Hemophagocytic lymphohistiocytosis following an acute HIV infection, in a known immunosuppressed patient: A case report

Francisca Beires a, Joana Laranjinha b,*, Ana Pinho a, Frederico Duarte b

a Internal Medicine Department, Unidade Local de Saúde de Matosinhos, Rua Dr. Eduardo Torres, 4464-513 Senhora da Hora, Matosinhos, Portugal
b Infectious Diseases Department, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Rua Dr. Eduardo Torres, 4464-513 Senhora da Hora, Matosinhos, Portugal

ARTICLE INFO

Keywords: Acute HIV infection Hemophagocytic lymphohistiocytosis Infection

ABSTRACT

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory condition with a wide range of causes, being frequently associated with infections in adults. The association between HLH and acute HIV infection has been rarely described.

Case presentation: A 62-year-old male, with a past medical history of Henoch-Schönlein purpura under immunosuppressive treatment, presented with a two-week history of fever, asthenia, anorexia, cough and purpuric rash. Initial blood tests showed pancytopenia, elevated C-reactive protein and renal failure. Microbiological investigations were negative, but persistent fever and pancytopenia led to HLH suspicion. This diagnosis was supported by hyperferritinemia, hypertriglyceridemia, high soluble-interleukin-2 receptor levels and hepatosplenomegaly, fulfilling 5/8 diagnostic criteria of the Histiocyte Society-2004. Further investigation revealed a positive HIV-1 antibody and the patient reported recent sexual risks, with TCD4+ lymphocytes below 100/mL and HIV-1 viremia above 10 million copies/mL, confirming an acute HIV infection. Antiretroviral therapy (ART) and glucocorticoids were started with full clinical recovery.

Conclusion: HLH occurrence can be obscured by the features of a primary disease and can mimic other clinical conditions. In this patient, the prompt identification of an acute HIV infection as the cause of HLH allowed the early initiation of antiretroviral treatment and corticosteroids, with an efficient control of the viral replication and inflammatory response, preventing a potentially fatal evolution.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare hematologic dysfunction characterized by a dysregulation of the immune response [1]. It has a higher incidence in childhood, and it can be primary (due to a genetic defect) or secondary (triggered by another disease process). In the primary form, a hereditary and fatal disease, there is an inability to stop or suspend the immune response. As a result, there is a continuous and uncontrolled proliferation and activation of the immune system [1]. Secondary HLH, on the other hand, has no underlying genetic cause or predisposition, and there is a strong immunological activation of the immune system, which may, for example, be caused by a severe infection [2]. It has been described most commonly in association with viral infections, especially Epstein Barr virus (EBV), but it may also have malignancies or autoimmunity as trigger factors. Although it occurs typically in immunocompromised hosts, they are usually not obviously immunosuppressed [3].

In the inflammatory vortex, there is an excess of IL (interleukin) – 1, IL-6, IL-10, IL-12, interferon (IFN) gamma, tumor necrosis factor(TNF)-alpha and TNF-gamma, in addition to other cytokines, which are at the basis of the clinical scenario [4]. The most typical clinical findings are fever, hepatosplenomegaly and cytopenias, but other initial clinical findings may be present [1]. The broad differential diagnosis complicates its management, leading to a life-threatening outcome. The prompt initiation of therapy can drastically change the outcome.

Diagnostic guidelines have been published by the Histiocyte Society in 2004 (HLH-2004) based on common clinical, laboratory and histologic abnormalities. Accordingly, five of eight criteria are required for the diagnosis of HLH: fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis on

* Corresponding author.
E-mail addresses: beires.francisca@gmail.com (F. Beires), larinjoana@gmail.com (J. Laranjinha), pinho.aoliveira@gmail.com (A. Pinho), frederico.duarte1@gmail.com (F. Duarte).

https://doi.org/10.1016/j.idcr.2022.e01534
Received 31 January 2022; Received in revised form 29 May 2022; Accepted 13 June 2022
Available online 15 June 2022
2214-2509/© 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
biopsy, low/absent natural killer (NK) cell activity, hyperferritinemia, and high-soluble interleukin-2-receptor levels. Furthermore, HLH-2004 recommend chemo-immunotherapy, including etoposide and dexamethasone [1].

The body of literature describing the link between HIV and HLH is limited to case reports and small case series, usually in patients with chronic HIV infection with simultaneous opportunistic infections. Only a few reports describe HLH in acute HIV infection [8–15].

Case description

A 62-year-old male presented to the emergency room with a two-week history of fever, asthenia, anorexia, productive cough and a non pruriginous rash covering the thorax and progressing to the upper extremitities. He had a medical history of Henoch-Schönlein purpura, stable under steroids and azathioprine, and a known renal impairment due to IgA nephropathy. On physical examination, the patient was hemodynamically stable, with a peripheral oxygen saturation of 87% on ambient air, an auricular temperature of 38.9°C, and a confluent disseminated purpuric rash. Arterial blood gas showed a hypoxemia with a PaO2 of 56 mmHg (pO2/FiO2 ratio of 264). Initial blood tests revealed a pancytopenia (hemoglobin 11 g/dL, leucocytes 1795 u/L and thrombocytopenia 73,000 u/L), an elevated C-reactive protein (180 mg/dL), elevated lactate dehydrogenase (634 U/L) and a worsening of the renal function (creatinine 3.7 mg/dL). Azathioprine was stopped on the basis of a possible link to the pancytopenia. A respiratory infection was the presumed cause of the dehydration and acute kidney injury. Microbiological samples (blood, urine and sputum cultures) were therefore collected. A thoracic CT scan showed bilateral pulmonary opacities and bronchiectasis, not suggestive of infection. Nevertheless, considering the fever and elevated inflammatory markers, antibiotic therapy was started empirically with ev ceftriaxone 2 g/day and ev azithromycin 500 mg/day. The patient was admitted to the ward and a broader study was performed, which revealed a normal immunological study, an hyperferritenemia of 15,840 ng/mL and an hypertriglyceridemia of more than 400 mg/dL. Moreover, the patient underwent an abdominal ultrasound, revealing hepatosplenomegaly. Considering the possibility of HLH, the interleukin-2 receptor (soluble CD25) was measured. An elevated soluble CD25 of 2400 U/L firmed the diagnosis of HLH, with 5 HLH-2004 criteria fulfilled. During 3 days, the patient received pulses of metilprednisolone, with a subsequent weaning. During hospitalization the patient reported a non-negligible sexual exposure, which motivated a complete serologic study. A positive antibody for human immunodeficiency virus extremely challenging [7–15]. In this case, a persistent fever of unknown origin and pancytopenia, with negative extensive microbiological investigations, in a previously immunosuppressed patient, increased suspicion for HLH and prompted further investigation, which led to the diagnosis confirmation based on the HLH-2004 criteria. With the patient and family collaboration, as well as a multidisciplinary medical team, the identification of an acute HIV infection as the primary cause for the development of HLH was possible, allowing a rapid and successful treatment strategy. HLH treatment in non-HIV patients usually mandates systemic steroids and sometimes HIV-induced HLH can be addressed uniquely via prompt initiation of anti-retroviral therapy (ART) [4,5]. Nonetheless, in our patient, the severe clinical evolution reasoned a strategy of both potent ART and steroids initiation, which conducted to a favorable outcome.

Along with other case reports, this case underlines the importance of considering all HLH etiologies with appropriate diagnostic testing. Furthermore, acute HIV infection needs to be considered when the cause of HLH is not apparent and the patient personal history is suggestive.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

This case report has been elaborated according to the institutional ethical committee rules with respect to scientific content and complies with applicable research and human subjects regulations.

Conflict of interest statement

The authors declare no conflicting interests.

Acknowledgements

The authors would like to thank the patient for accepting to share his clinical case with the scientific community. The consent for publication was obtained from patient during time of hospitalization. Available upon journal request.

References

[1] Henter J-L, Horne A, Aricić M, Egelius RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–31. https://doi.org/10.1002/blc.21038.
[2] Bhatia S, Bauer F, Bilgrami SA. Candidiasis-associated hemophagocytic lymphohistiocytosis in a patient infected with human immunodeficiency virus. Clin Infect Dis 2003;37:e161–6. https://doi.org/10.1086/379615.
[3] Sun Hsin-Yun*, Chen Mao-Yun*, Fang Chi-Tai*, Hsieh Shu-Min*, Hung Chien-Ching*, Chang Shan-Chwen*. Hemophagocytic lymphohistiocytosis: an unusual initial presentation of acute HIV infection. JAIDS J Acquir Immune Defic Syndr 2004;37(4):1539–40. https://doi.org/10.1097/01.qai.0000136725.92886.b8.
[4] Doyle T, Bhagani S, Cwynarski K. Haemophagocytic syndrome and HIV. Curr Opin Infect Dis 2009;22(1):1–6. https://doi.org/10.1097/QCO.0b013e3282221896.
Nguyen D, Nacher M, Melzani A, Demar M, Blanchet D, et al. Hemophagocytic lymphohistiocytosis during HIV infection in Cayenne Hospital 2012–2015: first think histoplasmosis. Front Cell Infect Microbiol 2020;10:574584. https://doi.org/10.3389/fcimb.2020.574584.

Timothy J Brown, Bonnie C Prokesch, Srikanth Nagalla, Christian Wysocki. Overall survival of HIV-positive patients with HLH. Blood 2018;132(Supplement 1):4957. https://doi.org/10.1182/blood-2018-99-116479.

Manji F, Wilson E, Mahe E. Acute HIV infection presenting as hemophagocytic lymphohistiocytosis: case report and review of the literature. BMC Infect Dis 2017;17(1 December):633.

Pellegrin JL, Merlio JP, Lacoste D, et al. Syndrome of macrophagic activation with hemophagocytosis in human immunodeficiency virus infection. Rev Med Interne 1992;13:438–40. https://doi.org/10.1016/0228-8663(92)80025-

Martínez-Escribano JA, Pedro F, Sabater V, et al. Acute exanthem and pancreatic panniculitis in a patient with primary HIV infection and haemophagocytic syndrome. Br J Dermatol 1996;134:804–7. https://doi.org/10.1111/j.1365-2133.1996.tb06997.x.

Chen TL, Wong WW, Chiu T.J. Hemophagocytic syndrome: an unusual manifestation of acute human immunodeficiency virus infection. Int J Hematol 2005;78:450–2. https://doi.org/10.1007/s11282-005-1290-6.

Park KH, Yu HS, Jung SI, Shin DH, Shin JH. Acute human immunodeficiency virus syndrome presenting with hemophagocytic lymphohistiocytosis. Yonsei Med J 2008;49(2):325–8. https://doi.org/10.3349/ymj.2008.49.2.325.

Sun HY, Chen MV, Fang CT, Heiel SM, Hung CC, Chang SC. Hemophagocytic lymphohistiocytosis: an unusual initial presentation of acute HIV infection. J Acquir Immune Defic Syndr 2004;37(4):1539–40. https://doi.org/10.1097/01. qai.0000136725.92886.b6.

Concetta G, Roberta P, Giuliana B, Antonio C, Vito G, Silvia C, Orlando A. Hemophagocytic syndrome in a patient with acute human immunodeficiency virus infection. Clin Infect Dis 2004;38(12):1792–3. https://doi.org/10.1086/392512.

Adachi E, Koibuchi T, Imai K, Kikuchi T, Shimizu S, Koga M, Nakamura H, Iwamoto A, Fuji T. Hemophagocytic syndrome in an acute human immunodeficiency virus infection. Intern Med 2013;52(5):629–32. https://doi.org/10.2169/internalmedicine.52.7544.