopathology and culture.²⁸

Prompt aggressive surgical debridement of the affected tissues and systemic antifungal therapy are the mainstay of the treatment. Rigid nasal endoscopy and biopsy of suspicious areas are advocated for early diagnosis.²⁹

The global guidelines for diagnosis and management of mucormycosis in 2019 by the European Confederation of Medical Mycology ECMM and Mycoses Study Group Education and Research Consortium (MSG ERC) strongly recommend an early complete surgical treatment whenever possible in addition to systemic antifungal treatment.³⁰ The World Health Organization also strongly recommends systemic corticosteroids (intravenous or oral) rather than no corticosteroids for the treatment of patients with severe and critical COVID-19. Thus, a high level of clinical suspicion, prompt and proactive initiation with aggressive systemic corticosteroids, and early complete surgical treatment can alleviate morbidity as well as mortality.

Conclusion

The COVID-19 pandemic has resulted in widespread turmoil not only creating socioeconomic turbulence but also greatly affecting the health conditions of the masses. Active surveillance and vigilant detection are especially important in the vulnerable group of patients with COVID-19 infections to reduce mortality and morbidity. The incidence of rhinoorbital fungal infections is likely to rise, as a coinfection and as a sequel of COVID-19, thus, a high level of suspicion among physicians, early diagnosis by imaging, laboratory investigations, and appropriate timely management will help the society to cope better.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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