CLINICAL PROFILE OF CENTRAL NERVOUS SYSTEM INVOLVEMENT IN PATIENTS WITH RHINO ORBITAL CEREBRAL MUCORMYCOSIS

Arvind MN[1], Sumesh Yadav[2], Nagaraja B S[3], Ambresh Ayyali[4]

[1]Arvind MN, Professor of General Medicine, SABVMCRI, Shivajinagar, Bangalore, Karanataka, India

[2]Sumesh Yadav, Post Graduate Student, Department of Medicine, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India.

[3]Dr Nagaraja B S, Professor , Department of Medicine, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India.

[4]Dr. Ambresh Ayyali, Assistant Professor of General Medicine, SABVMCRI, Shivajinagar, Bangalore, Karanataka, India

Corresponding Author:

Dr Sumesh Yadav, Post Graduate Student, Department of Medicine, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India

Abstract

Background: Mucormycosis is life threatening fungal infection that occurs in immunocompromised patients. Patients at risk are those with poorly controlled diabetes mellitus, immunosuppressed patients such as those undergoing treatment for haematological cancer or recipients of solid organ and hematopoietic stem cell transplantation. COVID 19 infection is known to produce a state of hyper inflammation with release of various cytokinesthis state of immune dysfunction is associated with development of opportunistic infections, of which Mucormycosis is on the rise currently**.** The widespread use of corticosteroids can cause secondary infections including mucormycosis**.** CNS penetration typically starts with nasal involvement followed by the paranasal sinuses and palate, ultimately invading the orbit and brain or by direct haematological spread which is called as Rhino-orbito-cerebral Mucormycosis (ROCM). **Material and Methods:** This is a cross sectional study conducted on 50 patients diagnosed with COVID 19 associated mucormycosis admitted to the hospitals attached to BMCRI from May2021 to August 2021.All the ROCM cases with CNS manifestation were included The relevant demographic data, clinical presentation, neurologic manifestations, underlying co morbidity, medical treatments, and surgical interventions done were recorded and analyzed. **Results:** A total of 50 patients were included mean age 49.3 year with 38 males and 12 females. Most common comorbidity was diabetes (94%) followed by hypertension (26%). Most common symptom was headache (86%) followed by facial swelling (68%), facial pain (66%).40% Patients had CNS symptom among which most common was hemiparesis. EOM restriction (70%) and abnormal vision (70%) being most common examination finding. Most common sinus being

involved was maxillary 94% followed by ethmoid sinus 92%. Neurological manifestation included acute infarct (56%), Cavernous sinus thrombosis (28%), ICA occlusion (10%) abscess (34%), 3 patients had dual fungal infection. 26% patient underwent craniotomy, 6% carniotomy with Denkers procedure, 30% underwent maxillectomy. Among the mortality group, average duration of diabetes was 11.5 years, average steroid use of 9.53 days, CRP was 104mg/l, D Dimer 755ng/dl, as compared to 5.89 years, 5.3 days, 58.9mg/l, 419ng/dl, respectively among recovered patients. Most patient were left with morbidity like vision loss and facial disfigurement (40%) being most common while hemiparesis in (14%) patients. **Conclusion:** Diabetes mellitus being the main predisposing factor for ROCM. Delayed diagnosis or inappropriate treatment may result in massive tissue destruction and possible extension into the cranial base and/or vault and orbit. Despite advances in imaging and the availability of novel drugs, cerebral mucormycosis continues to be associated with high rates of death and disability.

Keywords: Diabetes Mellitus, COVID-19, ROCM, CNS.

Introduction

Mucormycosis is life threatening fungal infection that occurs in immunocompromised patients.[1] Second most common invasive fungal disease after Aspergillosis.[2] Patients at risk are those with poorly controlled diabetes mellitus, immunosuppressed patients such as those undergoing treatment for haematological cancer or recipients of solid organ and hematopoietic stem cell transplantation. COVID 19 infection is known to produce a state of hyper inflammation with release of various cytokinesthis state of immune dysfunction is associated with development of opportunistic infections, of which Mucormycosis is on the rise currently. 33.3%–80% mortality in COVID-19 erahave been reported to be due to mucormycosis.[3] Proposed mechanism of pathogenesis of rhino-ocular-cerebral–mucor-mycosis (ROCM) is through colonization of nasal mucosa; sinuses than spreading to adjacent structures.[4]

Commonest clinical feature at presentation were nasal block, ocular pain, or swelling of lid rare presentations like sudden loss of vision was also seen as presenting feature.[5,6] Primary investigation could be done by potassium hydroxide (KOH) mount and calcofluor white stain then the confirmatory test could be done by contrast-enhanced computed tomography (CECT) paranasal sinus, orbit and brain.[7-9]

Gadolinium-enhanced magnetic resonance imaging (MRI) reserved for suspected intracranial spread and microbiological culture or biopsy.[7-9]

The widespread use of corticosteroids can cause secondary infections including mucormycosis. CNS penetration typically starts with nasal involvement followed by the paranasal sinuses and palate, ultimately invading the orbit and brain or by direct haematological spread which is called as Rhino-orbito-cerebral Mucor-mycosis (ROCM).[10,11] The present study aimed at analysing the clinical profile of central nervous system involvement in COVID 19 patients with rhino orbital cerebral mucormycosis.

Material and Methods

This is a cross sectional study conducted on 50 patients diagnosed with COVID 19 associated mucormycosis admitted to the hospitals attached to BMCRI from May2021 to August 2021. All the ROCM cases with CNS manifestation were included the relevant demographic data, clinical presentation, neurologic manifestations, underlying co morbidity, medical treatments, and surgical interventions done were recorded and analyzed.

Statistical Analysis: SPSS (Statistical Package for Social Sciences) version 20. [IBM SPSS statistics (IBM corp. Armonk, NY, USA released 2011)] was used to perform the statistical analysis.

- Descriptive statistics of the explanatory and outcome variables were calculated by mean, standard deviation for quantitative variables, frequency and proportions for qualitative variables.
- Chi square test was applied between outcome and quantitative variables
- Independent t test was applied to test the mean difference between the variables and outcome of the disease.

Results

Table 1: Comparison of outcome of the disease with respect to gender

Gender	Outcome		Total
	Survived	**Expired**	
Female	6	6	12
	16.2%	46.2%	24.0%
Male	31	7	38
	83.8%	53.8%	76.0%
Total	37	13	50
	100.0%	100.0%	100.0%

p value 0.03

There was significantly higher number of male patients involved and also the number of male patients survived was comparatively higher than the females.

Table 2: Correlation between the age and survival rate of ROCM

Outcome	N	Age (years)		Mean Difference	p value
		Mean	**Std. Deviation**		
Survived	37	48.81	12.76	-1.881	.640
Expired	13	50.69	11.33		
Total	50	49.3	12.318		

Mean age of the patients survived and the expired patients was 48.81±12.76and 50.69±11.33 respectively with no statistical significance.

Table 3: Distribution of the comorbid conditions among the patients with ROCM

Co Morbidities	Outcome		Total
	Survived	Expired	
T2DM	5	2	7
	13.5%	15.4%	14.0%
CKD, ITP, HTN, T2DM	0	1	1
	0.0%	7.7%	2.0%
IHD, CVA, HTN	0	1	1
	0.0%	7.7%	2.0%
LEUKEMIA, SPLEENIC ABSCESS	1	0	1
	2.7%	0.0%	2.0%
OLD PTB, T2DM	1	0	1
	2.7%	0.0%	2.0%
T2DM	17	5	22
	45.9%	38.5%	44.0%
T2DM HTN IHD	2	0	2
	5.4%	0.0%	4.0%
T2DM IHD, HERPES LIBIALS	1	0	1
	2.7%	0.0%	2.0%
T2DM, HTN	6	3	9
	16.2%	23.1%	18.0%
T2DM, HTN, CKD	1	0	1
	2.7%	0.0%	2.0%
T2DM, IHD	2	1	3
	5.4%	7.7%	6.0%
T2DM, OLD CVA	1	0	1
	2.7%	0.0%	2.0%
Total	37	13	50
	100.0%	100.0%	100.0%

Associated comorbid conditions were widely distributed among the study participants.

Table 4: Correlation between the of duration of diabetes, usage of steroids and the survival rate

Variables	Outcome	N	Mean	Std. Dev	Mean Difference	p value*
Duration of Diabetes	Survived	37	5.90	8.20	-5.65520	0.035
	Expired	13	11.55	7.75		
Duration of Steroids In Days	Survived	37	5.32	6.11	-4.21414	0.02990
	Expired	13	9.54	4.93		

*Independent t test

Patients with known history of diabetes and those who were on steroid usage had strong positive correlation with the mortality with significant p values of 0.035 and 0.0299 respectively.

Table 5: Correlation between the survival rate and the symptoms of ROCM

Symptoms	Outcome		Total	p value
	Survived	Expired		
Nasal block	22	8	30	0.895
	59.50%	61.50%	60.00%	
Nasal discharge	24	8	32	0.83
	64.90%	61.50%	64.00%	
Headache	32	11	43	0.867
	86.50%	84.60%	86.00%	
Vision loss	22	8	30	0.895
	59.50%	61.50%	60.00%	
Facial pain	25	8	33	0.693
	67.60%	61.50%	66.00%	
Facial swelling	26	8	34	0.562
	70.30%	61.50%	68.00%	
CNS symptoms	14	6	20	0.598
	37.8	46.2	40%	

Most of the patients had presented with multiple symptoms. Of which the most common symptom was headache, accounting for about 86% followed by facial swelling in about 68% of the patients. There was no correlation between the symptoms and the survival rate of the ROCM.

Table 6: Correlation between the disease outcome and the clinical examination

Examination findings	Outcome		Total	p value
	Survived	Expired		
Palatal involvement	13	8	21	0.097
	35.10%	61.50%	42.00%	
Proptosis	20	6	26	0.624
	54.10%	46.20%	52.00%	
EOM restriction	27	8	35	0.439
	73.00%	61.50%	70.00%	
Abnormal vision	25	10	35	0.526
	67.50%	77%	70%	

Table 7: Correlation between the type of sinus involved and the survival rate of ROCM

Types of sinus involved	Outcome		Total	p value
	Survived	Expired		
Maxillary	35	12	47	0.765
	94.60%	92.30%	94.00%	
Ethmoid	34	12	46	0.962
	91.90%	92.30%	92.00%	
Frontal	23	7	30	0.599
	62.20%	53.80%	60.00%	
Sphenoid	30	8	38	0.156
	81.10%	61.50%	76.00%	
Orbit	31	9	40	0.259
	83.80%	69.20%	80.00%	

There was significant association found between the involvement of the sinus and the survival rate of the study population.

Table 8: Correlation between the type of fungus and the clinical outcome

HPE	Outcome		Total	p value
	Survived	Expired		
Aspergillus Fumigatus	1	1	2	0.354
	2.7%	7.7%	4.0%	
Mucor	25	7	32	
	67.6%	53.8%	64.0%	
Mucor And Aspergillus Fumigatus	1	1	2	
	2.7%	7.7%	4.0%	
Mucormycosis With Angioinvasion	1	2	3	
	2.7%	15.4%	6.0%	
NEG	9	2	11	
	24.3%	15.4%	22.0%	
Total	37	13	50	
	100.0%	100.0%	100.0%	

There was no significant difference found between the type of fungus affecting the patients and the survival rate. Most common fungus found on HPE mount was mucor with the prevalence of 64% and the least common were aspergillus, mucor with aspergillus among two patients each.

Table 9: Correlation between the outcome of ROCM and the operation required.

Operated	Outcome		Total	p value
	Survived	**Expired**		
No	1	1	2	0.43
	2.7%	7.7%	4.0%	
Yes	36	12	48	
	97.3%	92.3%	96.0%	
Total	37	13	50	
	100.0%	100.0%	100.0%	

There was no correlation between the patients who had operated and those who were managed with conventional COVID protocol for mucor cases.

Table 10: Correlation between the COVID markers and the survival rate of ROCM patients

Variables	Outcome	N	Mean	Std. Dev	Mean Difference	p value*
HB	Survived	37	11.38	1.53	0.455	0.359
	Expired	13	10.92	1.50		
TC	Survived	37	10,106.22	3,943.06	-1627.091	0.225
	Expired	13	11,733.31	4,555.76		
CRP	Survived	37	58.91	22.65	-45.60279	0.00045
	Expired	13	104.51	64.06		
D DIMER	Survived	37	419.59	169.15	-335.71310	0.00000
	Expired	13	755.31	180.89		
LDH	Survived	37	183.49	59.77	-142.06736	0.00000
	Expired	13	325.55	82.53		
HBA1C	Survived	37	8.93	2.05	-2.64220	0.00036
	Expired	13	11.57	2.37		
UREA	Survived	37	22.62	16.81	-9.268	0.145
	Expired	13	31.88	25.70		
CREATININE	Survived	37	3.50	16.14	1.991	0.661
	Expired	13	1.51	1.70		
ALB	Survived	37	3.06	0.50	0.231	0.151
	Expired	13	2.83	0.47		

There was significantly higher level of D dimer, HbA1c, CRP and LDH among the recruited study population and the mortality was higher among those who had not found with higher level of COVID inflammatory markers.

Discussion

Prevalence of ROCM was rare in the pre-COVID-19 era which was most commonly seen among immunocompromised patients.[12] But later as there was increase in administration of the steroids in COVID 19, the cases of mucor mycosis also increased due to immunosuppression. There was sudden surge in mortality due to mucor cases among the patients with COVID 19. Hence the present study was conducted to analyse the association of various factors and the survival rate of the patients with ROCM.

A total of 50 patients were included mean age 49.3 year with 38 males and 12 females. Most common comorbidity was diabetes (94%) followed by hypertension (26%). Among the mortality group, average duration of diabetes was 11.5 years, average steroid use of 9.53 days. Similar to present study Garg D et al in their case report has discussed that the random blood sugar of their patient was 140 mg/dl at the time of admission which had increased to 400 mg/dl when the clinical symptoms of mucor mycosis had occurred.[13] The patient was administered with dexamethasone 6 mg once daily for 14 days. The probable reason they had mentioned was the steroid induced hyperglycemia in that patient had created an environment for the growth of mucor mycosis. The immunocompromised and the increased sugar levels have synergistically aggravated the spread of the infection.

Most common symptom was headache (86%) followed by facial swelling (68%), facial pain (66%). 40% Patients had CNS symptom among which most common was hemiparesis. EOM restriction (70%) and abnormal vision (70%) being most common examination finding. Whereas in the study by Bhattacharya et al, nasal block, ocular pain, or swelling of lidwere the commonest symptoms.[14] Majority of the patients (53.7%) in their study had complied of unilateral visual impairment as seen in our study. Pakdel F et al and Bayram N et al had reported nasal block as the commonest symptoms observed among their study population. By which we can analyse that the symptoms of ROCM varies widely.[15,16]

Most common sinus being involved was maxillary 94% followed by ethmoid sinus 92%. Neurological manifestation included acute infarct (56%), Cavernous sinus thrombosis (28%), ICA occlusion (10%) abscess (34%), 3 patients had dual fungal infection. 26% patient underwent craniotomy, 6%carniotomy with Denkers procedure, 30% underwent maxillectomy. Contrary to the present study, Sharma et al. reported the significantly higher prevalence of involvement of the ethmoid sinus.

The average CRP of our study population was 104mg/l, D Dimer 755ng/dl, as compared to5.89 years, 5.3 days, 58.9mg/l, 419ng/dl, respectively among recovered patients. Most patient were left with morbidity like vision loss and facial disfigurement (40%) being most common while hemiparesis in (14%) patients.

Out of 13 patients died due to COVID 19 in the present study, 11 (84.6%) and 2 (15.4%) were with and without mucor mycosis respectively. White et al reported that the overall mortality rate of their patients was 38%, of which the 53% and 31% were with and without fungal disease respectively.

Conclusion

Diabetes mellitus being the main predisposing factor for ROCM. Delayed diagnosis or inappropriate treatment may result in massive tissue destruction and possible extension into the cranial base and/or vault and orbit. Despite advances in imaging and the availability of

novel drugs, cerebral mucormycosis continues to be associated with high rates of death and disability.

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