

## Chronic Pulmonary Histoplasmosis Diagnosed in a Nonimmunosuppressed Patient 10 Years After Returning From an Endemic Area

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We report the case of a Spanish nonimmunosuppressed patient who was a chronic alcoholic and who developed chronic cavitary pulmonary histoplasmosis. He had been living in Venezuela until 10 years ago. The diagnosis was established when *Histoplasma capsulatum* was cultured from bronchoscopy samples. The patient was treated with itraconazole and progressed favorably until cure. This case suggests that histoplasmosis can reactivate years after exposure, even when significant immunodeficiency is not present. In the absence of another immunosuppressive factor, alcoholism may have played a role in the development of the condition.

**Key words:** *Histoplasmosis*. *Histoplasma capsulatum*. *Diagnosis*. *Treatment*.

### Introduction

Histoplasmosis is a disease caused by *Histoplasma capsulatum*, a dimorphic fungus whose 2 different phases or forms correspond to a soil-borne mycelial form at ambient temperature and a yeast form at body temperature. The fungus is found in certain warm climates in several American countries (United States, Mexico, Caribbean region, and South America), as well as in Africa, Oceania, Eastern Asia, and the Near East (Egypt, Israel). It is not usually found in Spain or Europe. In fact, only a few cases have been described, practically all of them imported. Such cases correspond to acute forms after recent exposure or to disseminated forms in immunosuppressed patients, and presentation as chronic cavitary pulmonary histoplasmosis is rare in nonendemic areas. Although most

Histoplasmosis pulmonar crónica en un paciente no inmunodeprimido, residente 10 años antes en una zona endémica

Se presenta el caso de un paciente español, no inmunodeprimido, con alcoholismo crónico e histoplasmosis pulmonar cavitaria, crónica, que había residido 10 años antes en Venezuela. El diagnóstico se estableció por cultivo de *Histoplasma capsulatum* en muestras de broncoscopia y el tratamiento consistió en itraconazol, con buena evolución y curación. Este caso apoya la posibilidad de que la histoplasmosis pueda reactivarse años después de la exposición y sin que haya inmunodepresión clínicamente importante. Se plantea que, en ausencia de otro factor inmunodepresor, el alcoholismo podría haber desempeñado algún papel en el desarrollo del cuadro.

**Palabras clave:** *Histoplasmosis*. *Histoplasma capsulatum*. *Diagnóstico*. *Tratamiento*.

of the chronic pulmonary forms are attributed to reinfections in endemic areas,<sup>1</sup> in Spain the disease is more likely to be reactivation, in the absence of recent exposure. We describe a patient with chronic cavitary pulmonary histoplasmosis, probably secondary to reactivation of a latent infection acquired after residing 10 years earlier in Venezuela.

### Case Description

The patient was a 46-year-old man who came to the emergency department in 1999 for respiratory infection symptoms and general deterioration. He had smoked 1 to 3 packs of cigarettes a day since he was 17 years old and had considerable, although unspecified, alcohol intake. He had worked as a clerk and in furnace repair for a number of years. Ten years earlier, he had returned from Venezuela, where he had resided in Caracas and Maracaibo for the previous 10 years. The patient did not recall any major illnesses during that period. In 1992 he had been admitted to our hospital for seizures in relation to alcohol consumption. A cranial computed tomography (CT) scan was normal. However, pneumonia was observed in the right middle field and resolved completely during follow-up.

On admission, the patient reported that from some weeks or months earlier, he had presented coughing with scant, purulent

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Figure 1. Chest radiograph showing various cavitations and loss of volume in the right lung.

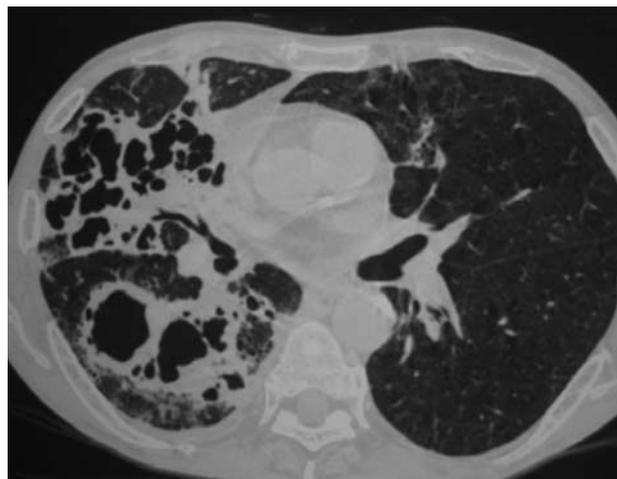


Figure 2. Computed tomography scan of the thorax showing an alveolar pattern with cavitations affecting the 3 lobes of the right lung and the lingula.

expectoration, dyspnea on exertion, unspecified weight loss, and malaise, but no fever. According to family members, he consumed considerable amounts of alcohol and was often intoxicated, but they had no knowledge of vomiting or suspected bronchial aspiration. The examination revealed poor overall condition, with signs of malnutrition. The patient was eupneic and afebrile, with normal blood pressure and pulse rate; the teeth were in poor condition. Lung auscultation revealed crackles in the right chest, and the liver edge was palpable 3 cm below the costal margin.

The chest radiograph showed a mixed (alveolointerstitial) pattern that affected most of the right lung. The laboratory workup showed 5090 leukocytes/ $\mu\text{L}$  with left shift (23% band neutrophils), abnormal liver tests (aspartate-transaminase, 76 U/L; alkaline phosphatase, 403 U/L;  $\gamma$ -glutamyl transpeptidase, 152 U/L), and hypoalbuminemia (albumin, 2.44 g/dL). Arterial blood gases measured on admission with the patient breathing room air showed a  $\text{PaO}_2$  of 54 mmHg,  $\text{PaCO}_2$  of 34 mmHg, and pH of 7.48. Spirometry at discharge showed a forced expiratory volume in 1 second ( $\text{FEV}_1$ ) of 2700 mL (77%), forced vital capacity (FVC) of 3440 mL (81%), and  $\text{FEV}_1/\text{FVC}$  ratio of 78%.

Pneumonia was diagnosed, possibly in relation to inadvertent bronchial aspiration, and amoxicillin-clavulanic acid (2 g/8 h by intravenous route) was prescribed. Progress was favorable with improvement in the patient's overall condition, respiratory symptoms, respiratory failure, and abnormal liver tests. The radiograph showed slight improvement and the patient was discharged with antibiotic therapy. At a follow-up visit 1 month later, the patient presented clear overall deterioration and weight loss of 4 kg, and reported abundant, purulent, hemoptitic sputum production, but no fever. The chest radiograph revealed considerable worsening, with various cavitations in the right lung and loss of right lung volume (Figure 1). An alveolar pattern with cavitations that affected the 3 lobes of the right lung and the lingula was observed in the chest CT scan (Figure 2). Two serologic tests for human immunodeficiency virus were negative. Sputum smears and polymerase chain reaction tests for *Mycobacterium tuberculosis* in sputum were repeatedly negative; mycobacterial cultures were also negative. Immunodiffusion-based immunoglobulin G serology tests for *H capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Paracoccidioides brasiliensis* were negative. Bronchoscopy showed no endobronchial abnormalities. Samples obtained by telescoping catheter, bronchoalveolar lavage, and bronchial aspirate were negative for aerobic bacteria, anaerobic bacteria, and mycobacteria. Lastly, all samples obtained by bronchoscopy

and transthoracic puncture (performed after the initially negative bronchoscopy results) showed growth of a dimorphic fungus identified some weeks later at the National Microbiology Center of Majadahonda, Spain, as *H capsulatum*.

Following the initial observation of growth of the fungus described, the patient was treated with itraconazole 400 mg/day and progressed favorably. This course of treatment lasted 1 year; the dose was then reduced to 200 mg/day for a further 2 years; until the pulmonary parenchymatous abnormalities had resolved and the cavitations had closed. Once treatment was discontinued, the patient was followed up for more than 3 years, during which time the residual pulmonary abnormalities remained stable. The patient was unable to give up drinking completely. In April 2005 the patient was admitted for diminished level of consciousness. The cranial CT scan showed pneumocephalus, probably in relation to brain injuries. He died at another hospital several days later as a result. The tests performed during this hospitalization found no evidence of a recurrence of histoplasmosis.

## Discussion

Histoplasmosis is acquired by inhaling mycelium spores or fragments when soil containing the fungus is disturbed. The risk is particularly high in soils rich with bird droppings and in caves where bats live. If the inhaled particles evade the nonspecific lung defenses, the microorganism begins to develop in the lung parenchyma, where inflammation occurs. In this inflammatory process, the macrophages initially phagocytize, but do not destroy, the fungus involved, allowing the microorganism to disseminate hematogenously. In the following weeks, *H capsulatum*-specific cellular immunity develops, any symptoms remit, and histoplasmic reactivity appears. The process may be asymptomatic or may manifest clinically as general and respiratory symptoms of highly variable severity, depending on the extent of exposure, the patient's immune status (general and *H capsulatum*-specific) and overall health, the presence of prior lung disease, and possibly host-related genetic factors and the virulence of the fungus.<sup>1</sup> In immunosuppressed and very elderly patients, or after heavy exposure, the acute form may be clinically important.

Asymptomatic forms are extremely common in endemic areas and 50% to 80% of adults have a positive reaction to histoplasmin.<sup>1</sup> In immunosuppressed patients, particularly those with AIDS, *H capsulatum* behaves as an opportunist and can cause disseminated forms of disease in both initial and repeat infections. Reactivation has also been recognized as a mechanism that produces disseminated forms, although it is apparently not the most important, given the low incidence (<5%) of disseminated histoplasmosis in patients with AIDS who reside in endemic areas.<sup>2</sup>

Chronic pulmonary histoplasmosis tends to occur mainly in patients with chronic lung disease and is characterized by infiltrations and cavitations predominantly in the upper fields, similar to tuberculosis. In some cases, some degree of immunosuppression may exist and, occasionally, there may be systemic dissemination.<sup>3</sup>

The pathogenic and clinical course is obviously parallel to that of tuberculosis, although there are differences between the two diseases.<sup>1,4</sup> In histoplasmosis, negative results for histoplasmin in skin tests (15% of negative results at 2 years) are much more common than in tuberculosis.<sup>4</sup> In addition, it appears that reinfection, rather than reactivation, is the main mechanism causing the disease after primary infection in endemic areas, both in disseminated forms seen in patients with AIDS and in chronic cavitary forms. In nonendemic areas, however, reactivation would explain why these forms appear in patients with a past history of exposure. Exposure to localized microfocal areas that could appear in any geographic area is also possible. Although few reports have been published in Europe, several, possibly indigenous, cases have been described in the Po Valley, Italy.<sup>5</sup>

Our patient showed chronic cavitary pulmonary histoplasmosis, with no systemic dissemination. This presentation is very uncommon in nonendemic areas. In fact, the cases reported in Spain correspond to acute forms that occurred while the patients were staying in the country where they acquired the disease or immediately after they returned from the country<sup>6-11</sup> or to disseminated forms in patients who are immunosuppressed, usually because of AIDS, in some cases among immigrants originally from endemic areas.<sup>12-18</sup> In our patient, because of the time between the alleged exposure to *H capsulatum* and the onset of symptoms, the disease apparently developed due to reactivation of a previous infection, most certainly asymptomatic.

The cause of reactivation is evident in immunosuppressed patients with abnormal cellular immunity. In chronic forms, immunosuppression is not as common<sup>3</sup> and the development of the disease is usually associated with chronic respiratory diseases (mainly emphysema).<sup>1,4</sup> However, our patient did not present signs of emphysema, at least to a significant degree, and there was no evidence of immunosuppression. The only factor potentially implicated as a cause of reactivation was alcohol consumption, although this is not recognized as an important risk factor for cavitary histoplasmosis.<sup>3</sup> Nevertheless, there is increasing evidence that alcohol depresses various components of cellular immunity that

are needed for defense against other intracellular pathogens, such as *Listeria monocytogenes* or *M tuberculosis*,<sup>19,20</sup> which resemble *H capsulatum* in terms of the importance of cellular immunity in its pathogenesis.

In chronic pulmonary presentation, the diagnosis is mainly established by the isolation of the fungus in respiratory samples, as in our case. This technique has a sensitivity of 50% to 85%,<sup>1</sup> although 2 to 4 weeks may be needed to detect growth, and identification of the fungus may take longer still. Serologic studies may be more useful, because they are faster and more sensitive, with a sensitivity of almost 100% in chronic forms.<sup>1</sup> In our case, immunodiffusion serology, which is less sensitive than complement fixation, was negative. Antigen detection in various samples (blood, urine, bronchoscopy samples) appears to be useful; however, the technique is less sensitive in chronic cases.<sup>1</sup> Nevertheless, this diagnostic method is not sold in Spain and is only available at referral hospitals in the United States. In nonendemic areas, an intradermal histoplasmin test, if available, may also guide diagnosis.<sup>8,9</sup> The treatment of choice in chronic forms is itraconazole for a recommended course of 1 to 2 years.<sup>1</sup> There is a relapse rate of 10% to 20% after discontinuation of treatment and, therefore, follow-up is recommended for a further 2 years.

Although this cavitary pulmonary form of histoplasmosis is apparently rare in our setting at this time, its importance may increase. This is also true of other clinical forms, due to the growing number of Spaniards who travel to endemic areas and increasing immigration from these same areas. Hence, this diagnostic possibility should be considered when patients present symptoms of this kind and the usual etiologies are not confirmed, if there is a history of exposure.

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GARCÍA-MARRÓN M ET AL. CHRONIC PULMONARY HISTOPLASMOSIS DIAGNOSED IN A NONIMMUNOSUPPRESSED PATIENT 10 YEARS AFTER RETURNING FROM AN ENDEMIC AREA

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