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Case report

Disseminated histoplasmosis with bone marrow infiltration in a newly diagnosed HIV patient

Histoplasmosis diseminada con infiltración de médula ósea en un paciente con VIH de reciente diagnóstico

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Sir,

A 41-year-old male patient experienced unintended weight loss of 8 kg for several months and progressive vomiting. The patient was born in Colombia but had been living in Spain for three years (did not travel to Colombia during this 3-year period), and he was not aware of any pre-existing conditions. He had no occupational or recreational history of environmental exposure to organic or inorganic hazardous agents. His blood pressure was 115/68 mmHg, heart rate 89 bpm, 96% oxygen saturation on room air, and he was afebrile. Cardiorespiratory auscultation was unremarkable. Abdominal examination only revealed mild hepatomegaly, and no peripheral lymphadenopathy was detected. An initial blood test in the emergency department revealed Hb 11.8 g/dL, 82,000 platelets/mcL, elevated ferritin (2,886 ng/mL), high LDH (731 U/L), low haptoglobin (17 mg/dL), C-reactive protein of 83 mg/L and procalcitonin at 0.19 ng/ml. Human immunodeficiency virus (HIV) serology was positive and he was admitted to our Infectious Diseases Unit for further study and treatment.

Aerobic, anaerobic and mycobacterial blood cultures were negative. HIV viral load of 216,000 copies/mL and CD4-T lymphocytes count was 67/mcL (13%). Both beta-D-glucan and galactomannan in a blood sample were positive (with values of 8.8 pg/mL and 5.9 mcg/L respectively). Serum Cryptococcal antigen, Quantiferon-TB Gold Plus® (interferon-gamma release assay or IGRA test), and hepatitis B, hepatitis C and *Treponema pallidum* serologies were all negative. Toxoplasma IgG, CMV IgG and hepatitis A IgG serologies were all positive. CMV serum viral load was 38 copies/mL. EBV viral load was not performed.

A chest X-ray was normal. A chest CT showed a 15 mm short-axis right hilar lymphadenopathy, a 6 mm right apical calcified nodule, and a 3 mm nodule in the middle lobe. Due to the poor quality of the sputum, neither culture nor molecular techniques could be performed in any respiratory sample. A bone marrow aspirate was performed. The smear is shown in **Figure 1**.

Based on clinical suspicion and the visualization of structures highly compatible with histoplasmosis, the

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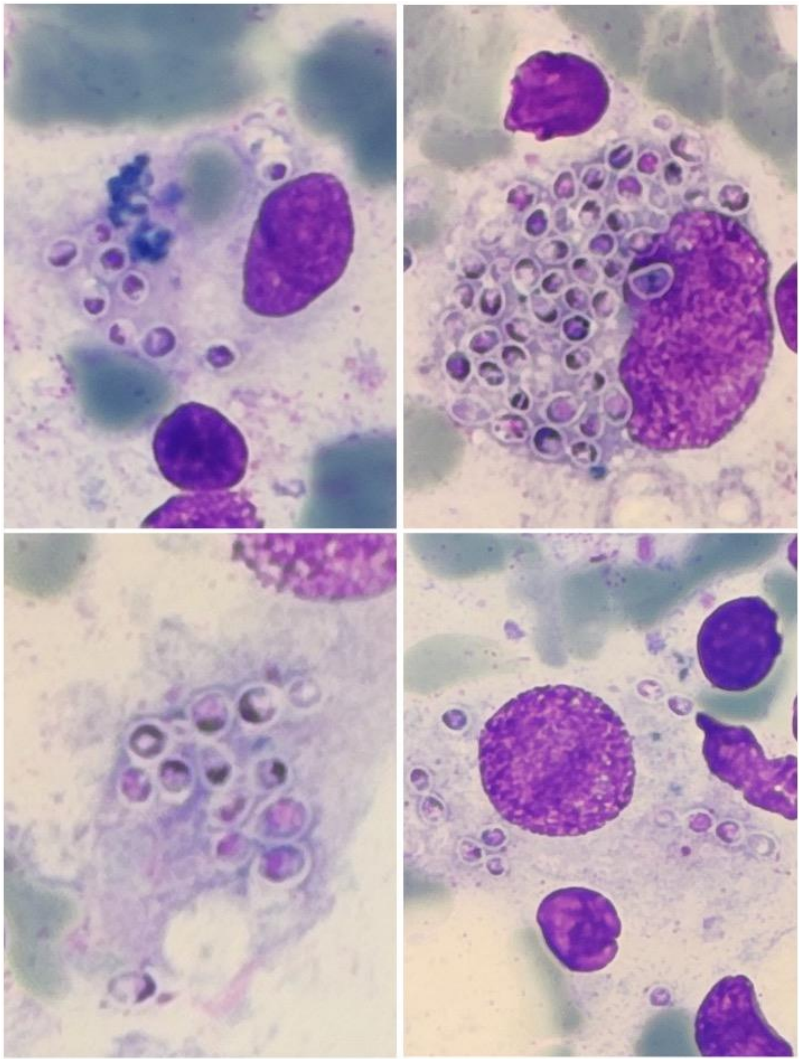

Figure 1. Bone marrow aspirate smear showing small (2-4 µm) budding yeasts within macrophages and free in the tissue, compatible with histoplasmosis. Halo effect is characteristic of *Histoplasma capsulatum* since it does not stain with May-Grünwald Giemsa stain, resembling a false capsule. Microscope magnification x100.

patient was started on treatment, pending definitive results: liposomal amphotericin B (L-AmB) 4 mg/kg/24h to treat a possible histoplasmosis, as well as bictegravir/emtricitabine/tenofovir alafenamide (for HIV infection) and cotrimoxazole prophylaxis (to prevent *Pneumocystis jirovecii* pneumonia) were initiated. The patient's general condition improved, and cytopenias began to resolve rapidly under antifungal therapy.

Leishmania spp and Parvovirus B19 PCR were performed in the bone marrow sample, and both were negative.

Bone marrow samples were sent to the National Center for Microbiology in Madrid, for further microbiological analysis. Culture on Sabouraud dextrose agar at 25-30°C from bone marrow aspirate sample revealed fungal structures, including tuberculate macroconidia with thick walls, surface projections and smooth-surfaced microconidia, compatible with *Histoplasma capsulatum*. In this culture sample, DNA extraction and molecular identification of *H. capsulatum* were performed by amplifying and sequencing the rDNA internal transcribed spacer region and the result was positive. Neither blood PCR for *H. capsulatum* nor urinary antigen tests were performed.

H. capsulatum var. *capsulatum* is a dimorphic fungus found in many parts of the world, mainly in humid climate regions (including countries in America, Africa, and Asia as well as some parts of central Europe, though not in Spain) [1]. Approximately 32% of histoplasmin skin test positivity has been reported throughout Latin America, with important differences between regions [2]. This implies that a significant proportion of the population from endemic countries has been previously infected and is susceptible to reactivation through any type of immunosuppression (HIV, solid organ transplantation, anti-TNF, etc.).

Primary infection is acquired via inhalation of microconidia from soil contaminated with bird or bat guano. Histoplasmosis can develop as an acute infection (usually asymptomatic, self-limited fever or pneumonia in both immunocompromised and immunocompetent individuals), reactivation (in which immunocompromised patients may develop disseminated disease via this etiopathogenic route) or reinfection. Immunity to *H. capsulatum* is mediated by INF-gamma, produced by macrophages and CD4 T lymphocytes, so severely immunocompromised patients, like those with advanced HIV, are prone to severe disease. Disseminated disease forms develop over 2-4 weeks and can produce a wide variety of symptoms: fever, fatigue, weight loss, shortness of breath, diarrhea with or without bleeding, and skin eruptions. At physical examination, some signs are common: lymphadenopathies, hepatomegaly or splenomegaly, skin or oral lesions ranging from maculopapular eruptions to ulcerations.

Pancytopenia, transaminitis and high LDH are common laboratory findings [3]. Hemophagocytic lymphohistiocytosis, disseminated intravascular coagulation and septic shock have been associated with histoplasmosis [3–5].

Serological testing lacks sensitivity in HIV patients. Diagnosis relies on culture and molecular techniques; however, culture takes 2 to 8 weeks to yield results [6]. Samples for culture or PCR can be obtained from bone marrow, blood, sputum/bronchoscopy, or CSF, each with different sensitivities. Where available, histoplasma antigen testing can accelerate diagnosis. This latter test can be performed on urine, blood, bronchoalveolar lavage fluid, or cerebrospinal fluid. Serum biomarkers like beta-glucan and galactomannan can both be positive, but there is limited data regarding the sensitivity and specificity of these serological markers [7]. It would be interesting to know their role as a first step when bone marrow aspiration cannot be performed early, and the patient is unstable. When antifungal treatment must be promptly initiated, a serum sample can be obtained first for fungal biomarkers (beta-D-glucan and galactomannan), so a positive result can later support the diagnosis of histoplasmosis.

We followed the classical liposomal amphotericin-B regimen, which is dosed as 3-5 mg/kg/day for 1-2 weeks, followed by oral itraconazole 200 mg twice daily for at least 12 months [8]. A single 10 mg/kg L-AmB induction dose (followed by oral itraconazole therapy) may be sufficient to achieve clinical and microbiological cure, based on a recent phase II clinical trial [9].

This case report emphasizes the role of early bone marrow aspiration in HIV patients with cytopenias and low CD4 counts. This diagnostic technique can lead to a final diagnosis in other infections like visceral leishmaniasis, disseminated MAC infection or CMV. Histoplasmosis is an uncommon opportunistic infection in Spain but should be taken into consideration in those patients from endemic regions. The increase in international travels may cause asymptomatic infections in individuals from non-endemic countries, which could later reactivate under immunosuppressive conditions. We aim to highlight this opportunistic fungal infection as a potentially life-threatening condition that is rarely diagnosed in Spain. However, it should be considered, given the evolving epidemiology of infectious diseases driven by migration, climate change, and tourism.

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Conflict of interest

Authors declare no conflicts of interest.

Author contributions

Conceptualization, E. G-A. and N. C-P.; methodology, E. G-A.; resources, N. C-P.; writing—original draft preparation, E. G-A., E. C-C. and L. A-F.; writing—review and editing, E. G-A. and A. R-S.; image acquisition: E. C-C.; supervision, E. G-A. All authors have read and agreed to the published version of the manuscript.

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