

Imported and autochthonous histoplasmosis in Italy: new cases and old problems

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Summary

In the past the Italian soil was considered as a low-endemic pabulum for *H. capsulatum* var. *capsulatum* and only few autochthonous cases of histoplasmosis were reported in Italy, especially in the Po valley. The aim of the paper was to evaluate this possibility by reviewing the literature and providing our own personal data. Four additional cases of histoplasmosis were observed during 1999-2003 in AIDS immigrant or in Italian citizens, and in travellers to endemic areas. One of the AIDS patients was an autochthonous case of histoplasmosis. The Italian literature was reviewed. Recent cases and literature data confirm the possible autochthonous presence of histoplasmosis in Italy, especially in the Northern regions.

Key words

Histoplasmosis, Italy, Travel, AIDS, Endemic disease

Histoplasmosis importada y autóctona en Italia: nuevos casos y viejos problemas

Resumen

En el pasado el suelo italiano era considerado un área de baja endemicidad para *Histoplasma capsulatum* var. *capsulatum* y únicamente unos pocos casos autóctonos de histoplasmosis fueron descritos en Italia, particularmente en el valle del Po. El objetivo de este trabajo es la valoración de esta posibilidad, haciendo una revisión de la bibliografía y de los datos personales. Cuatro nuevos casos de histoplasmosis han sido observados durante los años 1999-2003 en pacientes con sida inmigrantes o italianos y en viajeros a áreas endémicas. Uno de los pacientes con sida era un caso autóctono de histoplasmosis. Se revisa la bibliografía italiana. Los casos recientes y los datos de literatura confirman la posible presencia de histoplasmosis autóctona también en Italia, particularmente en las regiones del norte.

Palabras clave

Histoplasmosis, Italia, Viaje, Sida, Enfermedad endémica

Histoplasma capsulatum var. *capsulatum* is an environmental dimorphic mould endemic in extended geographic areas of the Americas, East Asia and Oceania, Sub-Saharan Africa and Middle-East Countries. Its presence as autochthonous fungus in Europe is still controversial.

Human activities associated to microfoci where *H. capsulatum* is a saprophytic inhabitant is very often related to a respiratory inhalation of aleurioconidia: speleology, mining and building sites works, as agricultural activities or living in rural areas are highly exposed to histoplasmosis.

The medical records of four Italian patients affected by histoplasmosis during the period August 1999 - March 2003 have been retrospectively reviewed utilizing the data base of the Microbiology Institute, Azienda Ospedaliera (A.O.) 'Ospedali Riuniti di Bergamo', Bergamo, Italy. The epidemiological and clinical profile of the patients was evaluated.

The patients were admitted to hospitals in Bergamo (1 patient), Brescia (1 patient), Reggio Emilia (2 patients): all cases were examined by the Microbiology Institute, A.O. Ospedali Riuniti di Bergamo for diagnosis or confirmation.

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Aceptado para publicación el 12 de septiembre de 2005

Case 1. APG, a 37 year-old woman, born in Ivory Coast, had been living in Italy since 1993. In 2001, six months after a visit to her native country, she complained of high fever, cough, weight loss, pharyngodinia, and diarrhoea: for these reasons she was admitted to hospital. Laboratory findings showed a severe immunosuppression (total WBC = 3.500/cc; CD4+ = 2/cc) because of a previously unknown HIV infection, but no kidney and liver abnormalities. A chest x-ray revealed diffuse bilateral reticulonodular infiltrates. Blood cultures and culture of stool were positive for group E *Salmonella*. A bronchial biopsy showed a myriad of conidia inside and outside phagocytic cells and yielded *H. capsulatum* var. *capsulatum*. Two blood cultures yielded *Histoplasma* too. The patient was successfully treated with amphotericin B for seven weeks. Then itraconazole was added as maintenance treatment.

Case 2. VM, a 41-year-old woman living in a town of the Po valley in Bergamo province, suffering from oral, vaginal and tracheo-bronchial candidiasis, was admitted in November 2002 because of wasting syndrome. She never went outside Italy. An HIV serology resulted positive, and antiretroviral therapy was initiated. Laboratory findings showed a severe immunosuppression (total WBC = 2.840/cc; CD4+ = 7/cc). Her chest x-ray revealed mild multiple opacities. A broncho-alveolar lavage was positive for *Pneumocystis carinii*, cultures for bacteria, mycobacteria, and fungi were always negative. Three blood cultures yielded *H. capsulatum* var. *capsulatum*, but *Histoplasma* serology was negative. The patient was successfully treated with amphotericin B (total dose: 1050 mg) then shifted to itraconazole oral solution 200 mg/day for two months.

Case 3. KB, a 48 year-old man, born in Ivory Coast, who had been living in Italy since 1993, HIV infected since 2001. After a trip to his Country, he was admitted to hospital because of fever, epigastralgia and pain at the right hypochondrium, and hemithorax. Laboratory findings showed a severe immunosuppression (total WBC = 5.700/cc; CD4+ = 9/cc), and liver abnormalities. A pulmonar CT revealed multiple bilateral reticulonodular infiltrates, with opacities at the upper right lobe, pleural effusion, and adenopathy. *Pneumocystis carinii* was found in a broncho-alveolar lavage. A blood culture yielded *H. capsulatum* var. *capsulatum*. He was treated with itraconazole 400 mg/day but he suddenly died. Autopsy was done, and *H. capsulatum* var. *capsulatum* was seen and yielded in lung.

Case 4. RA, a 45 year-old man from Italy, had spent two months in Nicaragua working in a Antigua rural, heavily dusty area. One week after his return, he referred asthenia, fever, pneumonia and loss weight (more than 10 kg in ten days). He was admitted to hospital where a chest x-ray showed multiple mild infiltrates bilaterally. All cultures for bacteria and fungi were negative. A Mantoux test was negative. An *Histoplasma* serology was positive. An antifungal therapy with itraconazole (600 mg/day during six weeks, then 800 mg/day for three months) was successful.

Till the 1980's, histoplasmosis was only a sporadic pathology in Italy [1-2,6,9-10,18,21,24-25,28-30,40]. In the '80s six additional imported cases were described: two in AIDS-patients [14,20], and four in immunocompetent people coming from Central Africa [32,39] and Mexico led to full recovery [36].

In the last fifteen years thirty-six cases have been reported in Italy. Of these, eleven were diagnosed in the Microbiology Institute of Bergamo, and four are described in this paper. Eighteen cases were AIDS-patients

returning from the Americas (twelve) or Africa (five) [12,14,17,27,35,38] and eleven cases were immunocompetent subjects returning from the Dominican Republic (two), Ecuador, Nicaragua, Guatemala, San Salvador, Brazil, Tanzania and Pakistan (one each) and Peru (four) [11,22-23,26,35,37].

Even if the large majority of histoplasmosis are imported, Europe has been long suspected to be an endemic region for *H. capsulatum* var. *capsulatum*: it is long-time, before 1965', that more than twenty autochthonous cases were described in Albania, Austria, France, United Kingdom, Hungary, Portugal, Romania, Switzerland, Turkey and Russia [33].

The epidemiological Italian situation for histoplasmosis was discussed firstly in the 1950' by Sotgiu et al. who confirmed the presence in soils of *H. capsulatum* [31,33] and in 1960' from animals [19]. In addition, from 1955 to 1960 seven autochthonous sporadic clinical cases were described in the Emilia Romagna, Piedmont and Venetia regions [9-10,28-29]. The epidemiology of histoplasmosis as autochthonous pathology was confirmed by histoplasmin reactivity surveys in Lombardy, Tuscany and Apulia [4,8,15,34]. Since then, no additional autochthonous cases of histoplasmosis were described in Italy till 1989 [13]. Then, in 1990 a Sicilian housewife presented a lung histoplasmosis [5], in 1992 a greengrocer from Cremona was diagnosed with deep histoplasmosis [7] and in 1996 two AIDS patient living in the Bergamo and Milano provinces, respectively, had a diagnosis of disseminated histoplasmosis [3,12]. All of them denied any travel abroad in the past.

The case report no. 2 describes the occurrence of histoplasmosis in a woman with no travel history: this appears to be a new autochthonous case of histoplasmosis, adding to a number of cases which have been diagnosed over the years in the south-eastern part of Lombardy, not far from the cluster of cases described in Emilia in the 1950s. This finding tend to confirm the existence of an endemic focus of histoplasmosis in the central part of the Po valley [33].

The same epidemiological profile of histoplasmosis is well-defined in immunocompetent subjects. Actually, histoplasmosis can be considered also as a travel-related pathology in people coming from endemic areas both for travelling reasons [16-17]. The case report n° 4 of the present series to confirm this condition: a medical doctor working in rural areas of Nicaragua presented typical signs of histoplasmosis after a long staying in that very dusty region.

If histoplasmosis may be autochthonous in our country, a few patients (such as patient n° 4) still acquire the infection while travelling in highly endemic areas, where the exposure to rural habitats, caves and dusty sites represents a well known risk factor. Other imported cases of histoplasmosis are diagnosed in people born in highly endemic countries (as in reports 1 and 3): this will probably happens more and more frequently, in relation with the dynamics of people migration.

Finally, immunodeficiency is a well known factor predisposing to histoplasmosis, and the HIV/AIDS epidemic has contributed to an increase in the number of cases of histoplasmosis in persons from endemic areas; in our report, three out of four patients had concomitant HIV infection.

In conclusion, the occurrence of histoplasmosis in Italy is well documented, with 55 reported cases in about fifty years. While HIV infection is an important underlying condition, which occurs in 20 out of 55 patients, travel to or migration from highly endemic areas are also to be regarded as important epidemiological factors. Autochthonous cases are well documented (13/55 patients), especially in recent years in Northern Italy.

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