

Histoplasmosis in Italy

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L'istoplasmosi in Italia
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In loving memory of Professor Aldo Mazzoni, MD, 1927-2007

HISTOPLASMOSES

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum* var. *capsulatum* and *Histoplasma capsulatum* var. *duboisii* (in Africa) [1].

These infective agents are present mainly in the soil, particularly if contaminated with bird or bat droppings. The infection, acquired via inhalation, is generally asymptomatic, but in a small percentage of cases (1%) it may result in influenza-like symptoms, often self-limiting. It affects mainly immunocompromised patients and worsens in case of high exposure level. It may involve all organs and systems, and may mimic many other infectious and non-infectious disorders, which are more frequent just in these immunocompromised hosts. In the most severe cases, disseminated histoplasmosis may be life-threatening [1].

Among systemic and cutaneous mycoses diffused worldwide, histoplasmosis is still a present threat for people living in endemic countries, travelers, immigrants, and in some cases also in non-endemic countries, especially when immunocompromised patients are of concern.

The most widely used diagnostic tests are *Histoplasma* antigen detection in urine and/or serum, but also culture, antibody tests, and microscopy may be performed, even if each of them present important drawbacks [1].

Histoplasmosis belongs to a particular group of pathogenic fungi, which are called "dimorphic", since they present as yeasts at body temperature (37°C) and as fungal hyphae at room temperature (25°C). This distinction is also very useful for the standard diagnostic techniques, since it is sufficient to change the temperature of the culture vial to allow the observation of this relevant morphologic change.

In cases of mild to moderate pulmonary histoplasmosis, the infection will resolve spontaneously, without treatments. For severe infections, an effective antifungal therapy (amphotericin B or itraconazole) is available, but a prompt diagnosis plays also a significant role in rapidly achieving a complete cure [1,2].

THE DIAGNOSIS OF HISTOPLASMOSES IN ITALY

Since 1950s, histoplasmosis was retrieved in the Po river valley. Most cases concerned imported histoplasmosis, but also native histoplasmosis was found, as confirmed by studies on soil [3] and animals [4]. From 1955 to 1960, 7 cases of native histoplasmosis were reported in the Emilia Romagna, Piedmont, and Venetia regions [5]. Afterwards, no cases of native histoplasmosis were published until 1989.

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During mid-1980s, the number of episodes of histoplasmosis among immunocompromised patients (especially those with HIV infection and AIDS) [6] grew and the number of cases of histoplasmosis occurring among travelers increased. At that time, the diagnosis of histoplasmosis was still based on the standard techniques, and missed or delayed diagnosis were common, when a skilled expertise in this field was lacking.

The diagnostic problems dealing with the frequent cutaneous localization of histoplasmosis [7] became even more difficult in immunocompromised patients. Particularly hard was the differential diagnosis with other opportunisms and underlying disorders [8,9]. Cutaneous forms may be especially challenging, and often require histopathologic studies to achieve a diagnosis, which leads to an appropriate clinical treatment.

A paper published in 2005 [5] calculated 55 cases of histoplasmosis reported in Italy in around 50 years. 20 of these patients were coinfecting by HIV. Native histoplasmosis was detected in 13 cases, that were concentrated in the Northern regions and in the most recent years.

Lately, more advanced molecular biology techniques to obtain diagnosis of histoplasmosis have been developed: mycoarrays [10].

It comes of a serological assay built up on a protein microarray platform specifically developed to detect antibodies against histoplasmin (for the diagnosis of histoplasmosis) and other antigens of *Coccidioides immitis* (for the diagnosis of coccidioidomycosis).

In my opinion, especially when imported histoplasmosis does not appear to have a life-threatening course, it continues to be borne by very relevant epidemiological, clinical, imaging, and histopathologic clues. Tissue samples available after biopsy may be needed for an histopathological examination, and especially a relevant history and a diagnostic suspicion are non-negligible clues, as just in a recently described Italian traveler who acquired imported histoplasmosis after his trip in the Mato Grosso region, Brazil [11].

Finally, I believe that the traditional mycological techniques (including microscopy and culture at the two key different temperatures where *Histoplasma* spp. show their yeast and hyphal forms, respectively), especially in conjunction with a timely diagnostic suspicion, may allow to expect that an endemic, imported (but sometime autochthonous) mycosis like histoplasmosis can be easily and promptly recognized also in Institutions where extremely advanced laboratory techniques are not still available.

The role of Professor Aldo Mazzoni

*The University of Bologna represents since over 60 years a national reference center for dimorphic mycoses, especially for both imported and native histoplasmosis. *H. capsulatum*, in fact, was retrieved in the Po river valley since 1950s by Professor Aldo Mazzoni and other researchers. He carried out systematic studies [3,4,6,12-14] in humans, animals, and in soil specimens, recognized also by a report published in Science in the year 1965 [3], among others. His personal engagement covered several vocations: he was clinician, microbiologist, mycologist, and finally bioethical expert [3,4,6,13-15]. His expertise, in particular in the field of histoplasmosis, was widely recognized, to the point that he frequently acted as "second opinion" for cases coming from the entire country.*

During mid-1980s, the University of Bologna carefully collected and discussed all cases of histoplasmosis capsulatum and duboisii reported by the scientific literature since the year 1980, distinguishing them from their presumably native or imported origin [16]. At that time, when a skilled expertise in this field was lacking, this systematic work has been acknowledged also by many institutional, epidemiological organisms, in Italy and abroad. Prof. Mazzoni gave also his valuable contribution in solving the diagnostic problems dealing with the frequent cutaneous localization of histoplasmosis [7] in the immunocompromised patients, which required a differential diagnosis with other opportunisms and underlying disorders [8,9].

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Conflicts of Interest

The author declares he worked in Professor Mazzoni's team described in the article.

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