

Clinical spectrum and treatment of classic histoplasmosis

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Summary

Classic histoplasmosis, or histoplasmosis capsulati, is a systemic mycosis produced by the dimorphic fungus *Histoplasma capsulatum* var. *capsulatum*. The infection in humans and animals is produced by the inhalation of microconidia of the mycelial phase. Primary infection tends to be asymptomatic or mild and usually remits spontaneously. Serious primary infections are associated with massive spore inhalation or immunodeficiencies. Three weeks after infection occurs, the cell-mediated immunity generates changes in the host's inflammatory responses which, in turn, regulate the evolutionary course of the disease. The wide range of clinical manifestations produced are the subject of this work.

Primary lung infection is seen in immunocompetent hosts. Beside the respiratory symptoms, the infection produces various manifestations resulting from hypersensitivity to causal agent antigens, characterized by erythema nodosum, arthritis, pleuresy and pericarditis; alterations resulting from the invasion of mediastinal lymph nodes; and histoplasmosomas. The chronic, cavitory form of pulmonary histoplasmosis occurs in males, older than 50 years of age, with chronic obstructive bronchopulmonary disease.

The disseminated, progressive forms of the disease are produced in persons with defective cell-mediated immunity. These evolve more rapidly and tend to be more serious, depending on the severity of the host's immunosuppression. Over the past years, organ transplants, lymphoma chemotherapy and the AIDS pandemic have contributed importantly to the increase in the acute and subacute forms of disseminated histoplasmosis. Focal lesions, especially mucocutaneous ulcers, predominate in the chronic, disseminated forms of the disease. The predominant clinical manifestations of the acute and subacute forms resemble those of a grave infectious process and include fever, weight loss, hepatosplenomegaly, micronodular interstitial lung infiltrates, generalized adenopathies, diarrhea and cytopenia. Fulminant cases present respiratory distress, shock, disseminated intravascular coagulation and multi-organ failure.

Currently, itraconazole and amphotericin B are the two drugs most frequently employed to combat this disease. These two antifungal agents are generally used for the chronic pulmonary and disseminated forms of histoplasmosis. Amphotericin B is usually reserved for the most serious cases or for patients receiving other drugs which interact with itraconazole.

A preventive vaccine is not currently available. Primary prophylaxis treatment for high-risk patients has not been universally accepted.

Key words

Histoplasmosis, *Histoplasma capsulatum*, Treatment, Clinical forms

Classic histoplasmosis, or histoplasmosis capsulati, is an endemic, systemic mycosis produced by the dimorphic fungus *Histoplasma capsulatum* var. *capsulatum*. The mycelial form of the microorganism is found in organically rich, acid pH soil, in humid, temperate or tropical climates [1]. Droppings of barnyard fowl, black birds, such as starlings, and bats increase soil contamination

which, in turn, generates sites of high spore density and the development of microepidemics [2,3]. Primary infection is usually produced by spore inhalation. The course of the disease largely depends on the number of inhaled microconidia and the immune status of the host. Table 1 summarizes the wide range of clinical manifestations of the disease.

Table 1. Clinical presentations of histoplasmosis.

1. Histoplasmosis in immunocompetent hosts
 - 1.1. Asymptomatic form of primary infection
 - 1.2. Acute pulmonary infection
2. Histoplasmosis in patients with chronic obstructive pulmonary disease
 - 2.1. Chronic cavitory pulmonary histoplasmosis
3. Histoplasmosis in immunocompromised hosts
 - 3.1. Chronic disseminated form
 - 3.2. Acute disseminated form
 - 3.3. Subacute disseminated form
4. Immunologically-mediated disease

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Pathogenesis

The infective elements of *H. capsulatum* are the microconidia of the mycelial form. These are inhaled by humans and other susceptible animal species as they float through the air. The inhaled spores penetrate the airways until they reach the pulmonary alveoli where they are phagocytized, but not lysed, by alveolar macrophages. In three to five days, the spores transform into yeast-like elements inside the alveolar macrophages and multiply by budding [4,5].

The regulatory genes controlling production of heat shock proteins play a fundamental role in changing the mycelial form to the yeast form. The enzymes produced participate in cysteine metabolism. These, in addition to the temperature of 37°C, are the two fundamental factors in the dimorphic process [6,7].

The yeast forms of *H. capsulatum* are initially found inside alveolar macrophages and polymorphonuclear neutrophils. The initial stages of the inflammatory response involve polymorphonuclear neutrophils, which are unable to dominate the infection but do limit its extension. Fungicide activity against the microconidia is exerted by these leukocytes through the action of the azurophilic granules. This is not related to nitric oxide nor to the action of toxic radicals of oxygen, but rather through the lack of activity against the yeast forms of *H. capsulatum*. Before the mechanisms of acquired cell-mediated immunity are put into play, macrophages permit rapid reproduction of the yeast forms of *H. capsulatum*, even though these are within the phagosomes which fuse with lysosomes. When the number of yeasts inside the macrophages is very high, they are liberated and rapidly captured by other macrophages to which they adhere by $\beta 2$ integrin [5,8]. Specific cellular immunity may be diminished when excessive number of yeasts is present. Lung infection during this phase progresses by contiguity, continuing through the lymphatic system to mediastinal lymph nodes and, finally, to the bloodstream. Hematogenous dissemination may be asymptomatic.

Activation of specific cell-mediated immunity in immunocompetent hosts is evident within two or three weeks after infection. The response produced is of the Th1 type, which effectively dominates the infectious process [8,9]. Maturation of cell-mediated immunity translates into production of compact, epithelioid granulomas in affected tissues, with the delayed hypersensitivity skin test with histoplasmin turning positive, and the blastogenic response of the lymphocytes against specific antigen becoming evident [8,9]. The important role of T CD4+ cells in the defensive mechanisms against histoplasmosis is seen in athymic mice and AIDS patients, both of whom have serious forms of the disease [5,6,8]. The role of T CD8+ cells does not appear to be significant in host survival but, apparently, these cells are necessary for optimal defense [2,5]. The importance of NK cells, which kill extracellular yeasts, is not absolutely clear, nor is the mechanism by which cytokines influence the transformation of macrophages into activated macrophages. Nevertheless, γ -interferon plays a protective role in experimental animal models of histoplasmosis [8,9].

When cellular immunity mechanisms are normal, the infection progresses to a latent state in which epithelioid granulomas with caseous centers which present viable yeast-like elements inside. The granulomas are surrounded by a fibrous capsule which calcifies over time.

Histoplasmosis in the immunocompetent host

Most of the primary infections are asymptomatic or present self-limited, mild, flu-like, respiratory symptoms. The course of the primary infection depends upon the number of inhaled microconidia, as well as on age and the previous clinical and immune status of the host.

The incubation period varies between three and 21 days. This period is shorter in reinfections and in massive infections [2,4].

The most frequently observed symptoms in the acute respiratory forms of the disease are: fever, headache, asthenia, dry cough, anorexia, weight loss, myalgias and, rarely, substernal, non-pleuritic pain. In extremely serious cases, respiratory distress requires mechanical respiratory assistance.

Hepatosplenomegaly is present in some patients, of whom approximately 5%-6% exhibit clinical manifestations associated with hypersensitivity, such as arthralgias with articular swelling and xanthochromic fluid, pericarditis and/or pleuresy and erythema nodosum or multiform. The fluid from the pericardium, pleura or articulations is serofibrinous and contains lymphocytes and polymorphonuclear cells. Sixty percent of the patients with pericarditis also present pleuresy.

The chest x-ray usually reveals diffuse infiltrates in both lung bases and an increase in the size of hilar and mediastinal lymph nodes. Serious cases may have disseminated miliary-type, micronodular infiltrates or confluent infiltrates which cavitate and later resolve without sequelae [5,10].

Independent of the severity of the disease, the acute, symptomatic forms seen in the primary infection tend to remit spontaneously in four to six weeks. The sequelae of the primary infection include fibrous nodules which calcify over time and contain caseous centers with yeast elements of *H. capsulatum* which are either dead or alive. Approximately one-third of the infected patients present calcified nodules in the lungs and lymph nodes of the pulmonary hili or in the mediastinum; less frequently, these nodules are also seen in the liver and spleen [3]. The calcifications can be multiple and uniformly distributed in both lungs [10] (Figure 1).

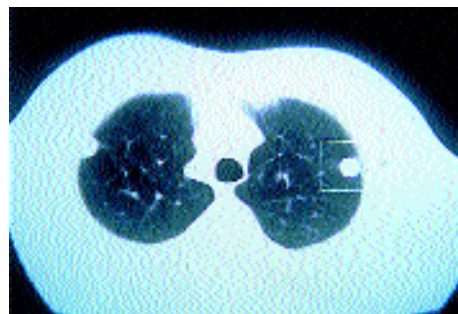


Figure 1. Calcified nodules of the lungs in a healthy young man as a sequela of primary infection.

During the course of symptomatic primary infection, the complementary laboratory studies reveal acceleration of the sedimentation rate, neutrophilia and elevation of alkaline phosphatase levels [2,5].



Figure 2. Granulomatous mediastinitis in a 68 year old man.

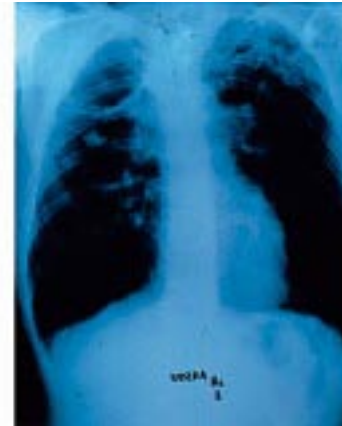


Figure 3. Chronic pulmonary histoplasmosis with a large cavity in the right lung in a 56 year old man.

Three to four weeks after infection, the serological tests for *H. capsulatum* antigens become positive. Specific antibodies can be demonstrated by immunodiffusion reactions, counterimmunoelectrophoresis, complement fixation and ELISA, although only the first two are sufficiently specific. The role of antibodies in host protection is unknown. Antibody titers tend to diminish after domination of the primary infection. The skin test with histoplasmin becomes positive three or four weeks after the first infective contact. Specific delayed hypersensitivity is maintained for two or more years and becomes negative if there are no new infections occur.

People who have had either symptomatic or asymptomatic primary *H. capsulatum* infections react in different manners to new infection. The incubation period is shorter, the respiratory symptomatology is more serious, and miliary-type micronodules and/or hilar adenopathies are seen on the chest x-ray. Clinical manifestations regress more rapidly, usually in seven to 14 days [10].

Primary histoplasmosis infection may infrequently lead to complications. Granulomatous mediastinitis, produced by invasion of lymphatic ganglia, leads to compression of the esophagus, bronchi, trachea and large blood vessels, especially the superior vena cava (Figure 2). When spontaneous remission occurs, fibrosis eventually replaces the granulomas. Fibrosis of the peribronchial region results in stenosis, bronchiectasis, pneumonia and bronchopleural fistulae [2,5]. Broncholithiasis, which is produced when calcified granulomas are eliminated via the bronchi, can also occur. Clinically, this translates into spasmodic cough, hemoptysis and atelectasis. Asymptomatic cases have been reported. Periesophageal fibrosis causes lumen stenosis, diverticuli and bronchoesophageal fistulae [5,6].

A serious consequence of granulomas in the carina lymph nodes is serofibrinous pericarditis. The inflammatory response is caused by hypersensitivity to *H. capsulatum* antigens; cultures of pericardial fluid are negative. The clinical course of pericarditis is usually benign, remitting in a few weeks and only rarely causing cardiac tamponade or constrictive pericarditis. Nevertheless, this complication incapacitates patients for several weeks [2,5].

Elevated hypersensitivity reactions to *H. capsulatum* antigens may produce massive mediastinal fibrosis and extrinsic compression of important anatomical structures in the area, especially the superior vena cava [11,12]. Histoplasmoses are residual lesions from the

pneumonitis which occurs during primary infection. These lesions are stable or slow-growing, usually asymptomatic and appear radiologically as solitary, subpleural nodules, 1-4 cm in diameter. The major problem with histoplasmoses, particularly those with no signs of calcification, is their potential confusion with lung neoplasms. Calcification is usually centric or in a target configuration [13]. As with the case of massive mediastinal fibrosis, hypersensitivity plays a fundamental role in the production of histoplasmoses. These lesions are thought to be mediated immunologically [12,13].

In patients with chronic, obstructive bronchopulmonary disease, *H. capsulatum* infection adopts a chronic, progressive course leading to chronic, cavitary pulmonary histoplasmosis [10,12]. This clinical form is present in approximately 10% of the patients with symptomatic primary infection. Nearly all cases are in Caucasian males, who are heavy smokers and older than 50 years of age (Figure 3). Defective lung architecture is considered a predisposing factor for this clinical form of the disease. These defects impede complete resolution of the mycosis, even in immunologically normal hosts [11]. Chronic pulmonary histoplasmosis may result from exogenous reinfection or reactivation of endogenous foci [10,13].

Inflammatory infiltrates, consisting of macrophages and lymphocytes, subsequently give rise to the formation of epithelioid granulomas which contain caseous material and are situated around emphysematous bullae. When the granulomas involute, lung parenchyma is destroyed and areas of fibrosis develop. This is a continuous process. The same cycle repeats in adjacent zones and, in this manner, extensive areas of both lungs are compromised. Involvement is usually symmetrical, affecting the apices and producing pleural thickening. Over time, this inflammatory process produces cavitations whose walls progressively thicken [5,12].

Clinical and radiological manifestations of the disease are similar to those seen in tuberculosis, but of lesser severity. The disease evolves over several years, with periods of progression and remission. More than 50% of the cases with lung infiltrates without cavitations remit spontaneously. A similar finding is seen in patients with cavitations with thin walls measuring 1-2 mm. On the other hand, the disease is chronic and progressive in patients who exhibit cavitations with walls measuring 3-4 mm in thickness [5].

The most frequent symptoms are evening fever, cough, mucopurulent or bloody expectoration, dyspnea on exertion, thoracic pain, asthenia, anorexia and weight loss.

Radiologically, heterogeneous, diffuse or nodular infiltrates are seen which are accompanied by pleural thickening. The functional capacity of the lungs is significantly reduced as a result of the cavitations and fibrosis which develop over time [10]. Two-thirds of the patients present calcified nodules in the lungs or lymph nodes.

The forced expiratory flow in functional respiratory capacity tests is markedly reduced, while complementary laboratory tests tend to reveal marked acceleration of the sedimentation rate, mild normocytic anemia (anemia of chronic diseases), neutrophilia in one-third of the cases and elevation of alkaline phosphatase values [5,6].

Diagnosis is ascertained by microscopic observation of *H. capsulatum* yeasts in mycological or histopathological studies or cultures of sputum, bronchoalveolar lavage and surgical specimens. The scarcity of yeasts in affected tissues and the rapid development of contaminant fungi in the upper airways makes both the microscopic observations and the isolation of *H. capsulatum* difficult [4,13].

Serological studies, especially immunodiffusion and complement fixation, constitute a valuable aid in the diagnosis of the disease. While not sensitive, immunodiffusion is a highly specific test. The result is defined as positive in the presence of M and H bands when histoplasmin is the antigen employed. Complement fixation may produce false-positive results in 5% of the inhabitants in endemic regions, as well as cross-reactions with other mycoses and a low percentage of false-negative results. All reactions with titers equaling or greater than 1/32, or reactions with progressive elevations in the titers, are strong indicators of progressive disease [4,8,9].

Chronic pulmonary histoplasmosis is an invalidating disease, leading to functional respiratory insufficiency, fatal hemoptysis, secondary bacterial infections and cor pulmonale. The spontaneous evolution of the disease is associated with high rates of mortality [5,10,13].

Histoplasmosis in immunocompromised hosts

The disseminated, progressive forms are seen in 1:2000 of persons infected with histoplasmosis. Proportions may be smaller, depending on the particular endemic zone. An important predisposing factor is age; many patients with the disease are younger than one year of age or older than 53 years of age and are predominantly males in proportion of 3-10:1 [14-17]. The most important conditioning factor is a deficit in cell-mediated immunity. This deficit may be mild, such as that produced by advanced age, type 2 diabetes, use of non-steroidal anti-inflammatory agents or small doses of corticosteroids, alcoholism and chronic smoking. The cell-mediated immunity may be seriously deficient in AIDS patients, organ transplant recipients, patients undergoing chemotherapy for hemato-oncological diseases and in those receiving high-dose corticosteroids [15-17].

Disseminated, progressive histoplasmosis in immunocompromised hosts may result from exogenous infection or from the reactivation of latent foci after a prolonged period of asymptomatic infection. The symptoms and evolution of the disease are conditioned by the degree of alteration in immunity. Mild defects can lead to chronic, localized processes, while serious immune defects produce multifocal processes with an acute or subacute evolution. The clinical panorama ranges from skin or mucous membrane ulcers, which mildly impact the

general health of the patient, to respiratory distress, shock and disseminated intravascular coagulation in the most severe cases [2,5,15].

The chronic, disseminated form of the disease predominates in males older than 50 years of age. In this group of patients, mucocutaneous lesions are the manifestations most frequently seen. Laryngeal compromise is present in approximately 50% of the patients. The symptoms are dysphonia, odynophagia, obstructive dyspnea, cough and mucopurulent expectoration. Laryngoscopy reveals a predominance of supraglottic lesions with red-violet infiltrates of the epiglottis and ventricular bands, erythematous nodules and ulcers with granulomatous bases, partially covered by white-yellow secretions [18]. The granulomatous, infiltrative infraglottic lesions frequently produce stenosis which necessitates tracheotomies [13].

Lesions are present on the mouth and pharynx in 40% of the cases. These lesions are sharp-edged ulcers with a smooth base or peaked, red granulomas partially covered with yellow-white secretions. Occasionally, the base is vegetated. White lesions, with the same appearance as those produced by lichen planus or leukoplakia but which are, in fact, superficial necrobioses, are also observable in the mucosa [18]. The lesions are polymorphic in one-third of the patients, with nodules, erosions with granulomatous bases and hemorrhagic dotting similar to the mulberry-like stomatitis of paracoccidioidomycosis. Chancroid lesions and aphtae may also be present [13,18]. Tongue involvement occurs in 10% of the patients. The presence of a fissured ulcer, situated on the union between the anterior two-thirds and the posterior third part of the tongue, is characteristic (Figure 4). Sublingual and lateral tongue ulcers are also common (Figure 5). Oropharyngeal lesions are accompanied by pain, odynophagia, sialorrhea, macroglossia and poor dental condition. General manifestations include asthenia, weight loss and, rarely, hepatosplenomegaly [19].

The destruction of the subnasal septum by granulomatous, ulcerated, scabbed lesions occurs in 15% of the cases and can be confused with mucocutaneous leishmaniasis [18].

Skin lesions occur less frequently than mucosal lesions in this clinical form of the disease, appearing in approximately 10% of the cases (Figure 6). These lesions have several presentations: deep ulcers with sharp edges and a granulomatous base; fissured ulcerations, seen predominantly on the feet, with abundant, purulent secretions; chancroid-like ulcers on the genitals; and acneiform papules with ulcerated vertex containing pus covered with scabs, similar to those observed in the acute, disseminated forms. Patients on high-dose corticosteroid treatment develop a nodular cellulitis which tends to ulcerate. These alterations are seen in organ transplant recipients and in persons affected by systemic lupus [11,13].

Pulmonary lesions are observed in only 10% to 20% of the cases. These consist of diffuse infiltrates, localized in the middle and inferior fields of the lung. Ultrasonographic abdominal studies tend to show heterogeneous hepatomegaly compatible with the presence of granulomas, fibrosis, steatosis and, rarely, retroperitoneal adenopathies.

Clinical involvement of the adrenal glands has been reported to be approximately 10%; however, autopsy studies reveal that involvement of these glands is much more frequent. A typical Addison syndrome is produced. Computerized abdominal tomography reveals both enlargement and destruction of the gland.



Figure 4. Ulcerated lesion of the tongue in a case of chronic disseminated histoplasmosis.



Figure 5. Chancroid ulcer of the tongue in a patient who presented a subacute disseminated histoplasmosis associated to a pleural mesothelioma.



Figure 6. Granulomatous skin lesions on the face of a patient who presented a chronic disseminated histoplasmosis.

Central nervous system (CNS) involvement is rare, but when it does occur, the clinical presentation is not characteristic. A chronically-evolving meningo-encephalitis is seen which selectively compromises the nuclei in the base of the brain. The cerebrospinal fluid (CSF) is non-purulent. Clinically, CNS involvement translates into behavior changes, headaches, convulsions and, in the most advanced cases, internal hydrocephaly. Tomographic brain studies are indispensable to detect the latter clinical manifestation. Cerebrospinal fluid presents increased proteins, positive globulin reaction and discrete lymphocytic pleocytosis (<50 cells/ μ l). Rarely, *H. capsulatum* can be isolated from the CSF; frequently, complement fixation and immunodiffusion tests performed on CSF yield positive results. The presence of histoplasmosis meningo-encephalitis can only be established when other locations of the disease are apparent (skin, mucosal or pulmonary) or when other possible causes of these clinical manifestations have been eliminated [12,13]. Occasionally, CNS histoplasmosis presents as an occupying brain mass, associated with headache, convulsions and focal signs. The computerized tomography brain study demonstrates the location of the lesion around which ring enhancement is present when contrast is used.

Endocarditis caused by *H. capsulatum* is infrequently observed. The clinical manifestations are the same as those associated with endocarditis produced by other entities: prolonged fever, heart murmurs, splenomegaly and septic emboli. Bidimensional echocardiography shows large-caliber vegetations. Most cases have been identified through the use of mycological and histopathological studies of surgical specimens [2,5,12]. Endovascular invasion, especially of the aorta, can also occur.

The clinical symptoms of gastrointestinal compromise are similar to those of gastric cancer or chronic intestinal diseases, such as tuberculosis, Crohn's disease, adenocarcinoma of the colon, etc. Gastrointestinal histoplasmosis produces ulcerations of the mucous membranes which are detectable by endoscopy. Hemorrhage, perforation or intestinal obstruction can occur. Radiology studies of the digestive tract using contrast are useful for identifying the different locations of the lesions [2,5].

Less frequently, the chronic, progressive forms of histoplasmosis produce arthritis, tendinitis, orchitis and chorioretinitis.

In the majority of the cases, the diagnosis can be confirmed by mycological studies and histopathological biopsies of skin and mucosal lesions. Rarely, when this clinical form is present, *H. capsulatum* can be isolated from bone marrow aspiration. Blood cultures are usually negative. The classic serological reactions, such as agar immunodiffusion and complement fixation, are positive in the majority of the cases. The results of the histoplasmin skin test are variable and frequently negative in the most serious cases [9,11,16].

The acute and subacute, disseminated forms of histoplasmosis are observed in infants in some endemic areas, as well as in patients whose cellular immunity is seriously deficient, such as those with AIDS, lymphomas, leukemias or organ transplant recipients [17,20-22].

AIDS constitutes an important predisposing factor for the disseminated form of histoplasmosis in endemic areas. This mycosis is associated with an estimated ten-fold increase in the frequency of complications in HIV infection in endemic versus non-endemic zones [20]. Approximately 5% of the AIDS patients in Buenos Aires have histoplasmosis disease, while in Indianapolis this figure rises to 27% in HIV-positive patients requiring hospitalization [22].

The clinical manifestations of histoplasmosis in AIDS patients are those which occur in other serious infectious processes: prolonged, high fever; weight loss; asthenia; anorexia; diarrhea or vomiting; hepatosplenomegaly; multiple adenomegalies; skin lesions and pancytopenia. Occasionally, symptoms are predominantly respiratory in nature: cough, mucous expectoration, dyspnea and interstitial, micronodular infiltrates on radiological chest studies [24] (Figure 7). Acute respiratory insufficiency requiring mechanical breathing assistance may be present in severe cases.

Ten percent of the cases follow a fulminant clinical course leading to shock and adult respiratory distress, encephalopathy, multi-organ failure and disseminated intravascular coagulation [5].

Central nervous system compromise is seen in one-fifth of the patients with acute and subacute disseminated processes. Meningo-encephalitis is clinically similar to that described for the chronic form of the disease, but with higher degrees of compromise in states of consciousness and a more rapid course of evolution [24].



Figure 7. Chest film of a young woman suffering an acute disseminated histoplasmosis with respiratory distress and HIV infection.



Figure 8. Disseminated papular lesions of the skin in an AIDS related histoplasmosis.

Endoscopic studies of the digestive tract demonstrate ulcerated lesions in the gastric and colonic mucosa. The symptoms are uncharacteristic, often presenting only as epigastric pain, emesis or diarrhea.

Bone lesions are frequent in pediatric patients, they preferentially localize in the long bones and produce pain, functional impotence and swelling of soft adjacent regions. Osteolytic images, usually localized on the metaphysis, can be seen on radiology studies [11,13].

Ultrasonography and computerized tomography of the abdomen show heterogeneous hepatomegaly, homogeneous splenomegaly and abdominal and retroperitoneal adenopathies.

In Latin America, mucocutaneous skin lesions appear in 80% of the patients with acute or subacute disseminated histoplasmosis. In the United States, mucocutaneous involvement has been reported in 6% to 10% of the patients suffering from this form of the disease [22]. The lesions manifest as small, multiple papules, 3-4 millimeters in diameter, on various body parts (Figure 8). The vertex are usually ulcerated and covered with scabs; however, the lesions can also be vegetated ulcers, large ulcers with granulomatous bases and sharp edges, nodules or diffuse hypodermatitis, molluscoid papules and lupoid lesions [24]. Mucosal lesions are less frequent than skin lesions and appear as ulcers covered by white secretions localized on the oropharyngeal mucosa in either the larynx or on the penis [24].

Complementary laboratory studies reveal accentuated acceleration of the sedimentation rate, thrombocytopenia and elevation of hepatic enzymes (especially alkaline phosphatase) [5].

In the F. J. Muñoz Infectious Disease Hospital in the city of Buenos Aires, significant numbers of HIV-positive patients have been treated for disseminated histoplasmosis. Results from the last three years are discussed. Ninety-three patients were studied, 75 of whom were males and 18 females, aged 23 to 56 years of age ($X=37.12$). Risk factors for HIV infection included intravenous drug use (54 patients), homosexuality or bisexuality (25 patients), heterosexual transmission (12 patients) and blood transfusions (two patients). Histoplasmosis was a late complication of HIV infection. Positive CD4 cell counts varied between 0 cells/ μ l and 290 cells/ μ l. Only eight patients (less than 10%) had CD4+ cell counts above 100 cells/ μ l. The clinical mani-

festations in the group of patients studied were: fever and weight loss (86 patients), lung infiltrates (71 patients), hepatosplenomegaly (66 patients), adenopathies (60 patients), skin lesions (54 patients), mucosal lesions (33 patients), diarrhea (15 patients), pericardial effusion (six patients), meningitis, endocarditis, adrenal insufficiency, serious jaundice and diabetes (one patient each). Radiological chest studies showed a predominance of micronodular pulmonary infiltrates with a miliary aspect (43 patients), diffuse infiltrates (21 cases), pleural effusions and cavitations (two and one patients, respectively). An important finding was the frequency with which mucocutaneous manifestations were identified. The lesions consisted of ulcerated papules covered with scabs in 39 patients, vegetated ulcers in five patients, isolated ulcers in four patients, molluscoid lesions in two patients, nodules and diffuse hypodermatitis in two patients and lupoid lesions in one patient. Mucosal alterations included oropharyngeal ulcers in 20 patients; laryngeal granulomas (three patients); and penile ulcers in three patients. The morbid clinical associations diagnosed in this group of patients included: tuberculosis (32 patients), hepatitis B (19 patients), hepatitis C (16 patients), herpes simplex (12 patients), oropharyngeal candidiasis (10 patients), *Pneumocystis carinii* pneumonia (nine patients), cerebral toxoplasmosis (eight patients), herpes zoster (five patients), gastric and esophageal candidiasis (six patients), neurosyphilis (six patients), pulmonary nocardiosis, meningeal cryptococcosis, *Streptococcus pneumoniae* septicemia and Kaposi's sarcoma (two patients, respectively). The large number of concomitant diseases poses difficulties and complications for diagnosing and treating AIDS-related histoplasmosis, especially in the absence of mucocutaneous lesions. The prognosis for these patients is poor.

Histoplasma capsulatum is easily identified and cultured from various active lesions using techniques such as scraping and biopsy of skin and mucous membranes, puncture and biopsy of lymph nodes, bronchoalveolar lavage, etc. (Figures 9 and 10). In a recent study, 78% of the patients with acute or subacute AIDS-related histoplasmosis were diagnosed with skin or mucosal lesion studies. Tzanck's cytodiagnosis is a useful and rapid diagnostic technique when skin alterations are present. Blood cultures by the lysis-centrifugation technique have been shown to be highly efficient, yielding positive results

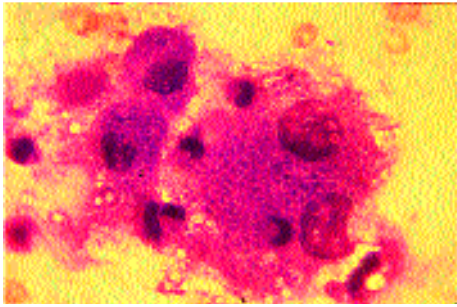


Figure 9. Giemsa smear showing macrophages with a large amount of intracellular yeast-like elements of *H. capsulatum*.

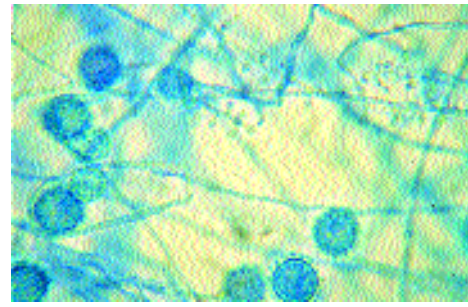


Figure 10. Mycelial form of *H. capsulatum* showing microconidia and macroconidia.

in 75% of the patients; blood cultures constitute the first diagnostic element in 20% of the cases [24]. The other techniques which permit observation or isolation of the causal agent, but are not routinely done, are: bone marrow or lymph node aspiration; microscopic observation of the leukocyte layer of the hematocrit and bronchoalveolar lavage [24,25].

Serology studies for antibodies yield elevated false-negative results in the acute, disseminated forms of the disease. When classical techniques are used, such as immunodiffusion, counter immunoelectrophoresis or complement fixation, only 25%-35% of the patients have positive reactions [24]. The ELISA technique, using an exoantigen of the yeast phase of *H. capsulatum*, increases the positive results to approximately 75% in patients with AIDS-related histoplasmosis. Radioimmunoassay or ELISA techniques are useful for identifying the glucoprotein antigen of *H. capsulatum* in organic fluid samples. Urine samples yield better results than serum samples and sensitivity increases when several concentrated urine samples are used from the same patient, even though specificity is not absolute [8,9,22]. Skin tests using histoplasmin are usually negative.

The experience in the F.J. Muñiz Infectious Disease Hospital in Buenos Aires over the past three years serves to underscore the utility of various diagnostic methods for AIDS-related histoplasmosis. Tzanck's cytodagnostic method for skin lesions identified *H. capsulatum* in 54 patients (58%). The same technique applied to mucosal lesions achieved diagnosis in 33 patients (34.5%). Blood cultures by the lysis-centrifugation technique isolated *H. capsulatum* in 68 patients (73.1%). Bronchoalveolar lavage was positive in seven patients and lymph node puncture and aspiration was positive in five patients. Serological studies for *H. capsulatum* antibodies yielded positive results in 34.8% of the patients when counterimmunoelectrophoresis was employed; ELISA yielded a positive rate of 77%.

The time frames in which the spontaneous evolution of acute or subacute disseminated histoplasmosis proves to be fatal are variable and determined by the immunological status of the host and the coexistence of other pathologies.

Immunologically-mediated disease

As previously mentioned, mediastinal fibrosis and histoplasmosis – both sequelae of primary infections – are considered to be mediated by exaggerated hypersensitivity to *H. capsulatum* antigens. Worthy of mention is the chorioretinitis presumably associated with histoplasmosis. The incidence of this disease in endemic areas oscillates between 1% and 10%, predominantly affecting white women between the ages of 30 and 40 years. Most of these patients possess the HLA-B7 histocompatibility

complex antigen. Skin tests with histoplasmin are strongly positive; however, *H. capsulatum* has neither been observed nor cultivated from the enucleated eyes of these patients. The assumption is that chorioretinitis results from the deposition of antigens liberated on the choroid from pulmonary or ganglionic foci. In as much as histoplasmosis-related chorioretinitis has also been reported in non-endemic areas, the suspicion arises as to whether or not there are other causes for this clinical syndrome. Clinically, a non-specific, inflammatory reaction produces local hemorrhages and detachment of the retina. Later, yellow scars with sharp edges are observed surrounded by inflammatory choroiditis. Patients refer loss of visual acuity and permanent scotomas. Fifty percent of the untreated cases result in blindness. Histopathological studies show the presence of mononuclear cellular infiltrates in which B lymphocytes and CD8+ cells predominate [2,5,11,13].

This clinical form of the disease does not cause general compromise of the patient, nor is antifungal treatment indicated. Corticosteroid treatment and laser photocoagulation improve the outcome; however, these treatment procedures are not advisable when involvement occurs near the fovea.

Treatment

Azolic compounds, such as itraconazole, ketoconazole, fluconazole and the polyenic antibiotic amphotericin B, are active *in vitro* and *in vivo* against *H. capsulatum* [27]. Indications for antifungal treatment vary according to the clinical presentation of the disease and the individual characteristics of the patient. The most frequently implemented therapeutic schemes are summarized in table 2.

Symptomatic primary infections do not usually require antifungal treatment; rather, treatment for these infections is only required when spontaneous remission does not occur within four to six weeks or for patients with immunological compromise [3,12,28].

Serious cases with marked respiratory insufficiency require mechanical respiratory assistance and corticosteroids in doses equivalent to 60-80 mg/day of prednisone [5]. During corticosteroid treatment, the patient requires protection with itraconazole in doses of 200-400 mg/day.

Hypersensitivity reactions, such as erythema nodosum, arthritis, pericarditis or pleuresy, warrant the use of non-steroidal anti-inflammatory drugs, aspirin and, in serious cases, corticosteroids. Antifungal protection is an absolute requirement in these cases [5].

Ketoconazole is a useful drug, but does not possess the therapeutic advantages of itraconazole for the treatment of histoplasmosis, even though it is the less expensive of the two drugs.

Table 2. Therapeutic schemes for histoplasmosis.

Clinical Form	Drug	Administration	Dose	Duration
Symptomatic Primary Infection	Itraconazole	Oral	400 mg	2 weeks(*)
	Itraconazole	Oral	200 mg	3 months
	Amphotericin B	IV	0.7 mg/kg	3 weeks
Pulmonary Chronic Cavitary	Itraconazole	Oral	200-400 mg	6-12 months
	Amphotericin B	IV	0.7 mg/kg	to 35 mg/kg
Chronic Disseminated	Itraconazole	Oral	100-200 mg	6-12 months
	Ketoconazole	Oral	400 mg	6-12 months
Subacute Disseminated	Itraconazole	Oral	400 mg	12 months
	Amphotericin B	IV	0.7 mg/kg	To 35 mg/kg
Acute Disseminated	Amphotericin B	IV	0.8-1.0 mg/kg	To 40 mg/kg
Mediastinal Granulomas	Itraconazole	Oral	100-200 mg	6 months

(*) Treatment is initiated with 400 mg/day of itraconazole. Dose is reduced to half in two weeks and is continued for three months.

Mediastinal granulomas which initially respond to itraconazole during the first six months of treatment tend to continue responding to the same drug during an additional year. The cases which do not respond to medical treatment need surgical evaluation, even though the latter is a high-risk procedure with high failure rates [2,5].

Histoplasmosis is often surgically resected by lobectomy because of the high risk for confusing the lesion with a lung neoplasm. Histoplasmosis with calcified centers are not usually considered for surgical resection because the risk for confusing the lesion with lung cancer is much less [5].

Chronic, cavitary histoplasmosis of the lung is treated successfully with antifungal drugs in 90% of the cases, although there are recurrences in one-fifth of these patients. The use of itraconazole requires attention to drug interactions. Surgical resection of the cavitation is indicated only in exceptional cases because of the high risk for developing chronic respiratory insufficiency and bronchopleural sinus tracts [2,5,6].

Chronic, disseminated forms of the disease respond favorably to antifungal treatment, especially itraconazole, which is well-tolerated and effective [27]. Amphotericin B is indicated only for patients receiving other drugs which interact negatively with itraconazole, such as rifampin, antacids, H₂ receptor blockers, cyclosporin, phenytoin, terfenadine etc. While ketoconazole is active against this form of the disease and less expensive, itraconazole is more effective and better tolerated.

Patients with suprarenal insufficiency can usually be stabilized with 30 mg/day of oral hydrocortisone.

Histoplasmosis meningitis responds poorly to medical treatment. Amphotericin B, in the doses summarized in table 2, is the drug of choice; however, the total dose required is 40 mg/kg or more. The effectiveness of this drug is somewhat higher than 50% and frequently requires the use of a ventricular-atrial or ventricular-peritoneal shunt. Relapses are frequent and may necessitate secondary prophylaxis with itraconazole or fluconazole in doses of 200 mg/day orally. In extremely serious cases, the intrathecal or intraventricular administration of amphotericin B may be considered. This procedure carries the inherent risk of chemical arachnoiditis or meningeal hemorrhage. The drug should be administered in doses of 0.1 to 0.5 mg, dissolved in 5 ml of CSF with 20 mg of hydrocortisone, twice weekly [14].

Endocarditis is a rare clinical event associated with chronic, disseminated histoplasmosis. The prognosis is

very poor; the mortality in treated patients is 50%. Treatment consists of amphotericin B in total doses of 35 mg/kg. Surgical valve replacement is required. Some authors suggest secondary prophylaxis for one year with itraconazole in doses of 200 mg/day. Amphotericin B is indicated in patients with subacute, disseminated histoplasmosis when emesis and diarrhea are present, in patients receiving drugs which interact with itraconazole, or those with meningo-encephalitis. The remainder of the cases respond well to itraconazole. During the first three or four days of treatment, doses of 600 mg/day are required to achieve rapid tissue saturation with this compound [28].

Liposomal amphotericin B, as well as amphotericin B bound to other lipid formulations, is not routinely indicated for the treatment of this mycosis because of its elevated cost. The same criteria should be applied to liposomal amphotericin B as that used for opportunistic mycoses when amphotericin B desoxycolate fails, or in patients with renal failure and creatinine blood levels equal to or higher than 3 mg/dl.

In AIDS-related histoplasmosis, life-long secondary prophylaxis with itraconazole in doses of 100-200 mg/day is indispensable. Complications may arise from concomitant administration of a protease inhibitor because of the negative pharmacological interactions between the two drugs [29]. No clear consensus exists concerning the administration of primary prophylaxis in HIV-positive patients living in endemic areas for histoplasmosis. One study, in which HIV-positive patients with CD4+ counts less than 150/μl were given 200 mg/day of itraconazole, found a marked reduction in the incidence of histoplasmosis when compared with non-treated patients. Treatment in this group of patients did not influence mortality, nor did it prevent the development of oropharyngeal or esophageal candidiasis [2,5].

Several indications for surgical intervention have been mentioned previously. Occasionally, it is also necessary to perform a tracheotomy on the laryngeal lesions or debride mediastinal fibrosis in order to free organs or blood vessels in the affected area.

For the moment, an effective vaccine for histoplasmosis has not been developed. The 62 and 80 kDa thermic shock glucoproteins are considered important candidates for this vaccine [5].

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