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Medical Mycology

OPPORTUNISTIC MYCOSES

Patients with compromised host defenses are susceptible to ubiquitous fungi to which healthy people are exposed but usually resistant. In many cases, the type of fungus and the natural history of the mycotic infection are determined by the underlying predisposing condition of the host. As members of the normal mammalian microbiota, Candida and related yeasts are endogenous opportunists. Other opportunistic mycoses are caused by exogenous fungi that are globally present in soil, water, and air. The coverage here will focus on the more common pathogens and the diseases they cause—**candidiasis, cryptococcosis, aspergillosis, mucormycosis, Pneumocystis pneumonia, and penicilliosis**. However, the incidence and the roster of fungal species causing serious mycotic infections in compromised individuals continue to increase. In patients with HIV/AIDS, the susceptibility and incidence of opportunistic mycoses are inversely correlated with the **CD4+ lymphocyte count**. In general, AIDS patients with **CD4+ counts less than 200 cells/µL are highly susceptible to infection with opportunistic fungi**.

-CANDIDIASIS

Several species of the yeast genus Candida are capable of causing **candidiasis**. They are members of the normal flora of the skin, mucous membranes, and gastrointestinal tract. **Candida species colonize the mucosal surfaces of all humans soon after birth**, and **the risk of endogenous infection is ever-present. Candidiasis is the most prevalent systemic mycosis, and the most common agents are C albicans, C**

parapsilosis, C glabrata, C tropicalis, C guilliermondii, and C dubliniensis.
The widespread use of fluconazole has precipitated the emergence of more azole-resistant species, such as C krusei and C lusitaniae. As indicated , species of Candida cause both cutaneous and systemic infections, and these clinical manifestations have different mechanisms of pathogenesis. In addition, there are several other types of candidal infectious syndromes.

In culture or tissue, Candida species grow as **oval, budding yeast cells** (3–6 μm in size). They also form **pseudohypha**e when the buds continue to grow but fail to detach, producing chains of elongated cells that are pinched or constricted at the septations between cells. Unlike other species of Candida, **C albicans is dimorphic**; in addition to yeasts and pseudo-hyphae, it can also produce true hyphae (Figure A). **On agar media or within 24 hours at 37°C or room temperature, Candida species produce soft, cream-colored colonies with a yeasty odor. Pseudohyphae are apparent as submerged growth below the agar** surface. Two simple morphologic tests distinguish **C albicans, the most common pathogen, from other species of Candida: After incubation in serum for about 90 minutes at 37°C, yeast cells of C albicans will begin to form true hyphae or germ tubes (Figure B**), and on nutritionally deficient media C albicans produces large, spherical **chlamydospores**. Sugar fermentation and assimilation tests can be used to confirm the identification and speciate the more common Candida isolates, such as C tropicalis, C parapsilosis, C guilliermondii, C kefyr, C krusei, and C lusitaniae; C glabrata is unique among these pathogens because it produces only yeast cells and no pseudohyphal forms.

-Antigenic Structure

The use of adsorbed antisera have defined two serotypes of C albicans: A (which includes C tropicalis) and B. During infection, cell wall components, such as mannans, glucans, other polysaccharides and glycoproteins, as well as enzymes, are released. These macromolecules typically elicit innate host defenses and Th1 and Th2 immune responses. For example, sera from patients with systemic candidiasis often contain detectable antibodies to candidal enolase,

secretory proteases and heat shock proteins.

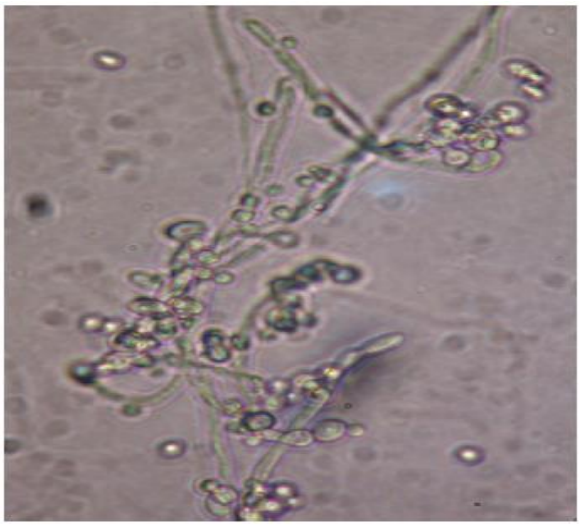

Fig. A :- Candida albicans. Budding yeast cells (blastoconidia), hyphae, and pseudohyphae. 400×.

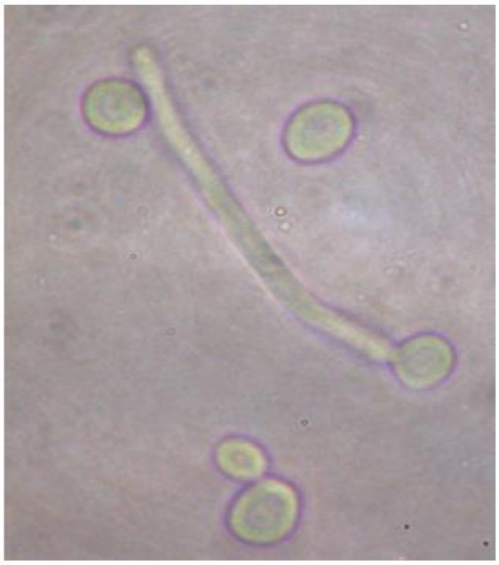

Fig. B :- Germ tube. Unlike other species of Candida, Candida albicans produces true hyphae as well as budding yeast cells and pseudohyphae. After incubation in serum at 37°C for 60–90 minutes in the laboratory, clinical isolates of Candida albicans are stimulated to form hyphae, and this process is initiated by the production of germ tubes, which are thinner and more uniform than pseudohyphae . 1000×.

-Pathogenesis and Pathology

Superficial (cutaneous or mucosal) candidiasis is established by an increase in the local census of Candida and damage to the skin or epithelium that permits local invasion by the yeasts and pseudohyphae. Systemic candidiasis occurs when Candida enters the bloodstream and the phagocytic host defenses are inadequate to contain the growth and dissemination of the yeasts. From the circulation, Candida can infect the kidneys, attach to prosthetic heart valves, or produce can-didal infections almost anywhere (eg, arthritis, meningitis, endophthalmitis). The local histology of cutaneous or muco-cutaneous lesions is characterized by inflammatory reactions varying from pyogenic abscesses to chronic granulomas. The lesions contain abundant budding yeast cells and pseudohy-phae. Large increases of Candida in the intestinal tract oſten follow the administration of oral antibacterial antibiotics, and the yeasts can enter the circulation by crossing the intestinal mucosa.

As mentioned above, Candida cells elaborate polysaccharides, proteins, and glycoproteins that not only stimulate host defenses but facilitate the attachment and invasion of host cells. Candida albicans and other **Candidia species produce a family of agglutinin-like sequence (ALS) surface glycoproteins, some of which are adhesins that bind host receptors and mediate attachment to epithelial or endothelial cells.** The innate host defense mechanisms include pattern recognition receptors (eg, lectins, toll-like receptors, macrophage mannose receptor) that bind to pathogen-associated molecular patterns. A key example is the host cell lectin, dectin-1, which binds to the β-1,3-glucan of C albicans and other fungi to stimulate a robust inflammatory response. This response is characterized by the production of cytokines, especially tumor necrosis factor-α, interferon-γ , and granulocyte colony-stimulating factor, which activate anti-fungal effector cells, neutrophils, and monocytes. In addition, the binding of β-glucan to dectin 1 on dendritic cells induces the Th17 lymphocytes, which secrete interleukin-17. Th17 lymphocytes differ from T and B cells. They are activated by innate, usually mucosal defense mechanisms as well as adaptive immune responses.

A. Cutaneous and Mucosal Candidiasis

The risk factors associated with superficial candidiasis include AIDS, pregnancy, diabetes, young or old age, birth control pills, and trauma (burns, maceration of the skin). Thrush can occur on the tongue, lips, gums, or palate. It is a patchy to confluent, whitish pseudomembranous lesion composed of epithelial cells, yeasts, and pseudohyphae. Thrush develops in most patients with AIDS. Other risk factors include treatment with corticosteroids or antibiotics, high levels of glucose, and cellular immunodeficiency. Yeast invasion of the vaginal mucosa leads to vulvovaginitis, characterized by irritation, pruritus, and vaginal discharge. This condition is often preceded by factors such as diabetes, pregnancy, or antibacterial drugs that alter the microbial flora, local acidity, or secretions. Other forms of cutaneous candidiasis include invasion of the skin. This occurs when the skin is

weakened by trauma, burns, or maceration. Intertriginous infection occurs in moist, warm parts of the body such as the axillae, groin, and intergluteal or inframammary folds; it is most common in obese and diabetic individuals. The infected areas become red and moist and may develop vesicles.

Interdigital involvement between the fingers follows repeated prolonged immersion in water; it is most common in homemakers, bartenders, cooks, and vegetable and fish handlers. Candidal invasion of the nails and around the nail plate causes onychomycosis, a painful, erythematous swelling of the nail fold resembling a pyogenic paronychia, which may eventually destroy the nail.

B. Systemic Candidiasis

Candidemia can be caused by **indwelling catheters,** surgery, intravenous drug abuse, aspiration, or damage to the skin or gastrointestinal tract. In most patients with normal host defenses, the yeasts are eliminated and candidemia is transient. However, patients with compromised innate phagocytic defenses may develop occult lesions anywhere, especially the kidney, skin (maculonodular lesions), eye, heart, and meninges. Systemic candidiasis is most often associated with chronic administration of corticosteroids or other immunosuppres-sive agents; with hematologic diseases such as leukemia, lymphoma, and aplastic anemia; or with chronic granuloma-tous disease. Candidal endocarditis is frequently associated with deposition and growth of the yeasts and pseudohyphae on prosthetic heart valves or vegetations. Kidney infections are usually a systemic manifestation, whereas urinary tract infections are often associated with Foley catheters, diabetes, pregnancy, and antibacterial antibiotics.

C. Chronic Mucocutaneous Candidiasis

Most forms of this rare disease have onset in early childhood, are associated with cellular immunodeficiencies and endo-crinopathies, and result in chronic superficial disfiguring infections of any or all areas of skin or mucosa. Many patients with chronic mucocutaneous candidiasis are unable to mount an effective Th17 response to Candida.

Diagnostic Laboratory Tests

A. Specimens

Specimens include swabs and scrapings from superficial lesions,

blood, spinal fluid, tissue biopsies, urine, exudates, and material from removed intravenous catheters.

B. Microscopic Examination

Tissue biopsies, centrifuged spinal fluid, and other specimens may be examined in Gram-stained smears or histopathologic slides for pseudohyphae and budding cells (Figure C). Skin or nail scrapings are first placed in a drop of 10% KOH and calcofluor white.

C. Culture

All specimens are cultured on fungal or bacteriologic media at room temperature or at 37°C. Yeast colonies are examined for the presence of pseudohyphae. Candida albicans is identified by the production of germ tubes or chlamydospores. Other Candida isolates are speciated with a battery of biochemical reactions. The interpretation of positive cultures varies with the specimen. Positive cultures from normally sterile body sites are significant. The diagnostic value of a quantitative urine culture depends on the integrity of the specimen and the yeast census. Contaminated Foley catheters may lead to “false-positive” urine cultures. Positive blood cultures may

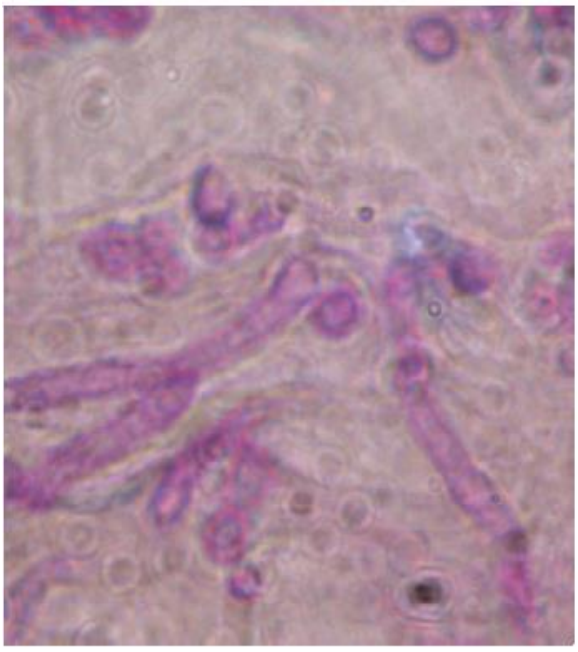

Fig C :- Candidiasis. Yeasts and pseudohyphae in tissue, stained with periodic acid-Schiff. 1000×.

eflect systemic candidiasis or transient candidemia due to a contaminated intravenous line. Sputum cultures have no value because Candida species are part of the oral microbiota. Cultures of skin lesions are confirmatory.

D. Serology

In general, the currently available serologic tests have limited specificity or sensitivity. Serum antibodies and cell-mediated immunity are demonstrable in most people as a result of lifelong exposure to Candida. In systemic candidiasis, antibody titers to various candidal antigens may be elevated, but there are no clear criteria for establishing a diagnosis serologically.The detection of circulating cell wall mannan, **using a latex agglutination test** or an enzyme immunoassay, is much more specific, but the test lacks sensitivity because many patients are only transiently positive or because they do not develop significant and detectable antigen titers until late in the disease. A serologic test for circulating β-glucan, which is found in the cell walls of many fungal species, is not specific for Candida. However, this test can be very helpful when considered with other laboratory and clinical data.

Immunity

The basis of resistance to candidiasis is complex and incompletely understood. Cell-mediated immune responses, especially CD4 cells, are important in controlling mucocutaneous candidiasis, and the neutrophil is probably crucial for resistance to systemic candidiasis.

Treatment

Thrush and other mucocutaneous forms of candidiasis are usually treated with topical nystatin or oral ketoconazole or fluconazole. Systemic candidiasis is treated with amphoteri-cin B, sometimes in conjunction with oral flucytosine, fluco-nazole, or caspofungin. The clearing of cutaneous lesions is accelerated by eliminating contributing factors such as excessive moisture or antibacterial drugs. Chronic mucocutaneous candidiasis responds well to oral ketoconazole and other azoles, but patients have a genetic cellular immune defect and oſten require lifelong treatment.

It is oſten difficult to establish an early diagnosis of systemic candidiasis—the clinical signs are not definitive, and cultures are oſten negative. Furthermore, there is no established prophylactic regimen for patients at risk, though treatment with an azole or with a short course of low-dose amphotericin B is oſten indicated for febrile or debilitated patients who are

immune compromised and do not respond to antibacterial therapy .

Epidemiology and Control

The most important preventive measure is to avoid disturbing the normal balance of microbiota and intact host defenses. Candidiasis is not communicable, since virtually all persons normally harbor the organism. However, molecular epidemiological studies have documented outbreaks caused by the osocomial transmission of particular strains to susceptible patients (e.g., leukemics, neonates, ICU patients).

CRYPTOCOCCOSIS

Cryptococcus neoformans and Cryptococcus gattii are environmental, basidiomycetous yeasts. Unlike other pathogenic fungi, these yeast cells possess large polysac-charide capsules (Figure D). Cryptococcus neoformans occurs worldwide in nature and is isolated readily from dry **pigeon feces, as well as trees, soil, and other sites**. Cryptococcus gattii is less common and typically **associated with trees in tropical areas**. Both species cause cryp-tococcosis, which follows inhalation of desiccated yeast cells or possibly the smaller basidiospores. From the lungs, these neurotropic yeasts typically migrate to the **central nervous system where they cause meningoencephalitis (Figure E).** However, they also have the capacity to infect many other organs (eg, **skin, eyes, prostate**). Cryptococcus neo-formans occurs in **immunocompetent persons but more often in patients with HIV/AIDS, hematogenous malignancies, and other immunosuppressive conditions**. Cryptococcosis due to C gattii is rarer and usually associated with apparently normal hosts. Overall, approximately one million new cases of cryptococcosis occur annually, and the mortality approaches 50%. More than 90% of these infections are caused by C neo-formans. Although C gattii is less prevalent globally, for the past decade, there has been an expanding outbreak of infections with this species in the Pacific Northwest.

Morphology and Identification

In culture, Cryptococcus species produce **whitish mucoid colonies within 2–3 days.** Microscopically, in culture or clinical material, the spherical budding yeast cells (5–10 μm in diameter) are surrounded by a thick nonstaining capsule (Fig. D). All species of Cryptococcus, including several nonpathogenic species, are encapsulated and possess urease. However, C neoformans and C gattii differ from non-pathogenic species

by the abilities to grow at 37°C and the production of laccase, a phenol oxidase, which catalyzes the formation of melanin from appropriate phenolic substrates (eg, catecholamines). Both the capsule and laccase are well-characterized virulence factors. Clinical isolates are identified by demonstrating the production of laccase or a specific pattern of carbohydrate assimilations. Adsorbed antisera have defined five serotypes (A–D and AD); strains of C neoformans may possess serotype A, D, or AD, and isolates of C gattii may have serotype B or C. In addition to their capsular serotypes, the two species differ in their genotypes, ecology, some biochemical reactions, and clinical manifestations. Sexual reproduction can be demonstrated in the laboratory, and successful mating results in the production of mycelia and basidiospores; the corresponding teleomorphs of the two varieties are Filobasidiella neoformans var neofor-mans (serotypes A and D) and Filobasidiella neoformans var bacillispora (serotypes B and C).

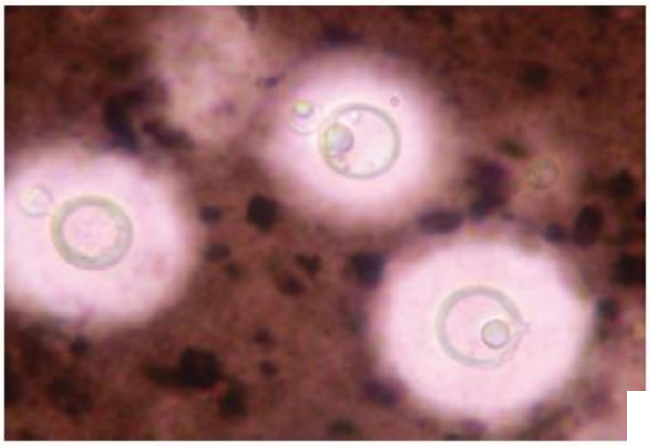

Fig. D :- Cryptococcosis. The capsule of Cryptococcus neoformans is notably apparent in this pulmonary lavage specimen. Giemsa's stain. 1000×.

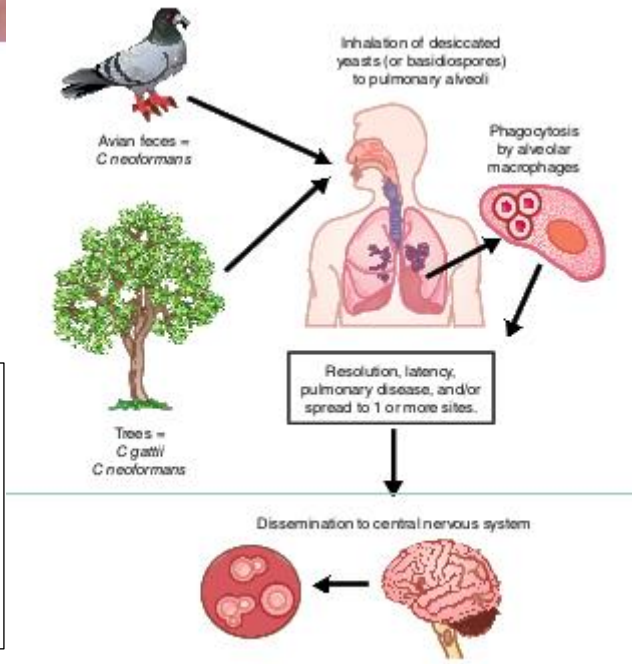

Fig E :- Natural history of cryptococcosis. (Reproduced with permission from Heitman J, Kozel TR, Kwon-Chung KJ, Perfect JR, Casadevall A [editors]: Cryptococcus. From Human Pathogen to Model Yeast. Washington, DC, ASM Press, 2011, Figure 1, p. 238.)

-Antigenic Structure

The capsular polysaccharides, regardless of serotype, have a similar structure: They are long, unbranched polymers consisting of an α-1,3-linked polymannose backbone with β-linked monomeric branches of xylose and glucuronic acid. During infection, the capsular polysaccharide is solubilized in **spinal fluid, serum, or urine and can be detected by an enzyme immunoassay or by the agglutination of latex particles coated with antibody to the polysaccharide. With proper controls, this test is diagnostic of cryptococcosis.** Patient antibodies to the capsule can also be measured, but they are not used in diagnosis.

-Pathogenesis

Infection is initiated by inhalation of the yeast cells, which in nature are dry, minimally encapsulated, and easily aerosol-ized. The primary pulmonary infection may be asymptomatic or may mimic an influenza-like respiratory infection, oſten resolving spontaneously. In patients who are compromised, the yeasts may multiply and disseminate to other parts of the body but **preferentially to the central nervous system, causing cryptococcal meningoencephalitis (Figure E). Other common sites of dissemination include the skin, adrenals, bone, eye, and prostate gland. The inflammatory reaction is usually minimal or granulomatous.**

Clinical Findings

The major clinical manifestation is chronic meningitis, which can resemble a brain tumor, brain abscess, degenerative central nervous system disease, or any mycobacterial or fungal meningitis. Cerebrospinal fluid pressure and protein may be increased and the cell count elevated, whereas the glucose is normal or low. Patients may complain of headache, neck stiff-ness, and disorientation. In addition, there may be lesions in skin, lungs, or other organs.The course of cryptococcal meningitis may fluctuate over long periods, but all untreated cases are ultimately fatal. Globally, about 58% of patients with AIDS

develop crypto-coccal meningitis. The infection is not transmitted from person to person.

Diagnostic Laboratory Tests

A. Specimens, Microscopic Examination, and Culture

Specimens include cerebrospinal fluid, tissue, exudates, sputum, blood, cutaneous scrapings, and urine. Spinal fluid is centrifuged before microscopic examination and culture. For direct microscopy, specimens are often examined in wet mounts, both directly and after mixing with India ink, which delineates the capsule (Figure D).

Colonies develop within a few days on most media at room temperature or 37°C. Media with cycloheximide inhibit Cryptococcus and should be avoided. Cultures can be identified by growth at 37°C and detection of urease. Alternatively, on an appropriate diphenolic substrate, the phenol oxidase (or laccase) of C neoformans and C gattii produces melanin in the cell walls and colonies develop a brown pigment.

B. Serology

Tests for capsular antigen can be performed on cerebrospinal fluid, serum and urine. The latex slide agglutination test or enzyme immunoassay for cryptococcal antigen is positive in 90% of patients with cryptococcal meningitis. With effective treatment, the antigen titer drops—except in AIDS patients, who often maintain high antigen titers for long periods.

Treatment

Combination therapy of amphotericin B and flucytosine has been considered the standard treatment for cryptococ-cal meningitis, though the benefit from adding flucytosine remains controversial. Amphotericin B (with or without flucytosine) is curative in non-AIDS most patients. Inadequately treated AIDS patients will almost always relapse when amphotericin B is withdrawn and require suppressive therapy with fluconazole, which offers excellent penetration of the central nervous system.

HIV/AIDS patients treated with highly active antiretrovi-ral therapy (HAART) have a lower incidence of cryptococco-sis, and cases have a much better prognosis. Unfortunately, up to a third of HAART-treated AIDS patients with cryptococcal meningitis develop immune reconstitution inflammatory syndrome (IRIS), which greatly exacerbates the illness. The diagnosis, pathogenesis, and management of IRIS are

problematic. In addition to causing a paradoxical relapse of cryptococ-cal disease, IRIS may “unmask” undiagnosed cryptococcosis. IRIS also occurs in AIDS patients with tuberculosis.

Epidemiology and Ecology

Bird droppings (particularly pigeon droppings) enrich for the growth of C neoformans and serve as a reservoir of infection. The organism grows luxuriantly in pigeon excreta, but the birds are not infected. In addition to patients with AIDS or hematologic malignancies, patients being maintained on corticosteroids are highly susceptible to cryptococcosis. In sub-Saharan Africa, the epicenter of HIV/AIDS, C neoformans is the leading cause of meningitis with an estimated one million new cases and 600,000 deaths per year. The vast majority of global cases of cryptococcosis are caused by C neoformans (serotype A). However, the normally tropical species C gattii has emerged in the Pacific Northwest, where it has been isolated from several local species of trees, soil, and water. Since 2000, human and veterinary cases have expanded from Vancouver Island to mainland British Columbia, Washington, Oregon, California, and Idaho.

ASPERGILLOSIS

Aspergillosis is a spectrum of diseases that may be caused by a number of Aspergillus species. Aspergillus species are ubiquitous saprobes in nature, and aspergillosis occurs worldwide. A fumigatus is the most common human pathogen, but many others, including A flavus, A niger, A terreus, and A lentulus may cause disease. This mold produces abundant small conidia that are easily aerosolized. Following inhalation of these conidia, atopic individuals often develop severe allergic reactions to the conidial antigens. In immunocom-promised patients—especially those with leukemia, stem cell transplant patients, and individuals taking corticosteroids— the conidia may germinate to produce hyphae that invade the lungs and other tissues.

Morphology and Identification

Aspergillus species grow rapidly, producing aerial hyphae that bear characteristic conidial structures: long conidiophores with terminal vesicles on which phialides produce basipetal chains of conidia . The species are identified according to morphologic differences in these structures, including the size, shape, texture, and color of the conidia.

Pathogenesis

In the lungs, alveolar macrophages are able to engulf and destroy the conidia. However, macrophages from corticosteroid-treated animals or immune compromised patients have a diminished ability to contain the

inoculum. In the lung, conidia swell and germinate to produce hyphae that have a tendency to invade preexisting cavities (aspergilloma or fungus ball) or blood vessels.

Clinical Findings

A. Allergic Forms

In some atopic individuals, development of IgE antibodies to the surface antigens of Aspergillus conidia elicits an immediate asthmatic reaction upon subsequent exposure. In others, the conidia germinate and hyphae colonize the bronchial tree without invading the lung parenchyma. This phenomenon is characteristic of **allergic bronchopulmonary aspergillosis,** which is clinically defined **as asthma**, recurrent chest infiltrates, eosinophilia, and both type I (immediate) and type III (Arthus) skin test hypersensitivity to Aspergillus antigen. Many patients produce sputum with Aspergillus and serum precipitins. They have difficulty breathing and may develop permanent lung scarring. Normal hosts exposed to massive doses of conidia can develop extrinsic allergic alveolitis.

B. Aspergilloma and Extrapulmonary Colonization

Aspergilloma occurs when inhaled conidia enter an existing cavity, germinate, and produce abundant hyphae in the abnormal pulmonary space. Patients with previous cavitary disease (eg, tuberculosis, sarcoidosis, emphysema) are at risk. Some patients are asymptomatic; others develop cough, dys-pnea, weight loss, fatigue, and hemoptysis. Cases of asper-gilloma rarely become invasive. Localized, noninvasive infections (colonization) by Aspergillus species may involve the nasal sinuses, the ear canal, the cornea, or the nails.

C. Invasive Aspergillosis

Following inhalation and germination of the conidia, invasive disease develops as an acute pneumonic process with or without dissemination. Patients at risk are those with lym-phocytic or myelogenous leukemia and lymphoma, stem cell transplant recipients, and especially individuals taking corticosteroids. The risk is much greater for patients receiving allogeneic (rather than autologous) hematopoietic stem cell transplants. In addition, AIDS patients with CD4 cell counts less than 50 CD4 cells/μL are predisposed to invasive asper-gillosis. Symptoms include fever, cough, dyspnea, and hemop-tysis. Hyphae invade the lumens and walls of blood vessels, causing thrombosis, infarction, and necrosis. From the lungs, the disease may spread to the gastrointestinal tract, kidney, liver,

brain, or other organs, producing abscesses and necrotic lesions. Without rapid treatment, the prognosis for patients with invasive aspergillosis is grave. Persons with less compromising underlying disease may develop chronic nec-rotizing pulmonary aspergillosis, which is a milder disease.

Diagnostic Laboratory Tests

A. Specimens, Microscopic Examination, and Culture

Sputum, other respiratory tract specimens, and lung biopsy tissue provide good specimens. Blood samples are rarely positive. On direct examination of sputum with KOH or calcofluor white or in histologic sections, the hyphae of Aspergillus species are hyaline, septate, and uniform in width (about 4 μm) and branch dichotomously (Figure F). Aspergillus species grow within a few days on most media at room temperature. Species are identified according to the morphology of their conidial structures .

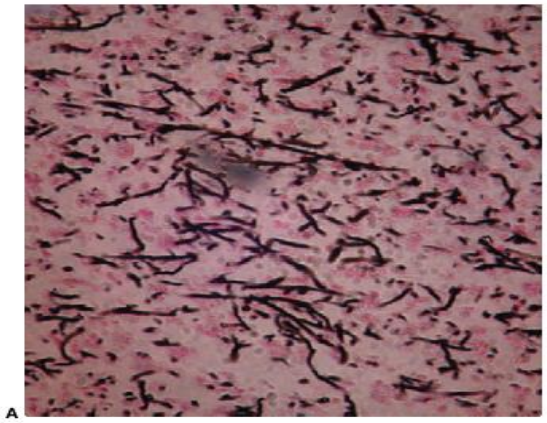

Fig F A Invasive aspergillosis. A: Uniform, branching septate hyphae (ca. 4 μm in width) of Aspergillus fumigatus in lung tissue stained with Gomori methenamine silver. 400×.

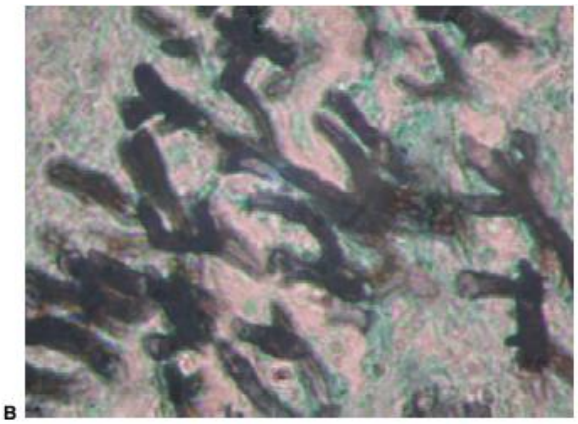

Fig F Invasive aspergillosis B: Similar preparation with Grocott stain. 1000×.

B. Serology

The ID test for precipitins to A fumigatus is positive in over 80% of patients with aspergilloma or allergic forms of asper-gillosis, but antibody tests are not helpful in the diagnosis of invasive aspergillosis. For the

latter, the serologic test for circulating cell wall galactomannan is diagnostic, although not entirely specific, for aspergillosis. In addition to testing for circulating galactomannan, the detection of β-glucan is also helpful in diagnosing invasive aspergillosis as well as candidiasis.

Treatment

Aspergilloma is treated with itraconazole or amphotericin B and surgery. Invasive aspergillosis requires rapid administration of either the native or lipid formulation of amphotericin B or voriconazole, often supplemented with cytokine immu-notherapy (eg, granulocyte-macrophage colony-stimulating factor or interferon γ). Amphotericin B-resistant strains of A terreus and other species, including A flavus and A lentulus, have emerged at several leukemia treatment centers, and the new triazole, posaconazole, may be more effective for these infections. The less severe chronic necrotizing pulmonary disease may be treatable with voriconazole or itraconazole. Allergic forms of aspergillosis are treated with corticosteroids or disodium cromoglycate.

Epidemiology and Control

For persons at risk for allergic disease or invasive aspergil-losis, 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 institute other measures to isolate patients and minimize their risk of exposure to the conidia of Aspergillus and other molds. Some patients at risk for invasive aspergillosis are given prophylactic low-dose amphotericin B or itraconazole.

MUCORMYCOSIS

Mucormycosis (zygomycosis) is an opportunistic myco-sis caused by a number of molds classified in the order Mucorales of the Phylum Glomerulomycota and Subphylum Mucoromycotina. These fungi are ubiquitous thermotolerant saprobes. The leading pathogens among this group are species of the genera Rhizopus , Rhizomucor, Lichtheimia, Cunninghamella , Mucor, et al. The most prevalent agent is Rhizopus oryzae. The conditions that place patients at risk include acidosis—especially that associated with diabetes mellitus—leukemias, lymphoma, corticosteroid treatment, severe burns, immune deficiencies, and other debilitating diseases as well as dialysis with the iron chelator deferoxamine. The major clinical form is rhinocerebral mucormycosis, which results from germination of the sporangiospores in the nasal

passages and invasion of the hyphae into the blood vessels, causing thrombosis, infarction, and necrosis. The disease can progress rapidly with invasion of the sinuses, eyes, cranial bones, and brain. Blood vessels and nerves are damaged, and patients develop edema of the inv

olved facial area, a bloody nasal exudate, and orbital cellulitis. Thoracic mucormyco-sis follows inhalation of the sporangiospores with invasion of the lung parenchyma and vasculature. In both locations, ischemic necrosis causes massive tissue destruction. Less frequently, this process has been associated with contaminated wound dressings and other situations. Direct examination or culture of nasal discharge, tissue, or sputum will reveal broad hyphae (10–15 μm) with uneven thickness, irregular branching, and sparse septations (Figure G). These fungi grow rapidly on laboratory media, producing abundant cottony colonies.

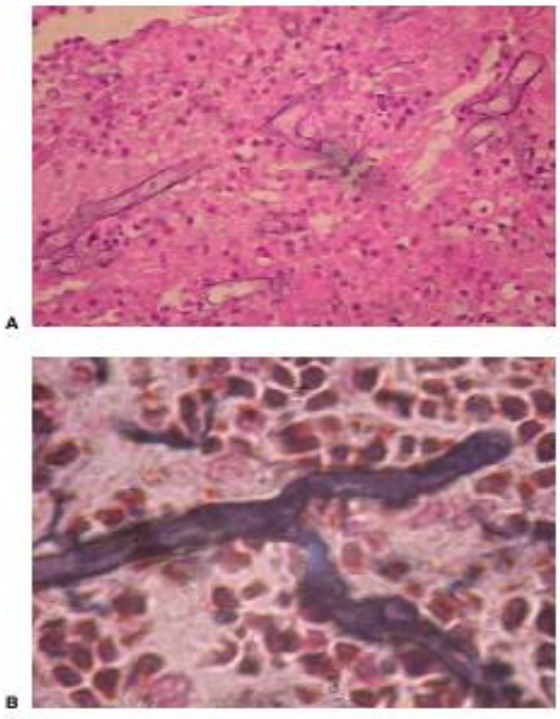

Fig G :- Mucormycosis A: Broad, ribbon-like sparsely septate hyphae (10–15 μm in width) of Rhizopus oryzae in lung tissue. H&E 400×. B: Similar histopathologic specimen, stained with Gomori methenamine silver. 1000×.

based on the sporangial structures. Treatment consists of aggressive surgical debridement, rapid administration of amphotericin B, and control of the underlying disease. Many patients survive, but there may be residual effects such as partial facial paralysis or loss of an eye.

PNEUMOCYSTIS PNEUMONIA

Pneumocystis jiroveci causes pneumonia in immune com-promised patients; dissemination is rare. For years, P jiroveci was thought to be a protozoan, but molecular biologic studies have proved that it is a fungus with a close relationship to ascomycetes. Pneumocystis species are

present in the lungs of many animals (rats, mice, dogs, cats, ferrets, rabbits) but rarely cause disease unless the host is immunosuppressed. Pneumocystis jiroveci is the human species, and the more familiar P carinii is found only in rats. Until the AIDS epidemic, human disease was confined to interstitial plasma cell pneumonitis in malnourished infants and immunosup-pressed patients (corticosteroid therapy, antineoplastic therapy, and transplant recipients). Prior to the introduction of effective chemoprophylactic regimens, it was a major cause of death among AIDS patients. Chemoprophylaxis has resulted in a dramatic decrease in the incidence of pneumonia, but infections are increasing in other organs, primarily the spleen, lymph nodes, and bone marrow.

Pneumocystis jiroveci has morphologically distinct forms: thin-walled trophozoites and cysts, which are thick-walled, spherical to elliptical (4–6 μm), and contain four to eight nuclei. Cysts can be stained with silver stain, toluidine blue, and calcofluor white. In most clinical specimens, the trophozoites and cysts are present in a tight mass that probably reflects their mode of growth in the host. Pneumocystis jiroveci contains a surface glycoprotein that can be detected in sera from acutely ill or normal individuals.

Pneumocystis jiroveci is an extracellular pathogen. Growth in the lung is limited to the surfactant layer above alveolar epithelium. In non-AIDS patients, infiltration of the alveolar spaces with plasma cells leads to interstitial plasma cell pneumonitis. Plasma cells are absent in AIDS-related Pneumocystis pneumonia. Blockage of the oxygen exchange interface results in cyanosis.

To establish the diagnosis of Pneumocystis pneumonia, specimens of bronchoalveolar lavage, lung biopsy tissue, or induced sputum are stained and examined for the presence of cysts or trophozoites. Appropriate stains include Giemsa, toluidine blue, methenamine silver, and calcofluor white. A specific monoclonal antibody is available for direct fluorescent examination of specimens. Pneumocystis cannot be cultured. While not clinically useful, serologic testing has been used to establish the prevalence of infection.

In the absence of immunosuppression, P jiroveci does not cause disease. Serologic evidence suggests that most individuals are infected in early childhood, and the organism has worldwide distribution. Cell-mediated immunity presumably plays a dominant role in resistance to disease, as AIDS patients often have significant antibody titers, and Pneumocystis pneumonia is not usually seen until the CD4 lymphocyte count drops below 400/μL.

Acute cases of Pneumocystis pneumonia are treated with trimethoprim-sulfamethoxazole or pentamidine isethionate. Prophylaxis can be achieved with daily trimethoprim-sulfamethoxazole or aerosolized pentamidine. Other drugs are also available.

No natural reservoir has been demonstrated, and the agent may be an obligate member of the normal flora. Persons at risk are provided with chemoprophylaxis. The mode of infection is unclear, and transmission by aerosols may be possible.

PENICILLIOSIS

Only one of the numerous and ubiquitous environmental species of Penicillium is dimorphic, Penicillium marneffei, and this species has emerged as an endemic, opportunistic pathogen. Penicillium marneffei is found in several regions of southeast Asia, including southeastern China, Thailand, Vietnam, Indonesia, Hong Kong, Taiwan, and the Manipur state of India. Within these endemic areas, P marneffei has been isolated from soil and especially soil that is associated with bamboo rats and their habitats. At ambient temperatures, the mold form grows rapidly to develop a **green-yellow colony with a diffusible reddish pigment.** The septate, branching hyphae produce aerial conidiophores bearing phialides and basipetal chains of conidia, similar to the structures . In tissue, the hyphal forms convert to unicellular yeast-like cells (ca. 2 × 6 μm) that divide by fission. The major risk for infection is immunodeficiency due to HIV/AIDS, tuberculosis, corticosteroid treatment, or lymphoproliferative diseases. The clinical manifestations include fungemia, skin lesions, and systemic involvement of multiple organs, especially the reticuloendothelial system. Early signs and symptoms are non specific and may include cough, fever, fatigue, weight loss, and lymphadenopathy. However, 70% of patients, with or without AIDS, develop cutaneous or subcutaneous papules, pustules, or rashes, which are often located on the face. From specimens of skin, blood, or tissue biopsies, the diagnosis can be established by microscopic observation of the yeast-like cells and positive cultures. The treatment usually entails a defined course of amphotericin B followed by itra-conazole. Without treatment, the mortality has exceeded 90%.