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COVID-19 Associated Pulmonary Aspergillosis (CAPA): A Narrative Review

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ABSTRACT

COVID-19 is pulmonary infection caused by Coronavirus, which result in inflammatory process in the lungs and lead to cytokine storm in the individual which finally results in immunocopromised patient and further the drugs (tocilizumab and steroids) used in the treatment of COVID-19 also suppress the immunity of the individual. This transient immuno compromised condition of the individual makes the secondary or supra added infection that might be either bacterial or fungal. One such fungal infection is COVID associated pulmonary aspergillosis. The cases of this deadly fungus are more found in the immuno compromised patients like who are severely ill and are admitted on intensive care unit and are on mechanical ventilation. The patients to get infected by this infection mostly by the 4^{th} day of the intensive care unit admission. Symptoms and signs of the infection are similar to that of COVID-19. Three grades have been proposed for this infection such as probable, possible and proven. Usage of corticosteroids, broad spectrum antibiotics used in the treatment of COVID-19 infection and presence of any other lung disease are the risk factor for the development of this infection. Symptoms and signs of the infection are similar to that of COVID-19. Early diagnosis with the help of various diagnostic procedures like culture, serum or broncho alveolar lavage fluid galactomannan levels and histopathological finding from biopsy is very useful for treating this infection and saving the life and reducing the mortality rate. Voriconazole and isavuconazole is the first line drug used in the treatment of this infection. Prevention is done by immunomodulation.

Key words: COVID-19, COVID associated pulmonary aspergillosis, Voriconazole, Galactomannan Immunomodulation, Isavuconazole

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INTRODUCTION

Coronavirus popularly known as COVID-19 declared a pandemic by who on 11 march 2020 [1]. Almost after 2.5 months of the first case which was reported in Wuhan, china on 31 December, 2019 [2]. In India, the first case was reported on 27 January, 2020 in Kerala. After the first case reported, this deadly disease was speeded all through the country and Maharashtra was the most affected state of India [3].

COVID-19 was presented as a viral pneumonia. Many complications are associated with COVID-19 in which one of the complications is "COVID-19 associated pulmonary aspergillosis" also known as CAPA. This is a superadded fungal infection associated with COVID-19. Many bacterial and fungal infections as a superadded infection are associated with COVID-19 as it is a viral pneumonia so it hampers the immunity of the individual which makes it easier for other organisms to take advantage of it. This deadly super infection has also increased the mortality rate and there was a significant rise in the mortality rate of the patients affected with the COVID associated pulmonary aspergillosis as compared to the patients who were not affected with COVID associated pulmonary aspergillosis.

The most common fungus or COVID-19 pulmonary aspergi llosis is *Aspergillus fumigatus*. Different grades of COVID associated pulmonary aspergillosis are:

- Probable COVID associated pulmonary aspergillosis.
- Possible COVID associated pulmonary aspergillosis.
- Proven COVID associated pulmonary aspergillosis.

LITERATURE REVIEW

Pathophysiology

COVID-19 is a viral disease that affects the lungs of the individual and it is a contagious disease, commonly spread through the aerosols of the infected patient if the healthy individual comes in the close contact of the infected individual.

Firstly, COVID-19 affects the epithelium of the lung and vandalise it, which makes this fungus to easily take the charge and produce it affects.

Secondly, the COVID-19 virus also hinders the function of respiratory cilia; it leads to improper clearance and thus leads to immune affliction.

Thirdly, the COVID-19 also leads to the dropping of T lymphocyte count and T lymphocyte cell plays a vital role in the immunity of the individual, so dropping down of T lymphocyte cell count leads to severe immune affliction and makes it very easy this deadly fungus to take the charge and produce its effects. So, all three effects are seen in the individual infected with COVID-19 infection and make the individual immuno compromised and make the easy pathway foe this deadly fungus to the charge and produce its affects [4].

Epidemiology

The prospective study was carried out at the various centres and it was found out that the incidence of COVID associated pulmonary aspergillosis was more in the severely ill patients who was requiring the need of mechanical ventilation. All individuals undergone through a screening test for CAPA with broncho alveolar lavage galactomannan and cultures were performed after the 7^{th} day of the admission in intensive care unit and in the patients who were progressively deteriorating and all were found positive for COVID associated pulmonary aspergillosis. The screening tests was done on many patients and out of them 27.8% were found to be infected with probable COVID associated pulmonary aspergillosis on the 4^{th} day out of the 7^{th} day of the intensive care unit admission. It was also noted that the mortality rate was also higher in the COVID associated pulmonary aspergillosis as compared to the one who were not infected with the COVID associated pulmonary aspergillosis. The positive point is that the individual infected with the COVID associated pulmonary aspergillosis and got treated with anti-fungal drug "variconazole" tends to have the lower mortality rate as compared to the one who are not treated with variconazole [5]. Risk factors in the development of COVID associated pulmonary aspergillosis in the general health condition of the individual, seasonal variations for the spread of aspergillosis spores, the early diagnosis of the condition and the immunity of the individual [6].

Risk factors: Risk factors involved in the development of COVID associated pulmonary aspergillosis are:

- The extent to which the COVID-19 has damaged it.
- The patients taking corticosteroids who were infected with COVID-19.
- The patients who were on broad spectrum antibiotics.
- The patient infected with any other structural lung disease [7].

Symptoms and signs

The symptoms and signs of COVID-19 and COVID associated pulmonary aspergillosis are same and it is very difficult to differentiate whether the individual is suffering from COVID-19 disease or has developed COVID associated pulmonary aspergillosis as its complication. Furthermore, the radiological appearance of individual infected with COVID-19 and COVID associated pulmonary aspergillosis is also same. In both of them we get the maundering infiltrates in both the lungs. It becomes very difficult for the physician to differentiate whether the individual has developed COVID associated pulmonary aspergillosis or it is a COVID-19 infection. So one cannot rely on just the clinical symptoms and the signs and has to do the definitive diagnostic procedure to confirm the development of COVID associated pulmonary aspergillosis as early as possible. It is mandatory to perform the definitive diagnostic test in an individual who is severely infected with COVID-19 and requiring mechanical ventilation admitted in intensive care unit for more than 7 days [8].

Diagnostic procedures: It is mandatory to do the diagnostic procedures as the clinical symptoms and signs resembles to that of COVID-19. So it becomes very difficult to distinguish and that could be done only by doing diagnostic procedures. The presence of COVID associated pulmonary aspergillosis in a patient of COVID-19 can be confirmed by:

- Culture of sterile site sample.
- Histopathological findings from biopsy.
- Serum galactomannan optical density index.

Galactomannan optical density index of the bronchoalveo lar lavage fluid/endotracheal aspirates. Samples that can be used to diagnose the COVID associated pulmonary aspergillosis are:

- Biopsy from lung.
- Serum.
- Broncho alveolar lavage fluid.
- Endotracheal aspirates.

Serum galactomannan has a low sensitivity in non-neutropenia patients. As the patients of COVID associated pulmonary aspergillosis are severely ill and are not stable haemodynamically, so the invasive procedures like bronchoscopy is very difficult to do in this patients. Further, there is a lot of risk to both patient and health worker doing bronchoscopy as it will generate aerosols so the spread of infection is possible which might put the life of health worker in danger. Till now the endotracheal aspirates are considered as the safest sample to be taken to diagnose the COVID associated pulmonary aspergillosis in COVID infected patient as it will not generate the aerosols, so the chances of spread of infection to health worker also decreases. There is also drawback in endotracheal aspirate sample as their use for galactomannan levels finding is not yet proven till now. Other is that culturing fungus from endotracheal aspirate sample gives the result as colonization only. New test which were found useful in early detection of COVID associated pulmonary aspergillosis is *Aspergillus* specific antigen found from the sample of endotracheal aspirate

in lateral flow assay. One more test can be performed for diagnosis but that is not specific for pulmonary aspergillosis but found positive in fungal infection, the test is detecting the levels of serum 1-3 Beta-D Glucan (BDG). *Aspergillus* DNA was also found in serum/ respiratory samples of the patient in which real time PCR was done.

The more practical approach in diagnosing the COVID associated pulmonary aspergillosis in COVID-19 infected patients is to combine >2 mycological criteria from the following:

- Detection of galactomannan from serum/broncho alveolar lavage fluid/endotracheal aspirates.
- Growth of *Aspergillus* SPP from sputum/ bronchoalveolar lavage fluid/endotracheal aspirates.
- Detection of BDG in serum.

Aspergillus DNA detection in blood or respiratory samples by real time PCR.

Treatment: Once the diagnosis of COVID associated pulmonary aspergillosis is confirmed as a superadded infection of COVID-19, then the anti-fungal therapy should be started stat. If there is delay in diagnosis or in starting of anti-fungal therapy, it may lead to the complications like multi organ failure, sepsis and finally the death. The first line therapy in the patients of COVID associated pulmonary aspergillosis is the triazoles like variconazole or isavuconazole. Challenges are coming in the way of treatment of COVID associated pulmonary aspergillosis like the patients are getting resistant to the triazoles treatment thus making it difficult to treat this deadly COVID-19 associated super infection, the reason behind this resistance is that the physicians are using structurally same compounds for the treatment of other fungal infections. To counter attack this resistance and make the treatment more effective and to increase the chances of survival, the COVID infected patient has to undergo Anti-Fungal Susceptibility Testing (AFST) either through one that is phenotypic or genotypic methods that will surely help in finding if the COVID infected patient is resistant to triazole treatment or not and will the patient will be benefitted by it as a proper definitive treatment for the COVID infected patients. The above mentioned genotypic testing that we do for determining resistance against the triazole works on principle of molecular assay and helps to depict *Aspergillus* species and its involved changes in chromosomal mutations linked with triazoles resistance straight away from the sample collected and it will be a very useful in the treatment of COVID associated pulmonary aspergillosis. It has been suggested that the area where resistance to triazole is more than 10%, we can use the combination therapy like voriconazole and echinocandins or voriconazole and liposomal amphotericin-B as the first line therapy. Major challenges were there to determine the prevalence of triazoles resistance, as no surveillance system is there in many countries to depict the triazoles resistance in *Aspergillus fumigatus* which is the most common cause of fungal super infection in COVID.

As this super added fungal infections is common in severely ill COVID patients admitted in intensive care unit and requiring mechanical ventilation so prophylaxis can be confirmed by giving aerosolised liposomal amphotericin B to all these patients in order to decrease the mortality and save the patient from this hazardous super added fungal infection. It is suggested to include the aerosolised liposomal amphotericin B in the treatment of the patients suffering from COVID-19 and admitted in intensive care unit and requiring mechanical ventilation for respiratory support. Precautionary diagnostic procedures can be done to find out the presence of COVID-19 associated pulmonary aspergillosis like screening of galactomannan levels in serum and broncho alveolar lavage fluid twice in a week. To counter attack the risk of COVID associated pulmonary aspergillosis, high efficiency particulate air filters were put on in the intensive care unit.

To overcome this deadly fungus, new anti-fungal agents with unique mechanism of action are in process to counter attack the issue of resistance to triazoles and to treat the invasive pulmonary aspergillosis. There are three anti-fungal drugs named:

- Ibrexafungerp
- Olorofim
- Fosmanogepix

Structurally, ibrexafungerp is similar to echinocandins, hampers the making of beta-1,3 glucan synthase and effective against *Aspergillus* species resistant to triazoles. Other two drugs named olorofim and fasmanogepix have other unique targets such as fungal dihydro orotate dehydrogenase, which is mandate enzyme in synthesis of fungal DNA and hampers the activity of gwt1 enzyme leading to deactivation of manno proteins modification, an integral component in maintaining the integrity of fungal cell wall. All these three agents are equally effective against the *Aspergillus* species involving *Aspergillus fumigatus* which is the most common cause of COVID associated pulmonary aspergillosis and counter attack the challenge of triazole resistance [9].

DISCUSSION

Prevention: It is important to prevent COVID associated pulmonary aspergillosis and for that we have to restore the immune homeostasis. For immune homeostasis we have to decrease the pathology linked with its increased inflammatory response and its side effects with it. Pulmonary aspergillosis is the result of immunosuppression and the drugs used in treatment of COVID-19 infection like toclizumab and steroids also leads to immunosuppression. A different pathway can be taken to restore immune response by restoring to the endogenous pathways of immunomodulation. In COVID-19 infection there is cytokine storm by the release of inflammatory cytokine like interleukin-1 as a result of damage to epithelium by the virus. There is release of interleukin-1 alpha and interleukin beta which will lead to the amplified response resulting in cytokine storm.

To overcome this we have to administer the patient with interleukin-1 antagonist and the drug for that is anakinra which is the recombinant version of interleukin-1 receptor antagonist and it is proven beneficial in COVID-19 infection. Anakinra is also proven beneficial in reducing the chances of secondary or superadded infection like pulmonary aspergillosis in the COVID-19 infected patients.

One another by which the immunomodulation can be done is by activating the aryl hydro carbon receptor, a xenobiotic receptor, which has shown positive result in modulation of immune response. Stimulation of aryl hydro carbon receptor leads to protection of mucosa by activating the synthesis of interleukin-22 and also increases the barrier function in the gut. It also works by the similar mechanism in the respiratory tract and protect the individual from the infection.

Another example by which the immunomodulation can be done is thymosin alpha-1, it is an endogenous thymic peptide with a good range of immuno modulatory activities and has the capacity to regulate immune response in a very good manner. It works by activating the indole amine 2,3-dioxygenase 1 pathway or by inducing the autophagy. The autophagy as the mechanism of action of thymosin alpha-1 is being more recognized as compared to the activation of indole amine 2,3-di oxygenise pathway [10].

Miscellaneous: Once the individual gets infected with COVID-19 infection, it causes the damage to the lung due to the replication of Coronavirus resulting in cytokine storm and initiation of inflammatory process. The lung gets severely damaged and the chances of secondary infections that might be bacterial or fungal increases. The chances of super added or secondary infections in immune competent host are less but the immune competent host infected with COVID-19 might be suffering from other co morbid conditions such as chronic obstructive pulmonary disease, diabetes, hypertension etc., but there is no link of supra added fungal infection in a host suffering from these comorbidities [11].

CONCLUSION

COVID associated pulmonary aspergillosis is a superadded infection in COVID-19 infection mainly found in the immune compromised patients who are on mechanical ventilation and are admitted in intensive care unit. Symptoms and signs of this infection is almost same as those of COVID-19 infection, so the diagnosis of this deadly supra added infection on the basis of clinical symptoms and signs is very difficult to make. Early diagnosis of this deadly fungus can lead to proper treatment of this infection and can save the life of the patient; otherwise if the diagnosis is delayed the death is inevitable. Diagnostic procedures which can be done to diagnose this infection are culture and histopathological finding from biopsy or sterile site sample. Samples used to diagnose this condition are serum, broncho alveolar lavage fluid and endotracheal aspirates. Levels of galactomannan in serum or broncho alveolar lavage fluid can also be useful in making the diagnosis of this deadly fungal infection. Voriconazole or isavuconazole which belong to triazole group of anti-fungal drugs can be given as the first line drug in these patients. In triazole resistant cases, combination therapy can be given such as voriconazole and echino candins or voriconazole and liposomal amphotericin B. To prevent this deadly fungus, we have to modulate the immune response as this infection is found more in immune compromised individuals. At last, we should avoid this infection as much as possible.

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