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Laura Suárez-Hormiga[1,2]
María-Nieves Jaén-Sánchez[1,2]
Edwin-Andrés Verdugo-Espinosa[3]
Cristina Carranza-Rodríguez[1,2]
Pilar-Michele Hernández-Cabrera[1,2]
Elena Pisos-Álamo[1,2]
Adela Francés-Urmeneta[1]
José-Luis Pérez-Arellano[1,2]

Hemophagocytic syndrome in patients infected with the human immunodeficiency virus: A study of 15 consecutive patients

[1]Unidad de Enfermedades Infecciosas y Medicina Tropical. Hospital Universitario Insular de Gran Canaria. Las Palmas de Gran Canaria. Spain
[2]Departamento de Ciencias Médicas y Quirúrgicas. Universidad de Las Palmas de Gran Canaria. Las Palmas de Gran Canaria. Spain
[3]Servicio de Medicina Interna. Hospital Universitario Insular de Gran Canaria. Las Palmas de Gran Canaria. Spain

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ABSTRACT

Objectives. Hemophagocytic syndrome (HPS) is characterized by various clinical and biological data derived from cytokine hyperproduction and cell proliferation. The objectives of this study were to evaluate the epidemiological, etiological, clinical and evolutionary characteristics of patients diagnosed with hemophagocytic syndrome and HIV infection, as well as their comparison with data from the literature.

Methods- A retrospective descriptive observational study was performed, including all adult patients with a diagnosis of HPS and HIV infection treated in the Infectious Diseases and Tropical Medicine Unit of the Hospital Universitario Insular, Las Palmas, Gran Canaria from June 1, 1998 to December 31, 2018.

Results. An analysis of this series of case reports of 15 patients showed a higher percentage of males than females, with a mean age of 42 years. With respect to the diagnostic criteria for HPS, presence of fever, cytopenias and hyperferritinemia were a constant in all patients. Clinical neurological manifestations were frequent and clinical respiratory signs and symptoms absent. HPS was confirmed in some patients who were not severely immune-depressed and had undetectable viral loads. Furthermore, 40% of cases were not receiving ART. The most frequent triggering causes of HPS were viral, especially HHV-8. In addition, two new HPS triggers were identified: *Blastocystis dermatitidis* and *Mycobacterium chelonae*.

Conclusion. Administration of treatment in HPS is arbitrary. This, together with the high mortality rate and the fact that it is underdiagnosed, indicates the importance of conducting future studies.

Key-words: Hemophagocytic syndrome, HIV, Acquired immunodeficiency syndrome, Antiretroviral therapy, Human herpes virus 8

Correspondence:
Cristina Carranza Rodríguez.
Unidad de Enfermedades Infecciosas y Medicina Tropical. Hospital Universitario Insular de Gran Canaria. Las Palmas de Gran Canaria.
Av. Marítima del Sur s/n 35016 Las Palmas de Gran Canaria. Spain.
Phone: +34 928441251 - Fax: +34 928441413
E-mail: cristinacarranzarodriguez@gmail.com

Síndrome hemofagocítico en pacientes infectados con el virus de la inmunodeficiencia humana: un estudio en 15 pacientes consecutivos

RESUMEN

Objetivos. El síndrome hemofagocítico (HPS) se caracteriza por varios datos clínicos y biológicos derivados de la hiperproducción de citocinas y proliferación celular. Los objetivos fueron evaluar las características epidemiológicas, etiológicas, clínicas y evolutivas de los pacientes con diagnóstico de síndrome hemofagocítico e infección por VIH así como su comparación con los datos bibliográficos.

Pacientes y métodos. Se realizó un estudio observacional descriptivo retrospectivo incluyendo todos los pacientes adultos con diagnóstico de HPS e infección por VIH, atendidos en la Unidad de Enfermedades Infecciosas y Medicina Tropical del Hospital Universitario Insular de Las Palmas de Gran Canaria desde 1 de junio 1998 hasta 31 de diciembre de 2018.

Resultados. Se analizó una serie de casos de 15 pacientes, observando un mayor porcentaje de varones con edad media de 42 años. En cuanto a los criterios de HPS se observa que la presencia de fiebre, citopenias e hiperferritinemia era constante en todos los pacientes. Las manifestaciones clínicas neurológicas fueron frecuentes y ausente la clínica respiratoria. Se confirmó HPS en algunos pacientes sin inmunodepresión grave y carga viral indetectable. Además, un 40% de los casos no recibían ART. Las causas desencadenantes de HPS más frecuentes fueron las víricas, especialmente HHV-8. Además, se identificaron dos nuevos agentes desencadenantes de HPS: *Blastocystis dermatitidis y Mycobacterium chelonae*

Conclusión. La administración de tratamiento en HPS es arbitraria lo que unido a su alta tasa de mortalidad e infradiagnóstico indican la importancia de continuar realizando estudios futuros.

Palabras clave: Síndrome hemofagocítico, VIH, Síndrome de inmunodeficiencia adquirida, Terapia antirretroviral, Herpesvirus humano 8.

INTRODUCTION

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis (HLH), is characterized by the association of various clinical (fever and splenomegaly) and biological (cytopenias, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and hemophagocytosis) features, whose common pathophysiological basis is the reduction of cytotoxic activity and hyperproduction of inflammatory cytokines [1-3].

HPS has traditionally been categorized as primary (or genetic) or secondary (or reactive) [1-3]. Primary forms appear in childhood and are usually the result of genetic alterations affecting the cytotoxic T lymphocyte granules and natural killer (NK) cells. Secondary forms can develop at any age and are associated with a number of triggering factors, indicated below. HPS, especially its secondary forms, present data that overlap with macrophage activation syndrome [4]

HPS is not a common process in adults (1 case per 800,000 people/year) with major geographical variations [2]. The highest number of cases has been reported in Japan (>500), followed by France (150-500), Spain, Italy and the United States (50-149) [2]. The three main groups of triggering agents of HPS in adults are infections, malignancies and autoimmune processes, with major differences depending on the geographical region. Among infections, the most frequently involved agents are viruses (particularly the Epstein Barr virus [EBV] and cytomegalovirus [CMV]), followed by bacteria (mainly *Mycobacterium tuberculosis*), protozoa (above all *Leishmania* spp.) and fungi (typically *Histoplasma* spp.) [2, 5-7]. The malignancies most frequently associated with HPS are lymphomas and related autoimmune disorders such as systemic lupus erythematosus (SLE) and adult Still's disease (ASD).

In the context of adult HPS, from the early years of HIV as an endemic infection, cases were reported of patients with HIV infection [8] who presented certain distinctive characteristics from the standpoint of etiology, progression and therapy [9-11]. Although there are some case series of patients and individual case (tables 1-2), the information is scarce, so that it is worth reviewing the experience in our center and comparing the characteristics in our series (clinical and microbiological features, and outcome) with those published by other authors.

METHODS

Study design. A retrospective descriptive observational analysis of a case series was performed.

Scope of study. To evaluate epidemiological, etiological, clinical and evolutionary characteristics of patients diagnosed with hemophagocytic syndrome and HIV infection.

Inclusion and exclusion criteria. Included were all adult patients (>14 years) with a diagnosis at discharge of HPS and HIV infection who were treated in the Infectious Diseases and Tropical Medicine Unit (IDTMU) of the Hospital Universitario Insular in Las Palmas, Gran Canaria. between June 1, 1998 and December 31, 2018. Henter's criteria were used for the HPS diagnosis (table 3) [12]. Mutations in genes compatible with a molecular diagnosis of HLH, increased levels of soluble CD25, and NK cell activity were not analyzed because of difficulties of access in our environment. Data were obtained after a detailed, comprehensive review of the clinical history of each patient. Excluded were patients who did not present HIV infection.

Methodology. For each patient, the following demographic data were recorded: age at the time of diagnosis, sex, geographic origin. Other essential data about HIV infection were also included, such as year of diagnosis, risk practices for acquiring HIV infection, medical history of interest, opportunistic infections prior to current HPS admission and co-infections. Other measures evaluated were: type of HIV, subtype and antiretroviral drug resistance, nadir CD4/µL count, viral load at the time of HIV infection diagnosis, antiretroviral therapy (ART) at admission, time in follow-up and compliance with ART. The time interval between diagnosis of HIV infection and the presence of HPS was also noted, indicating whether the HIV infection diagnosis was recent. For confirmation of the HPS diagnosis, the following variables were recorded: fever, presence of splenomegaly, cytopenias, triglycerides in blood, fibrinogen levels, presence of hyperferritinemia, bone marrow aspiration performed and observation of hemophagocytosis. Other data recorded included: time from onset of symptoms until HPS diagnosis, neurological symptoms, hepatomegaly, lymphadenopathies, basic analytic data (procalcitonin, erythrocyte sedimentation rate, C-reactive protein, total proteins in blood plasma, transaminases, LDH activity, urea, creatinine, natremia and Quick index). With respect to HIV, the following lymphocyte subpopulation values (total and percentage) were analyzed: B lymphocytes (CD19), T lymphocytes (CD3), CD4 and CD8 lymphocytes, CD4/CD8 ratio and NK cells (CD3-/CD56+). Finally, the etiology of HPS was evaluated, the specific therapy used to treat HPS, as well as the etiological therapy, the need for ICU admission, total days spent in hospital, and prognosis (survival after diagnosis of HPS, survival or mortality in the first 30 days).

Limitations. The present study has certain limitations. First, it is likely that some cases of HPS were not suspected or were mistaken for sepsis or immune reconstitution inflammatory syndrome. Second, various patients with a probable diagnosis (only 4 of Henter's criteria) were not included in the interests of methodological rigor (one was triggered by *Histoplasma capsulatum).* Third, the retrospective study design and the fact that it spanned a period of 20 years made it difficult to obtain some information, either to recover records or because of the limitation of additional tests available at any one time. Finally, therapeutic strategies were not clear and unambiguous, so that patient progress and prognosis may have been influenced by this heterogeneity.

Statistical analysis. Statistical analysis of the data obtained in the course of the present study was carried out using the SPSS statistical package, V22. Descriptive data were expressed as percentages (qualitative) or using measures of central tendency and dispersion (arithmetic mean and standard deviation, for normal distributions, or median and interquartile range for non-normal distributions).

Table 1 Case series of hemophagocytic syndrome in HIV-infected patients. General characteristics.

	Pellegrin [18]	Bourquelot [19]	Tiab [10]	Sailler [20]	Grateau [21]	Fardet [22]	Stebbing [23]	Fardet [24][a]	Townsend [25]	Lerolle [26][b]	Telles [27]
Year	1992	1993	1996	1997	1997	2003	2008	2010	2015	2015	2018
Nº patients	2	5	5	16	9	5	4	43	9	19	21
Age (years). Mean	31	33	35	-	46	-	40	-	42	-	36
Sex (M/F). Number	2/0	4/1	5/0	-	7/2	1/4	4/0	-	7/2	-	19/2
Origin. %	-	-	-	-	-	• Africa: 60% • Caribbean:20% • Europe:20%	• Africa: 50% • Europe: 50%	-	• North America: 78% • Central America:11% • Unknown: 11%	-	-
Fever	2 (100%)	5 (100%)	-	15 (94%)	7 (78%)	5 (100%)	4 (100%)	43 (100%)	7 (78%)	19 (100%)	21 (100%)
Splenomegaly	1 (50%)	4 (80%)[d]	-	-	3 (33%)	5 (100%)	3 (75%)	36 (84%)	9 (100%)	-	19 (90%)
Hemoglobin < 9 g/dL	1 (50%)	5 (100%)	-	-	6 (67%)	5 (100%)	4 (100%)	-	9 (100%)	-	-
Neutrophils < 1000/mL	0	3 (60%)	-	-	2 (22%)	2 (40%)	-	-	-	-	-
Platelets < 100000/mL	1 (50%)	5 (100%)	-	-	2 (22%)	3 (60%)	2 (50%)	-	9 (100%)	-	-
Triglyceridemia > 265 mg/dL	1 (50%)	3 (60%)	-	-	0	5 (100%)	3 (75%)	-	-	-	
Fibrinogen levels< 1,5 g/L	0	2 (40%)	-	-	-	3 (60%)	0	-	-	-	
Hemophagocytosis	2 (100%)	5 (100%)	5 (100%)	-	9 (100%)	5 (100%	4 (100%)	-	7 (78%)	-	
Elevated ferritin	1 (50%)	2 (40%)	-	-	1 (11%)	5 (100%)	4 (100%)	-	8 (89%)	-	21 (100%)
Respiratory symptoms	1 (50%)	4 (80%)	-	-	-	5 (100%)	-	-	-	-	-
Neurological symptoms	-	2 (40%)	-	-	4 (44%)	2 (40%)	-	-	-	-	-
Hepatomegaly	2 (100%)	4 (80%)	-	-	8 (89%)	3 (60%)	4 (100%)	-	-	-	-
Lymphadenopathy	1 (50%)	4 (80%)	-	-	4 (44%)	5 (100%)	4 (100%)	-	-	-	8 (38%)
Disseminated intravascular coagulation	-	2 (40%)	-	-	4 (44%)	-	-	-	-	-	-
Hypertransaminasemia	0	3 (60%)	-	-	7 (78%)	-	-	-	-	-	-
Risk practices for HIV infection (%)	MSM:100%	MSM: 80% IDU: 20%	-	-	MSM: 56% HTX : 33% IDU:11%	MSM: 20% HTX: 80%	-	-	-	-	-
Duration of HIV infection in months (mean and interval)	-[c]	-	65 (36-120)	-	-	-	-	48 (0-240)	-	-	96
Plasma HIV RNA at diagnosis of HPS (copies/mL). Interval	-	-	-	-	-	50-25.000	50-500.000	20-2.800.000	0-10.000.000	50- 316.000	-
ART admission	1 (50%)	-	-	-	-	-	2 (50%)	25 (58%)	4 (44%)	-	-
CD4/µL (mean and interval)	78[e]	305 (11-818)	36 (0-70)	30 (6-475)	16 (0-64)	200 (165-234)	247 (71-492)	104 (2-387)	13 (1-50)	21 (16-101)	82
CD8/µL (mean and interval)	-	1053 (200-3500)	-	-	-	-	-	391 (33-2618)	-	-	-
Specific treatment for HPS	-	Corticosteroids Splenectomy	-	-	-	Etoposide Splenectomy	Etoposide Splenectomy Rituximab	-	Corticosteroids Intravenous immunoglobulin	-	-
Mortality in the first 30 days	1 (50%)	4 (80%)	3 (60%)	8 (50%)	9 (100%)	2 (40%)	0	-	5 (56%)	-	-
Survival (days) in patients who died (mean and interval)	43	60-150	30 (10-50)	-	198 (60-360)	-	-	-	54 (9-221)	-	-

The data has been expressed in number of patients (n) and frequencies (%)

[a]Only the data referring to patients with confirmed HPS diagnosis are provided (n: 43 patients). [b]Only the data referring to patients with HPS and HIV infection are provided (no: 19 patients). [c]Primary infection [d]One patient was splenectomized. [e]Value obtained from a single patient. MSM: Men who have sex with men; HTX: Heterosexual contact; IDU: Injecting Drug Users.

Table 2 **Characteristics of single cases of hemophagocytic syndrome in HIV-infected patients.**

Group	Subgroup	Author	References	Year	HIV-infected admission	Age	Sex	Origin	CD4/µL	ART	Treatment *	Mortality
Virus	HIV	Gotoh	Br J Haematol. 2001;112:1090	2001	No	35	Male	-	100	Yes	No	No
		Alliot	Hematology. 2001;5:4758	2001	No	51	Male	North Africa	42	Yes	No	Yes
		Castilleti	Clin Infect Dis. 2004;38:17923	2004	Yes (acute HIV infection)	27	Male	Italy	138	No	No	No
		Chen	Int J Hematol. 2003;78:4502	2004	Yes	18	Male		590	No	IVIG	No
		Adachi	Intern Med. 2013;52: 62932	2013	Yes (acute HIV infection)	48	Male	Japan	98	No	No	No
		Ferraz	BMC Infect Dis. 2016;16:619	2016	Yes (acute HIV infection)	27	Female		13	No	Co	No
		Usman	Int J STD AIDS. 2016;27:4113	2016	Yes	24	Male		331	No	Co	No
		Manji	BMC Infect Dis. 2017;17:633	2017	Yes (acute HIV infection)		Male		137	No	No	No
		Fitzgerald	Case Rep Crit Care. 2017;2017:8630609	2017	No	30	Female	Caucasian	4	No	Co	No
	EBV	Albretch	Arch Pathol Lab Med. 1997;121:8538	1997	No	26	Male		70	No	Co + S+ IVIG	Yes
		Wong	Arch Intern Med. 2007;167:19013	2007	No	46	Male	China	204	Yes	Et +IVIG	Yes
		Flew	Int J STD AIDS. 2010;21:6013	2010	No	46	Male	Africa	314	Yes	Co	No
		Thoden	J Infect. 2012;64:1102	2012	No	70	Male		284	Yes	Co + Et + Ri	Yes
		Khagi	Clin Adv Hematol Oncol. 2012;10(4):260-2	2012	No	58	Male		40	Yes	Co + Ri	Yes
		Sculier	J Int AIDS Soc. 2014;17(4 Suppl 3):19650	2014	No	29	Male		438	Yes	Co + Et + Ri	
		Koizumi	J Clin Immunol. 2018;38:478483	2018	No	53	Male	Japan	7	Yes	No	Yes
		Shaikh	BMJ Case Rep. 2018;2018. pii: bcr2018224424	2018	Yes	33	Male		42	No	Co	No
	HHV-8	Yates	AIDS Read. 2007;17:5968	2007	No	45	Male		64	Yes	Cf + Co + S+ Ri	Yes
		Seliem	Am J Surg Pathol. 2007;31:143945	2007	No	45	Male		64	Yes	Cf + S + Ri	Yes
		Ramon	Acta Clin Belg. 2010;65:2768	2010	No	40	Male	Congo	90	Yes	No	No
		Shah	Clin Lymphoma Myeloma Leuk. 2014;14:e15760	2014	No	33	Male		60	No	Co + Ri	No
		Zorzou	Hematol Rep. 2016;8:6581	2016	No	40	Male		39	No	Co + IVIG	No
		Bangaru	BMJ Case Rep. 2017;2017. pii: bcr2017222382	2017	No	45	Male		17	Yes	Co	Yes
	CMV	Ohkuma	BMJ Case Rep. 2013;2013. pii: bcr2013200983	2013	No	29	Male		156	No	No	No
	Parvovirus	Alliot	Eur J Clin Microbiol Infect Dis. 2001;20:435	2001	No	34	Male	South America	34	Yes	No	Yes
Fungi	*Histoplasma* spp.	Guiot	Diagn Microbiol Infect Dis. 2007;57:42933	2007	Yes	43	Male	Puerto Rico	66	No	No	No
		Sánchez	AIDS Read. 2007;17:4969	2007	Yes	61	Male	Mexico	4	No	No	No
		De Lavaissière	J Infect. 2009;58:2457	2009	No	33	Male	Guyana	13	No	IVIG	No
		Subedee	J Int Assoc Provid AIDS Care. 2015;14:3917	2015	No	42	Female	USA	40	No	No	No
		Castelli	Open Forum Infect Dis. 2015;2:ofv140	2015	No	32	Male	Mexico	3	No	Co + Et	No
		Nieto	Biomedica. 2016;36:914	2016	No	33	Male	-	16	No	No	No
		Gómez	Myco-pathologia. 2017;182:767770	2017	Yes	23	Male	Venezuela	7	Yes	Co + IVIG	No
		Ocon	BMJ Case Rep. 2017;2017. pii: bcr2017221264	2017	No	49	Male	Guyana	7	No	A + Co + IVIG	No
		Loganantharaj	Int J STD AIDS.2018;29: 925928	2018	No	46	Male	D. Republic	54	No	No	No
		Zanotti	Mediterr J Hematol Infect Dis. 2018;10:e2018040	2018	Yes	19	Female	Ivory Coast	19	No	Co	No
		Tsuboi	Am J Trop Med Hyg. 2019;100:365367	2019	Yes	56	Female	Venezuela	13	No	No	No
	Penicillium spp.	Pei	Am J Trop Med Hyg. 2008;78:113	2008	Yes	34	Male		119	No	Co + IVIG	No
	Candida spp.	Bathia	Clin Infect Dis. 2003;37:e1616	2003	No	38	Female		65	Yes	Co + IVIG	Yes
	Aspergillus spp.	Delcroix	Rev Med Liege. 2006;61:7138	2006	Yes	31	Female	Yugoslavia		No	Co + IVIG	Yes
Protozoan parasites	*Leishmania* spp.	Patel	J Int Assoc Physicians AIDS Care (Chic). 2009;8:21720	2009	No	35	Male		234	No	No	No
	Toxoplasma spp.	Guillaume	Eur J Intern Med. 2006;17:5034	2006	No	33	Male	Rwanda	6	Yes	Co + IVIG	Yes
Bacteria	*Bartonella* spp.	Le Joncour	Clin Infect Dis. 2016;62:8046	2016	Yes	69	Male	Mali	20	No	Et	No
	Ehrlichia spp.	Naqash	Ann Hematol. 2017;96: 17551758	2017	No	66	Female	Africa	0	Yes	Co + Et	Yes
Mycobacteria	*M. xenopi*	Nuño	Enferm Infecc Microbiol Clin. 2000;18:967	2000	No	25	Female	-	9	No	Co	Yes

*A: Anakinra; Cf: Cyclophosphamide; Co: Corticosteroids; S: Splenectomy; Et: Etoposide; IVIG: Intravenous immunoglobulin; Ri: Rituximab

Table 3 Diagnostic criteria of hemophagocytic syndrome*

1. Fever > 38.5º C
2. Splenomegaly
3. Peripheral blood cytopenia, along with at least two of the following:
   - Hemoglobin < 9g/dL
   - Neutrophils < 1,000/µL
   - Platelets < 100,000/µL
4. Hypertriglyceridemia > 265 mg/dl, or fibrinogen levels < 1.5 g/L
5. Hemophagocytosis (bone marrow, lymph nodes or spleen) without evidence of malignancy
6. Low or absent NK cell activity
7. Ferritin levels > 500 ng/mL
8. Elevated soluble CD25 levels (> 2,400 U/mL)

*** If 5 of the 8 criteria listed are fulfilled.**

Table 4 Clinical characteristics and laboratory findings of hemophagocytic syndrome

DIAGNOSTIC CRITERIA OF HPS	n (%)	Range
Fever	15 (100)	
Splenomegaly	11 (73.3)	
Cytopenias	15 (100)	
(along with at least two of the following):		
Hemoglobin <9 g/dL	14 (93.3)	5.6-8.7
Neutrophils <1,000/mL	8 (53.3)	0-600
Platelets <100,000/mL	15 (100)	2,000-9,200
Triglycerides >265 mg/dL	11 (73.3)	283-900
Hemophagocytosis	11 (73.3)	
Elevated ferritin levels > 500 ng/mL	15 (100)	550-10,105
OTHER CHARACTERISTICS	**n (%)**	**Range**
Neurological symptoms	5 (33.3)	
Hepatomegaly	6 (40)	
Lymphadenopathy	7 (46.6)	
Procalcitonin > 0.5 ng/mL	7 (46.6)	1.5-75.7
Erythrocyte sedimentation rate >12 mm	11 (73.3)	20-132
C-reactive protein >0.5 mg/dL	14 (93.3)	0.6-30.6
Total protein < 6.4 g/dL	11 (73.3)	3.6-5.8
Aspartate aminotransferase >37 U/L	8 (53.3)	45-143
Alanine aminotransferase>45 U/L	5 (33.3)	47-195
Gamma-glutamyl transpeptidase > 55 U/L	10 (66.6)	75-1,112
Lactate dehydrogenase >248 U/L	10 (66.6)	256-5,984
Urea >43 mg/dL	10 (66.6)	60-512
Creatinine > 1.17 mg/dL	6 (40)	1.2-4.8
Serum sodium < 135 mM/L	9 (60)	127-134
Indice Quick <70%	8 (53.3)	44-66

The data has been expressed in number of patients (n) and frequencies (%)

RESULTS

Clinical cohort. Of the 3,066 HIV-infected cases followed between June 1, 1998 and December 31, 2018, 15 fulfilled the criteria for HPS. The distribution of cases according to year was: 1 patient in each of the following years: 2003, 2006, 2010, 2012, 2014, 2015 and 2018; 2 patients in 2011 and 2016, and 4 patients in 2013.

Epidemiological characteristics. 11 of the 15 patients were male and the mean age was 42 years (range 20-67). Ten patients were European (7 from Spain) and the rest came from sub-Saharan Africa (4) and the Caribbean (1).

Clinical characteristics and laboratory findings. Table 4 shows the diagnostic criteria for HPS present in the study group and other clinical and biological data of patients included in this series. Table 5 indicates characteristics related to HIV infection in this group of patients. The study of blood lymphocyte subpopulations is shown in table 6.

Etiological triggers. In 8 patients, the trigger was HHV type 8 (isolated in 5 cases and associated with *P. jirovecii* in two patients and Epstein Barr virus in another). The rest of the cases corresponded to other viruses (Cytomegalovirus in 2 cases), mycobacteria (*M. tuberculosis* and *M. chelonae*), fungi (*Blastocystis dermatitidis*) and neoplasms (Hodgkin's disease). No other triggering agent was found in one patient.

Treatment and follow-up. The main aspects of patient management and patient outcomes are shown in (tables 7-8).

DISCUSSION

Thanks to the efficacy of ART, a large number of patients with HIV infection currently remain asymptomatic during the course of the illness. In another group of patients, principally those with late diagnosis (starting CD4 count of <350 cells/µL), infections develop (both opportunistic and not) that can be controlled with specific treatment. There is however another group of patients with HIV infection whose clinical manifestations are serious or very serious. The three main situations that lead to this picture are septic hemophagocytic syndrome [8-11], shock [13] and immune reconstitution inflammatory syndrome [14]. Nevertheless, the boundaries between them are not always clear cut, and situations may arise in which various of the diagnostic criteria coexist [15-17].

The characteristics of the patients in our series present certain similarities to and also various differences from those described in the literature, both in case series and isolated communications.

The incidence of HPS in our series of patients was 5/1,000 HIV-infected persons. There are no equivalent data in the lit-

Table 5 **Clinical characteristics and laboratory findings of HIV infection.**

Risk practices for HIV infection	MSM: 7 (46.6) HTX: 7 (46.6) IDU: 1 (6.6)
Coinfection	No: 11 (73.3) Yes: 3 (20) (Chronic hepatitis B) Unknown: 1 (6.6)
Type of HIV	Type 1: 11 (73.3) Type 2: 1 (6.6) Unknown: 3 (20)
Subtype of HIV-1	B: 8 (72.7) Circulating Recombinant Forms: 3 (27)
Genotypic resistance test	Yes: 11 (73.3) Unknown: 4 (26.6)
Nadir CD4/ µL (mean and standard deviation)	303 (409)
Plasma HIV RNA (copies/mL) (median and range)	411,000 (9,989,200)
HIV recent diagnosis	7 (46.6)*
Duration of HIV infection in months (mean and standard deviation)	27 (38)
Plasma HIV RNA at diagnosis of HPS <50 copies	3 (20)
Plasma HIV RNA at diagnosis of HPS (copies/mL) (median and range)	20,670 (7,299,999)
ART at admission	9 (60)
ART schedule	
NRTIs	9 (100)
NNRTIs	5 (55)
PIs	4 (44)
INSTIs	2 (22)
Duration of ART in days (mean and standard deviation)	84 (90)

The data has been expressed in number of patients (n) and frequencies (%)
***One patient had acute HIV infection.**
N and %: Number of patients (n) and frequencies (%), MSM: Men who have sex with men; HTX: Heterosexual contact; IDU: Injecting Drug Users; NRTIs: Nucleoside reverse transcriptase inhibitors; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; PIs: Protease inhibitors; INSTIs: Integrase inhibitors.

erature to make comparisons. The number of patients included in the different case series ranges between 2 and 43, with the majority of studies being single-center [18-27].

In our series, the ratio of males to females was 2.75:1 and the mean age was 42 years, similar to those indicated in the literature, although males were less predominant (4:1 overall). The patients studied were of very diverse origins, with a third being of non-European origin (sub-Saharan Africa and the Caribbean), which is of importance primarily for type of triggering factor.

In our study, all the patients presented fever, cytopenias and elevated ferritin levels. Fever is one of the characteristic manifestations of HPS and appears in 100% of patients in most of the series [18, 19, 22-24, 26, 27], and at least 75% of patients in others [20, 21, 25]. The presence of cytopenia (especially anemia and thrombocytopenia) is usual in the published series, although the percentage of patients in which it is reported ranges from 22 to 100% [18, 19, 21-23, 25]. Elevated serum ferritin is a distinctive marker with a negative prognostic value in HPS [27]. The results in different series are variable, principally because this measure was not evaluated in all the patients included. Whilst it is reasonable to assume, given its name (hemophagocytic syndrome), that it is present in all patients by demonstrating its presence in bone marrow, lymph nodes, liver and spleen, it is possible to diagnose HPS without histologic evidence of hemophagocytosis. In our series, 73% of patients presented splenomegaly, and in other series, it varied from 0 to 100% [18, 19, 21-25, 27]. Three quarters of patients included in this study presented hypertriglyceridemia, which is similar to figures indicated in the literature [18, 19, 22, 23]. Measurements of fibrinogen, NK cell activity and soluble CD25 receptor levels are unusual in the bibliography.

In our series, the most frequently encountered clinical manifestations of HPS not included in its definition were neurological (33% of patients). Respiratory manifestations were not observed. In the literature, the frequency of neurological alterations is similar to that found in our study [19, 21, 22], whereas respiratory affectation varies considerably (0-100%) [18, 19, 22]. The presence of hepatomegaly, lymphadenopathies and liver function test alterations was observed in 40-60% of patients studied, with similar values to those found in other series [18, 19, 21-23, 27].

There was no single pattern of HIV infection in our patients. Consequently, the risk practices for acquiring HIV infection were different and probably reflected local epidemiological patterns [18, 19, 22, 23]. In general, severe immunosuppression (<200 CD4/ µL) and a detectable viral load at the time of diagnosis were common, although in our series and also in the literature, some cases of HPS presented higher CD4 values and undetectable viral loads [18-27]. Approximately half the patients were not in receipt of antiretroviral treatment, although the remainder were being treated [18, 23-25]. The interval between diagnosis of HIV infection and HPS varied considerably (0-240 days), which has also been described in the literature [10, 24, 27]. Finally, it should be mentioned that one of the patients in our series presented HPS at the same time as primary HIV infection. This has been described in the literature and is generally associated with a better prognosis.

The analysis of factors that trigger HPS in patients with HIV infection is complex for a number of reasons: *i)* The diagnostic methodology varies depending on the date and the

scope of the study, and consequently, in certain patients, the precipitating factor appears as undetermined; *ii)* In quite a few cases, categorizing the trigger as malignancy or infection is arbitrary. This is particularly common in EBV infections and Hodgkin's disease, and also in those due to HHV-8 and a number of associated malignancies (Kaposi's sarcoma, Castleman's disease); *iii)* Some causative agents (e.g. *Histoplasma* spp.) have a restricted geographic distribution, and *iv)* Frequently, two or more triggering agents are associated together in the same patient. Bearing these considerations in mind, several conclusions can be drawn from the analysis of triggering factors in patients included in our study: *i)* In three patients, two or more triggering factors were identified; *ii)* The most common *triggers* were infections, particularly, viral infections; *iii)* Apart from HIV itself, the most frequently involved virus in our series was *HHV-8*; *iv)* Among fungi, three triggering agents were found in our series: *Pneumocystis jirovecii*, *Candida albicans* and *B. dermatitidis*. In this context, it should be pointed out that we have not found any references to the participation of *B. dermatitidis* in triggering HPS; v) The two mycobacteria related to HPS in our series were *M. tuberculosis* and *M. chelonae*. We also point out that we have not found bibliography on the role of *M. chelonae* as a trigger of HPS.

Table 6 Blood lymphoid subsets*

CD3/ µL	648 (50-1656)
CD4/µL	1332 (3-996)
CD4/ µL <500	14 (93%)
CD4/ µL <200	12 (80%)
CD8/µL	475 (44-1056)
CD8/µL low	3 (20%)
CD8/µL normal	6 (40%)
CD8/µL high	3 (20%)
CD4/CD8 ratio	0.27 (0-1.7)
CD19/µL	146 (17-530)
CD19/µL low	6 (40%)
CD19/µL normal	5 (33%)
CD19/µL high	1 (7%)
CD3-/CD56 +/µL	62 (5-219)

*Subset data are expressed as mean and range.

Table 7 Treatment of hemophagocytic syndrome

Specific treatment for HPS	15 (100)
Corticosteroids	6 (40)
Corticosteroids + etoposide	3 (20)
Corticosteroids + intravenous immunoglobulin	2 (13.3)
Corticosteroids + cyclosporine	1 (6.6)
Corticosteroids + liposomal adriamycin	1 (6.6)
Corticosteroids + doxorubicin	1 (6.6)
Corticosteroids + cyclophosphamide	1 (6.6)

The data has been expressed in number of patients (n) and frequencies (%)

Table 8 Follow-up of hemophagocytic syndrome

Duration of symptoms until confirmation of HPS, in days (mean and standard deviation)	32 (37.7)
Transfer to intensive care unit *	7 (46.6)
Length of hospital stay in days (mean and standard deviation)	34 (21.3)
Survival after diagnosis of HPS in patients who died, in days (mean and standard deviation)	14.7 (10.4)
Mortality in the first 30 days after diagnosis of HPS *	11 (73.3)

*The data has been expressed in number of patients (n) and frequencies (%)

The three main pillars of treatment of HPS are [2, 12]: etiological, pathogenic and symptomatic. In entities where there is a causal treatment, the elimination or control of the triggering agent helps reduce the inflammatory stimulus. In this context, the limited therapeutic options in EBV and HHV-8 infections determine a worse prognosis. Pathogenic (sometimes called specific) treatment includes measures aimed at controlling the inflammatory response. The so-called HLH-2004 protocol (dexamethasone, cyclosporine, etoposide) [28] constitutes the accepted basis for treatment, although it is rare in practice, both in our series and in other published cases. Other measures employed, alone or in combination, included intravenous immunoglobulins, cyclophosphamide or rituximab. Splenectomy may have a role in cases of splenomegaly and/or hypersplenism. In the presence of neurological symptoms, a neuroimaging scan and lumbar puncture are mandatory to identify the mechanism and, if there is affectation, prednisone and intrathecal methotrexate should be used. In addition, the beneficial role of "personalized therapy" should be mentioned, as well as the use of anakinra/tocilizumab for the treatment of HPS, although more studies are necessary [4]. Finally, symptomatic or support treatment includes platelet transfusion, fresh frozen plasma, transfusion of red blood cells and granulocyte colony-stimulating factors (G-CSF) for cases of severe neutropenia (although in isolated cases, administration of GSFs has been associated with exacerbation of HPS).

Thirty-day mortality due to HPS in our series was 75%, a figure intermediate between 40 and 100% described in other series [10, 18-22, 25]. Although it is impossible to be certain, various factors can influence this outcome (such as triggering factor, control of HIV infection, basal state of the immune system), which means that hospital stays are longer, as well as admission to ICU.

In conclusion, HPS is not so infrequent among HIV patients and should be suspected in the presence of fever and cytopenias. There is no characteristic onset profile and it can appear at different times, with different degrees of immune-suppression, in the presence or absence of ART. HIV infection and HHV-8 are the main triggers and other causative agents such as *B. dermatitidis* and *M. chelonae* also play a role in this context. Treatment is ill-defined, and is one of the reasons for poor patient outcomes.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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