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HISTOPLASMOSIS: DIAGNOSTIC CHALLENGES

Editorial

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Histoplasmosis is an infection usually caused by a fungal pathogen that, in most cases, occurs in the respiratory tract, which explains the high frequency of clinical manifestations in the lungs. (1) This mycosis is endemic in the Americas (Mississippi and Ohio River Valley, USA; Central and South America; and the West Indies), while reports in areas of Asia, Africa, Australia, and Oceania are mainly associated with the pandemic of acquired immune deficiency syndrome (AIDS). In Europe, cases are on the rise because of the speculation of a global distribution of histoplasmosis, and emphasis has been on improving methods for its diagnosis. (2,3)

The etiological agent of histoplasmosis is the dimorphic fungus *Histoplasma capsulatum*, which is widely distributed in soils with high nitrogen content (contaminated with droppings from bats or birds) both in endemic areas and outside them. (2) From a taxonomic standpoint and based on molecular tests, Sepúlveda *et al.* (1) proposed a new classification of the species of *Histoplasma*. They were previously classified into three varieties: *H. capsulatum* var. *capsulatum*, pathogen for humans in America; *H. capsulatum* var. *duboisii*, pathogen for humans in Africa; and *H. capsulatum* var. *farciminosum*, pathogen for equines. Currently, the following classification is used: *H. capsulatum sensu stricto*, in Panama; *H. mississippiense sp.* nov. and *H. ohiense sp.* nov. in North America; and *H. suramericanum sp.* nov. in South America. The description of these species has clinical and epidemiological implications, as there are differences between them in terms of virulence and resistance to antifungal agents, as is the case of *H. mississippiense,* which is less virulent but has greater resistance to the most used antifungal antibiotics. (1)

Histoplasmosis mostly affects the lungs; however, the clinical presentation depends on two variables: the load of infectious particles in the inoculum and the immune status of the patient. It has been reported that in 5-10% of cases, the infection spreads systemically to other organs to be controlled by an immune system without alteration. Progressive disseminated disease occurs more often in patients with human immunodeficiency virus (HIV) infection and lower CD4 T-cell counts (<200 cells/mm^3), or in therapy with tumor necrosis factor inhibiting agents, in which mortality rates are high if diagnosis and treatment are not timely.

The symptoms of progressive histoplasmosis are nonspecific, so its differentiation with other infections, especially tuberculosis, is a challenge, even to determine the presence of coinfections that occur frequently in patients with HIV/AIDS. (1,2,4)

The laboratory tests available for the conventional diagnosis of this fungal infection have several limitations:

1) Collecting blood, respiratory tract or tissue samples for cultures is the golden standard, but sensitivity is variable based on the immunity of the patient, so the culture sometimes yields false-negative results. In addition, *Histoplasma* isolation may require up to six weeks for optimal growth.
2) Immunological tests can detect antigens or antibodies in serum and other biological fluids, but the detection of antibodies can give false-negative results due to its low sensitivity in immunosuppressed patients (particularly patients with AIDS, in whom the production of antibodies decreases); however, antigen detection in these individuals is more sensitive. Antigenic cross-reactivity with other fungi may also occur, causing

false-positive results in patients with other mycoses such as paracoccidioidomycosis, blastomycosis, aspergillosis, candidiasis and coccidioidomycosis. The detection of these antibodies is of great value to diagnose meningeal involvement in histoplasmosis. The detection of antigens in progressive disseminated histoplasmosis is more sensitive than the detection of antibodies, especially in urine. The detection of galactomannan antigen by enzyme immunoassay is the only commercially available methodology that has been validated and approved by the European Community for in vitro diagnosis. (5)

3) Histopathological analysis with different stains (Wright, Giemsa, Schiff periodic acid and methenamine silver) is a useful tool, but can have a sensitivity lower than 50%, depending on the experience of the observer since the *Histoplama* yeasts may be mistaken for *Candida spp., Penicillium marneffei, Pneumocystis jirovecii, Cryptococcus neoformans, Blastomyces dermatitidis* and *Leishmania spp.*, or for artifacts.
4) Molecular methods, in particular polymerase chain reaction (PCR), are a diagnostic alternative with suitable sensitivity and specificity to detect and identify *Histoplasma spp.* in biological and environmental samples in a rapid manner (6,7); however, their diagnostic use has not been approved by the Food and Drug Administration (FDA). (5,8)

All these limitations cause a delay in the diagnosis and subsequent mismanagement of patients. For this reason, a multiple approach to diagnosis is recommended, involving epidemiological and, especially, working knowledge of the patient, as well as laboratory, radiographic, histopathological, microbiological, serological and even molecular test results in complicated cases.

The initial treatment of choice for progressive disseminated histoplasmosis in immunocompromised individuals is lysosomal amphotericin B, while itraconazole is used in mild presentations of the disease and as reduction therapy. (4) Primary prophylaxis with itraconazole (200 mg/day) is recommended to reduce the risk of histoplasmosis in HIV-infected patients with CD4 cell counts <150 cells/mm^3 living in endemic areas. (9)

It is worth mentioning that since 1987 histoplasmosis has been considered an AIDS-defining infection because it is the first manifestation of the syndrome in 50-75% of HIV-infected patients; furthermore, disseminated infection may occur in 2-5% of them, particularly in patients living in endemic areas. (10) In Latin America, where there are areas of high endemicity (Colombia, Argentina, Mexico, Brazil, Venezuela, etc.), it has been estimated that about 1 600 000 people live with HIV, of which 24 000 develop disseminated histoplasmosis with a mortality rate of ≥40%. Although antiretroviral therapy has helped to reduce the incidence of histoplasmosis, it is a fact that in Latin America this infection continues to be a serious health problem, since there are still many people who do not have access to this therapy, which, together with the lack of tests that would allow a timely diagnosis, increases the risk of death. (11)

With all this in mind, it is evident that histoplasmosis is a disease of great medical interest due to its association with the population of individuals living with HIV/AIDS and its clinical similarity with tuberculosis. The public health problem posed by this fungal infection should be addressed comprehensively, considering that it is not a disease that is compulsorily reported

and its real incidence is unknown, reason why prevention and control programs have not been developed for the population most vulnerable to developing it. It is important that, in the presence of clinical suspicion, physicians have knowledge of the set of tests that can be used, as well as of their limitations, in order to confirm the diagnosis, provide the most appropriate therapeutic management for each patient, and influence the reduction of the mortality rate.

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