SPECIAL REVIEW

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Deep Fungal Infections in the Elderly

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As the population ages but continues to be active and to travel extensively, it is likely that more elderly people will be exposed to and infected with deep fungi endemic in certain areas of the country. Travel to the rural Midwest may lead to contact with *Histoplasma capsulatum,* whereas exposure to southwestern desert country may result in infection with *Coccidioides immitis.* Leisure activities, such as gardening, expose the elderly person to infection with *Sporothrix schenckii.*

The elderly person is at risk, not only for new infection, but also for reactivation of prior infection with certain deep fungi. This reactivation may occur years after the initial exposure to the organism. For example, histoplasmosis in a retiree who was originally from Kentucky but who now lives in Arizona may be missed unless one remembers to seek evidence for infection with organisms found in the original place of residence.

The natural history of certain fungal infections, such as histoplasmosis, is such that manifestations of disease are more severe at the extremes of age. Histoplasmosis is more likely to present as a disseminated infection in the very young and in the elderly, and the mortality from this infection is greater at the extremes of age.[1] On the other hand, other fungal infections, such as blastomycosis, do not appear to show an age-related worsening in the severity of illness. The four major deep fungal infections endemic in the United States—histoplasmosis, blastomycosis, coccidioidomycosis, and sporotrichosis—will be reviewed. Those aspects of infection in which age appears to play a significant role will be emphasized.

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HISTOPLASMOSIS

General Characteristics of Infection *Histoplasma capsulatum* is a dimorphic fungus which is endemic to the Ohio and Mississippi river valleys and is also common in scattered foci in southeastern and midwestern states.[2] The organism grows to high numbers in environments such as caves, deserted buildings, and other areas in which birds and bats may congregate and fertilize the soil. *H. capsulatum* is a true pathogen, infecting the normal person who inhales the spores of the mycelial form of the fungus. Once in the host, the fungus shows its dimorphic characteristics and assumes a yeast-like form in tissues.

Although initially causing pulmonary infection, in almost all hosts the organism disseminates widely, albeit silently, to cells of the reticuloendothelial system, parasitizing macrophages in spleen, liver, bone marrow, and other organs.[3] In over 99% of patients infected with *H. capsulatum,* cell-mediated immunity develops with T-cell sensitization and macrophage activation, resulting in the death of the fungus.[4] In certain hosts, the macrophage remains unable to kill the ingested yeast and clinical disease results. The two major forms of clinical disease due to *H. capsulatum* are pulmonary and disseminated infection. In both forms, there is a disproportionate number of elderly individuals affected, especially in the chronic cavitary type of pulmonary infection and the progressive type of disseminated infection.

CHRONIC CAVITARY PULMONARY HISTOPLASMOSIS

Risk of Infection in the Elderly Chronic cavitary pulmonary histoplasmosis affects almost entirely middle-aged to elderly men who have a history of chronic obstructive pulmonary disease.[5] In a 20-year study in Tennessee, Goodwin et al[6] found that 23% of 228 patients with chronic cavitary pulmonary histoplasmosis were over the age of 60 and 30% were aged 50 to 59 years.[6] Data from the late 1940s through the early 1960s showed a similar trend, with the chronic cavitary pulmonary form of histoplasmosis clustered almost entirely

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in those over the age of 50 and with at least one quarter of all the cases in those over the age of 60.[7,8] In Wheat's study of the massive outbreak of histoplasmosis in Indianapolis in 1978,[9] patients over the age of 60 were clearly at risk for the development of cavitary pulmonary histoplasmosis. Twenty-three of 71 patients over the age of 60 (32%) developed cavitary lesions compared with 23 of 139 patients aged 40 to 59 years (16%) and 14 of 358 patients aged 20 to 39 years (4%). The combination of chronic obstructive pulmonary disease plus age over 60 characterized those at greatest risk of cavitation; 70% of patients with these two risk factors developed cavitary pulmonary histoplasmosis.[9]

Clinical Manifestations Patients with this form of histoplasmosis are often mistakenly thought to have tuberculosis. The major pulmonary symptoms are cough, sputum production, and dyspnea. In addition, constitutional symptoms, such as malaise, fatigue, weakness, fever, night sweats, and weight loss are common.[6] The chest roentgenogram shows unilateral or bilateral upper lobe infiltrates with one or more cavities, similar to the findings in tuberculosis (Figure 1).

Diagnosis The diagnosis of chronic cavitary pulmonary histoplasmosis is usually made with a combination of microbiological and serological studies. The organism can be cultured from sputum; the yield is increased greatly if the microbiology laboratory uses special media to eliminate other contaminating fungi, such as Candida and Aspergillus.[10] *H. capsulatum* may take as long as 6 to 8 weeks to grow in culture, but may also appear in 2 weeks. The usual serologic studies performed are those which detect either complement fixing or precipitating antibodies to *H. capsulatum*. Serology can provide presumptive evidence for a diagnosis of histoplasmosis before the cultures have yielded any growth.[6,11] Skin tests are not used in the diagnosis of histoplasmosis because most persons living in the endemic area will have a positive skin test, regardless of whether they have active or inactive infection with *H. capsulatum*.

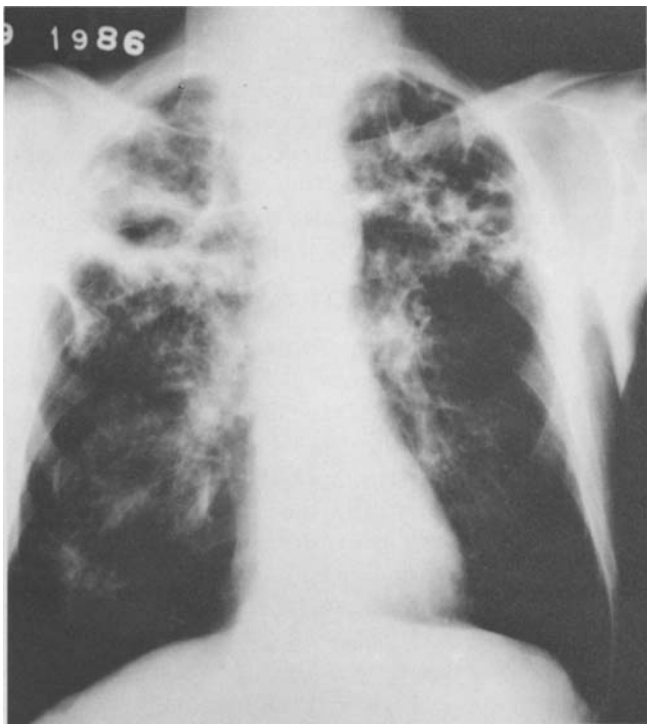

FIGURE 1. *Chest roentgenogram of a 65-year-old patient with chronic cavitary pulmonary histoplasmosis. Extensive bilateral cavitary disease is present in this man who had severe chronic obstructive pulmonary disease.*

Treatment Studies performed after the introduction of amphotericin B showed that the chronic cavitary form of histoplasmosis was frequently associated with a fatal outcome and that treatment with amphotericin B significantly reduced the mortality rate.[7,12] However, as pointed out by Goodwin et al, the overall mortality rate remains high even with therapy because of the serious underlying chronic obstructive pulmonary disease manifested by almost all patients with the chronic cavitary form of histoplasmosis. Treatment with amphotericin B generally requires administration of 25 mg/kg of drug over 6 to 8 weeks.[7,12] Ketoconazole administration is an effective alternative therapy for patients with chronic cavitary pulmonary histoplasmosis. The dose usually given is 400 mg daily for 6 to 12 months, although some patients will require 800 mg daily to control the infection.[13] Relapses can occur after therapy with ketoconazole, as well as after amphotericin B therapy.[7,12,13]

PROGRESSIVE DISSEMINATED HISTOPLASMOSIS

Risk of Infection in the Elderly Progressive disseminated infection with *H. capsulatum* is a rare manifestation of histoplasmosis, occurring almost entirely at the extremes of age. Children less than one year old and the elderly are most likely to develop this form of histoplasmosis. In a large series of 84 cases of disseminated histoplasmosis seen over a period of 46 years, Goodwin et al found that 42% of the adults were over the age of 60.[1] This is similar to previous data in which anywhere from 30% to 50% of adults with progressive disseminated histoplasmosis were over the age of 60 years.[14,15] In their study of the Indianapolis outbreak, Wheat et al included 60 patients with disseminated infection.[16] They found that age greater than 54 years and immunosuppression were the major risk factors for development of disseminated infection.

The reasons for the increased risk of progressive disease in elderly individuals are not entirely clear. Most likely, the waning of cell-mediated immunity, which occurs with aging, plays a role. Whether the defect is entirely within the T lymphocyte or whether macrophage dysfunction is important in allowing *H. capsula-*

tum to multiply is not known. The patient with this form of histoplasmosis shows continued parasitization of macrophages and an inability to kill the organism.[1,3] In some instances it is likely that dissemination is the result of reactivation of prior infection in an elderly individual.[17]

Clinical Manifestations Symptoms manifested by patients with progressive disseminated histoplasmosis include fever, fatigue, weakness, anorexia, and weight loss. Patients may present with a history of non-healing mucosal ulcerations.[3,14,15] Addison's disease is seen with involvement of the adrenal glands, and the initial presentation may be that of Addisonian crisis[14] (Figure 2). The disease may be slowly progressive over a period of years or may be subacute with significant disease manifestations occurring within several months of infection. Oropharyngeal ulcerations may appear anywhere on the buccal mucosa, palate, tongue, or oropharynx. Hepatosplenomegaly is common, whereas lymphadenopathy and skin lesions occur less often.[1,14,15] Laboratory studies will often reveal anemia, leukopenia, and thrombocytopenia, as well as an increase in the alkaline phosphatase if liver involvement is prominent. The chest roentgenogram may show diffuse pulmonary lesions or may appear normal.

Diagnosis The diagnosis of progressive disseminated histoplasmosis is best made by pathologic examination of the involved tissues. Bone marrow aspiration and biopsy are especially useful; liver or lymph node biopsy may also show the organism in macrophages. Intracellular *H. capsulatum* may be identified with the use of the methenamine silver or Giemsa stain[18] (Figure 3). In addition to pathologic examination, all biopsy material should be submitted for fungal cultures. A positive culture provides definitive proof of histoplasmosis, but generally takes weeks to grow. Both the complement fixation and the precipitin antibody tests are positive in most patients with disseminated histoplasmosis, providing suggestive evidence for the diagnosis before cultures have shown the organism.[11] A biopsy should always be sought in order to confirm the diagnosis in patients with positive serologies.

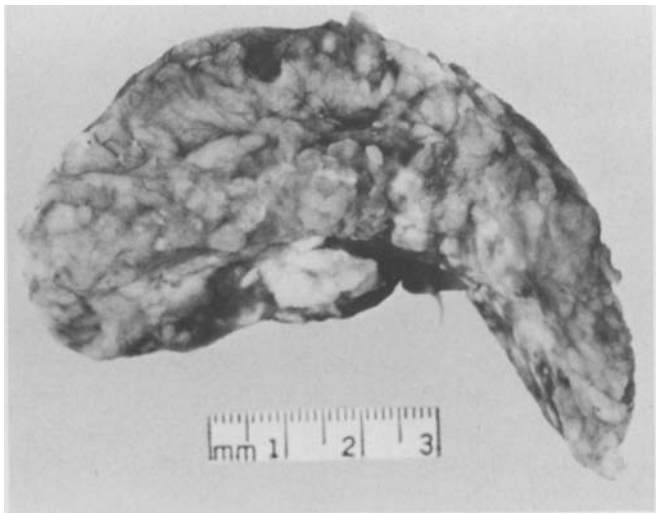

FIGURE 2. *Adrenal gland from a 60-year-old man who died in Addisonian crisis secondary to histoplasmosis. The adrenal is approximately five times normal size; on microscopic examination there was extensive replacement of the entire gland with* Histoplasma capsulatum.

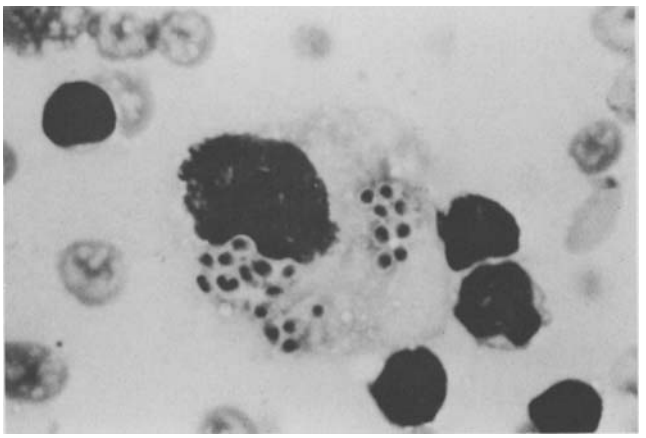

FIGURE 3. *Bone marrow aspirate from a 68-year-old man with pancytopenia, adrenal insufficiency, and a tongue ulcer. The macrophage is parasitized with* Histoplasma capsulatum. *Giemsa stain.*

Treatment The progressive disseminated form of histoplasmosis is generally fatal unless treated, although in some patients the disease may run a protracted course for many years before death occurs.[1,7,19] Treatment with amphotericin B has been the standard therapy, although ketoconazole has also been shown to be effective at a dose of 400 mg or 800 mg daily.[13]

BLASTOMYCOSIS

General Characteristics of Infection *Blastomyces dermatitidis* is a dimorphic fungus found along the Mississippi River basin from Canada to the Gulf of Mexico and throughout the southeastern United States. Presumably, the organism's ecological niche is in soil, although it has been difficult to grow the organism from soil samples, even in areas where outbreaks have occurred.[20]

The spores (mycelial phase) are inhaled, causing pulmonary infection; the organism assumes the yeast phase in tissues. Although *Blastomyces* may remain localized to the lungs, presenting as pneumonitis, the organism may spread hematogenously, manifesting as cutaneous lesions, osteomyelitis, genitourinary tract infection, or other less common presentations.[21,22] The host response is both neutrophilic (suppurative) and granulomatous with sensitized lymphocytes and activated macro-

phages.[21] Both phagocytic systems appear to be important in eliminating the organism.[23,24]

Risk of Infection in the Elderly In contrast to histoplasmosis, in which chronic cavitary pulmonary infection and progressive disseminated infection are heavily skewed toward those aged over 60 years, there seems to be no disproportionate number of cases of blastomycosis in the elderly population. Most reports from the 1940s through the 1970s show the major group at risk to be 30- to 40-year-old men.[21,22,25-27] Many have been engaged in outdoor occupations and presumably were exposed to *Blastomyces* in work-related activities.[26]

The effect of age as a factor leading to a worse outcome in blastomycosis has not been addressed specifically in most reports containing large numbers of cases.[21,22,25,26] It would appear that blastomycosis is different from histoplasmosis in that there is little evidence for increased morbidity as a function of age. For example, careful review of all the case histories listed in Gonyea's review of central nervous systems blastomycosis[28] showed no increase of this serious manifestation of blastomycosis in those over 60 years of age. The majority of cases were in those 30 to 40 years of age. On the other hand, fatal adult respiratory distress syndrome due to blastomycosis has occurred more often than expected in elderly patients.[29]

Clinical Manifestations The clinical manifestations of blastomycosis may be those of pulmonary infection, reflecting the portal of entry, or those of disseminated infection, usually with cutaneous, bone, and genitourinary involvement predominating. Pulmonary infection, especially in those involved in an outbreak, may be an acute pneumonitis with fever, myalgias and either a dry or a productive cough.[27,30] In contrast, many patients present with a clinical picture similar to that seen in tuberculosis, with low-grade fever, night sweats, anorexia, weight loss, and a chronic productive cough.[22,27] The chest roentgenogram may show a patchy pneumonitis, upper lobe cavitary lesions, or bilateral extensive infiltrates (Figure 4).

Cutaneous involvement is quite common, and the lesions are usually distinctive in appearance. They are usually slowly enlarging, verrucous, reddish to purplish lesions with crusting; microabscesses and granulomatous components are both present (Figure 5). Some patients develop more acute postular or ulcerated lesions. The lesions may occur anywhere, but often the face and arms are involved.

Bone and genitourinary tract are the next most common organ systems involved.[22] The patient may have symptoms, such as pain, swelling, and erythema of the skin overlying the involved bone. Genitourinary involvement is often asymptomatic but may present as dysuria, hesitancy, pyuria, or epididymal or testicular swelling.

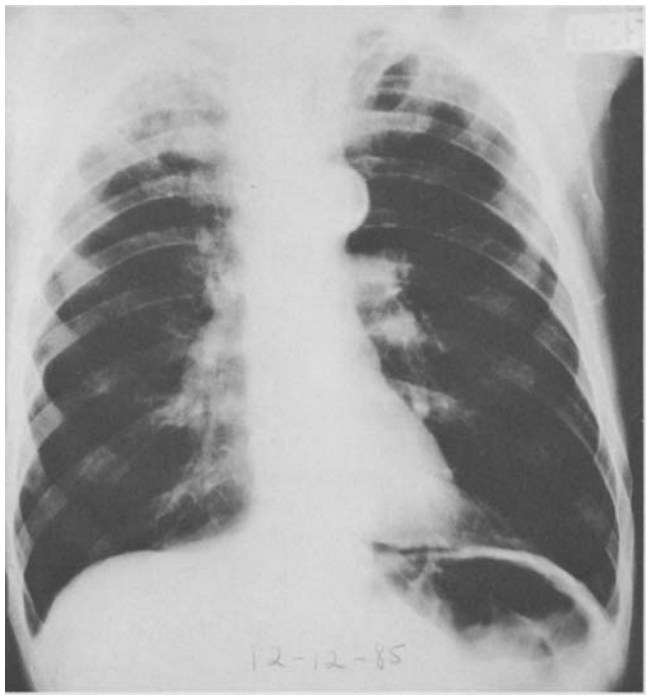

FIGURE 4. *Chest roentgenogram of a 72-year-old man with blastomycosis. Cutaneous and articular involvement was also present.*

Diagnosis Blastomycosis can be diagnosed by direct examination of infected body fluids or tissues or by growth of *B. dermatitidis* in culture. *B. dermatitidis* is a large thick-walled yeast with a single broad-based bud. Cytologic preparations of sputum or bronchial washings often are positive (Figure 6), and direct smears or KOH preparations of purulent material, synovial fluid, sputum, or centrifuged urine may show the organism readily. Skin lesions typically show pseudoepitheliomatous hyperplasia on routine hematoxylin and eosin

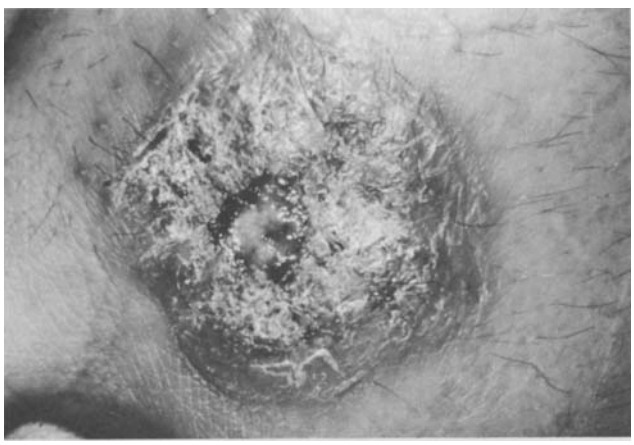

FIGURE 5. *Typical verrucous lesion of blastomycosis. Biopsy revealed broad-based budding yeasts and culture yielded* B. dermatitidis.

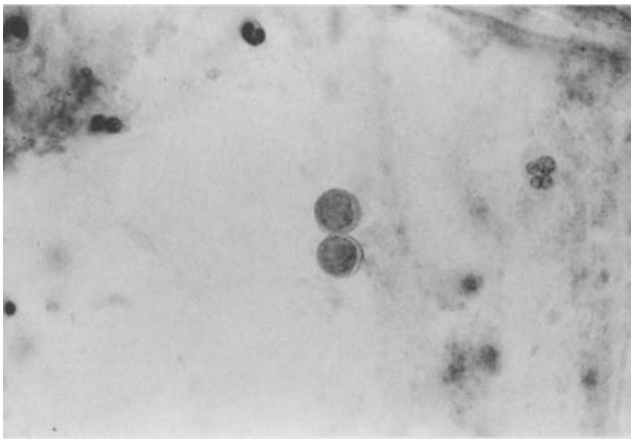

FIGURE 6. *Cytological preparation of washings obtained at the time of bronchoscopy in a patient with blastomycosis. Note the broad-based single bud attached to the yeast cell. Papanicolaou stain.*

stain; organisms are best seen with PAS or methenamine silver stains of tissue.

B. dermatitidis is generally more easily and more quickly grown than *H. capsulatum* on Sabouraud's agar or Smith's media. Useful serologic assays for blastomycosis have lagged behind those for histoplasmosis. However, recently ELISA and precipitin tests have appeared, which show much better specificity and sensitivity than the complement fixation assay for the diagnosis of blastomycosis.[31]

Treatment Amphotericin B is effective therapy for blastomycosis, reducing the mortality rate from near 80% to approximately 10%.[26] Although most agree that amphotericin B should be given for life-threatening blastomycosis, for less severe disease ketoconazole has proved to be an effective therapeutic agent, which is less toxic than amphotericin B and easier to administer, as it is given orally.[13,32] Thus, a patient with overwhelming pulmonary blastomycosis, central nervous system involvement, or widespread disseminated infection should be treated with 2 grams of amphotericin B, whereas patients with cutaneous lesions, osteomyelitis, or mild pulmonary infection can be treated quite effectively with ketoconazole 400 mg daily, increased to 800 mg daily if no response has occurred.[13,32]

Whether acute pulmonary blastomycosis needs to be treated is still debated. Certainly, in some outbreaks, patients have cleared their infection without any antifungal therapy before the diagnosis was established.[30,33] Most of these patients have been children and young adults; an elderly person in this situation probably should receive ketoconazole therapy.

COCCIDIOIDOMYCOSIS

General Characteristics of Infection *Coccidioides immitis* is a fungus endemic to the semiarid desert areas of the southwestern United States. The organism is very common in the lower Sonoran life zone in Southern California, Arizona, and Texas. Like *H. capsulatum* and *B. dermatitidis, C. immitis* is a true pathogen, causing infection in healthy hosts who inhale the highly infectious spores.[34] Any activity which stirs up dust in an endemic area may lead to an outbreak of coccidioidomycosis. Isolated cases, as well as epidemics, have been reported in association with archeological digs, construction work, and even activities as simple as driving through a contaminated site.[35,36]

In its usual form, coccidioidomycosis presents as an acute respiratory illness with fever and sometimes joint and skin manifestations.[37] However, in susceptible patients, widespread dissemination occurs and fatal infection is possible. The organism is dimorphic, as are *H. capsulatum* and *B. dermatitidis,* but in the case of *C. immitis,* the tissue form is a large spherule containing many endospores.[38] The host response to infection is both neutrophilic and granulomatous, with cell-mediated immunity necessary for control of infection.[34]

Risk of Infection in the Elderly There is debate about whether older persons are more susceptible than younger persons to *C. immitis.* Although Fiese found no clear-cut influence of advancing age on dissemination,[39] Sievers found, in a Native American population, that the highest mortality from disseminated coccidioidomycosis was in the very young and in adults over 50 years of age.[40] Although patients over 50 years old made up only 13% of the population, 25% of the patients with disseminated disease and 40% of the deaths due to coccidioidomycosis were in that group. Sievers postulated that the older patient may have a higher mortality because cell-mediated immunity to *C. immitis,* as well as other intracellular pathogens, decreases with increasing age.[40,41]

Although older persons in endemic areas may have reactivation of disease acquired in their youth, an increasingly large group of elderly persons at risk for developing coccidioidomycosis are travelers to the Southwest from nonendemic areas and elderly persons moving into the endemic area when they retire. Thus, it is important for physicians in all parts of the United States to be cognizant of the disease manifestations of coccidiodomycosis, which may appear in an elderly retiree just returned from wintering in Arizona or southern California.

Clinical Manifestations Many patients exposed to *C. immitis* will have a flulike illness with fever, chills, cough, headache, and chest pain.[35] The respiratory illness may be accompanied by erythema nodosum, erythema multiforme, and arthalgias ("Valley Fever"). Patients may also have a fine erythematous, macular rash with primary coccidioidomycosis.[37]

Persons with primary pulmonary coccidioidomycosis

which does not clear within several weeks time may go on to develop persistent pulmonary infection. Chronic progressive pneumonia may occur with fever, chest pain, productive cough, and progressive downhill course.[42] Miliary, nodular, and cavitary pulmonary lesions have been described, and in some cases, patients can develop rapidly progressive respiratory failure.[42,43] This rapid progression is more common in immunosuppressed hosts, but can occur in persons with apparently normal host defenses as well. Pulmonary nodules may occur after the primary infection is cleared and are usually noted as an incidental finding on the chest roentgenogram. Coccidioidal cavities may persist; long-term studies by Winn suggest that in most cases these cavities are contained by the patient, even when sputum is positive for *C. immitis.*[44] Dissemination may occur from late cavities, however, and they may be associated with hemorrhage, pleural spread, and superinfection.

Dissemination, the most feared complication of infection with *C. immitis,* occurs more often in certain dark-skinned races—blacks, Filipinos, and Native Americans.[37,40] Immunosuppressed patients and pregnant women also are at risk for disseminated infection.[45,46] Dissemination may occur in any organ of the body, but often involves skin, bones, joints, meninges, and genitourinary systems.

Skin lesions are common in disseminated coccidioidomycosis. The most common is the verruccous granuloma. Subcutaneous abscesses may occur anywhere, but on the back or hip, they may be mistaken for an incipient decubitus ulcer (Figure 7). Osteomyelitis, occurring in up to 50% of patients with disseminated coccidioidomycosis, frequently affects areas of tendon insertion, such as the malleolus, the tibial tubercle, and the patella. The genitourinary tract may be extensively involved in coccidioidal infection. Lesions of the renal parenchyma are common at autopsy, and men may have infection of prostate, epididymis, spermatic cord, or testicle. Many patients have fungi in the urine without dysuria or frequency.[47]

Although meningitis is often diagnosed within months of the onset of infection, it may remain latent and appear years after the initial infection. The clinical presentation includes severe headaches, confusion, and lethargy; these symptoms may be more common in older persons with fungal meningitis.[48]

Diagnosis The diagnosis of coccidioidomycosis usually is accomplished by the use of serology, skin testing, histopathology, or culture of the organism. As with the other deep fungi, the most definitive diagnosis is growth of the fungus in culture. However, this is not always possible, especially in the case of meningitis; other modalities may provide an excellent presumptive diagnosis.

Tube precipitin, latex agglutination, immunodiffusion and complement fixation tests are available with complement fixation being the standard antibody assay.[34] The delayed hypersensitivity skin test using spherulin or coccidioidin as the antigen is a helpful adjunct in diagnosing coccidioidomycosis, in contradistinction to skin tests for *H. capsulatum* and *B. dermatitidis.*

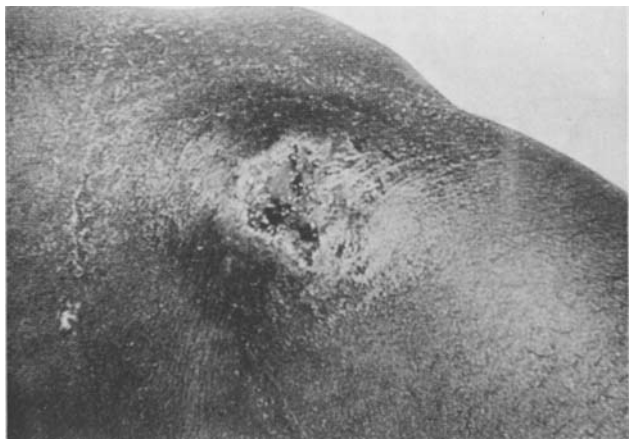

FIGURE 7. *Subcutaneous abscess next to the knee and overlying an area of osteomyelitis due to* C. immitis. *Smear of the purulent material from the site showed a large spherule characteristic of* C. immitis.

Although both skin tests and serology are helpful diagnostically, finding the organism in tissue and growing it in culture are definitive. The distinctive large (80 to 100μ) spherules of *C. immitis* can be seen in purulent material aspirated from draining sinuses, as well as on histopathologic examination of tissue sections. *C. immitis* is not difficult to grow in vitro. The physician should always notify the laboratory, especially in an area outside the area endemic for *C. immitis,* that coccidioidomycosis is a possible diagnosis so that lab accidents with this highly contagious fungus do not occur.

Treatment Amphotericin B remains the standard therapy for severe pulmonary and disseminated coccidioidomycosis.[49] In general, coccidioidomycosis is more difficult to treat than histoplasmosis and blastomycosis. When the infection is disseminated, it may be impossible to cure. With meningitis, intrathecal therapy is almost always needed, and the prognosis is dismal.[50] Ketoconazole has been shown to be effective in treating certain forms of coccidiodomycosis and is probably the first drug to be used in non-life-threatening infections.[51]

SPOROTRICHOSIS

General Characteristics of Infection *Sporothrix schenckii* is a dimorphic fungus which inhabits the soil in many areas of the United States; most cases have been reported from the midwestern and eastern half of the country. Outbreaks have been described in association

with both occupational and leisure activities[52,53]; sphagnum moss, soil, and wood have been contaminated with the spores of Sporothrix.[53,54] The pathogenesis of infection differs from the preceding deep fungi in that inhalation of spores is relatively uncommon, whereas direct cutaneous and subcutaneous inoculation is the usual mode of acquiring the disease.[55]

Once in the host, the fungus assumes the yeast form; localized disease, either cutaneous or lymphocutaneous, usually results, but occasionally widespread dissemination occurs. The tissue reaction is usually a mixed neutrophilic and granulomatous response, but the specifics of the host defense mechanisms important in sporothrichosis are not completely known.[56,57]

Risk of Infection in the Elderly There does not appear to be an increased propensity for sporotrichosis to occur in the elderly. The most important factor appears to be environmental exposure to the fungus. Not surprisingly, most of the reported cases have been in men aged 20 to 40 years who have been exposed to the fungus in their occupation. However, with increased participation in activities such as gardening, the elderly will be placed at greater risk of exposure to *S. schenckii* and will be more likely to acquire sporotrichosis.

When one reviews cases of extracutaneous sporotrichosis, it appears that extracutaneous spread of infection is more likely in older persons. For example, most patients with involvement of bones, joints, and tendons are over 50 years of age and many are over 60 years old.[58-60] Disseminated infection has been reported most often in men over 45 years of age[61,62]; in fact, 35% of the 30 patients with disseminated infection reported by Wilson et al were men over 60 years of age.[62] Thus, there appears to be a clustering of cases in the older age-range with more serious deep tissue involvement from *S. schenckii.*

Clinical Manifestations The most common clinical manifestation of sporotrichosis is a subcutaneous nodule or cutaneous ulceration with involvement of the lymphatics draining the area. The initial lesion is generally at the site of traumatic inoculation of the fungus, followed by the development of multiple ulcerated and nodular lesions along the lymphatics draining the area. The lesions may be painful or painless, they are frequently purplish or pink in color, and they may drain seropurulent fluid (Figure 8). The patient generally is afebrile and without systemic symptoms. Progression is slow, and the lesions frequently persist for months if untreated.

Extracutaneous focal or disseminated infection is uncommon.[62] In some instances it appears that the organism disseminates from the primary site of subcutaneous inoculation. In other instances, it appear likely that primary pulmonary infection occurs following inhalation of the spores of *S. schenckii.* Isolated articular or bony involvement has been reported. In these instances, the illness is generally protracted and frequently misdiagnosed for years.[58-60] Pulmonary infection is generally chronic with cavitary or nodular lesions, low-grade fever, weight loss, and fatigue—not unlike tuberculosis.[63]

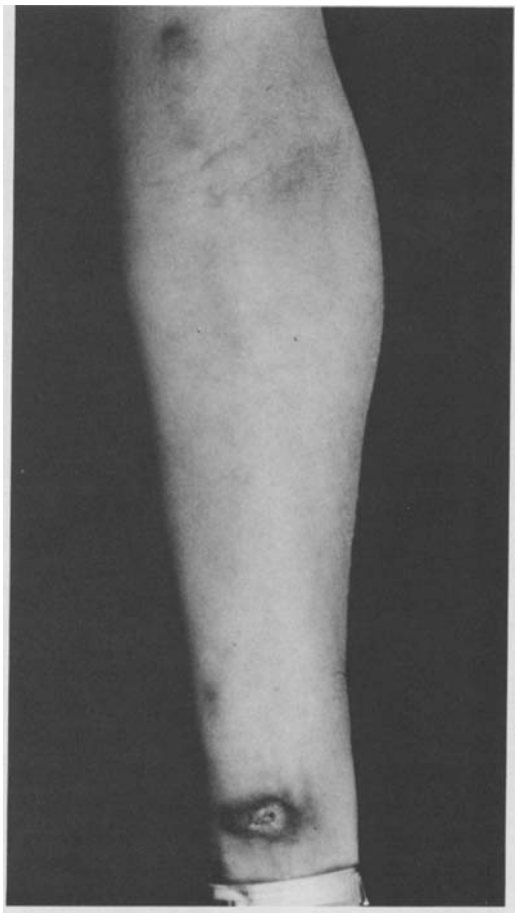

FIGURE 8. *Lymphocutaneous sporotrichosis in a farmer's wife, who had been scratched by cornstalks at several sites on arms and legs.*

Disseminated infection occurs only rarely. Most of these patients have multiple widespread cutaneous and subcutaneous lesions in addition to articular, pulmonary, genitourinary, and other visceral involvement.[62]

Diagnosis *S. schenckii* grows rather easily after several days in culture. Cutaneous and subcutaneous lesions should be aspirated or biopsied in order to obtain material for culture. This is the most definitive method for diagnosing sporotrichosis. Serology has been less useful than in other deep fungal infections. However, recent studies suggest that an ELISA and a latex agglutination assay may be quite useful in certain invasive forms of the disease, such as meningitis, in which it may be very difficult to isolate the fungus in culture.[64]

Direct examination of purulent material often does not reveal the organism, and histopathology may show only a mixed pyogenic-granulomatous reaction with-

out the fungus being noted. Usually the organism is present in rather small numbers; when seen they are small cigar-shaped or round yeastlike structures with irregular buds.[65]

Treatment The cutaneous and lymphocutaneous forms of sporotrichosis may be treated successfully by several methods. The time-honored therapy, a saturated solution of potassium iodide (SSKI), is still the therapy of choice, but side effects are noted in the majority of patients receiving the drug for the typical course of 3 to 6 months. A recent study showed itraconazole, an experimental oral triazole compound, to be quite effective in treating localized sporotrichosis and to be free of significant side effects.[66] Ketoconazole has not been effective in treating sporotrichosis.[63] In certain instances, for example, in a pregnant woman with localized sporotrichosis, in whom antifungal agents such as SSKI or azoles should not be given, local heat therapy applied to the lesions may be effective in eliminating the organism, which is heat sensitive, thus curing the infection.[67]

Disseminated or visceral infections with *S. schenckii* should not be treated with iodides; amphotericin B is the treatment of choice in disseminated infection.[62,68] It is not known whether the newer azoles will be useful in treating disseminated sporotrichosis.

DISCUSSION

There is evidence for increased severity of infection in elderly patients for all four major deep fungal infections occurring in the United States. The correlation between increased severity of infection and advancing age is strongest for histoplasmosis, in which the chronic cavitary pulmonary and progressive disseminated forms of the disease occur almost entirely in elderly men. Coccidioidomycosis appears to be a worse infection in elderly persons in at least one of the high risk groups, that of Native Americans. The rarer manifestations of sporotrichosis—disseminated infection and articular involvement—occur mostly in older men; however, in the case of blastomycosis only minimal data exist suggesting the disease takes on more serious manifestations in the elderly.

The reasons for the increased severity of infection with some of the deep fungi in the elderly have not been specifically investigated in humans or in animal models of aging. Presumably, decreased cell-mediated immunity, which occurs in some elderly persons, is related to the increased severity of infection in the elderly. This would explain infection best in the case of histoplasmosis, in which the data are clear that cell-mediated immunity is crucial to resolution of the infection. It is of interest that for those infections in which age-related severity is not as clear-cut, as with blastomycosis and sporotrichosis, cell-mediated immunity alone is probably not the sole host defense to eradicate the organism.

Of importance to the geriatrician is the fact that infection with deep fungi can be reactivated later in life. Again, the data are most clear for *H. capsulatum*. Thus, when a patient presents with fever, pulmonary infiltrates, or evidence of disseminated granulomatous infection, the history should include prior residence and past travel to areas endemic for the deep fungi. Histoplasmosis acquired, for example, while the patient served in the armed services in Arkansas or lived in Kentucky as a teenager may reactivate years later when the patient is a retiree in Arizona, a state in which the organism does not occur in the environment.

Because the deep fungi are acquired from the environment, newly-acquired disease is always possible in elderly persons who remain active in leisure activities. For example, an elderly gardener might encounter *S. schenckii* while spreading mulch, or an elderly person venturing into the desert in southern California might be exposed for the first time to *C. immitis*. Thus, not only reactivation infection but also primary infection with the deep fungi may occur in elderly persons who encounter a new environment after they move to retirement communities. It is likely that infection with the deep fungi will increase in the years ahead as elderly people live longer and more active lives.

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