Paparella: Volume I: Basic Sciences and Related Disciplines

Section 5: Microbiology

Chapter 26: Mycoses

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Although they were at one time largely medical curiosities, mycotic infections of the head and neck have been recognized with increased frequency over the past two decades. Enhanced imaging with computed tomography and magnetic resonance scanning and improvements in serology testing have led to an increase in diagnostic capabilities. Increased use of broad-spectrum antibiotics has contributed by enhancing fungal growth via alteration of normal flora. However, the most important factor leading to the rise in incidence of mycotic infections has been the increase in the number of immunocompromised individuals.

Most potentially pathogenic fungi are ubiquitous soil saprophytes or even normal human commensals. They are capable of causing isolated limited disease if local defense mechanisms are compromised such as with an obstructed sinus or an implanted foreign body, but in general, invasive systemic disease is possible only in the presence of immunodeficiency. The number of patients at risk for invasive fungal disease is on the rise because of (1) improvements in the care of premature infants and the elderly, leading to increased numbers of patients at the extremes of age; (2) new chemotherapeutic agents and protocols with improved survival rates, especially among patients with lymphoreticular malignancies; (3) advances in organ transplantation with the increasing necessity for chronic immunosuppressive therapy; and (4) the increasing number of patients with the diagnosis of acquired immunodeficiency syndrome.

The diagnosis of fungal infections is predicated on physician suspicion based on an awareness of the types of patients at greatest risk and the typical clinical presentation of fungal illnesses. Biopsy is the most important diagnostic tool and every specimen should be divided into two parts for staining and for culture. Overall, the most sensitive fungal stains are the methenamine-silver stains, although Gram's stain is useful in identifying infection with *Candida* and mucicarmine stain can be diagnostic for cryptococcal infection. Repeat biopsies are indicated when initial attempts are nondiagnostic. In addition, the clinical must keep in mind that histologic findings may mimic other disease entities such as squamous cell carcinoma. Close communication between the clinician and the pathologist is extremely important in order to have the best chance for early diagnosis. The patient's overall condition may be too serious to allow the luxury of awaiting culture results in order to confirm tissue diagnosis before beginning therapy.

The cornerstone of treatment of fungal infections is correction of the underlying predisposing pathophysiology such as with aeration and drainage of infected sinuses, removal of contaminated indwelling catheters, or treatment of acidosis and dehydration in diabetic patients. Unfortunately, correction of underlying immunodeficiencies is often not possible, and with the presence of invasive or disseminated disease, systemic antifungal drug therapy becomes the

mainstay of treatment. Amphotericin B remains the gold standard of systemic antifungal drugs, although problems with toxicity with this drug require constant careful patient monitoring. Although not primarily excreted by the kidneys, the drug is nephrotoxic and causes usually reversible tubular acidosis with the potential for hypokalemia and azotemia. All patients should be followed with laboratory studies of serum creatinine, BUN, electrolytes, and complete blood counts on a regular basis. 5-Flucytosine is often used in conjunction with amphotericin B for severe or resistant infection, and because it is primarily excreted by the kidneys, alterations in dosage levels may be necessitated because of changing renal function. Newer antifungal azoles such as ketokonazole and fluconazole have the advantages of lower levels of toxicity and the capacity to be administered orally, and are effective for some infections. Overall, the treatment of systemic fungal infections is complex and difficult, and the otolaryngologist should enlist the help of infectious disease specialists and other appropriate medical specialists whenever possible.

Aspergillosis

Aspergillus species are ubiquitous in soil and may cause disease in humans via inhalation of spores. Histologically, *Aspergillus* organisms appear as septate hyphae of uniform diameter with 45-degree angle branching. Aspergillosis has been recognized with increasing frequency in recent years, and it now represents the most common diagnosis in cases of fungal sinusitis. In immunocompromised patients, aspergillosis is second only to candidiasis in overall frequency of fungal infections.

In the sinuses, aspergillosis may become manifest in four different forms. Isolated noninvasive disease may be in the form of a solitary fungus ball, similar to intracavitary pulmonary mycetoma. Most commonly, chronic disease of a single maxillary sinus without evidence of bone destruction can be cured by a surgical drainage procedure. Histologically, a mass of fungal hyphae is seen adjacent to normal mucosa with little inflammatory reaction. Presumably, obstruction of the sinus ostium from mechanical or inflammatory causes leads to a low oxygen environment favorable for fungal growth.

Invasive fungal disease may be either slowly progressive or fulminant. Slowly progressive disease should be suspected in an apparently immunocompetent person with chronic sinusitis that progresses despite multiple medical and surgical treatments. One such patient treated by the author demonstrated progression of disease over a 25-year period, which finally involve the entire upper aerodigestive tract despite multiple surgical debridements and courses of antifungal drugs. Diagnosis is based on biopsies demonstrating tissue invasion by fungal hyphae with a granulomatous and fibrous tissue response.

Fulminant invasive aspergillosis is seen only in immunocompromised patients, and it has become relatively common in large cancer and transplant centers. Patients with a diagnosis of acute leukemia, lymphoma, or aplastic anemia and patients who have undergone bone marrow transplants and renal transplants during the first 6 months after surgery are at highest risk. Predisposing factors include steroid and broad-spectrum antibiotic use, low granulocyte count, and prolonged hospitalization. In immunocompromised patients, aspergillosis has a propensity

to invade vascular walls, leading to thrombosis and ischemic tissue necrosis. Early diagnosis is mandatory because the fungus tends to rapidly disseminate locally to the orbit and brain and systemically to lungs, liver, and spleen. Again, promptly performing a biopsy to demonstrate the presence or absence of tissue invasion by fungal hyphae is the key. A nasal smear or sinus aspirate with KOH preparation demonstrating fungi should be considered sufficient for diagnosis when clinical signs and symptoms, such as increasing nasal discharge and congestion with high spiking fevers, neuralgic facial and orbital pain, and headache, are present. Early on, the nasal or oral examination may demonstrate areas of pale grayish, relatively insensate mucosa. The physician should not wait for the appearance of the classic turbinate or palatal black necrosis to confirm the diagnosis. Similarly, sinus radiographs may be unremarkable due to the lack of immune response. Computed tomography is indicated as soon as the possibility of invasive disease is considered in order to attempt to demonstrate bony erosion or soft tissue involvement.

The most effective treatment, though it is not often possible, consists of prompt resolution of the underlying immunodeficiency. Immediate surgical debridement of devitalized tissue and aeration of involved sinuses should be undertaken. Amphotericin B remains the mainstay of medical therapy, with 5-flucytosine added when the initial response is poor. Newer drugs such as liposomal-amphotericin B are currently undergoing evaluation. Overall, the prognosis for fulminant aspergillosis remains poor. Patients with favorable initial responses to treatment often show recurrence when additional immunosuppressive therapy becomes necessary.

Finally, sinus aspergillosis may be exhibited as an allergic phenomenon analogous to allergic bronchopulmonary aspergillosis. This relatively newly described entity is most commonly seen in young patients with nasal polyps and a history of asthma and pansinusitis that is refractory to medical treatment. The underlying pathology appears to be a local immunologic reactivity to *Aspergillus antigens.* Computed tomography demonstrates a very characteristic picture of diffuse expansile sinus involvement with areas of dense concretions. Bony erosion may be present. Initial treatment consists of careful complete sinus drainage. Grossly, the sinuses are filled with thick, inspissated, greenish black mucus. Eosinophils, Charcot-Leyden crystals, and scattered fungal hyphae are seen histologically, although cultures are usually negative. Recurrences after surgery alone are common; therefore, most authors recommend additional treatment with nasal steroid preparations and appropriate allergy regimens.

Zygomycosis (Mucormycosis or Phycomycosis)

Like *Aspergillus* species, fungi of the class *Zygomycetes* are saprophytes found widely throughout nature that may cause a variety of diseases in humans. The most commonly cultured organisms are those of the genera *Mucor, Rhizopus,* and *Absidia.* Histologically, they appear as irregularly sized and shaped, broad non-septated hyphae. Again, as with *Aspergillus* species, they have a propensity to invade arterial walls in immunocompromised patients, leading to thrombosis and tissue infarction.

Pulmonary, gastrointestinal, and cardiac forms of zygomycosis are well described but over one half of all reported cases in recent years are of the rhino-orbito-cerebral type. Seventy per

cent of patients with this form of disease have uncontrolled diabetes mellitus at presentation. Presumably, hyperglycemia and acidosis enhance tissue invasion and fungal growth. The remainder of cases generally occur in cancer or transplant patients with profound immunosuppression. Risk factors include severe neutropenia, recent chemotherapy, and the use of steroids and broad-spectrum antibiotics. The disease begins in the nose or sinuses and, if unchecked, may rapidly spread along vascular channels to involve first the orbital apex and then the cavernous sinus. Invasion of the carotid arteries can lead rapidly to cerebral ischemia and death.

As with all invasive fungal diseases, early diagnosis is of paramount importance. A recent onset of nasal congestion, rhinorrhea, or facial pain, with unexplained fever, lethargy, or headache should rapidly prompt a nasal biopsy in patients at risk. Signs of orbital involvement such as proptosis, ptosis, orbital fixation, and blindness portend a grave prognosis. Sinus radiographs may be very nonspecific, with bony erosion becoming apparent only after extensive soft tissue necrosis has occurred.

Management should consist of treatment of the underlying disease, is possible; correction of dehydration and acidosis; wide surgical debridement of devitalized tissue; and administration of amphotericin B. *Zygomycetes* organisms are generally resistant to 5-flucytosine. Overall survival in diabetic patients approaches 70 to 80 per cent when the underlying ketoacidosis is corrected. Survival rates in nondiabetic immunosuppressed patients are very poor.

Candidiasis

Candida species are normal human commensals that commonly can be cultured from the oral cavities of healthy individuals. In general, *Candida* species do not cause disease unless the normal bacterial flora has been altered by the use of broad-spectrum antibiotics or the patient has become immunocompromised in some manner. By far, the most common form of candidiasis in the head and neck is thrush, or oral candidiasis. Thrush usually is exhibited as a white curd-like pseudomembrane in the oropharynx, which, when wiped away, reveals red, inflamed underlying mucosa. Thrush can also involve the buccal areas and, if untreated, may eventually result in angular cheilitis. Predisposing factors include diabetes mellitus, vitamin deficiencies, drooling, and chronic irritation from denture plates as well as the administration of antibiotics and steroids. The diagnosis can be made easily from oral smears or scrapings that demonstrate broad pseudohyphae (actually budding yeast forms) and small yeast forms with Gram's stain or KOH preparation. Treatment consists of topical antifungal medication, such as oral nystatin rinses or clotrimazole troches, and general measures, such as improved oral hygiene and the discontinuation of antibiotics.

Thrush is most commonly a disease of the very young and the very old, and the diagnosis in other age groups should raise the suspicion of an underlying immune system disorder. Specifically, when the diagnosis of oral candidiasis is made in a previously healthy adult with a history of risk factors for AIDS, then progression to serious opportunistic AIDS-associated infections is likely within 6 months. T-cell immunity is critical for protection from fungal

infection, and up to 30 per cent of AIDS patients have evidence of candidiasis at the time of their initial diagnosis. AIDS patients with oral thrush and odynophagia demonstrate a high likelihood of having esophageal candidiasis. When esophagitis is suspected, a barium swallow is indicated to reveal the characteristic "cobblestone" pattern. Oral clotrimazole troches are often effective; however, intravenous medication may be necessary when swallowing is impossible.

Laryngeal candidiasis is rare in otherwise healthy individuals, but it has been increasingly reported in immunocompromised patients. The diagnosis of laryngeal candidiasis should be strongly considered in any patient with a serious underlying illness who develops unexplained hoarseness or dysphasia, especially if they have received broad-spectrum antibiotics or steroids. Laryngoscopy reveals edema, ulcerations, and sometimes pseudomembranes. The diagnosis is confirmed by a biopsy that demonstrates tissue invasion by *Candida* organisms. Treatment consists of systemic and topical antifungal agents, with careful observation for the possible development of airway obstruction.

Systemic Mycoses

Histoplasmosis

Histoplasmosis is endemic in some areas of North America, especially in the Mississippi and Ohio River valleys, where up to 90 per cent of adults may acquire some type of infection via inhalation of fungal spores. By far, the most common type of histoplasmosis is acute pulmonary disease, which generally runs a benign self-limiting course with symptoms similar to that of a viral upper respiratory illness. On occasion, primary pulmonary disease may fail to arrest and may disseminate hematogenously to other organ systems either during the acute phase of disease or years after the primary infection. Factors influencing progression to disseminated disease include age (infant or elderly individual), nutritional status, and overall level of immunocompetence.

In its mucocutaneous form, chronic disseminated histoplasmosis may involve the head and neck area. Any portion of the upper aerodigestive tract may be involved, including the nasal mucosa, the oral cavity, the larynx, and the esophagus. Patients may exhibit ulcerations, edema with mass effect, or cutaneous lesions, and possible symptoms including dysphasia, hoarseness, and dyspnea from airway obstruction. Patients with disseminated disease generally have a history of intermittent low-grade fever, fatigue, and weight loss. Other manifestations of disseminated histoplasmosis include endocarditis, hepatosplenomegaly, and meningitis.

Disseminated histoplasmosis may mimic many other disease, including tuberculosis, syphilis, lymphoma, and squamous cell carcinoma, and a high index of suspicion is required for diagnosis. Skin tests are almost worthless in patients older than 6 months of age because of the high incidence of primary disease. Calcified densities on chest radiographs are suggestive of primary disease, and multiple calcifications are almost pathognomonic of previous disease. Rising or high complement fixation titers are highly suggestive of active disease, although false-positive findings may result from other fungal infections such as blastomycosis. The only laboratory tool

available for unequivocal diagnosis is culture of the organism, but this is sometimes difficult even after repeated attempts. A biopsy that demonstrates intracellular round-to-ovoid encapsulated yeast with a clinical picture suggestive of disseminated disease is sufficient for diagnosis and treatment. The demonstration of tissue reaction, including granulomas and caseous necrosis, may help to support the diagnosis. The clinician must keep in mind that fungal infection may cause pseudoepitheliomatous hyperplasia and may mimic squamous cell carcinoma, both grossly and microscopically. More than one patient has undergone a laryngectomy because of a missed diagnosis of laryngeal fungal infection.

Disseminated histoplasmosis is a systemic disease requiring systemic treatment with amphotericin B. Mucosal lesions usually respond in 6 to 8 weeks, and patients with laryngeal involvement may require a temporary tracheotomy for relief of airway obstruction. The patient must be followed closely after treatment for development of sudden exacerbations or relapses.

Blastomycosis

Like histoplasmosis, blastomycosis is fundamentally a pulmonary disease caused by inhalation of fungal spores. The initial lung involvement is usually mild and self-limiting, although occasionally severe pneumonia is seen. A minority of patients have late onset disseminated disease, with the skin as the most common site of involvement. Skin lesions usually include large verrucous ulcers with indurated borders, which may mimic squamous cell carcinoma. Mucosal lesions are less common in blastomycosis than in histoplasmosis and may involve any site in the upper aerodigestive tract.

The possibility of laryngeal blastomycosis is important to keep in mind when evaluating patients with chronic unexplained cough and hoarseness, especially when the patients have a history of low-grade fevers, occasionally hemoptysis, weight loss, and skin lesions. Grossly, laryngeal involvement may appear as ulcerations, edema, erythema, or fungating masses. Microscopically, pseudoepitheliomatous hyperplasia and microabscesses may be present. The diagnosis is confirmed by culturing *Blastomyces dermatitidis* on Sabouraud's agar or by demonstrating thick-walled refractile yeasts with single broad-based buds inside giant cells. Skin tests are unreliable, and serologic tests may cross react with other fungal diseases. Any manifestation of disseminated disease requires systemic treatment. Subacute or chronic progressive disease may be treated with oral ketoconazole, but patients with meningitis or evidence of respiratory compromise should be treated with amphotericin B due to the sometimes slow initial response to ketoconazole.

Coccidiomycosis

Coccidiomycosis is also a primary pulmonary disease, in this case caused by inhalation of arthrospores of *Coccidioides immitis.* The disease is endemic in parts of the southwestern USA, Mexico, and Central and South America. Most patients have a self-limiting illness with symptoms of cough, fever, headache, sore throat, and chest pains, but a few go on to have disseminated disease with the possibility of developing meningitis or destructive ulcerative facial

lesions. Laryngeal involvement is possible and granulomatous cervical adenopathy has been described.

The diagnosis of coccidioidomycosis can be confirmed by culture or by the demonstration of large endospore-packed spherules, possibly in association with caseating granulomas on biopsy. Rising complement fixation titers help to confirm the diagnosis of active disease. Again, disseminated disease should be treated with systemic therapy such as amphotericin B, micoconazole, or ketoconazole.

Cryptococcosis

Cryptococcosis may rarely be exhibited as an isolated pulmonary or sinus disease in an otherwise healthy patient, but the majority of cases are found in severely immunocompromised individuals. The organism is neurotropic, and 90 per cent of cryptococcosis is seen in the form of a meningeal infection. It should be strongly suspected when meningeal symptoms occur in patients with AIDS or lymphoreticular malignancies. The diagnosis is confirmed by demonstrating the organism in cerebrospinal fluid through stain or culture. Overall, 10 per cent of patients with cryptococcosis have mucocutaneous lesions. Morphologically, the organisms of *Cryptococcus neoformans* or *C. immitis* appear as yeast cells surrounded by clear halos on India ink preparations. The halo effect is due to yeast's mucopolysaccharide capsule. Relatively specific serologic tests are available for *C. immitis*, with a high or rising complement fixation indicating disseminated disease. The best available therapy for disseminated cryptococcosis consists of amphotericin B and 5-flucytosine, although the former has poor cerebrospinal fluid penetration and the latter is extremely myelotoxic in AIDS patients. Cryptococcal meningitis in a severely immunocompromised patient is often a terminal complication, with remissions occurring during systemic antifungal therapy and relapses occurring soon after drugs are discontinued.

Otomycoses

The external ear canal is a moist warm cavity that provides a potentially favorable environment for fungal growth. In fact, culture studies have demonstrated that up to 30 per cent of healthy individuals have saprophytic fungi on the surface of the skin of the ear canal. The layer of acidic wax overlying the epithelium of the lateral canal normally provides a barrier to disease. However, when the wax and superficial epithelium are disrupted by local trauma, as occurs with scratching or Q-tips or by bacterial or other forms of dermatitis, then fungal invasion and deep tissue disease are possible. The most common fungi cultured from infected ears are various *Aspergillus* species and *Candida albicans.*

The most common symptom of fungal external otitis, at least initially, is pruritus as opposed to the deep-seated pain and tenderness usually seen with predominantly bacterial infections. Initially, the ear examination may reveal mild erythema and edema only. An established infection shows desquamated epithelial debris with pus and overlying filamentous fungi with spores. The underlying skin may be extremely tender, red, and edematous.

Initial treatment consists of careful removal of all infected debris either with direct suctioning under magnification or via gentle irrigation with mildly acidic solution. Ear cleansing should be repeated frequently until the infection is resolved. Topical therapy generally consists of the administration of mildly acidic drops, such as boric acid and alcohol, or modified Burow's solution. For refractory cases, some authors recommend tolanftate cream, gentian violet, or amphotericin-B/chloramphenicol/boric acid topical powder application. At least as important as topical antifungal agents are general measures, such as advising the patient to avoid local trauma from scratching and to keep the ear dry when bathing.

The temporal bone can be involved with systemic fungal infection, again usually in immunocompromised patients. Up to 25 per cent of patients with cryptococcal meningitis develop significant neurosensory hearing loss. The most common histologic finding with invasive fungal disease of the temporal bone is fungal infiltration of the eight nerve in the internal auditory canal. Infiltration of the sensory organs of the membranous labyrinth has also been associated with disseminated fungal disease.