International Journal of Otorhinolaryngology and Head and Neck Surgery
Mittal M et al. Int J Otorhinolaryngol Head Neck Surg. 2021 Nov;7(11):1738-1743
http://www.ijorl.com
pISSN 2454-5929 | eISSN 2454-5937

DOI: https://dx.doi.org/10.18203/issn.2454-5929.ijohns20214223

Original Research Article

Mucormycosis during the second wave of COVID-19 in India

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Received: 03 July 2021
Revised: 20 August 2021
Accepted: 24 August 2021

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ABSTRACT

Background: The so called "black fungus epidemic" struck India during the second wave of COVID-19 pandemic. Large numbers of patients were being reported, posing a challenging situation for clinicians. The treatment options were limited, and rescue surgery was mutilating, anti-fungal medicines became short of supply soon, prognosis remained poor. Objective was to understand a unifying pathophysiological picture with a framework to check this post Covid epidemic, especially in context with South-east-Asia.
Methods: The clinical, radiological, surgical data of patients presented with symptoms of rhino-orbito-cerebral complications, collected and analyzed.
Results: 80.9% of operated patient had thrombosis of identifiable major vessels. The 76.7% patient had cerebral venous thrombosis. The 30% patient had internal carotid artery narrowing on imaging. Fungal staining was positive in 72% patient. We found level of D dimer was high in 81.3% patients and 83.9% patients had blood sugar level raised at the time of presentation.
Conclusions: Hyper thrombotic state of COVID-19 in diabetes and injudicious use of steroids predisposed susceptible patients to thromboembolic phenomena, leading to necrosis of tissue and secondary fungal infection.

Keywords: COVID-19, Hypercoagulability, Mucormycosis, Orbital cellulitis, Cavernous sinus thrombosis

INTRODUCTION

The second wave of the COVID-19 pandemic in March to May 2021 in India saw a sudden rise in cases of rhino-orbito-cerebral mucormycosis with orbital complications, palatal ulcers, dental or gingival pain, sinusitis and cerebral complications (Table 1). Presenting symptoms included lid swelling, congested eyes, decreased/lost vision, pressure in eye, restricted eye movements, proptosis, diplopia, dental pain, gingival swelling, zygomatic numbness and trismus, characteristic dry black crust in nose, palatal necrosis and black eschar (Figure 1). The government of India declared it an epidemic and a notifiable disease. It was labeled as "Black fungus" because of characteristic dry black crust in nose, palatal necrosis and black eschar.

Global prevalence of mucormycosis varies from 0.002 to 0.95 per million population, while its prevalence is nearly 70 times higher (14 per 100,000) in India compared to developed countries, in a recent estimate of year 2019-2020.[1]

Table 1: Distribution according to complaints.

Rhinological	Orbital	Maxillary	Head-ache	Other
3	57	60	81	5

We share our observational findings and attempt to understand a unifying pathophysiological picture with a framework to check this post COVID epidemic, especially in context with South-east-Asia.

Figure 1 (A-F): Engorgement of right facial vessels, pupillary dilatation and ophthalmoplegia, palatal lesions on right half of the palate, hard palatal necrosis with sharp well-defined margins, upper gingival necrosis with sharp margins and palatal submucosal blanched lesion.

METHODS

This work has been done after appropriate institutional review board, ethical committee approval (P-2010-M16) and informed consent from patients.

The observational study design included data starting from month of March, 2021 and concluded in May, 2021at Ankush Medicare and health sciences, Bhopal (M. P.). A Non-probability purposive sampling was done and all patients who were treated for COVID-19, and presented with either of rhino-orbito-cerebral symptoms like deep-seated headache, proptosis, diminished vision, ophthalmoplegia, loss of sensation over cheek, trismus, and palatal ulcers, were included in study. All those patients who were treated for COVID-19 but didn't have the mentioned symptoms or left the treatment in between were excluded from study. The sample size was 81 for this study.

The patient's symptomatology, co-morbidities, hematological, imaging findings, management details which include surgical findings also, and follow-up information were obtained, recorded and all the data thus collected, analyzed.

RESULTS

We are presenting here the observational data of 81 patients, studied during the period of March to May 2021. Out of these 81 patients, 5 died during treatment. The cause of death was septicemia, sudden cardiac arrest, or cerebral hemorrhage.

The majority of patients presenting with rhino-orbito-cerebral complaints were male constituting 72.8% (59), rest 27.1% (22) were female. One patient had diabetes mellitus type I and this was the only patient which was below 30 years of the age in this study.

Diminished vision was noticed in 29 (35.8%), ptosis in 20 (24.6%) restricted eye movements in 49 (60.4%) patients, and deep-seated headache in all the patients as the earliest complaint (Figure 2). Out of 49 patients, lateral rectus palsy was observed in 79.5%. Zygomatic area numbness was present in 60 patients, due to involvement of branches trigeminal nerve. The 13 patients presented with trismus, another 13 with palatal lesions, 4 had isolated facial nerve palsy and 1 had isolated trigeminal nerve palsy. All of those 76 patients who survived 24 had permanent loss of vision from one or both the eyes and 42 developed ophthalmoplegia of one eye (Table 1).

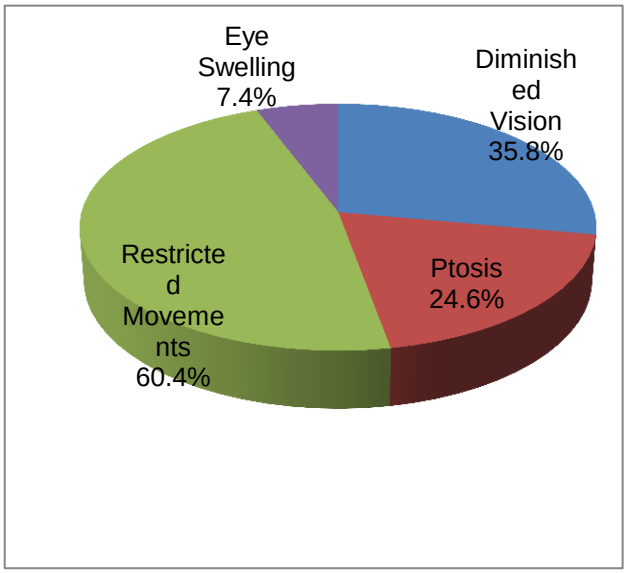

Figure 2: Distribution according to orbital complaints.

During treatment for COVID-19, only 16 (19.7%) patients were on oxygen support. The 33 patients were at home without oxygen support while taking treatment. Patients with high blood sugar levels at the time of presentation were 68 (83.9%). Out of these 68 patients, 38 (55.8%) patients had diabetes as a comorbidity before COVID-19 infection. D-dimer levels were raised in 81.3% (65) patients at the time of presentation. In 6 patients D-dimer records were not available.

History of recent intake of broad-spectrum antibiotics for COVID-19, was present in 77 (97.4%) patients. Two patients were unaware of their recent medications. Brief (less than 5 days) or prolonged (more than 3 weeks) use of steroids was present in 65 (80.2%) patients (Figure 3).

MR imaging and venograms could be performed in 73 patients. We found cavernous sinus thrombosis (CST) in 37(50.6%) patients. Of these CST patients 89% had high D-dimer levels. Head and neck venogram studies in 56 (76.7%) patients showed thrombotic patches in multiple cerebral venous sinuses, facial, maxillary artery and internal carotid artery (ICA). We observed carotid arteries narrowing and intraluminal clot in 22 (30%) of our patients, in the region of cavernous sinuses (Figure 4). Hemiplegia developed in four of these patients.

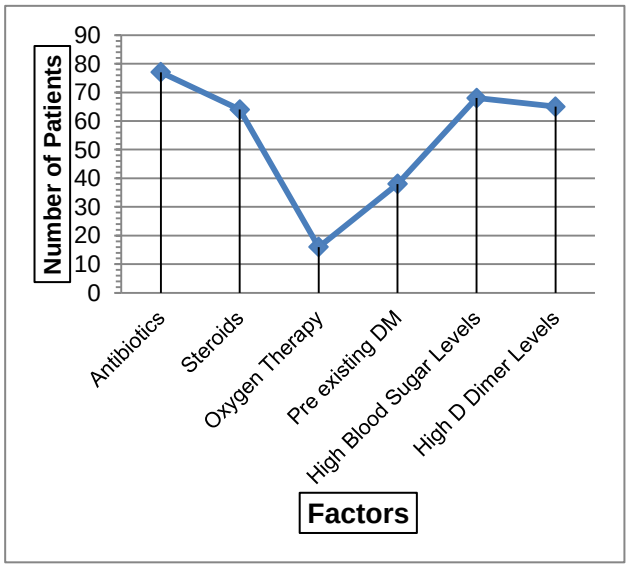

Figure 3: Predisposing factors.

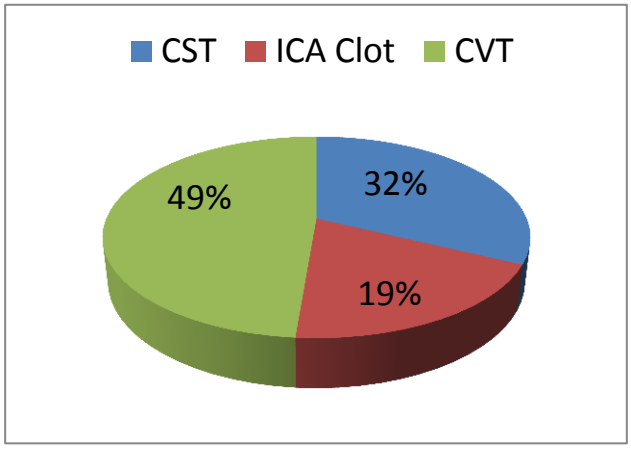

Figure 4: MRI venogram findings.
CST: Cavernus sinus thrombosis, ICA: Internal carotid artery, CVT: Cerebral venous thrombosis

We also observed gangrene in nose as discolored or black tissue (black eschar) with well-defined margins over turbinate, septum, palate, skull base and hard palate in 74 (91.3%) patients. Out of all these patients, 42 underwent endoscopic debridement. Thrombosed sphenopalatine vessel was found in 7, greater palatine artery in 5 and maxillary artery thrombosis in 22 patients was observed.

All the specimen debrided were sent for KOH staining, 72% came out positive for fungal hyphae. Only 4 specimens could culture mucor. On histology none of the specimen had tissue or angioinvasion.

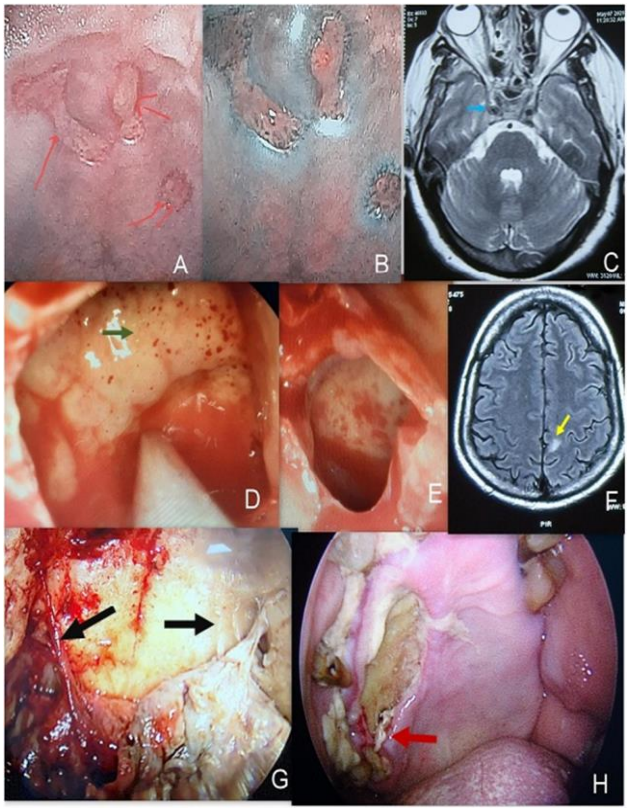

Figure 5 (A-F): White light: Few well defined palatal patches, NBI images- same lesions with cyan coloured borders suggestive of submucosal hemorrhage. Central part of lesion with normal looking brownish mucosa with cyan coloured hemorrhagic spots in between indicative of underlying hemorrhage or interrupted submucosal blood supply, right internal carotid artery and cavernous sinus thrombosis, sphenoid sinus and maxillary sinus submucosal hemorrhage, right parietal infarction, bilateral thrombosed greater palatine artery and necrosis of area supplied by thrombosed greater palatine artery.

DISCUSSION

COVID-19, a multi-systemic infection, is known to cause endothelial dysfunction, leading to the loss of fibrinolytic function, predisposing to thrombus formation. Activation of innate and adaptative immune cells and insufficient clearance of chemokine induce progressive thrombo-inflammatory response and hypercoagulability.[2]

During endoscopic debridement, our observation of the thrombosed sphenopalatine vessel, greater palatine artery, and maxillary artery was similar to the observations made by Omar et al (Figure 5 G and H). This corresponds to the well-demarcated area of necrosis of palate, nasal turbinate, or septal mucosa which later becomes

susceptible to infection and tissue death.[2] One of the main pathophysiological mechanisms of COVID-19 is the occurrence of a generalized pro-thrombotic state with resultant microvascular and macrovascular thromboembolism. Abou-Ismail et al proposed multiple mechanisms for inflammatory thrombosis that included localized intravascular coagulopathy, inflammatory cytokines, endothelial activation and dysfunction, mononuclear phagocytes, neutrophil extracellular traps, complement-mediated microangiopathy, and dysregulated renin-angiotensin system. Underlying diabetes causes over activation of the coagulation cascade in susceptible patients.[3]

Head and neck venogram studies in the majority of patients showed cascade of thrombosis which explain thrombotic patches in multiple cerebral venous sinuses, facial, maxillary, and internal carotid artery, seen in our study. Several cases of cerebral venous sinus thrombosis in patients of COVID-19 infection have also been reported by Thompson et al.[4] Four of our patients also presented with hemiparesis. This may be due to the extension of microthrombi to other venous sinuses, or may be a consequence of internal carotid artery occlusion. This has also been observed in cavernous sinus thrombosis (CST).[5] Various presentations of CST are possible due to the variable pattern of venous tributaries and drainage of cavernous sinus. Inflammation of the intra-cavernous segment of carotid artery and presence of intraluminal clot increases the risk of thromboembolism to many sites through various interconnections of internal carotid artery and external carotid artery, which are often not visualized in diagnostic arteriograms as of small caliber.[6,7] In few of our cases, carotid arteries narrowing in the region of cavernous sinuses and intraluminal clot was also observed (Figure 5 C). In very late and long-standing cases of COVID-19, complicated fungal sinusitis may develop, which may cause thrombosis of internal carotid artery and cavernous sinus.[8,9]

In our patients we observed diminished vision and restricted eye movements as the earliest complaint while swelling around the eye with proptosis developing later (Figure 1B). This is a feature of CST where parasympathetic and VI cranial nerve palsy has been seen initially, also engorgement of retinal and orbital vessels may contribute to loss of vision due to increased pressure at orbital apex, arteritis of internal carotid, retinal artery embolus, toxic neuropathy and ischemia of vasa nervosum of optic nerve.[5,10] In long-standing cases of COVID-19 associated complicated fungal sinusitis, when thrombosis of ICA and CST develops, it progressively involve cranial nerves as the infection spreads further and visual loss may develop from central retinal occlusion or direct orbital extension.[11] It is prudent to differentiate it from pre-septal cellulitis which does not cause proptosis and ophthalmoplegia in early cases.[5]

In many cases peculiar petechiae like blanched acro-ischemic lesions (AIL) were noticed over palate, sphenoid and maxillary sinus mucosa.[12] White light and narrow band imaging (NBI) of these lesions suggest submucosal haemorrhage of cyan color during very initial phase of the disease (Figure 5 A and B). Samples collected from these sites were negative for fungal growth. These lesions turn blackish later and get infected with mucor. Abou-Ismail et al have listed the multiple patterns of thrombotic outcome in COVID-19 patients at unusual sites in the human body e.g., mesenteric ischemia, purpuric rash on body, renal infarct, stroke, myocardial infarction, arterial and venous thromboembolism.[3] Many of our study patients with vision loss were having a normal extra-conal component of orbit without involvement by mucor. They were having superior ophthalmic vein thrombophlebitis and central retinal vein obstruction. The biopsy from orbital fat was also negative for fungus. Turbin et al reported two cases of COVID-19-associated complicated sinusitis with orbital cellulitis. One case developed along a sub-periosteal collection, while the other demonstrated superior ophthalmic vein thrombophlebitis. In both patients, bacterial, fungal smears and cultures remained repeatedly negative.[13] Invasion of blood vessels by mucor hyphae, damages the endothelium causing blood clots that occlude the blood vessels leading to ischemia and necrosis of surrounding tissue. Invasion of rhinocerebral mucormycosis to brain and orbit is through the involvement of sphenopalatine and internal maxillary arteries.[8]

Some patients presented with trismus, retro maxillary and mandibular pain. This may provide some clue about infection or inflammation of the pterygoid muscles in infratemporal fossa and pterygopalatine fossa, which may cause swelling in this region.[14] Contrast MRI of these patients, also confirmed inflammation in this region and thrombosis of maxillary artery in 3 of them. During surgery of 10 of these patients, thrombosis of the maxillary artery or one of its branches was confirmed in 5. Because of progressive CST, one patient developed engorgement of middle third of the face along with proptosis on right side and trismus due to venous stasis of facial vessels which are interconnected to the cavernous sinus through the pterygoid plexus and ophthalmic veins.[15] (Figure 1).

In our study use of steroids and broad-spectrum antibiotics were the commonest predisposing factors. The 83.9% of patients had high blood sugar levels at the time of presentation. It is known that the overall prevalence of prediabetes in all fifteen states of India is 10.3% which is quite high and alarming.[16] The presenting symptoms and complications were more severe in those with pre-existing diabetes mellitus or pre-diabetic patients. This happens because COVID-19 predisposes to over activation of coagulation cascade of already underlying pro-thrombotic hypercoagulable state in diabetic patients and this may further lead to fatal thrombo-embolic complications.[17]

We also noticed high "D-dimer" levels in 81·3% of the patients in this study. Of all those patients who had CST, D-dimer levels were high in 89%. Tang et al reported hypercoagulability of COVID-19, manifesting as an increase in D-dimer, fibrinogen and mild thrombocytopenia as well. He noticed overt DIC (Disseminated intravascular coagulation) in 71.4% of non-survivors and 0.6% in survivors of COVID-19 infection.[18]

More than half of the patients in this study were in home isolation without oxygen support. Thus, no obvious clinical correlation was found between the mucormycosis and mode of oxygen delivery as usage of non-sterile oxygen prong or industrial oxygen use had been suggested as a predisposing factor.

COVID-19 infection and diabetes cause arterial thrombose and subsequent gangrene. This dry gangrene was noticed as discolored, black tissue or eschar in nose with well-defined margins over turbinate, septum and skull base. This was also present on hard palate. Diabetic patients are more susceptible to infections because of poor wound healing. This triggers a cycle of micro thrombosis. Due to the ischemic environment, localized cellular dysregulation limits the ability to have adequate wound healing, set the tissue up for continued damage and infection.[19] Hyperglycemic condition, acidic medium and iron overload favors fungal growth and fungus flourishes more in hot and humid climate.[8] The black necrotic intranasal or palatal eschar is highly suggestive of fungal disease but it occurs in only 40% of those affected.[11] Treatment of ischemic gangrene is focused on restoring blood flow to help reduce pain and heal ischemic wounds.[19]

Limitations

Repeated hematological assessments and Imaging studies were required, which was not possible as medical infrastructure was overwhelmed with the rising number of patients and to avoid the cost further on already struggling medical system during pandemic. Investigations were also distributed to multiple centers, to avoid the possibility of single lab running out of resources. This may lead to confounding bias. A multi-centre study may help to confirm present findings and reduce bias.

CONCLUSION

Our findings match with the various studies done during the past one year on pathophysiology of covid-19 like thrombosis of small, medium and large sized vessels. Thrombosis of internal maxillary artery and its branches causes gangrene of tissue, often there was an absence of fungal hyphae, raised D -dimer and high blood sugar levels. Also, there was involvement of various venous sinuses and internal carotid artery in cerebrum.

Recommendations

Preliminary observations in our study explain the cascade of events beginning with hyper-coagulopathy triggered by COVID-19 infection progressing to multiple thrombotic events with possible migration of it into various cerebral sinuses, orbit and maxillary artery. Obstruction of multiple small and medium size vessels in rhino orbital and cerebral region causes dry gangrene superimposed with ubiquitous sinonasal zygomycetes in nose. Based on our findings, we propose the following: Irrational and improper use of steroids should be stopped, use of antiplatelets and antithrombotic agents early in the course of illness to prevent from such complications of COVID-19, Screening of pre-diabetic and diabetic patients. Good glycemic control by switching the patient on insulin therapy, Nasal saline irrigation and judicial use of prophylactic antifungal medication in the form of nebulization (Amphotericin-B) and oral medication (Posaconazole), A high index of suspicion for cavernous sinus thrombosis while investigating every case of suspected mucormycosis and specific criteria to label a case as mucormycosis should be considered: a). Demonstration of fungal element in diseased tissue on histopathology as fungus invading mucosa, blood vessels, soft tissue, or bone, b). Other evidence like radiological findings or venograms can be considered for inclusion only if they were validated and standardized.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Mittal M, Shrivastava R. Mucormycosis during the second wave of COVID-19 in India. Int J Otorhinolaryngol Head Neck Surg 2021;7:1738-43.