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Review Article

Pulmonary fungal infections

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ABSTRACT

Fungi are a major pathogen not only in critically ill patients in intensive care units but also in immunocompromised hosts or susceptible hosts. Susceptible hosts are increasing continuously in the present era of organ transplants, biologic immune suppressant agents for inflammatory conditions, and widespread use of prophylactic antimicrobial regimens in various immune suppressed hosts. Larger use of broad spectrum antibiotics in critical care setting leads to fungal overgrowth syndrome and infections. Literature strongly indicates that the clinician must remain vigilant for invasive and serious fungal lung infections and expand diagnostic consideration, even to individuals who were once considered only moderately immunocompromised.

Emergence of various fungi as deadly bugs in ever increasing subset of patients with compromised immunity is a matter of concern. Preventive measures are of limited use, as most fungi are ubiquitous in environment and enter through inhalation. Early suspicion and aggressive treatment in the susceptible host is the only answer to these newer enemies. In this review, we discuss the opportunistic and endemic fungi, their disease process, evaluation, and treatment options. The newer treatment modalities and surgical approach where applicable are discussed here.

1. Introduction

Lungs are the target organ of many infective agents and fungi are one of them. Fungal lung infections, though less common than bacterial or viral infections, have a serious impact on patients' morbidity and mortality. In the era of a boom in therapy for oncology and extensive use of immunosuppressive therapies, not only in cancer patients but also for organ transplant patients,[1] various fungi find a place to act and assert. Use of biological agents, as tumor necrosis factor inhibitors and other agents, significantly increases the number of susceptible hosts. These fungal infections are a real challenge not only in terms of making definitive diagnosis but also for treatment.

Recently, we have seen an improving understanding of fungal cell wall and cell membrane structure and development of molecular epidemiological techniques. This has led to better and quick diagnosis and arrival of newer antifungal agents like Echinocandins, such as Anadulafungin, Mycafungin, and new azoles like Voriconazole and Posaconazole. This has also been instrumental in the development of antigen-based diagnostic tests for Aspergillus, Histoplasma, etc. in relevant samples as blood, sputum, urine, and bronchoalveolar lavage (BAL). Their

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specificity and sensitivity is better over antibody detection tests as antibody response is poor in immunocompromised hosts.

1.1. *Changing epidemiology of fungal lung infections*

Fungi are a major pathogen not only in critically ill patients in intensive care units but also in non-critically ill immunocompromised hosts or susceptible hosts. The number of susceptible hosts are increasing exponentially in the present era of organ transplants, biologic immune suppressive agents for inflammatory conditions, and widespread use of prophylactic antimicrobial regimens in various immune suppressed hosts. Larger use of broad spectrum antibiotics in critical care setting leads to fungal overgrowth syndrome and infections. Literature strongly indicates that the clinician must remain vigilant for invasive and serious fungal lung infections and expand diagnostic consideration, even to individuals who were once considered only moderately immunocompromised.[2]

1.2. *What are the common culprits?*

Fungi are a small part of the large plant kingdom that survives on decaying organic matter. Out of a large number of species, only a few pose threats to human health. Fungi, affecting human lungs, can be divided as (a) opportunistic invaders; (b) endemic invaders.

Opportunistic invaders most commonly seen are *Aspergillus, Candida sp, Cryptococcus*, etc. These are mostly seen in immunocompromised hosts and in individuals with diseased or scarred lungs. Less virulent fungi like *Tricosporon, Fusarium, Alternaria, Pseudallescheria*, and dematiaceous fungi are also being recognized more frequently as the disease-causing pathogens today.

Endemic fungi are specifically seen in a restricted geographic area based on environment and other factors that favors their growth in that soil. For example, Histoplasmosis and Blastomycosis are mostly seen in Ohio and Mississippi river valleys whereas Coccidioidomycosis is seen in Southwest United States Desert area. Endemic fungi *Penicillium marneffei* is seen mostly in Manipur state of India.

Opportunistic fungi	Endemic fungi
Aspergillus	Histoplasmosis
Candida	Blastomycosis
Cryptococcus	Coccidiomycosis
Mucormycosis	
Fusarium	
Scedosporium sp	

2. Major opportunistic mycosis

2.1. *Aspergillus in lungs*

Aspergillus is a universal saprophytic fungus important for recycling of carbon and nitrogen. It has high sporulating capacity and its conidia has a diameter of 2–3 μm (can easily reach lung alveoli). These conidias can be easily eliminated in an immunocompetent host but not so in a person with faulty immune functions. There are approx. 200 species of this mold; however, only 20 are pathogenic to humans. *Aspergillus fumigatus* is the most common of the identified species but others are *Aspergillus flavus, Aspergillus niger, Aspergillus terrus, and Aspergillus nidulans*. It has been noted that *A. fumigatus* is virtually always the cause of allergic pulmonary disease.[3] Microbiologically, these are identified by examining spore bearing structures and appearance of the colony. These produce 4–6 μm wide hyphae with parallel walls and distinct septa and dichotomous branching occurring at 45°.

Disease profile of Aspergillus is decided by the individuals' immunity rather than the mold. In a normal healthy individual, Aspergillus in sputum or BAL is a mere colonizer and not infectious. In patients with a history of Atopy, Aspergillus can cause

1. Allergic rhinitis
2. Bronchial asthma
3. Hypersensitivity pneumonitis and
4. Allergic bronchopulmonary aspergillosis (ABPA).

Patients with lung cavities can develop Aspergilloma due to saprophytic growth of Aspergillus sp.

The invasive form of Aspergillus is the hyphae and in immunocompromised host conidia germinate into hyphae and cause fatal infections. There is also a wide spectrum of invasive forms: acute, subacute (seen in patients with Acquired immunodeficiency syndrome or chronic granulomatous disease), and chronic. The degree of invasion, response to therapy, and final outcome of invasion is guided by the severity and type of immunodeficiency.

The first case of invasive aspergillosis was described in 1940, and since then it has emerged as a major threat to life in severely immunocompromised hosts with Leukemia and hematopoietic stem cell transplants (HSCTs) with a mortality as high as 70–90%. *A. fumigatus* followed by *A. flavus* are the most commonly found species. *A. niger*, usually found in respiratory tract secretions, is a commensal. *A. terrus* is a serious problem due to its inherent resistance to amphotericin B, and *A. ustusis* is resistant to many azoles and amphotericin B.

The patient usually has fever, cough, chest pain, hemoptysis, and other symptoms based on the site of dissemination (dissemination more common in hematological malignancy).[4]

Radiology has evolved over the past decades and features suggestive of invasive aspergillosis, specially in neutropenic patients, are well recognized. Halo sign (nodules surrounded by ground glass haze) and air crescent signs due to cavitation of nodes are now hallmark of invasive fungal infection on CT scans of hematological malignancy patients. Lung transplant recipients differ from the above-mentioned class and more commonly have non-specific patchy infiltrates and consolidation.[5]

Diagnosis of invasive pulmonary aspergillosis is a big challenge as initial clinical and radiological picture is non-specific. Development of Galactomannan assays (Galactomannan being a polysaccharide cell wall component) in the past decade by an enzyme immunoassay (EIA) method in serum