Original Article

Mortality of Mucormycosis during Coronavirus Disease Pandemic

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Abstract

Background: Acute invasive fungal rhinosinusitis is an aggressive, mutilating, and in many cases life-threatening infection that results in rapid devitalization of tissues in the area of the nasal cavity and paranasal sinuses. Diabetic ketoacidosis, renal impairment, and hematological malignancies used to be the main predisposing factors for this serious infection. During the second wave of the pandemic of coronavirus disease (COVID-19), there has been an increment in these cases, in a manner that has not been witnessed before, and hence the interest in studying this topic. **Objectives:** Review of management outcomes and mortality in patients diagnosed with "possible invasive fungal rhinosinusitis" during the 2nd wave of COVID-19 pandemic and compare these with the outcomes observed before the pandemic in Iraq and other countries. **Materials and Methods:** A cross-sectional study of all patients with clinically possible invasive fungal rhinosinusitis (30 patients) presenting or referred to the ear nose and throat outpatient unit during the period from June 1st 2021 to December 31st 2021. **Results:** 30 patients were included, 53.3% male, 73.33% had mucormycosis following COVID-19 infection. Diabetes was the underlying condition in 57.67% of the cases. Fever, facial pain, nasal obstruction and headache were the most prevalent symptoms at presentation. The mortality rate was 16.7%. **Conclusion:** A reduced mortality rate was observed despite the increased number of cases, and this is mostly related to the early initiation of antifungal therapy.

Keywords: Acute invasive fungal rhinosinusitis, mucormycosis, mucormycosis mortality

Introduction

Acute sinonasal mucormycosis is a fungal infection of the nose and paranasal sinuses caused by molds from the order mucorales.

These organism are ubiquitous in the environment and on human nasal mucosal surfaces. Mucormycosis is non-pathologic in immunocompetent individuals as the functioning neutrophils act to eliminate their spores[1] pathological invasion is observed mostly in immunocompromised patients especially those with uncontrolled diabetes mellitus, hematological malignancies, renal failure, conditions requiring high doses of steroids, and iron overload.[2-6]

Once the organism penetrates the tissue, vascular and perineural spread with the resultant coagulative necrosis, will account for the insensate necrotic black tissue appearance that characterizes the infection. And being saprophytic organism, it tends to flourish in this environment of dead tissue, acidic pH, and low O_2 tension accounting for the rapid spread of this mutilating destructive and life-threatening condition.[7,8]

Initially the prevalent symptoms are those of sinus infection, ocular or facial pain, facial paresthesia, and impaired vision.[9] Features suggestive of mucormycosis in predisposed cases include cranial nerve palsy, diplopia, sinus pain, proptosis, ptosis, periorbital swelling, orbital inflammation, eyelid edema, internal or external ophthalmoplegia, headache, acute vision loss, or a palatine ulcer.[4,10]

As understood so far, coronavirus disease (COVID-19) infection may induce significant and persistent

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lymphopenia. The lower absolute number of T lymphocytes (CD4+T and CD8+ T cells) in COVID-19 patients might render them highly susceptible to fungal co-infections.[11]

The altered iron metabolism, observed in those patients along with the low O_2 tension, may have also played a role in prevalence of this invasive infection during the pandemic.[12]

Management of mucormycosis is underscored by three key strategies

The three key strategies: (1) rapid initiation of effective antifungal therapy and concomitant aggressive attempts for diagnosis, (2) extensive "early" surgical debridement of necrotic lesions, and (3) rapid control of underlying medical condition, when feasible.[13]

Whereas culture remains the most common method for identification, this method is hampered by the low yield in mold infections generally, the possibility of contamination by environmental spores, and the time required.[10,14]

Importantly, there are no biomarkers to identify this disease. β-D-glucan test and *Aspergillus galactomannan* tests do not detect antigen components of the Mucorales cell wall.[13]

The histopathological diagnosis is based on the shape of fungi in tissue. Therefore, identifying some species might be difficult only by assessment of the shape, and the accuracy of diagnosis could largely depend on the pathologist's skill.[15,16]

With these diagnostic difficulties, we are therefore left with cases that have predisposing factors, clinical features of the disease, but fall short in providing a mycological evidence, the so called "possible invasive fungal disease".[17]

Corzo-Leon *et al*.[10] proposed an algorithm for the diagnosis and treatment of rhino-orbito-cerebral mucormycosis in patients with diabetes mellitus, in which the finding of any of the suggestive features of the disease should prompt immediate further testing, including blood tests, imaging, ocular and, or sinus surgery or endoscopic revision and initiation of antifungal treatment.

In 2021, Honavar[18] suggested a four-stage system for disease stratification, to guide management utilizing the natural spread of the infection from the nasal mucosa (stage I), to the nose and paranasal sinuses (stage II), to the orbit (stage III), and the brain stage IV.

During summer and autumn 2021, and with the rise in COVID-19 cases during the 2nd wave of the pandemic, we witnessed unprecedented increment in cases of invasive fungal rhinosinusitis.

The average mortality of COVID-19-associated mucormycosis in a systematic review in 2021 is reported to be around 34%, a figure that is similar to what has been reported before the pandemic.[19]

We were motivated by this work to examine the effects the pandemic exerted on management of mucormycosis in our facility.

Study questions

Has COVID-19 pandemic and reliance on clinical impression adversely affected management outcomes of invasive rhino-orbito-cerebral mucormycosis?

Objectives

Review of management outcomes and mortality in patients diagnosed with "possible invasive fungal rhinosinusitis" during the 2nd wave of COVID-19 pandemic and compare these with the outcomes observed before the pandemic in Iraq and other countries.

Materials and Methods

A cross-sectional study of patients with clinically "possible" mucormycosis consulting the ear, nose, and throat outpatient department, or referred from other departments in 7 months period, from the 1st of June 2021 till the 31st of December 2021.

All participants gave their verbal consent before enrolment.

Patients were interviewed and their previous medical records were reviewed.

Information about demographic data, presentation, associated symptoms, past medical history, and comorbidities were collected.

Details of recent COVID-19 infection as documented by a positive RT-PCR (reverse transcription polymerase chain reaction assay) were obtained including severity, use of steroids, duration between the infection and the diagnosis of mucormycosis, and vaccination status of the patients were also obtained.

A complete ear, nose, and throat examination, involving anterior rhinoscopy, rigid nasal endoscopy, ear and throat examination, and evaluation for cranial nerve involvement was the standard.

Examination findings, including the sites involved and stage of the disease were documented. At the same session, debridement of dead tissues was performed, and tissue samples taken for histopathological evaluation, and mycological cultures. On the waiting, antifungal therapy was initiated in all patients upon clinical judgment of "possible invasive fungal disease."

Debridement sessions were arranged daily for the first week, then twice weekly until complete resolution of all necrotic tissues. Survivors were followed by history, examination and rigid nasal endoscopy every 2 weeks for the next 6 months.

Data analysis

The collected data were summarized, analyzed, and presented using statistical package for social sciences (SPSS) version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) and Microsoft Office Excel 2019 (Redmond, Washington). Qualitative (categorical) variables were expressed as numbers and percentages, whereas, quantitative (numeric) variables were expressed as means and standard deviations. The level of significance was considered at P-value of equal or less than 0.05.

Ethical approval

The research has complied with the items of the "declaration of Helsinki" developed by the World Medical Association, and with the national regulations and institutional policies and has been approved by the Institutional Review Board in College of Medicine, Al-Nahrain University in the decision Numbered 20230382 on April 2, 2023.

Results

Demographics

The study involved 30 patients, comprising 16 male patients (53.3%), and 14 female patients (46.7%) [Figure 1], with a mean age of 51.07 ± 15.47 years. The youngest patient was aged 20, whereas the oldest was 80 years old.

Most of the sample consisted of middle-aged adults between 36 and 64 years old, with gender composition of the age groups being nearly homogenous as is depicted in Figure 1.

COVID-19 and comorbid illness in the sample

From the 30 patients involved in the study, 22 (73.33%) gave history of recent COVID-19 infection confirmed by a positive PCR. The remaining 8 (26.67%) did not report such history. The mean age of COVID associated mucormycosis (CAM) was 53.86 years, compared to 43.375years in non-CAM cases; however, the difference was insignificant using the Mann-Whitney test [Figures 2 and 3].

The initial presentation in 20 CAM cases took place after a mild to moderate infection [Table 1], with interval ranging from 8 to 120 days.

The remaining two cases presented within the first week of the infection.

Comorbid illness was prevalent among both CAM and non-CAM cases, diabetes mellitus being the most prevalent present in 56.67% [Table 2]. In CAM cases, 9 (40.91%) experienced hypoxia in the course of their illness and were managed with short duration of steroid therapy.

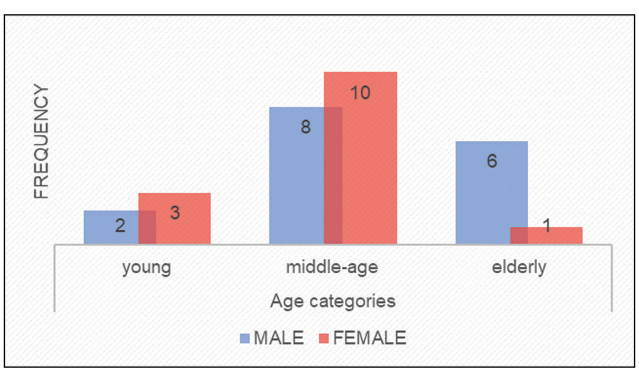

Figure 1: Age/gender distribution

Presentation

Cranial nerve palsies and otological symptoms were relatively more common in those with no previous history of COVID-19; however, this finding was statistically insignificant as the P values were 0.9 and 0.6, respectively [Tables 3-6].

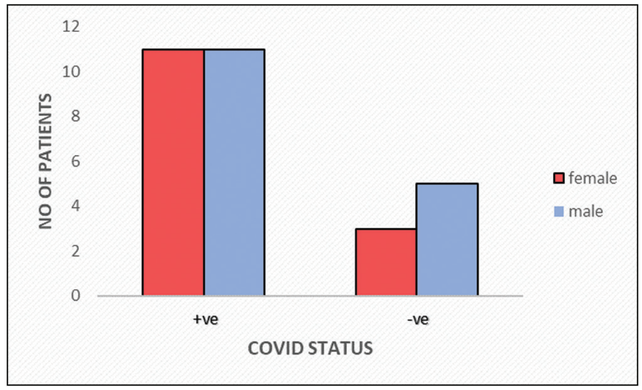

Figure 2: Gender/COVID distribution of mucormycosis cases

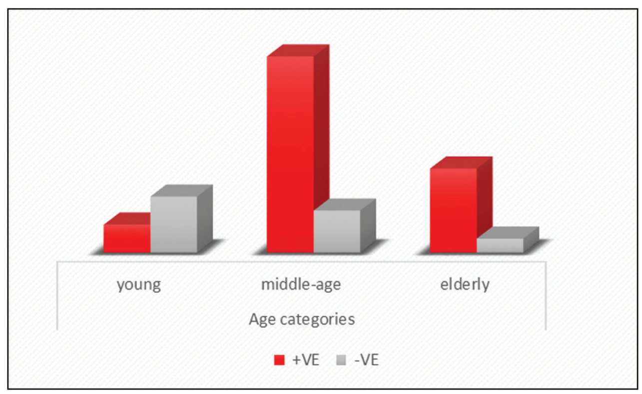

Figure 3: COVID status in different age categories.A part from one patient, all those with COVID associated mucormycosis (CAM) were unvaccinated against COVID-19, and the same is noticed in non CAM cases

Table 1: The severity of COVID-19 in patients with CAM

	Severity of COVID infection	
Mild	13	59.10 %
Moderate	8	36.4 %
Severe	1	4.50 %

Table 2: Comorbid illnesses

Comorbid illness	No.
DM [a]	17(56.67%)
DKA [b]	2(6.67%)
Renal failure	4(13.33%)
Hematological malignancy	3(10%)
Other (CA [c] Colon)	1(3.33%)
Mixed	4(13.33%)
None	2(6.67%)

[a:] Diabetes Mellites, [b:] Diabetic Ketoacidosis, [c:] Carcinoma of the Colon

Table 3: Frequency of symptoms and signs in the study population

Presentations	COVID +VE (n=22)	%	COVID -VE (n=8)	%
Fever	20	90.91%	7	87.50%
Facial pain	17	77.27%	7	87.50%
Nasal discharge/ obstruction	17	77.27%	6	75.00%
Headache	15	68.18%	6	75.00%
Otological symptoms	4	18.18%	2	25.00%
Acute loss of vision	3	13.64%	1	12.50%
Black necrotic turbinate	22	100.00%	8	100.00%
Facial swelling	20	90.91%	7	87.50%
Eyelid edema	14	63.64%	4	50.00%
Proptosis	10	45.45%	3	37.50%
Cranial nerve palsies	9	40.91%	5	62.50%
Palatal necrosis	5	22.73%	1	12.50%

Table 4: Symptom frequency by disease stage in the sample

Symptoms	Stage 1	Stage 2	Stage 3	Total	%
Fever	1	13	13	27	90
Facial pain	1	12	11	24	80
Nasal discharge/ obstruction	1	10	12	23	76.67
Headache	1	10	10	21	70
Otological symptoms	0	4	2	6	20
Acute loss of vision	0	0	6	6	20

Table 5: Frequency of examination findings in different stages

Signs	Stage 1	Stage 2	Stage 3	Total	%
Black necrotic eschar	1	15	14	30	100
Facial swelling	1	12	14	27	90
Eyelid edema	0	6	12	18	60
Proptosis	0	1	12	13	43.33
CN palsy	0	6	8	14	46.67
Palatal necrosis	0	2	4	6	20

Table 6: Outcome of mucormycosis in the sample

Outcome	CAM	Non-CAM	Total
Black necrotic eschar	6	2	8 (26.7%)
Frozen orbit	3	0	3 (10%)
CN*	1	0	1 (3.3%)
CN + palatal necrosis	4	3	7 (23.3%)
CN + frozen orbit	3	1	4 (13.3%)
Complete resolution	1	1	2(6.7%)
Death	4	1	5 (16.7%)
Total	22	8	30 (100%)

Fever accompanied with facial pain, nasal obstruction ± nasal discharge, and headache were the most prevalent symptom-combination in all stages occurring in 23.3% of the sample [Table 4].

Table 7: Stages of infection and stage specific mortality in COVID associated mucormycosis (CAM) and non-CAM groups

	CAM	Mortality %	non-CAM	Mortality %	Stage mortality
1	1 1	100%	0	0%	(1) 3.33%
2	10 1	10%	5	0%	(1) 3.33%
3	11 2	18.2%	3 1	33.3%	(3) 10%
TOTAL	22 4	18.2%	8 1	12.5%	(5) 16.7%

*Deceased cases are represented in grey

Outcome and mortality

The effect of age on disease mortality was found to be insignificant (*P* value = 0.069) [Table 7] [Figures 4-6].

Comparing the mortality in the different stages of mucormycosis, the *P* value was 0.069, and therefore, insignificant [Figure 7].

Discussion

A total of 30 cases with mucormycosis were managed in a 6-month period during the 2nd wave of COVID-19 pandemic. This is five times more than what Samir A. found in his unpublished series in 2005, and much higher than what is published by Stemler *et al.* [20]

Most of these cases (73.3%) had a history of recent COVID-19 infection. Similar increments were reported from other areas in the world, and especially from the India.[21-26]

The complex biochemical and physiological changes affecting those infected with COVID-19 might have furnished the floor for fungal growth.

A slight preponderance of male gender was noted [Figures 1 and 2]. This is also reported in many studies.[10,19,20,23,24,27-29] The difference however was insignificant in our study, and the gender gap appeared to be closed in those with history of COVID-19.

Robinson *et al*. (1990) as cited in Ribes *et al*.[9] suggested that this gender predilection of the disease might point to

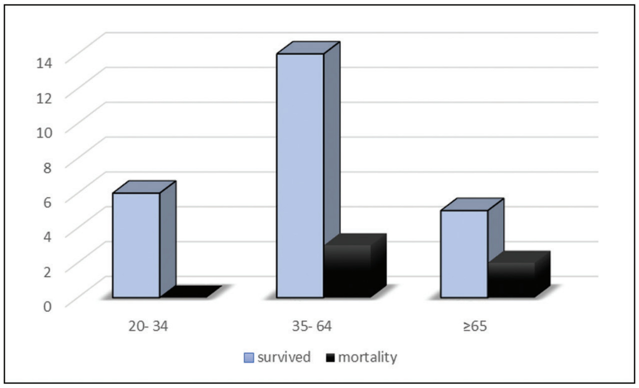

Figure 4: Age distribution of fatalities

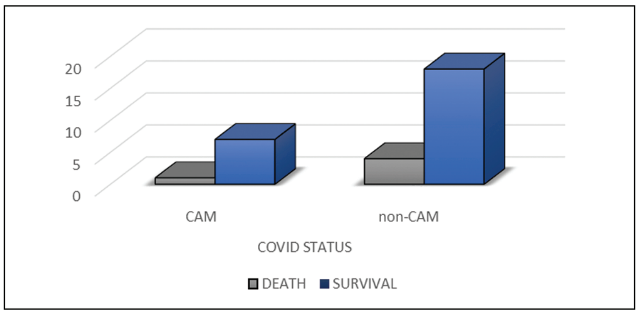

Figure 5: Distribution of mortality in COVID associated mucormycosis (CAM) and non-CAM patients

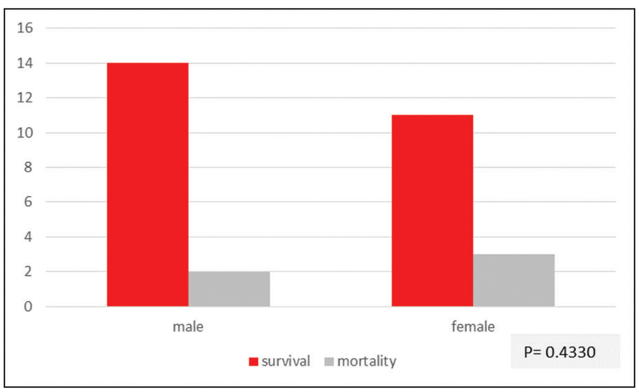

Figure 6: Gender distribution of mortality

involvement of male hormones as a predisposing factor for the infection.

The mean age of the population is similar to what have been previously reported,[23,27,30] and no significant difference was noted between CAM and non-CAM cases. Arjmand *et al*.,[24] however, found a significant difference in the mean age of cases reported in the pre-pandemic compared with those during the pandemic.

No sufficient data were available to compare the disease in vaccinated and unvaccinated patients, because only two of the victims received COVID vaccines. Mahla and Shrivastava[28] in 2021 reported 91.5% of their study population being unvaccinated.

In two Indian studies, the percentages of steroid use in CAM cases were 77.7% and 76.3%, respectively[28,29]; this is higher than the 40.91% observed in our study, and this might reflect the severity of COVID-19 infection as most of the cases had mild-to-moderate severity of infection [Table 1].

In concordance with studies from other parts of the world,[10,19,21,23-29,31-34] diabetes mellitus was the most prevalent comorbid illness in our sample (56.67%), diabetic keto acidosis being present in only two cases (6.67%). Chronic renal failure and hematological malignancies followed diabetes accounting for 13% and 10%, respectively. This is slightly different from what was noticed before the pandemic, where hematological malignancies dominated chronic renal failure. However this may only be caused by the short duration of the study.

From Table 2, we are able to identify that two of the CAM cases were immunocompetent and had no risk factors other than COVID-19 infection. Regardless of being statistically insignificant (P value = 0.815), this remains an interesting finding.

Fever and facial pain were the most prevalent presenting symptoms in both CAM, and non- CAM cases, occurring in 90% and 80%, respectively. Acute loss of vision occurred only in those with stage 3 disease (20% of the sample). That is somewhat different from what was reported by Iranian researchers with fever occurring in only 27% of the sample, and acute loss of vision in 73%.[33] This is related to difference in sample composition were stage 3 disease predominated in the Iranian sample.

The (16.67%) mortality rate in our sample is strikingly lower than that of most of the studies in our country before the pandemic, and in many other studies.[5,19,30,35]

Reflecting on this, we think that this was the effect of increased awareness of the condition, the medical authorities in Iraq fostered a preemptive strategy with early referral of suspected patients to otolaryngology departments for detailed evaluation, and provided the hospitals with liposomal amphotericin B, free of charge for the patients, factors that resulted in early initiation of treatment upon clinical judgement, before availability of tissue studies, that took on average 3-5 days.

The average fatalities of the infection show wide range of variations depending on the geographical area, the predisposing condition, comorbid illness, time of initiation of treatment, and the formulation of amphotericin available in the individual facilities.

Conclusions

Despite the challenge of increased number of cases of acute invasive mucormycosis during COVID-19 pandemic, a proactive policy based on detailed examination of suspected, high risk individuals with timely initiation of

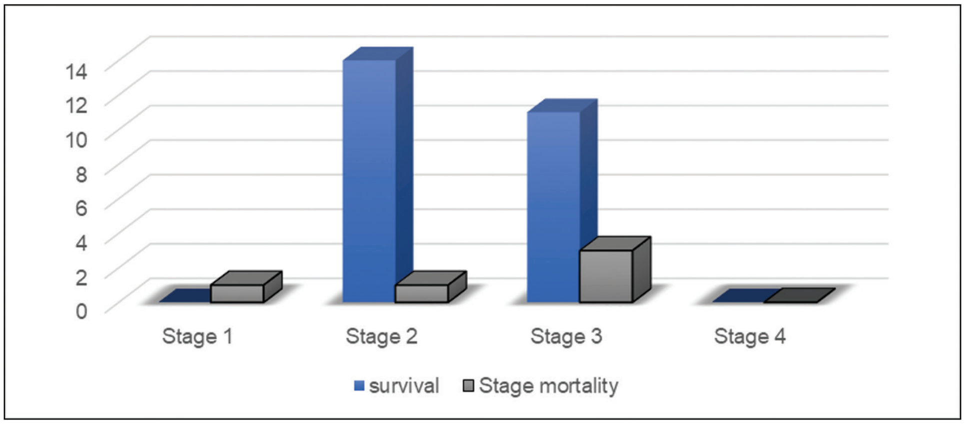

Figure 7: Stage specific mortality in the sample

antifungal therapy, in combination with local debridement can reduce the fatality of the condition.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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