

MUCORMYCOSIS (BLACK FUNGUS): A SERIOUS THREAT DURING COVID-19

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ABSTRACT

COVID19 patients generally suffer from reduced levels of lymphocytes, especially helper T lymphocytes and cytotoxic T lymphocytes. These cells play a vital role in the body's inflammation-mediated immune response, and their reduced levels make COVID19 patients extremely susceptible to secondary bacterial and fungal infections. In addition, doctors will give patients immunosuppressive steroids COVID19, which will further weaken their immunity. However, steroids reduced the phagocytic activity of neutrophils and macrophages in COVID19 patients. Also, steroids can cause a sudden spike in blood sugar levels in diabetic patients, which is another major risk factor for mucormycosis. In addition, an iron-rich environment is conducive to this fungal infection. Elevated levels of cytokines, such as interleukin, will increase ferritin levels in COVID19 patients, making them more susceptible to mucormycosis. In addition, oxygen cylinders and unsanitary fans may be the cause of this fungus outbreak. During the second wave of the epidemic, some hospitals shared ventilators. Some oxygen cylinders in use are contaminated, and this unsanitary condition may cause a sudden increase in mucormycosis cases. Indian doctors have previously warned about the use of cow dung and urine to enhance immunity against covid19. This is because animal droppings can contain different fungi. Therefore, diabetic patients with covid19 and those who have been treated with immunosuppressive corticosteroids are the most susceptible to mucormycosis.

KEYWORDS: Black Fungus, COVID-19, Infection, Disease, Immunity

INTRODUCTION

Fungi (Like Moulds and yeast) are unique groups of those micro-organisms which are responsible for numerous types of infections especially with those belong to immunocompromised host. Additionally, for those of medical importance these micro-organisms are associated with those of contamination on surface or spoilage of pharmaceuticals products, cosmetic and some food products.

Mostly fungal contamination on pharmaceutical products can cause not only serious economic losses to the manufacturer but can also lead to serious health issues to patients.

Black fungus is that one type of fungal infection which is caused by those type of mould known as 'mucoromycete's' which belongs to the order "Mucorales". That's why it is also known as Mucormycosis or sometimes it is named as zygomycosis. Black fungus is found in the environment in many forms like in soil, water, air, vegetables, rotten vegetables, organic matter. So, it is also called as environmental contamination but not a contagious disease.

Black fungus is not a novel disease basically it comes to know when it affects those peoples which have weaker immune system of recovered corona patients. Basically, they enter in to the body through nasal passage and affects our White blood cells (WBC which is responsible for fighting against any pathogens that affects our normal physiology of human system) that why it comes under opportunistic infection category (Means when the bacteria, virus or fungus when gets opportunity like weaker immunity or open wound they attack and start responding inside the body).

It is a rare disease but dangerous infection. Black fungus is caused by getting into contact with fungal spores present in the environment. It can also be spread through the skin through which the fungal spores enters either through a cut, scratch, burn, or may be through another type of skin trauma or who use drugs that weaken the body's ability to fight the infections.

About 150000 species of fungi but only 300 species of fungi are responsible for human fate.

Depending upon the site of infection caused by black fungus it is further classified as Rhino cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated or other, which includes uncommon rare forms, such as endocarditis, osteomyelitis, peritonitis, renal, etc ¹.

Currently, Mucorales fungi are the next most common mould pathogens after *Aspergillus*, leading to invasive fungal disease in patients with malignancies or transplantation ². The incidence of mucormycosis has also increased significantly in patients with diabetes ³, which is the commonest underlying risk factor globally.

Mostly, Black fungal infection is usually seen among Covid recovered patients with co morbidities such as diabetes or kidney, heart failure, or cancer ⁴.

The sign of this infection mimic those of Covid-19 and customary flu. If it's ignored or untreated infection originates nostril to eye and brain and produce life threatening complications ⁵.

EPIDEMIOLOGY

The presence of this invasive opportunistic mycoses had increased due to the expanding population especially of immunosuppressed patients which includes Solid Organ Transplant (SOT) In some cases it is also seen in Hematopoietic Stem Cell Transplant (HSCT) recipients' patients belong to cancer as well as it is also seen in patients with AIDS followed by Premature Neonates and generally seen in Elderly patients who are recovering from major surgery. Despite of some effective treatment options of mycoses are associated with high morbidity and mortality rates.

This invasive mucormycosis that shows a specific regional occurrence patterns across the world and there it exhibits different epidemiologic features that depend upon the geographical region. These may be specifically true for mycoses (specially mold infections) that are acquired from the environment.

In most of the cases human infections results from inhalation of fungal sporangiospores that have been released in the surrounding air or it may be in direct inoculation of organisms mainly in to the disrupted skin or mucosa ⁵. These Mucorales are ubiquitous in nature, but their precise ecology remains to be determined. In most of the cases it's been seen to be thermotolerant as well as they are also found in decaying organic matter. Cases with mucormycosis have also been reported from across the world. Seasonal variation in Mucorales infection is also possible as these spores have differences in the manifestation of mucormycosis seems to exist between developed and developing countries. In developed countries, this disease remains uncommon but at present these are mostly seen in those patients with diabetes mellitus and Haematological Malignancies (HMs) are undergoing chemotherapy and those who had received allogeneic stem cell transplants ⁶. In contrast, in developing countries, especially in India, mucormycosis cases, although sporadic, occur mainly in patients with uncontrolled diabetes or trauma ^{2, 6}.

In the review of mucormycosis cases mentioned in English-language literature written by Roden et al had compiled about 929 cases of mucormycosis during 1885 to 2004 which shows a rising proportions of especially immunocompromised patients with mucormycosis was reported in the year 1980s and 1990s ⁷. Patients with HMs or who underwent hematopoietic stem cell transplantation (HSCT) represented 22% of the cases (17% and 5%, respectively).

In the largest registry of the European Confederation of Medical Mycology Working Group had reported about 230 cases occurring between 2005 and 2007 were analysed and found to occur in patients with haematological malignancies (44%), trauma (15%), HSCT (9%), and diabetes mellitus (9%). During this a comprehensive analysis was performed at the country level in all hospitals of France and revealed a total of 101 cases of mucormycosis (60 proven/41 probable), mostly in men (58%) ⁸.

SOURCE

Black Fungal is a type of fungus that is spread through spores of fungus that are present either on the surface or any other present in various niche of numerous habitat that are present

on the environment in various forms like on the soils or through any other means by rotten vegetables.

The most prominent source of spreading fungal infection is through the patients having lower immunity and that individual comes in contact with the infected floor on which spores may be spread ⁹.

Entering lungs are sporangiospores i.e., of about 3-11 micrometre

These spores are very sensitive regarding weather changes as they are dispersed in environment mostly during summer season than in monsoon i.e., around 800 – 4800spores per cubic meter present compared to approximately 80 – 280 spores per cubic meter inside house.

As around 5 – 10 fungi species dispersed in the environment through air.

Basically, mucor fungi produce a million of spores (Generally dark-hued, microscopic spherical structures) that are dispersed in air. When these spores landed on moist surfaces such as on plant materials, compost piles, animal dung or it may be on soil surfaces they start to germinate and produce a thread like structure usually a mycelium.

The mycelia then branch out and feed on sugars in their surrounding and finally grew on the favourable sites where it has to proliferate ^{10, 11}.

As per Mucormycosis is not contagious disease and thus it cannot be transmitted either by direct or indirect contact between people or between people and animals.

Since, these are those types of fungus that are harmless but can take benefit with weakened immune system and invaded tissue. This is why these “Mucormycosis” infections are also known as opportunistic infection ¹¹.

That’s why it is transmitted through either by inhalation or by the ingestion of fungal spores in air. As it is a rare disease it is also found to be entering inside body through either from cuts or scratches on the surface of skin. It can also be seen during trauma.

ETIOLOGY

The chief cause of black fungus to spread among human is its spores which are present around the environment in many forms such as in soil, rotten vegetable peels or damp places.

In most of the cases it have been reported that this fungus enters in to the body through nasal passage and causes a most threatened disease named pulmonary mucormycosis which is a most rapidly progressive infection caused by mucormycosis when an individual accidentally inhaled the spores of fungi through nasal passage and directly reaches the bronchial associated with trachea and finally reaches alveoli in this cases the opportunistic ways may be pneumonia with infraction or necrosis in alveoli and get converted in to contagious structure which may result into mediastinum and the heart may disseminate hematogenously with other associated organs of the body ¹².

Generally, this fungus is clinically presented as Rhino orbital cerebral mucormycosis which is caused by inhalation of spores of fungi into the paranasal sinuses of the susceptible host and most probably the cause of black fungi is hyperglycaemia i.e. Diabetes mellitus which is associated with its metabolic acidosis is considered to be the most common underlying cause for the enhancement of dreadful disease named mucor mycosis.

Thus, black fungus infection usually infects those patients or those individuals which are either recovered patients from corona virus or those having high dose of steroids which been taken during treatment procedure of steroids. These fungi are also seen with the diabetes patient (Or those having low sugar level), in kidney, Angio invasive patients (Heart failure). It is also seen in cancer patients and rarely seen in HIV/AIDS patients ^{13,14}.

Fungal infection that affects Central Nervous System is rarely come to consideration especially with those associated with significant morbidity as well as mortality. Clinically CNS fungal infection is seen at intraparenchymal abscess i.e., approximately 87% and near meningitis it is about only 10%. Sometime Cerebral Phaeohyphomycotic also referred as Black mould and Phacoid fungi. Thus, it is considered that black fungus can cause about three kinds of diseases these are: The former is Mycetoma which is recognized by tumefaction, draining and granules associated with chromoblastomycosis and later is phaeohyphomycotic ¹⁵.

It has been observed that black fungi that causes cerebral phaeohyphomycosis are of different forms these are *Cladophialophora bantiana*, *Rhinochloidiella mackenziei*, *Verruconis gallopavum*, *Bipolar spicifera* etc. Among them the most dreadful species is *C. bontiana* it is generally causing about 48% of cerebral phaeohyphomycosis. In most of the cases the common cause of this fungus is seen during structural breaches i.e., during traumatic cutaneous inoculation that leads to mucormycosis. So, in most of the cases it been observed that these fungal species exist as spores with unique characteristics like in their colour, structure, size and their shape specially in their mycelium and these are thrive of dry, humid and arid conditions as shown in figure 1 ¹⁴.

It is considered to be pandemic across worldwide because this mucormycosis is much more common in COVID patients specially who are recovered but even before the COVID-19 pandemic this incidence in India was as such as approximately 70% times higher than the global average but it was in a recessive condition or in rare patients ^{14,15}.

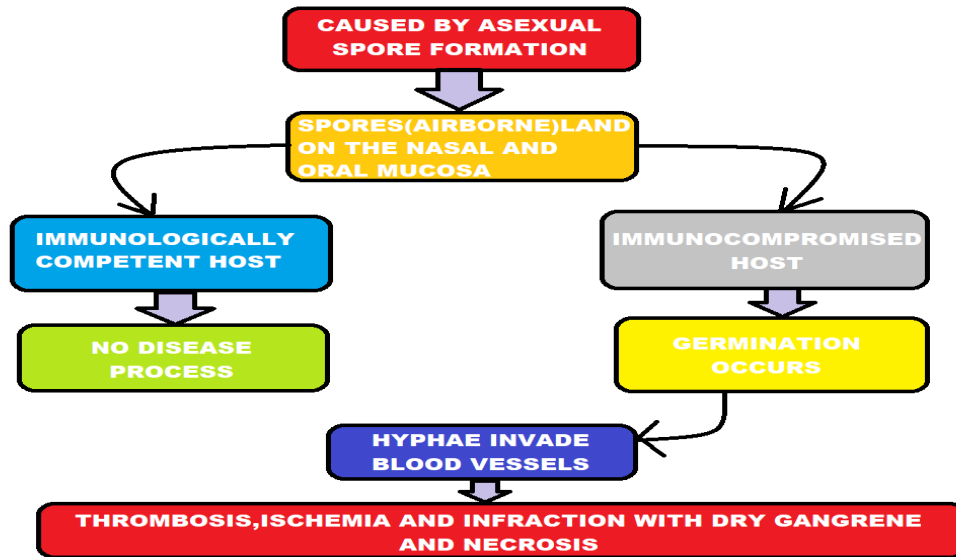


Fig. 1: Etiology of Mucormycosis

PATHOGENESIS

The pathogenesis of black fungus starts from nasal passage which is followed by sinuses which then enter into the eyes and sometimes reaches towards the brain in fatal cases.

In most of the cases this fungus is seen in the patients who are suffering from diabetes mellitus ¹⁶.

As we know that the patients having diabetes mellitus in their body one chemical forms name ketones in other way we know that in our body iron is responsible for forming blood but during diabetes mellitus these ketones affects the formation of blood through iron instead of synthesising the blood they start helping these fungus to grow because these fungus also need host iron to grow inside the body and this situation help fungus to grow inside the body and as it starts growing adversely in the body then it can enter into blood vessels and can cause Angio invasive disease as well as in fatal situation it may enters into the nerve and cause perineural spread. Its pathogenesis is also seen during organ transplant in that cases immunosuppressants are prescribed which may be the better pathways for this fungus to grow as its immune is low ¹⁷.

In most of the cases it's been reported that these fungi spread in following stages inside the body these are

Stage I: Starting from the nasal mucosa which is followed by

Stage II: Entering of fungal spores into the paranasal sinuses like maxillary sinuses or frontal sinuses then it enters into

Stage III: The orbits that consists of eye then from eye

Stage IV: Beyond which via optic nerves it can enter into the brain especially Central Nervous system.

The pathogenesis of these fungal diseases during COVID-19 is seen due to excess use of steroid especially corticosteroids due to which there is increment in cytokinin especially Interleukin-6 which is followed by the increment in the ferritin in the presence of ferritin synthesis which is enhances more and more iron transport across the body which leads to the enhancement of more and more intracellular free iron and thus causes the free passage of fungal to spread inside the body and lastly cause mucormycosis as shown in figure 2^{16,18}.

It can also be seen in the condition of Hypoxia (less oxygen condition) as well as lymphopenia in which there is decrease CD4+ and CDS+T cells which may cause endothelialitis it happens due to increase Endothelial receptor glucose regulated protein-78(GRP-78) and also increase in a Mucorales adhesin spore coat protein homologs (Cot-H) which also leads to mucormycosis¹⁹.

As the entering of these organisms through endothelial cells as well as through the extracellular matrix are the most important steps in the pathogenesis of most of the fungal spores it can be better be observed that this fungus enters into the body through burn site of any organ because at that there is removal of skin due to which the spores may enter into blood stream and through it circulate across the different part of the body²⁰.

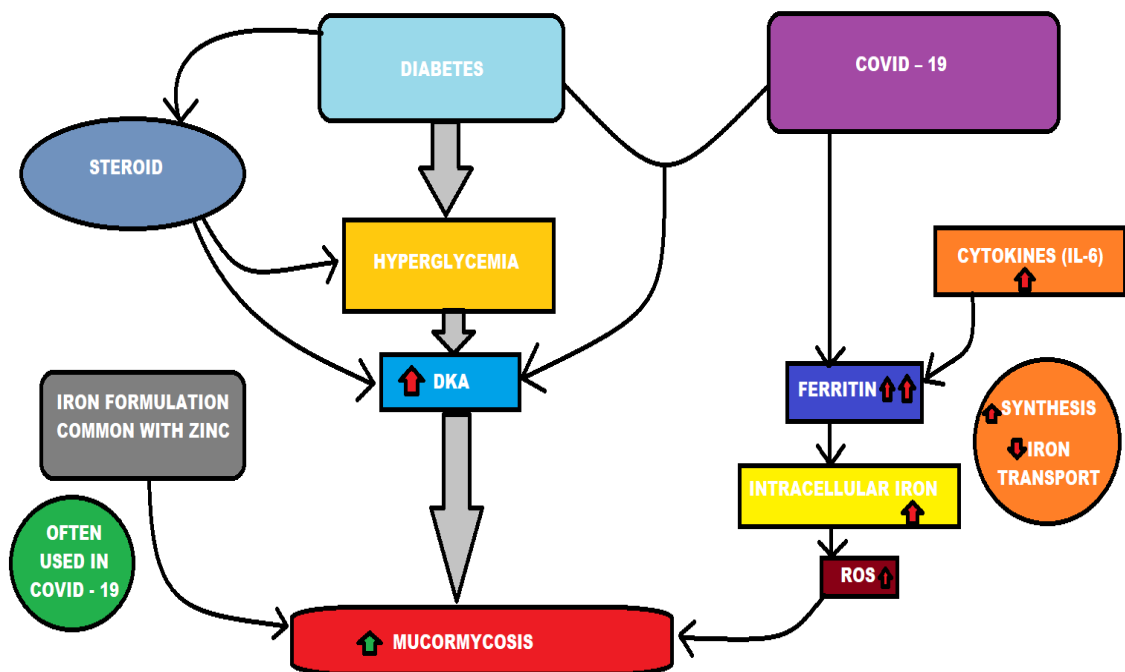


Fig. 2: Pathogenesis of Mucormycosis

SIGN AND SYMPTOMS

This may lead to severe disease if its sign and symptoms not seen earlier these are as indicated:

- Pain and redness around affected eyes or nose.
- Fever.
- Headache.
- Coughing.
- Shortness in breathing.
- Bloody vomit which may be brown or red.
- Altered mental status.
- Facial pain.
- Numbness or swelling.
- Toothache.
- Blackish Discolouration over the bridge of the nose or mouth palate.
- Jaw involvement.
- Blurred or double vision with pain
- Paraesthesia.
- Skin lesion.
- Black spots-on faces.
- Thrombosis.
- Necrosis (Eschar).

FACTORS

The most prominent factors for this fungal disease to spread among human to human is their weakness in their immunity which may be due numerous of problems like recently recovered corona patients or those patients who are under the medications of rather health issue in which they have lose their ability of fighting against wide variety of dreadful pathogen in such cases they may be affected in their sinus, lungs and can be life threatening in diabetes or severely immunocompromised individuals like it can be seen in cancer patients or those patients who are affected by HIV or AIDS ²¹.

This Fungal disease is most probably is seen under those patients who are in their elderly age groups or middle age groups or who have low immunity against any pathogens or they affected by diabetes.

Its factor may include the widespread use or misuse of steroid during the treatment of covid due to it vigorously decrease the immunity of the individuals, probably it may through mucosal damage from the virus or it may be through wide spread SARS-CoVs-2 infection. Its factor is also seen in the patients who are under antifungal therapy which leads to loss of the vision ²².

In most of the cases this fungus disease is seen under the patients who are suffering from malignant disease specially a haematological disease either with or may be without stem cells transplantations^{22,23}.

The mortality rate of this dreadful fungal infection varies with their site of action i.e.

- In case of gastrointestinal infection, it is about 85%.
- In case of pulmonary infection, it is approximately 76%.
- In case of children affected specially by former cutaneous it is about 27%, gastrointestinal it is approximately 21%, by rhino cerebral it is about 18% and later by pulmonary infection it is approximately 16%.

HOW IT IS LINKED WITH COVID 19

This fungal infection is spread in covid 19 patients because during the manifestations of covid 19 the patients lose a large number of lymphocytes count and Over The Counter (OTC) misuse of steroids in this case their sugar level becomes high beyond which the covid it increases the chances of black fungus to grow.

These cases emerged in second wave because of high number use of steroids which is relatively less used in first wave of covid 19²⁴.

This happens because while using of steroids it suppresses the immunity of individuals that makes more prone to fungal disease although this steroid especially corticosteroids are life saving drugs during covid treatment but they indirectly loosen the patient's immunity which worsen the condition as black fungus.

During the covid situation this fungal disease spread very rapidly as it can be seen inside the patient body as there is drastic change occurs due to entrance of the host for the fungus in the form of spores as its medical treatment of this covid situation gives the opportunistic for fungus to grow which leads to harm the air way mucosa followed by blood vessels²⁵.

In some cases, it's been observed that in blood there is increment in serum iron which also leads to the growth of fungus inside the body.

During this pandemic covid situation some medication related to broad spectrum antibiotics were also used as medication in covid situation as we know that these drugs are helpful against any types of bacterial born diseases as well as these drugs are beneficial in commensals with fungus to grow.

In some cases, it's been also reported that the fungal growth is also enhanced by the excess use of zinc which usually acts as catalyst for the fungal growth²⁶.

In most of the cases it's been observed that the prolonged use of oxygen during the ventilation for covid patients is also the reason for the growth of fungal disease because its steam leads to the growth of fungal infection.

COMPLICATIONS

The major complication of this fungal disease is mostly seen in immune suppressive patients, cancer patients especially to those are undergoing through regular chemo radiation, uncontrolled diabetes, Patients who are under the treatment of erratic using strong steroid medication. Sometimes this complication may occur with those patients who are under the treatment with antifungal therapy or regimes ^{26,27}.

The most complication factor with these fungal disease is that these fungal infection when enter into the body they starts to clump at one location which commonly known as thrombotic invasion in which the black fungal spores enters into the blood vessels and start to clump at one location which leads to degrade the other associated vessels or other parts by making a plaques like structure at the sites and sometimes they flow along with blood vessels and enters into other parts like eyes ,brain, nasal passage and many other associated organ or organ system and there it may be either forms a plaque at location or starts to degrade it which causes a painful effects on the body system.

Several other associated complication factors are due Diabetes mellitus, ketoacidosis, In most of the cases it's been seen in Haematological malignancy and hematopoietic stem cell transplantation. Some time it is seen during Solid organ malignancies and Solid organ transplantation, Corticosteroid and others immunosuppressive agents, iron overload, Breakthrough mucormycosis ²⁸.

DIAGNOSIS

For the prominent diagnosis of this invasive fungal diseases there are some basic tests were used in order to detect its manifestation inside the body as well as their presence can be detected initially and foremost used test for fungal infection is nasal endoscopy in which by the help of camera it can be helpful to determine which types of disease is spread around the nose and also it is helpful in determining that whether the nose is healthy or disease prone by fungal infection ²⁹.

This test is followed by another test known as MRI (Magnetic Resonance Imaging) of different affected organs like eye, nose and brain. This is helpful in determining the manifestation of disease i.e., how much the disease had been spread inside the body.

Usually, MRI is done after the nose endoscopy test gets positive result i.e., the nose is affected then it is followed by the next test which may be the final test in order to detect that this fungal infection is infected the nose or it is infected by other disease it is done by taking the small tissue during nose biopsy and send it to the laboratory to detect whether this part is infected by black fungal or by another and make their comprehensive report.

In other way it can be diagnosed at laboratory level by taking only a fluid sample from nasal passage ³⁰.

Since form the many existing reports of black fungus it's been seen that the test was differing form region to region as these affect many other organs specially associated organs like that

of sinus and lungs so their way of diagnosis was different i.e., it can be diagnosed through CT scan.

TREATMENT

The treatment for this invasive disease of mucormycosis should be done in multidisciplinary ways as this disease is not sited at only one location or site it is spread throughout the body in different organs like eye ,brain and many other associated parts so it requires treatment through different specialist like starting with the ENT (Eye, Nose ,Tongue) specialist which is followed by physician in order to control the blood sugar level , if required nephrologist because it is also spread across kidney of affected patients . In some severe cases Eye surgeon is also required because this fungal disease also spread across eye that may cause blurred vision or blindness in eye ³¹.

After diagnosis of this mucormycosis there is need to prescribe the high dose of antifungal medicine like amphotericin B (IV), Posaconazole. In some severe cases like during rhino cerebral mucormycosis there is need of surgery. Surgery is also helpful in treatment during necrosis in tissue in order to treat it the infected tissues which may leads to the removal of jaw or in many cases eye is also removed. In most cases it's been also seen that this invasive fungal disease can be treated by the use of hyperbaric oxygen in order to make the more oxygen rich environment so that this fungal infection can't be grown at the site.

The medical treatment for this invasive disease may be lasting for 4-6 weeks or it may extend on the basis of the condition of patients after the preferred surgery of the patient's during this the medication duration may extend from week to months ³².

There must discontinue of the immune-modulating drugs in order to save the life of the patients.

PRECAUTION

Precaution of any disease is its personal hygiene of an individual regarding it and it surrounding in order to eradicate the spread of any type of dreadful disease either it is a fungal spore or any contagious pathogen which directly or indirectly enter the body ³³.

The chief and foremost precaution of these fungal diseases is to protect our self from the pathogen by making the environment hygiene as well as personal hygiene is must by following ways like:

- Wearing a mask which must be always be change at regular interval,
- Always try to wear full sleeves shirts in order to cover the whole parts of the body,
- try to wear a shoe,
- Always take warm bath after having any type of contact from patients and always wear
- Always wear a glove while doing any type of work related to chemicals,
- Also try to wear full gloves during cultivation or gardening when you come in contact with soils.

Apart from these all the patient with fungal infection must have to manage their lifestyle by following some of the useful measure in order to treat this invasive fungal disease like

- There should be control and always monitor the blood sugar level in case of diabetic patients.
- Try to avoid self-medication like the use of steroids or any type of antibiotics or may be taking any type of antifungal therapy instead of going to hospitals at alarming time of fungal disease.
- Try to immediate contact doctors who are giving appropriate treatment of this invasive fungal disease.
- Always take the medicine at its scheduled time and follow up the other co-morbidities.
- There should be regular examination of patients having invasive fungal disease like having facial swelling or black coloration due to fungal infection.
- Regular check-up of oral and nasal examination must be done.
- Always use clean and sterile water for humidifiers at the time of ventilation or intake of oxygen as prescribed by physician.
- Try to avoid those medications which are related to immune-modulating drugs.
- Always maintain required amount of systemic hydration.

So, it is important to maintain a healthy diet as well as scheduled lifestyle must be there to prevent any type of disease^{34, 35, 36}.

CONCLUSION

This fungal spores are not a novel type of disease but it is a rare disease which comes to know in recently occurred second wave of COVID-19 it is also been seen in the first wave but it is not so spread like second wave duration in India it is spread due to poor hygiene condition of environment as well as not taking serious straps against in earlier period these can also be seen during earlier which is in the form of comorbidities with other type of disease specially with those that reduces the immunity of the individual like during diabetes mellitus or it may be through any respiratory problems, in some time it is observed with another disease like that of skin problem i.e. burning of skin or any scratches on skin surface.

The mortality rate of this invasive fungal disease is about 50%-54% across the world which is mostly be seen with those patients who lies within the range elder age group or suffering with that of diabetes melilites or with cancer related to blood or immunosuppressive treatment during grafting or transplanting of organs. Mostly this invasive fungal disease is treated by inversely the use of steroids judicially and the way of treatment of this invasive disease is to control of sugar in case of diabetic patient.

Additionally there are several other preventive measures were taken in order to treat this invasive fungal disease apart from the medicine these may be done after the reaction at the injection site that may be after vaccination at that site try to use only a clean or cool wet wash cloth followed by compression this gives a relief from muscle and joint ache in order to get ease from soreness or any types of stiffness in the arm try to move it as much as possible this

helps to get counterintuitive. While in case of chill or low-grade fever try to wear light clothing, which helps in preventing the body from overheating.

Availability of data and material- All the data collected through the review and research articles

Funding- Not applicable

Acknowledgements-

This research was supported by the Quantum University. We thank the Management for their moral support and for providing insight expertise that greatly assisted the research.

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