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Case Report

Triple whammy in pandemic: COVID-19, mucormycosis and myiasis

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ABSTRACT

Background: Mucormycosis is a fatal opportunistic fungal infection most commonly seen in immunocompromised individuals. The mortality can vary depending on the extent of the disease, starting in the paranasal sinuses, reaching the orbit, and eventually spreading intracranially. The sudden surge of Mucormycosis along with COVID-19 infections has rightfully been described as an epidemic amidst a pandemic. While the exact etiological factor is still being investigated, uncontrolled diabetes seems to be the most common inciting factor. Mucormycosis being angioinvasive, often leads to thrombus formation in the vessels, which leads to the necrosis of the tissues and bones, most commonly the maxilla. This necrotic tissue forms an ideal culture for various organisms and is a potential source for maggots' infestation. The presence of nasal myiasis further worsens the clinical status of the patients, making them prone to life-threatening complications. Thus, nasal myiasis seems to be an independent prognosticating factor in such cases. Here, we have described two such cases, our approach to management and mortality despite the best possible management.

Case Presentation: Two cases are being presented of elderly patients with comorbidities of type 2 diabetes mellitus and coronary artery disease. Both patients had a recent onset of COVID-19 and presented with intraorbital and intracranial disease extension along with nasal myiasis. Both patients succumbed to the fulminant pathology despite aggressive management.

Conclusion: Mucormycosis, COVID-19 and nasal myiasis combine together to form a fatal triad, which despite early identification and aggressive management, carries a poor prognosis.

1. Background

In December 2019, A cluster of viral pneumonia cases was reported in Wuhan, China which was labelled as Coronavirus 2019 (COVID-19). A month later, 1^{st} case of COVID-19 was reported outside China in Thailand. The first case in India was reported in Kerala on 30^{th} January 2020. This was then declared by World Health Organization (WHO) as a Public Health Emergency of International Concern (PHEIC) on 30^{th} January 2020 and subsequently declared as a Pandemic on 11^{th} March, 2020.[1]

The number of cases quickly peaked worldwide, bringing everything to a standstill. As of 14^{th} December 2021, 27,00,31,622 confirmed cases had been reported, of which 3,47,03,644 are from India.[2] COVID-19 and type 2 diabetes mellitus (T2DM) share a very close relationship. The cytokine storm in COVID-19 results in insulin resistance and worsens glycemic control. Hyperglycemia further promotes viral replication resulting in a vicious cycle that results in significant morbidity and mortality. Furthermore,

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the widespread and poorly monitored use of corticosteroids has resulted in neglected glycemic control for a significant proportion of the infected population.[3]

A sudden surge of a rare but fatal opportunistic fungal infection, Mucormycosis, was seen in India during the 2^{nd} wave of COVID-19. An astonishing 41,512 cases of mucormycosis were reported between 5^{th} May and 12^{th} July, out of which 3,554 patients expired. The Government of India declared this rare but fatal disease endemic on 10^{th} May 2021. Mucormycosis is an aerobic saprophytic infection caused by a fungus of Class Zygomycetes and order Mucorales, found in decaying vegetations and soils and as a commensal in the mucosa of the nasal and oral cavity. It was first described by "Paltauf" in 1885 as "mycosis mucorina". It most commonly begins as sinonasal and can rapidly progress to orbital and intracranial, resulting in a fatal outcome.[4]

Rhino-Orbito-Cerebral Mucormycosis (ROCM) can be diagnostically categorized into Possible, Probable, or Proven. Possible ROCM is when the patient presents with typical signs and symptoms along with a recent history of COVID-19, diabetes mellitus, systemic corticosteroids, immunosuppressants, supplemental oxygen, or mechanical ventilation. When these presentations are supported by typical diagnostic nasal endoscopy or radiological findings, they can be categorized into a Probable ROCM. When these findings are supplemented with microbiological or histopathological or culture, or molecular diagnostic evidence, it can be termed Proven ROCM.[5]

The sudden surge of COVID-19 cases overwhelmed the existing health infrastructure, leading to the inability to maintain hygiene. Poor hygiene and the widespread use of humidified oxygen may be deemed responsible for the rise in mucormycosis cases. The angioinvasive nature of Mucormycosis causes a significant risk of thromboembolism, leading to necrosis and bony erosion.

Tissue necrosis in mucormycosis can be an ideal culture media for the larvae leading to myiasis. The bony erosion can further provide a pathway for the spread of larvae. Myiasis, caused by Diptera larvae, is a rare disease. Laurence first described it in 1909. Poor hygiene, infected wounds, and halitosis are some predisposing factors that can lead to myiasis. Flies deposit the eggs. These eggs grow into larvae, penetrating the tissue by a chitinous apparatus in the anterior end of it. Proteolytic enzymes help the further movement of the larva and feed on damaged tissue. The larvae eventually grow into a pupa, transforming into an adult in 1 to 3 weeks. A poor hygienic environment attracts flies which mead maggots infestation.[6,7]

Diabetes mellitus is a prothrombotic state attributed to low-grade inflammation, oxidative stress, endothelial dysfunction, and platelet hyperreactivity.[8] This thrombosis further leads to necrosis which complements the angioinvasive nature of Mucormycosis. The presence of nasal myiasis also indicates the neglect of symptoms and a delayed intervention which can further lead to devastating systemic, orbital, and intracranial complications of mucormycosis. These include Central Retinal Artery Occlusion, Cavernous sinus thrombosis, and intracranial infarcts.[9] Here, we aim to- describe the fulminant nature of 2 such cases, which presented to us with the coexistence of Mucormycosis, Nasal Myiasis, Uncontrolled diabetes, and a history of COVID-19.

2. Case Presentation

2.1. Case 1

A 46-year-old female presented with complaints of drooping of the right eyelid for 20 days and vision loss in the right eye for the past seven days. On examination, there was complete ophthalmoplegia, ptosis, and an absent perception of light in the right eye. Crusting with foul-smelling debris was visualized in nasal cavities. She was on irregular medications for type 2 diabetes mellitus for one year with HbA1c 9.3%; diagnosed as SARS-CoV-2 positive three months back, which was managed at home in isolation without the requirement of steroid or oxygen therapy. She was seropositive for Hepatitis C. Contrast-Enhanced Magnetic Resonance Imaging (CEMRI) showed mucosal thickening in all sinuses bilaterally, appearing hyperintense on T2 weighted and hypointense on T1 weighted images; with non-enhancing right middle and inferior turbinates showing the typical "black turbinate sign" suggestive of mucormycosis (Figure 1).

On MRI, extraconal involvement of the right orbit and minimal dural enhancement were seen along the medial aspect of the right anterior temporal lobe. The patient underwent a right total maxillectomy with right orbital exenteration, left medial maxillectomy, and bilateral pan-sinus clearance. Intraoperatively live wriggling maggots were seen in bilateral maxillary sinuses, which were removed. Postoperatively, the patient was kept on Conventional Amphotericin B (at 1 mg/kg/day) and Injectable Ceftriaxone 1 g 12^{th} hourly. Blood sugar and renal functions were monitored daily, and appropriate medical corrections were given. Diagnostic nasal endoscopy was done on post-operative day 3, which showed a healthy cavity with no maggots. On post-operative day 7, the patient developed respiratory distress and persistent tachypnea and was intubated. Chest radiograph showed patchy ground-glass attenuation in bilateral upper lobes, the lateral segment of the middle lobe, and the anteromedial segment of the left lower lobe. Her C-reactive protein was 111.1 mg/L, and her serum Procalcitonin was 24.97 ng/ml.

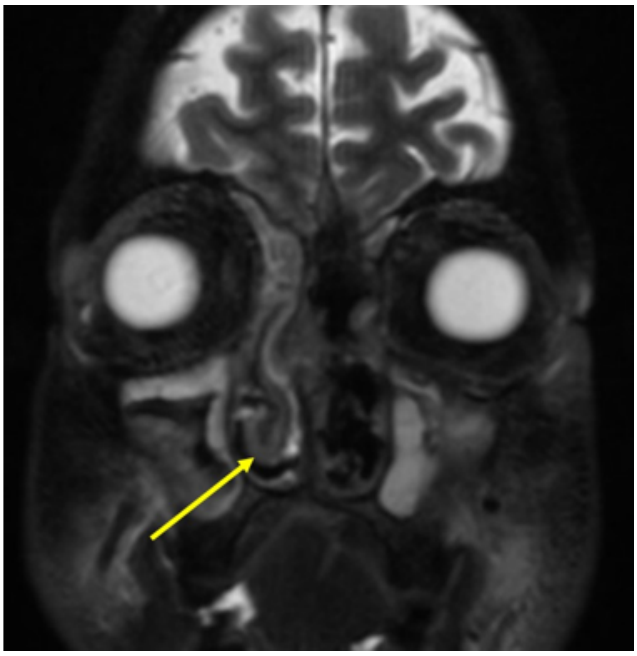

Fig. 1: The black turbinate sign

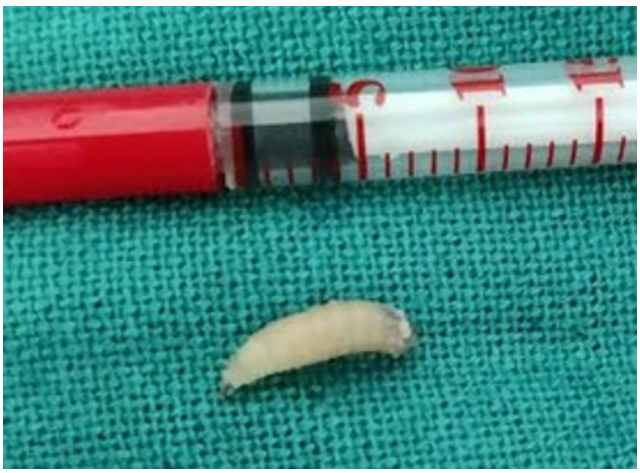

Fig. 2: Third instar larva of chrysomya bezziana

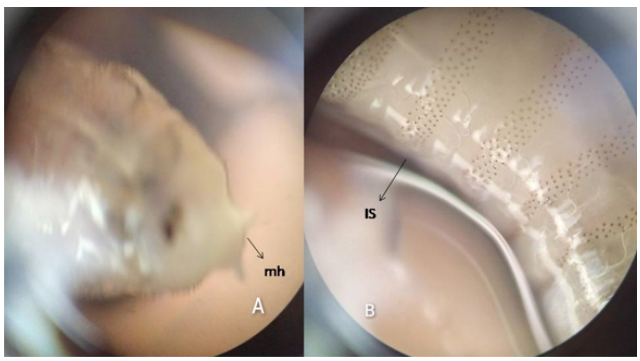

Fig. 3: Morphology of the third-instar larva of Chrysomya bezziana is seen with strong mouth hooks (mh) and intersegmental spines (IS)

She developed refractory septic shock and respiratory acidosis. Her inotropic requirement kept increasing, and she developed asystole and expired on the 15^{th} post-operative day.

2.2. Case 2

A 60-year-old male patient presented with pain over the right side of the face and swelling of the right eye for two months. He was a known case of Coronary Artery Disease (CAD) and was on anticoagulants and statins (Tab. Atorvastatin 10 mg and Tab. Aspirin 75 mg once daily) for the past two months. His HbA1C was 13% at the presentation. He was diagnosed as SARS-CoV-2 positive six months back and was managed at home. There was no perception of light in the right eye, and the right side of the palate was eroded with an oroantral fistula. Live wriggling maggots were seen in the right nasal cavity, which was removed. CEMRI revealed T2 hyperintense contents with heterogeneous enhancement in all sinuses bilaterally, right pterygopalatine fossa, and infratemporal fossa. There was intracranial extension through the defect in the posterior wall of the frontal sinus into the right frontal lobe. Right extra conal and intraconal orbital involvement was seen with retrobulbar fat stranding. He received a total dose of 600 mg of Conventional Amphotericin B (1 mg/kg/day) until the 8^{th} day of admission when he suddenly developed Atrial Fibrillation and was revived with cardioversion. Following this, the patient developed refractory shock and was on inotropic support. Daily blood sugar and renal profiles were monitored with corrections. The patient developed asystole on the 12^{th} day of admission and could not be revived despite best efforts.

Both patients had live maggots seen with wriggling movements. After applying turpentine oil drops in sinonasal cavities, they were removed manually under endoscopic vision. For myiasis, a single dose of 12 mg oral Ivermectin was given in both patients. On microbiological examination, the larvae were creamy white, with cuticular spines, and varied in size due to different stages of presentation, from 5 to 15 mm. They had strong, robust mouth hooks, four to six papillae on the anterior spiracles, incomplete posterior spiracular peritreme, and segmented rings. Based on these findings, they were confirmed to be the third instar larvae of Chrysomya bezziana (Figures 2 and 3). Direct KOH wet mount revealed obtuse-angled aseptate fungal hyphae suggestive of mucormycosis. Fungal culture was done on Sabouraud's Dextrose Agar (SDA) and was inoculated and incubated at 37°C and 25°C, respectively. It showed a mixture of cotton growth. The culture's Lactophenol Cotton Blue (LPCB) mount showed the presence of Mucor spp.

3. Discussion

The exact a etiology of mucormycosis has been a topic of debate. The most commonly associated risk factors seen are diabetes mellitus (36%), hematological malignancies (17%), organ transplantation (7%), desferrioxamine therapy (6%), and bone marrow transplantation (5%), renal failure (5%), etc. Numerous cases have been reported in immunocompetent patients without any of the above-mentioned risk factors. Although such patients are known to have better survival than that immunocompromised ones.[10] Overburdened health infrastructure leading to radical use of systemic steroids, inhalational oxygen, and poor hygiene in the COVID-19 pandemic could have probably led to the surge of mucormycosis cases. This leads to microangiopathy, which is responsible for diabetic neuropathy, nephropathy, and retinopathy. This poses a higher risk of coronary artery disease, one of the leading causes of mortality.[8]

Both our patients were poorly controlled diabetics with HbA1c of 9.3% and 13% and had a history of COVID-19 in the recent past (3 months and 6 months back). Additional morbidity of Hepatitis C and CAD was present in the 1^{st} and 2^{nd} patients, respectively. Numerous studies have established a strong link of diabetes mellitus (78%[11], 79%[12], 96.7%[13]) as an aetiology for COVID-19-associated Rhino-Orbito-Cerebral Mucormycosis. Poorly controlled Diabetes Mellitus can lead to acidosis and hyperglycemia. Severe acidosis elevates the free iron levels, which promotes the growth of Mucorales. Hence, acidosis is considered an independent risk factor for mucormycosis.[14]

Hepatitis C is associated with a higher risk of thrombotic events such as stroke, myocardial infarction, and venous thromboembolism. This can be attributed to several factors, which include chronic inflammation, decreased anticoagulants (protein C, protein S, antithrombin III), and the presence of antiphospholipid and anticardiolipin antibodies in these patients.[15]

COVID-19 is primarily known to affect the respiratory system, leading to significant morbidity and mortality. The release of pro-inflammatory cytokines, platelet activation, and endothelial injury predisposes the patients to prothrombotic events. A meta-analysis of 8271 patients through 42 studies showed a very high rate of venous thromboembolism at 21% with a 20% rate of Deep Vein Thrombosis and a 13% rate of Pulmonary Embolism. This increases the odds of mortality by 74%. The International Society of Thrombosis and Hemostasis (ISTH) and the American Society of Hematology recommend the prophylactic use of Low Molecular Weight Heparin (LMWH) for all hospitalized COVID-19 patients.[16]

The prothrombotic nature of mucormycosis frequently results in tissue necrosis, which can predispose to nasal myiasis. The acidotic pH caused by diabetic ketoacidosis and septic lactic acidosis also creates an ideal culture media for nasal myiasis, which through bony erosion, further provides a pathway for the spread of the disease. Myiasis has been classified in the literature based on host dependence, mode of infestation, and anatomical sites. Based on host dependence, it can be Obligatory – when maggots need living tissues for survival and Facultative – when flies incubate the larva in necrotic areas. Based on the mode of infestation, it can be Accidental – when the larva is accidentally ingested, Semi-specific – when the larva enters a necrotic wound or Obligatory – when the larva affects normal skin. Anatomically myiasis can be Cutaneous, External orifices – in oral, ocular, nasal, or anal orifices or of Internal organs.

The foul smell from the necrotic mucosa of the host attracts the flies. The laid eggs then hatch into the larvae in 24 hours. These larvae should be removed and preserved in 70-95% ethanol when they are sent for microbiological examination. The larvae are photophobic, and hence they move deeper into the wound when they are exposed to light. Turpentine oil acts by irritating the maggots, forcing them to crawl out. Liquid paraffin, Chloroform, and mineral oil act as asphyxiating agents, killing the maggots by cutting off their oxygen supply. A single dose of oral Ivermectin at 200 mcg/kg has also been effective. Oral Ivermectin stimulates the release of Gama Amino Butyric Acid (GABA) by the endoparasites, which activates Chloride channels. Increased chloride concentration in the cells leads to hyperpolarization, paralysis, and, eventually, the death of the parasites.[17,18] In both cases, a single dose of oral Ivermectin was given, and maggots were removed using turpentine oil. Mosquito nets were used to prevent flies, and good hygiene was ensured. Poor personal hygiene and lack of sanitization are common risk factors for mucormycosis and nasal myiasis. It is essential to note that a high index of suspicion should be kept for nasal myiasis in at-risk patients, as they have a profound negative impact on the overall prognosis and progression of the disease. In both of our cases, the larva was identified to be Chrysomya bezziana.[19]

The European Confederation of Medical Mycology (ECMM) recommends histopathological evidence of tissue invasion as the gold standard for diagnosis and CEMRI as the imaging of choice. KOH fungal staining of both of our patients showed the presence of broad aseptate hyphae with broad-angle branching. The presence of heavy metals in fungal elements appears as a hypointense on T2 weight MRI. The lack of enhancement with gadolinium and diffusion restriction occurs due to the infarcted mucosa.

Early complete surgical debridement followed by intravenous Liposomal Amphotericin B (5 to 10 mg/kg/day) is the first-line management recommended by ECMM.[20] This is generally continued for 3 to 4 weeks. Oral antifungals follow this, either with a tablet of Isavuconazole (200 mg thrice a day for the first two days, followed by 200 mg once a day) or a tablet of Posaconazole (300

mg twice a day for one day, followed by 300 mg once a day). Depending on disease regression, this step-down therapy must be given for 3 to 6 months. There is limited literature available on the role of combination antifungal therapy, and hence is not recommended.[21] A strict glycemic control, good personal hygiene and improvement of the underlying immunosuppression are needed. Both of our cases were given Conventional Amphotericin B due to the high cost and non-availability of Liposomal formulation. Surgical debridement was done in the first case. However, the 2^{nd} case could not be taken up for debridement because of preexisting cardiovascular morbidity and hemodynamic instability.

The preceding history of COVID-19 and uncontrolled diabetes in both our patients, advanced stage at presentation, coupled with comorbidities of Hepatitis C (in 1^{st} patient) and CAD (in 2^{nd} patient), along with the presence of nasal myiasis and sepsis in both, can be held responsible for the fulminant course of the disease. Hemodynamic instability is a major limiting factor that increases risks intraoperatively and might even delay the debridement. Multiple factors seem to work synergistically and converge on a common pathology of thromboembolism, which caused cardiovascular collapse leading to the demise of both of our cases. Even with a multidisciplinary approach of strict glycemic control, aggressive surgical debridement with adequate antifungals, and empirical antibiotics, the prognosis remains abysmal. Both of our patients belonged to a low socio-economic background. Poor personal hygiene and lack of awareness about the disease can significantly delay the diagnosis and worsen the prognosis.

4. Conclusion

There is heightened susceptibility of immune-compromised hosts with uncontrolled diabetes mellitus who suffer from a myriad of SARS-CoV-2 infections with opportunistic infections like sinonasal mucormycosis, followed by nasal myiasis; all of which may have inferior and fatal outcomes if not timely detected and managed. There exists a desperate need for increasing awareness amongst the general public as well as health care workers for the identification of such at-risk immunocompromised individuals.

5. Source of Funding

None.

6. Conflict of Interest

None.

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