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Aspergillus fumigatus a major infectious cause of invasive aspergillosis: advances in pathogenesis

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ABSTRACT

Infections are at the increase all over the world. Bearing in mind that these infections do occur in both human and animals and infections are at the increase all over the world. So, it calls for the provision of better means of preventing if not cutting down the number of people that are infected in the various parts of the body. Therefore, before setting foot on these fields and seeking solutions to the infections, one needs to know the causes, the conditions and the affected areas. In this topic, the emphasis inclines to the causes of infections of aspergillosis and the conditions under which they affect the humans and animals. Aspergillosis is a disease that is associated with human and animals beings and its proponent is the Aspergillus fungi. The disease is a respiratory tract infection that is more specifically caused by the Aspergillus fumigatus species. This species is described to be in the form of spores and does reproduce through asexual means. Due to its high affinity for water, it is dispersed in a very fast manner when in the air. Therefore, in this paper, the causative agent (*Aspergillus fumigatus*) of aspergillosis; a disease or infection that attacks the human respiratory system and the disease itself is the area of focus.

KEYWORDS

Aspergillosis;
Infection;
Aspergillus fumigates;
Disease;
Human;
Animal.

INTRODUCTION

Aspergillus is considered to be a group of molds found in countries located in the Northern Hemisphere. The reason for existing largely in the northern hemisphere is because of the cold weather conditions. These conditions primarily occur in autumn and winter. Much of the northern hemisphere experiences these seasons nearly throughout the year. The fungi can cause illnesses to both humans and animals such as dogs though most people seem to be naturally immune in connection to these impressions[1]. In case the disease caused by these fungi occurs in humans, it takes several forms that may be very dangerous to the health of the patient. Hence, it starts from mild to an invasive form that has proved to be very challenging in terms of treatment.

This invasive form of the disease is termed as

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aspergillosis. *Aspergillus* has different specific fungi. They comprise of *Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger and Aspergillus penicillium*. The disease affects that respiratory system especially for those humans that are asthmatic. Its primary cause is *Aspergillus fumigatus*. Aspergillosis, on the other hand is an invasive untreatable form of fungi[2]. These fungi cause the disease on condition that the immune system is weak. Various human body parts are affected by the disease, but the most common parts infected are the lungs and the sinuses. The types of diseases caused by *Aspergillus* do differ in terms of allergy-type of illness and life-threatening frequent infections. The different types of aspergillum do include aspergillorma, chronic pulmonary aspergillosis, allergic broncho-pulmonary aspergillosis (ABPA), and invasive aspergillosis and Aspergillus sinusitis[3].

Types of aspergillosis

Aspergillorma and chronic pulmonary aspergillosis

In this disease, the spores of the fungus *Aspergillus fumigatus* are inhaled through the respiratory tract and grow within the cavity of the lung. The most vulnerable lung cavities are those that have been damaged before by lung diseases such as tuberculosis, asthma, and even sarcoidosis. On penetrating through the cavities, they reproduce and germinate on the holes[4]. During germination, the spores accumulate to form a fungal ball that is called aspergillorma. It majorly occurs in pits that had been caused before by a lung illness that left the cavities open. In some people, cavity openings in the lung and parts of the respiratory system are formed by Aspergillus, therefore, no possibility of a fungal ball developing in them. The person affected might fall sick or rather feel ill due to the allergic toxic products that the fungus secretes[2].

Allergic bronchopulmonary aspergillosis (ABPA)

It is a condition, whereby a person's respiratory tract develops an allergy to the spores of the fungus Aspergillus. Asthmatic patients and those that are TB positive are the most vulnerable people to allergies from the Aspergillus spores[1]. This aspergillosis disease attacks the patients as they reach adulthood. Worse enough, their symptoms are similar to those of asthma that makes it difficult to come up with findings on the actual condition to be treating after diagnosis. The symptoms include:

- Intermittent episodes of the patient feeling unwell whereby joints ache,
- Regular coughing and wheezing[2].

Invasive pulmonary aspergillosis

The fever of people with invasive aspergillosis together with disturbing coughs, breathlessness and pains inside the chest. These are symptoms of the diseaseIt does not respond in any way to common antibiotics that patients are administered with. The low count of the white blood cells that help in defending the body against bacteria is the major cause of this unresponsive behavior portrayed by patients of invasive aspergillosis[1].This condition is usually only diagnosed in bone marrow transplant patients, those that are following cancer treatment procedures, HIV/ AIDS patients and lastly those with chief burns cases. Another group categorized as being prone to this condition is the *chronic granulomatous disease* that is an inherited condition. Their risk of being infected though is moderate[5].

In order to make a diagnosis of invasive aspergillosis, one has to undergo Chest X-rays and CT scans that will enable the doctors to indicate possible abnormalities and help to locate the disease. Bronchoscopy is the process that refers to the inspection of the inside of the lung that is done through inserting a relatively small tube into the nose[6]. In addition to these methods of disease diagnosis, cultures and blood tests are recommended for absolute surety.

People with relatively feeble immune systems can be victims of attacks by the infections in the brain and other parts of the body. This scenario occurs when the fungus transfers its spores from the lung via the blood stream to the brain or to any other organs that the blood is carrying the fungus circulates[6]. These body parts are inclusive of the eye, the heart, the kidneys and the skin. In ordinary circumstances, this is an indication of a fatal circumstance as the situation gets more severe due to diseases in numerous body parts, and this makes the patient very ill. This condition is considered fatal at

this stage, and the best chance of survival for the patient is of performing an early diagnosis, thus an early treatment by applying anti-fungal drugs especially antibiotics[5].

Aspergillus sinusitis

Aspergillus disease can be diagnosed in the sinuses causing a disease named *Aspergillus sinusitis*. Just as in the lungs, Aspergillus causes the three diseases in the sinus[6].

- Allergic sinusitis,
- A fungal ball or
- Invasive sinus aspergillosis.

The fungal ball caused by Aspergillus occurs in a similar manner to that of an aspergillorma. The symptoms associated with this ball are stuffiness of the nose, intensive headaches or discomfort in the face[7]. Those with normal immune systems also experience the same symptoms.

On the other hand, patients possessing damaged immune systems are more prone to fatal deaths. The case applies to those that are affected by other ailments such as cancer or the ones that are operated on in order to receive a heart transplant. Casualties that die as a result of this fungus are one of the cases that the aspergillosis is declared to be a form of invasive aspergillosis in the sinusitis[8]. The disease's symptoms comprise of fever, pain in the face (facial pain), running nose and regular nasal discharge together with constant headaches. Performing scans of the fluid discharges and tissue that comes from the sinuses helps in quick identification of the aspergillosis sinusitis by the fungus that causes it.

The primary focus in this topic discussion is to have an insight of the particular fungus of Aspergillus that causes invasive aspergillosis in the lungs. Therefore, without a doubt as stated above the *Aspergillus fumigatus* is the topic of discussion here. Aspergillus fumigatus has been put into consideration as it has been found to be that most dangerous of all the other Aspergillus molds because of its fast formation of spores[7]. These spores are typically resistant to any antibody or lysis chemicals that the respiratory tract walls produce that aim at digesting intrusive objects; the spores. They further subdivide into globose and subglobose for easy maneuvering through the respiratory tract to the lungs and even the sinuses.

Aspergillus fumigates

Aspergillus fumigatus is one of the major species of *Aspergillus* that do bring about diseases to human beings[5]. Most of the human attacking diseases live within this mold that seems to be rampant and possesses a characteristic of stubbornness. The mold accounts for at least 85 percent of these diseases. It is an invasive mold that brings about infection through one inhaling conidia[9]. Furthermore, it's not identifiable when it is in the tissue of a person since it resembles the other pathogens available. Since its channel of contraction is through inhalation due to its high hydrophobicity, it e primary cause of *aspergillosis*.

In pathogenesis, it has been observed through feasible experiments that this mold disperses very fast at the slightest current of air. Its conidia, further enhances the mold's survivability by forming a melanin cell wall that prevents ultraviolet irradiations from the environment. It is considered to be the mildest in spore production since it compared to other aspergilli is more hydrophobic[9]. For this reason alone, one can readily accept that *Aspergillus fumigatus* can be quick in invading the respiratory system and causing the associated diseases; respiratory tract diseases. The air that humans breathe daily is accompanied by mass molecules of aerosols. Therefore, this accounts for the existence of this mold because it is part of these particles since its concentration indoors and the outside environment estimates at 91cm[8].

As mentioned early its cell wall is resistant to the host cells, protection chemicals released called lysis when they sense the mold's presence[8]. They also have a shape and spore size advantage over the respiratory tract; they assume shapes such as from globose to suglobose for easy navigation through the human respiratory tract. Considering that they are they change to smaller than they had dispersed before, their spore radius becomes even smaller than the original one[9]. The conclusion is; the fungal infection is dangerous and invasive thus bringing about severe respiratory tract complications.

Invasive aspergillosis life cycle

The life cycle of *Aspergillus* commences when

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conidia is produced that are subject to easy distribution into the air that we breath. Conidia are asexual spores that can comfortably survive in houses and outside environments as explained in adaptation. They grow up to form haploid mycelia, and they go on reproducing by creating foot cells again. This process further enhances asexual reproduction, and they increase in numbers. Their smooth dispersion into the air enables them to be available inside and outside structures[10]. Since they are ever present in the air, inhalation by human beings together with animals acts as the as the primary means of their introduction into the human respiratory system. Therefore, they cause airborne infections via their conidia.

Going back to the asexual cycle, we get information that haploid hyphae form foot cells that are projections off of the hyphae. The tip of the foot cell swells, leading to the formation of a conidiophores vesicle[10]. A series of mitotic budding occurs in this vesicle meaning that the end results are chains of haploid spores called conidia as mentioned above form. Secondary metabolites are produced in a different kind in terms of variety by A. *fumigatus,* and they include the mycotoxin, and *gliotoxin that enable it to survive for a considerably long time in its environment*[11]. *Its* fungi proliferate into moulds that are sometimes termed as colonies when the conditions under which they form are favorable. That is the period when mycotoxin levels increase at a high speeds. These mycotoxins' main function is to weaken host's immune and therefore do not help the fungi to grow nor develop[10]. They usually are very useful in their functioning, and they result in making a person the A. fumigatus has invaded fall ill and weaker. In addition, the mycotoxin, *gliotoxin*, possesses immunosuppressive characteristics. These symptoms cause apoptosis that is a condition of inactiveness of the defense cells. Some of the cells of the immune system are mentioned;

a) neutrophils,
b) eosinophils,
c) granulocytes,
d) macrophages, and
e) thymocytes.

This type of the Aspergillus species A. fumigatus is considered the most proficient gliotoxin producer among all the other pathogens. For this reason, it provides the largest platform for chronic and invasive infections caused by these moulds. After entering the respiratory organs and the sinuses, they deposit themselves on the alveolar spaces and the bronchioles, as well[12]. Antibodies fight them and kill them, but not fully in a healthy person's body. Mucociliary clearance removes the dead spores and conidia depositions. Conidial depositions now and then cleanse the lungs and respiratory tract. Those that escape this means encounter alveolar macrophages also known as phagocytes. The function of these primary resident phagocytes of the lung is to kill Aspergillus conidia and on encountering them they perform their purpose of killing as many spores as they can in the process of pyrolysis. Their other function lies in the subsequent initiation of pro-inflammatory response that in turn helps in recruiting of neutrophils[13].

These are nuclear cells that are polymorphic in nature, and they congest themselves in the site of infection. They at last infiltrate as they kill their targets; hyphae that had evaded phagocytes. A problem sometimes arises when a dysfunction occurs in the host defenses that combine with the fungal traits allowing Aspergillus fumigatus survive[13]. They further grow in the pulmonary arteries and veins. At this point, they can be moved through the blood stream. They travel through the heart, the kidney, the lymph nodes, sinuses pancreas and the liver. As discussed early in this paper, they affect these parts by causing inflammations that are the primary inhibitors to functionality of these parts. Whether the individual infected by these hyphae is healthy or unhealthy, there is a high probability of one experiencing dysfunction in the defense cells[13]. On compromising the defense cells of the invaded person, they are most likely to cause Invasive Aspergillosis (IA).

Pathology and the risks involved there of

The primary host's immunodeficiency's that are responsible for the increased risk of IA are neutropenia. The immunodeficiency's that are responsible for the increased exposure to infections such as invasive aspergillosis is neutropenia. When comparing the immuno-suppresion that offer protection by being induced, phagocytes fighting conidia together with corticosteroid-induced immunosuppressant, the

pathological consequences of IPA under these conditions do differ significantly[14]. The explanation is in the models created in the past discussing on human patients and animals. The most dominant risk factor is prolonged neutropenia that is Invasive Aspergillosis and is often the result of highly cytotoxic therapies. The models are used used for heart and kidney transplant patients or those with hematological diseases.

Cyclophosphamide interferes with cellular replication when it binds with a DNA-alkylation agent and in return depletes circulating white blood cells including neutrophils[14]. Inadequate numbers of inflammatory infiltrates affect the levels of inflammation despite the production of necrosis factor-alpha of tumor. Without the recovery of neutrophils, angioinvasion and dissemination to other organs via the blood occur.

A variety of non-neutropenic patients, most commonly those on corticosteroid therapy such as allergenic transplant patients are the most probable IPA patients[12]. The difference in the pathology of this disease they are suffering makes then the most vulnerable to IPA. Corticosteroids have significant consequences for phagocyte function. They include impairment of phagocytosis, phagocyte oxidative burst, production of cytokines, as well as, chemokines, and cellular migration[14].

The recruitment of neutrophils to the lung and helps prevent hyphal invasion, but also creates an inflammatory environment that results in tissue injury. The exacerbated inflammatory response results into death.

Importance of aspergillus species of pathogens

Besides, Aspergillus species containing very harmful pathogens to both humans and animals, it has also proved to be so helpful and beneficial to humans as the genus Aspergillus is used during biomedical and industrial activities[15]. A. indulines is both an essential fungal model system that is used in genetics and cell biology. On the other hand, A. niger that is a milder type of Aspergillus species is employed and widely exploited by the manufacturers in the process of fermentation. The end product is for the production is citric acid[11].

In the fermentation industry, the use of Aspergillus species is a very common aspect in countries that practice beverage production in large scale. In Japan, beverages that are consumed by majority of the population are subjected under the fermentation; A. *oryzae* is one of the components that are put into use to help in the process of fermenting these beverages[15]. Its application is also extended into the sauce production industry bearing in mind that these are the most valued fast foods and food additives. The other species are considered as harmful to the health of human beings that are already struggling with asthma, cancer and heart attacks. Just to mention some of these species comprise of A. terreus, and A. fumigates[16].

Treatment of invasive aspergillosis

IA can also occur in nonneutropenic critically ill patients that have the following diseases[15]:

- Chronic obstructive pulmonary disease,
- Long-term steroid therapy,
- Hepatic cirrhosis,
- Dialysis,
- Near drowning,
- Diabetes,
- Sepsis due to bacterial, viral, and
- Severe post sepsis immunoparalysis[17]

IPA's presence can only be confirmed by the Histopathology, but obtaining a lung biopsy still stand to be a challenge. In hematology patients, means have been obtained of performing strict diagnosis, and the criteria have worked out. IPA diagnoses in patients by observing and recording host factors and clinical signs into probing the possibility of diagnosing IPA in those who also exhibit *Aspergillus*-positive characteristics, as well as, Aspergillus galactomannan antigen[17]. Such a criterion may not be appropriate for immune competent critically ill patients; especially with those that have are nonspecific findings when considering the clinical signs together with a computerized tomography (CT). Indicators show that the galactomannan antigen lacks sensitivity. Unpleasant outcomes of IPA and the low sensitivity and specificity of diagnostic tests make patients receive medication based on a diagnosis of possible ailment. In the bone marrow transplant patients that also are victims of leukemia the infection of the pulmonary of undetermined etiology has a high

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probability of indicating IPA positivity unless other samples are carried out with patients of prolonged neutropenia[17].

In contrast with the point in the previous paragraph, an *Aspergillus*-positive respiratory specimen is immune competent that you cannot interpret. The patient's condition was worse during the experiment[16]. In both of these scenarios, IPA is an event that dreads, but IPA occurs in less than 1% of immune competent ICU patients. It is in comparison to about 25% of patients with acute leukemia and 10% of those suffering from bone marrow transplants. The reported figures of *Aspergillus*-positive respiratory specimens found in 1–2% of non-neutropenic mechanically ventilated patients. Of these patients, 80% of them are colonized which 20% are believed to have IPA[18].

Reports and results of a multicenter observational study that reached nearly to a thousand interviewees, portrayed that critically ill patients with *Aspergillus*-positive have end tracheal aspirate cultures. To discriminate and separate Aspergillus from IPA, and especially the respiratory tract colonization a clinical algorithm had to be discovered and applied. The conducted research is one of the largest taken from ICUs[18]. It is important not to ignore the outcomes and recommendations made from it.

ICU patients might not possess the host criteria that is necessary for carrying out samples' therefore, exhibiting nonspecific CT patterns. This is the cause of IPA and the other diseases associated conditions (bacterial infection, fluid overload and atelectasis). Serum galactomannan antigen essays are rarely of assistance in this case[3]. Hence, an explicit algorithm for critically ill patients should be formulated to curb delays in therapeutic overuse of the antifungal. The chief purpose of this algorithm is to keep track of the patients with *Aspergillus*-positive lower respiratory tract traits. In connection to that, they should be put under high-resolution CT and Bronchoscopy with BAL fluid analysis and cytology to look for hyphae that might be growing.

In a more interesting manner, this algorithm has the capability of discovering patients with possible IPA counts. When this algorithm is performed without neutropenia, the primary or secondary malignancy and chemotherapy-related immune-suppression, or steroid therapy does apply and can be employed. The point that has been stated last here carries more weight than any other because it highlights the probability of IPA occurring as a complication of post-sepsis immunoparalysis or severe acute respiratory distress syndrome (ARDS)[18].

Prominently, in a comprehensive perspective, the algorithm had a near to 70% specificity and positive predictive value. Sensitivity and negative predictive value recorded at 88%. Making observations from these figures, it may be more efficient when IPA includes in these tests than in diagnosing it[11]. Immunocompetent patients with *Aspergillus*-positive, an observation that kept repeating itself were the lower respiratory tract cultures and respiratory symptoms. They seemed to worsen the respiratory sufficiency, persistent fever, and nonspecific CT abnormalities, during the diagnosis of IPA that required a positive semi-quantitative BAL culture[19]. This process was to exclude bacterial growth and a cytological smear showing branching hyphae from the results since they never came out.

Considering the low specificity of the algorithm, the researchers preferred to perform experiments for both patients with hematology malignancies, as well as, those of immunocompetent ailments such as immune-suppression. Prospective studies are given the go ahead to verify and approve these diagnostic criteria in immune-competent patients[20]. The test is performed using either a binary endpoint. This endpoint comprises the determining of putative IPA by indicating a Yes/No. It can also be determined by putting into use the IPA score that has high scores. The model is conducted for better results, that is, IPA reported to be absent in the set samples. It is not clear for researchers to have room for suspicion as a result of the presence of IPA[18]. When most procedures are met that is host factors, clinical symptoms, CT patterns, and the absence of pneumonia, without *Aspergillus*-positive samples, IPA should also be counted to be present.

In an autopsy studies, up to an estimated 4% of uninspected patients that met their death in a tertiary-care hospital had IPA[19]. This proportion might probably be subject to an increase. The reason behind this increase is that therapeutic advances pro-

vide a platform for survivability for a variety of malignant diseases. Doctors that have experience show that IPA can occur in the absence of Aspergillus-positive respiratory samples. In addition to, casualties with hematological malignancies show experience that IPA can occur in the absence of Aspergillus-positive respiratory samples[20].

The steps operating and features of this algorithm should be looked in casualties with few entry criteria but not dependant on *Aspergillus*-positive lower respiratory tract specimen cultures.

Importantly, unlike hematology patients, patients that are immunocompetent and critically ill subjects who are under mechanical ventilation most assuredly a low IPA preference will be recorded (less than 0.5). Evidently, prophylactic or pre-emptive therapy cannot be trusted as an appropriate criterion in the diagnosis of IPA in these patients[1]. Instead, the algorithm developed needs prospectively to seek evaluation in immune-competent mechanically ventilated patients with and without considering the using Aspergillus-positive respiratory samples at baseline of performing the tests[17]. For studies conducted in the field of lung biopsy no clear indications of critically ill patients having any IPA cultures. Therefore, to come out with results that are more satisfactorily, the tests should include the use of acute lung injury. The lung injury should include etiology accompanied by new autopsy to determine the proportion of immunocompetent critically ill patients that are IPA positive[19]. As always it has been stated in the previous samples done above, the aspects of Aspergillus-positive respiratory samples that have IPA are more complicated and dangerous to the immune system.

CONCLUSION

As we have learned from this topic, it is at our best interest to understand the dangers associated with A. fumigatus. This fungus is very dangerous to the human beings especially to those that are affected by incurable diseases. The pathogen may result into weakening the immune system as well as destroying the white blood cells. Individuals who are immunosuppressive are very susceptible to invasive fumigates. It further leads to invasive pulmonary aspergillosis. The most efficient cure is to administer antibiotics to the human body right before further infection. The ability of the fungi to genetically change its strain can result in the weakening of antibiotics. Thus doctors may find it difficult to treat the disease if it progressively regenerates.

Aspergillum fumigatus is the most known agent of the aspergillosis in human beings. Especially in those that have a weak immune system. A. fumigatus reacts well at a temperature of 37ºCelcius and germinates faster than other species.

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