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Scientific letter

# Hemophagocytic lymphohistiocytosis (HLH) caused by disseminated histoplasmosis by *H. capsulatum* var. duboisii in HIV patient: A case report

## *Síndrome hemofacítico causado por histoplasmosis diseminada por H. capsulatum var. duboisii en paciente VIH: caso clínico*

We report the case of a 46-year-old-man, originally from Ghana, who had been living in Spain for 18 months and with no serious illnesses and no history of smoking, drinking or drug abuse. He went to the Emergency Department because of weakness, malaise, fever and a cough without expectoration for a week. He also explained sexual risk behavior 7 years previously with his partner, who was infected with HIV, with both HIV tests (Western Blot (WB) and ELISA) being negative then.

At hospital admission, physical examination revealed cachexia, hepatosplenomegaly and inguinal lymphadenopathy with no other important findings. The chest X-ray was also normal and the blood test showed pancytopenia (Hemoglobin 11 g/dL, 55,000 platelets/mm$^3$, 800 leukocytes/mm$^3$ with 521 neutrophils/mm$^3$, 186 lymphocytes/mm$^3$ and 70 monocytes/mm$^3$), acute renal failure (Glomerular filtrate rate 19 mL/min/1.73 m$^2$, Creatinine 3.68 mg/dL), liver biochemical alterations, LDH 2290 IU/L and C-reactive protein (CRP) 51.2 mg/dL.

The anemia test revealed very high ferritin levels (>14,683 μg/L). Additionally, the patient presented continuous LDH elevation (maximum of 17,800 IU/L), very low levels of albumin (0.9 g/dL), progressive elevation of lactate and persistent unspecific inflammatory changes such as CRP, procalcitonin and fibrinogen. All blood, sputum, urine and mycobacterium cultures were negative. EBV-IgG and HBV serology were positive, with 94,100,000 copies. HIV infection was confirmed by Western Blood (WB) and ELISA and the total amount of CD4 lymphocytes was 10 CD4/mm$^3$ (1.4%) and HLA-B*5701 was negative. Entecavir, Ritonavir, Raltegravir, Darunavir and Lamivudine were started as well as prophylaxis with Trimethoprim-Sulfamethoxazole and Ganciclovir.

Abdominal ultrasound showed clinical nephropathy and splenomegaly and a body scan (TC) revealed anasarca with bilateral pleural effusion and pulmonary edema.

The patient was deteriorating becoming anuric, confused and agitated. A new blood test showed high levels of triglycerides (up to 717 mg/dL) with progressive deterioration of the liver and renal functions and aggravated pancytopenia, requiring platelets and blood transfusion. These findings, including the persistent fever, suggested a hemophagocytic lymphohistiocytosis (HLH).

Due to the lack of a causing agent, a bone marrow aspirate was obtained, revealing a large number of oval cells between red blood cells and inside macrophages and granulocytes, suggesting fungal infection (Fig. 1).

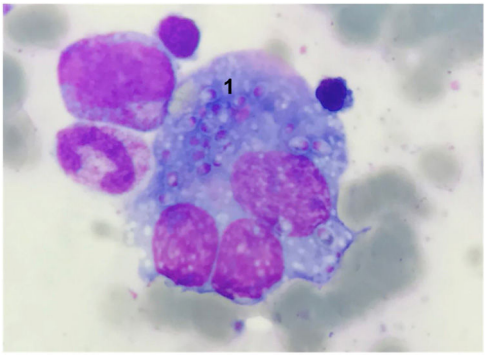


**Fig. 1.** Smear of peripheral blood with histoplasma inclusions (number 1) inside the macrophage.

A direct polymerase chain reaction (PCR) was performed to amplify the internal transcribed spacer 1 (ITS1) and ITS2. A Histoplasma capsulatum var duboisii was identified when the sequences obtained were analyzed using the BLAST alignment program of the GenBank database (National Institutes of Health) and liposomal amphotericine B by 4 mg/kg/day doses were started.

However, the patient deteriorated further, requiring intensive care including hemodialysis, vasoactive drugs (norepinephrine), albumin and K-vitamin. The progression of the disease was very fast causing hepatic liver failure progressing to multiple organ failure (MOF) and, unfortunately, death.

A total of 30 cases of HLH associated with disseminated-histoplasmosis with HIV infection were identified through the Pubmed search, being reported 23 cases reported in Spanish by Gil-Brusola et al.[1] Because of this, disseminated histoplasmosis is an uncommon presentation of HIV/AIDS in Spain, where there were 24 cases in HIV+ patients published in bibliography from 1988 to 2004,[1] and 19 cases reported in the first decade of this century.[2] Despite this, histoplasmosis is the most frequent, imported micosis in Spanish HIV patients, with most cases coming from America, and with only one case from Africa reported, where the most frequent variant is Histoplasma duboisii, as with the current case.[1–4]

HLH was described in 1939 and is divided into genetic or acquired forms, both characterized by an extreme inflammatory response due to natural killer (NK) cell dysfunction which activates the macrophage system.[3,5–7] It is caused by underlying processes such as infections, autoimmune diseases or malignancy. The estimated incidence is 1.2-cases/million inhabitants/year, maybe underestimated.[3] The diagnostic of HLH is defined by fulfilling one of the following: a molecular diagnosis consistent with HLH or 5 out of the 8 criteria below: fever, splenomegaly, cytopenia (affecting ≥ 2 lineages in the peripheral blood), hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow or spleen or lymph nodes, no evidence of malignancy, low or absent

NK cell activity, ferritin ≥ 500 μg/L and soluble CD25 ≥ 2400 U/mL, being the last three considered as new criteria.[3,8]

The initial management to secondary HLH includes the administration of etoposide and dexamethasone, both of which could be restarted and increased gradually in case of reactivation.[3]

Additionally, disseminated histoplasmosis is an uncommon opportunistic infection in HIV patients caused by Histoplasma capsulatum fungi, with the Capsulatum variant being more likely in America and the Duboisii variant more likely in Africa.[1,4,8] Some cases of HLH due to disseminated histoplasmosis have been described, mostly of them caused by *H. capsulatum* var. capsulatum, but they are infrequent.

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## Anterior bilateral uveitis and acute parvovirus B19 infection☆

### *Uveítis anterior bilateral e infección aguda por parvovirus B19*

Parvoviruses are single-stranded DNA viruses, the only one of which known to affect humans is B19. Parvovirus B19 is a ubiquitous micro-organism that causes common infections of respiratory transmission. The prevalence of the virus in the general adult population ranges from 50% to 80%.[1]

The course of the infection usually features two phases: a viraemia phase, in which the patient presents flu-like signs and symptoms with malaise, myalgia, fever, headache and chills; and a second phase, characterised by the onset of dermatosis, vasculitis, joint diseases and other general symptoms.[2] In healthy subjects, the infection may go unnoticed or be concomitant with infectious erythema or joint diseases. In adults, skin lesions are usually absent and joint impairment is most notable, with a particular propensity for the cervical spinal vertebrae, shoulders, elbows, wrists, ankles and feet.[3]

The infection can be diagnosed in the early phase with the demonstration of IgM antibodies against the virus, and in the disease resolution period by seroconversion to specific IgG antibodies. Treatment of this infection is symptomatic and based on analgesics and anti-inflammatory agents.

We report the case of a 46-year-old male who visited the emergency department due to headache radiating towards the cervical area with night sweats and measurable fever. The patient had also been suffering from back pain and joint pain in the knees and ankles for several weeks. He had already sought treatment for these symptoms and been diagnosed with influenza. Laboratory testing in the emergency department showed C-reactive protein (CRP) 1.6 mg/dl and leukocytosis 12,400/mm.[3] A lumbar puncture ruled out meningitis.

As the patient presented significant bilateral conjunctival hyperaemia, he was assessed by Ophthalmology. The ophthalmological examination showed bilateral Tyndall++ with visual acuity of the unit, and examination of the eye fundus revealed no signs of vitritis or retinitis. The patient was diagnosed with bilateral anterior uveitis.

A decision was made to admit him to the internal medicinal department to continue evaluating his systemic condition. He underwent an echocardiogram which, along with negative blood cultures, ruled out endocarditis. Urine sediment and urine culture were also normal. No influenza virus or respiratory syncytial virus (RSV) was detected in the patient's pharyngeal exudate, and a Mantoux test was negative. A chest X-ray showed no pleural effusion, and the patient's knees and shoulders showed no abnormalities. Serologies were all negative (*Brucella* spp., Toxoplasma, syphilis, hepatitis B and C, human immunodeficiency virus [HIV], *Coxiella* spp., *Borrelia* spp. and *Rickettsia* spp.) with IgG positivity for herpes simplex virus, Epstein–Barr virus and IgG and IgM antibodies for parvovirus. Autoimmunity was also negative (antinuclear antibodies [ANAs], antimitochondrial antibodies [AMAs] and extractable nuclear antibodies [ENAs]). Ultimately, the patient's diagnosis was probable acute infection due to parvovirus B19 and bilateral anterior uveitis.

It is estimated that only 20% of cases of anterior uveitis are of infectious origin; they are largely caused by viruses belonging to the family Herpesviridae.[4] However, there are few reported cases of infection with parvovirus B19 and uveitis. The four previously published cases (Table 1) were patients under 18 years of age; this case was the first one in an adult.[5–8] There are

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