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Post-COVID Mucormycosis: A Parallel Pandemic

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Abstract:

As many as 47% of the population in India are unaware of their diabetes status. many of them get accidentally diagnosed with diabetes on routine blood investigation for covid. Their diabetes status worsens after taking steroids for covid infection putting them at risk for severe mucor and bacterial infections.

COVID itself causes immunodisregulation (i.e alteration in immunity). Added to it, the large number of diabetic patients getting serious covid infections and rampant use of immunosuppressant medications and steroids has increased the number of mucormycosis cases. Mucormycosis is not a new disease. It's a fungal disease caused by moulds, which affect the nose and paranasal sinuses. The article explains about causes, symptoms, preventions that should be taken care along with the treatment.

The prognosis of mucormycosis is usually depends upon the overall health of the patient, speed of diagnosis and treatment, the patient's ability to respond treatment. So here in this paper some herbs are discussed which can be used in covid as well as post covid patients to improve immune status which will reduce the risk of further complications such as mucormycosis.

Keywords: mucormycosis, Post COVID symptoms, fungus

Introduction:

By the time you read this article some of you would have experienced the pain and suffering associated with mucormycosis, some of you might have just heard about it and many of you might be in sheer denial - now what's this new thing? What's the relevance to me? Why should researcher be bothered about it? or Is it one more conspiracy as COVID? And something like this? Well, we all know how badly we are affected by the COVID pandemic. And if COVID is a frying pan then mucormycosis is nothing less than a burning fire itself. It's not only devastating, but it also attacks you when you are already broke and just gathering all your energies to come back to normal. So why aren't we aware of it, if it's so dangerous? Is it something new like COVID? Let us unfold the issue, understand the disease, the science behind it, and get educated. This will go a long way to protect ourselves and help us to take appropriate measures to fight against it.

Mucormycosis is not a new disease. It's a fungal disease caused by moulds, which affect the nose and paranasal sinuses. Less commonly it can affect the lungs and skin. This fungus, which is present everywhere in the environment normally does not cause human disease. However, when the immunity of the person decreases this fungus starts growing inside the body. It rapidly spreads to the surrounding structures by destroying them. It tends to spread to the eyes and brain. Once the eye is involved it needs to be taken out to save the life. Brain involvement is the sign of advanced disease and the chances of survival in such patients are only 15%.

The very logical question that arises here is if this is such a dangerous disease why there is no awareness about it. It's because in the pre-covid time it was not a common disease. Though the exact figures are not known, due to the lack of population-based studies in India, it is estimated that the pre-covid case burden was around 14 cases per 1 lac ICU patient. When the covid pandemic started the number of patients affected by this disease has increased significantly. Most of the tertiary care centers in the major cities in India are now seeing approximately 25 to 30 cases a month (as against 12 to 18 cases a year in pre-covid time).

Alarming and bothering post Covid 19 Situation:

1. It's a matter of worry because Mucormycosis is a very fatal disease. Left untreated the survival rate is only 3%. With combined medical and surgical treatment the survival rate is not better than 60%. This means that despite the best possible treatment 40% of the patients succumb to the disease.
2. The part of the body which is invaded by the fungus needs to be removed for the patient to survive (Removal of such fungus-infected dead part is called surgical debridement). That means if the eye is involved, it will be required to remove the eye for saving the life and if the brain is involved then that part of the brain needs to be removed, likewise for any other organ in the body which gets infected with the fungus.
3. Is surgical debridement of the affected tissue the only treatment option?
4. No. It is just one part of the treatment. After thorough surgical debridement, the patient needs to take antifungal medicine for 15 days to 6 weeks. The preferred antifungal medicine is Amphotericin-
5. B. It is available in two varieties, the regular lyophilized amphotericin, and the newer liposomal amphotericin. The lyophilized amphotericin is cheaper but has toxic effects on the kidney and has chances of some serious side effects. Moreover, it cannot be given in higher doses in kidney failure patients. The Liposomal amphotericin is less toxic to the kidney and has fewer side effects, however, it is too costly. A single-day treatment cost with the Liposomal Amphotericin-B ranges from INR 30000 to 60000 (Average cost of medicine alone ranges from 7 to 12 lacs).
6. What if surgical debridement is not done? Can mucormycosis be treated with medicine alone? No. Mucormycosis infects and spreads by invading and blocking the blood vessels (this is called angioinvasion). As a result, the area of tissue supplied by the particular blood vessels dies and becomes black. The fungus further multiplies and grows on this dead tissue and rapidly spreads to the surrounding normal tissue whatever comes in contact with it. It has also the property of spreading

via blood vessels to distant sites in the body. Hence when the antifungal medicine is given to the patients through the veins it is able to kill the microscopic fungus present in the body, but as the medicine cannot reach the site of dead tissue (due to blood vessel destruction and blockage), it fails to kill the fungus completely. Therefore it is necessary that the dead tissue is removed aggressively by surgical debridement and the antifungal medicine be given for 15 days to 6 weeks so that the fungus can be killed optimally. This gives the best chance of survival.

Risk factors for mucormycosis:

Cytokine storm is the condition where the body responds to the covid virus infection by producing a huge number of inflammatory cells to fight against the virus. However, these inflammatory cells, along with killing the virus also destroy the normal body structures affecting lungs, heart, kidney, etc. Research has proved that low-dose short course steroids are helpful in treating cytokine storms thereby preventing serious covid complications and saving life.

When used injudiciously steroids significantly lowers immunity, increases blood sugar, and predisposes to mucormycosis and other serious fungal infections. In the following cases it may get critical and increase the risk of mucormycosis,

1. ***Mucormycosis infects people who are really low on immunity.***
 - a. Mucor can not infect normal healthy individuals
 - b. Cancer patients, Organ transplant patients taking immunosuppressive medications, chronic kidney, liver, and lung disease patients are at increased risk of invasive mucormycosis.
2. ***Diabetes and high blood sugar.***
 - a. Persistent high blood sugar favors invasive mucormycosis
 - b. Moreover, many diabetes patients have chronic kidney and liver disease which lowers their immunity.
 - c. Many diabetes patients are on dialysis with increased chances of acquiring hepatitis B and hepatitis C infections - further lowering their immunity and favoring the fungal diseases.
3. ***Steroids***
 - a. Steroids are wonder drugs in experienced hands, however, when used injudiciously by the inexperienced they can wreak havoc.
 - b. Steroids primarily work by reducing inflammation and the immune response of the body. Hence they are very helpful in the 2nd phase of covid where there is cytokine storm.
4. ***Mucor is abundant in damp, ill-ventilated, and unhygienic conditions.***
 - a. Mucor is ubiquitous, meaning it is present everywhere in the environment. However, it grows in abundance in humid & ill-ventilated places.
 - b. Many hospitals, nursing homes, and ICU in India, barring the big corporate hospitals, have poor

infrastructure and hygiene conditions.

- c. Many hospitalized covid patients who are seriously ill do not take bath or change the clothes for days together owing to their illness. This problem is aggravated by overcrowded hospitals, poor nursing personnel to patient ratio, and inadequate hospital infrastructures at many places, resulting in poor patient hygiene who are already immunocompromised thereby favoring the chances of deadly fungal and infections.

More Risk for Post covid patients:

Many seriously ill covid patients have an average hospital stay of 2 to 3 weeks, jeopardizing adequate hygiene.

Many of these patients are known diabetics with chronic kidney and liver disease with low immunity.

As many as 47% of the population in India are unaware of their diabetes status. many of them get accidentally diagnosed with diabetes on routine blood investigation for covid. Their diabetes status worsens after taking steroids for covid infection putting them at risk for severe mucor and bacterial infections.

COVID itself causes immunodisregulation (i.e alteration in immunity). Added to it, the large number of diabetic patients getting serious covid infections and rampant use of immunosuppressant medications and steroids has increased the number of mucormycosis cases.

Symptoms of Mucormycosis:

How can I know if I have post covid Mucormycosis?

Keep a high degree of suspicion for mucormycosis if you are diabetic, had been treated with steroids and other immunosuppressant medications had prolonged hospital stay, or if you have any disease with lowers the body immunity. Even if you are not known diabetics if you had recent covid and have received steroids and immunosuppressants for treatment, be suspicious of mucormycosis if you notice any of the following symptoms (in such case you can be either pre-diabetic or undiagnosed diabetic).

1. **Nasal discharge:** Runny nose for initial few days followed by dryness in the nose and crusting in the nose- this is usually the first symptom but may not be noticed by everyone. The dryness and crusting inside the nose gradually increase causing nasal blockage, very foul-smelling nasal discharge at times mixed with blood. After few days there can be blackish crusts visible inside the nostril.
2. **Loose teeth:** Loosing of teeth cap, blackish discoloration of the upper jaw gumline or the roof of the mouth.
3. Some people who have upper jaw bone (maxilla) involvement by the fungus can present with these signs. This generally happens when the disease advances from the nose to the upper jaw bone. This is not a good sign. When seen it signifies that the disease has crossed the confines of the nose and has involved the paranasal sinuses and the surrounding structures.

4. Swelling and redness over the cheek, side of the nose. This is again not a good sign. It signifies that the disease has now spread outside the nose and paranasal sinus to involve the eye and the skin surrounding the nose and cheek.
5. Intense pain over the face and around the eye

6. Drooping of eyelid
7. Inability to move the eye in any or all the directions
8. Diminution of the vision
9. All the above there are very ominous signs (no. 4 to 7). This signifies the involvement of internal muscles and nerves of the eyes. In such a condition, the Eye cannot be preserved and it needs to be removed to save life.
10. Intense persistent headache
11. Paralysis
12. Epilepsy or Fits
13. These all are the signs of brain involvement by the fungus and are very dangerous (no. 8 to 10). This is an advanced disease now and the chances of survival in such conditions are very low, not more than 15%. If brain involvement is not much then aggressive surgical debridement can still help in saving the life.

Prevention Techniques:

What care can be taken to prevent post- covid mucormycosis?

- Since steroids and immunosuppressants are the mainstays of treatment in the inflammatory phase of covid (inflammatory phase generally starts at the end of 1st week of the disease, but can vary), not using them is not the option proven their life-saving benefit. However judicious use of these drugs is definitely warranted particularly in those patients who are diabetics and low on immunity due to any of the health conditions.
- Maintaining good personal and environmental hygiene during the covid illness is very much imperative.
- Checking your blood sugars during the covid illness, even when you are not diabetic, will help in the early detection of diabetes and will help in managing the blood sugars tightly during the steroid treatment if required. For this, your doctor can advise you to do blood tests for detecting diabetes namely fasting and Post-meal Blood Sugar levels and HbA1c levels.
- Avoid nose-picking. Nose packing can inoculate the invisible fungal spores stuck to the fingernails directly inside the nostril.
- Be highly suspicious of mucormycosis if you have any of the risk factors and symptoms as mentioned in the previous section. Consult your ENT as early as possible. Wasting the time

- here is like sitting on a ticking bomb as mucormycosis is a rapidly spreading fungal disease. Your ENT surgeon may perform a diagnostic nasal endoscopy and may ask you to do a CT scan and MRI for diagnosing the condition. Early diagnosed mucormycosis can still save a lot of lives and late diagnosis can be equally devastating.
- Doing regular saltwater gargles and nasal washes during and after the covid illness can be helpful as alkaline solutions halt the fungal growth to a certain extent. Also, it will help to wash away any minute fungal particles and other organisms if present in the nose. Sometimes doctors may advise you to do the nasal wash with dilute betadine solution.
- Do not take any regular over the counter antifungal medications just as a preventive measure for mucormycosis. This disease requires very specific antifungal medicines which are very costly and also have serious side effects. Some antifungal medications can actually do more harm than benefit by promoting mucor growth. Therefore don't self-medicate yourself and always consult your ENT when in doubt.

Proposed Ayurvedic Management of Mucormycosis:

The prognosis of mucormycosis usually depends upon the overall health of the patient, speed of diagnosis and treatment, the patient's ability to respond to treatment. So here in this paper some herbs are discussed which can be used in covid as well as post covid patients to improve immune status which will reduce the risk of further complications such as mucormycosis.

Nowadays, Viral and fungal infections are affecting human health disastrously. We have to give stress upon building immunity. Ayurveda has the unique concept of '**Rasayana**' which helps to increase the body's capacity to fight against such infections.

Use of steroids reduces the activity of the immune system, which is the body's natural defense against illness and infection. Ayurvedic treatment certainly helps in this condition. Ayurvedic drugs should be included in the management of covid and post covid as well as prophylaxis for the comorbid.

Here are some herbs having krumighna (antimicrobial), pramehaghna (antidiabetic), Rasayana (immunity booster).

NEEM : Azadirachta indica:

Figure No. 1: NEEM : Azadirachta indica.



Neem (*Azadirachta indica*) tree has attracted worldwide prominence owing to its wide range of medicinal properties. Neem leaf and its constituents have been demonstrated to exhibit immunomodulatory, anti-inflammatory, antihyperglycemic, antiulcer, antimalarial, antifungal, antibacterial, antioxidant, antimutagenic and anticarcinogenic properties.

Neem whole plant is extensively used in Ayurvedic System Medicine for various skin disorders and diabetes. Nature has served this plant with various organic Compounds that are used as insecticides and pesticides. Neem is a Major herb with anti-fungal, anti-bacterial ,anti-diabetic, anti-viral and anti-Helminthic Properties in Ayurveda.

Doses- Powder : 3-6 gm
Juice : 10-20ml.
Decoction : 20-50ml.

Some important uses as home remedies of Neem are :

1. Skin Disease - 10ml of juice of leaves with honey twice a day . It is advisable to take bath with water of boiled Neem leaves.
2. Wounds/Ulcer - Application of paste prepared from leaves of Neem on the affected part helps in healing of wounds/Ulcers.
3. Intestinal wounds - 20ml of Decoction made from handful of leaves should be given empty stomach for 3 days.

4. Loss of appetite - 20ml Decoction made from handful of leaves should be given empty stomach for 3 days.
5. Dandruff/ring worm - Decoction made from handful of leaves may be applied to scalp and affected area one hour before bath to alleviate dandruff.
6. Diabetics- 5gm dry leaves /fruit power with lukewarm water empty stomach twice in a day helps in certain cases of NIDDM (initial stages).

Vidanga -Emblia ribes:

Figure No.2: Vidanga -Emblia ribes



Vidanga, commonly known as false black pepper, has various medicinal properties and is used in various ayurvedic formulations.

Vidanga is generally used to expel worms and parasites from the stomach due to its anthelmintic properties. It is beneficial for indigestion and also helps to manage constipation due to its laxative property. Taking Vidanga churna regularly might help manage weight by lowering lipid levels and improving the metabolism of the body. It might also protect the heart against free cell damage by

free radicals due to its cardioprotective and antioxidant activities. Vidanga might also be useful in managing depression by improving mood as well as brain functions due to its antidepressant activity.

Other applications of vidanga :

1. Intestinal Worms-Vidanga is a useful herb to manage worm infestation that includes threadworms, roundworm and types of worms due to its Krimighna property.

Indigestion

Vidanga controls vomiting, nausea, indigestion, and flatulence due to its hot potency. It also helps manage constipation due to its Rechana (laxative) property.

Depression

Vidanga has an antidepressant effect which helps in managing depression due to its Vata balancing property.

Throat infection

Vidanga has Kapha pacifying property as a result of which it reduces cough and throat infection.

Obesity

Vidanga also works on reducing fat and clearing all toxins present in the body because of its hot potency that improves digestion and helps in the elimination of undigested foods.

Skin disease

Vidanga helps to control skin diseases by reducing toxins from the blood due to its Shodhan (purification) property.

Some important uses as home remedies of vidanga are :

1. Vidanga seed paste can be applied on the skin to help get rid of acne due to its antibacterial property.
2. You can also apply Vidanga seed paste along with rose water on the skin to improve your complexion[1-3].

3. Preparation of VIDANGA

Vidanga Seed Paste

- a. Take ½-1 teaspoon of Vidanga seed paste.
- b. Mix it with rose water and apply evenly on the skin.
- c. Let it sit for 5-7 minutes.
- d. Wash thoroughly with tap water.
- e. Use this remedy 1-2 times a week to improve your skin complexion.

4. Vidanga Seeds Powder

- a. Take ½-1 teaspoon of Vidanga seeds powder.
- b. Mix it with honey and apply evenly on the affected area.
- c. Let it sit for 7-10 minutes.

- d. Wash thoroughly with water.
- e. Use this remedy 2-3 times a week to get rid of skin diseases[3].

Karanja- Pongamia Pinnata:

Figure No 3 : Karanja -Pongamia Pinnata



Pongamia pinnata (Linn.), popularly known as Karanja or Indian Beech, is a medicinal plant known for its multitude of benefits. Its seeds contain about 28-34% oil with a high percentage of polyunsaturated fatty acids. *Pongamia* is rich in phenylated flavonoids. *Pongamia* seed oil contains a bioactive molecule known as karanjin. Six compounds (two sterols, three sterol derivatives and one disaccharide) and eight fatty acids (three saturated and five unsaturated) have also been isolated from the seeds of *Pongamia pinnata*.

Applications of karanja:

1. *Pongamia* is used for the treatment of various inflammatory and infectious diseases.
2. The antifungal and antibacterial activity of Karanja is attributed to Pongarotene, a rotenoid, and karanjin, a flavonol.
3. Karanja has traditionally been prescribed for cutaneous affections and vaginal discharge.
4. Wagh et al assessed the antifungal and antibacterial activity of *Pongamia* oil against *Aspergillus niger*, *A. fumigatus*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The oil exhibited high degree of antimycotic and antibacterial activity.
5. A study investigated the antibacterial activity of Karanj (*Pongamia pinnata*) and Neem (*Azadirachta indica*) seed oil *in vitro* against 14 strains of pathogenic bacteria. About 57.14% and 21.42% of the pathogens were inhibited at 500 microl/ml; 14.28% and 71.42% at 125 microl/ml; and 28.57% and 7.14% at

- 250 microl/ml of Karanj and Neem oils, respectively. Pongamia oil was found to have potential bactericidal activity. This could be attributed to the inhibition of cell-membrane synthesis in the bacteria.
6. Ujwal and colleagues evaluated the antimicrobial activity of Pongamia against *Bacillus subtilis*, *Escherichia coli*, *P. aeruginosa*, *S. aureus* and *Candida albicans*. Extracts of petroleum ether and ethyl acetate from seeds exhibited maximum inhibition zone on *Bacillus subtilis* while leaf extract of petroleum ether and ethyl acetate had comparable activity against *S. aureus*. The bark extract of petroleum ether exhibited a zone of inhibition on *Escherichia coli*.
 7. Bajpai et al² noted in their study that *P. pinnata* extracts exhibited potential antibacterial effect against *B. Subtilis* ATCC6633, *S. aureus* ATCC6538, *Listeria monocytogenes* ATCC19118, *L. monocytogenes* ATCC19166, *Pseudomonas aeruginosa* ATCC6432 and *Salmonella typhimurium* ATCC2512. The chloroform, ethyl acetate and methanol extracts exhibited significantly higher antibacterial activity as compared to streptomycin.
 8. Methanol extract of Pongamia has been found to cause moderate inhibition of *C. albicans* and significant inhibition of *C. tropicalis* fungal isolates.³ In an evaluation of antifungal activity of Pongamia pinnata extracts on *C. albicans* strains, the extracts were found to have significant anticandidal activity.⁸
 9. Pongamia extracts thus show potential antibacterial and antifungal effects and be used to manage infections caused by a range of bacteria and fungus.

Research gap & limitations of research:

Laboratory studies and Clinical trials are required to include these herbs in the covid management protocol.

Conclusion:

In conclusion, it should be noted that Mucormycosis is a potentially life-threatening fungal disease. It is devastating to the patient and family who is just about to recover from the bone-breaking COVID. The treatment can be mutilating and costly with some serious side effects. Good personal hygiene during and after the illness, tight control of blood sugar levels and, judicious use of steroids & immunosuppressant medications can prevent the disease. A high level of suspicions for the symptoms of mucormycosis particularly in the late phase of covid illness and even after recovery from covid infection can help in early diagnosis of the disease. Once the diagnosis of mucormycosis is made it is important not to waste the time in taking the call for the treatment as it is a very aggressive disease.

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