Enferm Infecc Microbiol Clin. (2021);39(2):102–110

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

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).

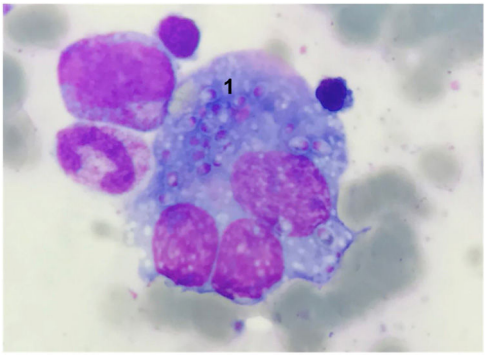

Fig. 1. Smear of peripheral blood with histoplasma inclusions (number 1) inside the macrophage.

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.

Acknowledgements

We thank our colleagues from Center de Diagnóstic Biomèdic (CDB), Hospital Clínic (Barcelona), who provided the specific diagnosis and especially to Francesc Marco for useful conversations.

References

1. Gil-Brusola A, Pemán J, Santos M, Salavert M, Lacruz J, Gobernado M. Disseminated histoplasmosis with hemophagocytic syndrome in a patient with AIDS: description of one case and review of the Spanish literature. Rev Iberoam Micol. 2007;24:312–6.
2. Ministerio de Sanidad Servicios Sociales e Igualdad; Ministerio de Economía y Competitividad; Instituto de Salud CarlosIII; Vigilancia Epidemiológica del VIH y SIDA en España. Sist Inf Sobre Nuevos Diagnósticos VIH y Regist Nac Casos Sida. 2016;1–35.
3. Espinosa Bautista KA, Fossas PG, Rodríguez EL. Síndrome hemofagocítico Conceptos actuales. Gac Med Mex. 2013;149:431–7.
4. Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev. 2007;20:115–32.
5. Castelli AA, Rosenthal DG, Bender Ignacio R, Chu HY. Hemophagocytic lymphohistiocytosis secondary to human immunodeficiency virus-associated histoplasmosis. Open Forum Infect Dis. 2015;2:1–4.
6. Phillips J, Staszewski H, Garrison M. Successful treatment of secondary hemophagocytic lymphohistiocytosis in a patient with disseminated histoplasmosis. Hematology. 2008;13:282–5.
7. Townsend JL, Shanbhag S, Hancock J, Bowman K, Nijhawan AE. Histoplasmosis-induced hemophagocytic syndrome: a case series and review of the literature. Open Forum Infect Dis. 2015;2, ofv055.
8. Subedee A, Van Sickels N. Hemophagocytic syndrome in the setting of AIDS and disseminated histoplasmosis: case report and a review of literature. J Int Assoc Provid AIDS Care. 2015;14:391–7.

Santiago Castejón-Hernández[a,*,1], Esteban A. Reynaga-Sosa[a,1], Marian Navarro-Aguirre[b,1], Anna Vilamala-Bastarras[b,1]

[a] *Department of Internal Medicine, Hospital Universitari de Vic, Barcelona, Spain*
[b] *Microbiology Department, Hospital Universitari de Vic, Barcelona, Spain*

* Corresponding author.
E-mail address: scastejon@chv.cat (S. Castejón-Hernández).
[1] These authors have contributed equally to the work.

https://doi.org/10.1016/j.eimc.2020.04.001

Uveítis anterior bilateral e infección aguda por parvovirus B19

Anterior bilateral uveitis and acute parvovirus B19 infection

Los parvovirus son virus ADN de cadena única, de los que el único conocido que afecta a los seres humanos es el B19. El parvovirus B19 es un microorganismo muy ubicuo, que provoca infecciones frecuentes, extendidas por vía respiratoria. La prevalencia del virus en la población general adulta oscila de 50-80%[1].

La infección suele desarrollarse en dos fases, una primera de viremia en la que el paciente presenta un cuadro seudogripal con malestar, mialgia, fiebre, cefalea y escalofríos, y una segunda fase caracterizada por la aparición de dermatosis, vasculitis, artropatías u otros síntomas generales[2]. En sujetos sanos, la infección puede pasar desapercibida o cursar únicamente con eritema infeccioso o artropatías. En adultos, las lesiones cutáneas suelen estar ausentes siendo la afección articular la más notable, con especial predilección por la columna vertebral cervical, hombros, codos, muñecas, tobillos y pies[3].

El diagnóstico se puede realizar en la fase temprana de la infección mediante la demostración de anticuerpos IgM contra el virus y en el periodo de resolución de la enfermedad mediante la seroconversión a anticuerpos IgG específicos. El tratamiento de esta infección es sintomático, de manera que se emplean fundamentalmente analgésicos y los antiinflamatorios.

Presentamos el caso de un varón de 46 años que acudió a Urgencias por presentar cefalea irradiada hacia la zona cervical con sudoración nocturna y fiebre termometrada. Así mismo, el paciente presentaba dorsalgia y artralgias en rodillas y tobillos de varias semanas de evolución. El paciente ya había ido a consulta por este motivo y se le diagnosticó cuadro gripal. La analítica extraída en Urgencias mostraba una PCR de 1,6 mg/dL con una leucocitosis de 12.400/mm^3. Se realizó punción lumbar que descartó meningitis.

Dado que el paciente presentaba una hiperemia conjuntival bilateral importante, fue valorado por Oftalmología. En la exploración oftalmológica presentaba Tyndall++ bilateral con agudeza visual de la unidad y una exploración de fondo de ojo sin signos de vitritis ni retinitis; se le diagnosticó uveítis anterior bilateral.

Se decidió ingresarlo en Medicina Interna para continuar con el estudio del cuadro sistémico. Se realizó un ecocardiograma que junto con hemocultivos negativos descartó endocarditis. El sedimento urinario y cultivo de orina también fueron normales. En el exudado faríngeo no se detectaron virus de la gripe ni VRS y el Mantoux fue negativo. En la radiografía de tórax no se observó derrame pleural y las de rodillas y hombros no mostraron alteraciones.

Tabla 1
Casos publicados de uveítis asociada a infección por parvovirus B19

Paciente	Edad (años)	Sexo	Eritema	Autoanticuerpos	Tratamiento de uveítis	Referencia
1	18	Mujer	Sí	Desconocido	Corticoide tópico	5
2	6	Mujer	No	Factor reumatoide	Corticoide tópico	6
3	5	Mujer	Sí	ANA	Corticoide tópico	7
4	9	Hombre	Sí	Negativos	Corticoide tópico	8
5	46	Hombre	No	Negativos	Corticoide tópico	Caso presentado