Impact of COVID-19 on Acute Invasive Fungal Rhinosinusitis: A Comparative Study

Original Article

Kamal Ebeid[1], Mohamed Gamea[2], Alzahraa A. Allam[3] and Emad Shehata[1]

Department of Otorhinolaryngology, [1]Faculty of Medicine, Tanta University, [2]Misr University for Science & Technology, Faculty of Medicine, Egypt.

[3]Department of Internal medicine, Faculty of Medicine Tanta University Hospital, Tanta, Gharbia.

ABSTRACT

Background: Acute invasive fungal rhinosinusitis (AIFR) is a potentially fatal infection that usually complicates immunosuppressive status like uncontrolled or newly discovered diabetes mellitus, during the coronavirus disease (COVID19) pandemic, worsening of underlying diabetes and newly discovered cases have been observed.

Aim: To highlight the impact of COVID-19 on emerging cases of AIFRS comparing this with AIFR before COVID-19 pandemic.

Methods: This is a retrospective comparative study between AIFR patients presenting to Tanta University Hospital, Egypt between July and December 2020 with a recent proven COVID-19 infection and AIFR patients presenting to the same institution prior to the covid-19 pandemic between January 2017 and December 2019.

Results: There was a dramatic increase in the rate of incidence of AIFR in patients with recent covid-19 infection in comparison with pre COVID-19 pandemic numbers. On the other hand, there was no statistical difference in the severity, extent of lesion or survival rate between the two groups.

Conclusion: A bidirectional relationship between Covid-19 and diabetes mellitus was observed together with immune dysregulation playing a possible role in subsequent increase in the rate of incidence of AIFR making it more emerging and more challenging.

Key Words: Acute invasive fungal rhinosinusitis, COVID-19, diabetic complications, rhinocerebral mucor mycosis, uncontrolled diabetes.

INTRODUCTION

Invasive Fungal Rhinosinusitis is a profoundly serious medical condition which includes three subcategories, the acute invasive fungal rhinosinusitis, the chronic invasive fungal rhinosinusitis, and the rare chronic granulomatous invasive fungal rhinosinusitis[1].

The acute invasive fungal rhinosinusitis (AIFR) is a highly fatal disease that affects severely immunocompromised patients due to mycotic invasion of the mucosa of the nasal cavity and paranasal sinuses. Poorly controlled type 1 diabetes mellitus (DM), new chemotherapeutic agents and long-term use of immunosuppressive agents following bone marrow or solid organ transplantation, hematological malignancies, long standing multi organ failure have resulted in an increase in the population at risk of developing AIFR.

Multiple fungal species have been identified in patients with AIFR: Mucoraceae and Aspergillus are the most common pathogens[2].

DM is well established as one of the major risk factors to develop severe degree of COVID-19 infection and to increase the mortality rate as well as development of new onset DM[3].

The relationship between Covid-19 and diabetes could be described as a bidirectional multi risk relation. Patients with DM seem to be more prone to severe affection and a higher mortality rate. Patients with DM can be attributed to a facilitated viral uptake assisted by the host's receptor angiotensin-converting enzyme 2 (ACE2). It can also be associated with a higher basal level of pro-inflammatory cytokines present in patients with diabetes, which enables a hyperinflammatory "cytokine storm" in response to the virus. Also, an observed relation between the increased

pro-inflammatory cytokines and insulin. Moreover, there is an observed poor control of DM in patients with covid 19 either due to the disease itself or the commonly used high doses of steroids which are routinely used in severe conditions to stop the disease process, which make the control of DM during covid 19 infection a real challenge[4].

This encouraged us to assess the impact of Covid-19 on the incidence of acute invasive fungal rhinosinusitis.

PATIENTS AND METHODS

Ethical considerations

This is study which was approved by the Ethical Committees of Faculty of Medicine, Tanta University, Egypt with approval code (34341/12/20). Confidentiality of the patients' data was warranted by keeping data anonymous (after assigning a code number to each patient that is known only by the investigators) and de-identification of images. Written consents were signed by patients or relatives.

Study design

This is a retrospective comparative study between AIFR patients presenting to Tanta University Hospital, Egypt between July and December 2020 with a recent proven COVID-19 infection and AIFR patients presenting to the same institution prior to the covid-19 pandemic between January 2017 and December 2019.

Diagnosis of AIFRS was based on history of recent manifestations of sinonasal infection, physical examination including meticulous endoscopic nasal examination, radiological modalities including coronal, axial, and sagittal CT scans, MRI, or both for sinonasal region in addition to histopathological assessment of nasal biopsies and fungal culture for identification of fungal species. Laboratory investigations to evaluate the general condition and diabetic control including fasting ,2hours post prandial blood sugar and glycosylated hemoglobin percentage.

The main stay of therapy is the proper diabetic control, all patients were admitted in ICU with close monitoring and proper control of diabetes. All patients were subjected to endoscopic Sino nasal tissue biopsies as office procedure for fungal and routine histopathological investigations, all patients were managed by amphotericin B infusion (Intravenous admixtures of amphotericin B 0.25 and 1.4 mg/mL in 5% dextrose injection, beginning intravenous therapy with a 1-mg test dose. The usual daily maintenance dose of amphotericin B is 0.5-1 mg/kg i.e. The infusion was given over 4 hours with close monitoring of serum electrolytes and kidney functions).

Surgical debridement was done once the patients were candidate, debridement of all necrotic gangrenous elements was done either endoscopic, external, or combined endoscopic assisted, the limit of debridement was achieving apparent healthy surgical site.

Close daily examination of surgical site and debridement of any new necrotic elements till complete epithelialization of surgical site and histopathological confirmation of fungal free tissue biopsies at this time amphotericin B can be stopped.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov- Smirnov was used to verify the normality of distribution of variables, Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). Student t-test was used to compare two groups for normally distributed quantitative variables while Mann Whitney test was used to compare between two groups for not normally distributed quantitative variables. Significance of the obtained results was judged at the 5% level.

RESULTS

During 6 months period between July and December 2020, Tanta university hospitals admitted 28 AIFR patients. All of them gave history of a recent covid-19 infection proven by PCR and CT chest imaging that was diagnosed 2-8 weeks prior to the date of their presentation with AIFR. 22 patients (78.6%) were known to be diabetic before their covid-19 infection, while 6 patients (21.4%) were diagnosed with diabetes after their infection. All patients gave history of steroid administration in the form prednisolone 20-60 mg/day for 10-30 days as part of covid-19 treatment.

Both male and female patients represented 50% of this group of patients. The mean age was 41.2 ± 15.8 years. 7 patients (25%) gave no history of comorbidities while 21patients (75%) had other comorbidities. 24 patients (85.7%) had no history of thromboembolic manifestations.

On admission of those patients, The median fasting blood sugar was 215 mg/dL (150 – 400), The median 2 hour post prandial blood sugar was 405 mg/dL (300 – 614). The mean Glycosylated HB% was 10.5 ± 2.9 patients (32.1%) have no diabetic ketoacidosis. while 19 (67.9%) patients had adiabatic ketoacidosis.

The median oxygen saturation was 89.5% (78 – 100). Severe lung affection of more than 40% was present in 7 patients (25%). The median C reactive protein level was 60 mg/L (28 – 90). The mean serum ferritin level was 224.9 ± 104.3 microgram/L. The median LDH serum level was 461.5 U/L (234 – 890).

Histopathological assessment of nasal biopsies and fungal culture for those patients showed that Mucor species was identified in 19 patients (68%) while Aspergillus species was found in 9 patients (32%). (Figure 1)
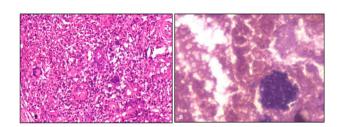
Fig. 1: Histopathological assessment of nasal biopsies showing mucosal and bony invasion by fungal colonies surrounded by dense inflammatory reactions

Encountered complications found through both examination and imaging included facial skin infarction in 15 patients (53.6%) (Figure 2), orbital affection with visual loss in 21 patients (75%), intracranial affection with disturbed conscious level in 3 patients (10.7%) (Figure 3), and cavernous sinus thrombosis was present in 11 patients (39.3%).

Fig. 2: Example of skin necrosis encountered with rhinocerebral mucormycosis
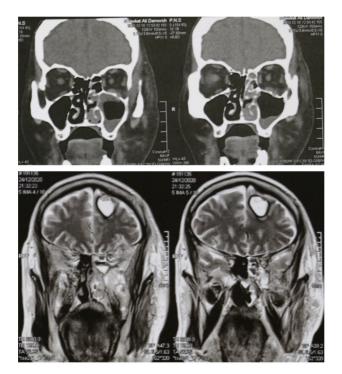

Fig. 3: A 54-year-old female patient with uncontrolled DM 1 month post COVID -19 infection presented with left facial pain and facial swelling A) CT scan of the nose and paranasal sinuses showing mucosal thickening of the left nasal cavity. B) MRI of this patient showing intracranial fungal abscess and marked swelling of the facial soft tissues

Surgical management varied according to the extent of infection. Hemi maxillectomy was done in 5 patients (17.9%). Orbit exenteration was done in 7 patients (25%). Endoscopic debridement was done in 7 patients (25%) while external approach was adopted in 15patients (53.6%) and combined external and endoscopic approaches were done in 5 patients (17.9%). (Figures 4,5).
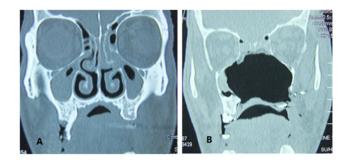

Fig. 4: A, pre-operative CT scan coronal cuts showing bilateral sinonasal tissues affection with AIFRS from second group of patients without COVID-19 affection, B post-operative CT scan coronal cuts showing extensive debridement after 2 months.
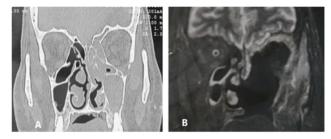

Fig. 5: A, pre-operative CT scan coronal cuts showing left side sinonasal tissues affection with AIFRS from first group of patients with COVID-19 affection, B post-operative MRI coronal cuts showing extensive debridement with maxillectomy and orbital exenteration cavity after 4 weeks

Proper diabetic control was achieved in 22 patients (78.6%) using insulin infusion. Systemic intravenous Amphotericin B was administered in 25 patients (89.3%). Thirteen patients died (46.4%) in this group of patients.

On the other hand, during a 3 years period between January 2017 and December 2019, only 20 AIFR patients were admitted in Tanta university hospital, 7 male patients (35%) and 13 females (65%) with a mean age of 39.7 ± 13.4 years. 4 patients (20%) had no comorbidities while16 (80%) had other comorbidities. 18 patients (90%) gave no history of thromboembolic manifestations.

On admission, The median fasting blood sugar was 285 mg/dL (170 – 400). The median 2 hour post prandial blood sugar was 411 mg/dL (300 – 614). The mean Glycosylated HB% was 10.3 ± 2 gm/L. 6 (30%) have no diabetic ketoacidosis. The median oxygen saturation was 99% (89 – 100).

Histopathological assessment of nasal biopsies and fungal culture for the pre-covid group identified Mucor species in 13 patients (65%) while Aspergillus species was found in 7 patients (35%).

Encountered complications that was found through examination and imaging included facial skin infarction in 11 patients (55%), orbital affection with visual loss in 10 patients (50%), intracranial extension with disturbed conscious level in 4 patients (20%) and cavernous sinus thrombosis in 7 patients (35%).

Surgical management included hemi maxillectomy in 4 patients (20%). Orbital exenteration in 6 patients (30%). Proper diabetic control was achieved in 16 patients (80%). 8 patients died ((40%)) in this group of patients.

DISCUSSION

This study represents the experience of a tertiary referral center (Tanta University Hospital, Egypt) with AIFRS during and prior to COVID19 pandemic.

According to our study, A recent dramatic increase in the rate of incidence of AIFR was noticed in comparison with pre COVID-19 pandemic numbers (Table 1,2). This may be explained by the impact of both COVID-19 infection and its associated steroid therapy on diabetic control. we even found out that 6 patients from the first group (21.4%) were diagnosed with diabetes after covid-19 infection with no history of diabetes at all prior to the onset of covid-19 infection. These data strongly support the impact of COVID-19 on diabetic control and its bidirectional relationship as proposed by previous reports[5-7] Also COVID-19 may be associated with increased risk of invasive fungal infection as reported by data from the UK National Mycology Reference Laboratory[8]. Also A dysregulated immune response to COVID-19 not only compromises the ability of the host to resolve the viral infection, but may also predispose the individual to secondary bacterial and fungal infections[9,10].

There was no significant impact of age, sex, other comorbidities, and diabetic control between first and second group of patients, also we noticed that no significant difference between the two groups regarding clinical and radiological presentations this suggests that COVID-19 does not affect AIFR in a direct mechanism but through its impact on diabetic status with consequent immunosuppression, but this issue needs further large case volume studies.

Although there was a significant difference in oxygen desaturation between two groups at time of presentations, most of lung conditions were not affected in severe degree by COVID-19 to stage of severe hypoxemia to impact mortality rate in first group. There was no significant impact of COVID-19 on local extent of AIFRS disease and extent of surgical resection (Table 3).

Early complete surgical debridement with frozen section control and antifungal therapy are the cornerstones of AIFR management reversing the underlying immunosuppression altogether[11,12].

According to our study results the survival rate was coinciding with that of the literature. With accordance to a systematic review on Fifty-two studies comprising a total of 807 patients, the overall survival rate was 49.7%[13]. but there was no significant difference between two groups of patients (Figure 6).

Fig. 6: Kaplan-Meier survival curve for overall Survival with groups

The main limitation of this study is the limited number of patients, also lack of postmortem examinations to defiantly detect mortalities etiologies.

In conclusion, ICU physicians, otolaryngologists should be aware that acute invasive fungal rhinosinusitis may be a fatal complication of critically ill COVID-19 patients and its early diagnosis and initiation of appropriate antifungal therapy for it is essential to reduce high mortality rate.

Table 1: Comparison between the two studied groups according to different parameters

	GROUP 1 (COVID + DM) (n = 28)	GROUP 2 (DM) (n = 20)	Test of Sig.	*p*
Sex				
Male	14 (50%)	7 (35%)	χ^2=1.067	0.302
Female	14 (50%)	13 (65%)		
Age (years)				
Mean ± SD.	41.2 ± 15.8	39.7 ± 13.4	t=0.340	0.735
Median (Min. – Max.)	43 (12 – 67)	41.5 (16 – 65)		
No	7 (25%)	4 (20%)	χ^2=0.165	FEp=0.741
Yes	21 (75%)	16 (80%)		
Hypertensive ischemic	14 (66.7%)	11 (68.8%)	χ^2=0.018	0.893
Renal impairment	6 (28.6%)	2 (12.5%)	χ^2=1.384	FEp=0.423
COPD	5 (23.8%)	4 (25%)	χ^2=0.007	FEp=1.000
Hepatic	1 (4.8%)	1 (6.3%)	χ^2=0.039	FEp=1.000
History of DVT and thrombotic accidents				
No history of thromboembolic manifestations	24 (85.7%)	18 (90%)	χ^2=0.196	FEp=1.000
Positive history of thromboembolic manifestations	4 (14.3%)	2 (10%)		
Diabteic condition				
Newly discovered DM with COVID	6 (21.4%)	0 (0%)	χ^2=4.898*	FEp=0.034*
Known to be diabetic uncontrolled with COVID	22 (78.6%)	20 (100%)		
Fasting Bs				
Mean ± SD.	249 ± 69.7	261.4 ± 68.7	U=251.0	0.543
Median (Min. – Max.)	215 (150 – 400)	285 (170 – 400)		
2 hPP blood sugar				
Mean ± SD.	410.6 ± 81.4	417.3 ± 88.3	t=0.273	0.786
Median (Min. – Max.)	405 (300 – 614)	411 (300 – 614)		
Diabetic ketoacidosis				
No	9 (32.1%)	6 (30%)	χ^2=0.025	0.875
DKA present	19 (67.9%)	14 (70%)		
COVID 19 PCR				
Recent positive PCR	14 (50%)	–	–	–
Previous positive PCR within 2 months	14 (50%)	–		
Glycoselated HB% (gm)				
Mean ± SD.	10.5 ± 2	10.3 ± 2	t=0.432	0.668
Median (Min. – Max.)	10.5 (7.5 – 14.4)	10 (7.5 – 13.9)		
Preoperative radiology				
CT scan	21 (75%)	14 (70%)		
CT and MRI	6 (21.4%)	5 (25%)	χ^2=0.488	MCp=1.000
MRI only	1 (3.6%)	1 (5%)		

χ^2: Chi square test   **MC:** Monte Carlo   **FE:** Fisher Exact   **t:** Student t-test   **U:** Mann Whitney test   **p:** *p value* for comparing between the studied groups.
*: Statistically significant at $p \leq 0.05$

Table 2: Comparison between the two studied groups according to different parameters

	GROUP 1 (COVID + DM) (n = 28)	GROUP 2 (DM) (n = 20)	Test of Sig.	*p*
Sinonasal tissues infarctions	28 (100%)	20 (100%)	–	–
Skin infarction				
No skin infarction	13 (46.4%)	9 (45%)	χ^2=0.010	0.922
Skin infarction present	15 (53.6%)	11 (55%)		
Orbital affection with visual loss				
No affection	7 (25%)	10 (50%)	χ^2=3.188	0.074
Orbital affection	21 (75%)	10 (50%)		
Intracranial affection with disturbed conscious level				
No affection	25 (89.3%)	16 (80%)	χ^2=0.808	FEp=0.429
Intracranial affection	3 (10.7%)	4 (20%)		
Cavernous sinus thrombosis				
No	17 (60.7%)	13 (65%)	χ^2=0.091	0.762
Present	11 (39.3%)	7 (35%)		
O_2 saturation at diagnosis (%)				
Median (Min. – Max.)	10.5 (7.5 – 14.4)	10 (7.5 – 13.9)	U=68.500*	<0.001*
Median (Min. – Max.)	89.5 (78 – 100)	99 (89 – 100)		
Initial c reactive protein (mg/L)				
Mean ± SD.	60.6 ± 17.5	61.3 ± 21.1	t=0.130	0.897
Median (Min. – Max.)	60 (28 – 90)	60 (28 – 105)		
Maxillectomy				
Not done	23 (82.1%)	16 (80%)	χ^2=0.035	FEp=1.000
Done	5 (17.9%)	4 (20%)		
Orbit exenteration				
Not done	21 (75%)	14 (70%)	χ^2=0.148	0.701
Done	7 (25%)	6 (30%)		
Diabetic control				
Controlled	22 (78.6%)	16 (80%)	χ^2=0.014	FEp=1.000
Poor control	6 (21.4%)	4 (20%)		
Systemic antifungal				
Patient not received antifungal treatment due to death	3 (10.7%)	3 (15%)	χ^2=0.196	FEp=0.683
Systemic amphotericin B	25 (89.3%)	17 (85%)		
Outcome				
Died	13 (46.4%)	8 (40%)	χ^2=0.196	0.658
Survived	15 (53.6%)	12 (60%)		

χ^2: Chi square test   **MC:** Monte Carlo   **FE:** Fisher Exact   **t:** Student t-test   **U:** Mann Whitney test   **p:** *p value* for comparing between the studied groups.
*: Statistically significant at $p \leq 0.05$

Table 3: Distribution of the studied cases according to different parameters COVID+ DM (n = 28)

	No. (%)
Lung affection degree of infiltration	
No lung affection	4 (14.3%)
Mild lung affection with COVID less than 20%	13 (46.4%)
Moderate 20-40%	4 (14.3%)
Severe more than 40%	7 (25%)
Serum ferritin micrograms (L)	
Mean ± SD.	224.9 ± 104.3
Median (Min. – Max.)	239.5 (56 – 456)
LDH serum level (U/L)	
Mean ± SD.	507.6 ± 153
Median (Min. – Max.)	461.5 (234 – 890)
Initial dose of steroid used for COVID 19 before and at the presentation	
Mean ± SD.	32.9 ± 9
Median (Min. – Max.)	40 (20 – 40)
Surgical approach	
Patient not received surgical treatment due to death	1 (3.6%)
Endoscopic debridement	7 (25%)
Debridement through external approach	15 (53.6%)
Combined external and endoscopic debridement	5 (17.9%)

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTERESTS

There are no Conflicts of Interest.

REFERENCES

1. Süslü AE · Öfretmenoflu O· Süslü N· Yücel OT· Önerci TM: Acute invasive fungal rhinosinusitis: our experience with 19 patients. Eur Arch Otorhinolaryngol (2009) 266:77–82

2. deShazo RD, O'Brien M, Chapin K, Soto-Aguilar M, Gardner L,Swain R (1997) A new classiWcation and diagnostic criteria for invasive fungal sinusitis. Arch Otolaryngol Head Neck Surg 123:1181–1188

3. Moazzami B, Chaichian S, Kasaeian A, Djalalinia S, Akhlaghdoust M, Eslami M, Broumand B. Metabolic risk factors and risk of Covid-19: A systematic review and meta-analysis. PLoS One. 2020 Dec 15;15(12): e0243600. doi: 10.1371/journal.pone.0243600. PMID: 33320875.

4. 4-Azar WS, Njeim R, Fares AH, *et al*. COVID-19 and diabetes mellitus: how one pandemic worsens the other. Rev Endocr Metab Disord. 2020;21(4):451-463. doi:10.1007/s11154-020-09573-6

5. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. Diabetes Obes Metab 2020 April 20 (Epub ahead of print).

6. Ren H, Yang Y, Wang F, *et al*. Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19. Cardiovasc Diabetol 2020; 19: 58.

7. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. J Pathol 2004; 203: 631-7.

8. Borman AM, Palmer MD, Fraser M, Patterson Z, Mann C, Oliver D, Linton CJ, Gough M, Brown P, Dzietczyk A, Hedley M, McLachlan S, King J, Johnson EM. COVID-19-Associated Invasive Aspergillosis: Data from the UK National Mycology Reference Laboratory. J Clin Microbiol. 2020 Dec 17;59(1)

9. Costantini C, van de Veerdonk FL, Romani L. Covid-19-Associated Pulmonary Aspergillosis: The Other Side of the Coin. Vaccines (Basel). 2020 Dec 1;8(4):713.

10. Hoenigl, M. Invasive Fungal Disease complicating COVID-19: When it rains it pours. Clin. Infect. Dis. 2020.

11. Zuniga, Maria G.; Turner, Justin H. Treatment outcomes in acute invasive fungal rhinosinusitis, Current Opinion in Otolaryngology & Head and Neck Surgery: June 2014 - Volume 22 - Issue 3 - p 242-248.

12. Craig, John R. Updates in management of acute invasive fungal rhinosinusitis, Current Opinion in Otolaryngology & Head and Neck Surgery: February 2019 - Volume 27 - Issue 1 - p 29-36.

13. Turner JH, Soudry E, Nayak JV, Hwang PH. Survival outcomes in acute invasive fungal sinusitis: a systematic review and quantitative synthesis of published evidence. The laryngoscope. 2013 May;123(5):1112-8.