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Invasive Fungal Sinusitis Associated with COVID-19

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Abstract

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According to WHO Coronavirus (COVID-19) Dashboard, as of 11th February 2022, there have been 404,910,528 confirmed cases of COVID-19, including 5,783,776 deaths. Coronavirus-2 (SARS-CoV-2) is the causative agent. It is caused by coronavirus-2 (SARS-CoV-2), the disease may cause acute respiratory distress syndrome (ARDS), that increases the susceptibility of co-infections with fungi. Acute invasive fungal sinusitis (AIFS) is a severe infection mostly affecting immune-compromised patients and carries high risk of mortality. COVID-19 patients admitted to the ICU have risk factors for AIFS, mainly chronic diseases of the respiratory tract, treatment with corticosteroid, intubation/mechanical ventilation, and cytokine storm. Aspergillus and Mucorales are the causative fungi of most AIFS cases, but other atypical fungi can be involved especially among patients receiving azole prophylaxis. Most AIFS cases have symptoms like fever, nasal congestion, and facial swelling. Diagnosis of AIFS is made by endoscopy and radiology associated with clinical examination. The gold standard test for diagnosis of AIFS is histopathology, though pan-fungal PCR plays an important role. Therapy of AIFS includes surgery, antifungal agents, and correction of immunosuppression status

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Introduction

The epidemic of respiratory infection caused by the new coronavirus SARS-CoV-2 that occurred by the end of 2019 in China and became a global pandemic associated with large number of deaths. The death rate varies between different regions, with unclear high rate in some countries.¹ Alongside Acute Respiratory Distress Syndromes (ARDS) caused by it, Coronavirus disease 2019 (COVID-19) patients are immunocompromised due to a lowered CD4 T and CD8 T cells.² This causes several bacterial and fungal infections that may occur simultaneously with a preexisting disease (diabetes mellitus, lung disease) or may suffer a hospital-acquired infection.³ Acute invasive fungal sinusitis (AIFS) is a lethal infection that develop in immune-suppressed patients and represent the most severe form of fungal sinusitis with following serious morbidity and mortality. It is highly frequent in individuals with malignancy, uncontrolled diabetes, AIDS, immunosuppressive, chemotherapeutic drugs and COVID-19.4,5 This review aims to demonstrate the possible association between invasive fungal sinusitis and COVID-19 pandemic highlighting the diagnostic and therapeutic challenges.

Origin of COVID 19 pandemic

The pandemic of COVID-19

By the end of 2019 in Wuhan, China, many cases of lower respiratory tract infections were caused by a new corona virus severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). The virus is of zoonotic origin and has high potential transmission from human to human leading to rapid epidemic in China and subsequent global pandemic.⁶

Virology of SARS- COV-2

SARS-CoV-2 is an enveloped β -coronavirus, with a nearly identical genome of SARS-CoV-1 and bat coronavirus.⁷ In the viral envelope, several proteins project from it including spike (S) glycoprotein, envelope (E), and membrane (M) proteins (fig 1). Several mutations have developed in the viral genome (RNA). SARS-CoV-2 has a higher number and much more affinity to host receptors than SARS-CoV-1, suggesting more easy spread.⁸



Figure 1: Schematic structure of SARS-CoV-2⁹

structural proteins such as spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The S, M, and E proteins are embedded in the viral envelope. The N protein interacts with viral RNA.

Transmission of SARS-COV-2

Transmission of SARS-COV-2 occurs via infected respiratory droplets, and infection occurs by

direct or indirect contact with nasal, conjunctival, or oral mucosa. The epithelium of the oropharynx and upper airway, the conjunctiva and gastrointestinal tracts harbor the target host receptors.¹⁰

Pathogenesis of COVID-19

The viral S protein mediates binding to target host cell receptor (angiotensin-converting enzyme 2) which is expressed on multiple human cells followed by viral entry. The ACE 2/angiotensin has an essential role in inflammation and tissue injury.¹¹ ACE 2 expression was reported to be attenuated in females compared to males¹² and was found to be age dependent.¹³ The level of inflammatory cytokines is related to the severity of COVID-19. Significant decrease in lymphocytes and natural killer cells count is detected in patients with severe disease. Also, an increase in expression of inhibitory receptor to natural killer cells is associated with attenuation of T lymphocytes.¹⁴

Clinical manifestations of COVID-19

The incubation period range from 1–14 days. Children and adolescents represent < 2% of cases¹⁵ who are mostly asymptomatic or have mild symptoms.¹⁶ Death is uncommon in this group of age. Symptoms include low-grade fever, cough and anorexia.¹⁷ Clinical manifestations of COVID-19 pneumonia in adults include pyrexia, dry cough, sore throat, headache, fatigue, myalgia and difficult breathing.¹⁸ Presentation ranges from mild (81%) to moderate pneumonia (14%), and critical illness (leading to invasive mechanical ventilation, multi-organ dysfunction or death). Mortality rate depends on age, underlying comorbidities and disease severity, reaching up to 49% in critically ill patients.¹⁹

Complications of COVID-19

Most complications are associated with cardiopulmonary systems. Cardiac complications include myocarditis, arrhythmia, and ischemia; while the most prevalent pulmonary complications are bacterial pneumonia, pneumothorax, and pleural effusion. Guillain–Barré syndrome, encephalitis, polyneuropathy, delirium, psychosis and tinnitus were also observed. Thrombotic problems such as deep-vein thrombosis and pulmonary embolism have also been described, association with acute kidney injury (AKI) and renal failure was also a possibility.²⁰

Prognosis of COVID-19

Worse outcomes are associated with ARDS, AKI and myocardial infarction. High inflammatory biomarkers (CRP, ferritin), lactate dehydrogenase, hypokalemia, hypophosphatemia and coagulopathy (elevated D-dimer and PT) are predictors of mortality.²¹

Assessment and diagnosis of COVID-19 Diagnostic Testing by Polymerase Chain Reaction and Serology

The standard for diagnosis is detection of Viral RNA by polymerase chain reaction (PCR) from respiratory samples (eg, nasopharynx). False-negative results are related to amount of the specimen, time from exposure, and specimen source. Lower respiratory samples are more sensitive than upper respiratory ones.²² Serology based on detection of antiviral antibodies can also be used.²³

Laboratory Findings

Typical laboratory abnormalities included high serum C-reactive protein (>60% of cases), lactate dehydrogenase (~50-60%), alanine aminotransferase (~25%), aspartate aminotransferase (~33%) and low albumin (~75%).²⁴ The most common hematological finding was lymphopenia (~83%) with absolute lymphocyte count <1.0 × 10⁹/L. Modest prolongation of prothrombin times (~ >5%), mild thrombocytopenia (~30%) and elevated D-dimer (43%-60%) were also observed.²⁵

Imaging

Early in the disease, chest computed tomographic (CT) findings and chest radiograph can be normal where abnormalities occur in the first 2 weeks. The chest CT imaging abnormalities were peripheral ground-glass opacities. They are nonspecific, so it is of limited diagnostic value.²⁴

Treatment of COVID-19

Respiratory Support

Supplemental oxygen is needed in more than 75% of hospitalized patients. If no response occurred, heated high-flow nasal cannula or invasive mechanical ventilation may be required. Patients should be moved to airborne isolation room and donning personal protective equipment should be performed prior to intubation.²⁶

Targeting the Virus and the Host Response

Antivirals (remdesivir, favipiravir) were found to be effective early, antibodies (convalescent plasma, immunoglobulins), anti-inflammatory drugs (dexamethasone), targeted immunomodulatory therapies (tocilizumab, anakinra), anticoagulants (heparin), and antifibrotics (tyrosine kinase inhibitors) have been used. Trials of chloroquine/hydroxychloroquine, compounds have been tested, but early data have not demonstrated clear benefit.²⁷

Post COVID invasive opportunistic fungal infections

Decreased CD4 T and CD8 T cells counts with over expressions of cytokines in COVID-19 patients make them vulnerable to fungal co-infections. Life threatening invasive fungal infections affects patients with hematologic malignancy, organ transplant recipients, immune-compromised patients and uncontrolled diabetics. Corticosteroid therapy increases secondary fungal infection risk. So it is likely that, coronavirus by itself may not raise the risk for fungal infections, but other factors may have. Also broad spectrum antibiotics usage raises the risk of endogenous fungal infections including candida species.²⁸

Acute invasive fungal sinusitis in the context of COVID-19

Definition of acute invasive fungal sinusitis (AIFS)

 Table (1): Prevalence of predisposing factors for AIFR ³⁴

Sinusitis caused by fungi may be invasive or not according to the extent of fungal extension into the sub-mucous layer and the nearby vascular system.²⁹ The non-invasive form comprises allergic types, superficial mycosis and sinus mycetoma. Invasive form is subdivided into chronic and acute and both occur in immune-compromised subjects. Chronic invasive fungal sinusitis continues over months to years, in diabetic patients or patients on low dose of corticosteroids.³⁰ While, AIFS progresses rapidly over less than one month and occurs in subjects with more severe immunocompromisation and associated with high mortality up to 50–80%.³¹

Incidence of AIFS

The incidence of AIFS showed a significant association (P < 0.05) with post-COVID-19 patients than in non-COVID-19.³² At least 10% of COVID-19 patients in ICU develop Aspergillus co-infection.³³

Risk factors of AIFS

One study detected the most prevalent predisposing factors for AIFS were leukemia, particularly acute myeloid leukemia, and diabetes (Table 1).³⁴ A meta-analysis showed that diabetes was the most common followed by hematologic malignancy, corticosteroid use, renal or liver failure, solid organ transplantation, acquired immunodeficiency syndrome (AIDS), and autoimmune disease.³¹ Hospitalized COVID-19 patients in intensive care units (ICU) share risk factors for AIFS, particularly chronic respiratory diseases, corticosteroid therapy, intubation/mechanical ventilation, and cytokinic storm.¹

1). I revalence of predisposing fue	arenee of preusposing factors for Arrive		
Variable	Prevalence in AIFR Group	Prevalence in Control Group	
Acute myeloid leukemia (AML)	42.9% (18/42)	38.1% (16/42)	
Diabetes	28.6%	9.5%	
Other leukemia (non-AML)	19.0%	21.4%	
Multiple myeloma	7.1%	7.1%	
Solid organ malignancy	7.1%	0%	
Solid organ transplant	4.8%	9.5%	
Myelodysplastic syndrome	2.4%	7.1%	
Non-Hodgkin lymphoma	2.4%	11.9%	
None	2.4%	0%	

Fungal spores are numerous in the atmosphere and easily cause disease in the nose and paranasal sinuses. Inhaled fungi form part of the normal sinonasal flora, but in conditions such as antibiotic use for long duration, bad ventilation and humid environment associated with immunocompromised patients, make fungal infection more likely.35 The high aggressive nature of the SARS-CoV-2 causing bilateral alveolointerstitial lesions in the lung make the occurrence of invasive fungal infections (IFI) more likely, including invasive pulmonary aspergillosis (IPA) and mucormycosis.³⁵ Additionally, absolute number of T lymphocytes, CD4+T and CD8+T are markedly lower in severe cases, together with markedly higher levels of interleukin 2 (IL-2), IL-6, IL-10, tumor necrosis factor (TNF) alpha and other inflammatory markers, all these

factors share in increasing susceptibility of IFI.³⁷ The condition starts in the nose and paranasal sinuses and spread to the orbit which explains bad prognosis. The invading fungus destroys the surrounding bone and soft tissue by vascular thrombosis and tissue infarction and may extend to brain.³⁸

Causative fungi

Many fungal species can cause AIFS, but the most commonly involved were Aspergillus, Rhizopus, Mucor, and Rhizomucor, figure (1).^{39,40} Aspergillus species predominate among hematologic malignancy patients, whereas mucor predominate among poorly controlled diabetes patients. less commonly atypical fungi are involved like Fusarium, and Alternaria species. ⁴¹ The frequency of cultured fugal pathogens is demonstrated in table (2).³⁴



Fig. (2): Aspergillus species ⁴²

A Colony morphology on specific culture medium. **B**: Branching septated hyphae on H&E tissue staining **C,D**: Lactophenol Cotton Blue staining, showing septate hyphae and swollen vesicle giving rise to phalides from which chains of conidia arise.



B

Fig. (3): Rhizopus species ⁴³A: Colony morphology on specific culture medium;

B: Zygospores on wet mount



Fig. (4): Mucor on Lactophenol Cotton Blue staining ⁴⁴

Broad aseptate hyphae, with extension of columella into sporangium and aggregation of sporangispores

Table 2: Cultured fungal pathogens in patients with AIFR ³⁴

Fungal Species	Frequency
Aspergillus species	42.9%
Mucor species	23.8%
Curvularia species	7.1%
Fusarium species	2.4%
Bipolaris species	2.4%
Alternaria species	2.4%
Unknown	19.0%

Clinical Manifestations of AIFS

Facial pain and swelling, pyrexia, nasal blockage, and feeling pain in the eye occur in > 50% of patients.³¹ Ocular changes, proptosis, and weaknning of the extraocular muscles are less common, but manifest in progressive disease.³⁹ When the disease spreads outside the sinuses, it may embrace the orbit, cavernous sinus, or intracranial space. Propagation to the **Table 3: Presenting Signs and Symptoms in AIFS**³¹

cavernous sinus and orbit causes complications including orbital apex syndrome, superior orbital fissure syndrome, or thrombosis of the cavernous sinus. Intracranial extension leads to change of the mental status or neuropathy of the cranial nerves.⁴⁴ The frequency of presenting signs and symptoms is demonstrated in table (3).³¹

Sign or symptom	Frequency
Swelling of the face	64.5%
pyrexia	62.9%
Nasal congestion	52.2%
Ocular pain	50.9%
Proptosis	48.9%
Decreased vision	48.9%
Nasal discharge	48.1%
Facial pain	46.8%
Headache	46.3%
Cranial nerve palsy	41.5%
Altered mental status	21.1%
Palatal necrosis/ulcer	20.8%

Mortality

It is under recorded how fungal co-infection during COVID-19 affects mortality. But the impact of influenza/IPA co-infection is well known with mortality reaching 23%.^{46,47} In a study by Schauwvlieghe, the 3month mortality rate of influenza is 51% when coupled with IPA and 28% without it.⁴⁸ In France, IFI causes 9.2 to 40% of mortality in patients with co-morbidities.⁴⁹ Mortality is high (50 - 80%) in intracranial or orbital affection, irreversible immune suppression, and mucormycosis.³⁵

Diagnosis of AIFS

Physical head and neck examination

Evaluation of nose, mouth (teeth and palate), soft tissue, ophthalmologic, and cranial nerves should be considered.. mucosa of the nose and mouth are examined for pallor or necrosis, the teeth are examined for looseness or increased sensitivity to hot and cold items, and the visual exam includes acuity of vision, pupil similarity, reactivity, and status of the sclera and conjunctiva.⁴⁵

Nasal Endoscopy

Endoscopic nasal examination provides information about health of mucosal surfaces. Pallor or decreased sensation suggest early signs of AIFS, whereas necrosis occurs in late stage. When AIFS is localized to paranasal sinuses, the nasal endoscopy may appear normal; that is why why if nasal endoscope examination is negative does not exclude possibility of AIFS. The radiology completes the diagnosis.⁴⁵

Radiology

CT and magnetic resonance imaging (MRI) are the ultimate popular used techniques. CT provides information about bone safety around nasal sinuses, orbits, and base of the skull. If there are abrasions of the bone or soft tissue extension seen by CT (Fig. 4), suggestion of AIFS remain high.⁴⁵ Fat stranding, lost fat planes, and inflammatory changes outside the sinuses could suggest spread outside the sinuses (Fig. 5).⁵⁰



Fig. (5): CT and nasal endoscopy of AIFS ⁴⁵

a CT detects demineralization of left inferior turbinate (arrow) and soft tissue thickening.

b View of necrotic left inferior turbinate (arrow) by the endoscope.

c View after turbinate resection (arrow).



Fig. (6): Non-contrast axial CT in AIFS ⁴⁵

Total opacity of right maxillary sinus with demineralization and impairement in the posterior lateral maxillary sinus wall. Also, loss of fat plane posterior to the maxillary sinus due to inflammation

146

MRI was proposed as the former techniques for diagnosis of AIFS. Although, limitations include difficulty, time length and cost.⁵¹ Loss of contrast enhancement on MRI occurs in ~50% of AIFS patients (Fig. 6).⁵² If there is doubt of intracranial or intraorbital extension, both CT and MRI are considered. Also, CT chest detect COVID-19 signs or concurrent pulmonary infection.⁵³



Fig. (7): MRI changes associated with AIFS $^{\rm 45}$

a Iso-intense lesion within the upper part of the sphenoid sinus. **b** Loss of contrast enhancement

Histopathology

Histopathology revealed a clue of angioinvasion and lumenal thrombosis. Angio-invasion is the gold standard for diagnosis of AIFS and is demonstrated filamentous parts on pathology specimens stained with hematoxylin and eosin (H&E) (Fig.7).^{54,55} Frozen section support operative decision and confirm fungal tissue invasion. Gomori methenamine silver (GMS) stain also confirm fungal presence in tissues.⁴⁵ whereas 39 were positive on frozen periodic acid-Schiff stain (PASF).²⁸



Fig. (8): Sinus histopathology ⁵⁴
A, Bone and sinus tissue (400×, H&E): Fungal forms infiltrating arteries (arrow).
B, Sinus tissue (400×, H&E): Area of acute inflammation and fungus infiltrating arterial wall (arrow).

In a review of 271 biopsies evaluated for AIFS, 41 were positive on H&E staining. Of those 41 positive specimens, 34 were found positive on frozen H&E pathology,

Fungal Markers

Measurement of Aspergillus galactomannan (GM) in the serum can help diagnosis of invasive Aspergillosis, but with imperfect sensitivity (< 50%) and specificity. Cross reactivity with other fungi causing AIFS leads to false positives results.⁵⁶ Beta-Dglucan is another component of most fungal cell walls except mucor mycosis and represents another serum marker which is used in diagnosis of invasive Aspergillosis, but with few details on its use in AIFS.⁵⁷

Microbiology techniques

Direct microscopic evidence of fungal hyphae using 10% KOH in endoscopic sample is done initially and later confirmed by fungal culture and histopathology if radiology is nonspecific.³⁵ Fungal stains performed on tissue specimens are positive in few cases.⁵⁸ Cultures are positive in 50 to 95% of cases. Pan-fungal PCR may elevate the sensitivity to > 70-80% and decrease the time needed to reach diagnosis.⁵⁹ The diagnosis by PCR lacks antifungal susceptibility results. The Identification of the species level together with antifungal susceptibility testing can guide antifungal therapy.⁴⁵

Medical Management

Urgent surgical debridement, antifungal therapy, and correction of immunosuppression are the pillars of treatment of AIFS. Management requires a multidisciplinary approach of different specialists according to extent of infection.⁴⁵ Additionally medical management for COVID-19 should also be started.

Antifungal Therapy

Immediate treatment with antifungal agents should be started emperically based on clinical suspicion for AIFS; late therapy may increases the mortality.⁶⁰ For all patients start treatment with liposomal amphotericin B, which is effective against mucormycosis. After identification of the causative fungus, start targeted antifungal therapy (Fig. 8).⁴⁵

For Aspergillus species, the first-line is voriconazole while second options include isavuconazole and liposomal amphotericin Β. Posaconazole is used in resistant or intolerant cases. Echinocandins is used only as one of combination or rescue therapy.⁶¹ Combination of antifungal drugs for invasive Aspergillus infection is not frequently considered, but used as salvage therapy or in critical cases. Monitoring of drugs must be done for azoles. About 3.2% of Aspergillus isolates are azole-resisant and Liposomal amphotericin B is recommended.⁶² For Mucor, the drug of choice is liposomal amphotericin B. For intolerant or refractory patients switch to isavuconazole and posaconazole.63 Combination of azole with activity against mucormycosis (posaconazole with isavuconazole) amphotericin is also or

considered.⁶⁴ Treatment of atypical fungal causes of AIFS should be guided by existing expert consensus guidelines.⁶⁵ Continue treatment until compete clinical and radiologic resolution and until no normal fungal biomarkers, and negative fungal cultures on repeat cultures).⁴⁰

Correction of Immunosuppression

Multi-institutional review showed that immune stimulating therapies (Granulocyte- colony stimulating factor [G-CSF], Granulocyte monocyte- colony stimulating factor [GM-CSF], granulocyte transfusion, or all of them)) lead to 70% lowering in one month death in AIFS patients.³⁹

Surgical Management

First of all, surgeons should decide if the patient needs surgery. Once the decision is made, the timing of surgery is also critical. Prompt surgical should be conducted if there is proof of serious complication (vision loss) but elective surgery is considered if the clinical presentation is minimal. Prior to surgery, appropriate imaging, no per oral (NPO) status and reversal of coagulopathy are important. The algorithm for surgical management is illustrated in figure (9).45 Endoscopic, open, and combined techniques are used with serial debridement to eradicate infection. The aim of operative intervention is to obtain representative tissue sample for histopathologic analysis, pathogen identification, fungal cultures and antifungal susceptibility. Also it aims at removing necrotic tissue and opening up any obstruction.⁴⁵ Infection control measures for COVID-19 included the use of powered air purifying respirators and the exclusion of trainees from OR.³⁹ Consult ophthalmology discipline if the orbit is involved. In intracranial involvement, neurosurgery should be consulted. Additionally, oral surgery should be consulted if there is loose dentition. A second surgery after 1-2 weeks is important if clinical picture is not getting better. Repeat CT scan if there is a plan for second surgery.⁴⁵





Fig. (9): Algorithm for medical management of AIFS⁴⁵



Fig. (10): Algorithm for surgical management in AIFS $^{\rm 45}$

Conclusion

Covid-19 patients developing pneumonia require intensive care, and have risk factors that make them susceptible to get AIFS. Mortality of AIFS is still high in spite of improvements in medical and surgical treatment,. Early diagnosis followed by surgical and medical treatment of AIFS and consideration of COVID-19 treatment recommendations are essential for bettering patient survival. Correction of immunosuppression is the most important predictor of survival. Also encouraging preventive measures like antifungal chemoprophylaxis and environmental precautions is essential to decrease morbidity and mortality.

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