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Secondary Hemophagocytic Syndrome: Differences between the Etiologies Autoimmunes and Hematological Malignancies Subgroup

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Abstract

Background: Hemophagocytic Syndrome (HPS) is an uncommon disorder with high mortality. HPS is reported to be usually related to some underlying conditions; autoimmune (AI) and hematological malignancies (HM) are two main underlying conditions. Here, we attempted to determine the clinical characteristics/ differences of HPS according to underlying conditions; AI vs. HM, based on our experience.

Methods: We studied all adult patients with HPS diagnosed at our institution from 2005 to 2019. Demographic, clinical characteristics, laboratory findings, underlying disorders, hospital stay and prognosis variables were examined and related to the underlying conditions.

Results: A total of 30 patients (median age of 55 years and male/female of 14/16) met the inclusion criteria which we analyzed: HM: 12 (40%), AI: 10 (33%), and others: 8 (27%). HM group, compared with AI group, showed a significantly longer length hospital stay (HM vs. AI: 61.5 vs. 30.5 (median)), more severe thrombocytopenia, leukocytopenias, and neutropenia, and importantly, higher mortality (with overall mortality and HM-related HPS-mortality being 43.3% and 66.7%, respectively). Contrarily, HM group, compared with AI group, showed less severe liver abnormalities (AST; 106 vs. 457 (median); ALT; 109 vs. 457 (median)).

Conclusion: The HM subgroup presented a greater mortality and a higher number and severe cytopenias but lower elevation of transaminases.

Keywords: Hemophagocytic syndrome; Hemophagocytic Lymphohistiocytosis; Autoimmune diseases; Hematological malignancies

Abbreviations: AP: Alkaline Phosphatase; AI: Autoimmune; ALT: Alanine Aminotransferase; ASD: Adult Still's Disease (ASD); AST: Aspartate Aminotransferase; BT: Total Bilirubin; BM: Bone Marrow; CMV: *Cytomegalovirus*; CSA: Cyclosporine A; EBV: *Epstein Barr*; Fb: Fibrinogen; Fer: Ferritin; GC: Glucocorticoids; GGT: Gamma-Glutamyl Transferase; GM: Glioblastoma Multiforme; GSR: Globular Sedimentation Rate; Hb: Hemoglobin; HC: Hemophagocytic Cells; HIV: Human Immunodeficiency Virus; HLH: Hemophagocytic Lymphohistiocytosis; HM: Hematological Malignancies; HPS: Hemophagocytic Syndrome; IL: interleukins; LDH: Lactate Dehydrogenase; INR: International Normalized Ratio; JIA: Juvenile Idiopathic Arthritis; Leu: Leukocytes; MAS: Macrophage Activation Syndrome; MST: Malignant Solid Tumors; Neu: Neutrophils; NK: Natural Killer; Pt: Platelets; SG: Subgroup; SLE: Systemic Lupus Erythematosus; TP: Total Protein; Tg: Triglycerides

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Introduction

Hemophagocytic Lymphohistiocytosis (HLH), also called Hemophagocytic Syndrome (HPS), is characterized by a clinical, inflammatory, acute and severe syndrome with high mortality without early treatment. To refer to this entity, in this study, we will use exclusively the acronym "HPS". The first cases of HPS in children and adults were published in 1952 and 1979 respectively [1,2]. The incidence of HPS is unknown, but in one hospital of Sweden the incidence was 0.12/100,000 patient/year for familial HPS and 0.36/100,000 patient/year for HPS associated with malignancy [3]. The HPS is expressed by a proliferation and activation of T cells and macrophages, producing a hypersecretion of cytokines such as interferon-gamma, tumor necrosis factor-alpha, interleukins (IL) 1, IL-6, IL-10, IL-12, IL-18 and macrophage colony-stimulating factor [4,5]. The HPS has been classified into 2 groups: primary or genetic, and secondary or acquired. Primary, usually called Familial Hemophagocytic Lymphohistiocytosis, is a rare disease that commonly affects infants and children [5,6]. It is inherited in an autosomal recessive manner, and 5 subtypes are known [7]. The secondary form is mainly associated with hematological malignancies (HM) such as lymphomas or leukemias, and autoimmune (AI) diseases such as Systemic Lupus Erythematosus (SLE) and Child or Adult Still's Disease (ASD). The HPS secondary to AI disease is called Macrophage Activation Syndrome (MAS). Less frequently, HPS can be associated with infections, either as etiology of HPS or as a trigger over AI or HM diseases. Others less frequent causes of secondary HPS are transplants, malignant solid tumors (MST) due to the production of cytokines by itself or under chemotherapy [4,8]. The most common manifestations are fever, hepatosplenomegaly, altered liver and coagulation function, hypertriglyceridemia, cytopenias, hyperferritinemia and the histological presence of hemophagocytic cells (HC) in bone marrow (BM), spleen or lymph nodes [4]. We are currently facing a rare entity with a high mortality rate. The diagnosis is complex and can affect different profiles of patients treated by various medical specialists, so having a basic knowledge of this entity, knowing the various clinical manifestations, laboratory findings, diagnostic criteria and differential diagnostic procedures can favor a timely approach. Autoimmune disorders and malignancy are two important underlying causes of HPS; however, clinical characteristics of HPS according to the underlying disorders are not well determined. Although there have been important advances in recent years, but are insufficient. The most relevant advances are the recommendations made by the American Society of Hematology and a scoring system to predict the probability of diagnosing HPS made by the American College of Rheumatology, published in 2019 and 2014 respectively [8,9]. The present study was an effort to determine this issue based on our own experience describing demographic, clinical manifestation, laboratory findings and prognostic characteristics according to underlying conditions (AI vs. HM).

Materials and Methods

We retrospectively analyzed a cohort of 30 adult patients over 17 years old with diagnosis of HPS during their admission in

the Donostia University Hospital between December 2005 and October 2019, based on the HLH-2004 criteria from the Histiocyte Society, or presented HC in the BM biopsy, or who had HPS diagnosis in the hospital discharge report. The diagnosis based on the HLH-2004 criteria required to meet at least five of the following criteria: 1 - prolonged fever (a temperature ≥ 38.5 °C for ≥ 7 days), 2 - splenomegaly (the costal margin exceeded 3 cm), 3 - cytopenia involving in at least two lineages of peripheral blood (neutrophil count $< 1.0 \times 10^9/L$, hemoglobin < 90 g/L or platelet $< 100 \times 10^9/L$), 4 - hypertriglyceridemia (fasting triglycerides ≥ 3 mmol/L) and/or hypo-fibrinogenemia (fibrinogen ≤ 1.5 g/L), 5 - hemophagocytosis in bone marrow, spleen or lymph nodes, 6 - low or absent NK cells activity, 7 - serum ferritin ≥ 500 $\mu\text{g/L}$ and 8 - soluble CD25 (soluble interleukin-2 receptor) ≥ 2400 IU/ml [4]. However, the tests for soluble CD25 levels and NK cell activity were not available in our institution. The study was approved by the ethics committee and given the retrospective nature of this study; informed consent was not obtained. However, after data collection, patients were anonymized. In addition, the study followed the guidelines of the Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights, which repealed the Organic Law 15/1999, of December 5, on the Protection of Personal Data in Spain. The demographics, clinical characteristics (etiology, underlying disorders, diagnostic criteria and hospital stay), relevant laboratory findings (complete blood count, biochemical profile, coagulation, ferritin and others), treatments and prognosis were extracted from the electronic medical record; examined and related to the underlying conditions. Data analysis was performed using SPSS 21.0 software. Categorical variables are shown as frequencies and percentages (n, %). Continuous variables are presented with the mean ($\bar{x} \pm s$) or median [interquartile rank (IQR)] according to the degree of normality of the variable distribution. Non-parametric tests were used for most quantitative variables because of the abnormal distribution. The analysis of inter-group differences (qualitative variables) was performed using the Fisher's test. The Kruskal Wallis' test was used in the analysis between continuous quantitative variables and the polynomial categorical variable "etiology". The analysis between continuous quantitative variables and the analysis of the 2 subgroups (AI and HM) the Mann-Whitney U test were used.

Results

Patient characteristics, etiologies, underlying disorders and treatments

Thirty patients with diagnosis of HPS were included [16 females; mean age, 55.5 years (± 18.3 years)]. Patients were distributed in 5 subgroups according to the etiology: AI, HM, MST, Infectious and HPS without defined etiology (**Table 1**). The debut of the primary etiology coincided with the diagnosis of HPS in 12 (57%) patients, and it was predominant in AI subgroup (60%). The coincidence of an infectious disease with the diagnosis of HPS was observed in 10 (33.3%) patients, 2 were considered to be the primary etiology of HPS and 8 were considered to be the trigger of HPS [AI: 5 (2 CMV, 2 probably viral respiratory infections and 1 bacterial infection) and HM: 3 (2 EBV and 1 bacterial infection)]. In 2 patients with

Table 1 Etiologies and underlying disorders during admission of patients with Hemophagocytic syndrome.

Etiological subgroups	N	Debut of etiology	Infectious trigger	Mortality
Autoimmune diseases	n=10	n=6	n=5	n=1
Systemic Lupus Erythematosus	5	3	3	1
Adult Still's Disease	3	2	1	0
Rheumatoid arthritis	1	0	1	0
IgG4 Sclerosing Disease	1	1	0	0
Hematological Malignancies Diseases	n=12	n=4	n=3	n=8*
Non-Hodgkin's Lymphoma	3	0	0	1
Myelodysplastic syndrome	3	1	1	2
Acute leukemia	3	1	1	3
Lymphoma extranodal NK cell	1	1	1	1
Multiple Myeloma	1	0	0	0
Probably lymphoproliferative disease	1	1	0	1
Infectious diseases	n=2	n=2	n=2	n=1
<i>Pneumocystis jirovecii</i> in patient with HIV	1	1	1	1
Gastroenteritis by <i>Campylobacter jejuni</i>	1	1	1	0
Malignant Solid tumor disease	n=1	n=0	n=0	n=0
Glioblastoma multiforme in treatment with temozolomide	1	0	0	0
HPS without defined etiology	n=5	5	0	3

HIV: Human Immunodeficiency Virus, NK: Natural Killer

*p=0.029

acute leukemia the allogeneic transplantation was associated as the trigger of HPS. In one patient with myelodysplastic syndrome the HPS was associated with the development of graft-versus-host disease. Finally, in one patient with glioblastoma multiforme (GM) the chemotherapy (temozolomide) was considered the trigger event. Five patients were included in the HPS without defined etiology subgroup. Three died from HPS during hospital admission. The other 2 cases continue to be followed by the Hematology Service without finding an etiological cause of the HPS (1523 and 1573 days of follow-up after discharge). Only one patient presented a reactivation of HPS (36 days after discharge). The diagnosis of first hospital admission was HPS secondary to autoimmune hemolytic anemia due to hot antibodies. At the second admission, when reactivation occurred, the diagnosis was HPS secondary to a probable lymphoproliferative disease, unconfirmed by histology or autopsy. Glucocorticoids (GC) were used in all patients and cyclosporine A (CSA) in 50% of patients (Table 2). In addition, supportive treatment such as transfusions of red blood cells and/or platelets were used almost in all patients. Broad-spectrum antibiotics were used in all patients except in 2 (Multiple Myeloma and HPS without defined etiology).

Clinical characteristics and laboratory findings of all subgroups

All patients presented high fever. Significant differences were observed in age, mortality, leukocytes, neutrophils, platelets,

transaminases and total proteins. Age at diagnosis of HPS was lower in AI [40 (26.5 - 56.3)] and Infection subgroups [45.5 (30 - 61); p 0.001]. The HM subgroup had severe cytopenias [platelets 4500 (650 - 15,750; p 0.009), leukocytes 2050 (20 - 728; p 0.0001) and neutrophils 0 (0 - 280; p 0.002)]. The AI subgroup had a highest elevation of AST [457 (289 - 1140; p 0.026). Tables 3 and 4 show the comparison of the demographic, clinical characteristics, laboratory findings, underlying disorders and mortality variables during hospital admission of the 5 subgroups.

Clinical characteristics and laboratory findings of the AI and HM subgroups

Compared the two most frequent subgroups, significant differences were observed according to the age, mortality, leukocytes, neutrophils, platelets, transaminases, total proteins, global hospital stay and hospital stay previous to the diagnosis by BM biopsy. The HM subgroup presented a higher number and more severe cytopenias (Figure 1) (Tables 3 and 4). The AI subgroup presented more severe liver abnormalities, such as higher elevation of AST [AI: 457 (289 - 1140) and HM: 106 (71 - 193); p 0.003] and ALT [AI: 432 (174 - 599) and HM: 109 (54 - 263); p 0.017]. The HM subgroup had a higher global hospital stay [HM: 61.5 days (29.3 - 93.3) and AI: 30.5 days (9.5 - 53.3); p 0.036] and hospital stay previous to the diagnosis by BM biopsy [HM: 26 days (10 - 39) and AI: 10 days (5 - 16.5); p 0.038].

Table 2 Treatments used during hospital admission in patients with hemophagocytic syndrome according to etiological subgroup.

Variables	AI	HM	Infectious	MST	HPS without defined etiology
n	10	12	2	1	5
Glucocorticoids	10 (100%)	12 (100%)	2 (100%)	1 (100%)	3 (60%)
Immunoglobulins	4 (40%)	4 (30%)	2 (100%)	1 (100%)	0
Cyclosporine A	8 (80%)	6 (50%)	0	0	1 (17%)
Anakinra	4 (40%)	3 (25%)	0	0	0
Others	0	Si*	0	0	0

*Rituximab (4 patients), Chemotherapy (4 patients), Etoposide (3 patients) and Tocilizumab (2 patients)

Table 3 Characteristics demographic, diagnostic criteria, underlying disorders and mortality of each etiological subgroups of Hemophagocytic Syndrome.

Variables	Total		AI		HM		Infectious		MST	HPS without defined etiology		p		
	n	30	10	12	2	1	5	*5 SG	**3 SG	***2 SG				
Age (x ± s)	55.5	±18.3	40	26.5-56.3	68	57.5-73.8	45.5	30-61	78	71	53.5-73.5	0.006	0.003	0.001
Gender, man	14	46.70%	3	30%	9	75%	1	50%	1	0	0%			
Gender, female	16	53.30%	7	70%	3	25%	1	50%	0	5	100%	0.013	0.008	0.084
Splenomegaly	16	53.30%	5	50%	8	66.70%	2	100%	0	1	20%	0.216	0.283	0.666
Hepatomegaly	10	33.30%	4	40%	4	33.3%	2	100%	0	0	0%	0.138	0.4	1
Bicitopenia	27	90%	9	90%	12	100%	2	100%	1	3	60%	0.156	0.038	0.455
Hb ≤ 9 g	27	90%	9	90%	12	100%	2	100%	1	3	60%	0.156	0.038	0.05
Pt ≤ 100 000	25	83.30%	7	70%	12	100%	2	100%	1	3	60%	0.157	0.071	0.004
Leu ≤ 4 000	25	83.30%	8	80%	12	100%	2	100%	1	2	40%	0.04	0.01	0
Neu ≤ 4 000	19	63.30%	5	50%	11	91.70%	1	50%	1	1	20%	0.018	0.01	0.001
Tg ≥ 160 mg/dl	25	83.30%	9	90%	11	91.70%	2	100%	0	3	60%	0.157	0.281	0.314
Fb ≤ 150 mg/dl (n=24)	11	45.80%	4	44.4%	5	55.60%	0	0%	1	1	25%	0.84	0.894	1
Fer ≥ 500 ug/L (n=28)	28	100%	10	100%	11	100%	2	100%	#	5	100%	0.115	1	0.314
Global hospital stay∞	35.5	20-60.8	30.5	9.5-53.3	61.5	29.3-93.3	23	16-30	28	23	16.5-59	0.191	0.083	0.036
Hospital stay previous to the diagnosis∞	16.5	8.5-29.8	10	5-16.5	26	Oct-39	14	Nov-17	13	36	11.5-50	0.191	0.067	0.038
ICU admission	7	23.30%	2	20%	4	33.30%	0	0%	0	1	20%	0.935	0.851	0.646
Mortality	13	43.30%	1	10%	8	66.70%	1	50%	0	3	60%	0.029	0.025	0.011

SG: subgroup, Hb: hemoglobin, Pt: platelets, Leu: leukocytes, Neu: Neutrophils, Tg: Triglycerides, Fb: Fibrinogen, Fer: Ferritin, ICU: Intensive Care Unit

*: Analysis of all SG.

**: Analysis of AI, HM and HPS without defined etiology SG.

***: Analysis of AI and HO SG.

#: No information in the medical record.

∞: [Median; RIQ]

Mortality

The overall mortality was 43.3% (Table 3). The HM subgroup had higher statistically significant mortality [8 patients (66.7%)] compared to all subgroups (p 0.029) and compared to the AI subgroup [one patient (10%); p 0.011].

Discussion

In our study the most frequent causes of secondary HPS were AI and HM diseases, similar to other published series [6,10-12]. In our study we found that the most frequent causes of HPS were lymphomas, SLE and ASD, like in other AI or HM series published

Table 4 Laboratory findings of each etiological subgroups of Hemophagocytic syndrome.

Variables	Total		AI		HM		Infectious		MST		HPS without defined etiology			p		
	n	30	10	12	12	2	2	1	1	5	*5 SG	**3 SG	***2 SG			
Hb (g/dL)	7.1	6.4-7.9	7.2	6.6-8.4	6.5	5.9-7.3	7.5	7.3-7.8	8.6	7.1	6.5-11.7	0.120	0.082	0.05		
Pt (x 10 ⁹ /L)	13 500	5 000-52 500	31 650	11 000-100 250	4 500	650-15 750	9 500	9 000-10 000	5 000	87 000	26 500-186 000	0.009	0.003	0.004		
Leu (x 10 ⁹ /L)	1 250	238-3 153	1 985	1 350-3 382	185	20 - 728	2 050	1 010-3 090	480	4 370	2 975-5 640	0.0001	0.000	0.000		
Neu (x 10 ⁹ /L)	615	0-1 550	948	633-1 808	0	0-280	1160	0 - 2 320	230	3 090	1 280-4 040	0.002	0.000	0.001		
Fb (mg/dL) (n=24)	171	111-358	212	90-450	167	114-354	214	214	117	195	105-261	0.940	0.983	1.00		
Fer (ng/mL) (n=28)	15 330	5 434-38 284	14 263	4 254-14 263	16 796	8 287 - 56 969	10 346	9 755-10 938	#	6 689	2 914-26 748	0.410	0.289	0.314		
Tg (mmol/L)	341	226-438	411.5	234-572	321	233.8-403.8	372.5	274-471	149	337	119-540	0.594	0.513	0.314		
AST (U/L)	139	78-406	457	289-1 140	106	71-193	79	23-134	54	111	57-485	0.026	0.012	0.003		
ALT (U/L)	162	46-388	432	174-599	109	54-263	133	32-234	88	41,0	28-287	0.054	0.017	0.017		
LDH (U/L)	737	521-1 126	884	684-1 228	680	339-1 351	597	441-752	426	657	379-2 635	0.564	0.634	0.418		
T.B. (mg/dL)	2.1	1-11	1.3	0.6-7.1	2.7	2.7-11.4	1.6	1.6-1.7	3.7	1.2	0.7-29	0.709	0.482	0.228		
INR (n=29)	1.5	1.1-1.9	1.5	1.1-1.8	1.7	1.3-2.1	1.2	1.1-1.4	1.9	1.3	1.2-3.7	0.615	0.511	0.31		
T.P. (n=29)	4.8	±1.04	5	4.5-5.8	4.3	3.9-4.5	5.5	5.4-5.6	3.1	5.2	4.8-6.7	0.003	0.002	0.003		
A.P.	234	121-413	275	102-419	304	158-496	123	73-172	68	158	120-382	0.263	0.587	0.456		
GGT	233	110-548	367	132-689	303	126-931	162	96-227	173	119	51-376	0.580	0.357	1.00		

AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, LDH: Lactate Dehydrogenase, B.T.: Total Bilirubin, INR: International Normalized Ratio, T.P.: Total Protein, A.P.: Alkaline Phosphatase, GGT: Gamma-Glutamyl Transferase.

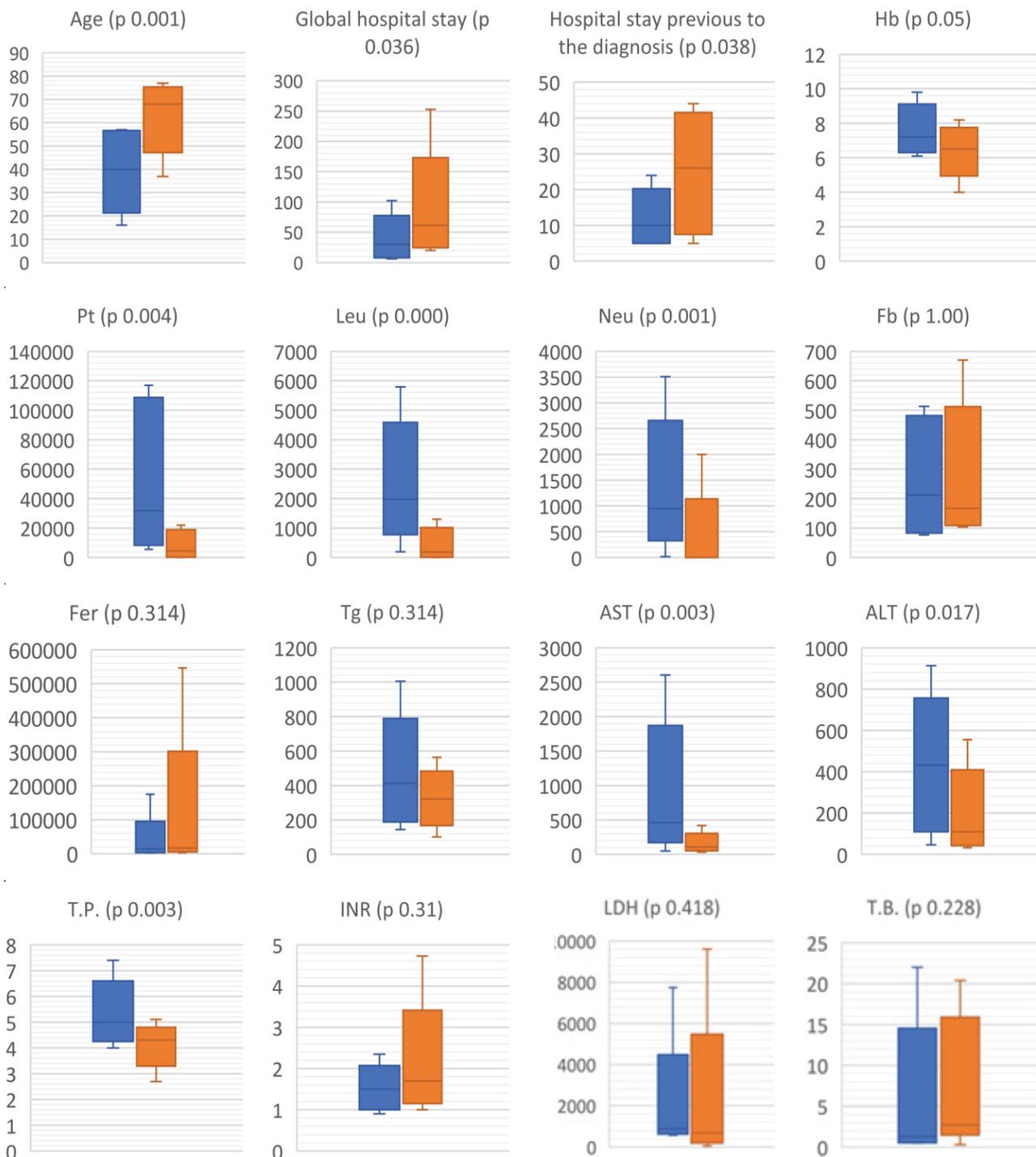


Figure 1 Demographic, clinical characteristics, laboratory findings and underlying disorders differences between AI (blue) and HM (orange) subgroups of Hemophagocytic Syndrome.

[13-15]. The JIA was excluded from the study because the age. The third most frequent subgroup in our cohort was HPS without defined etiology (16.7%). These patients were subjected to different diagnostic tests (X-rays, computerized axial tomography, analysis, serologies and bacterial cultures) during the hospital admission without concluding a final etiological diagnosis. The

etiological absence of HPS is quite frequent in some series, being almost 30% [16]. In our study, this subgroup had a greater, but not statistically significant hospital stays previous to diagnosis of HPS [(36 days (11.5-50; p=0.191)] compared to all subgroups, and compared with AI and HM subgroups (p 0.067). In addition, this subgroup had a high mortality rate of 60% (p 0.029). The absence

of an etiological diagnosis of HPS is likely to influence prognosis. In our study we found only one case of HPS secondary to MST probably to the initiation of temozolomide. This event is caused by a loss of immune homeostasis induced by chemotherapy, aggravating T-cell dysfunction [13,16,17]. The diagnosis of HPS secondary to chemotherapy is a challenge by the pre-existing neutropenia. In our opinion, HPS should be suspected in those patients who, after stopping chemotherapy, persist with neutropenia and fever that do not respond to broad-spectrum antibiotics. The presence of infections as an etiology of HPS is less frequent compared to HPS secondary to HM and AI disease. Usually the infections are more related as a trigger, usually on an AI and HM disease. The most frequent viruses associated as a trigger are *Epstein Barr (EBV)*, *Cytomegalovirus (CMV)* and *Influenza* [17-19]. In our cohort we found 10 cases of infections related to HPS, 8 as triggers (2 CMV, 2 EBV, 2 respiratory infections probably not filiated and 2 bacterial infections) and 2 as primary etiologies of HPS. In the HM diseases an adequate T and NK cell function is required for the elimination of antigenic and to end the inflammatory or autoimmune response. Aberrant activation of T and NK cells by lymphomas results in active, excessive, and sustained production of cytokines and macrophages, causing an HPS. The HPS also occurs in the course of other HM, such as B-cell lymphoma, Hodgkin's lymphoma, acute and chronic leukemias, acute myeloid leukemia, and myelodysplastic syndromes, as in our study [9,14-16].

The clinical features reflect an alteration of the immune system, induced by a hypercytokinaemia caused by highly activated lymphocytes and macrophages [20,21]. The clinical findings that suggest the presence of HPS are prolonged fever unresponsive to antibiotics and hepatosplenomegaly. The laboratory findings include the presence of cytopenias, which usually begin with a thrombocytopenia that progresses to severe pancytopenia. Other common findings include the presence of hyperferritinemia, hyponatremia, hypertransaminasemia, hypofibrinogenemia, hypertriglyceridemia, and hypoalbuminemia [22]. In our cohort, statistically significant differences were observed between the different subgroups in relation to the number and severity of cytopenias, being more severe in the HM subgroup. Also, a longer hospital stay previous to the diagnosis of HPS was observed in the HM subgroup compared to AI and Inf. subgroups, as observed in a Chinese study, which also showed an increased hypertriglyceridaemia and increased sCD25 activity in the HM subgroup [23].

The triglycerides may not increase until the liver has been damaged for a long period of time; that is, hypertriglyceridemia is a sign of severe and late liver failure. In our study, no statistically significant differences were observed between the different subgroups [24]. This may be due to the fact that the AI subgroup presented lower mortality and a greater liver alteration.

As we mentioned above, most of the patients included in our study presented an AI and HM disease, like in others published series [3,6,10,12,13,16,17,25]. We found a few studies in the literature that compare these two subgroup or differences that are not very relevant or significant. In our study we found in the

comparative analysis between these two subgroups, that the HM presented a higher number and more severe cytopenias, in which plaquetopenia is the most importance. In addition, the HM subgroup presented a higher age at the time of diagnosis of HPS, a longer hospital stays, a longer hospital stays previous to the diagnosis of HPS and a higher mortality. The prognosis of the HM subgroup was worse, this may be due to the sum of several factors: such as the complexity of the disease itself, older age, a delay in the diagnosis of HPS and the severity of cytopenias, especially plaquetopenia. On the other hand, the AI subgroup presented a higher elevation of transaminases, probably due to a more systemic component, characteristic of AI diseases. In contrast, the HM subgroup had a more pronounced hypoproteinemia, probably related more to the severe liver damage. There is a great heterogeneity in the prognosis of adult patients with HPS, the mortality rate varies between 20% and 90% [11,13,25-27]. In our study the overall mortality was 43.3%, with significant differences according to the subgroup. In general, the malignant neoplasms underlying HPS, especially lymphoma, are considered an adverse prognostic factor [10,11,24,27]. The aim of this study is not to analysis the differences between MAS and a flare of an AI disease, but we thought to mention some relevant data given the great similarity between these two. So far, there is no clinical and laboratory pathognomonic finding that would help us to suspect in a MAS [28-32]. But, there are some clinical data that could help us to differentiate between these two, for example, the fever in MAS is continuous and in a flare is usually intermittent; hepatosplenomegaly can be present in both, but more often occurs in MAS; and, the alteration of the central nervous system and bleeding disorders are more frequents and severe in MAS [33,34]. Also, the decreased of the platelet counts appear to be the most valuable data to differentiate, this finding being very suggestive of the appearance of a MAS. [35]. A decrease in the levels of globular sedimentation rate (GSR) or a disproportion between GSR and C-reactive protein increases the suspicion of MAS. However, this finding occurs in advanced stages concomitant with hypofibrinogenemia [35-37]. Generally, the current therapy is based on the combination of immunosuppressors and cytotoxics to treat the hyperinflammatory state, but the main goal of treatment is to control the underlying disease. In the HLH-94 and HLH-2004 protocols the induction treatment is dexamethasone and etoposide, and for maintenance CSA. In refractory or recurrent cases, intrathecal methotrexate and allogeneic hematopoietic cell transplantation can be used [3,7,38]. In the specific case of MAS the main treatment is GC, intravenous methylprednisolone at 30 mg/kg/dose (maximum 1 g) for 1-3 days. If patients respond well, GC is reduced to 2-3 mg/kg/day in divided doses. In the absence of response to GC, it is recommended to add CSA 2-7 mg/kg/day [39-41]. In refractory cases to high dose GC and CSA, the HLH-2004 protocol should be considered. However, etoposide is not recommended in MAS due to its serious side effects, such as severe BM suppression, liver and kidney toxicity [42]. Biological therapies, such as IL-1 and IL-6 inhibitors, is recommended in refractory cases [43,44]. Other therapies such as intravenous immunoglobulin, cyclophosphamide, and plasmapheresis have provided inconsistent results. The treatments used in our

patients do not differ from those reported in the literature. In the HM subgroup a greater number of treatments were used, probably due to the lack of early etiological diagnosis and the very complexity of the disease.

Conclusion

We found that the HM subgroup presented a greater mortality, and more number and severe cytopenias, compared to all subgroups and especially with AI subgroup. The AI subgroup had a higher elevation of transaminases and a better prognosis than all subgroups. The HPS with no defined etiology subgroup presented a high mortality and a delay diagnosis of HPS.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the Donostia University Hospital, and given the retrospective nature of this study; it was not necessary to obtain informed consent, as the

ethics committee did not require it or waived it. However, after data collection, patients were anonymized. In addition, the study followed the guidelines of the Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights, which repealed the Organic Law 15/1999, of December 5, on the Protection of Personal Data in Spain.

Consent for publication

Consent was not obtained because the retrospective nature of the study.

Availability of data and materials

Not applicable

Competing Interests

The authors declare that they have no competing interests.

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