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Covid 19- Therapeutics and Intrications Superintending to Mucormycosis- A Case Report and Review of Literature.

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Abstract

With ongoing global pandemic recently there has been an unexpected rise in sporadic cases of Mucormycosis in SARS CoV patients in India. This is most likely due to the use of high-dose steroids, which has created a transient hyperglycemic and immunocompromised state. We reported a case of middle aged non diabetic female who was diagnosed with Mucormycosis in her Covid state which could not only be due to high-dose steroid use but also other factors like significant lymphopenia, use of IL6 inhibitors, associated comorbidities (asthma), preexisting sinusitis, lack of personal hygiene and improper isolation. She had undergone FESS surgery under strict aseptic precautions. Appropriate use of steroids along with maintenance of tight glycemic control, boosting immunity and proper hygiene maintenance can aid in deterring one from contracting the fungus.

Keywords: Mucormycosis, COVID 19 Pneumonia, Paranasal sinusitis, Steroids.

INTRODUCTION

Mucormycosis is an uncommon but a fatal fungal infection that usually affects patients with altered immunity ⁽¹⁾. *Rhizopus Oryzae* is the most common type and accountable for nearly 60% of cases in humans and also reckons for 90% of the Rhino-orbitalcerebral Mucormycosis (ROCM) form, the mode of contamination being inhalation of the fungal spores ⁽²⁾. The recent surge of fungal infections in India, in COVID 19 patients has been due to their immunocompromised state, high blood sugar levels as well as related comorbidities. Diabetes Mellitus has been one of the common risks associated with Mucormycosis, along with the concomitant usage of steroids during the treatment period of SARS-CoV 19. But here we report a case of a non-diabetic female presenting with Mucormycosis. It is a clinical and histopathological diagnosis⁽³⁾.

CASE REPORT

A 44-year-old female patient, known case of asthma and hypothyroidism with no diabetes and hypertension started complaining of right eye pain, nausea and generalized weakness on 10th day of her admission for COVID pneumonia. Patient had no redness of eye, discharge, nasal blockage, headache, post nasal drip, fever and cough. She was admitted for COVID-19 in view of shortness of breath and decreasing saturations. She was diagnosed by real-time PCR (nasal and

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oropharyngeal swab), with HRCT CORADS Score-6 and severity score-10/25. She was initially treated with Supplementary Oxygen, HFNC, later shifted to CPAP in view of increased respiratory efforts on 5th day, gradually she maintained good saturation levels with intermittent CPAP and HFNC and weaned off on 8th day. She was started a course of IV Remdesivir for 5days along with IV Methylprednisolone for a period of 8 days. Tocilizumab was used in our patient in view of her elevated IL6 value. She was administered with antibiotics and anticoagulants to prevent secondary infections and blood clots.



Figure 1: HRCT of a 44-year-old female with patchy central and peripheral ground glass opacities with septal thickening noted in bilateral lungs in sub pleural location suggesting acute viral pneumonia.

On examination, patient was conscious, coherent, well oriented, afebrile. Pulse rate 82 bpm, Blood pressure 120/80 mmHg, Respiratory rate -22cpm, and oxygen saturation 94% on 4litres of oxygen. Systemic examination was unremarkable. Her otolaryngological and ophthalmological examinations were normal. She had no sinus tenderness. There were no neurological deficits.

Initial investigations on admission revealed random blood sugar- 136mg/dl, HbA1C-5.6% (<6%). Inflammatory markers like CRP-positive 68.04 (normal-<5.0 mg/l), IL-6- 40.38(normal-0-7.0pg/ml), D-dimer-942(normal-0-500ug/l), ferritin-296 (normal-23.9-336.2ng/ml), procalcitonin0.071(normal-0-0.5). Prothrombin time was elevated (18.7 control-13.0) with an INR of 1.40. Her renal function tests, liver function tests and serum electrolytes were within normal limits. The patient's TSH levels were raised, 9.89(0.5-5.0ml U/L), with T3 decreased and T4 increased. On her 6th day of admission her RBS: 356mg/dl, and Lymphopenia was noted with a total lymphocytic count of 820(normal-1000-5000 (0.8-5.0) lymphocytes/mcL). An MRI of Brain, Orbits and PNS (Plain and Contrast) was done, which revealed mucosal thickening in bilateral maxillary, ethmoidal and frontal sinuses which has enhanced when contrast was administered. Impression of sinusitis in the above areas was noted with no bony destructions or intracranial and infraorbital extensions.



Figure 2: Coronal T1-weighted MRI of 44 year old female with fungal infection of paranasal sinus -With contrast - A) Mucosal thickening of Maxillary, Frontal, Ethmoid sinuses on right side and mucosal edema on left side B) homogenous enhancement of thickened mucosa in maxillary sinuses.



Figure 3 and figure 4 : MRI Contrast showing Mucosal thickening of Maxillary Sinus and Ethmoid Sinus

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Given her elevated blood sugar levels, she was started on insulin therapy with continuous monitoring of her glucose levels. Functional Endoscopic Sinus Surgery was performed under general anesthesia revealing thick purulent discharge and white debris in the right middle meatus. Polypoidal mucosa was noticed in the anterior ethmoid, which was followed by an anterior ethmoidectomy. Middle meatus debris was sent for fungal stain, which was positive for Mucormycosis. Histopathological specimen was positive for fungal elements -showing broad aseptate hyphae with wideangle branching suggestive of Mucormycosis (Rhizopus species). She was further managed with INJ LIPOSOMAL AMPHOTERICIN B (0.5mg/kg/day), antibiotics, nasal douching and other supportive therapy. Patient improved clinically and followed up regularly. Vallivedu Chennakesavulu Pujitha et al International Journal of Medical Science and Current Research (IJMSCR)

DISCUSSION:

Mucormycosis is a grave opportunistic infection embracing elderly diabetic and immunocompromised population. As an asexual spore-forming mold it can taint the oral and nasal cavities through inhalation. In a healthy individual, there is phagocytic exclusion of mucormycosis spores. Some people are predisposed to germinate these spores into broad septate hyphae likely due to their suppressed immune system. The probability is high in those with diabetes, AIDS, Organ transplantation, usage of immunosuppressive drugs, kidney failure, and malignancies. It spreads rapidly causing necrosis of the tissues. The mold enters the host through droplets by respiratory tract and hematogenously spread to paranasal sinuses and they invade orbit and brain either directly or hematogenously from PNS⁽⁴⁾. Rhino orbital cerebral infection is the most common presentation. The unusual presentations of mucormycosis are involvement of skin, respiratory, gastrointestinal, and disseminated form.

We reported here a case of non-diabetic 44-year-old female, who started complaining of right eye pain on her tenth day of COVID 19 pneumonia. In our case the infection had no orbital or cerebral extensions and was restricted to the PNS, this could be due to timely and expeditious diagnosis with extensive treatment.

Astha et al study reported a case of 38-year-old male with no prior history of diabetes, with PPBS: 146mg/dl and HbA1c 6.3% (pre diabetic) on admission, whereas post treatment for Covid his FBS: 125mg/dl, PPBS: 352 mg/dl, HbA1c: 12.3%. He had complaints on his 18th day of admission, which led to his diagnosis of sino orbital Mucormycosis. This illustrates that a prediabetic patient with uncontrolled sugars solely due to high steroid use can attract the deadly fungus. He had an extensive involvement probably due his poor HbA1c and usage of both IV methylprednisolone 80mg/day for 18 days and also Inj Dexamethasone 4mg twice a day for 12 days. ⁽⁴⁾ In Marina et al study of a 32-year-old female with uncontrolled diabetes for 6 months, we can observe that her infection had confined involvement to the PNS leading to orbital apex syndrome ⁽⁵⁾.

Shweta et al study reported a ROCM in a middle-aged diabetic woman who presented with left eye pain and was diagnosed incidentally with Covid 19 Pneumonia ⁽⁶⁾. In their case, infection was unrestricted, due to her

uncontrolled sugars which were detected during the patient's hospital stay (glucose 378mg/dl; HBA1C of 12.39%) and also delayed diagnosis of COVID 19. This illustrates that Mucormycosis can present directly in uncontrolled diabetes mellitus without the usage of steroids for COVID 19 status. This parades that uncontrolled blood sugar levels are the main culprit for mucormycosis, which could either be due to heavy corticosteroid usage or diabetes mellitus.

In severe Covid-19, it has been discerned that lymphocyte progressively decreases. It is hypothesized that SARS-CoV infection may involve lymphocytes CD4+ and CD8+ T-cells, which plays a role in the pathological process of Covid-19 infection. In addition, increased sugar levels due to steroids, glycosylates proteins and leads to reduced activation of T lymphocytes, interferon gamma and cell mediated killing causing immune destruction.

Observed possible causes for lymphopenia in Covid 19 patients ⁽⁷⁾

- 1. The increased inflammatory cytokines have a possible correlation with the depleting lymphocytes as shown in Sohail Tavakolpour et al study.
- 2. Increased expression of Programmed cell death protein 1 (PD-1) and T cell immunoglobulin and mucin domain 3 (Tim-3) markers (T cell exhaustion markers) is associated with disease severity and mortality.
- 3. Usage of immunosuppressive agents also have a role in suppressing T cell activity.
- 4. ARDS is also one of the reasons for lymphopenia which can lead to opportunistic infections. This was similarly shown by Daniela Pasero et al study. ⁽⁸⁾ In our case patient had moderate ARDS (ie., PiO2 / FiO2 = 120.008), which significantly contributed to induce lymphopenia which further contributed to Mucormycosis.

It might be conjectured that lymphopenia could increase the risk of contracting invasive Mucormycosis, while the recovery of lymphocyte count could enhance the adaptive immune system and provoke the production of Mucorales-specific T-cells, which might have a part in improving the invasive infection.

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Anti-inflammatory therapies such as anti-IL-6 therapy have the capability to undermine viral clearance and pre-dispose to secondary infections. ⁽⁹⁾

Though numerous studies have shown that pre existing diabetes is the most potent risk factor for Mucormycosis ^(4,5,6), our study proves that high-dose steroid use without proper maintenance of sugar levels can solely make one susceptible to this infection. Along with her immune suppressive therapy, significant lymphopenia, use of IL6 inhibitors and her comorbidities like asthma, could have also played some role in triggering her infection. High blood sugar levels could be a nidus for the start of this deadly infection. Blood sugar levels are usually not monitored on regular basis in a non-diabetic patient. Therefore, irrespective of one's diabetic status use of high-dose steroids should inculcate the routine of measuring blood sugar levels on daily basis with maintenance of tight glycemic control by using insulin in hospitalized patients. The dire need for monitoring and extensive treatment is required to keep in check the high blood sugar levels in both diabetic and non-diabetic patients.

Due to high suspicion and growing awareness of budding fungal infections lately, our patient had extensive imaging done on the day of complaints and so her infection was noticed when the involvement was confined to sinuses with no intracranial and orbital extensions. Whereas the delayed time of presentation in Astha and Shwetha et al studies, led to extensive involvement. ^(4,6) This outcasts the importance of early diagnosis, extensive evaluation, and aggressive management in driving to a favorable prognosis.

Keeping her Covid positive status in mind and FESS surgery being an aerosol generating procedure with a high risk of transmission, our patient underwent surgery with debridement under complete aseptic precautions, along with subsequent histopathological confirmation.

There are other serious risk factors like that of a case presented by Akshay et al study, where a heart transplant patient succumbed to death due to SARS CoV infection and invasive Mucormycosis ⁽¹⁰⁾. Other risk factors like HIV, AIDS, DKA, Leukemias should also be acknowledged and assessed.

In a setting where steroids have become lifesaving drugs and there is an obvious certainty that one can misuse them, we should particularly concentrate on strict maintenance of blood sugar levels in both diabetic or non-diabetic patients. Steroids are a double-edged sword and so they need to be used judiciously only in patients with moderate and severe SARS CoV infection.

In addition to maintaining tight glycemic control, we should also focus on the stringent usage of cocktail of drugs like tocilizumab and steroids. Covid being a novel pandemic, had no much research and evidence. With time and new challenges, regimens used to treat SARS CoV infection were modified and followed. In such pandemics where no sufficient statistical evidence and research is available, we need to consider every person affected with the virus in a high-risk zone and attempt in giving equal attention without neglecting any person based on age, past history, complications and severity.

We are proffering this case so that suspicion of the disease remains equal in everyone when a disease like Covid with no proper fixed symptoms or any guidelines strikes the world. Everyone globally has fronted the deadly virus for the first time so it is essential for us to combat it with the most beneficial treatment possible. We seek to inflate physician perception of these concerns and highlight the necessity to adequately understand the ongoing pandemic.

Table 1:

We have systematically reviewed 12 PUBMED case report articles and attempted to assemble data from each one and summarized in the table below.

Sr.N o.	Author	Age	Diabetes	Presentat ion	CRP, IL-6	COVID treatment	Lymphop enia	Invasi on by Mucor	Outco me
1	Swetha et al (6)	Midd le aged fema le	Present Type 2 DM	Left eye ptosis Facial pain Fever	CRP:68. 35, IL-6: Not mention ed	Not mentioned	Present	Sinus, orbit, brain	Alive
2	Astha et al (4)	38 years Male	Pre diabetic	Swelling and pain in left eye	CRP:17. 84 mg/dl	IV Methyl Predinosolone- 80 mg per day - for 18 days Inj.	Present	Orbit, Sinus	Alive
					6:37.93 pg/ml	Dexamethasone - 4 mg - BD - for 12 days		PNS	
3	Marina et al (5)	32 years Male	Type 2 DM present for 6 months	Left eye complete ptosis and facial pain	Not mention ed	Not mentioned	Not mentioned	PNS and orbital apex syndro me	Alive
4	Deepak ak Garg et al (11)	55 Year s Male	Present Type 2 DM	Hemopty sis	Not mention ed	Dexamethasone	Present	Lungs	Alive
5	Werthm an Ehrenre ich (12)	33 year Fema le	Present but undiagno sed	DKA and eye pain	Not mention ed	Plasma therapy and Remedisvir, (not mentioned about steroids)	present	Rhino orbital and cerebra l	Dead

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6	Kirill Aleksey ev et al (13)	41 year old male	Type 1 Diabetes	Deep aching pain in nose radiating down to throat	Not mention ed	Steroids and hydroxychoroq uine	Not mentioned	PNS and brain	Alive
7	Hanley et al (14)	22 years Male	Not present	Hemopty sis	Not mention ed	Mechanical ventilation	Not mentioned	Lungs dead	Dead
8	Placik et al (15)	49 years Male	Not present	Hemopty sis	Not mention ed	Remedisvir, tocilizumab and Dexamethasone	not mentioned	Lungs	Dead
9	Daniela Pasero et al (8)	66 years male	Not present	none	CRP: 25 IL-6: Not mention ed	Hydroxychloro quine, lopinavir- ritonavir (not mentioned about steroids) Mechanical ventilation	Present	lung	Dead
10	Amirre za velsi et al (16)	40 year fema le	Not present	progressi ve bilateral visual loss, periorbita l pain.	Not mention ed.	Remedisvir, Dexamethasone	Not mentioned	Sinus, orbit, brain	Dead
11	Amirre za velsi et al (16)	54 year male	Present Type 2 DM	left orbital pain and periorbita l swelling	Not mention ed	Remedisvir, Dexamethasone	Not mentioned	Sinus, orbit.	Alive
12	Zesema yat et al (17)	60 years male	Present Type 2 DM	prominen ce of right eye	Not mention ed	Remedisvir, Dexamethasone	Present	sinus, orbit	Alive

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13	Index case	44 years Fema le	Not present	Right eye pain	CRP: 68.04.IL -6: 40.38	Remedisvir, tocilizumab and Methy prednisolone	Present	PNS only	Alive
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CONCLUSION –

Good prognosis in a Mucormycosis patient depends on various factors. We have noted few, which led to good outcomes in our patient that includes high index of suspicion, patient awareness, early diagnosis, comprehensive evaluation, aggressive management, and limited infection to PNS. These have contributed to complete resolution with no destruction and permanent loss.

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