

Chapter 4 – Histoplasmosis*

Capítulo 4 – Histoplasmose

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Abstract

Histoplasmosis is systemic mycosis caused by a small fungus, *Histoplasma capsulatum* var. *capsulatum*, whose natural habitat is soil contaminated by bat or bird excrement. The incidence of histoplasmosis is worldwide. In Brazil, the disease is found in all regions; however, the state of Rio de Janeiro is responsible for most of the microepidemics described. Human infection occurs when airborne spores of *H. capsulatum* are inhaled. The most common clinical presentation is asymptomatic. The symptoms of acute or epidemic histoplasmosis are high fever, cough, asthenia and retrosternal pain, as well as enlargement of the cervical lymph nodes, liver and spleen. The most common radiological findings are diffuse reticulonodular infiltrates in both lungs, as well as hilar and mediastinal lymph node enlargement. In chronic pulmonary histoplasmosis, the clinical and radiological manifestations are identical to those of reinfection with pulmonary tuberculosis. Histoplasmosis is diagnosed by means of the identification or culture growth of the fungus in sputum or fiberoptic bronchoscopy specimens. Histopathological examination reveals the fungus itself within or surrounding macrophages, as well as granulomatous lesions with or without caseous necrosis. Double agar gel immunodiffusion is the most easily used and readily available serologic test for making the immunological diagnosis. Acute histoplasmosis with prolonged symptoms requires treatment, as do the disseminated or chronic pulmonary forms of the disease. The drug of choice is itraconazole.

Keywords: Mycosis; Histoplasmosis; Lung diseases, fungal.

Resumo

Histoplasmose é uma micose sistêmica causada por um pequeno fungo, *Histoplasma capsulatum* var. *capsulatum*, cujo habitat é o solo rico em excrementos de pássaros e morcegos. A incidência da histoplasmose é mundial. No Brasil, a doença incide em todas as regiões; porém, o estado do Rio de Janeiro é responsável pelo maior número de microepidemias descritas até hoje. A infecção humana ocorre pela inalação de esporos do *H. capsulatum*. A forma clínica mais freqüente é a assintomática. Na histoplasmose aguda ou epidêmica, os sintomas são febre alta, tosse, astenia, dor retroesternal, acompanhados de aumento dos linfonodos cervicais, fígado e do baço. Os achados radiológicos mais frequentes são o infiltrado reticulonodular difuso em ambos os pulmões, associados a linfonomegalias hiliares e mediastinais. Na forma pulmonar crônica, o quadro clínico e radiológico é idêntico ao da tuberculose pulmonar do adulto. O diagnóstico da histoplasmose é feito pela identificação do fungo ou crescimento em cultura de escarro ou de material obtido por fibrobroncoscopia. A histopatologia identifica o fungo dentro e fora do macrófago em meio à lesão granulomatosa com ou sem necrose caseosa. A imunodifusão em duplo gel de ágar é o teste sorológico mais fácil e disponível para o diagnóstico imunológico. As formas agudas com sintomas prolongados, as formas disseminadas e a forma pulmonar crônica requerem tratamento. A droga de escolha é o itraconazol.

Descritores: Micoses; Histoplasmose; Pneumopatias fúngicas.

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Introduction

Histoplasmosis is a systemic mycosis caused by a small fungus, *Histoplasma capsulatum* var. *capsulatum*. Histoplasmosis has characteristics of granulomatous disease and primarily affects the lungs and the immune system. A variant of the disease is caused by *H. capsulatum* var. *duboisii*, which is found in Africa. *H. capsulatum* var. *capsulatum* is a dimorphic fungus. The natural habitat of *H. capsulatum* var. *capsulatum* is soil, principally soil that is rich in bat or bird excrement. In regular culture media at room temperature, *H. capsulatum* var. *capsulatum* grows as a saprophyte and presents filamentous growth, with hyphae that produce microconidia (infective elements) and tuberculate macroconidia. In regular culture media at 37°C, *H. capsulatum* var. *capsulatum* grows as a parasite and presents as a yeast-like, round, single-budding fungus of 2–4 µm in diameter. The fungus can be found in caves, sleeping trees, tree hollows, chicken coops, mines, water tanks, abandoned construction sites, basements and attics.⁽¹⁻³⁾

The incidence of histoplasmosis is worldwide, and the area in which the disease is most prevalent is the Midwestern United States, which is the region of the valleys of the largest American rivers, namely Ohio, Mississippi and Missouri. In Brazil, the disease is found in all regions; however, the state of Rio de Janeiro, where 18 microepidemics have been reported, accounts for most of the cases.^(1,2,4)

Human infection occurs when airborne spores of *H. capsulatum* are inhaled. The infective elements (microconidia) enter the airways (point of entry) and, upon reaching the alveoli, are phagocytosed, multiplying, in the parasitic form, within alveolar macrophages, resulting in focal pneumonitis or pneumonitis due to inoculation. Through the lymph nodes, the fungi reach the satellite regional ganglion, forming the bipolar pulmonary complex, similar to Ghon complex of tuberculosis. The fungus can then disseminate, through the blood, to any organ or system. This type of primary infection, which regresses spontaneously, usually occurs in immunocompetent individuals. In immunodeficient hosts, primary infection and reinfections can assume a progressive character of variable severity.⁽¹⁾

Clinical diagnosis

The severity of the disease depends on the intensity of the exposure, on the number of spores inhaled and on the immune status of the host. In healthy individuals, a low intensity of exposure commonly causes asymptomatic or nearly asymptomatic infection of self-limiting course. When the exposure is intense, individuals can develop severe pulmonary disease that can lead to respiratory failure and even death.⁽²⁾

The acute forms of histoplasmosis regress spontaneously. The asymptomatic or nearly asymptomatic form is the most common form of the disease and often goes unnoticed because it is mistaken for the flu. The so-called acute or epidemic pulmonary histoplasmosis presents to clinicians as isolated cases of difficult diagnosis or as microepidemics of easier diagnosis and benign course, the symptoms of which depend on the degree of exposure to the infective propagules. Fever, persistent and mildly productive cough, headache, asthenia, retrosternal pain and severe prostration are common. Pallor is a characteristic sign. Enlargement of superficial lymph nodes and hepatosplenomegaly are characteristic findings in the acute diffuse pulmonary form. Pulmonary physical signs are insignificant. The incubation period ranges from 3 to 14 days. The most common radiological findings in this form are bilateral hilar lymph node enlargement and bilateral reticulonodular infiltrate. When hilar lymph node enlargement is unilateral, this aspect is indistinguishable from the primary complex of pulmonary tuberculosis.^(2,5-8)

Chronic pulmonary histoplasmosis, also known as opportunistic histoplasmosis, affects individuals with abnormal air spaces, notably those with centrilobular emphysema or bullous emphysema, favoring the colonization of the fungus in these lesions. The fungus causes foci of segmental pneumonitis followed by pulmonary fibrosis and worsening of the underlying disease. The lesions commonly affect the upper lobes and are often mistaken for reinfection pulmonary tuberculosis or adult pulmonary tuberculosis, being treated as such.⁽²⁾

In the disseminated form, which affects patients with primary or secondary immunodeficiency, fever is always present and is generally persistent. Cough, dyspnea and asthenia are common complaints. In more advanced cases,

multiple organs are affected, resulting in polymorphic profiles. Hepatosplenomegaly, anemia, thrombocytopenia and leukopenia might be present. Acute disseminated histoplasmosis (infant form) and subacute disseminated histoplasmosis (juvenile form) are quite similar, and various organs and systems are affected. If left untreated, these forms progress to death. In chronic disseminated histoplasmosis (adult form), the lungs are often not affected.^(2,6,8)

Patients with the acute form can present arthralgia or arthritis, erythema nodosum or erythema multiforme, characterizing the rheumatic form of the disease. Pericarditis is another inflammatory complication of acute histoplasmosis that presents some months after the onset of the disease and manifests clinically as a subacute complication. Mediastinal involvement is part of the profile of the infection. Lymph node enlargement can compress important mediastinal structures, among which are the esophagus, the superior vena cava, the airways and the pulmonary vessels. This is the mediastinal granulomatous form of histoplasmosis. Fibrosing mediastinitis constitutes an abnormal form of fibrosis in response to past infection. It can obstruct or compress any structure in the mediastinum, forming a true fibrotic mass. Fortunately, the frequency of fibrosing mediastinitis is rare.⁽⁵⁾

Central nervous system (CNS) involvement is commonly associated with disseminated histoplasmosis in 40% of the cases and occurs in the form of isolated meningitis and local lesions in 25% of the cases, headache in 10% of the cases and spinal cord involvement in 2.5% of the cases. Histoplasmosis should be included in the differential diagnosis of patients with subacute or chronic disease of the CNS.⁽⁸⁾

Histoplasmosis can present to clinicians as a solitary pulmonary nodule, known as a histoplasma. The principal differential diagnosis is lung cancer. It is a lesion of necrotic or calcified (or a combination of the two) center, surrounded by a fibrotic capsule. It can rupture into a bronchus, causing broncholithiasis.^(1,6,8)

Laboratory diagnosis

The diagnosis of histoplasmosis is based on techniques for mycological examination, on techniques for histological examination, on techniques for immunological tests, on the clinical

history, on the epidemiological history and on the radiological findings. The fungus is not easily detected in organic secretions, even when special staining techniques are used (Giemsa, Wright, Grocott); even histopathology using the Grocott-Gomori methenamine-silver stain technique is unable to distinguish the fungus from other pathogens.^(3,6,8,9)

Mycological examination

The fungus is not easily detected by direct mycological examination of organic secretions, even when special staining techniques are employed. The fungus can be isolated from sputum or tracheobronchial secretion in 60-85% of the cases of chronic pulmonary histoplasmosis. *H. capsulatum* grows at 25°C, forming white (rat hair) colonies or brown, suede-like colonies on conventional Sabouraud agar medium or Mycosel agar. The time to growth is more than 30 days. The conversion into a yeast-like pattern occurs when the culture is incubated at 37°C, that is, the conversion from the mycelial form into the parasitic form confirms the diagnosis. Culture is commonly positive in cases of dissemination (to the blood, bone marrow or urine) and in cases of chronic pulmonary histoplasmosis, in which various samples obtained through fiberoptic bronchoscopy are analyzed. Biopsy samples (lung, lymph nodes, liver, skin and adrenal gland) can also be sent for culture.^(3,6,8)

Histopathological examination

The histopathological examination of various tissue samples (lung, lymph nodes, liver and bone marrow) reveals the presence of granulomas, with or without caseous necrosis, in immunocompetent individuals, whereas in immunocompromised individuals loose granuloma, lymphohistiocytic aggregates or diffuse mononuclear infiltrate in isolation are common. The yeast-like fungus is seen within and around macrophages. The differential diagnosis with *Toxoplasma gondii*, *Leishmania* sp. and *Pneumocystis carinii* is often difficult even for experienced pathologists.^(3,6,8)

H. capsulatum antigen detection

The detection of the polysaccharide antigen of the fungus in organic fluids can be performed through radioimmunoassay or ELISA,

although cross-reaction with *Paracoccidioides brasiliensis* and *Blastomyces dermatitidis* can occur. *H. capsulatum* antigen detection is quite useful in patients with acute histoplasmosis and in those with severe disseminated histoplasmosis. The greatest advantage of the antigen test is early detection: 24–48 h after sample collection (blood, urine, bronchoalveolar lavage fluid or cerebrospinal fluid). After acute exposure, the antigen is detected well before the anti-*Histoplasma* antibody is. The sensitivity of *H. capsulatum* antigen detection is greater in patients with acute disseminated histoplasmosis and in those with acute pulmonary histoplasmosis (epidemic histoplasmosis). The antigen is detected in urine in 92% of patients with the disseminated form and in more than 75% of those with acute histoplasmosis. In subacute histoplasmosis, the antigen is detected in only 25% of the cases, whereas in the chronic pulmonary form the antigen is detected in less than 10% of the cases. The *H. capsulatum* antigen is less commonly detected in the serum than in urine, that is, the antigen is detected in the serum in only 50% of the cases. In AIDS patients, antigenuria is 95%, and antigenemia is 85%. Rarely do patients with histoplasmosis exhibit antigenemia without antigenuria. The presence of rheumatoid factor in patients with positive antigenemia should be ruled out.^(3,6,9)

The analysis of the *H. capsulatum* var. *capsulatum* antigen is a valuable tool for the diagnosis of patients with severe acute histoplasmosis, who require early treatment. Screening for the antigen is useful not only for diagnosis, but also for monitoring the treatment and recurrence of the disease. A minimum of 5 mL of urine, serum or bronchoalveolar lavage fluid should be sent to a laboratory for antigen analysis, whereas 1 mL of cerebrospinal fluid is acceptable.^(6,9)

A PCR that allows a definitive diagnosis has recently been made available.⁽⁷⁾

Serologic tests

When correctly performed, serologic tests greatly aid in the diagnosis of histoplasmosis, and the sensitivity of the tests is greater than 90%. The serologic tests have certain limitations: 1. Seroconversion occurs late, 2 to 6 weeks being required for the antibodies to become detectable. 2. The immune response is weak in

immunocompromised patients. 3. In endemic areas, the prevalence of positive immunodiffusion (ID) results is 0.5%, and the prevalence of positive complement fixation (CF) test results is 40%. 4. The anti-*Histoplasma* antibody might be present in the blood of patients with other systemic mycoses.^(7,9)

Only 18% of asymptomatic patients present seropositivity, compared with 75–86% of symptomatic patients and as much as 100% of patients with severe symptoms, which denotes a correlation with the intensity of the exposure and the severity of the symptoms. Titers are less commonly positive and drop more rapidly in immunocompromised patients than in immunocompetent patients.

There are two tests to evaluate the antigen response of *H. capsulatum*: double agar gel ID and the CF test. Double agar gel ID is simple and more readily available in medical practice than the CF test. Double agar gel ID identifies M and H precipitation bands of the fungus. The M band can be detected in 75% of patients with acute histoplasmosis and in almost all of those with chronic histoplasmosis; the H band is present in only 20% of these patients. The H band indicates disease activity, and the M band indicates recent contact with the fungus. Precipitins appear 4–8 weeks after exposure and after the appearance of complement-fixing antibodies.^(7,9)

Approximately 95% of patients with acute or chronic histoplasmosis are positive for the CF test; however, 25% of these are weakly positive, presenting titers of 1:8 or 1:16. Although these titers are low, they represent active disease in one third of the cases. Although titers four times as high strengthen the significance of serologic test results, such titers are observed in 37% of patients with histoplasmosis.

It should be borne in mind that serologic test results should always be interpreted in light of the clinical signs and symptoms.^(6,7,9)

Histoplasmin skin test

Although the histoplasmin skin test should be used in epidemiological investigations, it should never be used to diagnose histoplasmosis. The test is positive (induration ≥ 5 mm) 48–72 h after intradermal reaction with 0.1 mL of *H. capsulatum* antigen. The test should not be performed before the serologic tests because

it induces the appearance of precipitin in the serum.^(3,6-8)

Radiological tests

Radiological tests are not specific for histoplasmosis. In acute pulmonary histoplasmosis, the most common radiological finding is the presence of bilateral and mediastinal hilar lymph node enlargement associated with bilateral perihilar reticulonodular infiltrate (Figure 1). However, unilateral hilar lymph node enlargement, diffuse reticulonodular interstitial infiltrate, cavitation and diffuse or isolated nodules can be found. In chronic pulmonary histoplasmosis, the radiological findings are similar to those in adult or reinfection tuberculosis, that is, progressive infiltrate in the upper lobe, cavitation and signs of fibrosis. Mediastinal enlargement can be seen principally on CT scans of the chest of patients with granulomatous histoplasmosis and mediastinal fibrosis. The presence of a solitary nodule or multiple nodules with central calcification is quite characteristic of the nodular form, that is, of histoplasmosis.⁽¹⁻⁵⁾

Treatment

Treatment is recommended according to the degree of severity of the disease and to the immunological competence of the patient.



Figure 1 - Anteroposterior chest X-ray showing diffuse micronodular infiltrate with bilateral and right paratracheal hilar lymph node enlargement.⁽¹⁾

There is strong evidence that most patients with acute histoplasmosis do not require treatment, as evidenced by the microepidemic that affected 17 children in the Pendotiba district of the city of Niterói, Brazil. All but one required no anti-fungal therapy.^(3,10,11)

Amphotericin B and its liposomal derivatives are probably more effective than itraconazole in cases of severe disease. Fungemia clearance is more rapid with amphotericin B, which has the advantage of being fungicidal; however, amphotericin B has many more side effects. Itraconazole is the drug of choice for home treatment; however, when patients require hospitalization, amphotericin B is recommended. The criteria for hospitalization are as follows: hypoxemia; systolic hypotension; bone marrow depression; blood creatinine three times as high as the upper normal limit; jaundice; serum transaminase levels five times as high as the upper normal limit; coagulation disorders; and CNS involvement.⁽¹⁰⁻¹³⁾

Acute pulmonary histoplasmosis

The disease is often self-limiting. However, persistent fever for more than 3 weeks or clinical conditions that persist for more than 30 days indicate progressive dissemination of the disease, which can be stopped with treatment. Treatment consists of a dose of 200 mg of itraconazole three times daily (breakfast, lunch and dinner) for three days in adults, followed by the same dose twice daily (lunch and dinner) for 6-12 weeks. The dose of itraconazole in children is $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, until the above-mentioned maximum dose for adults is reached. In patients with progressive disease who require hospitalization, as well as in cases of respiratory failure, a dose of 50 mg/day ($1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) of amphotericin B (or $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ i.v. in the liposomal form) is recommended. If there is clinical improvement, amphotericin B should be substituted for itraconazole for 12 more weeks. Some authors have recommended that a corticosteroid (prednisone/prednisolone) be also used for 2 weeks, at a dose of $0.5\text{-}1.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, in patients with hypoxemia or acute respiratory failure.^(6,8,10,11)

Chronic pulmonary histoplasmosis

All patients with chronic pulmonary histoplasmosis should be treated because the disease

is progressive and fatal. Ketoconazole or itraconazole can be used, and the response is effective in 75–85% of the cases; the recurrence rate, however, is 10%. The drug of choice is itraconazole, at a dose of 200 mg (three times daily for 3 days and then once or twice daily for 12–14 months). Amphotericin B is used in patients who require hospitalization, often due to the exacerbation of chronic respiratory failure or to the inability to absorb itraconazole given orally. There is no evidence as to whether i.v. itraconazole is more effective than amphotericin B. Fluconazole is less effective than ketoconazole and itraconazole.^(6,8,10,11)

Disseminated histoplasmosis

The mortality rate due to untreated disseminated histoplasmosis is 80%; however, it can be reduced to less than 25% with antifungal therapy. Among patient without AIDS, amphotericin B is effective in 68–72% of the cases, itraconazole is effective in 100% of the cases, ketoconazole is effective in 56–70% of the cases and fluconazole is effective in 86% of the cases. Among patients with AIDS, amphotericin B is effective in 74–88% of the cases, itraconazole is effective in 85% of the cases, ketoconazole is effective in 9% of the cases and fluconazole (high dose) is effective in 74% of the cases. Therefore, ketoconazole is not indicated for patients with AIDS. The mortality rate among AIDS patients with severe disease is 50%, compared with 2% among those with mild disease. In addition to being less toxic, the liposomal formulation of amphotericin B has the following advantages: it reduces mortality; it eradicates fungemia; and it lowers fever more rapidly than do conventional amphotericin B (deoxycholate), itraconazole and fluconazole. The disadvantage is its high cost.^(10–12)

In hospitalized patients, treatment prioritizes amphotericin B (deoxycholate or liposomal), which, within 1–2 weeks after having induced remission, is substituted for itraconazole, at a dose of 200 mg (three times daily for 3 days and then twice daily for 12 months). In patients with mild or moderate disease under outpatient treatment, itraconazole (200 mg three times daily for 3 days and then twice daily for 12 months) is used. In patients with AIDS, the remission induction phase is longer, lasting 12 weeks, and is

followed by the maintenance phase, in order to prevent recurrence, with 200 mg/day of itraconazole or 400–800 mg/day of fluconazole in case patients do not tolerate itraconazole. In the maintenance phase, amphotericin B is another alternative for patients with or without AIDS and is administered at a dose of 50 mg (once or twice weekly).^(10–12)

The evaluation of blood levels of itraconazole is important to ensure appropriate exposure to the drug.^(10,11)

H. capsulatum antigen detection should be performed during treatment and for 12 months after treatment in order to detect possible recurrence.^(10,11)

Prophylaxis with itraconazole is recommended in HIV-infected patients with CD4 count < 150 cells/mm³ in endemic areas in which the incidence of histoplasmosis is 10 cases/100 patients/year. Prophylaxis with itraconazole might be appropriate in immunocompromised HIV-negative patients.^(10,11)

Other forms

Granulomatous mediastinitis

Granulomatous mediastinitis treatment is usually not necessary (grade A recommendation). In symptomatic forms, treatment consists of 200 mg of itraconazole (three times daily and then once or twice daily for 6–12 weeks).⁽¹¹⁾

Mediastinal fibrosis

Antifungal therapy is not recommended. In cases of venous obstruction (superior vena cava syndrome), stents should be placed. If there is no distinction between mediastinitis and fibrosis, treatment with itraconazole is recommended.⁽¹¹⁾

Pericarditis

Pericarditis affects 5–10% of patients, more as an inflammatory response of the pericardium to the fungus than by direct effect. Pericarditis is treated with nonsteroidal anti-inflammatory drugs (NSAIDs), and the clinical response is excellent. If patients do not respond to NSAIDs, the use of corticosteroids (0.5–1 mg • kg⁻¹ • weight⁻¹ for 1–2 weeks) in combination with itraconazole

is indicated. Pericardial fluid removal is indicated for patients with hemodynamic alterations.⁽¹¹⁾

Rheumatologic syndromes

Joint involvement is, in half of the cases, bilateral and symmetric, affecting lower and upper limbs. Half of the patients with rheumatologic syndromes also present with erythema nodosum or erythema multiforme, or a combination of the two. The disease is treated with NSAIDs. If patients do not respond to NSAIDs, the use of corticosteroids (0.5-1 mg • kg⁻¹ • weight⁻¹ for 1-2 weeks) in combination with itraconazole is indicated.⁽¹¹⁾

CNS

Patients with CNS histoplasmosis do not respond to treatment as well as those with other forms of histoplasmosis, since 20-40% of patients die from the infection and half of those who respond to treatment present recurrence after the medication is discontinued. The use of amphotericin B deoxycholate (0.7-1 mg•kg⁻¹•day⁻¹ until a total dose of 35 mg•kg⁻¹•weight⁻¹ is reached) is recommended. The liposomal formulation does not seem to be more effective in reaching superior levels in brain tissue. These two formulations have not been evaluated in cases of meningitis, and their concentrations in the cerebrospinal fluid have not been assessed. After the dose of amphotericin B is completed, a dose of 800 mg/day of fluconazole for 9-12 months is prescribed in order to reduce the risk of recurrence. The dose should be adjusted according to blood concentration, which should remain in the 80- to 150-µg/mL range. Unfortunately, itraconazole cannot be used because it cannot cross the blood-brain barrier. In focal cases involving

the brain and the spinal cord without meningitis, treatment response is better. In such cases, itraconazole can be useful after a response has been induced by amphotericin B. Parenchymal lesions rarely require surgical treatment.^(10,11)

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