Dramatic response to HAART in HIV-induced hemophagocytic lymphohistiocytosis

Karan K. Topiwala, Ellen F. Eaton, Ricardo A. Franco

ABSTRACT

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a difficult diagnosis to make and carries with it a high mortality rate, yet it is treatable.

Case Report: We present a 48-year-old African-American male, recently diagnosed with AIDS who had not yet initiated HAART (highly active antiretroviral therapy). He presented with high fever and altered mental status with progressive liver failure and worsening cytopenias. He showed no response to broad spectrum anti-microbial coverage and no infectious etiology could be established. There was no evidence of an opportunist infection or hemophagocytosis (HPC) on a subsequent bone marrow biopsy. In view of his rapid clinical deterioration with multi-organ failure, in the absence of an infectious cause and a stable CD4 cell count, he was diagnosed with HIV induced HLH using the modified-2009 criteria. He was started on HAART and showed a dramatic response with clinical improvement over the next three days, without the need to resort to immunosuppressive agents. The patient was discharged two weeks later, and has remained free of problems over the last eight months.

Conclusion: This case report summarizes the importance of an early diagnosis of HIV induced HLH and the importance of early HAART initiation.

International Journal of Case Reports and Images (IJCRI)

International Journal of Case Reports and Images (IJCRI) is an international, peer reviewed, monthly, open access, online journal, publishing high-quality, articles in all areas of basic medical sciences and clinical specialties.

Aim of IJCRI is to encourage the publication of new information by providing a platform for reporting of unique, unusual and rare cases which enhance understanding of disease process, its diagnosis, management and clinico-pathologic correlations.

IJCRI publishes Review Articles, Case Series, Case Reports, Case in Images, Clinical Images and Letters to Editor.

Website: www.ijcasereportsandimages.com

CASE REPORT

OPEN ACCESS | PEER REVIEWED

Dramatic response to HAART in HIV-induced hemophagocytic lymphohistiocytosis

Karan K. Topiwala, Ellen F. Eaton, Ricardo A. Franco

ABSTRACT

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a difficult diagnosis to make and carries with it a high mortality rate, yet it is treatable. **Case Report:** We present a 48-year-old African-American male, recently diagnosed with AIDS who had not yet initiated HAART (highly active antiretroviral therapy). He presented with high fever and altered mental status with progressive liver failure and worsening cytopenias. He showed no response to broad spectrum anti-microbial coverage and no infectious etiology could be established. There was no evidence of an opportunist infection or hemophagocytosis (HPC) on a subsequent bone marrow biopsy. In view of his rapid clinical deterioration with multi-organ failure, in the absence of an infectious cause and a stable CD4 cell count, he was diagnosed with HIV induced HLH using the modified-2009 criteria. He was started on HAART and showed a dramatic response with clinical improvement over the next three days, without the need to resort to immunosuppressive agents. The patient was

discharged two weeks later, and has remained free of problems over the last eight months. **Conclusion:** This case report summarizes the importance of an early diagnosis of HIV induced HLH and the importance of early HAART initiation.

Keywords: Hemophagocytic lymphohistiocytosis (HLH), Hemophagocytosis, Highly active antiretroviral therapy (HAART) Hepatitis B, Herpes simplex virus (HSV), T lymphocytes

How to cite this article

Topiwala KK, Eaton EF, Franco RA. Dramatic response to HAART in HIV-induced hemophagocytic lymphohistiocytosis. Int J Case Rep Images 2015;6(2):65–69.

doi:10.5348/ijcri-201512-CR-10473

Karan K. Topiwala¹, Ellen F. Eaton², Ricardo A. Franco³

Affiliations: ¹Medical Student, Bharati Vidyapeeth Medical College, Pune, Maharashtra, India; ²Fellow, Division of Infectious Disease, University of Alabama, Birmingham, 229 Tinsley Harrison Tower, 1900 University Boulevard, Birmingham, AL, USA; ³MD, Assistant Professor, Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, AL, USA.

Corresponding Author: Karan Kaushik Topiwala, A-1303/1304 Hampton Park, Vesu, Surat, Gujarat, India 395007; Ph: 91 9687818564; Email: topiwala.karan@gmail.com

Received: 17 October 2014

Accepted: 19 November 2014

Published: 01 February 2015

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening syndrome characterized by an unregulated activation of antigen presenting cells, T lymphocytes, and macrophages, without their appropriate down-regulation by natural killer and cytotoxic cells. Although the frequency is unknown, HIV alone or in combination with infection or malignancy has been recognized as a cause of HLH since 1992 [1]. HLH in context of HIV can occur with acute or chronic HIV or even after initiation of HAART [2]. A dramatic resolution of HLH after the initiation of highly active antiretroviral therapy (HAART), as in our case report, is only infrequently reported. We thus hope to underscore the importance of rapid diagnosis and early initiation of HAART to treat the immune activation of HLH and the underlying viral process.

CASE REPORT

A 48-year-old African-American male presented with altered mental status and one week of fever, confusion and visual-tactile hallucinations. He reported malaise and subjective fever since one month. He had lost 40 pounds over the last two years which prompted a diagnosis of HIV/AIDS, made two months prior to his recent presentation. At that time his viral load was 630,000 copies/mL and CD4 count was 24/mm³. He had not yet initiated antiretroviral therapy and was on bactrim prophylaxis for *Pneumocystis pneumonia*. His only other medication was hydrochlorothiazide for hypertension, which was well controlled. He reported being sexually active with men. Physical examination was significant for fever of 103°F and a regular tachycardia. He was alert to person, place and location but deferred other questions to his mother due to confusion. There were no focal neurological findings. His initial laboratory workup showed pancytopenia (WBC 2.5x10³/μL, HCT 21, platelets 145x10³/μL) with markedly elevated serum ferritin (51,376 ng/mL, normal: 23–336 ng/mL) levels along with raised serum transaminases (ALT-450 IU/L, normal:15–58 IU/L; AST-790 IU/L, normal:14–40 IU/L) and normal alkaline phosphatase-109 IU/L (normal: 39–117). Routine cerebrospinal fluid (CSF) analysis, neuroimaging and chest X-ray were within normal limits.

An initial differential diagnosis included, disseminated histoplasmosis, hemophagocytic lymphohistiocytosis (HLH) due to HIV, leptospirosis, fulminant viral hepatitis from herpes simplex virus (HSV) or hepatitis B and disseminated Mycobacteriosis. Given the acuity of his presentation he was given an initial empirical coverage with vancomycin, piperacillin and tazobactam, acyclovir and amphotericin B for suspected sepsis and hepatitis. However, there was little improvement in his clinical status the following day with worsening pancytopenia (WBC, HCT and platelets are 1.9 x10³/μL, 25 and 90x10³/μL respectively) and liver function (ALT and AST rose to 1500 and 2000 IU/L, respectively with an INR at 2.2 (normal: 1). Additionally, he developed renal failure (serum creatinine 1.7 mg/dL, normal: 0.5–1.2 mg/dL). A comprehensive infectious workup including a viral hepatitis panel and others (CSF culture and cytology, CSF-AFB, HSV PCR and IgM, CMV antigen, HHV-6 DNA, adenovirus DNA, parvovirus PCR, VDRL, leptospirosis antibody, Bartonella IgG and IgM, AFB blood isolators, cryptococcal antigen, urine histoplasma antigen, blood and urine cultures, stool giardia and cryptosporidium tests) were checked and found to be negative. A bone marrow biopsy was subsequently performed to look for any evidence of an opportunistic infection or hemophagocytosis. The results were indicative of HIV/AIDS related changes including plasmacytosis, megaloblastic change, megakaryocyte hyperplasia, reticulin fibrosis, stromal damage, histiocyte hyperplasia, and hypercellularity (Figure 1).

In the absence of an infectious etiology, a diagnosis of HLH was made using the 2009 criteria (Table 1) and the patient was started on HAART (raltegravir, emtricitabine and tenofovir). He improved dramatically within three days of initiating HAART. His agitation resolved along with improvement in his fever and liver function tests. He was discharged two weeks after starting HAART. He is being followed in the clinic and is doing well, eight months later. Below is a figure demonstrating his laboratory trends after HAART initiation (Figure 2).

Figure 1: Slightly hypercellular marrow (50–60%) with trilineage hematopoiesis. Stromal changes consistent with history of HIV/AIDS effect on marrow: plasmacytosis, megaloblastic change, megakaryocyte hyperplasia, reticulin fibrosis, stromal damage, histiocyte hyperplasia, and hypercellularity. No morphologic evidence of malignancy. No evidence of opportunistic infection (special stains for fungus, cytomegalovirus, herpes simplex virus (HSV), mycobacteria, spirochetes and *Bartonella* were negative.

Table 1: 2009 HLH diagnostic criteria [9]

Identification of a HLH-associated gene mutation: (PRF1, UNC13D, STX11, STXBP2, Rab27A, SH2D1A, or BIRC4)

or

Three of the following four clinical criteria:

(i) Fever $\geq 38.5^{\circ}\text{C}$ (ii) Splenomegaly (iii) Peripheral blood cytopenia: at least two cell lines (iv) Hepatitis

and

one of the following four laboratory criteria:

(i) Hemophagocytosis in bone marrow, spleen, lymph node, or liver (ii) Ferritin >500 ng/mL (iii) Elevated soluble CD25 (iv) Low or absent NK cell activity

Supportive criteria:

(i) Hypertriglyceridemia (ii) Hypofibrinogenemia (iii) Hyponatremia

Abbreviations: [HLH Hemophagocytic lymphohistiocytosis].

Figure 2: Laboratory trends after highly active antiretroviral therapy (HAART) initiation. Note the extremely elevated levels of serum ferritin and its rapid decline along with aspartate aminotransferase and lactate dehydrogenase levels, after the initiation of HAART.

DISCUSSION

HLH is a life-threatening syndrome characterized by an unregulated activation of antigen presenting cells, T lymphocytes, and macrophages, without their appropriate down-regulation by natural killer and cytotoxic cells. The major manifestations include sepsis, fever, cytopenias, splenomegaly and hepatitis. The activated macrophages in HLH may also phagocytize host cells producing hemophagocytosis (HPC). HLH can be primary due to genetic predisposition or secondary to an infectious or rheumatologic processes. When HLH occurs in the setting of rheumatologic disorders such as lupus or rheumatoid arthritis, it is termed Macrophage Activation Syndrome (MAS). EBV was the most common infectious trigger in one study of 250 suspected HLH-cases (28% of the cases), followed by histoplasmosis (19%), cytomegalovirus (14%), bacteria (4%), mycobacteria (4%), blastomycosis (5%) [3]. Although the frequency is unknown HIV alone or in combination with an infection or malignancy has been recognized as a cause of HLH since 1992 [1]. Neidt et al. published autopsy reports of 56 AIDS patients in 1985, 20% of whom had HLH [4]. In 1997, Grateau et al. found a 0.6% incidence of HLH among HIV infected persons in one clinic, but this was likely an under-representation as it relied on bone marrow aspiration [5]. Of HIV infected patients with HLH, 56/58 had an additional hematologic or infectious etiology in one review: tuberculosis, cytomegalovirus and Hodgkin's disease were the most common associated conditions [1]. Several case reports, including ours, report HIV infection alone as the trigger for HLH, but the incidence is unknown [6]. HLH in context of HIV can occur with acute or chronic HIV or after initiation of HAART [2]. In advanced AIDS, HLH

is usually secondary to infection or malignancy [1, 5]. Diagnosis of HLH in HIV infected patients is also limited by poor sensitivity of bone marrow. Bone marrow biopsy is thought to be 60% sensitive [7] in all populations, and 63% sensitive in HIV infected patients [1]. Other reports of severe HIV-related HLH have failed to demonstrate biopsy-proven HPC [8]. As in our case, it is common for patients to present with only three or four of the eight diagnostic criteria, as initially laid down in 2004 [9]. Thus, experts proposed a modification (Table 1) necessitating only three of four physical findings and one of four laboratory derangements [10]. Lastly, treatment of HLH in the HIV infected patient should focus on treating the underlying cause. The HAART potentially plays an important role in reverting clinic-pathological changes of severe HLH as exemplified in our case report. The importance of HAART is also suggested, by the dramatically reduced mortality of HLH in the post-HAART era (31%) compared to the pre-HAART era (50–100%) [1]. Severe HLH usually requires conventional immunomodulatory agents such as corticosteroids, cyclosporin, intravenous immunoglobulin (IVIG), anti-thymocyte globulin and TNF antagonists. Refractory cases respond well to Alemtuzumab, where it is used as a bridge to allogeneic stem cell transplantation [11]. Two case reports of HIV related HLH with significant splenic involvement have also benefitted from splenectomy [8]. In our case, HAART alone could provide complete recovery of multi-organ failure without the use of further immunosuppressive therapies.

CONCLUSION

Our case highlights chronic HIV alone as a trigger for hemophagocytic lymphohistiocytosis (HLH). It stresses the use of more liberal diagnostic criteria as proposed in 2009. It further underscores the importance of an early treatment initiation with highly active antiretroviral therapy (HAART) in the HIV associated HLH cases, as it may potentially prevent the use of immuno-modulatory agents, in this immune-deficient population and provide complete recovery even in severe cases.

Author Contributions

Karan K. Topiwala – Acquisition of data, Analysis and interpretation of data, Drafting the article, Final approval of the version to be published

Ellen F. Eaton – Conception and design, Acquisition of data, Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published

Ricardo A. Franco – Conception and design, Analysis and interpretation of data, Critical revision of the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

Copyright

© 2015 Karan K. Topiwala et al. This article is distributed under the terms of Creative Commons Attribution License which permits unrestricted use, distribution and reproduction in any medium provided the original author(s) and original publisher are properly credited.

REFERENCES

1. Fardet L, Lambotte O, Meynard JL, et al. Reactive haemophagocytic syndrome in 58 HIV-1-infected patients: Clinical features, underlying diseases and prognosis. *AIDS* 2010 Jun 1;24(9):1299–306.
2. Huang DB, Wu JJ, Hamill RJ. Reactive hemophagocytosis associated with the initiation of highly active antiretroviral therapy (HAART) in a patient with AIDS. *Scand J Infect Dis* 2004;36(6-7):516–9.
3. Parikh SA, Kapoor P, Letendre L, Kumar S, Wolanskyj AP. Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis. *Mayo Clin Proc* 2014 Apr;89(4):484–92.
4. Niedt GW, Schinella RA. Acquired immunodeficiency syndrome. Clinico- pathologic study of 56 autopsies. *Arch Pathol Lab Med* 1985 Aug;109(8):727–34.
5. Grateau G, Bachmeyer C, Blanche P, et al. Haemophagocytic syndrome in patients infected with the human immunodeficiency virus: Nine cases and a review. *J Infect* 1997 May;34(3):219–25.

6. Martínez-Escribano JA, Pedro F, Sabater V, Quecedo E, Navarro V, Aliaga A. Acute exanthem and pancreatic panniculitis in a patient with primary HIV infection and haemophagocytic syndrome. *Br J Dermatol* 1996 Apr;134(4):804–7.
7. Gupta A, Weitzman S, Abdelhaleem M. The role of hemophagocytosis in bone marrow aspirates in the diagnosis of hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2008 Feb;50(2):192–4.
8. Sasadeusz J, Buchanan M, Speed B. Reactive haemophagocytic syndrome in human immunodeficiency virus infection. *J Infect* 1990 Jan;20(1):65–8.
9. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007 Feb;48(2):124–31.
10. Filipovich AH. Hemophagocytic lymphohistiocytosis (HLH) and related disorders. *Hematology Am Soc Hematol Educ Program* 2009:127–31.
11. Marsh RA, Allen CE, McClain KL, et al. Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab. *Pediatr Blood Cancer* 2013 Jan;60(1):101–9.

SUGGESTED READING

- Clinical features and diagnosis of hemophagocytic lymphohistiocytosis: UpToDate.
- Hemophagocytic Lymphohistiocytosis: An Update on Diagnosis and Pathogenesis, Flavia G. N. Rosado, MD, Annette S. Kim, MD, PhD, *Am J Clin Pathol* 2013;139(6):713–727.

ABOUT THE AUTHORS

Article citation: Topiwala KK, Eaton EF, Franco RA. Dramatic response to HAART in HIV-induced hemophagocytic lymphohistiocytosis. *Int J Case Rep Images* 2015;6(2):65–69.

Karan K. Topiwala is a final year medical student at Bharati Vidyapeeth Medical College, Pune, Maharashtra, India.

Ellen F. Eaton is Fellow, Division of Infectious Disease, University of Alabama, Birmingham, 229 Tinsley Harrison Tower, 1900 University Boulevard, Birmingham, AL, USA.

Ricardo A. Franco is Assistant Professor of Medicine at Division of Infectious Diseases, University of Alabama at Birmingham, USA.

Access full text article on
other devices

Access PDF of article on
other devices

Edorium Journals: An introduction

Edorium Journals Team

About Edorium Journals

Edorium Journals is a publisher of high-quality, open access, international scholarly journals covering subjects in basic sciences and clinical specialties and subspecialties.

Invitation for article submission

We sincerely invite you to submit your valuable research for publication to Edorium Journals.

But why should you publish with Edorium Journals?

In less than 10 words - we give you what no one does.

Vision of being the best

We have the vision of making our journals the best and the most authoritative journals in their respective specialties. We are working towards this goal every day of every week of every month of every year.

Exceptional services

We care for you, your work and your time. Our efficient, personalized and courteous services are a testimony to this.

Editorial Review

All manuscripts submitted to Edorium Journals undergo pre-processing review, first editorial review, peer review, second editorial review and finally third editorial review.

Peer Review

All manuscripts submitted to Edorium Journals undergo anonymous, double-blind, external peer review.

Early View version

Early View version of your manuscript will be published in the journal within 72 hours of final acceptance.

Manuscript status

From submission to publication of your article you will get regular updates (minimum six times) about status of your manuscripts directly in your email.

Our Commitment

Six weeks

You will get first decision on your manuscript within six weeks (42 days) of submission. If we fail to honor this by even one day, we will publish your manuscript free of charge.

Four weeks

After we receive page proofs, your manuscript will be published in the journal within four weeks (31 days). If we fail to honor this by even one day, we will publish your manuscript free of charge and refund you the full article publication charges you paid for your manuscript.

Mentored Review Articles (MRA)

Our academic program "Mentored Review Article" (MRA) gives you a unique opportunity to publish papers under mentorship of international faculty. These articles are published free of charges.

Favored Author program

One email is all it takes to become our favored author. You will not only get fee waivers but also get information and insights about scholarly publishing.

Institutional Membership program

Join our Institutional Memberships program and help scholars from your institute make their research accessible to all and save thousands of dollars in fees make their research accessible to all.

Our presence

We have some of the best designed publication formats. Our websites are very user friendly and enable you to do your work very easily with no hassle.

Something more...

We request you to have a look at our website to know more about us and our services.

We welcome you to interact with us, share with us, join us and of course publish with us.

Edorium Journals: On Web

Browse Journals

CONNECT WITH US