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Review Article

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SYSTEMIC INFECTION AND RELATED FUNGUS: AN OVERVIEW

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ABSTRACT
A fungus is a member of a large group of eukaryotic organisms that includes microorganisms such as yeasts and molds (British English: moulds), as well as the more familiar mushrooms. These organisms are classified as a kingdom, Fungi, which are separate from plants, animals, and bacteria. One major difference is that fungal cells have cell walls that contain chitin, unlike the cell walls of plants, which contain cellulose. Many fungi play a crucial role in decomposition (breaking things down) and returning nutrients to the soil. They are also used in medicine, an example is the antibiotic penicillin, as well as in industry and food preparation. In the present time the microbes are to be seen as disease causing organisms harming the mankind. The harm done by this community cannot be taken lightly as they are also useful in many ways. The above article is an effort to bring out the various fungal issued related to human.

KEYWORDS: Systematic infection, Fungal infection, Fungus, Meningitis.

INTRODUCTION

Fungi are considered to be low virulence organisms that generally cause opportunistic infection when the host's defenses are lowered. A fungus is a member of a large group of eukaryotic organisms that includes microorganisms such as yeasts and molds, as well as the more familiar mushrooms. This term can be used for all members of the Kingdom Fungi. Fungi are small, generally microscopic, eukaryotic, usually filamentous, branched, spore-bearing organisms that lack chlorophyll and have cell walls that contain chitin, cellulose, or both. They are heterotrophic and require a preformed organic source (i.e., they are not able to make their own food). When used as a common term, "fungus" can be used to include a mold, mildew, rust, smut, mushroom, or yeast[1].

Classification

Fungi are eukaryotic unicellular or multicellular organisms with absorptive nutrition and have been classified traditionally as members of the plant kingdom. More recently, a separate kingdom, Fungi was established for them, although species historically considered fungi are currently distributed among several kingdoms. Traditionally, fungal life cycles have been divided into perfect (sexual) and imperfect (asexual) states, depending upon the spore type produced. Current terminology refers to these states as the teleomorph and anamorph, respectively, which together are a holomorph. Conidium (plural, conidia) is a term used for an externally borne asexual spore produced by anamorphs of filamentous fungi. Some filamentous fungi predominantly or exclusively produce conidia rather than sexual spores. These have been referred to as Fungi Imperfecti or deuteromycetes but are termed anamorphic fungi in this review. Most of the species, including all those currently recognized as allergens, are ascomycetes. The species of fungi that produce airborne spores can be found within the divisions Dikaryomycota (ascomycetes and basidiomycetes), Zygomycota, and Oomycota (order Peronosporales)[2].

Fungal Infection

Fungi grow almost everywhere, even as lichens inside Antarctic rocks. Fungi grow over a wide temperature range (25°C to 508°C and greater), although individual species usually grow within a much narrower range. One of the most important physical parameters affecting fungal growth is moisture. Fungi cause a number of infectious diseases. These range from superficial skin lesions primarily of cosmetic concern to potentially fatal systemic mycoses.

Fungal infections or mycoses are classified depending on the degree of tissue involvement and mode of entry into the host. These are

- Superficial - localized to the skin, the hair, and the nails.
- Subcutaneous - Infection confined to the dermis, subcutaneous tissue or adjacent structures.
- Systemic - Deep infections of the internal organs.
- Opportunistic - cause infection only in the immunocompromised[3-5].

Systemic Fungal Infection

These are invasive infections of the internal organs with the organism gaining entry by the lungs, gastrointestinal tract or through intravenous lines. They may be caused by:

(i) Primary pathogenic fungi
(ii) By opportunistic fungi that are of marginal pathogenicity but can infect the immune compromised host[6,7].

Epidemiology of systemic infection via fungus

The epidemiology of systemic fungal diseases has evolved rapidly over the past 2 decades. Advances in medical treatment have led to improved survival in the general population, but these advances have also led to larger numbers of individuals (including those who have indwelling catheters, who are in intensive care, who have received various immunosuppressive therapies, and who are undergoing organ or stem cell transplantation) being at risk for fungal infection. The global human immunodeficiency virus (HIV) pandemic has led to unprecedented numbers of opportunistic fungal infections, including candidiasis, cryptococcosis, histoplasmosis, and penicilliosis. While the numbers have dropped dramatically in developed nations, many countries in sub-Saharan Africa and parts of Asia remain highly affected by these and other fungal diseases. Migration patterns, land use, and climate factors are thought to have contributed to a marked increase in the incidence of coccidioidomycosis in the endemic areas of the southwestern USA and in the emergence of *Cryptococcus gattii* infections in British Columbia, Canada, and the Pacific northwestern USA. This chapter will focus on public health aspects of systemic fungal diseases. It will discuss principles of epidemiology, risk factors, and prevention of infection by using specific fungal diseases as examples of broader public health principles[8].

CNS Fungal Infection

A number of parasitic infections that can involve the human Central Nervous System (including the brain, the spinal cord and the eyes). Of these, some infect the CNS as their primary infection site, but many others may only involve the CNS as an uncommon/rare complication or as an ectopic site of infection. Many of these infections are world-wide, some are confined to the tropics and others are more common in areas with poor hygiene and sanitation which are usually classed as developing areas. There are also a number of fungal pathogens and opportunists that can cause deep (systemic) mycotic infections which may involve the CNS. Most of these fungi have a wide geographical distribution although tending to result in sporadic infections only[9,10]. Fungus that may infect the CNS are summarized in Table 1.

Specific pathogens

Aspergillosis

Aspergillus brain abscess is a severe complication of hematological malignancies and cancer chemotherapy, and, until recently, was almost uniformly fatal. The Transplant Associated Infections Surveillance Network demonstrated that the incidence of proven or probable invasive Aspergillus at 12 months was 0.5% for autologous HSCT, 2.3% for allogeneic, human leukocyte antigen (HLA)-matched donor, 3.2% after an HLAmismatched related donor and 3.9% from an unrelated donor. Additional specific risk factors for CNS fungal infection include solid-organ transplant, GvHD, HIV, liver disease and sarcoidosis. Candida Candida species have emerged as important pathogens that are currently the fourth most common cause of hospital acquired blood stream infections.

CNS infections include the following:

1. Cerebral micro abscesses, which typically manifest with diffuse encephalopathy, often below the limits of detection by computed tomography (CT) and occult on lumbar puncture.
2. Cerebral abscesses, which are uncommon, present with focal neurological signs, seizures and biopsy is required for diagnosis.
3. Meningitis, which occurs in less than 15% of cases, and presents with sub acute fever and headache, and head imaging demonstrating hydrocephalus.
4. Vascular complications manifest by infarcts, mycotic aneurysms and subarachnoid hemorrhage, which have been found in up to 23% of necropsy after candidemia. In patients with an indwelling catheter and a fever unresponsive to antibacterial agents, consideration and investigation for invasive Candida infection may occur including fundoscopic examination of the retina. Culture data from urine, sputum and skin have little diagnostic value, but positive blood and CSF cultures are highly suggestive of infection. Of the greater than 200 Candida species, five are responsible for the majority of all infections: *C. albicans, C. glabrata, C. tropicalis* (particularly important in patients with hematologic malignancies and HSCT), *C. parapsilosis* and *C. krusei*[11].

Fungal Meningitis

Fungal meningitis, an infection that causes inflammation of the membranes covering the brain and spinal cord, is one of the most common life-threatening opportunistic infections of HIV patients. It is caused by *Cryptococcus*, a fungus that has been found throughout the world. Infections in people are acquired by inhalation of small fungal cells spread on air currents. The organisms survive and spread only in people with weakened immune systems. The symptoms of fungal meningitis differ from one patient to another, but can include headaches, drowsiness, and confusion. In order to differentiate fungal meningitis from bacterial and viral meningitis, blood and spinal fluid must be tested[12].

Infection of eye

Fungal infections of the cornea (mycotic or fungal keratitis, keratomycosis) present as suppurative, usually ulcerative, lesions. Such a corneal infection poses a challenge to the ophthalmologist because of its tendency to mimic other types of stromal inflammation, and because its management is restricted by the availability of effective antifungal agents and the extent to which they can penetrate into corneal tissue. Mycotic keratitis has been reported from many different parts of the world, particularly tropical areas, where it may account for more than 50% of all ocular mycoses, or of all cases of microbial keratitis. Two basic forms have been recognised: that due to filamentous fungi (especially *Fusarium* and *Aspergillus*), which commonly occurs in tropical and subtropical zones, and keratitis due to yeast like and related fungi (particularly *Candida*). More than 105 species of fungi, classified in 56 genera, have been reported to cause oculomycosis. However, species of *Fusarium*, *Aspergillus*, and other hyaline hyphomycetes, and species of *Curvularia* and other dematiaceous hyphomycetes, are the usual isolates from patients with filamentous fungal keratitis, while *Candida albicans* is the most frequent cause of keratitis due to yeast-like and related fungi[13].

Fungal infection of mouth

Candidosis is the most common mycosis of the mouth either in normal and immunodeficient persons. It is a superficial oportunistic infection, with local and systemic factors facilitating the development of the disease. *Candida albicans* is present in the oral cavity as a harmless commensal of about 50% of healthy persons, and it is involved in most cases of oral candidosis. Contrary to some deep mycosis the yeast changes to the pseudohyphal form to establish infection. Eventually, it can cause deep infections in patients with decreased resistance. Different biotypes of *C. albicans* were described, and sometimes associated with different areas of the world. Other species are more frequently isolated from the mouth as *C. parapsilosis, C. tropicalis, C. Krusei, C.glabrata, C. guilliermondii* and more recently *C. dubliniensis* .*C. albicans* seems to be the most pathogenic species, and the important factors considered are capacity of adherence and colonization, enzyme production and interactions with host defenses. In the mouth, epithelial physical barrier, indiginous bacterial flora, mechanical cleansing of saliva, salivary antibodies, lysozyme, histidine-rich polypeptides, lactoferrin, lactoperoxidase seem to play an important role to keep *Candida* under control[14]

Thyroid Dysfunction

Mycoses

The thyroid is resistant to microbial invasion because of its rich blood supply, iodine content, and capsule. Although several fungi may infect the thyroid, thyroid fungal infection occurs rarely and is clinically overt in a minority of patients. Of 415 previously reported cases of infectious thyroiditis (1900-1997), only 50 (12%) were fungal. The pathogenesis of fungal thyroiditis entails hematogenous or lymphatic spread. Although most cases of thyroid fungal involvement occur during dissemination in immunosuppressed patients, isolated thyroid histoplasmosis, *coccidioidomycosis*, and pneumocystosis have been reported[15].

Fungi as Aeroallergens

Fungal spores are universal atmospheric components indoors and outdoors and are now generally recognized as important causes of respiratory allergies. Allergic reactions associated with fungi involve the lower respiratory tract more frequently than do pollen allergies. Fungal spores and spore extracts, when administered during provocative inhalation challenge tests, can cause immediate bronchoconstriction in sensitive subjects. Reports of non respiratory symptoms, food allergy, or contact urticaria are anecdotal. More than 80 genera of fungi have been associated with symptoms of respiratory tract allergy. Aerobiologic surveys show that fungal spores are present in the atmosphere worldwide. Multiple species may be observed at any time of the year, but in temperate climates, spore numbers peak during summer and fall, decrease with cooler

temperatures, and are absent, at least outdoors, where snow cover occurs. Despite the clinical importance and abundant release of fungal spores, relatively few investigations have focused on the relationship between airborne spores and allergic disease. Allergic reactions normally occur at the site of allergen deposition. Most inhaled particles of 10 mm (most pollens and some larger spores) are deposited in the nasopharynx and are associated with nasal and/or ocular symptoms generally referred to as hay fever. Conversely, particles of 10 mm, especially those of 5 mm, can penetrate the lower airways, where allergic reactions tend to manifest as asthma. Fungal spores differ in size and are associated with both upper and lower respiratory symptoms. Additionally, there is now evidence that secondary dispersal of allergens, i.e., on other, smaller particles, possibly spore fragments, may serve as a vehicle for allergens. This would permit the deposition of allergens even from large spores such as *E. nigrum* into the lower airways[7].

Fungal infection of heart

Cardiac infection by fungi was rarely reported in the past. In 1915 Hurleyl described a patient with Blastomyces dermatitidis in the right atrium. In the first completely documented case of candidal endocarditis, reported in 1940, the patient was a heroin addict. A patient with postvalvulotomy endocarditis due to Candida albicans was described in l956.As Aspergillar valve endocarditis was first reported in 1950 in a patient with rheumatic heart disease who received large doses of penicillin for a leg wound. Systemic fungal infections have since been identified with increasing frequency. Cardiac involvement may be difficult to diagnose clinically, is frequently fatal and may first be discovered at autopsy. In this study we systematically examined the clinical setting, predisposing conditions, pathologic findings and consequences of endocarditis, myocarditis and pericarditis in 51 patients with postmortem examination.

Endocarditis

Manifestations were important clinical features in one third of the patients with endocarditis. Acute onset of a central neurologic deficit (hemiparesis, oculomotor palsy,for example), a fungus-laden maculopapular rash in nonintertrigenous regions, abrupt major arterial occlusion and fungal endophthalmitis. Among four patients whose eyes were examined postmortem, three had fungal chorioretinitis that would have been ophthalmologically visible during life. The typical discrete retinal lesion described elsewhere, It may be diagnosed early in the course of endocarditis before the onset of more catastrophic events[16].

Infection of lungs

Fungal infections of the lung are less common than bacterial and viral infections but pose significant problems in diagnosis and treatment. They mainly affect people living in certain geographic areas and those with immune deficiency. Their virulence varies from causing no symptoms to causing death.

Epidemiology

Rates of invasive fungal infections have surged during recent decades, largely because of the increasing size of the population at risk. This population includes patients who are immunosuppressed because of diseases, such as cancers of immune cells of the blood, bone marrow, and lymph nodes, and those with human immunodeficiency virus (HIV) infection. It also includes patients taking immunosuppressive drugs, which are given to avoid rejection of transplanted organs or stem cells and as treatment for autoimmune diseases, such as rheumatoid arthritis. Immunosuppressive drugs are also given to reduce inflammation. For example, corticosteroids are often prescribed for many different lung diseases. A new class of potent immunosuppressive agents includes compounds that block regulatory molecules produced by the immune system called cytokines. One of these cytokines, tumor necrosis factor, is key to many of the body's immune processes. In addition, patients with chronic debilitating diseases, who are in an immune-deficient state, make an attractive host for invasive fungi. Massive population growth, urban development, and climate change are also factors that have increased the prevalence of fungal infections in certain areas and are putting more people at risk of becoming infected with the fungi that is endemic to where they live. More recently, natural disasters such as tsunamis and hurricanes have also contributed to the changing epidemiology of fungal infections. The financial and social burdens of fungal infections are staggering. Using National Hospital Discharge Data Sets from 1998, the annual cost of fungal infections in the United States was estimated to be $2.6 billion, approximately 0.24 percent of total U.S. healthcare expenditures. That same year, the average added expenditure to treat a patient with a fungal infection in the United States was more than $31,000 above the average annual healthcare expenditure of $4,000 per person. Most of this expense was incurred caring for hospitalized patients with invasive aspergillosis, a fungal infection predominantly affecting the lungs. Generally speaking, invasive fungal infections (termed mycoses) can be divided into two broad categories: the opportunistic and the endemic mycoses. Opportunistic fungal infections involve ubiquitous fungi and occur predominantly in individuals whose immune systems are compromised. These infections do not follow any particular geographic distribution and are seen with increasing frequency worldwide. Invasive pulmonary aspergillosis and systemic candidiasis are the most prevalent opportunistic fungal infections. Mold infections that were once considered rare are now emerging as significant infectious complications.

Pathophysiology

Most pulmonary fungal infections occur after inhalation of fungi that have been aerosolized because their natural habitat was disturbed. Once in the lungs' alveoli (air sacs), the fungus is engulfed by macrophages and other cells involved in the primary immune response. Macrophages are usually able to neutralize and destroy the pathogens that they attack, but many fungi have developed a way to disable the macrophage's weapons, and some fungi have actually developed the ability to grow and multiply inside macrophages. Secondary or adaptive immunity cells are called to the site of infection, and in healthy individuals, this action can usually control the infection's spread. The fungus is contained, but the sites of initial infection can remain as granulomas, collections of different types of immune cells. The granulomas later degenerate to scars and often calcify. Calcified granulomas may be seen years later on x-ray images. When cellular immunity is impaired, as it is, for instance, in AIDS, infection with an endemic fungus cannot be controlled. Almost any organ can be involved as the infection spreads throughout the body. The presence of structural lung disease, such as emphysema, impairs the clearance of the infection and allows a chronic condition to take hold. White blood cells (especially neutrophils) are critical to fight certain fungal infections such as those due to the fungus Aspergillus. A number of recent studies suggest that climate changes have disrupted the natural habitat of some endemic fungi, leading to significant changes in their epidemiology. One revealing example is the noticeable increase in the incidence of the fungus coccidioidomycosis, which has been linked to distinct patterns of environmental and climatic change in parts of Arizona between 1998 and 2001[17-19].

Hematologic Infections

Histoplasmosis

The classic deep fungal infection associated with granuloma formation is histoplasmosis, caused by the dimorphic mold, *Histoplasma capsulatum* (also called *Emmonsiella capsulata).* Like mycobacterial infections, the lymph node involvement may be localized or part of a systemic infection. The budding yeast form of the organism may be seen in routine hematoxylin/eosin-stained

sections but can be made more easily visible with silver impregnation stains, of which Gomori methenamine silver (GMS) is most widely used.

Coccidioidomycosis

The other main fungal infection associated with a tuberculoid granulomatous response is coccidioidomycosis, caused by *Coccidioides immitis,* another dimorphic mold. Histoplasmosis is extremely common in the Mississippi river valley, while coccidioidomycosis is more common in the desert Southwest.

Other fungal infections

Some fungal infections may produce a peculiar reaction characterized by a mixture of loosely arranged granulomas admixed with a prominent suppurative (neutrophilic) exudate. This so-called suppurative granulomatous response is characteristic of sporotrichosis (caused by the mold *Sporothrix schenckii)* and North American blastomycosis (caused by the dimorphic mold *Blastomyces dermatitidis).* Both of these infections may be localized or systemic[20].

Infection of Reproduction system

Candidiasis (referred to as thrush, or a yeast infection) is caused by the fungus candida. Some women appear to be naturally more prone to developing this type of infection for reasons that are not well understood. In addition, recent use of antibiotics, oral contraceptives that contain progesterone, or the presence of other conditions such as diabetes, pregnancy, or immune Suppression (such as that caused by HIV, the virus that causes AIDS) can also increase a woman's chances of developing candidiasis[21,22] .

Signs Observed by Clinician

- White, thick, curd-like discharge
- Redness of vulva, vaginal, and cervical tissue Symptoms Experienced by Women
- Thick, curd-like discharge
- Itching, soreness of the vulva
- and vaginal area (vaginitis)
- Painful intercourse

CONCLUSION

We have discussed systemic fungal infection and there causes. So it is seems that immunosuppressed person need extra attention about their diagnosis and treatment. HIV infection is a fast growing disease at present time which cause deficiency of immune system. Infections due to *Histoplasma capsulatum* and *Penicillium marneffei* are increasingly reported in patients with AIDS in India. *H. capsulatum* is found country wide, but *P. marneffei* remains restricted to Manipur state. Global warming could have a significant effect on fungal populations which may cause a high risk of systemic fungal infection and may cause severe diseased condition. This global change in systemic fungal infections has emphasized the need to develop good diagnostic mycology laboratories in this country and to recognize this increasingly large group of potential fungal pathogens.

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Table 1. Summary of Fungus that may infect the CNS

Fungus	Geog. Area	Mode of infection	Clinical association
Aspergillus spp.	Widespread	Inhalation	Brain abscess, Meningitis
Mucor spp.	"	"	Brain abscess
Yeasts:			
Cryptococccus neoformans	Widespread	Inhalation	Meningitis
Candida spp .	"	"	Brain abscess, Meningitis

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