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Chronic Pulmonary Histoplasmosis: Case Report

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ABSTRACT

Introduction: Histoplasmosis is a fungal infection acquired by inhaling spores, which can progress from a primary form to a chronic cavitary form.

Objetive: To present a case of clinical and radiological manifestations of histoplasmosis, which can be non-specific and easily confused with other pathologies.

Clinical Case: A 56-year-old man presented with symptoms persisting for five months, including a 5-kilogram weight loss, asthenia, exertional dyspnea, and dry cough. He had a 30-pack-year history of smoking. A chest computed tomography scan revealed polymorphic, cavitated, bilateral nodular images. A percutaneous lung biopsy was performed without complications. Histological analysis showed granulomatous disease with fungal structures consistent with histoplasma.

Conclusion: Multiple pulmonary nodules require further investigation through bronchoscopy and percutaneous lung biopsy to evaluate various pathologies. In cases of mycoses, specific staining is essential for targeted treatment.

Keywords: chronic pulmonary histoplasmosis; pulmonary cavitation; percutaneous biopsy.

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Histoplasmosis pulmonar crónica: presentación de caso

RESUMEN

Introducción: La histoplasmosis es una infección micótica adquirida por la inhalación de esporas, que puede progresar de una forma primaria a una crónica cavitaria.

Objetivo: Dar a conocer un caso sobre la presentación clínica e imágenes radiológicas de la histoplasmosis que pueden ser inespecíficas y confundirse con otras patologías.

Caso clínico: Se presenta un caso de hombre de 56 años con síntomas de 5 meses de evolución, pérdida de peso de 5 kilos, astenia, disnea de esfuerzo y tos seca. Historia de tabaquismo de 30 paquetes/año. La tomografía computada de tórax evidenciaba imágenes nodulares polimorfas cavitadas bilaterales. Se le realizó una biopsia percutánea pulmonar, sin complicaciones. Los análisis histológicos mostraron una enfermedad granulomatosa con estructuras fúngicas compatibles con histoplasma.

Conclusión: Los nódulos pulmonares múltiples requieren estudios mediante broncoscopia y biopsia pulmonar percutánea para analizar diversas patologías, y en el caso de micosis, sus respectivas coloraciones para un tratamiento específico.

Palabras clave: histoplasmosis pulmonar crónica; cavitación pulmonar; biopsia percutánea.

Histoplasmose pulmonar crónica: apresentação de caso

Resumo

Introdução: A Histoplasmose é uma infecção fúngica adquirida pela inalação de esporos, que pode progredir de uma forma primaria para uma forma crónica cavitaria.

Objetivo: Apresentar um caso sobre a manifestação clínica e as imagens radiológicas da Histoplasmose que podem ser inespecíficas e se confundir com outras patologias.

Caso clínico: Apresenta-se o caso de um homem de 56 anos com sintomas de 5 meses de evolução, perda de peso de 5 quilos, astenia, dispneia ao esforço e tosse seca. História de tabagismo de 30 pacotes/ano. A tomografia computorizada de tórax evidenciava imagens nodulares polimorfas cavitadas bilaterais. Foi realizada uma biópsia percutânea pulmonar, sem complicações. As análises histológicas mostraram uma doença granulomatosa com estruturas fúngicas compatíveis com histoplasma.

Conclusão: Os nódulos pulmonares múltiplos requerem estudos por meio de broncoscopia e biopsia pulmonar percutânea para analisar diversas patologias, e, no caso de micose, suas respectivas colorações para um tratamento especifico.

Palavras-chave: Histoplasmose pulmonar crónica; cavitação pulmonar; biópsia percutânea,

INTRODUCTION

Histoplasmosis has a worldwide distribution and is an endemic mycosis in the Americas. The causative agent is *Histoplasma capsulatum*, a dimorphic fungus that behaves as a mold in the environment and in cultures at 25°C, while in tissues and cultures at 37°C, it takes on a yeast form. There is no human-to-human transmission (1).

The infection is acquired through the inhalation of infectious structures (microconidia or mycelial fragments) dispersed in the air. The natural habitat of *H. capsulatum* is soil, particularly acidic soils enriched with nitrogen, phosphates, and carbohydrates (such as bat and bird guano), in temperate and tropical climates, and in humid places such as caves, abandoned houses, mines, tunnels, church crypts, and abandoned chicken coops (2).

The occurrence of isolated cases or epidemics is influenced by the infectious inoculum, immune status, and strain virulence. Following initial exposure, the host's immune system may fail to destroy the yeast, allowing it to remain latent in tissues (such as the spleen, liver, and lymph nodes) and reactivate later to cause disease. This endogenous reinfection may occur years after the primary infection.

The human defense mechanism is based on cellular immunity, primarily involving CD4 T lymphocytes and macrophages. The main cytokines involved include interleukin-12, interferon-γ, and tumor necrosis factor-α. In immunosuppressed individuals, there is a higher prevalence of the disseminated form of the disease (3).

Histoplasma is an intracellular pathogen located within macrophages. In immunocompetent individuals, macrophages induce the formation of granulomas, which help control the infection (4).

Most immunocompetent individuals infected with *Histoplasma* are asymptomatic. On average, symptoms appear 10 days after exposure and resemble a flu-like syndrome. This may be accompanied by arthralgias, erythema nodosum, or erythema multiforme, and patients typically recover spontaneously. Histoplasmosis presents in three main forms: acute primary, chronic cavitary, and progressive disseminated. Radiological diagnosis varies according to the form of the disease, and is made by identifying the microorganism in tissue or sputum or through specific tests to detect the antigen in serum and urine (5).

CASE PRESENTATION

We present the case of a 56-year-old man from an urban area who sought medical attention due to a five-month history of exertional dyspnea,

progressively worsening with moderate physical activity, asthenia, a five-kilogram weight loss, frequent cough, afebrile, without wheezing, sputum production, or chest pain.

He had a history of active smoking with a 30 pack-year index and arterial hypertension. He worked with wrought iron and welding and also sold coke coal. His medication history included the use of verapamil, hydrochlorothiazide, and enalapril.

On physical examination, the patient appeared in generally good condition: height 167 cm, weight 55 kg, body mass index 19.7, respiratory rate 18 breaths per minute, and oxygen saturation of 98%. Cardiopulmonary auscultation was normal.

The chest X-ray revealed multiple bilateral nodular images with diameters ranging from 15 to 20 mm. A contrast-enhanced chest computed tomography (CT) scan showed polymorphic, cavitated nodular opacities, well-defined, of varying densities; some with a ground-glass appearance, predominantly bibasilar, peripheral, and bilateral (Figure 1). Additionally, there was right parahilar lymphadenopathy (Figure 2).

Figure 1. Computed tomography scan showing multiple cavitated nodules and areas with ground-glass opacity

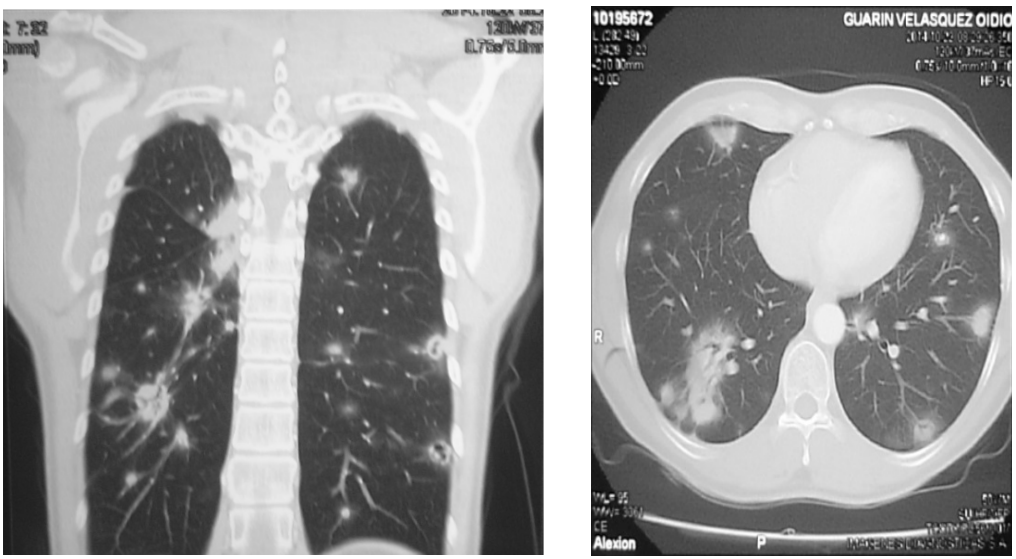
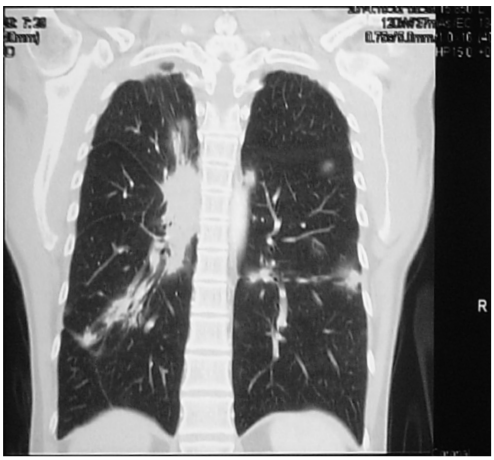


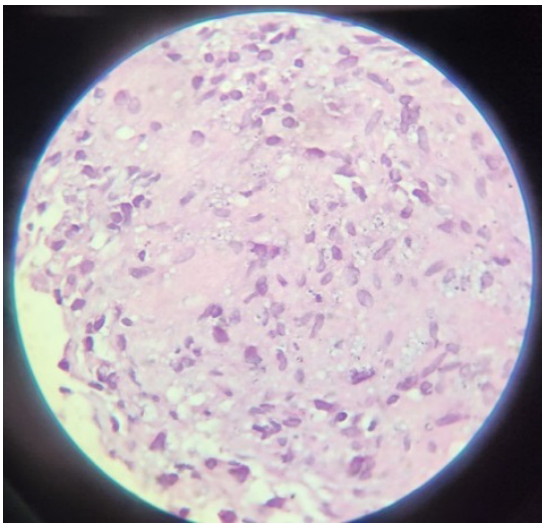
Figure 2. Computed tomography scan showing right parahilar lymphadenopathy



Diagnostic bronchoscopy revealed severe edema at the spur of the entry to the posterior segment of the right upper lobe. A Gene Xpert MTB/RIF molecular biology test on a sample of bronchial wash was negative for *Mycobacterium tuberculosis* complex. Sputum smear microscopy and culture were ordered, both of which were negative for acid-fast bacilli. Cytology from the bronchial wash and brushing was negative for malignancy. Potassium hydroxide (KOH) staining and fungal cultures were also negative.

A percutaneous lung biopsy under CT guidance and the pathological report showed multiple epithelioid granulomas with areas of necrosis, within which small yeast forms were present inside the cytoplasm of histiocytes. PAS and Gomori stains highlighted small spherical yeasts, consistent with histoplasmosis (Figures 3 and 4).

Figure 3. Lung biopsy of the patient stained with hematoxylin-eosin (X1000). Granulomas containing numerous Histoplasma yeasts are observed. In a broader view, granulomatous areas are defined (X100).



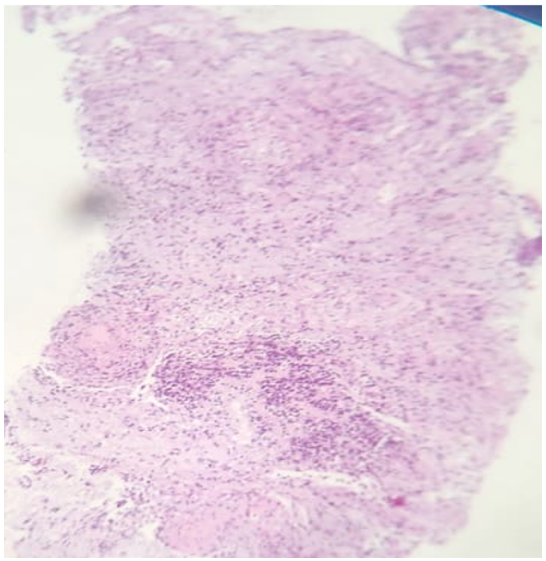
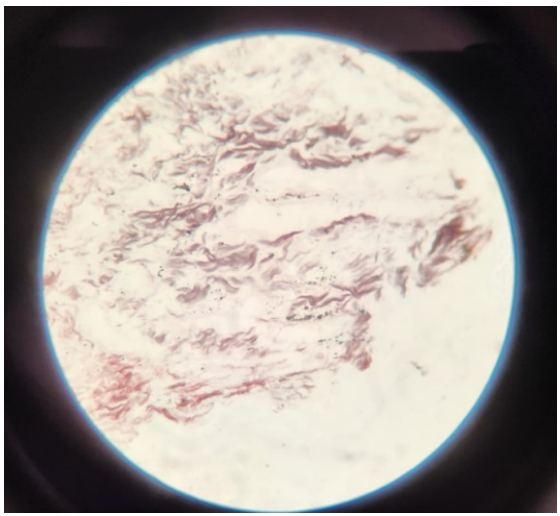


Figure 4. Grocott stain. Small oval yeast structures of Histoplasma are seen (X400).



Source: Laboratorio Clínico Patológico López Correa (Pereira, Colombia).

Additionally, a contrast-enhanced CT scan of the abdomen and pelvis was performed and was normal. A contrast-enhanced neck CT scan showed degenerative disc disease at C5-C7. Liver function tests, kidney function tests, complete blood count, and spirometry were normal, and the HIV test was negative. The patient was treated with 400 mg/day of itraconazole for six months, resulting in clinical and radiological improvement.

DISCUSSION

In Colombia, a national survey conducted between 1992 and 2008 collected confirmed cases of histoplasmosis. Although histoplasmosis is not a notifiable disease in the country, 434 cases were reported, with 96.1% of cases occurring in adults. Of these, 70.5% had AIDS, and 7% had other forms of immunosuppression. The department of Antioquia accounted for 59.2% of the reported cases (6).

The infection rate varies according to different sources. According to a survey by the Centers for Disease Control and Prevention (CDC), it is estimated that around 500,000 new cases occur each year. In a study involving U.S. Navy soldiers, it was found that 20% tested positive for histoplasmin skin tests, suggesting that up to 3 million cases may occur annually in the population (7).

Several occupations are associated with an increased risk of contracting the disease, including agriculture, construction, demolition, roofing, and gardening. However, our patient did not work in a field associated with these risk factors.

Chronic cavitary pulmonary histoplasmosis typically occurs in men over 50 years of age with a history of lung damage related to smoking. Symptoms include productive cough, dyspnea, fever, night sweats, and weight loss. The lesions,

with central necrosis and peripheral fibrosis, tend to form cavities that can persist for months or years. Our patient fit this profile: a 56-year-old male smoker with the described symptoms over a five-month period.

The disseminated form of histoplasmosis almost exclusively occurs in immunosuppressed individuals, such as those with AIDS, lymphoma, or leukemia. The most severe forms present with sepsis, acute respiratory distress syndrome, disseminated intravascular coagulation, and acute adrenal failure. Skin and mucosal involvement may also occur, along with elevated liver enzymes and pancytopenia.

The clinical presentation depends on the patient's age, degree of immunosuppression, and the size of the inoculum. Histoplasmosis can be mistaken for other diseases, delaying diagnosis. Contributing factors include prior antibiotic use or the coexistence of other lung diseases (8). Approximately 90% of cases involve acute pulmonary histoplasmosis, which presents with mild, self-limiting symptoms similar to those of the flu, often going unnoticed. Around 6% of cases will have rheumatologic manifestations, such as arthralgias, arthritis, or erythema nodosum, and symptoms usually resolve within one to two weeks (9).

When histoplasmosis presents with multiple nodules, it can mimic metastatic neoplastic lesions, as in two cases reported by Azevedo and colleagues (10). Other conditions with similar presentations include sarcoidosis, Wegener's granulomatosis, rheumatoid arthritis, Churg-Strauss syndrome, multiple hamartomas, and granulomatous infections. Empirical treatment can be ineffective and dangerous. In our case, the patient presented with multiple nodules, and histopathological confirmation was achieved through Gomori and PAS stains, which detected *Histoplasma*.

Radiological findings vary according to the clinical presentation. In acute and subacute pulmonary histoplasmosis, diffuse opacities are predominant, which may be focal or bilateral, and hilar and mediastinal lymphadenopathy is commonly observed (11). Radiological patterns vary and include unilateral or bilateral interstitial infiltrates, typically parahilar, or single or multiple disseminated lesions with hilar or mediastinal adenomegaly, with or without pleural effusion. The disease may leave sequelae such as pulmonary or extrapulmonary calcifications. Cavitary lesions may present with thickened walls, air-fluid levels, or pleural thickening adjacent to the cavity.

In the chronic form, cavitation, fibrosis, or pleural thickening can be observed, with the upper lobes being more commonly affected. Calcifications may also be present, and pulmonary tuberculosis should be ruled out as a differential diagnosis (12).

Diagnosis is made through direct observation or pathogen isolation (culture, histopathology, and cytopathology) or by detecting antigens, antibodies, and nucleic acids (13). The isolation of specimens is the gold standard and is considered a definitive diagnosis. Initial histopathology shows an inflammatory reaction with numerous polymorphonuclear cells and macrophages. Later, granulomas, with or without caseation, as well as multinucleated giant cells and areas of necrosis, are observed. PAS and Grocott stains are recommended, although fungal structures can also be seen with hematoxylin and eosin staining (14).

Since *H. capsulatum* is an intracellular fungus, it is difficult to detect in fresh direct examinations. However, the use of calcofluor-white stain and identifying the fungus inside cells using fluorescence microscopy are very useful in diagnosis.

Culture is considered the definitive diagnostic method for histoplasmosis, but it takes four to six weeks for the fungus to grow. Culture is most useful in disseminated disease, when samples are taken from bone marrow or blood, with a positivity rate of about 74%, and in chronic pulmonary disease, with a 67% positivity rate from sputum or bronchoscopy specimens.

Fungal antigens are detected in urine, serum, or other body fluids, but urine is preferred due to its higher sensitivity. In urine, the progressive disseminated form has demonstrated up to 90% sensitivity in immunocompromised patients, but sensitivity is lower in severe chronic forms (75%) and only about 10% in mild forms (15).

Antibodies in serum and cerebrospinal fluid become detectable six weeks after infection and may be negative in immunosuppressed patients, potentially delaying treatment.

Complement fixation titers ≥1:32 are indicative of active histoplasmosis, with a sensitivity between 73% and 95%. Immunodiffusion detects precipitin bands with a sensitivity of 55% (16).

In a study published in 2013 by Arango-Bustamante and colleagues (17), records of 391 Colombian patients with histoplasmosis were reviewed. The diagnostic value of culture and serological tests (complement fixation and immunodiffusion) was observed. Of these patients, 184 were infected with HIV (47.1%). In the HIV-negative population, positive cultures were obtained in 35.7% of cases, and serological tests were reactive in 95.2%. In comparison, the HIV-positive population showed higher culture positivity (75%) and serological reactivity at 92.4% (17).

In pathology, yeast cells measuring 2 to 4 mm, intracellular, have been observed in tissue samples stained with methenamine silver. Granulomatous inflammation with caseation may also be found.

In the present case, complementary studies for dissemination, including a neck and abdominal CT scan, were negative.

According to the management guidelines of the Infectious Diseases Society of America, treatment varies depending on the clinical presentation. In mild cases, treatment for *H. capsulatum* is not recommended as most cases resolve spontaneously. Only if symptoms persist for more than a month is treatment with 200 mg of itraconazole, three times daily for three days, followed by 200 mg once or twice daily for 6 to 12 weeks, recommended.

For severe acute cases, treatment involves intravenous amphotericin B at 3-5 mg/kg per day for one to two weeks, followed by 200 mg of itraconazole for 12 weeks. It should not be assumed that severe disease only affects immunocompromised individuals (18).

For chronic pulmonary histoplasmosis, the recommended regimen is 200 mg of itraconazole three times daily for three days, followed by 200 mg once or twice daily for a year. Some authors recommend extending treatment to 18-24 months to prevent relapse (19). Liposomal amphotericin B is the preferred agent for severe or disseminated disease (20).

The prognosis for the acute primary form is almost always self-limiting, and death due to massive infection is very rare. Chronic cavitary histoplasmosis may lead to respiratory failure. Untreated disseminated disease is associated with a mortality rate exceeding 90%. The risk of histoplasmosis is higher in HIV patients, particularly those with CD4 counts below 200 cells/μL (21).

CONCLUSION

Histoplasmosis is a fungal infection with variable clinical presentations and radiological findings, such as multiple nodules that may cavitate and mimic other pathologies. For diagnosis, bronchoscopy may not be definitive and often requires histopathological examination and appropriate staining for mycoses. Percutaneous biopsy is safe and conclusive.

INFORMED CONSENT

The authors declare that this work does not contain any personal information that could lead to the identification of the patient. This is a no-risk study based on retrospective data review. Additionally, informed consent was obtained from the patient, which is in the authors' possession.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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