中文題目：新冠肺炎相關侵犯性麴菌性鼻竇炎：病例報告

英文題目：COVID-19 Associated Invasive Sinus Aspergillosis: A case report

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Introduction:

The co-infection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and fungus had been reported extensively worldwide. Traditionally, patients in an immunocompromised state were susceptible to fungal infections. Coronavirus disease 2019 (COVID-19) patients had significantly lower type I and III interferon responses, which were crucial in innate and adaptive immune responses against infectious diseases. In addition, the use of steroids and IL-6 inhibitors such as tocilizumab in COVID-19 treatment may increase the incidence and mortality of invasive fungal diseases in patients with co-existing SARS-CoV-2 infection.

We report a case of invasive sinus aspergillosis with orbital fossa involvement who was infected with COVID-19. The patient underwent early surgical debridement and was treated with a novel second-generation triazole, isavuconazole.

Case Report:

The 69-year-old female had underlying diseases of poorly controlled diabetes mellitus (DM), chronic kidney disease (stage 3b), and hypertension. The patient was brought to the emergency room due to cough and general weakness for 3 days. She was diagnosed with COVID-19 pneumonia. The patient was treated with the combination of remdesivir and dexamethasone for 5 days. Empirical ceftriaxone was used for pneumonia.

During hospitalization, she complained of progressive right orbital swelling with periocular pain. Right periocular redness and tenderness were also noticed. Limited extraocular movement and decreased visual acuity were detected 7 days after admission. Computed tomography (CT) of paranasal sinuses disclosed right ethmoid and maxillary sinusitis with extension to the right orbital fossa and inferior rectus muscle of the right eye. Invasive fungal sinusitis was suspected. Empirical antifungal agent of intravenous (IV) liposomal amphotericin B (250mg daily) was administered initially for suspected invasive mucormycosis or aspergillosis. Ceftriaxone was changed to piperacillin/tazobactam for broader coverage of nosocomial pathogens.

Right multiple sinusectomy with right orbital wall decompression was performed. Upon the surgery, pus and the fungal ball were noted in the right maxillary sinus. Pathology report of the tissue fragments disclosed acute and chronic inflammatory infiltrates, necrotic debris, and fungal hyphae. Gomori methenamine-silver (GMS) and periodic acid–Schiff (PAS) stains revealed fungal microorganisms with sharp angled branching and septate hyphae, suggestive of *Aspergillus* species. The patient had a positive serum galactomannan antigen test (0.698; reference index< 0.5) as well.

After the operation, right periorbital swelling and pain were alleviated. Because of deteriorated renal function, the antifungal agent was changed to IV isavuconazonium sulfate after 5 days of liposomal amphotericin B. The dosage of such medication was 200mg every eight hours for 2 days followed by 200mg daily. Repeated sinus CT revealed decreased effusion in the right maxillary sinus and infiltration into orbital fossa. The patient was discharged after a total of 8 days of IV isavuconazole treatment. She had not noticed right orbital swelling or pain when visiting the outpatient department after 14 days of oral isavuconazole treatment.

Discussion:

Fungal rhinosinusitis was broadly divided into two groups, non-invasive and invasive. The course of acute invasive fungal rhinosinusitis (AIFR) developed in a month or less. Patients with AIFR usually had more severe immunocompromised status and bore a higher risk of mortality (around 50%). *Mucor* and *Rhizopus* spp. and *Aspergillus* spp. lead to most cases of AIFR.

Aspergillus spp. and *Mucor s*pp. had several differences in morphology under a microscope. Aspergillus had an acute angle, dichotomous branching, and septate hyphae. Mucor and Rhizopus spp. had wide and non-septate (or pauci-septate) hyphae with larger angles. People with neutropenia were prone to aspergillus infections. Genes encoding pentraxin-3, toll-like receptors 2 and 4, and dectin-1 have been associated with increased risk. DM was the predominant risk factor for mucormycosis. Moreover, *Mucor* spp. was usually more aggressive and had more frequent angiovascular or orbital invasion. It was often reported with higher mortality than aspergillosis.

There are three major components in the treatment of AIFR, reversal of the pre-disposing condition, early surgical intervention, and anti-fungal medications.

Antifungal therapy should be initiated as soon as AIFR was diagnosed. Among all antifungal agents, amphotericin B was traditionally the main empirical AIFR treatment. If aspergillus was proved to be the causative pathogen, triazole can replace amphotericin B as the mainstay of treatment. Isavuconazole is an efficient and relatively safe option for aspergillosis treatment. Moreover, isavuconazole is also recommended as the savage treatment of mucormycosis, especially when the patient suffered from intolerable adverse events from amphotericin B.

Conclusion*:*

We present a case of a COVID-19 patient with invasive sinus aspergillosis, who recovered under isavuconazole treatment. The case had distinct features of its fulminant progression, co-existing SARS-CoV-2, and anti-fungal treatment by a novel triazole, isavuconazole. To our knowledge, there have been many reports about invasive fungal rhinosinusitis with SARS-CoV-2. However, there was a lack of experience on isavuconazole treatment of COVID-19 associated AIFR. Further study should be conducted to examine the efficacy of this novel anti-fungal agent on COVID-19 associated AIFR.