Histoplasmosis

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Histoplasmosis, the most common endemic mycosis in the United States, is caused by *Histoplasma capsulatum* var. *capsulatum*. *Histoplasma capsulatum* var. *duboisii* causes African histoplasmosis, which has different clinical manifestations. *Histoplasma capsulatum* is a thermally dimorphic fungus; in the environment and at temperatures below 35°C, it exists as a mould, and in tissues and at 35–37°C, as a yeast. In the highly endemic area, along the Mississippi and Ohio River valleys in the United States, most persons are infected in childhood. The primary site of infection is the lungs following inhalation of the conidia from the environment. The severity of disease is related to the number of conidia inhaled and the immune response of the host; the primary host defense mechanism against *H. capsulatum* is cell-mediated immunity. Pulmonary infection is asymptomatic or only mildly symptomatic in most persons who have been infected; acute severe pneumonia and chronic progressive pulmonary infection also can occur. Asymptomatic dissemination of *H. capsulatum* to the organs of the reticuloendothelial system occurs in most infected individuals; however, symptomatic acute or chronic disseminated histoplasmosis, which is a life-threatening infection, occurs almost entirely in persons who have deficient cell-mediated immunity. Antifungal therapy is highly effective. For patients with mild-to-moderate histoplasmosis, itraconazole is the treatment of choice; for patients with severe infection, amphotericin B is required.

Organism

Histoplasmosis was first described and the organism given its name in 1904 by Samuel Darling, a physician working at the Canal Zone Hospital in Panama. He erroneously thought the organism, which in tissues resembles *Leishmania*, was a parasite. Within a few years it became clear that this organism was indeed a fungus. Several decades later it was shown that *H. capsulatum* was a thermally dimorphic fungus, and by 1949, an environmental reservoir for *H. capsulatum* had been proved by Emmons.

Two varieties of *H. capsulatum* are pathogenic for humans: *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii.* These organisms mate in the laboratory and thus have been assigned varietal, rather than species, status. At 25–30°C, the organism exists in the mycelial form; the colony is white to tan in color. The aerial hyphae produce two types of conidia: Macroconidia (tuberculate conidia) are thick-walled, 8–15 μm in diameter, and have distinctive projections on their surfaces. Microconidia are smooth-walled, 2–4 μm in diameter, and are the infectious form (Fig. 1). *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii* are indistinguishable in the mycelial phase.

At 37°C in tissues and in vitro, the organism undergoes transformation to the yeast phase. In vitro, the colony is cream-colored and becomes gray with age. In tissues, the two varieties of *H. capsulatum* differ in their appearance. *H. capsulatum* var. *capsulatum* appears as tiny 2–4 μm oval budding yeasts often found inside macrophages (Fig. 2a and b). *Histoplasma capsulatum* var. *duboisii* is larger, 8–15 μm, thick-walled, may appear as short chains in tissues, and shows the "scar" from which its bud has been released at one end [1] (Fig. 2c).

In addition to the above two human pathogens, there is a third variety, *Histoplasma capsulatum* var. *farciminosum,* which is a pathogen of horses and mules. This organism causes lymphangitis in equines from the Middle East, northern Africa, central and southern Europe, Japan, the Philippines, and southern Asia [2]. The disease is characterized by multifocal suppurative lymphangitis and ulcerated cutaneous lesions that usually affect the head and forequarters; mucous membranes of the nares and oropharynx can also become ulcerated. Systemic infection does not occur.

In this chapter, *H. capsulatum* var. *capsulatum* is referred to simply as *H. capsulatum* and *H. capsulatum* var. *duboisii* as *H. duboisii.* Most of the chapter focuses on *H. capsulatum*, with additional comments, when relevant, regarding infection due to *H. duboisii.*

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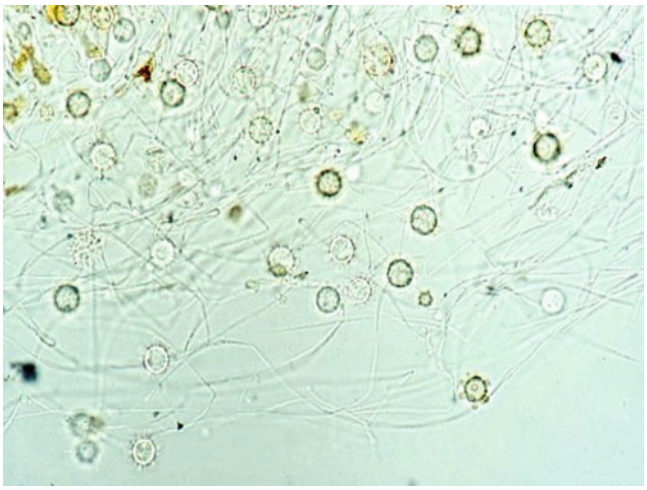

Fig. 1 Mycelial phase of *H. capsulatum* grown at 25°C showing mostly tuberculate macroconidia and a few smaller microconidia

Ecology and Epidemiology

Histoplasmosis occurs throughout the world, but is most common in North and Central America. Isolated cases have been reported from Southeast Asia, Africa, and the Mediterranean Basin [3]. In the United States, *H. capsulatum* is endemic in the Mississippi and Ohio River valleys and in localized areas in several mideastern states (Fig. 3). In the environment, *H. capsulatum* appears to have precise growth requirements related to humidity, acidity, temperature, and nitrogen content, but all of the specific conditions needed for growth in the soil have not been completely elucidated. What is known, however, is that soil containing large amounts of droppings from birds or bats supports luxuriant mycelial growth [4]. The soil under blackbird roosts and around chicken coops is especially likely to harbor *H. capsulatum*. Birds themselves are not infected with *H. capsulatum,* but can transiently carry the organism on beaks and feet and contribute to its spread. Once contaminated, soil yields *H. capsulatum* for many years after birds no longer roost in the area. Bats, in contradistinction to birds, can become infected with *H. capsulatum* and excrete the organism in their feces [5]. Intestinal carriage by bats and their migratory patterns help to ensure expansion of geographic areas yielding *H. capsulatum.*

Infection with *H. capsulatum* results from passive exposure that occurs during typical day-to-day activities or from active exposure related to occupational or recreational activities. Most cases are sporadic, related to passive exposure, and not associated with a known source. Every year hundreds of thousands of individuals in the United States are infected with *H. capsulatum*; most of these individuals are not aware of this event. The two largest outbreaks ever reported were both associated with passive exposure of hundreds of thousands of people to *H. capsulatum* during urban construction projects in Indianapolis [6, 7]. In other outbreaks, workers became infected after involvement in specific activities, such as cleaning

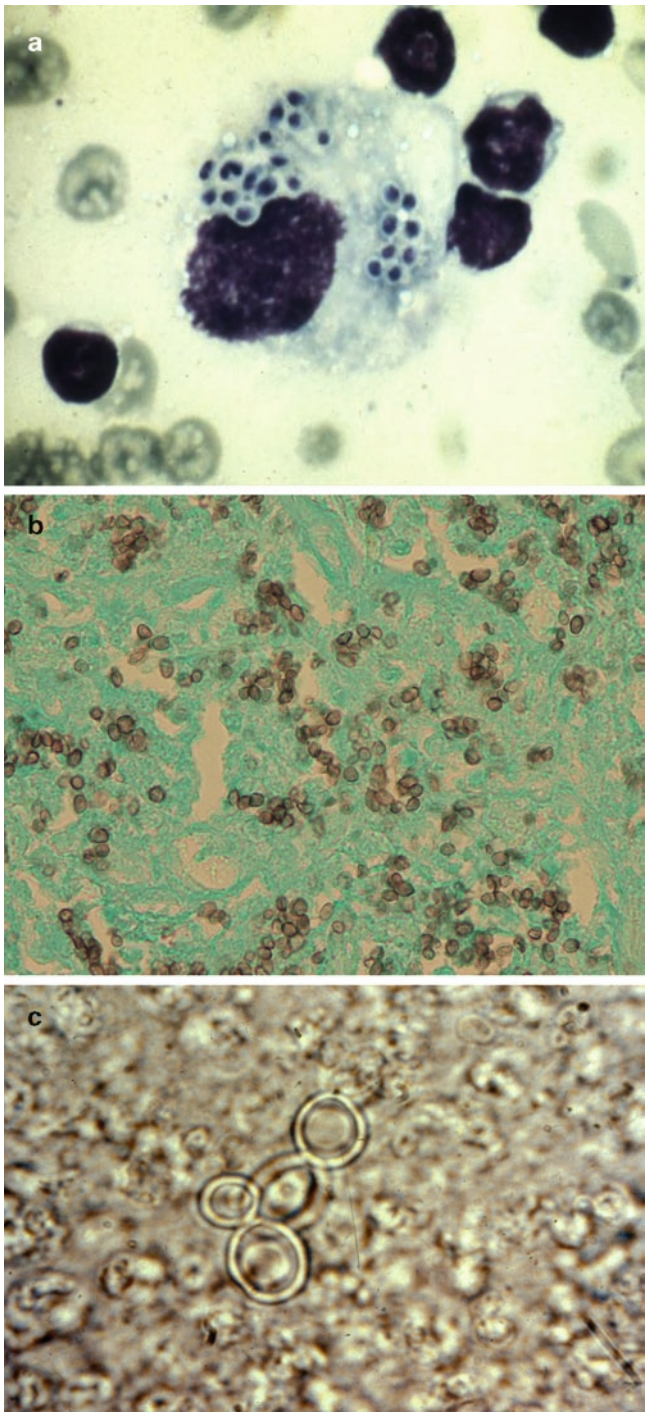

Fig. 2 Yeast phase of *Histoplasma*. (**a**) Smear of lung biopsy specimen stained with Giemsa stain showing 2–4 μm yeasts within an alveolar macrophage, typical of *Histoplasma capsulatum*; (**b**) Lung biopsy specimen stained with methenamine silver stain showing numerous budding yeasts of *H. capsulatum*; (**c**) KOH preparation of an aspirate taken from an abscess in bone showing thick-walled yeast forms typical of *H. duboisii* (Photo courtesy of Dr. Bertrand Dupont)

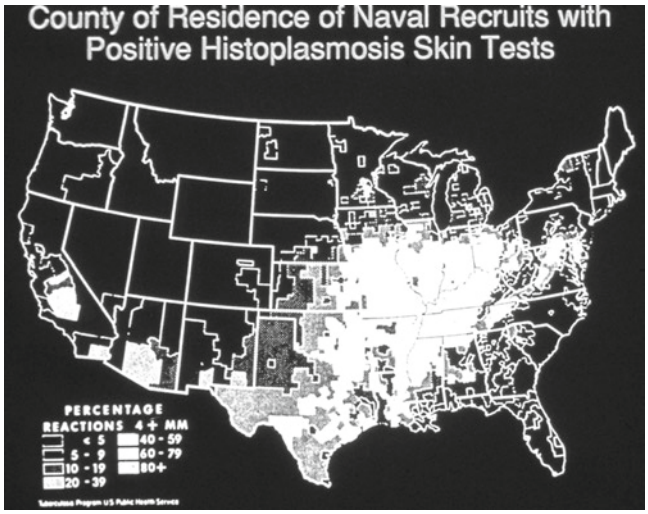

Fig. 3 Histoplasmin reactivity in the continental United States among 275,558 white male naval recruits, ages 17–21 years [112]

bird or bat guano from bridges or heavy equipment or tearing down or cleaning out old buildings, especially chicken coops [8, 9]. Other outbreaks have been associated with recreational pursuits, such as spelunking [10] and ecologic volunteer efforts [11].

AIDS has had a significant effect on the epidemiology of histoplasmosis in the highly endemic areas [12–14]. In the early 1990s, the rates of histoplasmosis in AIDS patients were as high as 12/100 patient-years in Kansas City, and 10/1,000 AIDS patients in Houston [12]. This has decreased markedly with antiretroviral therapy. Most cases of histoplasmosis in AIDS patients now are seen in those who are newly diagnosed with HIV infection [14]. Increasingly, histoplasmosis is reported among patients who have received solid organ transplants, corticosteroids, and tumor necrosis factor (TNF) antagonists [15–18].

Histoplasma duboisii is more restricted in its geography, and occurs only in Africa between the Tropic of Cancer and the Tropic of Capricorn. Within these boundaries, most cases occur in Nigeria, Mali, Senegal, and Zaire. The exact ecologic niche the organism occupies has not been determined, but cases have been described in association with bat guano [1, 19]. Cases of African histoplasmosis reported outside the endemic area have all been among travelers or immigrants from Africa [20]. *H. duboisii* has been reported to cause more severe disseminated infection in patients with HIV infection [20, 21].

Pathogenesis

The microcondia of the mycelial phase of *H. capsulatum* are 2–4 μm, a size that allows them to be easily aerosolized and inhaled into the alveoli of the host. At 37°C, the organism undergoes transformation to the yeast phase from the mycelial phase. Phagocytosis of either form (conidia or yeast) by alveolar macrophages and neutrophils occurs through binding of the organism to the CD18 family of adhesion promoting glycoproteins [22]. The yeast form of *H. capsulatum* is uniquely able to survive within the phagolysosome of macrophages through several mechanisms, including the ability to resist killing by toxic oxygen radicals and to modulate the intraphagosomal pH [23–25]. Iron and calcium acquisition by the yeast are important survival tools, allowing growth within the macrophage [25]. Surviving within the macrophage, *H. capsulatum* is transported to the hilar and mediastinal lymph nodes and subsequently disseminates hematogenously throughout the reticuloendothelial system in most cases of histoplasmosis.

After several weeks, specific T-cell immunity develops, macrophages become activated, and then killing of the organism ensues [24]. At this point, long-lasting immunity to *H. capsulatum* occurs. Experimental animal models show the importance of CD4 cells in developing specific immunity to *H. capsulatum* [26]. Interferon-gamma produced by CD4 cells is probably the most important factor for activation of macrophages, but TNF-alpha also plays a central role in immunity to *H. capsulatum* [27]. Other cytokines (IL-1, IL-12, GM-CSF) also aid in containing the organism [24, 28].

The clinical corollary in humans to the studies in the murine model is that most patients with severe infection with *H. capsulatum* are those with cellular immune deficiencies, especially those who have advanced HIV infection and low CD4 counts [29], transplant recipients [15, 18], those receiving TNF antagonists [16, 17], and rarely persons with genetic defects, such as interferon-gamma receptor deficiency [30]. Of all the human mycoses, histoplasmosis appears to be the most pure example of the pivotal importance of the cell-mediated immune system in limiting infection.

The extent of disease is determined both by the immune response of the host and the number of conidia that are inhaled. A healthy individual can develop severe life-threatening pulmonary infection if a large number of conidia are inhaled. This might occur during demolition of or renovations to old buildings or as a result of spelunking in a heavily infested cave. Conversely, a small inoculum can cause severe pulmonary infection or progress to acute symptomatic disseminated histoplasmosis in a host whose cell-mediated immune system is unable to contain the organism.

Most persons who have been infected have asymptomatic dissemination; only rarely will this lead to symptomatic disseminated histoplasmosis [5]. However, because dissemination is the rule, latent infection probably persists for a lifetime, and reactivation can result if the host becomes immunosuppressed. Presumably, this is the mechanism by which persons who were born in the endemic area and had not returned for years develop histoplasmosis years later [31, 32].

In immunosuppressed patients, histoplasmosis is most often acquired as a new infection from an environmental exposure, but also can result from reactivation of a latent infection that was acquired years before. In solid organ transplant recipients, *H. capsulatum* has rarely been transmitted with the donor organ [15].

Although uncommon, reinfection histoplasmosis can occur in persons who previously were infected and occurs most often after exposure to a heavily contaminated point source [33]. Reinfection histoplasmosis is usually less severe than primary infection because there is residual immunity induced by the initial episode.

Clinical Manifestations

Acute Pulmonary Histoplasmosis

The usual result of exposure of a normal host to *H. capsulatum* is asymptomatic infection (Table 1). In the highly endemic area, as many as 85% of adults have been infected with *H. capsulatum*, and most have not had symptoms that were attributed to histoplasmosis. Symptomatic acute pulmonary histoplasmosis is most often manifested as a self-limited illness characterized by dry cough, fever, and fatigue. Approximately 5% of patients will develop erythema nodosum [34], and 5–10% will develop myalgias and arthralgias/arthritis [35]. Joint involvement is usually polyarticular and symmetric. Chest radiographs show a patchy pneumonitis in one or more lobes, often accompanied by hilar or mediastinal lymphadenopathy [36] (Fig. 4). Some patients have only hilar lymphadenopathy; when this is accompanied by arthralgias and erythema nodosum, the clinical picture can mimic sarcoidosis and the two must be differentiated. Improvement within several weeks is typical, but in some individuals fatigue may linger for months. Joint symptoms usually resolve over several weeks in response to anti-inflammatory therapy.

When a person is exposed to a heavy inoculum of *H. capsulatum*, acute severe pulmonary infection, sometimes termed epidemic histoplasmosis, can ensue [36, 37]. Symptoms include high fever, chills, fatigue, dyspnea, cough, and chest pain. Acute respiratory failure and death can ensue. Chest radiographs show diffuse reticulonodular pulmonary infiltrates; mediastinal lymphadenopathy may or may not be present (Fig. 5). Over the ensuing months to years following resolution of the pneumonia, calcified nodules may develop throughout the lung fields [38] (Fig. 6).

If a physician sees several cases that appear to be similar and that share a possible exposure or if the patient recounts that several of his or her associates have a similar illness, then the possibility of a fungal etiology is more likely to be

Table 1 Classification of clinical manifestations of histoplasmosis

Acute pulmonary
Chronic cavitary pulmonary
Complications of pulmonary histoplasmosis
Mediastinal granuloma
Fibrosing mediastinitis
Broncholithiasis
Pericarditis
Disseminated
Acute
Chronic progressive
Endocarditis
Central nervous system

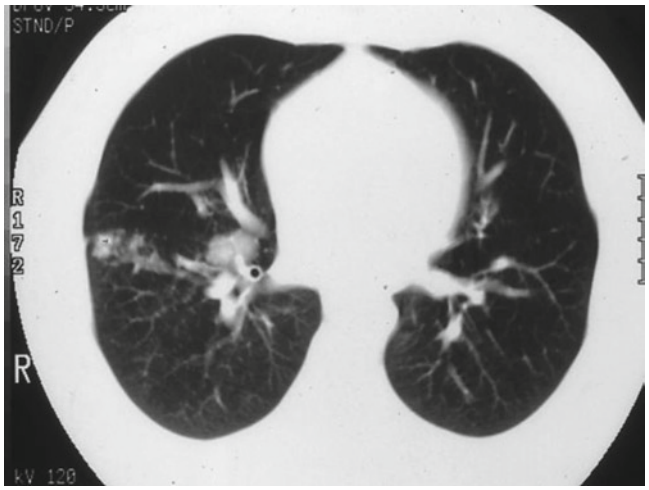

Fig. 4 CT scan of a patient with acute pulmonary histoplasmosis. Note hilar adenopathy and patchy pneumonitis

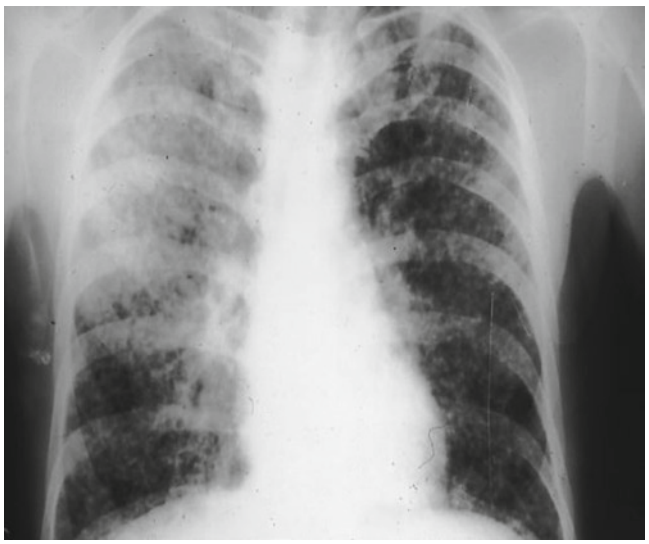

Fig. 5 Acute severe pulmonary histoplasmosis occurring in a construction worker who cleaned bird and bat guano from a bridge prior to painting the structure. The patient responded quickly to amphotericin B therapy

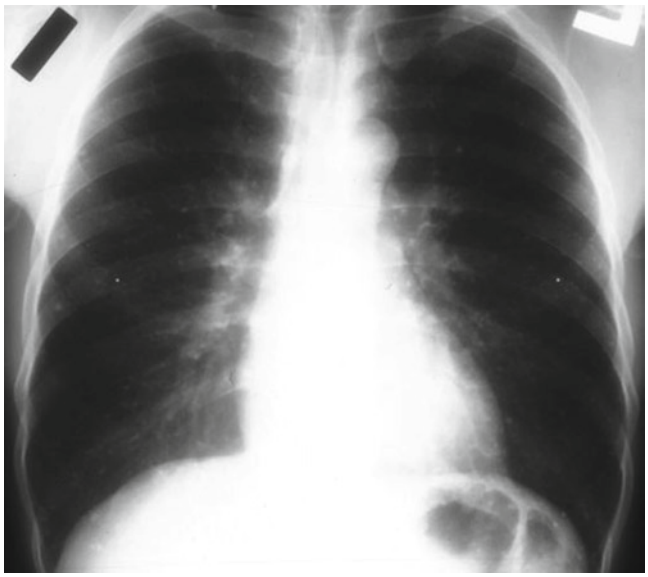

Fig. 6 Diffuse calcified nodules throughout the lung fields in a patient who had acute pulmonary histoplasmosis 20 years earlier

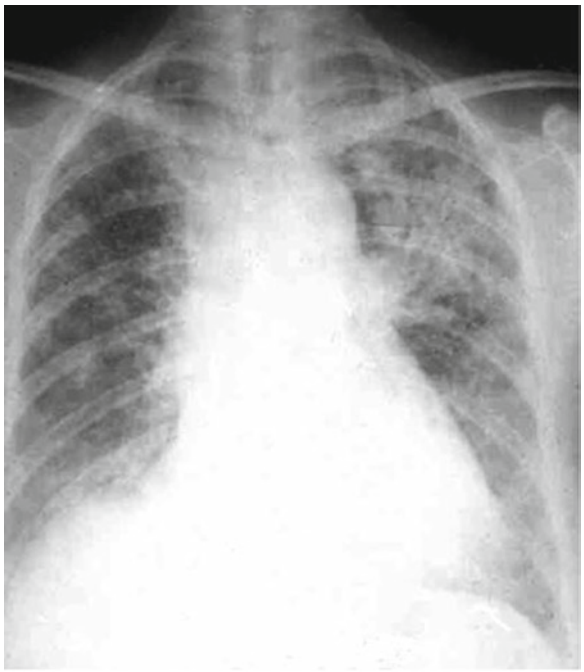

Fig. 7 Acute severe pulmonary histoplasmosis occurring in a kidney transplant recipient. Diffuse pulmonary infiltrates are present and the patient was markedly hypoxemic

entertained. Sporadic cases almost always are initially thought to be due to one of the usual causes of community-acquired pneumonia. Only after the patient fails to respond to several courses of antibiotics is the possibility of a fungal pneumonia raised. A history of activities in an area endemic for *H. capsulatum* that are likely to lead to exposure to the organism several weeks prior to the onset of symptoms should lead to further diagnostic tests for histoplasmosis. Included in the differential diagnosis of acute pulmonary histoplasmosis are acute pulmonary blastomycosis and pneumonias due to *Mycoplasma*, *Legionella*, and *Chlamydia.* Hilar and mediastinal lymphadenopathy, common with histoplasmosis, are occasionally seen with blastomycosis but are rarely, if ever, noted with pneumonia due to the other organisms.

Acute pulmonary histoplasmosis in patients who have cell-mediated immune defects is more severe than in normal hosts. Prostration, fever, chills, and sweats are prominent; marked dyspnea and hypoxemia can progress quickly to acute respiratory distress syndrome (ARDS). Chest radiographs show diffuse bilateral infiltrates (Fig. 7). Dissemination to other organs is common.

Chronic Pulmonary Histoplasmosis

Chronic pulmonary histoplasmosis occurs almost entirely in older persons, predominantly men, with underlying chronic obstructive pulmonary disease (COPD) [39, 40]. The clinical manifestations include fatigue, fever, night sweats, chronic cough, sputum production, hemoptysis, dyspnea, and weight loss. This form of histoplasmosis is characterized by cavity formation in the upper lobes and progressive fibrosis in the lower lung fields (Fig. 8). The extensive scarring is thought to be related to the host's response to *H. capsulatum* antigens. Pleural involvement is uncommon. The disease is manifested by progressive respiratory insufficiency and if not treated is fatal in about 40% of patients [39, 41, 42]. A more recent study from the Mayo Clinic that was far less proscriptive in its definition of chronic pulmonary histoplasmosis, found that 48% of the cases were in women, and only 20% of patients had COPD [43]. In many aspects, chronic cavitary pulmonary histoplasmosis mimics reactivation tuberculosis. The differential diagnosis of chronic pulmonary histoplasmosis also includes nontuberculous mycobacterial infections, blastomycosis, sporotrichosis, and coccidioidomycosis.

Complications of Pulmonary Histoplasmosis

Mediastinal Granuloma. Involvement of mediastinal lymph nodes is common during the course of acute pulmonary histoplasmosis. However, mediastinal granuloma, characterized by massive enlargement of mediastinal lymph nodes that frequently undergo caseation necrosis, is distinctly uncommon. These nodes can remain enlarged for months to years and can lead to impingement on airways or major vessels, displacement of the esophagus, or formation of fistulae between the nodes and adjacent structures in the mediastinum [36, 44].

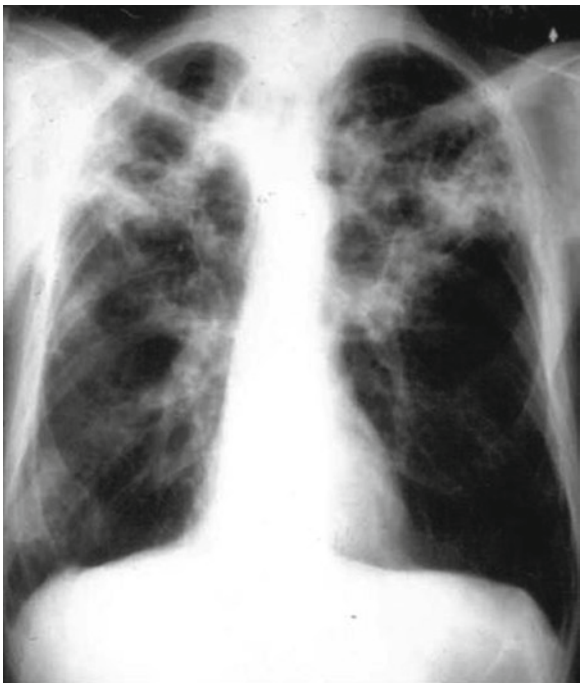

Fig. 8 Chronic cavitary pulmonary histoplasmosis in an elderly man with severe underlying emphysema

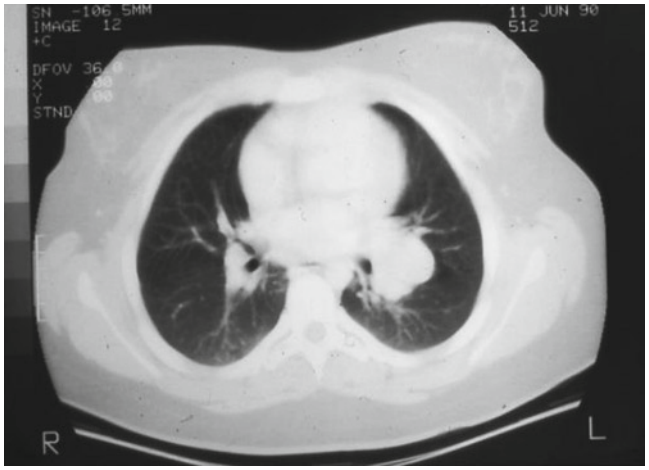

Fig. 9 CT scan of a young woman who developed mediastinal granuloma due to *Histoplasma capsulatum*. The multiple enlarged mediastinal and left hilar lymph nodes had been present for at least 1 year at the time this scan was performed

Compression of a bronchus can result in intermittent obstruction and pneumonia. In some cases, the nodes will spontaneously drain into adjacent soft tissues of the neck. Patients may be asymptomatic, have nonspecific systemic complaints of fatigue and not feeling well, or have symptoms such as dyspnea, cough, or odynophagia related to the effects of the nodes on adjacent structures. Although it was initially thought that mediastinal granuloma progressed to fibrosing mediastinitis, current thinking is that these are two separate complications of pulmonary histoplasmosis [37, 45].

Radiographs show only enlarged lymph nodes, sometimes with calcification noted. Computed tomography scans of the chest are more helpful, showing nodal enlargement, the presence of necrosis, and impingement on mediastinal structures [37, 38] (Fig. 9). Bronchoscopy or esophagoscopy can document extrinsic compression, traction diverticulae, or fistulae. Mediastinal granuloma as a complication of histoplasmosis must be differentiated from lymphoma and other tumors that cause mediastinal lymphadenopathy.

Fibrosing Mediastinitis. Fibrosing mediastinitis, an entity distinct from and much less common than mediastinal granuloma, is characterized by excessive fibrosis that progressively envelops the structures of the mediastinum [45–47]. The condition arises following infection with *H. capsulatum*, occurs mostly in young adults, and is caused by an abnormal fibrotic response to *H. capsulatum* in these individuals. When patients present with symptoms of fibrosing mediastinitis, there is rarely any sign of active histoplasmosis. The fibrosis can lead to obstruction of the superior vena cava or pulmonary arteries or veins; there may be occlusion of the bronchi. Rarely, the thoracic duct, recurrent laryngeal nerve, or right atrium are involved. Hemoptysis, dyspnea, and cough are common symptoms. Signs of superior vena cava syndrome or right heart failure may be prominent. Most patients have involvement of predominantly one side, but some have bilateral involvement, which is often fatal. Chest radiographs show subcarinal or superior mediastinal widening. Computed tomography scans and angiography are needed to reveal the extent of invasion of mediastinal structures and great vessels.

Broncholithiasis. Broncholithiasis occurs when calcified nodes or pulmonary granulomas erode into the bronchi. Ulceration into the bronchus with hemoptysis and expectoration of "stones" can ensue. Postobstructive pneumonia occurs if the node obstructs the bronchus. Computed tomography scans show the calcified node and its impingement on the bronchus, and bronchoscopy will usually confirm the diagnosis and rule out other endobronchial lesions [48].

Pericarditis. Pericarditis occurs in the setting of acute pulmonary histoplasmosis, is seen mostly in young persons, and is thought to be due to an inflammatory reaction to *H. capsulatum* in adjacent mediastinal nodes [49, 50] (Fig. 10). Pericardial fluid is often hemorrhagic with a predominance of lymphocytes, and *H. capsulatum* cannot be grown from the fluid. Pleural effusions are also common in this setting, and the fluid is exudative and frequently bloody. The majority of patients exhibit no hemodynamic consequences; however, tamponade can occur and requires immediate drainage. Outcome is excellent; only rarely does acute pericarditis progress to constriction requiring a surgical procedure for relief of symptoms.

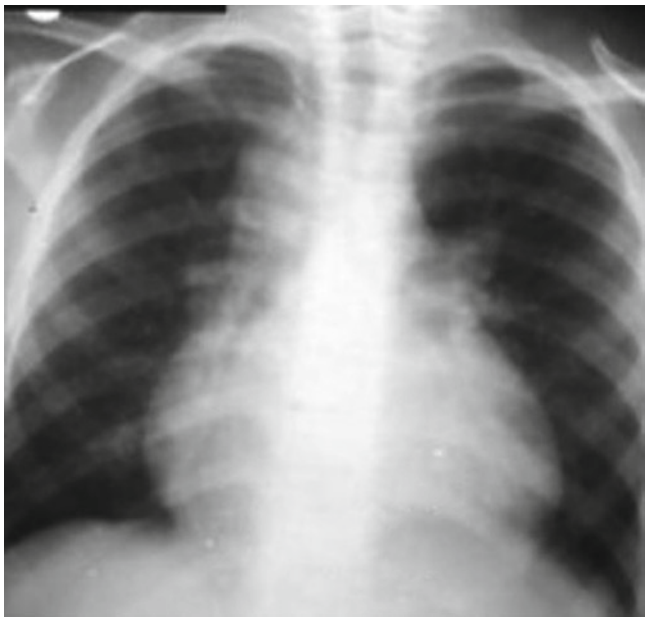

Fig. 10 Chest radiograph of a young girl with pericarditis complicating acute histoplasmosis. This resolved within a few weeks and she had no sequelae

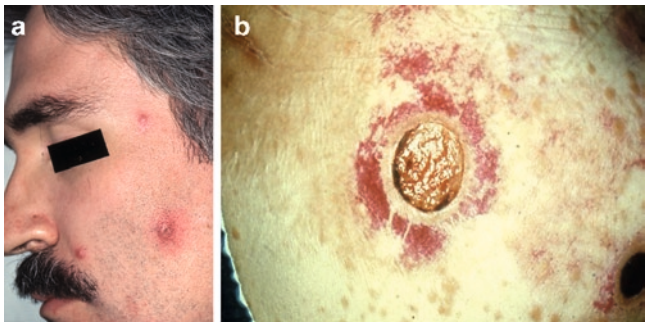

Fig. 11 Skin lesions noted in patients with disseminated histoplasmosis. (**a**) Multiple papulopustules which appeared on the face and chest in a patient with HIV infection; (**b**) chronic ulcer on the thigh of an elderly man with chronic progressive disseminated histoplasmosis

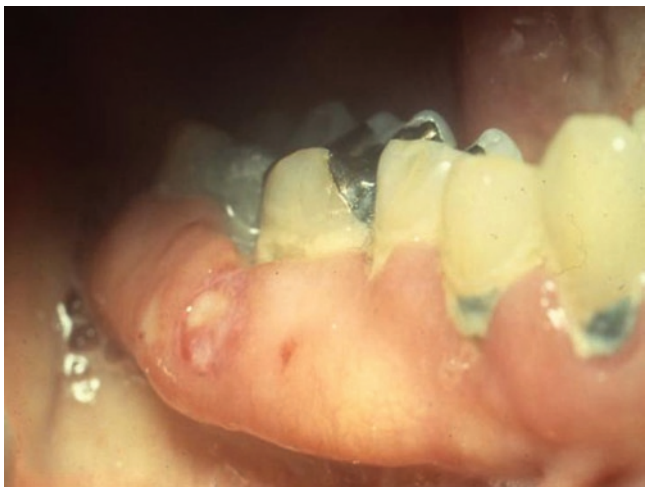

Fig. 12 Painful, slowly enlarging gingival ulcer that was present for 4 months in an elderly man who had chronic progressive histoplasmosis

Disseminated Histoplasmosis

Although dissemination is common during the course of most infections with *H. capsulatum,* symptomatic dissemination occurs primarily in immunosuppressed patients and infants [7, 51–53]. In persons with HIV-1 infection and histoplasmosis, a CD4 count <150/μL is associated with increased risk of disseminated histoplasmosis [29]. A rapidly fatal course with diffuse involvement of multiple organs characterizes the infection in most immunosuppressed patients [16, 18, 31, 53, 54]. Patients may present with dyspnea, renal failure, hepatic failure, coagulopathy, hypotension, and obtundation. Chest radiographs show diffuse interstitial or reticulonodular infiltrates, but may progress quickly to the findings associated with ARDS. Hemophagocytic syndrome has been associated with acute disseminated histoplasmosis [55, 56].

A chronic progressive course is typical of disseminated histoplasmosis in nonimmunocompromised middle-aged to older adults [51, 57]. This form of histoplasmosis is more common in men than women. A history of recent exposure often cannot be elicited, and overt defects in immune function have not been identified in these patients. However, because such patients are unable to eradicate the organism from their macrophages, it is presumed that they have a specific immune defect against *H. capsulatum* [51]. Fever, night sweats, anorexia, weight loss, and fatigue are prominent. Pulmonary symptoms may or may not be present, but usually are not prominent.

In both acute and chronic disseminated histoplasmosis, hepatosplenomegaly, lymphadenopathy, and skin and mucous membrane lesions are frequently noted. A variety of different skin lesions, including papules, pustules, ulcers, and subcutaneous nodules, have been noted in patients with disseminated histoplasmosis (Fig. 11a and b). Oropharyngeal ulcers or, less commonly, nodules can be found on the tongue, buccal and gingival mucosa, larynx, or lips in patients with either acute or chronic dissemination (Fig. 12). Patients with disseminated histoplasmosis can develop adrenal insufficiency as a result of destruction of the adrenal glands by infiltration with *H. capsulatum*. Addisonian crisis has been reported as the presenting manifestation of disseminated histoplasmosis.

Laboratory abnormalities noted with disseminated disease include an elevated erythrocyte sedimentation rate, pancytopenia, elevation of hepatic enzymes, especially alkaline phosphatase, and hyperbilirubinemia. Hypercalcemia has been associated with disseminated histoplasmosis, as it has with other granulomatous diseases, such as tuberculosis, coccidioidomycosis, and sarcoidosis. Patients with adrenal insufficiency may have hyponatremia, hyperkalemia, and

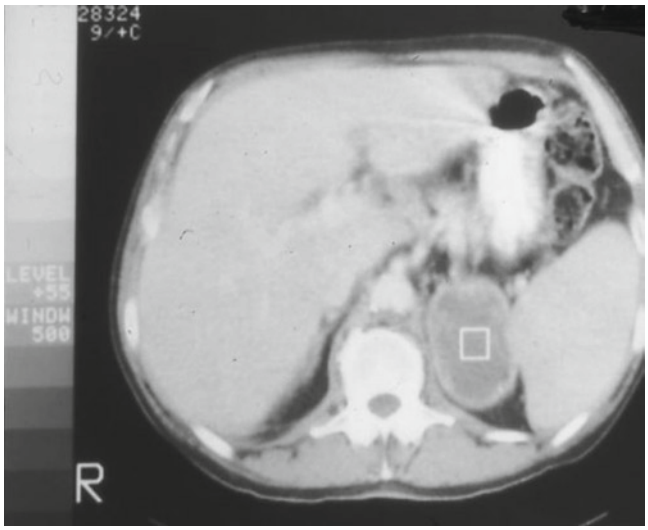

Fig. 13 Abdominal CT scan showing adrenal enlargement with central necrosis in a patient with chronic progressive histoplasmosis complicated by Addison's disease

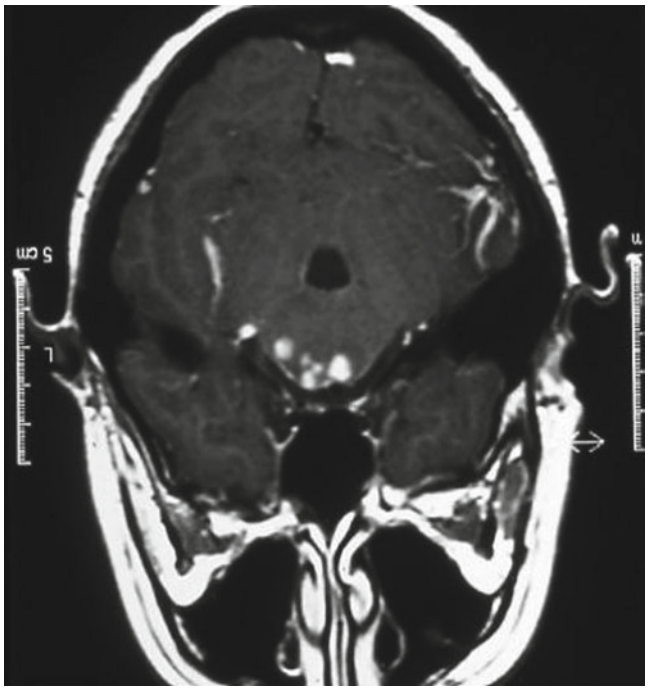

Fig. 14 MRI scan of a woman with isolated central nervous system histoplasmosis. The scan shows meningeal enhancement as well as several enhancing lesions in the midbrain

hypoglycemia. Abdominal CT scans show adrenal enlargement and sometimes necrosis in those with adrenal involvement [58] (Fig. 13). Bone marrow, liver, and lymph node biopsy specimens often reveal granulomas and budding yeast.

Disseminated histoplasmosis must always be considered as a possible cause of fever of unknown origin in any person who has ever lived in the endemic area. Lymphomas, sarcoidosis, and mycobacterial infections must be differentiated from disseminated histoplasmosis. Whether the patient has histoplasmosis or sarcoidosis is a difficult diagnostic conundrum. The use of corticosteroids for presumed sarcoidosis without excluding active histoplasmosis can be risky. Although patients may initially appear to improve with corticosteroid treatment, they subsequently experience progressive illness and can die of overwhelming histoplasmosis [59].

Endocarditis is an uncommon manifestation of disseminated histoplasmosis. Both native and prosthetic valve endocarditis have been reported [60, 61], as well as an infected left atrial myxoma [62]. The disease is manifested by major embolic episodes and poor outcomes if the infected valve cannot be replaced. *H. capsulatum* has also been described as a cause of infection of an aortofemoral prosthetic graft [63].

Specific Organ System Involvement

Histoplasmosis of the central nervous system can be manifested as subacute or chronic meningitis or as an acute event that is just one manifestation of disseminated infection [64, 65]. Basilar meningeal involvement is typical and can lead to communicating hydrocephalus. Focal brain or spinal cord lesions can occur in those with meningitis, and in other patients, they appear as isolated lesions without meningitis [65, 66]. In patients with meningitis, the typical CSF abnormalities include lymphocytic pleocytosis, elevated protein, and hypoglycorrachia; in those with focal lesions, the CSF findings are either within normal limits or show slight pleocytosis and elevated protein concentrations. Computed tomography or MRI scans show single or multiple enhancing brain lesions in those with focal infection and meningeal enhancement in those who have meningitis only (Fig. 14). *Histoplasma* meningitis must be differentiated from other causes of chronic lymphocytic meningitis, notably tuberculosis, coccidioidomycosis and, less commonly, blastomycosis, sporotrichosis, brucellosis, and sarcoidosis. Mass lesions must be differentiated from other infectious processes as well as tumors [66].

Osteoarticular histoplasmosis is not common. Typically, the manifestations are those of chronic tenosynovitis and, less commonly, osteomyelitis and septic arthritis of a native joint or, rarely, a prosthetic joint [67, 68]. Infection of osteoarticular structures must be differentiated from the self-limited arthralgias and arthritis that are noted during the course of acute histoplasmosis and that are presumed secondary to the immune response to *H. capsulatum* [35].

Isolated infection of the GI tract is an uncommon manifestation of histoplasmosis, but GI involvement as one manifestation of disseminated infection, especially among immunosuppressed patients, is common [69, 70]. Diffuse infiltration of the bowel wall is usually noted; abdominal pain and diarrhea are prominent, and malabsorption can result.

Genitourinary tract infection with *H. capsulatum* can be manifested as epididymal, testicular, or prostatic nodules [71–73]. Placental infection with spread to the fetus has been described rarely [74]. Other sites at which *H. capsulatum* has been reported to cause focal infection or in which involvement has been noted in association with widespread dissemination include kidneys, peritoneum, omentum, gallbladder, common bile duct, panniculus, breast, thymus, sinuses, optic nerve, eyes, and ears.

Presumed Ocular Histoplasmosis

Ocular histoplasmosis is a diagnosis based on ophthalmologic findings of discrete yellow-white lesions in the retina, so-called "histo spots"; these lesions are sight threatening when they occur in the macula [75]. However, there is little scientific evidence linking this syndrome to histoplasmosis [5]. The association is based primarily on residence in an area endemic for histoplasmosis and positive histoplasmin skin tests and not by demonstration of fungus in the eye. Similar ophthalmologic findings have been noted in patients who have never lived in the endemic area [76]. Rarely, *H. capsulatum* can be recovered from the eye in patients with disseminated histoplasmosis, but the clinical and ophthalmologic findings are not those described with ocular histoplasmosis [77].

Histoplasmosis due to H. duboisii

Infection with *H. duboisii* differs from that due to *H. capsulatum* in that bones and skin are the two major organs affected [20, 21] (Figs. 15a and b). Osteolytic lesions are often found in association with subcutaneous nodules and abscesses; skin nodules can ulcerate and drain. Lung involvement is more common than previously thought, and lymphadenopathy is prominent in some cases. The infection is frequently indolent and not life threatening, but in the exceptional patient, widespread visceral dissemination occurs, and the disease resembles progressive disseminated histoplasmosis due to *H. capsulatum*; this is especially seen in patients who have HIV infection [20].

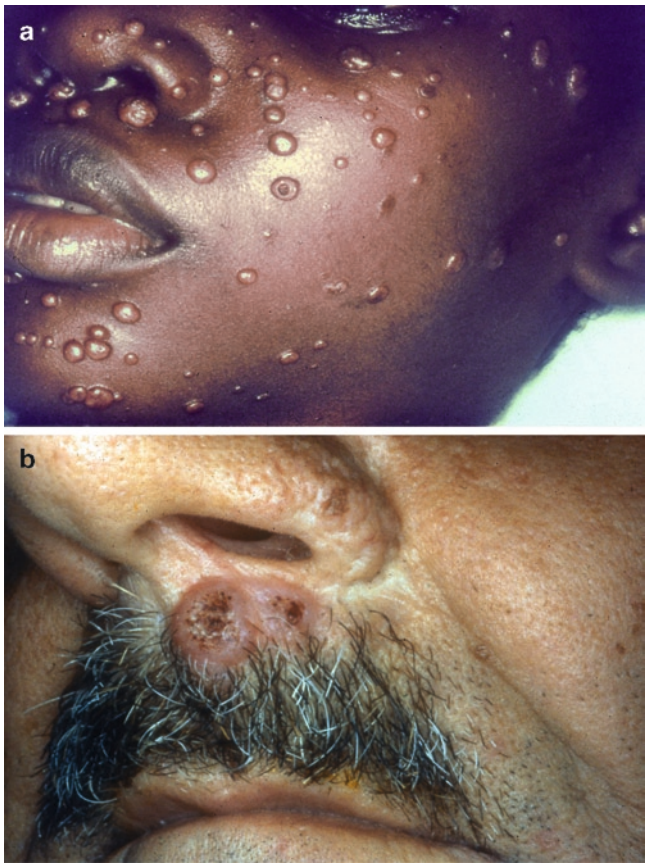

Fig. 15 (**a**) Numerous molluscum-type skin lesions that appeared on the face of an African child with disseminated infection due to *Histoplasma duboisii*; (**b**) solitary skin lesion typical of those seen with *H. duboisii* (Photos courtesy of Dr. Bertrand Dupont)

Diagnosis

Culture Methods

The definitive diagnostic test for histoplasmosis is growth of *H. capsulatum* from tissue or body fluids. For patients who have disseminated infection, samples taken from blood, bone marrow, liver, skin, or mucosal lesions often yield the organism. The lysis-centrifugation (Isolator tube) system is more sensitive than automated systems for growing *H. capsulatum* from blood [78]. When sputum or bronchoalveolar lavage fluid is sent for culture, the laboratory should be informed that histoplasmosis is a possibility; use of a selective medium that uses ammonium hydroxide decreases the growth of commensal fungi and increases the yield of *H. capsulatum* [79].

H. capsulatum may take as long as 6 weeks to grow at 30°C in the mould phase in vitro. Identifying tuberculate macroconidia allows a presumptive diagnosis of histoplasmosis, but a confirmatory test should always be performed. A chemiluminescent DNA probe specific for *H. capsulatum* is used to rapidly confirm the identification of the organism [80]. The laborious task of converting the mould phase to the yeast phase in vitro is no longer required for definitive identification of *H. capsulatum*. Cultures yield the organism in most cases of disseminated infection, in chronic pulmonary histoplasmosis, and in those cases of acute pulmonary histoplasmosis following a heavy-inoculum exposure. However, in many patients who have acute pulmonary histoplasmosis, and in most patients who have mediastinal granuloma or meningitis, cultures rarely yield *H. capsulatum*.

Antigen Detection

Detection of circulating *H. capsulatum* polysaccharide antigen in urine and serum has proved extremely useful in patients, especially those with AIDS, who have disseminated infection with a large burden of organisms [81, 82]. Originally developed as a radioimmunoassay, antigen detection is now performed by enzyme immunoassay with greater ease and equivalent sensitivity and specificity [83]. The sensitivity for antigen detection is higher in urine than in serum. Antigen can be detected in the urine of approximately 90% and in the serum of approximately 50% of AIDS patients with disseminated infection [82]. Antigen can be detected in urine or serum within the first few weeks of illness in approximately 65% of patients who have acute pulmonary histoplasmosis, especially in those who had been exposed to a high inoculum of organisms [84]. However, antigen is detected in only 10–20% of patients with less severe and chronic forms of pulmonary histoplasmosis and in patients who have complications of pulmonary histoplasmosis. Antigen detection has also proved useful in AIDS patients undergoing bronchoalveolar lavage for pneumonia due to histoplasmosis [85]. Antigen can be detected in CSF from some patients with *Histoplasma* meningitis [65].

False-positive reactions have been noted in a majority of samples of urine and serum taken from patients with blastomycosis, paracoccidioidomycosis, and penicilliosis [86], and have been described less commonly in patients with coccidioidomycosis [87]. The major diagnostic dilemma in the United States is obviously with blastomycosis. Samples from patients who have either histoplasmosis or blastomycosis show reactivity with antigen assays for both fungi [86, 88]. Antigen detection can be used to follow a patient's response to antifungal therapy. Levels should fall to below the level of detection with successful therapy, and a rise in antigen level may signal relapse [82].

PCR Assays

Several polymerase chain reaction (PCR) assays that might help with more rapid identification of *H. capsulatum* have been developed [89–92]. To date, there is no standardization, and none are commercially available. A real-time PCR assay correctly identified *H. capsulatum* from among a variety of culture extracts from different fungi grown in the laboratory [89]. This assay was used to identify *H. capsulatum* in tissue biopsies and bronchoalveolar lavage fluid from three patients who had documented histoplasmosis. Semi-nested PCR assays were shown to be very sensitive for detecting *H. capsulatum* in tissues from infected mice [90], and other similar assays have been used in a small number of samples of blood or tissues obtained from a few patients who had documented histoplasmosis [91, 92]. It is likely that PCR will assume an increasing role in the diagnosis of histoplasmosis in the future.

Serologic Tests

Although antigen detection has led to a less important role for antibody assays, these tests still play a role in the diagnosis of several forms of histoplasmosis [82]. The standard assays for antibodies to *H. capsulatum* are the complement fixation (CF) test that uses two separate antigens – yeast and mycelial (or histoplasmin) – and the immunodiffusion (ID) assay. A fourfold rise in CF antibody titer is considered indicative of active histoplasmosis. It is also frequently stated that a CF titer equal to 1:32 indicates active infection with *H. capsulatum*, but a diagnosis should never be based solely on such a titer. CF antibodies frequently persist for years after infection; thus, the presence of a single low CF titer means little other than that the patient was exposed to *H. capsulatum* at some time.

The ID assay tests for the presence of M and H precipitin bands. An M band develops with acute infection, is often present in chronic forms of histoplasmosis, and persists for months to years after the infection has resolved [93]. An H band is much less common, is rarely if ever found without an M band, and is indicative of chronic and progressive forms of histoplasmosis. The ID assay is more specific than the CF assay. Enzyme immunoassay methods are poorly standardized and are generally not recommended.

Serologic tests are most useful for patients with chronic pulmonary or disseminated histoplasmosis; in these forms of histoplasmosis, the chronicity of the infection ensures that sufficient time has elapsed for the patient to have developed antibodies. For acute pulmonary histoplasmosis, a rising antibody titer to *H. capsulatum* is diagnostic. Serologic tests are less definitive in patients who have mediastinal lymphadenopathy, and the diagnosis should always be confirmed by tissue biopsy. False-positive CF tests occur in patients with lymphoma, tuberculosis, sarcoidosis, and other fungal infections, all of which may present as a mediastinal mass. Because 2–4 weeks are required for appearance of antibodies, serologic assays are less helpful in establishing a diagnosis in patients who have severe acute infection, and they are rarely useful in immunosuppressed patients, who mount a poor antibody response. A special use for antibody detection is in patients who have *Histoplasma* meningitis. The presence of CF and/or ID antibodies against *H. capsulatum* in the CSF is adequate to make a diagnosis in the appropriate clinical setting, and frequently this is the only positive diagnostic test [65].

Histopathologic Examination

For the patient who is acutely ill, tissue biopsy should be done as soon as possible to look for *H. capsulatum*. Finding the distinctive 2–4 μm oval, budding yeasts allows a presumptive diagnosis of histoplasmosis. Routine hematoxylin and eosin stains rarely show the tiny yeasts; biopsy material

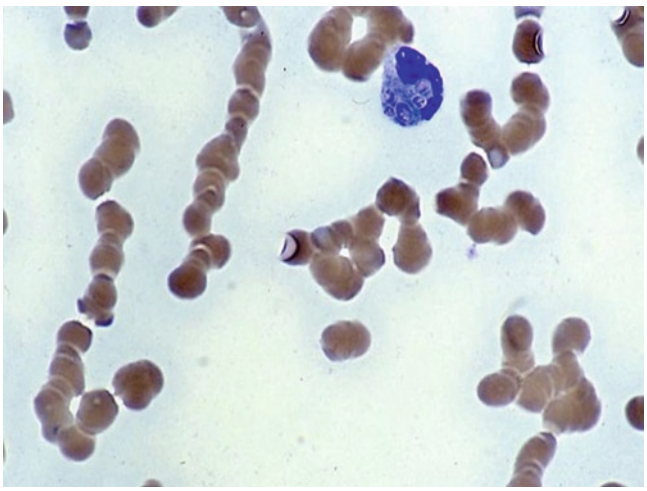

Fig. 16 Peripheral blood smear from an AIDS patient who was severely ill with disseminated histoplasmosis. Multiple tiny yeasts typical of *Histoplasma capsulatum* are seen within a monocyte

should be stained with methenamine silver or periodic acid–Schiff stains. Yeasts are typically found within macrophages, but also can be seen free in the tissues. In patients with disseminated infection, bone marrow, liver, skin, and mucocutaneous lesions usually reveal organisms, and in those with a large burden of organisms, routine peripheral blood smears may show yeasts within neutrophils (Fig. 16).

For patients with mediastinal granuloma, biopsy of nodes will often reveal caseous material, which may contain a few yeast-like organisms typical of *H. capsulatum.* It is unusual to find *H. capsulatum* on cytologic examination of sputum or bronchoalveolar lavage fluid unless there is a large organism burden.

In histopathology specimens, the yeast phase of *H. duboisii* is distinctly different from that of *H. capsulatum*. Yeast forms of *H. duboisii* are approximately fourfold larger than *H. capsulatum* and may be seen as short chains in tissues. The distinction between these two varieties of *Histoplasma* is clinically relevant only for a small number of patients who could have either infection because they live in areas of tropical Africa in which both organisms are found.

Treatment

Most patients infected with *H. capsulatum* are asymptomatic or have mild, self-limited disease and thus do not need treatment with an antifungal agent. However, patients who have severe acute pulmonary, chronic pulmonary, or disseminated histoplasmosis do require treatment with an antifungal agent. Guidelines for the treatment of histoplasmosis have been published recently by the Infectious Diseases Society of America [94].

Pulmonary Histoplasmosis

Acute pulmonary histoplasmosis. Most patients with acute pulmonary histoplasmosis do not require antifungal therapy; recovery usually occurs within a month. However, some patients remain symptomatic for longer periods of time and are likely to benefit from antifungal therapy. Oral itraconazole, 200 mg once or twice daily, for 6–12 weeks is recommended in such cases [94].

Patients who have moderately severe to severe acute pulmonary histoplasmosis should be treated initially with a lipid formulation of amphotericin B, 3–5 mg/kg daily, or with amphotericin B deoxycholate, 0.7–1 mg/kg daily. After the patient has shown improvement, usually in 1–2 weeks, therapy can be changed to oral itraconazole, 200 mg twice daily. Methylprednisolone, 0.5–1 mg/kg daily for the first 1–2 weeks is recommended for patients who are severely ill and for those with ARDS [94]. Antifungal treatment is usually given until the infiltrates resolve. For normal hosts, therapy may be as short as 12 weeks, but immunosuppressed hosts often require a longer course of therapy.

Chronic pulmonary histoplasmosis. Treatment is indicated for all patients with chronic pulmonary histoplasmosis [94]. Without therapy, inexorable progression to respiratory insufficiency is the usual course [39, 41, 42]. Most patients can be treated with itraconazole, 200 mg twice daily, and do not require therapy with amphotericin B [95]. Treatment should be given for at least 12 months, and some physicians recommend 18–24 months of azole therapy to decrease the risk of relapse. Fluconazole is less effective than itraconazole and is considered second-line therapy [96].

Complications of pulmonary histoplasmosis. It is not clear that antifungal agents alter the course of mediastinal granuloma. Most patients recover without treatment, but some continue to have symptoms, which usually leads to the use of antifungal agents. Reports of successful therapy with either azoles or amphotericin B remain anecdotal. Itraconazole, 200 mg once or twice daily for 6–12 weeks, is suggested for patients who are persistently symptomatic [94]. For some patients, surgical removal of the mass of obstructing nodes is necessary for symptomatic relief [37].

Antifungal therapy, corticosteroids, and anti-inflammatory agents are not useful for treating fibrosing mediastinitis. Surgery is considered to be risky and does not have a role in management of this condition [47, 94]. For some patients, placement of intravascular stents into obstructed pulmonary arteries or veins or the superior vena cava has been helpful [97]. Generally, stenting is performed in those patients who are more severely compromised with bilateral pulmonary vessel obstruction or superior vena cava syndrome [37, 97]. Unilateral occlusion of the pulmonary vessels is associated with a better prognosis, and stenting is generally not necessary.

Pericarditis is treated with nonsteroidal anti-inflammatory agents and, rarely, corticosteroids. Antifungal agents are not recommended unless corticosteroids are used, in which case itraconazole, 200 mg once or twice daily, is given for 6–12 weeks to prevent the possible occurrence of progressive infection with *H. capsulatum* [94]. In the exceptional case associated with tamponade, pericardiocentesis and creation of a pericardial window are important therapeutic measures.

Disseminated Histoplasmosis

All patients with disseminated histoplasmosis should be treated with an antifungal agent [94]. Patients with moderately severe to severe infection should be treated initially with liposomal amphotericin B, 3 mg/kg daily. Another lipid formulation at a dosage of 5 mg/kg daily or amphotericin B deoxycholate, 0.7–1 mg/kg daily, are alternatives. A randomized, blinded, controlled clinical trial in AIDS patients with moderately severe to severe disseminated histoplasmosis showed that liposomal amphotericin B, when compared with amphotericin B deoxycholate, resulted in faster resolution of fever and improved survival rates [98]. After clinical improvement is noted, which usually occurs within 2 weeks in most patients, therapy can be changed to oral itraconazole, 200 mg twice daily, to complete a course of 12 months of antifungal therapy [94]. Patients with mild-to-moderate disseminated histoplasmosis, including most patients who have the chronic progressive form of disseminated histoplasmosis, can be treated with oral itraconazole, 200 mg twice daily [94, 95, 99].

Fluconazole is less effective than itraconazole [96]; this has been most clearly shown in AIDS patients, in whom relapse rates while receiving fluconazole were noted to be unacceptably high [100]. Voriconazole and posaconazole have been reported to be effective for several different forms of histoplasmosis [18, 101–103]. However, there are no clinical trials to define the role of these newer agents in treating histoplasmosis, and most of these reports describe salvage therapy when other agents failed.

The length of therapy depends on the severity of the infection and the immune status of the host. The recommended treatment course is 12 months [94]. However, some patients with chronic progressive dissemination may respond slowly to antifungal therapy and require 18–24 months of therapy. For patients with AIDS, suppressive therapy with itraconazole, 200 mg daily, should continue beyond 12 months if the CD4 cell count remains <150 cells/μL [104]. For patients who are receiving effective antiretroviral therapy and whose CD4 cell counts are >150 cells/μL for at least 6 months, antifungal therapy can be stopped [105]. For patients whose immunosuppression cannot be reversed, life-long suppressive therapy with itraconazole may be prudent [94].

Histoplasma endocarditis should be treated with both surgical replacement of the valve and antifungal therapy [60, 61]. A lipid formulation of amphotericin B is the preferred treatment. If for any reason, surgical extirpation of the valve cannot be performed, lifelong suppression with itraconazole should be maintained.

Central Nervous System Histoplasmosis

Histoplasmosis involving the central nervous system is difficult to treat. Initial treatment should be with liposomal amphotericin B, 5 mg/kg daily for 4–6 weeks, and this is followed by oral azole therapy for at least 12 months. Itraconazole, 200 mg twice or three times daily, is the agent recommended in the IDSA guidelines [94]. Itraconazole does not achieve detectable CSF levels, but has been used successfully for *Histoplasma*, as well as other types of fungal meningitis [106, 107]. Conversely, fluconazole achieves higher CSF concentrations, but is less active against *H. capsulatum* than itraconazole. Fluconazole has been noted to be effective in a few case reports of *Histoplasma* meningitis [107, 108]. Anecdotal case reports show benefit for both voriconazole and posaconazole [101–103]. Antifungal therapy should continue for a total of at least 12 months and until all CSF abnormalities have resolved. Enhancing mass lesions in the brain or spinal cord appear to respond to antifungal agents and do not require excision in most patients. Magnetic resonance imaging scans should be followed to assure resolution.

Treatment of Infections Due to H. duboisii

Controlled trials have not been performed to determine the most efficacious treatment for *H. duboisii.* Anecdotal experience shows amphotericin B, ketoconazole, and itraconazole to be effective [21, 109]. There is no reason to doubt that the response to antifungal agents would be similar to that with *H. capsulatum*. However, osteoarticular involvement, which is common in this form of histoplasmosis, is slow to respond and requires long-term azole therapy.

Prevention

Persons who could be at risk for exposure to *H. capsulatum* through their occupation or leisure activities should be counseled to take appropriate precautions to prevent exposure [110].

Workers should wear a respirator when dismantling bird and bat roosts or chicken coops, refurbishing old structures that are found to have provided roosts for bats or birds, and moving large quantities of soil in areas known to be highly endemic for *H. capsulatum*. Soil or debris can be treated with formalin to inactivate the conidia prior to construction work, but this is rarely accomplished. Immunocompromised patients should be counseled to not undertake activities, such as spelunking or renovation projects, that might put them at risk for exposure to *H. capsulatum*.

Prophylactic use of antifungal agents has been studied only in persons with AIDS. In patients with CD4 counts <150 cells/μL, a placebo-controlled trial showed that prophylaxis with itraconazole, 200 mg daily, was effective at preventing histoplasmosis [111]. Prophylaxis should be considered only in highly endemic areas in which the rate of infection is at least ten cases/100 AIDS patient-years. There are no recommendations for the use of prophylaxis for other populations of immunosuppressed patients, such as those undergoing transplantation and those treated with TNF antagonists.

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