

# Fungal Infections Pathology: Implications for Immunosuppressive Activities

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## Description

Fungal infections of the Central Nervous System (CNS) present with protean clinical manifestations such as meningitis, encephalitis or mass lesions and are being increasingly recognized due to an increase in the at-risk population, increased awareness and better diagnostic modalities. However, due to lack of specific clinical and imaging features, diagnosis and treatment are often delayed, resulting in severe morbidity and mortality. The spectrum of aetiological fungi, the predisposing risk factors and clinical syndromes encountered in developing countries are different from those reported in the West. There are a few reports of large series from India. 1–10 In this paper, we present 130 cases of histologically verified fungal infections of the CNS seen at a University Hospital in Southern India over a period of 17 years and highlight the features seen in tropical countries such as India between mid-1981 and mid-1991, 64 cases of deep mycotic infections were found in 890 consecutive necropsies (incidence 7.2%). Among these there were 26 gastrointestinal infections, with 12 cases affecting the upper gastrointestinal tract (mouth, oesophagus, and stomach) alone, seven the lower intestinal tract (duodenum, jejunum, ileum and colon) alone, and seven both sites. These last 14 cases are the subject of this report. In the lower intestinal group the following variables were assessed from the clinical records: the age and sex of the patient; the underlying neoplastic condition; and the treatment administered. During the final illness any gastrointestinal symptoms and signs, drug intake, including antibiotics and steroids, the white cell count, results of fungal serological tests and blood and stool cultures were recorded. The degree of the clinician's awareness of an intestinal infection was assessed as well as the clinically perceived mode of death. The necropsy reports revealed information about the gross appearance and distribution of the lesions together with the extent of other organ disease. An assessment of the degree to which the intestinal disease contributed to death was made. Necropsy stool cultures were sent in three cases. Microscopic examination was undertaken on formalin fixed, paraffin wax embedded sections stained with haematoxylin and eosin, Periodic-Acid Schiff (PAS) with and without diastase, Grocott's methenamine silver stain, and the Gram stain. The sections were seen by two pathologists without prior knowledge of the clinical or necropsy data. The fungi were all classified confidently on morphological grounds as either *Candida* or *Aspergillus* sp. Because of the high degree of agreement between the pathologists, it was not felt necessary

to confirm the findings by immunohistochemical or lectin histochemical techniques. *Candida* organisms were characterised by blastospores and pseudohyphae with budding forms and *Aspergillus* organisms by regular septate hyphae which exhibited dichotomous branching

Systemic mycoses can be divided into two groups based on their ability to infect immunocompetent hosts. Infectious fungi, the first group, are classified as primary pathogens. These include *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces*, and *Paracoccidioides*. The second group includes the opportunistic pathogens such as *Candida*, *Aspergillus*, *Cryptococcus*, *Trichosporon* and *Fusarium*. These can cause invasive, deep infections only if additional specific predisposing risk factors, such as immune deficiency or other underlying severe disease, are concomitantly present. In the past, most fungi could be assigned to these two categories. However, recent findings clearly show that these two categories do not sufficiently discriminate among these species. For example, *Saccharomyces cerevisiae*, considered to be the least dangerous fungal species, was found to be responsible for invasive, life-threatening infection in several cases. *Fusarium*, a well-known plant pathogen, was also reported to cause severe infections in humans, particularly in leukaemic patients. Furthermore, *Penicillium marneffei*, a fungus endemic in Asia and Japan, can cause disseminated fungal infection, especially in Human Immunodeficiency Virus (HIV) patients. Therefore, it appears that fungi, previously regarded as nonpathogenic and harmless in humans, can cause life-threatening mycoses and be devastating in immunocompromised patients. Nevertheless, the precise nature of the immune defence cascade to pathogenic fungi and moulds still needs clarification. The association of fungal infections with certain forms of immune adequacy will contribute significantly to the understanding of natural defence mechanisms against mycoses. In addition to systemic and opportunistic mycoses, various fungi are associated with a large number of allergic disorders in humans that occur with increased prevalence. Among these, Allergic Broncho Pulmonary Aspergillosis (ABPA), a life threatening hypersensitivity disease associated with *A. fumigatus* colonization of the bronchial airway, was described as a lung disease with defined clinical, serological, radiological and pathological features difficult to diagnose especially in patients suffering from Cystic Fibrosis (CF). The first four of the eight criteria proposed for the diagnosis of ABPA do not cause significant problems to the experienced clinician; however, they are not sufficient for

reliable diagnosis of the syndrome. Moreover, independent of priority, not all of these criteria and symptoms must be fulfilled. Therefore, to improve diagnosis, serology should clearly contribute in order to either confirm or exclude ABPA as suspected from the clinical signs. It is evident that skin-test reactivity and serological findings largely depend on the quality of the fungal extract applied; indeed, there are significant batch-to-batch variations in the content and quality of allergenic components. Recent progress in molecular cloning of *A. fumigatus* allergens has not only generated new diagnostic tools, but it has also clarified the molecular background and nature of ABPA. In particular, molecular definition and recombinant production of major *A. fumigatus* allergens has enabled easy serological discrimination of ABPA from *A. fumigatus*-related allergic asthma by Immune Globulin (Ig)-E-specific detection techniques. Increased levels of serum IgE against the two allergens Asp f 4 and Asp f 6 clearly distinguishes ABPA from *A. fumigatus*-allergic asthma.

Despite the recent insights into the host–fungus relationship, which may help to accommodate the multifaceted role of Th17 cells in immunity and homeostasis during fungal infections, there are several unanswered questions. Because pathways that regulate IL-17 and IL-22 production by Th17 cells can be disparate, is the production of IL-22 distinguishing pathogenic Th17 from protective Th17 against fungi? How is IL-22 regulated in pathogenic Th17 responses? As IL-22 activates STAT3, and STAT3 activation in myeloid dendritic cells is sufficient and required for the activation of tolerogenic anti-fungal responses via IL-10, could IL-10 induction ameliorate the pathogenicity of Th17 cells? Naturally occurring Th17 cells are highly enriched at mucosa sites, where continuous exposure to ubiquitous fungi occurs (through inhalation or via commensalism). This demands for a sophisticated degree of adaptation to which integrated innate and adaptive immune responses contribute. In this scenario, the IFN-g/IDO axis, leading to sequential Th1/Treg activation upon exposure to fungi at mucosal sites, may have evolved to accommodate fungal persistence, i.e. commensalism, in an inflammatory environment rich in IFN-g. In contrast, the occurrence of IL-22<sup>hi</sup> Th17 cells, employing ancient effector mechanisms of immunity, may represent a primitive mechanism of resistance against the fungus under a condition of limited

inflammation. Thus, the exploitation of the IFN-g/IDO axis for functional specialization of antifungal effector and regulatory mechanisms may have allowed commensal or ubiquitous fungi to co-evolve with the mammalian immune system to survive in conditions of high-threat inflammation. Infectious agents can induce autoimmune diseases but paradoxically can also suppress allergic and autoimmune disorders. A central question here will be to determine whether fungal exposure/ colonization contributes to the burst of pathogenic autoimmunity or alternatively, but not mutually exclusive, whether dysregulation precedes, if not promotes, diseases caused by fungi. In this context, in their ability to subvert the inflammatory program through the activation of the IL-23/Th17 axis, fungi may eventually lead to immune dysregulation, including allergy and autoimmunity. However, their ability to activate Treg may represent a mechanism whereby dysregulated immunity is prevented in a manner similar to “protective” microbiota of the gastrointestinal tract.

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