

## Chronic or Recurrent Invasive Fungal Sinusitis after COVID-19 Infection

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### Abstract

**Background:** During the COVID-19 epidemic, we have witnessed numerous manifestations and complications after contracting this disease. One of these complications in patients with COVID-19 is the increased risk of invasive fungal infections due to the suppression of the immune system caused by the disease or due to the use of suppressive drugs such as corticosteroids.

**Case presentation:** Here we report three cases of invasive fungal sinusitis after contracting COVID-19 with recurrence after primary treatment and the measures taken for these patients.

**Discussion:** Invasive fungal sinusitis with involvement of orbit or brain is a known complication in COVID-19 patients especially in diabetics. Recurrence of manifestations of fungal infection after primary treatment and hospital discharge may be related to uncontrolled underlying disease and residual fungal infection especially in necrotic soft tissue or bone.

**Conclusion:** Early diagnosis and management with antifungal drugs and surgical debridement and also close follow up after discharge from hospital is essential for treatment and achieving higher survival in patients with invasive fungal sinusitis.

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### Introduction

Coronavirus 2019 (COVID-19), caused by the Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) can cause mild to severe respiratory disease and lead to an emergency pandemic in the world (1). COVID-19 may lead to acute respiratory distress syndrome (ARDS). In these patients, corticosteroids such as Dexamethasone and Methylprednisolone are prescribed to reduce lung inflammation caused by the disease and prevent its progression (2). Because these drugs suppress the immune system of COVID-19 patients, they are likely to cause opportunistic infections (3, 4). Studies have shown that the rate of opportunistic

infections are higher in patients with severe form of COVID-19 among them, about 10 to 30 percent are related to fungal infections (5).

The most commonly reported fungal infections in patients with COVID-19 include aspergillosis, invasive candidiasis, and mucormycosis (6–8). Antifungal-resistant infections have also been described in patients with severe COVID-19 (9).

Uncontrolled diabetes and overuse of steroids are important risk factors in treating COVID-19 (10).

Herein we present three cases of chronic or recurrent invasive fungal sinusitis in patients

referred to our otolaryngology department with history of COVID-19 infection.

**Case Presentation**

**Case 1**

A 42-year-old diabetic male with right pre-septal cellulitis referred from ophthalmology department. He had no past medical history. His past surgical history was also insignificant. He

claimed that before developing ophthalmological symptoms, he had an episode of COVID-19 infection. Except for pre-septal cellulitis, every other physical examination was normal. He had normal neurological examination and his eyes movements were normal.

Except for inflammatory markers, laboratory investigations were otherwise normal (Table 1).

**Table 1.** shows the details of laboratory investigations of the discussed patients

Laboratory investigation	Case 1	Case 2	Case 3
White blood cell count	5823	7625	6254
Hemoglobin	13.2	12.8	14.1
Platelet	398500	423000	345000
Fasting blood sugar	98	87	129
Erythrocyte sedimentation rate	78	66	48
C-reactive protein	Positive	Positive	Positive
COVID-19 IgM	Negative	Negative	Negative
COVID-19 IgG	Negative	Negative	Negative

Endoscopic examination showed necrosis of parts of right middle turbinate. There was opacity in the anterior and posterior ethmoids and right frontal sinus in CT images (Figure 1).



**Figure 1.** Bilateral opacity of maxillary sinus.

Right antrostomy and posterior and anterior ethmoidectomy was performed for the patient, and the necrotic tissue was completely removed. Pathology findings in this stage showed invasive fungal rhinosinusitis. Six weeks later, the patient again developed right periorbital edema and erythema, which again underwent endoscopic sinus surgery. In the second stage, the sphenoid sinus was opened

and cleared of fungal secretions and pterygopalatine space was examined and cleared of necrotic tissue. The pathology findings from the second stage showed sinonasal mucormycosis associated with mucromycotic osteomeilitis.

**Case 2**

A 58-year-old diabetic male with a history of COVID-19 referred to us. He complained of pain and decreased sensation of left cheek and decreased visual acuity of left eye. He had insignificant past medical and surgical history. He consumed no medication.

Except for the mentioned abnormal examinations, neurological examinations were otherwise normal. The eyes movements were normal. Sensation, strength, reflexes, and tone were unremarkable in the trunk and extremities. The patient's gait was normal. High inflammatory markers were evident in his laboratory investigations (Table 1). Endoscopic examination showed necrosis in the left middle turbinate. Opacity of maxillary sinus, anterior and posterior ethmoids and left sphenoid sinus was evident on CT images. In the first stage, the necrotic mucosa of the left anterior ethmoid and

maxillary sinuses were removed. Pathology findings showed invasive fungal rhinosinusitis. After the first surgery, serial endoscopic examinations with debridement of remained necrotic tissue were performed in 3 sessions. After 8 weeks of antifungal treatment and with significant improvement of symptoms, including vision, the patient discharged from hospital. He came back with complaint of swelling of the left periorbital area after 3 months. Then he underwent endoscopic sinus surgery again. Pathology findings of the second stage showed tiny necrotic tissue associated with some broad pauci-septated hyphae.

### Case 3

A 49-year-old diabetic male with a history of COVID-19 came to our clinic with complains of nasal obstruction and pain. He had no other medical illness. His past surgical history was insignificant. His drug history consisted of Metformin.

On physical examination, the only evident abnormal finding was nasal congestion. His facial movement and sensations were normal. There was necrosis of mucosa of right inferior turbinate during nasal endoscopy. The details of laboratory data are mentioned in Table 1. Imaging findings showed opacity of the right and left maxillary sinuses (Figure 2).



**Figure 2.** Bilateral opacity of sinuses.

In the first stage, the patient underwent endoscopic sinus surgery and debridement.

Pathology findings showed invasive fungal rhinosinusitis. The patient returned to the hospital after 2 months of discharge with symptoms of lip numbness and pain on the right side. Then he underwent endoscopic debridement again. In the second stage, bone sequestrations were removed from inside of right maxillary sinus. Pathology findings in the second stage showed invasive fungus in favor of Mucorales.

### Discussion

COVID-19 is a viral disease that can lead to a global emergency epidemic. This disease has killed more than 1 million people worldwide. The treatment of this disease varies according to the symptoms and severity. Along with specific antiviral treatments, supportive care plays an important role in controlling the disease of COVID-19. One of the treatments for these patients is the administration of glucocorticosteroids. These drugs improve the lung inflammation and reduce the mortality caused by it in patients suffering from hypoxia (11). Due to the reduction of CD8+ T and CD4+ T cells, COVID-19 suppresses the immune system in patients. Administering glucocorticosteroids further suppress the immune system in these patients (12). Therefore, it causes a susceptibility to opportunistic infections. One of the most common opportunistic infections is fungal infection.

Chronic Invasive Fungal Sinusitis (CIFS) is a subset of Invasive Fungal Rhinosinusitis (IFS) occurs due to the inhalation of fungi and their invasion of the sinuses. It caused by saprophytic fungi such as Zygomycetes (*Mucor*, *Rhizopus*, *Rhizomucor*) and numerous *Aspergillus* species (13). Among them, *Aspergillus* species such as *Aspergillus flavus* or *Aspergillus fumigatus* are the most common cause of CIFS in humans (14). CIFS is classified into granulomatous and non-granulomatous forms, which can be distinguished mainly based on the presence of

submucosal granuloma with fungal hyphae and multinuclear giant cells on histopathology (15). CIFS is a fatal but rare infection that usually manifests in immunocompetent patients or patients with mild immunosuppression, such as patients taking corticosteroids for a long time or patients with mild diabetes mellitus (16). In immunocompetent individuals, phagocytes destroy inhaled fungal spores, but in immunocompromised patients, these spores may act as opportunistic pathogens and cause disease. In diabetic patients, increased blood sugar levels facilitate the germination and formation of hyphae, followed by vascular invasion with local tissue proliferation (17). The rate of progression of CIFS is slow, often progressing gradually over weeks or months. A period of less than 4 weeks separates the acute form of the disease from the chronic form (18). Therefore, we think our patients cannot be categorized as classic CIFS cases because of different clinical course and especially existing underlying immunocompromised state. Presentation of invasive fungal sinusitis after initial resolution of manifestations and control of disease may be related to poor control of underlying disease or residual disease in tissues, like case 1, with fungal osteomyelitis. Thus, close follow up of patients in outpatient setting for early symptoms of recurrence of disease is important. Complete eradication of invasive fungus may be difficult and complicated and may need more prolonged periods of antifungals, drugs originally have many side effects and on the other hand more aggressive surgical debridement while preserving viable tissue.

Early diagnosis and treatment of this disease is very necessary, especially in patients with immunodeficiency. Treatment for invasive fungal sinusitis includes reversal of any immunosuppression, surgical debridement, and systemic antifungal therapy such as amphotericin B.

## Conclusion

In summary, physicians should be aware of the serious infections that can affect patients with COVID-19. Early diagnosis of invasive fungal disease in COVID-19 patients and appropriate measures are necessary to cure the disease. It is also essential to follow patient for early symptoms of recurrence along with control of underlying conditions.

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