Characteristics of Secondary Hemophagocytic Lymphohistiocytosis in People Living With HIV/AIDS

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1. INTRODUCTION

BACKGROUND:

Hemophagocytic lymphohistiocytosis (HLH), commonly known as hemophagocytic syndrome, is a rare and serious disease triggered by a myriad of stimuli. HLH is characterized by an uncontrolled cytokine production and persistent lymphocyte and macrophage activation which results in hemophagocytosis. Since people living with human immunodeficiency virus (PLWH) have an increased risk of coinfections, HLH has great relevance in the clinical field as it worsens patient's prognosis, and presents with 33% mortality.

OBJECTIVE:

The main objetive of this observational descriptive study was to elucidate the main clinical characteristics of PLWH and HLH.

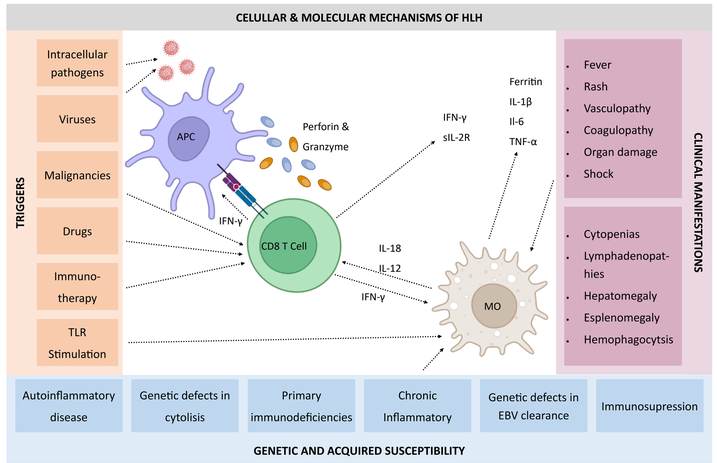


Figure 1. Pathogenesis of HLH. Abreviations: TLR: Toll-like receptors, EBV: Epstein-Barr virus, IL: Interleukin, TNF: Tumor necrosis factor, IFN: Interferon, APC: Antigen presenting cell. Figure adapted from Griffin et al., 2020 (1). Created in BioRender.com.

2. METHODS

Descriptive retrospective study in three reference centers in Mexico City from January 2018 to December 2023.

- Center for Research in Infectious Diseases (CIENI) of the National Institute of Respiratory Diseases "Ismael Cosio Villegas" (INER).
- Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" (INCMNSZ).
- Hospital General "Dr. Manuel Gea González".

The analysis included 16 participants living with human immunodeficiency virus hospitalized due to opportunistic infections or malignancies.

For this analysis only participants with more than 90% probability for HLH by HSCORE where included. Clinical and microbiological data were collected from clinical records, as well as bone diagnostic biopsies to perform Epstein–Barr virus–encoded small RNAs (EBER) in situ hybridization and to confirm infectious or neoplastic triggers.

3. RESULTS

One third of participants in the study died, exhibiting the importance of surveillance in PLWH with multiple infections and/or malignancies.

Viral and fungal infections where the most common trigger.

EBER in bone marrow was positive in all studied samples , depicting **the relevance of EBV in HLH development.**

Table 1. General characteristics and HLH diagnosis

	Total	Deceased	Recovered	*p*
	n = 26	n = 9	n = 17	
Age - years (SD)*	32 (29-36)	33 (31-36)	32 (26-39)	0.4990
Gender - no. (%)†				
Cisgender woman	4 (15)	2 (22)	2 (12)	
Cisgender men	19 (73)	7 (78)	12 (71)	0.1524
Transgender woman	3 (12)	0 (0)	3 (18)	
Antiretroviral therapy regimen - no. (%)†				
BIC/FTC/TAF	17 (65)	4 (44)	13 (76)	
DTG/FTC/TDF	5 (19)	2 (22)	3 (18)	
EFV/FTC/TDF	2 (8)	0 (0)	2 (12)	**0.0142**
DRVr/ETV/FTC/TDF	1 (4)	1 (11)	0 (0)	
DRVr/DTG/FTC/TDF	1 (4)	1 (11)	0 (0)	
HLH Criteria				
Fever - no. (%)†	24 (92)	8 (89)	16 (94)	0.9999
Organomegaly - no. (%)†	21 (81)	5 (56)	16 (94)	**0.0344**
Bicytopenia - no. (%)†	16 (62)	3 (33)	13 (76)	**0.0461**
Hypertriglyceridemia or hypofibrinogenemia - no. (%)†	18 (69)	6 (67)	12 (71)	0.9999
Hemophagocytosis in bone biopsy - no. (%)†	10 (38)	3 (33)	7 (41)	0.9999
Hyperferritinemia - no. (%)†	26 (100)	9 (100)	17 (100)	0.1166
Diagnosed by HLH 2004 criteria - no. (%)†	8 (31)	0 (0)	8 (47)	**0.0232**
Hscore - socore (SD)*	231.5 (36.06)	224.3 (42.48)	235.2 (32.95)	0.5140
HLH probability by Hscore - no. (%)†				
<88 %	1 (4)	1 (11)	0 (0)	
88-97 %	10 (38)	4 (44)	6 (35)	0.2878
98-99 %	15 (58)	4 (44)	11 (65)	
HIV and T cell laboratories				
Log. HIV viral load - copies/mcL (SD)*	4.9 (1.9)	4.9 (1.4)	4.9 (2.2)	0.7058
CD4+ T cells - cells/mL (IQR)*	24.5 (15-65)	29 (16-116)	21 (15-55)	0.5348
CD8+ T cells - cells/mL (IQR)*	153 (63-362)	181 (62-506)	99 (62-351)	0.4784

*For quantitative variables following a normal distribution (assessed with the Shapiro-Wilk test), Levene's test was conducted to evaluate variance homogeneity. Student's t-test with Welch's correction was utilized in cases of heterogeneity, while Student's t-test was used for homogeneity. The Mann-Whitney U test was applied for variables with non-normal distribution. †For qualitative variables, either the Chi-square test of independence or Fisher's exact test was employed.

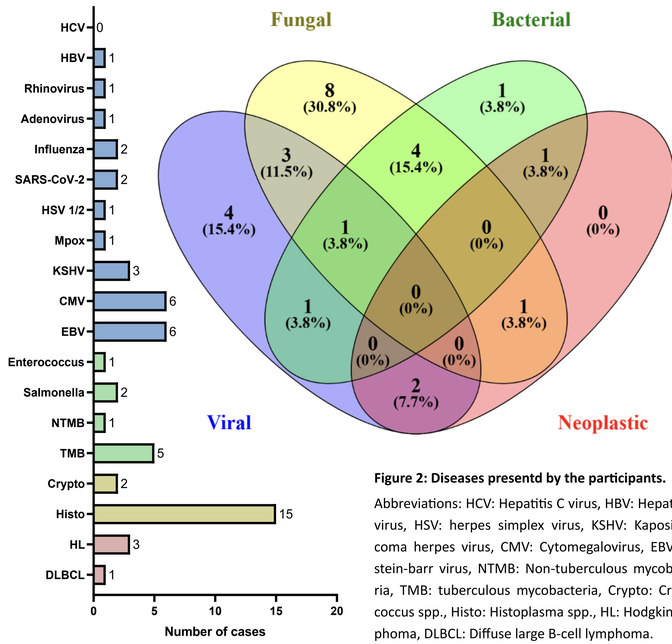


Figure 2: Diseases presentd by the participants.

Abbreviations: HCV: Hepatitis C virus, HBV: Hepatitis B virus, HSV: herpes simplex virus, KSHV: Kaposi sarcoma herpes virus, CMV: Cytomegalovirus, EBV: Epstein-barr virus, NTMB: Non-tuberculous mycobacteria, TMB: tuberculous mycobacteria, Crypto: Cryptococcus spp., Histo: Histoplasma spp., HL: Hodgkin lymphoma, DLBCL: Diffuse large B-cell lymphoma.

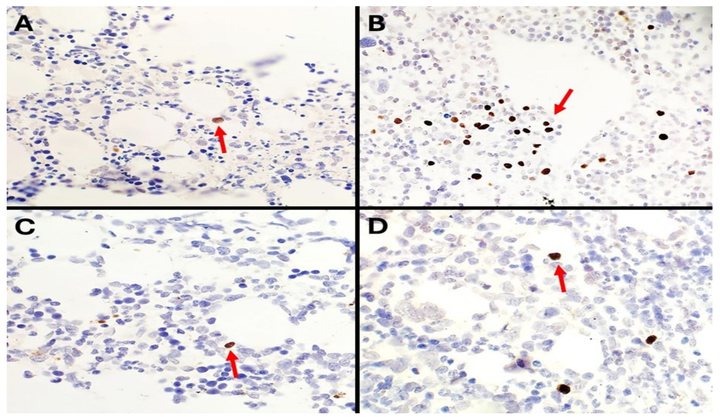


Figure 3. EBV-encoded small RNAs (EBER) in situ hybridization in bone marrow biopsies. A-D Microscopic examination (EBER) of bone marrow biopsies. Red arrows show the presence of EBV in bone marrow specimens. EBER expression was identified in medium and large lymphoid cells (red arrows) in all samples in different proportions: <1% (A and C, 10x), ~30% (B, 10x), and ~3% (D, 20x).

4. Conclusions

HLH, in conjunction with other severe diseases can progress to a devastating scenario putting the patient's life at risk. Surveillance of HLH is warranted, especially in PLWH presenting concomitant triggers such as fungal, viral, mycobacterial diseases, and neoplastic malignancies. Special attention should be driven to EBV coinfection which is a common trigger and coinfection among PLWH.