



SPECIAL ARTICLE COVID-19

Covid-19-Related Acute Invasive Fungal Sinusitis: Clinical Features and Outcomes

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Abstract

Introduction There is a noticeable increase in the incidence of acute invasive fungal sinusitis which coincides with the ongoing coronavirus pandemic. It is a potentially-lethal fungal infection, with the most common form being the rhino-orbito-cerebral presentation.

Objectives The aim of the present study is to discuss the different epidemiological factors, risk factors, clinical presentations and outcomes of acute invasive fungal sinusitis which is noticeably related to the coronavirus disease 2019 (Covid-19) pandemic.

Methods The present cross-sectional cohort study included 22 adult patients who presented with Covid-19-related acute invasive fungal sinusitis. The diagnosis of acute invasive fungal sinusitis was confirmed by histopathological biopsy. All data, including demographics, risk factors, clinical findings, different lines of treatment and their outcomes, were recorded and analyzed.

Results All patients had diabetes mellitus (100%), and 17 (77.3%) had been submitted to systemic steroids. All patients (100%) had unilateral sinonasal disease. Proptosis was found in 15 patients (68.2%), ophthalmoplegia was observed in 12 patients (54.5%), and intracranial affection occurred in 10 patients (45.5%). A total of 20 patients (90.9%) received liposomal amphotericin B. Surgical debridement was performed in 18 patients (45.5%). Non-septated mycelia was present in 19 biopsies (86.4%), while 3 (13.6%) showed septated mycelia. Total improvement was achieved in 10 patients (45.5%), while the mortality rate was of 27.3% (6 out of 22 participants).

Conclusion Diabetes mellitus is the most common preexisting medical condition associated with Covid-19-related acute invasive fungal sinusitis. Systemic corticosteroid therapy is considered a predisposing factor. It is necessary to raise the level of awareness to diagnose this condition, especially in patients with Covid-19 infection or those who have recently recovered from it.

Keywords

- ▶ Covid-19
- ▶ mucormycosis
- ▶ sinusitis

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Introduction

Coronavirus disease 2019 (Covid-19) is an infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Since the first case was discovered, in December 2019 in Wuhan, China, there have been various changes in terms of pathophysiology, diagnosis, treatment and arising complications.¹

The association between Covid-19 and invasive fungal sinusitis was noticed by Song et al.² in April 2020, and they concluded that many patients affected by or who had recovered from Covid-19 are at an increased risk of developing invasive fungal sinusitis.

There are many overlapping factors that lead to secondary infection that are increasingly being recognized due to their influence on morbidity and mortality, such as diabetes mellitus (DM), immunosuppressive therapy, any prior respiratory disease, and sources of nosocomial infections.³ Also, systemic immune changes due to Covid-19 infection itself play a role as the infected patients exhibit impaired cell-mediated immunity with decreased cluster of differentiation (CD) 4 and 8 positive T-helper (CD4+ T and CD8+ T) cell counts, making them more susceptible to fungal infections.⁴

Mucormycosis is an angioinvasive fungal infection caused by saprophytic aerobic fungi, transmitted environmentally via the inhalation of spores. The spores then colonize the nose or sinus mucosa, and, in immunocompetent individuals, phagocytes destroy the spores of inhaled fungi, but the spores may act as opportunistic pathogens in those with impaired immunity. In diabetic patients, the elevated blood sugar level facilitates germination and the formation of hyphae, followed by vascular invasion with local tissue proliferation.⁵ The most common type of *Mucorales* is *Rhizopus oryzae*, which is responsible for approximately 60% of the cases of mucormycosis cases in humans, and for 90% of the cases that present on the rhinocerebral form.⁶

Rhino-orbito-cerebral mucormycosis is the most common presentation of the disease. Some of its symptoms are non-ophthalmic, such as fever, headache, facial swelling, facial pain, nasal discharge, nasal and palatal eschar, toothache, and facial numbness and/or facial nerve palsy. The ophthalmic signs and symptoms, developed by direct extension of the disease from the paranasal sinuses, include eye pain, decreased vision, ophthalmoplegia, proptosis, chemosis, ptosis, orbital cellulitis, periorbital discoloration, and necrosis.⁷ Various neurological signs and symptoms may present if intracranial extension is developed.⁸

Aim

The aim of the present study is to discuss the different epidemiological, risk factors, clinical presentations and outcomes of the noticeable Covid-19-related acute invasive fungal sinusitis.

Patients and Methods

The present cross-sectional cohort study was conducted at a tertiary-level university hospital from April to July 2021. The

study was approved by the local ethics committee under number RC3.4.2021. Signed written informed consent was obtained from all patients.

We enrolled 22 adult patients presented with symptoms and signs of acute invasive fungal sinusitis which were related to recent Covid-19 infection. Patients were included as they presented with or developed acute invasive fungal sinusitis either while their Covid-19 infection was still active or after their recovery. The diagnosis of Covid-19 infection was based on a throat swab specimen with a positive result after real-time reverse transcription-polymerase chain reaction (rRT-PCR).

Patients who refused to participate in the study were excluded, and we also excluded those patients who needed transfer to other medical facilities and had unknown outcomes.

The complete medical history of all patients was taken, including; age, gender, duration and severity of the Covid-19, and place of isolation during COVID-19 illness. We also recorded the risk factors, such as DM, hypertension (HTN), and renal failure, and if the patient had received systemic steroids or immunomodulatory medications during the treatment course. Moreover, we recorded the probable risk factors, such as oxygen therapy and mechanical ventilation during the treatment for Covid-19. Essential clinical assessment and examination with appropriate protective measures were performed for all participants. All participants were subjected to full otorhinolaryngologic, head and neck examinations, including endoscopic endonasal examination by 4-mm zero-degree rigid endoscope. Physicians of different specialties were sought when needed, such as an ophthalmologist, a neurologist, and an internist.

All patients were subjected to axial and coronal computed tomography (CT) scans of the paranasal sinuses and orbits. Magnetic resonance imaging (MRI) scans were performed for those with suspected intracranial complications.

The patients were managed according to our institutional guidelines with medical treatment including systemic anti-fungal (liposomal amphotericin B) medication, unless contraindicated, and surgical debridement, either through the endoscopic, or combined open and endoscopic approaches. The diagnosis of acute invasive fungal sinusitis was confirmed by histopathological biopsy showing evidence of mucosal and angioinvasion. The surviving patients were followed regularly for one month postoperatively.

All data, including demographics, risk factors, clinical symptoms, and clinical examination findings on admission, were obtained. Hematological, laboratory and pathological data were also recorded. Different lines of treatment with the outcomes of all participants were recorded and analyzed.

Data management and statistical analysis were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, US) software, version 25.0. Quantitative data were assessed for normality using the Shapiro-Wilk test and direct data visualization methods. According to the normality testing, numerical data were expressed as means and standard

Table 1 General characteristics of the studied patients

General characteristics		
Age (years)	Mean \pm SD	59 \pm 8
Gender	Female	12 (54.5)
	Male	10 (45.5)
Covid-19 positive at time of onset	n (%)	4 (18.2)
History of ICU admission	n (%)	8 (36.4)
History of mechanical ventilation	n (%)	0 (0)
Diabetes mellitus	n (%)	22 (100)
Hypertension	n (%)	15 (68.2)
Renal failure	n (%)	2 (9.1)
Cardiac	n (%)	9 (40.9)
Hepatitis C virus	n (%)	10 (45.5)

Abbreviations: Covid-19, coronavirus disease 2019; ICU, intensive care unit; SD, standard deviation.

deviations or medians and ranges. Categorical data were expressed as numbers and percentages.

Results

The study included 22 patients; their mean age was 59 \pm 8 years. As shown in **Table 1**, there was a female predominance; more than half of the patients were female (54.5%). About one-third (36.4%) of the sample reported history of intensive care unit (ICU) admission, and none of the patients reported history of mechanical ventilation. All patients had DM (100%), and more than two thirds (68.2%) had hypertension. Renal failure, cardiac affection, and the hepatitis C virus were found in 2 (9.1%), 9 (40.9%), and 10 (45.5%) of the patients respectively.

Regarding the probable risk factors and the clinical and histopathological findings of the studied patients, **Table 2** shows that only 9.1% had received tocilizumab (an antagonist of the interleukin-6 receptor) during the course of their Covid-19 treatment, and about three quarters, 17 patients (77.3%), had received systemic steroids. The median duration of the Covid-19 was of 14 days, ranging from 10 to 28 days. Upon admission, the mean random blood sugar (RBS) was of 420 mg/dL, and the median total leucocyte count (TLC) was of $5.5 \times 10^9/L$, ranging from $2.2 \times 10^9/L$ to $24.0 \times 10^9/L$. Only 13.6% of the patients had leucopenia. The median serum creatinine level was of 1 mg/dl, ranging from 1 mg/dl to 7 mg/dl. All patients (100%) had unilateral sinonasal disease affecting the ethmoids and maxillary sinuses. Other clinical manifestations included facial numbness in 14 patients (63.6%), facial palsy in 7 patients (31.8%), palatal affection in 6 patients (27.3%), and intracranial affection in 10 patients (45.5%). The histopathological examination of the biopsies revealed non-septated or pauci-septated broad branching hyphae and spores in 19 out of 22 biopsies (86.4%). A total of 3 biopsies (13.6%) showed thin septated hyphae.

Table 2 Clinical and histopathological findings of the studied patients

Clinical findings		
Received tocilizumab	n (%)	2 (9.1)
Received systemic steroids	n (%)	17 (77.3)
Duration of Covid-19 (days)	Median (range)	14 (10–28)
RBS on admission (mg/dL)	Mean \pm SD	420 \pm 100
TLC on admission ($\times 10^9/L$)	Median (range)	5.5 (2.2–24.0)
Leukopenia	n (%)	3 (13.6)
Serum creatinine (mg/dL)	Median (range)	1 (1–7)
Fever	n (%)	19 (86.4)
Palatal affection	n (%)	6 (27.3)
Facial palsy	n (%)	7 (31.8)
Facial numbness	n (%)	14 (63.6)
Intracranial affection	n (%)	10 (45.5)
Histopathological findings		
Septated hyphae	n (%)	3 (13.6)
Non-septated hyphae	n (%)	19 (86.4)

Abbreviations: Covid-19, coronavirus disease 2019; RBS, random blood sugar; SD, standard deviation; TLC, total leucocyte count.

Regarding orbital symptoms, which were unilateral in all patients, proptosis was the most frequent, and was found in 15 patients (68.2%). Ophthalmoplegia was found in 12 patients (54.5%), and loss of vision in one eye and subperi-orbital abscess were observed in 10 (45.5%) and 2 (18.2%) of the patients respectively.

Most patients, 20 out of 22 patients (90.9%), received liposomal amphotericin B and/or underwent surgery 18 out of 22 patients (81.8%). In total 4 patients did not undergo surgical treatment because they died within the first 24 hours after admission to the ICU due to late presentation: 2 of them took only one dose of amphotericin B, and the other 2 (9.1%) patients did not received any.

Surgical debridement was performed in 18 patients. The median duration between the onset of the disease and surgery was of 7 days, ranging from 2 to 18 days. Regarding the type of surgery, most patients underwent endoscopic surgery 16 out of 18 patients (88.9%), and only 2 out of 18 patients (11.1%) underwent combined open and endoscopic surgery. Regarding orbital management, half of the patients (50.0%) underwent decompression. Regarding the outcome, 10 out of 22 patients (45.5%) improved, 6 patients (27.3%) died, and 6 patients (27.3%) showed morbidity in the form of ophthalmoplegia and loss of vision (**Table 3**).

Discussion

Cases of Covid-19 may be associated with and complicated by different bacterial and fungal infections due to associated

Table 3 Management and outcomes of the studied patients

Management and outcome			
Amphotericin B	n (%)		20 (90.9)
Surgical treatment	n (%)		18 (81.8)
Days between onset and surgery	Median (range)		7 (2–18)
Type of surgery*	Endoscopic	n (%)	16 (88.9)
	Open and endoscopic	n (%)	2 (11.1)
Orbital management	Decompression	n (%)	11 (50.0)
	No	n (%)	11 (50.0)
Outcome	Died	n (%)	6 (27.3)
	Improved	n (%)	10 (45.5)
	Morbidity	n (%)	6 (27.3)

Note: *The percentages were calculated based on the total of 18 patients who underwent surgery.

impaired immunity.⁹ Mucormycosis is a potentially lethal fungal infection affecting the nose and paranasal sinuses, with the most common form being the rhino-orbital-cerebral presentation.¹⁰

Despite its low incidence rate, varying from 0.005 to 1.7 per million inhabitants, many cases have been seen recently, and it is noticeable that this significant increase in incidence coincides with the ongoing coronavirus pandemic.¹¹

The steady increase in the number of cases of acute invasive fungal sinusitis and their clear firm association with Covid-19 must be studied in terms of the different epidemiological factors, risk factors, clinical presentations and outcomes.

The present cross-sectional cohort study was conducted at a tertiary-level university hospital, and it included 22 patients with acute invasive fungal sinusitis complicating previous diagnoses of Covid-19. Regarding the demographics of the sample, their ages ranged from 45 to 70 years (mean: 59 ± 8 years), and the male-to-female ratio was of 10/12; these findings are in line with the longitudinal prospective study by El-Kholy et al.,¹² in which the mean age of the 36 patients was 52.92 ± 11.3 years and the male-to-female ratio was of 19/17. Regarding the gender distribution, our results slightly differ from those of Sharma et al.,¹³ who reported a male predominance among 23 patients: 15 were male and 8 were female.

In the present study, less than one quarter of the patients (18.2% – 4 patients) were Covid-19 positive at the time of the onset of mucormycosis; this coincides with the study by Sharma et al.,¹³ who found that 4 out of 23 patients (17.9%) were Covid-19 positive, which means that mucormycosis occurred after the recovery from Covid-19 and during its active course as well.

The common predisposing factors found in patients with mucormycosis include DM with or without diabetic ketoacidosis, malignancies, being a transplant recipient, prolonged neutropenia, and immunosuppressive and corticosteroid therapies.¹⁴ Hemochromatosis, acquired immunodeficiency syndrome (AIDS), intravenous drug abuse, malnutrition and open wound following trauma are also predisposing factors.¹⁵

In the present study, all patients had DM (100%), either previously diagnosed or recently discovered, and about three quarters (77.3%) 17 patients reported history of treatment with systemic steroids. These findings are consistent with those of Singh et al.,¹⁶ whose sample comprised 80% of cases of DM, with more than two thirds (76.3%) of the patients receiving a course of corticosteroids. Our results also match those of the systematic review by John et al.,¹⁷ who reported the findings of 41 confirmed cases of mucormycosis cases in people with Covid-19, and DM in 93% of the cases, while 88% were receiving corticosteroids. Our results regarding DM and treatment with systemic corticosteroids as predisposing factors go in line with those of the study by Sharma et al.,¹³ who found that 21 out of 23 patients (91.3%) were diabetic, and all of the 23 patients (100%) had received systemic steroids.

In the present study, all patients (100%) had unilateral sinonasal disease affecting the ethmoids and maxillary sinuses, intracranial affection in 10 patients (45.5%), facial nerve palsy in 7 patients (31.8%), palatal affection in 6 patients (27.3%), and this matches the results of the study by Sharma et al.,¹³ who found that the ethmoids were the most common sinuses affected (100%), and palatal affection was noticed in 39.1% of the sample. But intracranial extension, was only observed in 8.69% of the patients.

Regarding the clinical presentations, our results nearly match those of the study by El-Kholy et al.,¹² who stated that the most involved sinonasal sites were the lateral nasal wall (86.1%) and ethmoid (72.2%); intracranial extension was only observed in 27.8% of the sample, facial nerve palsy, in 19.4%, and palatal necrosis and ulceration, in 33.3% of the patients.

Regarding the orbital symptoms, which were unilateral in all patients, proptosis was the most frequent (15 patients; 68.2%). Ophthalmoplegia was found in 12 patients (54.5%). Orbital involvement was observed in rates similar to those of previous studies; in the study by Singh et al.,¹⁶ the rate of orbital involvement was of 56.7%; El-Kholy et al.¹² found rates of ophthalmoplegia of 63.9%; and proptosis of 52.8%, and, in the study by Sharma et al.,¹³ intraorbital extension was seen in 43.47% of the cases. The relatively high incidence of orbital and intracranial extension can be

explained by the fact that the patients presented late, and, in this entity, we can say that hours, not days, play a big role in the outcome. Due to the late presentation, 4 patients (18.2%) in our sample did not receive surgical treatment because they died within the first 24 hours after ICU admission.

The best management for acute invasive fungal sinusitis is presumed to be aggressive surgical debridement combined with medical treatment and control of the predisposing factors.¹⁸ Most of the patients, 20 out of 22 (90.9%), in the present study received liposomal amphotericin B, and 18 out of 22 patients (81.8%) underwent surgery. Regarding the outcome and mortality, 6 patients (27.3%) died. Our results are in line with a previous study by Bala et al.,¹⁸ which was conducted in a tertiary hospital in India before the Covid-19 pandemic: the overall mortality rate in that study was of 23% of the 38 patients treated. Our results were slightly better than those of Meis and Chakrabarti,¹⁹ in whose study the overall mortality rate was of 45% of 53 patients. In the largest meta-analysis conducted by Roden et al.,²⁰ the overall mortality rate was of 46%.

The mortality rate found in the present study matches that of the study by Singh et al.¹⁶ (30.6%), a systematic review and meta-analysis which included 101 cases of Covid-19-related mucormycosis.

Limitation

Regarding mortality, six patients died out of 19 patients with non septated type according to their histopathology slides (31.6%) in the present study. No one died between the 3 patients with septated type (0%), but we cannot depend on the statistical significance due to small number of patients with septated type (only three cases 13.6%).

Conclusion

The incidence of acute invasive fungal sinusitis among Covid-19 patients is still unknown, but there is a noticeable increase that coincides with the ongoing Covid-19 pandemic. The most common preexisting medical condition associated with Covid-19-related acute invasive fungal sinusitis is DM, and systemic corticosteroid therapy is considered a predisposing factor.

To achieve the best treatment results for this potentially-lethal disease, it is necessary to raise the level of awareness and suspicion to diagnose it, especially in patients with active Covid-19 infection or those who have recently recovered. Proper diagnosis and rapid management are crucial to avoid complications, which usually involve the orbit and intracranial extension.

Financial Support and Sponsorship

The authors have no source of funding to declare.

Ethics and Consent

The present study was performed in accordance with the 1975 Helsinki Declaration and its amendments, and the study protocol was approved by the local ethical commit-

tee under number RC3.4.2021. All patients signed the written informed consent form to participate in the study.

Availability of Data and Material

The data that support the findings of the present study are available from the corresponding author upon reasonable request.

Conflict of Interests

The authors have no conflict of interests to declare.

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