

Review

The Changing Clinical Presentation of Fungal Infections

George S. Kobayashi

Washington University School of Medicine, Department of Internal Medicine
Division of Infectious Diseases, St. Louis, Missouri 63130

Statement of the problem:

Fungi, as all of us know, are extremely common in the environment and, with 2 exceptions; they exist as free-living organism in nature deriving no obvious benefits by parasitizing humans or animals. Since they are widespread in nature and are often cultured from diseased body surfaces, it is frequently difficult to assess whether a certain fungus isolated in cultures taken from a lesion is a pathogen or a transient environmental contaminant. To establish with certainty that a specific fungus is the cause of a disease process, the same fungus must be isolated from several serial specimens taken at well-spaced intervals of time, and fungal elements morphologically consistent with the isolate should be observed in tissues taken from the lesion.

In general, fungal infections and the diseases they cause are accidental. Healthy immunologically competent individuals have a high innate resistance to fungi. However, a few fungi have developed a balanced relationship with humans and are part of the normal microbial flora. We see this with species of *Candida*, *Malassezia furfur* and some of the dermatophytes. Whereas a great deal of information is available concerning the molecular basis of bacterial, viral and protozoal pathogenesis, at the present time little is known about molecular mechanisms of fungal pathogenesis. The primary goal of current research is to understand how fungal agents cause infection and disease. In order to examine the genetic and molecular basis of fungal pathogenicity several model systems have been employed. It is also important not to neglect the natural history of infectious diseases by looking at the molecular

organization of the genetic material of pathogens in endemic and epidemic settings. The research techniques that are currently being employed range from model infection in animal systems and cultured human cells to the cloning and sequencing of specific fungal genes.

As a result of great strides that are being made in the genomics of fungal pathogens and the application of molecular genetic techniques to study these organisms, inroads are being made to correct these shortcomings. The availability of genomic sequences of pathogenic fungi, microarray technology, and proteomics now provides techniques for scientists to work with fungal pathogens without having to deal with viable organisms and the fear of handling infectious materials. This, however, is not without its problems since an increasing number of researchers who have been attracted to study fungal pathogens are scientists who have great familiarity with yeasts such as *Saccharomyces cerevisiae* and molds such as *Aspergillus oryzae*. While they are superbly trained researchers, they have difficulties communicating with clinicians since they lack in depth knowledge of host-parasite interactions, diagnostic techniques and management of critically ill patients. In addition, there appears to be a trend in the United States towards training fewer medical mycologists in the traditional sense. There is a great need for well-trained medical mycologists in order to deal with the increasing numbers of patients who are at high risk to develop life threatening fungus diseases. In particular because of advances that are being made in therapy of cancers and organ transplantation, the aging population and the current AIDs pandemic.

In order to discuss the subject that I have chosen to present today, it is clear that a review of fungal infections is in order. For some of you this may be mundane and simplistic but I feel is

Address correspondence to: George S. Kobayashi

Washington University School of Medicine Department of
Internal Medicine
Division of Infectious Diseases St. Louis, Missouri 63130.

necessary in the face of the influx of basic scientists who now study fungal pathogens and the changing patterns of fungal diseases.

Infection:

Fungal infections are defined as entry into body tissues followed by multiplication of the organism. The infection may be clinically inapparent or it may result in disease due to cellular injury from competitive metabolism, elaboration of toxic metabolites, replication of the fungus, or an immune response. The immune response may be transient or prolonged, and may be cell-mediated, humoral (without production of specific antibodies to components of the infection organism), or both. Successful infection may result in disease, defined as a deviation from or interruption of the normal structure or function of body parts, organs, or systems (or a combination thereof) marked by a characteristic set of symptoms and signs and whose etiology, pathology, and prognosis may be known or unknown.

Entry:

Fungi may infect the body through several portals of entry. The first exposure of fungi that most humans experience occurs during birth, when they encounter the yeast *Candida albicans* while passing through the vaginal canal. During this process the fungus colonizes the buccal cavity and portions of the upper and lower gastrointestinal tract of the newborn, where they maintain a lifelong residence in healthy individuals as commensals.

Another fungus, *Malassezia furfur*, is commonly found in areas of skin rich in sebaceous glands. How it colonizes skin is not known, but both *M. furfur* and *C. albicans* are the only fungi that I am aware of, that exist as commensals of humans and are considered part of the indigenous flora. Only under certain unusual circumstances have they been the causative agents of disease. Other fungi that have been implicated in disease of humans come from exogenous sources where they exist as saprobes on decaying vegetation or as plant parasites.

Fungi rarely cause disease in healthy, immunocompetent hosts, even though we are constantly exposed to infectious propagules. It is only when fungi accidentally penetrate barriers such as intact skin and mucous membrane linings, or when immunologic defects or other debilitating conditions exist in the host, that conditions favorable for fungal colonization and growth occur. When *Candida albicans*, for example, is

implicated in disease processes, one must consider the possibility that the patient has a coexisting immunologic, endocrinologic, or other debilitating disorder. In most cases, the underlying disorder must be corrected to effectively manage the fungal disease.

Adaptation and propagation:

While most fungal diseases are the result of accidental encounters with the etiologic agent, many fungi have developed mechanisms that facilitate their multiplication within the host. For example, the dermatophytes that colonize skin, hairs, and nails elaborate enzymes that digest keratin. *Candida albicans* as a commensal organism exists in a unicellular yeast-like morphology but when it invades tissues it becomes filamentous. Conversely, the systemic fungi: *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Coccidioides immitis*, and *Penicillium marneffii* exist as molds in nature and change to a unicellular morphology when they cause disease. Similarly several dematiaceous fungi causing chromoblastomycosis have the ability to take on various morphologic forms in response to the immunologic status of the patient. They can exist in a hyphal morphology, take on bizarre yeastlike shapes or become sclerotic cells in order to survive and multiply. These and other properties such as capsule production by *Cryptococcus neoformans* and the adherence properties of *Candida* species to host tissue, contribute to their pathogenicity. In general, fungal pathogens must survive at host body temperatures in order to grow and multiply. Those unable to do so are not virulent.

Dissemination:

Disseminated fungal disease usually indicates that a breach exists in host defenses. Endocrinopathies or immunologic disorders may cause such a breach, or it may be induced iatrogenically. In order to manage effectively the fungal infection, a concerted effort must be made to uncover and correct the underlying defect.

Host factors:

The high degree of innate resistance that humans show to fungal invasion is based primarily on the various protective mechanisms that prevent fungi from entering host tissues. The intact skin and factors such as naturally occurring long-chain fatty acids, pH, competition with the normal bacterial flora, epithelial turnover rate, and the desiccated nature of the stratum corneum discourage fungal growth. Other body surface, such as the respiratory tree, gastrointestinal tract,

and vaginal vault are lined with mucous membranes bathed in fluids that contain microbicidal substances, and some of these membranes are lined with ciliated epithelial cells that actively remove foreign materials. Only when these protective barriers are breached can fungi gain access to host tissues by traumatic implantation or inhalation. The severity of disease that these organisms cause depends upon size of the inoculum, magnitude of tissue destruction, their ability to multiply in tissues, and the immunologic status of the host.

Fungal factors:

The definition of virulence always brings with it a certain amount of confusion and arguments about what is a "virulence" gene or factor. Doctor Jim Cutler proposed the following definition of virulence: "Virulence phenotypes or traits belong to a set of genes that within a given isolate express a finite number or subset of traits to make up the composite virulence phenotype of a particular strain". Much confusion occurs because virulence is considered a property of the microorganism and must be separated from its maintenance properties or functions required for surviving on a non-living host. However, Doctor John Perfect feels that virulence as a concept must encompass the entire host-parasite interaction, an interaction that can be complex and variable. In the current era of genomics, it remains important to frame a definition for a virulence gene as a starting point for any discussion. In this respect, a dictionary definition may simply suffice "it is the relative infectiousness of an organism causing disease and/or its ability to overcome the natural defenses of the host". There are three important principles of virulence included in this definition: (1) it has a

quantitative nature; (2) it embraces the concept of disease; and (3) it includes the importance of the host's contribution to the interaction. Doctor Perfect summarized this as follows: "A gene or set of genes might change in importance depending on the following criteria: (1) immune status of the host, (2) site of exposure, and (3) degree of exposure".

In general, fungi have not become highly specialized to be involved with the normal human hosts and as Paul Steele, a postdoctoral fellow of mine wrote; "A fungal infection is simply an accidental encounter in the life of a fungus. Fungi are not highly developed efficient pathogens. Some of the basic requirements for disease production can include such "housekeeping-like characteristics" as adaptation to temperature of growth (mammalian body temperature) and need for prototrophy. It is important not to limit our virulence studies to certain unique characteristics and disregard these important metabolic functions in the disease process. It is likely that some fungi have developed a series of specific metabolic functions that have been altered uniquely to create a pathogen".

Most of the fungi that infect humans and cause disease can be classified according to the tissue or organ levels that are the primary sites of colonization. In order to appreciate the tissue tropism that exists between fungal pathogens and their host, a brief review of the agents implicated in the disease of humans and animals must be understood, particularly in view of the changing faces of their clinical presentations.

The clinician needs to be aware of the changing clinical presentations of the mycoses as a result of the increased use of immuno-suppressive drug therapy and the AIDS pandemic.