

Mucormycosis in Covid-19 Cases; Is A Steroid A Lethal Factor

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ABSTRACT

In the year 2019 the world went down in the clutches of a new virus and was announced a pandemic in the year 2020 by the WHO. India being a country with a large population ranked in second in the total number of cases falling behind USA. With the growing number of cases, the virus kept mutating and the complications associated also went on increasing including a high vulnerability towards bacterial and fungal infections. Also the further degeneration of immune system added on to the susceptibility in patients with already concomitant condition such as diabetes. It has been also been found that it affects the sinus, brain and lungs in human body. The rate of fungal infection has been found to be 8 percent. Though India in the first phase of the infection had a decent performance but in the second phase due the condition was threatening. A total of more than 30000 cases of mucormycosis was detected every single day. The first case was identified in United Kingdom, the genomic surveillance showed that the UK variant was the dominant variant. The transmissibility increased and thus being able to evade the immune system.

I. INTRODUCTION

In 2019, the world was hit by a deadly virus initially considered just another virus. But having infected millions it was declared as a pandemic by the WHO. Initially said to have found affecting the respiratory system it has emerged a complex virus that leads to the multi-organ failure due to SARS Cov-2. With the increasing infection and mutation what increased is the opportunistic increase in the fungal infection and it increased due to the dysfunctional use of steroids. This fungal infection can be life threatening for patients suffering from diabetes and those with reduced immune or low innate immunity.(1) Black fungus or mucormycosis cases have been reported in large number in India. Mucormycosis is a fungal infection considered to be rare and can be found

almost everywhere ranging from the manure to the mucus of a human, decaying fruits primarily caused due to exposure to mucor cold. Basically these pathogens are to be found on any decayed matter. Physicians on conducting various tests have listed an alarming number of Mucormycosis cases among the COVID 19 patients (2). Most of them were given steroids in the course of the treatment of the infection and this condition made them more vulnerable to the fungal infection. The excess use of steroids often causes immune degeneration and leads to a significant spike in the blood sugar level often acting threatening to the patients suffering from diabetes.(3) The internal environment of the body also aids the growth of the fungal Mucorales. This pathogen is often linked with a high mortality rate whether it is a case of invasive or disseminated mucormycosis. (4) In case of disseminated mucormycosis it also affects the central nervous system, in such cases of pulmonary invasive mould the clinical diagnosis is still difficult to determine due to its rarity. Mucorales are responsible for the invasive mould diseases and often affects those who have either undergone an organ transplant or a stem cell transplant. The Rhino orbital mucormycosis mortality rate is till 50 percent.(5)

Fungal rhinosinusitis can be said to be invasive or non-invasive depending upon the tissue invasion caused by the fungal pathogen. This invasion can be chronic, acute. In a research conducted on COVID-19 patients having acute rhino – orbital – cerebral sinusitis there was found a presence of mucormycosis and the symptoms were mostly found at the last stage of the virus. (6) While conducting cross sectional imaging, different types of intracranial complications like that of infarctions, perineural /epidural spread were diagnosed in patients. These are the factors that result in high morbidity rate and mortality rate.(7) In the MR imaging shows the presence of elements in magnesium and iron in vitro this could be primarily due to the involvement of the Mucosa fungus. Acute invasive condition requires early diagnosis.(8)

The most common types still remain the rhino – orbital and the pulmonary. Timely diagnosis and using of antifungal drugs can aid to the betterment of the patients. A vast number of cases are still treated in the ICU but even after that the mortality rate is very high and complications like organ transplant complicate the anti-fungal therapy.

MUCORMYCOSIS : ORIGIN

Mucormycosis is a fungal disease caused by pathogens called mucormycetes and former nomenclature as zygomycosis also popularly known as the “black fungus”, it also belongs to the code Mucoromycotina and Mucorales. In case of any stem cell transplant the fungi mucorales are found in the malignancies.(9) There are 11 genes and different species under the order that cause mucormycosis. The most common species are *Rhizopus* , *Mucor*. The first human case was first came to be known in the year 1855 in a cancer patient with a haemorrhage infarct in the lung that showed fungal development as discovered by Fubringer, later the first time it was seen in an autopsy was in 1956. Thus the diagnosis pathway was setup by the European Confederation. They took into account several methodology that can used for the diagnosis process starting from imaging , MR and others.(10)

The main way through which the fungus enters the body is through consumption of either contaminated food or through the spores , also the contaminated ventilation system. Based on clinical manifestation it has 6 different forms.(11) Having the ability to evade the immunity system of those with already weak immune system. Diagnosis of it can occur by conducting a biopsy from the area of infection . The Rhino- orbital cerebral is the most common form usually begins with symptoms like numbness and pain around the eye and face, conjunctivitis , blurred vision. (12) If not properly controlled or dealt at the right time it may spread to the sinus causing proptosis with chemosis thus damaging the extraocular muscle. In most of the cases there is no fever and the symptoms occur very late , the initial phase is very normal. The progression of the disease may be with edema or without it as well. With the increased spread formation of ulcer on tongue has also be diagnosed. This clinical condition would mean that the fungal infection has reached the mouth. (13) For Pulmonary mucormycosis the patients usually have fever and persistent cough , at times it can be also be present in the endobronchial pathway thus obstructing the air way path. The fungal infection can further be categorised into deep extension or localised depending upon the area it is infecting , if

it's the skin it is local but if it relates to the bone , tendon it is the former.(14).

Gastrointestinal mucormycosis is a hard to diagnose form and is a rare case to begin with . It affects the colon, stomach and the ileum. In the mild stage it can cause neutropenic fever but in severe case leads to the spreading in other organs like that blood vessels in bowel(15)

MUCORMYCOSIS AND COVID- 19: An Inevitable Link

A. Link between COVID-19 and Mucormycosis

Generally the healthy individuals do not come under the vulnerable group susceptible to mucormycosis because of the ability of their immune system to destroy the spores and the hyphae , this work is mainly done by the polymorphnuclear cells. The study of SARS-COV2 shows how deadly it impacts the immune system.(16) Thus a clear relationship between the two would be of that of the reduction of T cells and the reduced CD4 and the injecting of steroids in the system to control the inflammation in the organs. Post Covid a number of pulmonary changes occurs in the system thus increasing the chances of being infected with a fungal infection.(17) More so over an increased stay in the hospital , and the continual staying on ventilation causes spores . The fungal infection can easily infect : those with comorbidity like diabetes and those with increases iron content in the body. (18)

Other factor that is causing a high rate of mortality is the associated condition of diabetes. These fungal pathogens are able to survive in a strong acidic and glucose environment due to their innate enzymatic properties. (19) Diabetes Ketoacidosis a severe infection most likely to develop in patients with COVID 19 due to the acidic condition that makes the mucorcyosis to grow further . studies have shown that the SARS virus deeply impact the pancreas thus causing acute diabetes.(20) It has also been found that these pathogen also increase the insulin resistance thus creating a diabetes like state in the COVID patients. The increased serum ferritin level can also show the sign of susceptibility. (21)The use of Corticosteroids as presented in a research conducted by the European Federation has found to be in particular very harmful for patients already suffering from diabetes as it increases the blood glucose level and the continual use of it poses a serious threat of fungal infection . Also the creation of diabetogenic state further causes hyperglycemia causes a growth in the mucormycosis. (22)

The only fungal pathogens that stores iron the ferritins are the zygomycetes. They damage the tissue by creating a high ferritin levels which often to the generation of high reactive oxygen species. (23) These high ferritin levels also causes intercellular iron acquisition and also the cytokines released during COVID 19 leads to the release of iron in the circulation thus creating an environment inside the body where the fungal infection can breed. The ways to detect the infection is usually biopsy of the infected area but such a time taking process cannot be useful in COVID-19 cases owing to the high rate of spread of disease. (24)

Endotheliatis also occurs in patients with COVID-19. Initially the mucormycosis progresses its way in the system by adhesion and penetration. (25) The mucorales penetrates to the endothelium in acidemic state, creating a condition that of hypoglycaemia where the the glucose regulated protein receptor come in adhesion with the mucorales spore coat protein homologs. This prepares a conducive environment for the overall penetration of the fungal pathogen. Various research conducted have also shown the patients being infected with mucormycosis as a post COVID-19 symptom. (26) It was observed that there is no period for the growth of this fungus, it can be weeks after the discharge or after immediate hospitalisation. Studies of various patients have been presented , in case of patients with no medical history.(27).

B. Factors aiding mucormycosis in COVID-19 patients:

Black fungus is a fatal infection and a rare infection that occurs due to long period of hospitalization and the continual use of ventilation system when patients are kept in ICU, in worst of the cases it can cost the life of an individual as well as lead to the loss of vision. This fungal infection enters the human body through inhalation of spores present in the air. These spores then get fixed in the nasal passage (28) . In the initial phase the symptoms of mucormycosis can be greyishness of eyes, blockage of nose and oral cavity. At a later stage it may make its way up to the brain making it more fatal and increasing the mortality rate by a considerable percentage. (29) The best way of the treatment is the giving of anti-fungal medicine also supportive therapy might be useful. In other circumstances one has to operate upon the patient. While giving this anti-fungal treatment a lot of things must kept in mind the technician and the support staff should be more than alert about sterilizing the oxygen tubing. (30) Apart from causing severe inflammatory exudation the

COVID-19 patients have formed decreased immune due to the depletion of the T cells and CD4 that controls the inflammatory response of the body and regulates the process of phagocytosis. Extreme depletion of the T cells can lead to harm of the Central Nervous System and becomes life threatening. (31) Early detection can lead to the saving of the lives of the individuals. Drugs like that of amphotericin- B injections can help in subsiding the effect. The symptoms of the infection may vary with different individuals. There are various factors that aid the process in COVID 19 patients. These are as follows (32)

- A. Depletion of organs: The mucormycosis can infect the sinuses, brain and lungs and also can harm the gasrointesitinaltract , skin. It has different outcomes when it affects different organs like when infected in the sinus it creates a black gryish mucus thereby blocking the nasal cavity. (33) Can also lead to one sided pain,numbness and the face – pain. The first effect is usually seen in the eye.
- Eye: the mucormycosis begins its journey inside the body from the sinus and then spreads on tot the sphenoid. There is formation of gangrene in the eye due to the lesion in the eye that happens due to the germinated hyphae. When angio invasion occurs as a result of the thrombosis or leads to the internal carotid artery it leads to the infraction and hematogenous disintegration. (34) When the ophthalmic artery is affected due to the blood vessel necrosis it can cause blindness and sensory defects.
 - Mouth : This is the easiest place for the mucormycosis to grow , it happens in humans when the humans inhale air full of spores it leads to oral activity and wounds in the mouth and can also lead to ulcer on the palate .(35) Diagnosis can be done on the basis of pressure sores in orbital – nasal region , from the mouth the fungal infection cam spread to the nose in the maxillofacial region and can even infect the CNS. Angioinvasion of the Mucorales in the blood tissues leads to the formation of the thrombus that can cause necrosis in hard and soft tissues. (36)
 - Brain: The clinical manifestation of mucormycosis in the CNS often poses a question on life and death of individuals. The invasion in the CNS occurs when the fungal is widespread in the body and enters through the hematogenous spread or from dispersion through the sinus gland. The CNS is the third most vulnerable site for spread of the fungal infection. (37) The fungal develops and grows

in the internal elastic lamina and then gets in various part by the arterial lumen. Hyphal invasion in the brain cell occurs in case of extreme case of CNS mucormycosis.

- B. Problem of Self-medication: With the high cases of COVID 19 what happened was the increase in the case of self-medication and home remedies being followed by the infected individuals which leads to the consumption of the wrong dose of the medicine. In India consumption of steroids in large quantity has been observed in the lockdown, which seems to be the most among all the countries in the world. There has also been a trend towards the use of zinc and the excess of which creates a circumstance and a condition that helps in the breeding of the fungal infection and may lead to nasal microbimes. (38) Steroids can function through the interaction with the receptors which causes the defects in the functioning of the macrophages. It also disregulates the pro inflammatory cytokines secreted by the macrophages causing the immune degeneration. These cytokines are mainly the TNF α , IL-1 β , IL-6, IL-8, and IL. (39)
- C. Tocilizumab therapy – During COVID 19 there was mass scale production of pro inflammatory cytokines to control the level of IL6 in the patients. This production occurs from the bronchial epithelial cells. the drug tocilizumab though cleared by the FDA had more detrimental effect than benefits. (40) When consumed along with dexamethasone for a long period of time, instead of controlling the inflammatory function it led to the creation of antibody that obstructed the respiratory system and increased the breathing problem thereby weakening the immunity even more and posing a greater threat to the patients. (41)
- D. Improper usage of oxygen cylinders – Also one of the reasons for the post COVID-19 mucormycosis is due to the use of non-sterilized oxygen cylinders and the low-quality tubing system that patients even after recovering also the use of unclean mask and contaminated water in nebulizers have led to the prolonged survival of the virus. (42)
- E. Excess consumption of vitamins – The excess consumption of vitamins can also a threat for example the excess consumption of vitamin A hampers the absorption of Vitamin D and cause various bone issues. Vitamin D is also connected with the absorption of the calcium. Excess use of it can also lead to increase in the toxicity level and the non-utilization of the

other vitamins. Excess of vitamin A is said to increase the production of the antibody that obstructs the response against a deadly virus. (43)

C. ABUSE OF STEROIDS AND ANTIBIOTICS

The exact picture of COVID-19 may vary from patient to patient and on the degree of the severity also depends on the conditions of the patients and which person is infected by what symptoms ranging from bacterial to fungal and to that of life-threatening pneumonia. There also have been instances of the development of infection like Gram negative bacteria,(44) the pulmonary aspergillosis. These infections are common in patients who apart from corona have several other illness or comorbidity such as bp and diabetes .

Due to lack of knowledge about the defined medicine for corona and the ever changing nature of the virus a trial and error method was used to get to a point as to which drug would be beneficial and which wouldn't.(45) This trial sometimes resulted in success and at times lead to the worsening of the situation one such condition was the use of Steroids. Though at times acting as lifesaving elements the excess use of it caused all the more harm. Corticosteroids were used to treat severe cases of COVID and to decrease the damage to the immunity system that had been caused due to the virus. But these steroids when given repeatedly lead to significant increase in the blood sugar level of the patients and thus harmful for patients with diabetes and also leads to the creation of a hypoglycemic environment reducing the efficiency of the innate immune system thereby creating an breeding ground for the fungal infection. It was also recommended by the ICMR that doctors must pay special attention to symptoms that might indicate the growth of the mucormycosis like swollen eye, mouth pain , numbness, redness of eye. (46) (47)

Also at the peak of the virus there were no availability of the vaccine and drugs like glucocorticoids and remdesivir were found to be of utmost help , While treating patients with hypoxemia glucocorticoids was found to be a good option and being inexpensive and easily available drug it acted as a boon. Despite all its benefits it opens the door for more secondary infections. Also, when one looks at the application of other drugs like tocilizumab injected in a patient with an already immune degenerated disorder and the property of the drug that also acts like immunomodulatory leads to the increment in the risk of the patients with COVID-19. The use of excess antibiotics leads to a sharp decline in the

lymphocytes while cause a sharp rise in neutrophils and the WBCs. (48)

In severe cases the T cells present in the body that work mostly on the controlling of the anti – inflammatory response of the body decreased and it lead to negative outcomes , also the CD4 and CD8 that lead to the phagocytosis and genomes like cytokines and chemokine level were found to be increase thereby causing a serious threat to the CNS. To control this problem of T cell reduction lymphopenia was used and it lead to a raise in the amount of lymphocyte thus being beneficial for the internal immune system. (49) Various case studies were conducted and has been analysed one of such studies was the case of a 40 year old woman who after being infected with COVID-19 was given remedesivir for 4 days followed by dexamethasone from 8th day to combat the immune loss and the issues associated and livoflaxcin. The patient complained of visual loss and orbital pain . Imaging and MRI and the histopathological examination showed the degenerated tissues from the sinuses showed cases of inflammation marked with necrosis and confirmed the diagnosis of mucormycosis. Endoscopy of the sinuses was conducted every day. The patient was monitored with on a continuous basis. (50)

Rhino orbitocerebral mucormycosis is a fatal infection the chances of survival only depends on the time of diagnosis. One of the first things that is prescribed under such condition is to stop the use of corticosteroid and sugar must be controlled. Systemic treatment is found to be beneficial and amphotericin B could be considered as the first drug choice. Posaconazole an oral antifungal agent can used as for less rigorous infection.

II. CONCLUSION

In the year 2019 the world went through testing times, with the unsurmountable number of cases and the high transferability rate of disease lead to the death of lakhs of individual. In the year 2020 WHO declared COVID 19 as a pandemic. Being a part of the SARs virus genesis it initially caused an obstruction in the breathing tracts and attacked the lungs and the respiratory system. It often lead to complications like that leading to organ transplant and once that situation arose , the virus weakened the immunity system of the body thus making body a ground for more external and secondary virus threat increased. In severe cases the T cells present in the body that work mostly on the controlling of the anti – inflammatory response of the body decreased and it lead to negative outcomes , also the CD4 and CD8 that lead to the

phagocytosis and genomes like cytokines and chemokine level were found to be increase thereby causing a serious threat to the CNS. To control this problem of T cell reduction lymphopenia was used and it lead to a raise in the amount of lymphocyte thus being beneficial for the internal immune system and can also lead to the production of the particular T cells that can aid the spreading of the virus.

This attack of the virus comes with several other secondary harms like that of the fungal infection and this harm often occurs in those patients that have comorbidity or those with low immunity. Mucormycosis or black fungus is a rare fungal infection and quite fatal as well.

Diagnosis of it can occur by conducting a biopsy from the area of infection . The Rhino-orbital cerebral is the most common form usually begins with symptoms like numbness and pain around the eye and face, conjunctivitis , blurred vision. If not properly controlled or dealt at the right time it may spread to the sinus causing protosis with chemosis thus damaging the extraocular muscle. In most of the cases there is no fever and the symptoms occur very late , the initial phase is very normal. The progression of the disease may be with edema or without it as well. With the increased spread formation of ulcer on tongue has also be diagnosed. This clinical condition would mean that the fungal infection has reached the mouth.

The study of SARS- COV2 shows how deadly it impacts the immune system. Thus a clear relationship between the two would be of that of the reduction of T cells and the reduced CD4 and the injecting of steroids in the system to control the inflammation in the organs. Post Covid a number of pulmonary changes occurs in the system thus increasing the chances of being infected with a fungal infection. More so over an increased stay in the hospital , and the continual staying on ventilation causes spores . The fungal infection can easily infect : those with comorbidity like diabetes and those with increases iron content in the body.

The best way of the treatment is the giving of anti-fungal medicine also supportive therapy might be useful. In other circumstances one has to operate upon the patient. While giving this anti-fungal treatment a lot of things have to kept in mind the technician and the support staff should be more than alert about sterilizing the oxygen tubing. Apart from causing severe inflammatory exudation the COVID 19 patients have formed decreased immune due to the depletion of the T cells and CD4 that controls the inflammatory response of the body and also regulates the process of phagocytosis.

Extreme depletion of the T cells can lead to harm of the Central Nervous System and becomes life threatening. Early detection can lead to the saving of the lives of the individuals.

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