



Facial Nerve Palsy as a Common Presentation during the Epidemic of Coronavirus Disease Associated Rhinocerebral Mucormycosis

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Received: 12 August 2021 / Accepted: 19 August 2022 / Published online: 4 September 2022
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Abstract

Purpose The main purpose of this study is to highlight the involvement of the facial nerve as one of the presenting symptoms in patients suspected of coronavirus disease associated mucormycosis (CAM).

Methods This is a retrospective observational study conducted at a tertiary care referral centre which included 300 patients with past history of being treated for coronavirus disease and who presented to our department with symptoms of invasive fungal sinusitis. All the patients were evaluated clinically and radiologically for presence of facial nerve palsy (FNP) in suspected cases of CAM. All the patients were managed with combined modality treatment with anti-fungal therapy and radical endoscopic debridement of the necrotic tissue and fungal debris.

Results The data were analysed to assess the possible epidemiological factors linked to CAM. Diabetes mellitus was the most common associated factor identified for aggravating of CAM. FNP is also one of the common presentation seen among 53 patients with CAM.

Conclusion FNP is an unusual but significant sign in presentation of mucormycosis. It could be easily misdiagnosed as cerebrovascular accident leading to delay in the treatment. During this era of Covid-19 pandemic where wearing of masks has become mandatory, there is a high probability of this finding to be missed. Thus, our study emphasises for

thorough cranial nerve examination in all cases of CAM, for an early and an immediate intervention to prevent the spread of the disease and also to improve the overall general condition of the patient.

Keyword Coronavirus · Mucormycosis · Invasive fungal sinusitis · Facial nerve palsy · Greater superficial petrosal nerve

Introduction

The global Coronavirus disease 2019 (Covid-19) pandemic has affected more than 30 million people in India till date and several have succumbed to the disease. As India continues to fight and gain stability over the existing scenario, another imminent threat has emerged as a challenge to India in the form of coronavirus disease associated mucormycosis (CAM). Covid-19 is an infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus, which principally binds to the angiotensin converting enzyme 2 receptors and thus invades the respiratory epithelium. The second stage of this disease is more severe caused by aggravation of systemic inflammation and coagulopathy causing direct endothelial damage to the blood vessels and microvascular thrombus formation. Moreover, affected patients likewise show an overexpression of inflammatory cytokines, and impaired cell mediated immunity thus leading to increased susceptibility to fungal infections.

Mucormycosis (the so called black fungus) is a rare, angioinvasive infection that typically affects immunocompromised individuals. Depending on the site affected it can manifest as one of seven different clinical syndromes such as rhino-orbito cerebral, pulmonary, gastrointestinal, central nervous system, cutaneous, disseminated, miscellaneous

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(bones, joints, heart, kidney, mediastinum). Rhino-orbit cerebral type is the commonest type accounting for about 30–50% of the cases and also rapidly progresses through the stages of rhinomaxillary, rhino-orbital and rhino-orbito-cerebral mucormycosis (ROCM). In the past 3 months, we have seen an immense increase in the numbers of cases of CAM at our nodal centre. The high incidence of diabetes in our Indian population alongside with excessive use of corticosteroids as a part of treatment for Covid-19 could also be a probability for increased numbers. Coagulopathy leading to several peripheral microthrombi, microangiopathy from diabetes mellitus in addition to immunosuppression from corticosteroids all could have been a cause in providing an ideal host for the fungus to grow. Typical presentation of ROCM includes nasal stuffiness, headache, facial pain, retro-orbital pain, orbital swelling, ophthalmoplegia and visual loss. Involvement of the cranial nerves although not very common, facial nerve palsy (FNP) is a rare finding which has been documented previously. The purpose of this article is to make ENT surgeons aware of this uncommon presentation of ROCM. Timely diagnosis and early recognition of the signs and symptoms, correction of underlying medical disorders, and aggressive medical treatment with antifungal and surgical intervention are necessary for successful therapeutic outcome.

Materials and Methods

This is a retrospective observational study which was conducted at our tertiary care nodal centre in India for the treatment of CAM between April 2021 and June 2021 after obtaining an institute ethical committee approval. This study included 300 patients with past history of recently being treated for Covid-19 infection and who presented to our department with symptoms and signs of ROCM. Patients were characterized as recovered from Covid-19 if they were tested negative on a repeat RT-PCR (reverse transcriptase polymerase chain reaction) or if fourteen days had elapsed since the diagnosis.

Patients were also assessed for the following history before deciding the treatment protocol 1. History of Covid-19 infection 2. Diabetes status of the patient (pre-existing or newly diagnosed) 3. History of steroid use during Covid-19 infection.

Patients with a history of radiotherapy, chemotherapy, osteoradionecrosis of the jaw, granulocytopenic patients or those on other immunomodulator drugs were excluded from the study. Patients with non Covid-19 associated ROCM were also excluded from the study.

The patients who presented with one or more of the following symptoms and signs of headache, facial pain, jaw pain or necrosis of the mucosa or the palatal bone,

retro-orbital pain, swelling of the eye or proptosis, ptosis and visual disturbances (Fig. 1) suspicious of ROCM were all included in the study.

Intervention

All patients underwent thorough ENT and cranial nerve examination. Patient were checked for swelling of the eye (proptosis), drooping of the upper eyelid (ptosis), loss of vision or visual disturbances, and facial nerve involvement with signs of drooping of the corner of the mouth, drooling of saliva and absence of wrinkles in half of the forehead (suggestive of lower motor neuron palsy). Aside from ascertaining the current Covid-19 status with RT-PCR test, routine blood investigations and high resolution computed tomography of the chest were done for all the patients. Diagnostic nasal endoscopy was performed to look for necrotic tissue, black eschar or fungal debris i.e., signs of invasive fungal sinusitis (Fig. 1). Magnetic resonance imaging (MRI) of the paranasal sinuses (PNS) including orbits and brain were performed for all cases (Fig. 2). Patients were taken up for surgical exploration and debridement, under endoscopic guidance and the infected tissue was sent for microbiological and histopathological examination (HPE) to determine and confirm the presence of fungal hyphae (Fig. 1). The surgical intervention varied from a simple surgical debridement to maxillectomy (partial/subtotal/total) to orbital exenteration depending on the extent of disease. Depending on the type of fungal organism, liposomal amphotericin therapy was instituted at 5 mg/kg for mucormycosis. Later at the time of discharge patients were started on oral posaconazole 300 mg every 8th hourly on the first day and then continued at once daily dosage. Due to high possibility of nephrotoxicity and electrolyte disturbances due to liposomal amphotericin B, daily renal function tests and serum electrolytes were performed, monitored and managed appropriately. The patients were followed up after discharge regularly at weekly intervals and were taken up for further surgical debridement if any suspicious lesions were noted.

Measurement

Patients were assessed for the presence of facial nerve palsy in ROCM, whether it was lower motor neurone type or upper motor neurone type. Radiologically the various sites of involvement of sinuses due to the spread of mucormycosis has also been studied.

Statistical Methods

Statistical analysis was performed by a department appointed statistician. The data of the patients demographic details, co-morbidities, history in regards to management with use

Fig. 1 (A, B) Clinical images showing drooping of the angle of mouth seen in lower motor neurone FNP, (C) Diagnostic nasal endoscopy image showing black necrotic tissue involving the middle turbinate and mucosa in the nasal cavity, (D) Histopathological image (Periodic Acid Schiff stain, 10× magnification) showing broad aseptate fungal hyphae confirming mucor species



of corticosteroids, Covid-19 infection, symptomatology and involvement of facial nerve were all collected, obtained and analysed. Descriptive statistics for patient characteristics included the mean, standard deviation, median and range for continuous variables, and frequencies and percentages for categorical items. Statistical analysis software STATA (StataCorp LLC, 4905 Lakeway Drive College Station, Texas) v.11.2 was used for data analysis.

Results

Among the 300 patients who were included in the study, 227 (75.6%) were males and 73 (24.33%) were females, with ratio between males to females to be 3.1:1. The age of the patients ranged from 18 to 80 years with a mean age of 47.05 ± 10.7 years.

Out of the 300 patients suspected CAM the most common epidemiological factor was diabetes mellitus. Majority 285 (95%) patients were either newly diagnosed 152 (50.67%) or pre-existing diabetics 133 (44.33%) and 253 (84.33%) received corticosteroids during management of Covid-19 infection.

Table 1 summarises the symptoms of CAM among 300 patients who were included in the study. FNP was seen among 53 (17.67%) out of 300 patients included in the study. Table 2 summarises distribution of signs of ptosis, loss of vision among patients with FNP. 45 out of 300 patients had ptosis, vision loss and facial nerve palsy. Table 3 summarises the involvement of various sinuses, premaxillary area, retromaxillary area, orbit, orbital apex, optic nerve, and cavernous sinus.

All patients underwent preoperative DNE, imaging, followed by immediate surgical management and the excised

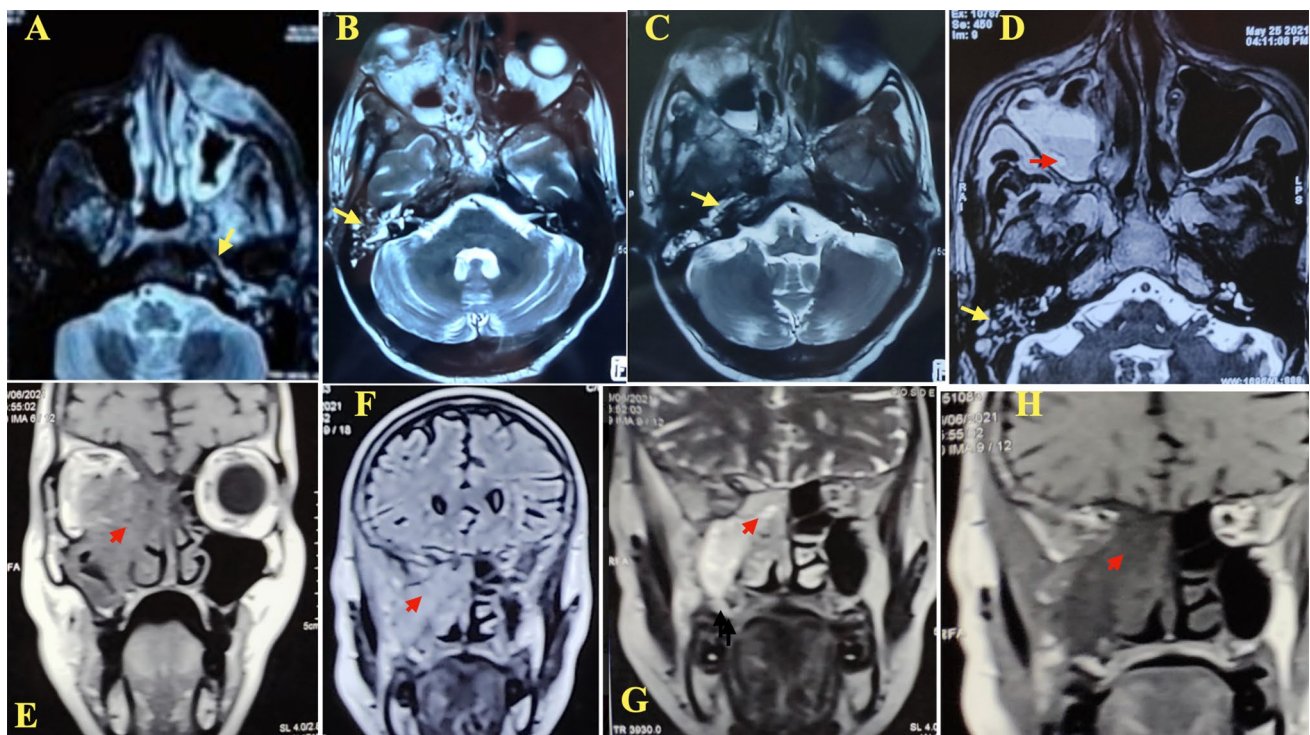


Fig. 2 MRI brain with orbit with PNS, showing features suggestive of invasive fungal sinusitis and its spread to involve the facial nerve and mastoid. (A, B, C, D) axial sections showing, (A) enhancement of the greater superficial petrosal nerve (yellow area) from maxillary

sinus. (B, D) extension from PNS (red arrow) to involve the mastoid cavity (yellow arrow) (C) spread via the eustachian tube (yellow arrow) to involve the mastoid cavity. (E, F, G, H) coronal sections showing involvement of the PNS (red arrow) and orbit

tissue was sent for HPE. HPE confirmed mucormycosis was seen in 262 (87.33%) patients, aspergillosis in 11 patients, mixed infection in 4 patients and rest others showed features of chronic sinusitis.

Table 4 summarises the association of FNP with DM and Mucormycosis. 52 out of the total 53 patients with FNP were diabetics.

Discussion

Mucormycosis is a rare, opportunistic, fulminant, angioinvasive fungal infection caused by rhizopus species of the order mucorales and was first described by Paultauf in 1885 [1]. It mainly affects immunocompromised individuals, predisposed by diabetes mellitus, corticosteroids, immunosuppressive therapy, haematological malignancies and organ transplantation [2]. The fungi are ubiquitous and are seen mainly on plants and animal matter. In patients with diabetes, hyperglycaemia along with low pH acidic environment produces a favourable environment for the spores to germinate. The inhaled spores of the fungi get inoculated into the nose and nasopharynx, leading to tissue invasion, thrombosis, and necrosis. The fungal hyphae are highly angioinvasive and have a great affinity towards the internal elastic lumina of the

arterial blood vessels thus ensuing thromboembolism and causing subsequent thrombotic infarction [3]. Most commonly seen is the thrombosis of the sphenopalatine artery or internal maxillary artery thus producing a characteristic black necrotic eschar on which the fungus thrives. This necrosis causes rapid spread of infection from the nose to the PNS, to the orbit, cavernous sinus and then to the intracranial cavity via angular, ethmoidal and lacrimal vessels. Intracranial spread can occur within days from the orbit via orbital vessels, or via cribriform plate [4].

Typical clinical presentation of ROCM includes headache, facial pain or swelling, retro-orbital pain and jaw pain. As the disease advances patients may present with ptosis, proptosis, palatal eschar with multiple cranial nerve palsy [5–7]. Ptosis could be due to direct involvement of retro-orbital tissues, levator palpable superiors muscle or the oculomotor nerve extending into the cavernous sinus. Loss of vision may result from direct involvement of the optic nerve or due to central retinal artery occlusion or endophthalmitis. Bilateral eye signs are suggestive of involvement of the cavernous sinus. The orbital findings in our study revealed ptosis, proptosis and vision disturbances. Retro-orbital pain or swelling was observed in 221 (73.67%) of patients by us compared with 43% by Yohai et al. [8]. Ptosis was reported in 96 (32%) of patients. In our study loss

Table 1 Distribution of symptoms and signs of ROCM among 300 patients of CAM

Symptoms/signs	Male	Female	Total
<i>Headache</i>			
Yes	160/227 (70.48%)	48/73 (65.75%)	208/300 (69.33%)
No	67/227 (29.52%)	25/73 (34.25%)	92/300 (30.67%)
<i>Eye pain</i>			
Yes	170/227 (74.89%)	51/73 (69.86%)	221/300 (73.67%)
No	57/227 (25.11%)	22/73 (30.14%)	79/300 (26.33%)
<i>Facial pain</i>			
Yes	193/227 (85.02%)	60/73 (82.19%)	253/300 (84.33%)
No	34/227 (14.98%)	13/73 (17.81%)	47/300 (15.67%)
<i>Jaw pain/palatal eschar</i>			
Present	46/227 (20.26%)	10/73 (13.70%)	56/300 (18.67%)
Absent	181/227 (79.74%)	63/73 (86.30%)	244/300 (81.33%)
<i>Loss of vision</i>			
Present	75/227 (33.04%)	25/73 (34.25%)	100/300 (33.33%)
Absent	152/227 (66.96%)	48/73 (65.75%)	200/300 (66.67%)
<i>Ptosis</i>			
Present	77/227 (33.92%)	19/73 (26.03%)	96/300 (32.00%)
Absent	150/227 (66.08%)	54/73 (73.97%)	204/300 (68.00%)
<i>Facial nerve palsy</i>			
Present	42/227 (18.50)	11/73 (15.07)	53/300 (17.67)
Absent	185/227 (81.50)	62/73 (84.93)	247/300 (82.33)
<i>Side of FNP</i>			
Right	31 (13.66%)	7 (9.59%)	38 (12.67%)
Left	11 (4.85%)	3 (4.11%)	14 (4.67%)
None	185 (81.50%)	63 (86.30%)	248 (82.67%)
<i>Present</i>			
Present	14 (6.17%)	3 (4.11%)	17 (5.67%)
<i>Absent</i>			
Absent	213 (93.83%)	70 (95.89%)	283 (94.33%)
<i>DNE—black eschar</i>			
Present	170/227 (74.89)	58/73 (79.45)	228/300 (76.00)
Absent	57/227 (25.11)	15/73(20.55)	72/300 (24.00)
<i>Mucormycosis HPE</i>			
Yes	200/227 (88.11%)	62/73 (84.93%)	262/300 (87.33%)
No	27/227 (11.89%)	11/73 (15.07%)	38/300 (12.67%)

Table 2 Distribution of association between ptosis, loss of vision and facial nerve palsy among 300 patients of CAM

Sign	Facial nerve palsy (FNP)			
	FNP Present 53 (17.67%)	FNP Absent 247 (82.33%)		
<i>Ptosis</i>				
Present (96)	51 (53.13%)	45 (46.88%)		
Absent (204)	2 (0.98%)	202 (99.02%)		
<i>Loss of Vision</i>				
Present 100	FNP Present 53 (17.67%)	FNP Absent 247 (82.33%)		
Present 100	45 (45.00%)	55 (55.00%)		
Absent 200	8 (4.00%)	192 (96.00%)		
<i>Loss of vision</i>				
	FNP absent ptosis absent	FNP absent ptosis present	FNP present ptosis absent	FNP present ptosis present
Present	28	27	0	45
Absent	174	18	2	6

Table 3 Distribution of various sites of involvement radiologically among 300 patients of CAM

Site of Involvement	RIGHT (n = 300)	LEFT (n=300)
Maxillary sinus	205 (68.3%)	174 (58%)
Ethmoid sinus	146 (48.6%)	119 (39.6%)
Sphenoid sinus	93 (31%)	74 (24.6%)
Frontal sinus	106 (35.3%)	89 (29.6%)
Premaxillary area	171 (57%)	148 (49.3%)
Retromaxillary area	130 (43.3%)	96 (32%)
Middle turbinate	151 (50.3%)	126 (42%)
Inferior turbinate	124 (41.3%)	104 (34.6%)
Superior turbinate	12 (4%)	7 (2.3%)
Orbit	151 (50.3%)	142 (47.3%)
Orbital apex	13 (4.3%)	19 (6.3%)
Cavernous sinus	16 (5.3%)	12 (4%)

of vision or visual disturbances were observed in 33.3% of the cases when compared with 65% reported by Yohai et al. [8] and 25% by Ferry et al. [9].

Significant neurological findings observed in our study was mainly LMN type facial nerve palsy with signs of drooping of the corner of the mouth, drooling of saliva and absence of wrinkles in the half of the forehead. With regards to symptomatology, our patients had more extensive involvement than reported by Yohai et al. [8] particularly with regard to facial swelling (84.33% vs. 30%), nasal ulceration or necrosis (76% vs. 48%) as seen on DNE, jaw pain or palatal necrosis (18.67% vs. 32%), and LMN facial palsy (17.67% vs. 22%). 51 patients had both ptosis and FNP, 45% had loss of vision with FNP and 45 of them had ptosis, FNP and loss of vision.

Involvement of cranial nerves albeit not common, facial nerve palsy is a rare finding. ROCM can mimic cerebrovascular accidents due to involvement of multiple

cranial nerves. Cranial nerve findings imply a much more severe infection and signal a grave prognosis. The previous reported literature showed frequency of unilateral LMN FNP in conjunction with ROCM to be 11% [10] however in our study, it was bit higher, we had 53 (17.7%) patients who presented with FNP with right side being more involved than the left.

The exact mechanism of involvement of the facial nerve in mucormycosis is unknown, and no definite pathology of the facial nerve has been identified. Recent studies have demonstrated spread of mucorales species along the peripheral nerves [11]. Some authors consider pterygopalatine fossa as a reservoir for the and route of spread of mucormycosis to the facial nerve [11]. The pathway of spread to involve the facial nerve is believed to start from the nasal mucosa, spreading to the maxillary, ethmoid sinuses, orbit, pterygopalatine fossa finally to the infra temporal fossa and then extending intracranially [10].

So, the infection reaching the pterygopalatine fossa can spread to the inferior orbital fissure, orbital apex, and infra temporal fossa. The juxtaposition of the Pterygopalatine fossa and presence of numerous vascular and neural tissue connections makes it a likely route of perineural invasion to the cranial tissues. Perineural spread through the vidian nerve is also one of the possibilities. The Vidian nerve is a continuation of the greater superficial petrosal nerve. An isolated involvement of the intracanalicular facial nerve within the temporal bone can occur along the nerve sheath of this nerve [12, 13]. Facial nerve may also be affected by direct spread through the Eustachian tube or through the vascular channels into middle ear. Another reason of involvement of facial nerve palsy can be the pathology of resistance arteries in diabetic patients which may cause oedema and localize facial nerve ischemia. This would compromise the blood supply to the nerve leading to palsy. Facial nerve palsy can also be incidental and may be idiopathic as in Bell's palsy.

Table 4 showing association between Diabetes and Facial nerve palsy, Mucormycosis and Facial nerve palsy

Variant	Facial nerve palsy (FNP)			
	FNP present (n = 53)	FNP absent (n = 247)	Total	
Diabetes Mellitus				
Denovo DM	23/53	129/247	152/300	
Chronic DM	29/53	104/247	133/300	
Absent	01/53	14/247	15/300	
Mucormycosis	FNP present (n = 53)	FNP absent (n = 247)		
Present	53	209		
Absent	0	38		
Diabetes Mellitus	FNP present HPE positive	FNP present HPE negative	FNP absent HPE positive	FNP absent HPE negative
Denovo DM	23/53	0	109	20
Chronic DM	29/53	0	86	18
Absent	1	0	14	0

In our study out of the 300 patients suspected of CAM the most common epidemiological factor was diabetes mellitus. Majority 285 (95%) patients were either newly diagnosed 152 (50.67%) or pre-existing diabetics 133(44.33%). 52 patients who developed FNP in our study were all diabetics with CAM. All the 53 patients with FNP had mucormycosis. Previous studies in literature have shown involvement of the facial nerve due to vascular ischaemia caused by microthrombi among Covid 19 positive patients[14, 15]. Various studies have also mentioned involvement of the facial nerve among diabetic patients. [16–18]

According to our study, the involvement of facial nerve could be mainly due to the extent and rapid spread of the disease, past Covid 19 Status and diabetes would be contributory. However there is also a possibility that it also could be coincidental and we need to collect more data that reflects FNP positive without mucormycosis among COVID 19 positive patients.

Computed tomography or magnetic resonance imaging are useful modalities to assess the extent of the disease. Bone erosion is not a typical finding seen in ROCM, as the fungus is highly angioinvasive which leads to extensive necrosis of tissues, and thus CT scan may fail in detecting early disease. In our series, contrast enhanced MRI of the paranasal sinuses, orbit and brain was the preferred imaging modality of choice. It detects early involvement of soft tissues especially in cases with extensive orbital and intracranial spread. On MRI, Facial nerve involvement may be diagnosed by widening of pterygopalatine fossa., Perineural invasion has been documented using contrast enhanced MRI [19].

In our study paranasal sinuses were involved in all patients, with ethmoid (right—48.6% and left—39.6) and maxillary (right—68% and left—58%) being the most frequent, while Ferry and Yohai reported sinuses involvement in 69% and 79% respectively. Cavernous sinus thrombosis usually results from spread of infection from the orbit and appears as a filling defect within the enhancing sinus or as a lateral convexity, and was evident in 5.3% on right side and 4% on the left side.

Diagnostic nasal endoscopy allows for quick inspection to look for a black eschar and thus allowing to take biopsy for microbiological and HPE. Diagnosis is confirmed histologically by detection of aseptate hyphae with right angled branching which is pathognomonic of mucormycosis. The impact of facial nerve palsy on the overall prognosis of patients with mucormycosis is yet to be determined and cannot be derived from our case series.

The management of mucormycosis essentially involves control of hyperglycemia or any other risk factor, optimal surgical debridement, and medical management with antifungal agents. Previous published literature showed that survival was 70% when treated with both amphotericin and

surgical debridement, 61% with amphotericin deoxycholate, 57% with surgery alone and only 3% in patients who underwent no treatment [20].

Amphotericin B is the antifungal drug of choice for mucormycosis. It has been used in 88% of the patients of CAM. Even in our series, almost all patients had received liposomal amphotericin B. The liposomal form is preferred since it is less nephrotoxic and, therefore, higher doses may be given for a prolonged duration. In patients with compromised renal functions, posaconazole and isavuconazole have been found to be effective alternatives. Endoscopic surgical debridement of paranasal sinuses was performed as a primary management in all of the cases in our series. Simultaneous PNS debridement with orbital exenteration or intraorbital amphotericin injection or maxillectomy was performed in cases based on the extent of disease. Orbital exenteration is conventionally done in cases with no visual potential, with diffuse orbital involvement, but with the disease limited to the orbit without or minimal extension to the cavernous sinus. CAM is a rapidly progressive disease, with a high 30—90% mortality rate in cases with intracranial involvement. For cases associated with Covid-19, the overall mortality has been estimated to be 31%.

Conclusion

CAM predominantly affects middle aged males and DM is the most common epidemiological factor for CAM. Good glycemic control is of paramount importance in a patients with Covid-19 in preventing rapid progression of the disease. The red flag signs and symptoms of severe headache, facial pain, eye pain, jaw pain and visual disturbances should be recognized promptly, followed by a confirmatory diagnosis by diagnostic nasal endoscopy and HPE. Contrast-enhanced MRI is the imaging modality of choice. Liposomal amphotericin B is the drug of choice for treatment of CAM. PNS debridement should be radical and may be combined with orbital exenteration/maxillectomy based on the extent of disease. To highlight involvement of facial nerve paresis as a presenting feature in rhino cerebral mucormycosis. A meticulous history, detailed workup, confirmation of diagnosis by histopathology and culture helps to make diagnosis. Aggressive management of these patients can reverse the adverse outcome. Prognosis of CAM is directly dependant on multiple factors and early initiation of treatment is an important element.

Acknowledgements The authors would like to gratefully acknowledge the medical postgraduates and consultants who contributed in collection of data for this article. We are also grateful to all the patients who volunteered to participate in this study. The authors would like to gratefully acknowledge and thank the medical superintendent and faculty for accepting for publication.

Funding The author(s) received no financial support for the research, authorship, and/or publication of this article.

Declarations

Conflict of interest The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Informed Consent Informed Consent was obtained from all the patients included in the study.

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