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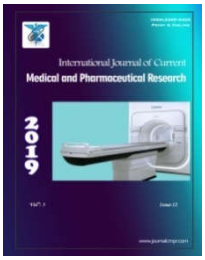

Research Article

"CHRONIC FIBROSING PULMONARY ASPERGILLOSIS A CAUSE OF "DESTROYED LUNG SYNDROME" AND THE MYSTERY OF ASPERGILLUS

Raghavendra Rao M.V[1*], Dilip Mathai[1], Vijay Kumar C[3] , Khizer Hussain Junaidy[2], Mahendra K.Verma[4], Badam Aruna Kumari[5], Mohammed Ismail Nizami[7] and Jithender Kumar Naik S[6]

[1]Department of Medicine, Apollo Institute of Medical Sciences and Research Institute, Jubilee Hills, Hyderabad, Telangana, India
[2]Department of Pharmacology,Gandhi Medical College, Secunderabad. Telangana, India
[3]Department of Pulmonology, Apollo Hospitals, Jubilee Hills, Hyderabad, Telangana, India
[4]Department of Biotechnology, Acharya Nagarjuna University, Guntur,AP,India
[5]Department of Respiratory Medicine, Apollo Institute of Medical sciences and Research, Hyderabad, TS, India
[6]Department of Zoology, University College of Science, Osmania University, Hyderabad, TS, India
[7]Department of Emergency Medicine NIMS, Punjagutta, Hyderabad, TS, India

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ABSTRACT

Aspergillus species constitute the second most common cause of hospital-acquired fungal infections after Candida. It may be seen up to 30% of patients with hematological malignancies A filamentous fungus, Aspergillus is omnipresent. It is found where ever organic debris occurs, especially in soil, decomposing plant matter, household dust, building materials some foods and water. It is almost impossible to avoid the daily inhalation of Aspergillus spores. "It's fairly uncommon, but still life-threatening,"

Aspergillosis is a disease caused by Aspergillus, a common mold that lives indoors and outdoors. Most people breathe in Aspergillus spores every day without getting sick. However, people with weakened immune systems or lung diseases are at a higher risk of developing health problems due to Aspergillus.

Allergic Bronchopulmonary Aspergillosis is a result of an immune reaction to the colonization of Aspergillus fumigatus within the airways of patients. "Invasive Pulmonary Aspergillosis-mimicking Tuberculosis". "Chronic fibrosing pulmonary aspergillosis: a cause of 'destroyed lung' syndrome"

INTRODUCTION

Aspergillus species are filamentous fungi that are commonly found in soil, decaying vegetation, and seeds and grains, where they thrive as saprophytes. *Aspergillus* species can be occasionally harmful to humans.(1)

Most *Aspergillus* species are found in a wide variety of environments and substrates on the Earth throughout the year.(2)

In humans, *Aspergillus fumigatus* is the most common and life-threatening airborne opportunistic fungal pathogen, which is particularly important among immunocompromised hosts (3) In normal host lungs, inhaled conidia are cleared by epithelial cells and alveolar macrophages. Conidia escaping these host defenses may germinate into branching filaments called hyphae, which is when Aspergillus becomes invasive. Inflammatory mediators released by alveolar macrophages lead to the recruitment of neutrophils, which can eliminate the hyphae (4)

The presence of numerous glycosylhydrolases and a group of extracellular proteinases in the *A. fumigatus* genome attest to the ability of the fungus to grow by the degradation of polysaccharides from plant cell walls and acquire nitrogen sources made available by the degradation of proteinaceous substrates (5)

The *A. fumigatus* genome is also rich in specific enzymes such as catalases, superoxide dismutases, and glutathione transferases for the detoxification of reactive oxygen species (ROS) (6) Fungal infections are not common in normal healthy persons; however, in the immunocompromised patients (ICP), opportunistic fungi can cause fatal infections.(7)

Corresponding author:* **Raghavendra Rao M.V
Department of Medicine, Apollo Institute of Medical Sciences and Research Institute,Jubilee Hills, Hyderabad, Telangana, India

Fungal can cause invasive infections in ICP when they invade the mucosal tissues. The ICP patients such as hematologic malignancies, aplastic anemia, Diabetes mellitus, AIDS, patients on chemotherapy, steroids, and organ transplantation (8)

The most common fungi which invade mucosal tissues including species like Aspergillus, Rhizopus, Mucor, Absidia and Rhizomucor. However, Bipolaris and Fusarium are less common. Fungi can reach to the sinonasal cavities by spores inhalation(9)

Filamentous saprophyte fungi have a wide distribution in nature, and their spore is abundant in the air and the transmission of infection occurs always through inhalation(10)

The extensive use of antibiotics and steroids has recently caused a widespread prevalence of fungal pulmonary infection. Some factors such as immunodeficiency, chronic diseases, malignancy are involved in worsening the diseases and these fungal pulmonary infections may be formed primary and secondary in TB infection (11)

Because the symptoms of chronic pulmonary aspergillosis are very similar to TB symptoms that physician often misdiagnoses it, unfortunately, the infection can grow steadily and undetectable for years, and its treatment is too late successfully. Therefore, timely diagnosis of fungal diseases is of great importance in treating patients (12)

Invasive aspergillosis (IA) is a life-threatening mycosis predominantly caused by *Aspergillus fumigatus*.Triazole antifungal drugs represent the first line of therapy. Azole blocks the ergosterol biosynthesis pathway via the inhibition of the *cyp* 51 A(ERG11) gene, which encodes the enzyme responsible for converting lanosterol to ergosterol (13)

Alterations in the *cyp* 51 A gene leading to amino acid substitutions in the target enzyme 14-alfa lanosterol demethylase are considered the primary mechanisms leading to azole resistance (14,15)

Since the early description of itraconazole-resistant Aspergillus fumigatus in 1997 in California, Azole resistance in A.fumigatus is increasingly observed worldwide and in various clinical contexts. The most recognized resistance mechanism involves mutations in the *cyp* 51 A gene that encodes for lanosterol 14-alfa-demethylase (16)

Because azole resistance could be associated with treatment failure, experts recently recommended the use of liposomal amphotericin B or a combination of voriconazole plus an echinocandin for the treatment of invasive aspergillosis in regions with a high resistance rate (less than 10%)or azole-resistance invasive aspergillosis (17,18)

Invasive fungal infections (IFI) caused by the mold of the genus *Aspergillus* are an important cause of morbidity and mortality in immunocompromised children, mainly including those with cancer or those who had to undergo hematopoietic stem cell transplantation (HSCT) (19)

A. fumigatus seems to be the most common species isolated in pulmonary infections, while *A. flavus* is predominantly found in skin infections (20)

Invasive aspergillosis (IA) is an increasingly common and fatal opportunistic fungal infection in patients with hematological diseases.Early diagnosis is difficult as mycological culture techniques have low sensitivity and the radio-logical tools have low specificity Galactomannon enzyme immunoassay (GEL) detects galactomannon in the human serum with a reported sensitivity and specificity between 30% and 100%.(21)

Invasive Aspergillosis(IA) is an increasingly common and often fatal opportunistic fungal infection inpatients with hematological disease due to the growing use of high dose chemotherapy and powerful immunosuppressive agents (22)

Galactmannan (GM) is a polysaccharide cell wall component released by Aspergillus hyphae during growth (23)

Galactomannon (GM),being water soluble carbohydrate can be detected in several body fluids (24)

Discovery of Aspergillus as a Human Pathogen

Aspergillus was named by Pier Antonio Micheli, an Italian priest, and biologist in 1729 when cataloging molds. Andral and Gavarret in 1843 and Mayer in 1844 first described fungal infections of the external auditory canal and subsequently Virchow suggested the term ‘otomycosis’. In 1851, Pacini was the first to describe a preparation for the treatment of otomycosis.(25) The histopathological findings of otomycosis were further elaborated by Vennewald *et al* 2002.(26)
How fungus can cripple your immune system?

Life threatening fungal infections have risen sharply in recent years, owing to the advances and intensity of medical care that may blunt immunity in patients. This emerging crisis has created the growing need to clarify immune defence mechanisms against fungi with the ultimate goal of therapeutic intervention.(27)

Mice inhalation of A*spergillus fumigatus* leads to a rapid increase in philosophic numbers in the spleen and blood but also in the lung (28)

This increase is IL-3 dependent.IL-3 is important for the recruitment of basophil into mediastinal lymph nodes following *Nippostrongylus basiliensis* infection.(29)

These insights create a foundation for the development of new immune-based strategies for prevention or enhanced clearance of fungal diseases.(30)

These experiments of nature offer a unique opportunity for developing new knowledge in immunological research and for devising immune-based therapeutic approaches for patients infected with fungal pathogens (31).

About Frontiers Aspergillus Research

Several immunotherapeutics and vaccines are in development to address this need, although one has yet to reach the clinic.(32)

Rapid Detection of Resistance

Resistance may be encountered in the antifungal drug-exposed or drug-naive patients and is particularly challenging when it concerns mycoses with acquired resistance that cannot be predicted from the species identification itself Owing to the expanding spectrum of causative agents, fast and accurate pathogen detection systems are necessary to identify resistant organisms (33)

Biotechnology for Molecular Diagnosis of Aspergillosis

10% KOH preparation of sputum, bronchoalveolar lavage, transbronchial biopsy, and other biopsies reveal non-pigmented septate hyphae,3-5 micro m in diameter with characteristic dichotomous branching at 45 degrees angles. The hyphae have a tendency to branch repeatedly. In a majority of pulmonary and disseminated lesions, only hyphal forms are seen.In allergic aspergillosis, there is usually abundant fungus in the sputum and mycelial plugs may be present. In aspergilloma, fungus may be difficult to find in sputum. In invasive aspergillosis, sputum smear often negative. The most reliable method for the diagnosis of acute invasive aspergillosis is the examination of stained tissue sections.

The morphology of Aspergillus is fairly characteristic, usually demonstrating nonpigmented, narrow, septate hyphae with acute angle branching. The histological section can be stained with hematoxylin and eosin(H&E) and Gomori methenamine silver(GMS) and examined for characteristic hyphae.In chronic lesions, short, distorted hyphae may be as wide as 12 mico m. Conidial heads may occasionally form in areas exposed to air.eg in pulmonary cavities and ear or skin infections.

Invasive aspergillus pneumonia, Galactomannan ELISA may be positive in the blood very early, prior to clinical suspicion of invasive fungal infection. Serological testing for antibodies to *Aspergillus* antigens is helpful to diagnose aspergilloma. or allergic bronchopulmonary aspergillosis in immunocompetent individuals, but unfortunately serology plays a little role for diagnosis in the immunocompromised patient because of *Aspergillus* growth does not correlate with an increase in anti- Aspergillus antibody titer (34)

Galactomannan (GM) is a major cell wall component of *Aspergillus* and it is known that the highest concentrations of GM are released in the terminal phases of the disease. An ELISA technique was introduced using a rat anti-GM monoclonal antibodies,EB-A2, which recognizes 1---5 Beta-D-Galactio furanoside side chains of the GM molecule (35)

This sandwich ELISA technique is used in current commercially available GM assay for the diagnosis of IA. In a meta-analysis conducted to characterize the clinical utility of GM assay,27 standing were identified and overall the GM assay had a sensitivity of 71 % and a specificity of 89% for proven cases of IA as defined by the specific clinical criteria (36)

Unfortunately, the GM assay has decreased sensitivity in the setting of a patient receiving Aspergillus antifungals, although specificity for detection does not change (37)

The sensitivity increases markedly when BAL fluid is tested instead of the patient's serum.false-positive results may be obtained in patients receiving piperacillin-tazobactam antibiotics or plasmalyte intravenous fluids. Beta-glucan testing is also helpful in diagnosing invasive aspergillosisThis is found to be comparable or more sensitive than galactomannan assays. False-positive results with beta-glucan assays have been observed in patients who were receiving fungal derived antibiotics. Sometimes false-positives may be noted with *Pseudomonas aerusinosa* infections. Perimonitoring of the galactomannan polymerase chain reaction is also useful. These assays are more sensitive than Enzyme immunoassays and latex agglutination techniques.
Radiological manifestations include nodular shadows, patchy infiltrates, cavitating lesions are the common findings on the chest radiograph. Computed tomography (CT) scan is useful in the evaluation of non-specific infiltrates in immunocompromised patients It is imperative to achieve an early diagnosis in order to avoid the development of long-standing complications and to reduce the mortality rates as much as possible. The ' halo sign' on CT is now regarded as an early indicator of invasive pulmonary Aspergillosis.(38)

The Need of New Anti fungal Agents

Potential pharmacological strategies include the use of (i) new formulations of antifungals, such as liposomal amphotericin B, amphotericin B lipid complex, amphotericin B colloidal dispersion, amphotericin B into a lipid nanosphere formulation, itraconazole, and **β**-cyclodextrin itraconazole or (ii) combination therapies of one or more antifungal compounds, for example, amphotericin B + flucytosine, fluconazole + flucytosine, amphotericin B + fluconazole, caspofungin + liposomal amphotericin B, and caspofungin + fluconazole

"Invasive Pulmonary Aspergillosis-mimicking Tuberculosis"

Aspergilloma,a fungal ball grows within and is usually restricted to an exiting lung cavity, for example,old tuberculosis or bronchiectasis.In this type colonizing *Aspergillosis* surgical removal becomes necessary as the disease commonly causes massive hemoptysis. In invasive Aspergillosis, fungus first causes pneumonia and later disseminates to involve other organs. Eg, the brain,kidney,or heart. Patient who develop this type of disease which may be fatal are usually immunocompromised or debilitated due to prolonged treatment with antibiotics,steroids and cytotoxic drugs. Obstructive bronchial aspergillosis usually occurs in the setting of underlying pulmonary disease such as cystic fibrosis,chronic bronchitis or bronchiectasis.The colonization of old fibrocavitary disease(eg.area of bronchiectasis due to healed tuberculosis or sarcoidosis,emphysematous bullae) by Aspergillus is the most common cause of a pulmonary fungus ball. Aspergillus fungus balls show heterogenous staining intensity on H&E stain. giving the impression of alternating zones of growth. The wall of fungus ball frequently shows increased number of tissue eosinophils.The walls of the cavity are lined with granulation tissue,granulomatous inflammation or metaplastic squamous epithelium depending on the activity of the disease (39)

Rapid expansion of a cavity is due to vascular thrombosis induced by a variety of Aspergillus species and most commonly Aspergillus niger. "Chronic fibrosing pulmonary aspergillosis: a cause of 'destroyed lung' syndrome" This condition is masked by the formation of bronchial casts or plugs composed of hyphal elements and mucinous material.

Treatment

Possible interactions with other drugs must be considered before Azoles are prescribed. In addition,plasma azole concentrations vary substantially from one patient to another,and many authorities recommend monitoring levels to ensure that drug concentrations are adequate,but not excessive,especially withitraconazole and voriconazole.Initial

IV administration is preferred for acute invasive aspergillosis and oral administration for all other diseases that require anti fungal therapy.(40)

Treatment of chronic necrotizing pulmonary aspergillosis (CNPA) and invasive aspergillosis differs significantly from treatment of allergic bronchopulmonary aspergillosis (ABPA) and aspergilloma Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction that requires treatment with oral corticosteroids. Inhaled steroids are not effective (41) Few studies have evaluated treatment options for chronic pulmonary aspergillosis (CPA), where long-term oral itraconazole or voriconazole remain the treatment of choice. (42)

Side Effects

All anti fungal drugs can have serious side effects, including kidney and liver damage.

The adverse effects of azoles are primarily related to their ability to inhibit mammalian cytochrome P450 enzymes. Ketoconazole is the most toxic, and therapeutic doses may inhibit the synthesis of testosterone and cortisol, which may cause a variety of reversible effects such as gynecomastia, decreased libido,impotence, menstrual irregularity and occasionally adrenal insufficiency. Fluconazole and itraconazole at recommended therapeutic doses do not cause significant impairment of mammalian steroidogenisis. All anti fungal azoles can cause both asymptomatic elevations in LFT and rare cases of hepatitis. Voriconazole causes reversible visual impairment in about 30% of patients.Since anti fungal azoles interact with P450 enzymes that are also responsible for drug metabolism, some important drug interactions occur. Increased antifungal azole concentrations can be seen when isoniazid, phenetoin or rifampin is used.

New and Future Developments in Microbial Biotechnology and Bio engineering

Many species of **Aspergillus** have economic importance ranging from harmful to beneficial effects. Their beneficial effects involve their use in industrial production of enzymes, therapeutic molecules like lovastatin, etc., and their harmful effects include them being the causative agents of diseases (aspergillosis, allergic reactions, etc.). Nevertheless, they are found to be the producers of several bio-active metabolites which include many anticancer compounds (43)

Control

Aspergillus species are the most common causes of invasive mold infections in immune compromised persons.

The available information regarding the rising incidence of invasive aspergillosis in different high-risk groups, including persons with acute leukemia, hematopoietic stem cell transplant recipients, and liver and lung transplant recipients. Molecular strain typing and other studies indicate that a significant number of Aspergillus infections are now being acquired outside the health care setting, either before patients are admitted to hospital, or after they have been discharged.(44)

Persons with high risk of allergic disease or invasive aspergillosis, efforts are made to avoid exposure to the conidia of *Aspergillus species*. Most bone marrow transplant units employ filtered air conditioning systems, monitor airborne contaminants in patients rooms, reduce visiting and other measures to isolate patients and minimize their risk of exposure to the Aspergillus and other molds. Some patients at risk for invasive aspergillosis are given prophylactic low dose amphotericin -B or itraconazole.

CONCLUSION

Infections caused by *Aspergillus* spp. remain associated with high morbidity and mortality. (45) or patients who receive biological therapies, such as tumor necrosis factor-α inhibitors, and new small molecule kinase inhibitors, such as ibrutinib (46)

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