

Increased acute invasive fungal rhinosinusitis in COVID-19 patients

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ABSTRACT

Aim: Acute invasive fungal rhinosinusitis (AIFRS) is a rare infection of the nose and paranasal sinuses that can be fatal. Infection may lead to tissue infarction, necrosis, and thrombosis and rapidly spread intracranially. The aim of this study is to highlight the increasing cases of AIFRS after covid-19 and to investigate the parameters affecting mortality.

Material and Method: Total 11 patients diagnosed with AIFRS after COVID-19 were included in this study. Patient age, gender, comorbid diseases, initial symptoms, time between COVID-19 diagnosis and AIFRS diagnosis, intensive care hospitalization history, medical treatments, surgical findings, antifungal treatment, fungal species grown in culture, mortality, and the relationships of these parameters with mortality were also evaluated.

Results: A total of 11 patients diagnosed with AIFRS after COVID-19 were included in the study. Among these patients, 81.8% were male, 18.2% were female, and ages ranged from 57 years to 89 years. The mean time between COVID-19 infection and development of IFRS in patients was 26.09 ± 18.04 days. The initial symptoms in 45.45% of the patients were unilateral periorbital edema, vision loss, and total ophthalmoplegia. The surgical approach was purely endoscopic in all patients. In our study, the mortality rate was 72.7% in COVID-19 related AIFRS patients.

Conclusion: As a result, in our study, we found an increase in AIFRS incidence and mortality due to the systemic effects of COVID 19 and the treatments used for it. AIFRS should be suspected when a patient presents acute sinusitis symptoms after COVID-19 infection.

Keywords: COVID-19, *Mucor*, AIFRS, ophthalmoplegia

INTRODUCTION

Acute invasive fungal rhinosinusitis (AIFRS) is a rare infection of the nose and paranasal sinuses that can be fatal. Infection may lead to tissue infarction, necrosis, and thrombosis and rapidly spread intracranially, resulting in fungemia and death; indeed, the mortality rates of AIFRS infection reported in the literature are between 40% and 80% in the studies of Chang et al. (1), Shanbag et al. (2), Fadda et al. (3), Ergun et al. (4).

Although many fungi can be causative agents of AIFRS, the most commonly isolated fungi are *Aspergillus* spp. (mainly *A. fumigatus* and *A. flavus*) and *Zygomycetes* (*Mucor*, *Rhizopus*, and *Absidia*); Singh et al. (5), Montone et al. (6).

AIFRS is caused by opportunistic pathogens that typically develop in immunocompromised patients, such as those with hematologic malignancies, acquired immunodeficiency syndrome, neutropenia, or diabetes;

those receiving bone marrow or organ transplant; or those on long-term steroids; Ryu et al. (7), Fernandez et al. (8), Wu et al. (9).

Patients with AIFRS present with fever and localized symptoms, the most common of which include facial swelling, nasal congestion, headache not responding to analgesics, ophthalmoplegia, proptosis, cranial nerve palsies, and vision disturbances or loss. Although early diagnosis can be achieved with the presence of predisposing factors in the patient and the support of clinical and radiological findings, microscopic examination and histopathological evaluation remain necessary to obtain a definitive diagnosis of AIFRS.

Severe COVID-19 is associated with immune dysregulation and may be associated with a wide range of bacterial and fungal co-infections. The literature reports several cases of invasive fungal infections, especially

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invasive pulmonary aspergillosis, after COVID-19 infection. However, limited studies on the development of IFRS in COVID-19 patients are available. The aim of this study is to investigate and report the clinical findings, diagnosis, treatment processes, and mortality and morbidity rates of AIFRS patients with COVID-19 infection during the pandemic to assist in early diagnosis and treatment development.

MATERIAL AND METHOD

A retrospective study was conducted on AIFRS patients with COVID-19 (2020–2021) who had sought treatment at the Ear, Nose, and Throat Department of University of Health Sciences Kayseri City Training and Research Hospital. The study was initiated with the approval by the University of Health Sciences Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 15/04/2021, Decision No: 373). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Total 11 patients diagnosed with IFRS after COVID-19 were included in this study. The diagnosis of all patients was achieved by mycological or direct examination or culture of biopsy materials. All patients were preoperatively evaluated by endoscopic examination and paranasal sinus computerised tomography (CT). Patient age, gender, comorbid diseases, initial symptoms, intensive care hospitalization history, medical treatments (e.g., steroidal and immunosuppressant treatments for COVID-19), surgical findings, antifungal treatment, fungal species grown in culture, mortality, and the relationships of these parameters with mortality were also evaluated.

The data were analyzed using the SPSS software package. Numbers and percentages were used when defining categorical variables, and mean±standard deviation (min–max) values were used when defining continuous variables. The Wilcoxon signed-rank test was used for dependent-group comparisons, and the Mann–Whitney U test was used for independent-group comparisons. Spearman correlation analysis was used to measure the relationship between variables; $p \leq 0.05$ was considered significant.

RESULTS

A total of 11 patients diagnosed with IFRS after COVID-19 were included in the study. Among these patients, 81.8% were male (n=9), 18.2% were female (n=2), and ages ranged from 57 years to 89 years (mean=73.73±9.10 years).

Diabetes mellitus (DM) was recorded in 9.09% of the patients (n=1), DM and hypertension(HT) were recorded in 18.18% (n=2); and DM, atrial fibrillation, and hypothyroidism were recorded in 9.09% (n=1). Moreover, 9.09% (n=1) had DM and chronic renal failure (CRF); 9.09% had (n=1) DM, coronary artery disease, Parkinson’s disease; 9.09% (n=1) had coronary artery disease, HT, asthma, hyperlipidemia, and previous ischemic cerebrovascular disease; 9.09% (n=1) had DM, HT, and CRF; and 9.09% (n=1) had DM, HT, and cerebrovascular disease. Finally, 9.09% of the patients (n=1) had coronary artery disease and HT, while 9.09% (n=1) had DM and thalassemia carriage (Table 1).

Table 1. Distribution of patients according to sociodemographic and clinical characteristics

Variables	Number (%)	Mean± standard deviation (min, max)
Age (year)	11 (100%)	73,73±9,10 (57-89)
Male (n)	9 (18.2%)	
Female (n)	2 (76.5%)	
DM (n)	1 (9.09%)	
DM+HT (n)	2 (18.18%)	
DM+AF+Hypo-thyroidism (n)	1 (9.09%)	
DM+CRF (n)	1 (9.09%)	
DM+ CAD+ Parkinson’s disease (n)	1 (9.09%)	
CAD+HT+asthma, hyperlipidemia, and previous ischemic cerebrovascular disease (n)	1 (9.09%)	
DM+HT+CRF (n)	1 (9.09%)	
DM+HT+CVH (n)	1 (9.09%)	
KAH+HT (n)	1 (9.09%)	
DM+thalassemia carrier (n)	1 (9.09%)	

The mean time between COVID-19 infection and development of IFRS in patients was 26.09±18.04 days (min=8 days; max=75 days). The initial symptoms in 45.45% of the patients (n=5) were unilateral periorbital edema, vision loss, and total ophthalmoplegia. In addition, 9.09% of the infected patients (n=1) had right facial swelling and fever, 9.09% (n=1) had abscess and endophthalmitis in the left buccal region, 9.09% (n=1) had soft tissue swelling in the left premaxillary region, 9.09% (n=1) had right facial numbness and pain, and 9.09% (n=1) had periorbital edema only. Pain in the right half of the face was reported by 9.09% (n=1) of the patients. Among the patients, 9.10% (n=1) remained in the intensive care unit for 4 days before the development of IFRS. Steroid treatment was applied to 90.90% of the patients. The steroid history of one patient was not known. Two of the three patients (66.66%) administered immunosuppressant treatment remained alive, while all other patients died (Table 2).

Table 2. Distribution of patients according to initial symptoms of invasive fungal rhinosinusitis

Variables	Number (%)
Unilateral periorbital edema, visual loss and total ophthalmoplegia	5 (45.45%)
Right facial swelling and fever	1 (9.09%)
Abscess and endophthalmitis in the left buccal region	1 (9.09%)
Soft tissue swelling in the left premaxillary region	1 (9.09%)
Right face numbness and pain	1 (9.09%)
Periorbital edema	1 (9.09%)
Pain in the right half of the face	1 (9.09%)

No significant correlation was found between age and time elapsed between COVID-19 infection and the development of IFRS ($p=0.840$; $r=-0.069$), between age and survival after the development of IFRS ($p=0.119$; $r=-0.498$), or between the lifespan of eight patients who died and the time elapsed between COVID-19 infection and the development of IFRS ($p=0.012$; $r=0.977$). After the development of IFR, no significant correlation between age and the survival of eight patients who died ($p=0.037$; $r=0.931$) was noted. Considering the life span of all patients from the development of IFRS to today, no significant correlation between life span and the time between COVID-19 infection and the development of IFRS ($p=0.979$, $r=0.009$) was found (Table 3).

Table 3. Correlations of various variables in patients included in the study (* $p\leq 0.05$ was considered significant)

Variable	p and r value	
	p value	r value
Age - time between COVID-19 and IFRS	0.840	-0.069
Age-life expectancy after IFRS	0.119	-0.498
Life expectancy after IFRS-time between COVID-19 and IFRS	0.979	0.009
Duration of steroid use-life expectancy after IFRS	0.355	0.309
Duration of steroid use time between COVID-19 and IFRS	0.498	-0.229

When life expectancy after the development of IFRS was examined by gender, no significant difference was found between genders ($p=0.334$). No significant difference in terms of the time elapsed between the development of COVID-19 infection and IFRS was found between genders ($p=0.813$). The mean duration of steroid use was 12.73 ± 5.08 days. No significant difference in terms of survival after the development of IFRS and the time elapsed between COVID-19 infection and the development of IFRS was found between patients using dexamethasone or prednisolone ($p=0.334$

and $p=0.748$, respectively; Table 4). No significant correlation between the duration of steroid use of the patients and the life span after the development of IFRS and between the duration of steroid use and the time between COVID infection and the development of IFRS was noted ($p=0.355$, $r=0.309$ and $p=0.498$, $r=-0.229$, respectively; Table 3). No significant difference in terms of survival after the development of IFRS and time elapsed between COVID infection and the development of IFRS was found between the groups using and not using immunosuppressants ($p=0.065$ and $p=0.539$, respectively; Table 4).

Table 4. Distribution of life expectancy and time elapsed between COVID-19 and IFRS development according to various variables (* $p\leq 0.05$ was considered significant).

Variables	Life expectancy after IFRS	p value	Time between COVID and IFRS	p value
Gender		0.334		0.813
Female	82.50±95.45		20.50±0.70	
Male	58.22±81.49		27.33±19.93	
Use of steroids		0.334		0.748
Dexamethasone	67.25±65.66		24.50±7.23	
Prednisolone	67.50±97.75		28.17±24.60	
Use of immuno- suppressants		0.065		0.539
Used	131±108.67		33±36.59	
Did not use	37±53.86		23.50±7.38	

In our examination findings, periorbital swelling, redness, exophthalmos and chemosis were the most common findings in patients presenting with eye involvement (Figure 1). In our endoscopic examination findings, most of the patients had widespread drying, discoloration in the middle turbinate (blackening), and purulent discharge in the middle meatus. Fungal hyphae were also seen on the middle turbinate in some of the patients (Figure 2).



Figure 1. IFRS patient with total ophthalmoplegia

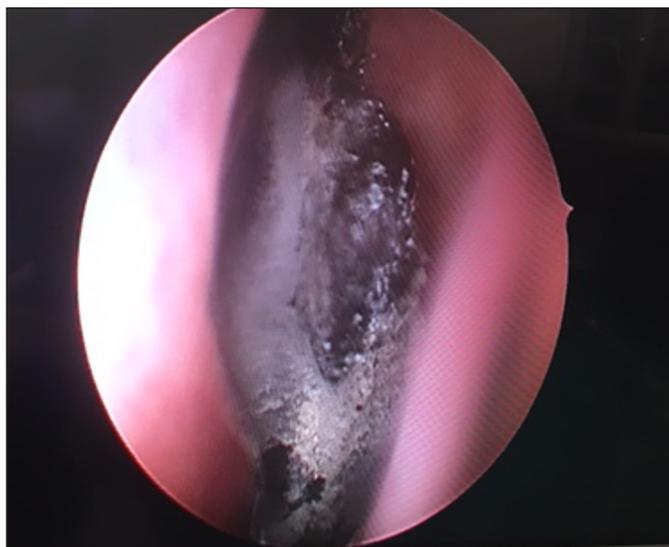


Figure 2. Necrotic middle turbinate and overlying fungal hyphae

Fungal hyphae were visible in the microscopic examination of the biopsy materials of all patients (**Figure 3**). *Mucor* grew in the fungal culture of most of the patients (n=10) (**Figure 4**), while *Exophiala* spp. grew in the culture of only one patient.

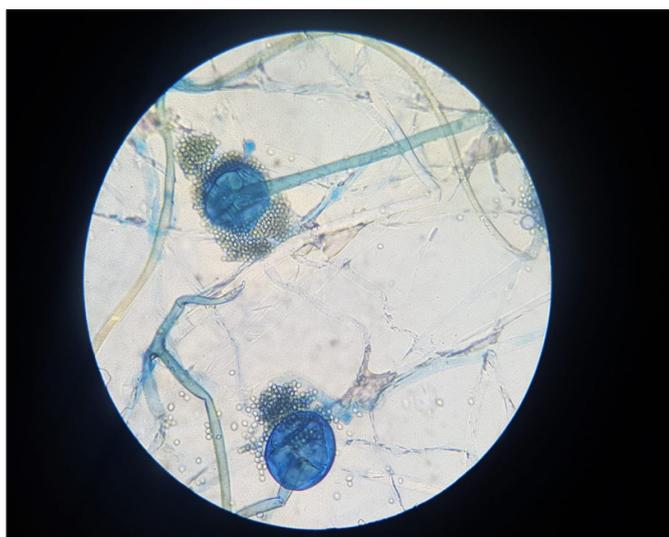


Figure 3. Microscopic image of fungal hyphae



Figure 4. Petri image of fungal hyphae

The surgical approach was purely endoscopic in all patients. Endoscopic debridement, including resection of the middle turbinate, wide middle meatal antrostomy, ethmoidectomy, nasal septectomy, and sphenoidotomy, was performed according to the involved sinuses. Repetitive endoscopic debridement was performed in all patients.

Amphotericin b treatment was given to all patients during their hospitalization, and oral posaconazole was given as maintenance therapy to patients who were successfully discharged.

DISCUSSION

Recent studies have reported that COVID-19 causes superinfections by affecting the immune system and exacerbating the effects of treatments used for the disease; Musuza et al. (10), Feldman et al. (11). Thus, the occurrence of invasive fungal infections after COVID-19 has drawn increased research attention. Although the most common type of infection recorded in the literature is invasive pulmonary fungal infection, some cases of IFRS have also been reported; Mekonnen et al. (12), Waizel-Haiat et al. (13), Turbin et al. (14). One study indicated that IFRS in post-COVID-19 patients is a new clinical condition; El-Kholy et al. (15). Similarly, we believe that IFRS after COVID-19 infection represents a new clinical situation on account of our multiple experiences of IFRS detected post-COVID over a short period of approximately 8 months. Specifically, over this period, we detected 11 IFRS cases in post-COVID-19 patients but diagnosed only 1 non-COVID-related IFRS case. Thus, COVID-19 may be inferred to increase the frequency of IFRS considerably; however, newer and larger studies are necessary to confirm this supposition.

The mean age of presentation of the patients was 73.73 ± 9.10 years. Although no report on differences in AIFRS infection between males and females has been published, the majority of our patients were male (9 males, 2 females).

All of the patients had comorbidities, the most common of which were diabetes mellitus (81%), hypertension (54%), chronic kidney disease (18%), coronary artery disease (18%), and cerebrovascular disease (18%); one patient was a thalassemia carrier. Most of the patients had controlled diabetes, and none had a history of ketoacidosis. None of our patients had a history of hematological disease or bone marrow and organ transplantation, which are among the most common comorbidities described in the literature; Jestin et al. (16), Pan et al. (17). These findings lead us to believe that COVID-19 may be the main cause of the development of AIFRS in these patients.

While all patients received steroid therapy following their diagnosis with AIFRS, none of them received long-term or high-dose therapy (3 patients, 40 mg/day prednisolone for 14 days; 1 patient, 10 mg/day prednisolone for 14 days; 6 patients, 8 mg/day dexamethasone for 14 days; 1 patient, 8 mg/day dexamethasone for 5 days). Steroids are believed to be highly likely to play a role in the development of AIFRS because of their detrimental effects on the immune system. However, few cases of *Mucor* infection while on systemic steroids has been reported in the literature; Pan et al. (17), Najafi et al. (18). To the best of our knowledge, no study showing that steroid use causes the development of AIFRS is yet available. In fact, we feel that a low dose and short duration of steroid use decreases the likelihood of treatment exerting any effect on the development of AIFRS in these cases.

Most of the patients presented symptoms such pain in the face and cheek (45.45%, five patients) and periorbital edema and vision loss (45.45%, five patients). Other symptoms included facial swelling (three patients). The symptoms reported are similar to those in the literature; Raizada et al. (19), Abdollahi et al. (20).

The time of first diagnosis of COVID-19 and AIFRS was between 8 and 75 days (average, 26.09±18.04 days). If the one patient who developed IFRS on the 75th day was excluded from the analysis, most of the patients demonstrated improvements in AIFRS symptoms within 2–4 weeks. A recently published study indicated that the development of AIFRS after COVID-19 could occur in the early post-COVID period (17.82±2.97 days after a negative result), except in two patients who developed AIFRS while actively infected with COVID-19, similar to our findings; El-Kholy et al. (15).

The literature indicates AIFRS mortality rates of 40%–80%. In our study, the mortality rate was 72.7%, which is close to the upper limit of mortality rates reported in previous studies. However, in these studies, the mortality rate of AIFRS after COVID-19 did not significantly differ from that of infection after other diseases; El-Kholy et al. (15), Ismaiel et al. (21).

CONCLUSION

AIFRS should be suspected when a patient presents acute sinusitis symptoms after COVID-19 infection.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences Kayseri City Training and Research Hospital Clinical Researches Ethics Committee (Date: 15/04/2021, Decision No: 373).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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