

Hemophagocytic Syndrome Secondary to Cytomegalovirus Infection in a Patient with Human Immunodeficiency Virus

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Abstract: Hemophagocytic Syndrome (HPS) or Hemophagocytic Lymphohistiocytosis is characterized by a dysregulation of the immune system with activation of macrophages and T lymphocytes, the product of an uncontrollable and excessive inflammatory response to different stimuli. The case of a patient with a history of Human Immunodeficiency Virus (HIV) under current treatment is presented, a clinical picture of 10 days of evolution characterized by fever, anorexia and asthenia, on physical examination skin-mucosa paleness, dehydration, generalized lymphadenopathy, hepatosplenomegaly. Paraclinical tests are performed suggesting reactivation of infection by Cytomegalovirus (CMV), in addition, during its in-hospital evolution, marked pancytopenia is evidenced, with elevated ferritin values, a bone marrow biopsy is performed, observing proliferation of Histiocytes, the patient meets the diagnostic criteria for HPS proposed by the Histiocyte Society in 2004, treatment was instituted, however it presented a torpid evolution and reached death. It is concluded that the diagnosis of HPS is complex; it is usually overlapped by the underlying diseases, as is the case of this HIV patient with reactivation of CMV infection; both viruses by themselves are related to HPS; therefore, knowledge of the clinical and laboratory criteria of this entity is necessary to make an early diagnosis and establish timely treatment, thus reducing mortality.

Keywords: Hemophagocytic Syndrome, Hemophagocytic Lymphohistiocytosis, Cytomegalovirus, Human Immunodeficiency Virus

1. Introduction

Hemophagocytic Syndrome (HPS) or Hemophagocytic Lymphohistiocytosis (HLH) is a disorder of the immune system, first described in 1939 by pediatricians Scott and Robb-Smith [1]. In 1952 it was linked to a familial immune disorder, called Familial Hemophagocytic Reticulocytosis. In 1979 Risdall et al described HPS associated with viral infection [2]. However, although its origin has been associated with autosomal recessive genetic factors, secondary forms were also later described, related to infections, malignant diseases, drugs or autoimmune diseases [1-6]. (Table 1).

There are few epidemiological studies about this disease, however, it is estimated that the worldwide incidence is 1,2 cases per million inhabitants, although this figure may be underestimated due to the difficulty in making the diagnosis and the symptoms and signs of the disease are not very

specific [7].

Hemophagocytic Syndrome is characterized by a dysregulation of the immune system with activation of macrophages and a failure in the function of natural killer cells and cytotoxic T lymphocytes, the product of an uncontrollable and excessive inflammatory response to different stimuli. It includes clinical (fever, splenomegaly) and hematological biochemical (bi -or pancytopenia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia and increased soluble interleukin 2 receptor, low natural killer cell activity) and histological changes (evidence of hemophagocytosis in bone marrow) that comprise the diagnostic criteria established by the Histiocyte Society in 2004 [8]. (Table 2).

The objective of these criteria is to standardize the diagnosis and not to underestimate the disease. A timely diagnosis allows provide an effective therapy which significantly reduces the mortality of the disease [7]. The

primary form generally manifests at an early age and forms a serious condition that requires early treatment with immunosuppressant or cytostatic. Secondary forms can be due to different causes such as neoplasms, autoimmune diseases and infections, of the latter, viral causes are the most frequent. In these cases, the treatment of the cause and the supportive measures play a fundamental role in the

management of the syndrome [8, 9], the treatment with corticosteroids, immunosuppressants and intravenous immunoglobulin can improve the prognosis [10]. HPS has a high mortality, with a survival of approximately 2 months without treatment, so it is a priority to start management as soon as the diagnosis is established [5, 11, 12].

Table 1. Etiology of Hemophagocytic Syndrome.

1. Familial Primary Hemophagocytic Lymphohistiocytosis
a) Immunodeficiency Syndrome
b) Chediak-Higashi Syndrome
c) Griscelli Syndrome
d) Wiskott-Aldrich Syndrome
e) Severe combined immunodeficiency
f) Hermansky-Pudlak Syndrome
2. Secondary Hemophagocytic Syndrome
a) Infections
i. Viral: Cytomegalovirus, Epstein-Barr Virus, Herpes Simplex Virus, Varicella-Zoster, Herpes Virus 6, Adenovirus, Rubella, Influenza, Parainfluenza, Human Immunodeficiency Virus, Arbovirus, Parvovirus, Dengue.
ii. Bacterial: Mycobacteria, Brucella, Pneumococcus, Staphylococcus, Haemophilus, Serratia, Mycoplasma, Legionella, Salmonella typhi, Gram-negative enteric bacilli, Rickettsia, Coxiella, Chlamydia
iii. Fungal: Candida, Histoplasma, Cryptococci.
iv. Parasitic: Leishmania, Babesia, Toxoplasma, Plasmodium.
b) Collagenopathies: Systemic Lupus Erythematosus, Juvenile Rheumatoid Arthritis, Kawasaki Disease.
c) Neoplasms: Hodgkin and non-Hodgkin Lymphomas, acute and chronic Leukemias, Myelodysplastic Syndromes, Multiple Myeloma, Carcinomas of the stomach, breast, ovary, lung, urinary bladder, nasopharynx, germ cell tumor
d) Others: Phenytoin, Treatment with immunosuppressants, Post-vaccination, Sarcoidosis, Hyperalimentation with lipids [2].

Table 2. Diagnostic Criteria for Hemophagocytic Syndrome.

The diagnosis is established if one or two of the criteria are met
1.- Molecular diagnosis consistent with HPS
2.- Diagnostic criteria for HPS (5 criteria)
a) Fever
b) Splenomegaly
c) Cytopenias (affecting 2 or 3 lines in peripheral blood):
i) Hemoglobin < 9 mg/dl (in children < 4 weeks: hemoglobin < 100 g/L
ii) Platelets < 100,000 /L
iii) Neutrophils < 1,000 /L
d) Hypertriglyceridemia and / or hypofibrinogenemia
i) Fasting triglycerides > 265 mg/dl
ii) Fibrinogen <1.5 g/L
e) Hemophagocytosis in bone marrow, lymph nodes or spleen
f) No evidence of malignancy
g) Low levels or absence of NK cell activity
h) Ferritin > 500 µg/l
i) CD 25 Soluble > 2,400 U/ml
Comments:
- If hemophagocytosis is not found at the time of presentation, it should be looked for later. If the bone marrow is not conclusive, it should be looked for in other organs. Multiple bone marrow aspirates may be helpful in confirming the diagnosis.
- The following findings may be supporting evidence for the diagnosis: a) CSF pleocytosis (mononuclear cells) and / or proteinorrachia, and b) liver biopsy with persistent chronic hepatitis.
- Other clinical or laboratory findings consistent with the diagnosis are: cerebromeningeal symptoms, lymphadenopathy, jaundice, edema, rash, alteration in liver enzymes, hypoproteinemia, hyponatremia, high VLDL, low HDL.

NK: natural killer. CSF: cerebrospinal fluid, VLDL: very low-density lipoprotein, HDL: high-density lipoprotein. [11].

2. Clinical Case

This is a 38-year-old male patient, from Mara Municipality, Zulia State, who presents a clinical picture of 10 days of evolution characterized by fever quantified at 39-40 ° C, without a predominance of hours, preceded by chills and night sweats, that yields with administration of Acetaminophen-type antipyretics, likewise, anorexia,

asthenia, reasons for which he goes to the Autonomous Service University Hospital of Maracaibo where he is evaluated and admitted.

In the anamnesis of his personal history, he refers to 2 previous hospitalizations in this institution: (1) Diagnosis of Malaria by *Plasmodium vivax*, 7 months prior to the current admission, under treatment with Chloroquine and Primaquine, provided by the Regional Malariology Service. (2) Diagnosis of Infective Endocarditis Valve Mitral, 1 month prior to

current admission, received treatment with Vancomycin and Ceftriaxone. In this same admission, Human Immunodeficiency Virus (HIV) infection was diagnosed in current treatment with Viraday (600 mg of Efavirenz + 200 mg of Emtricitabine + 245 mg of Tenofovir) 1 tablet orally daily. He reports a history of multiple blood transfusions in both hospitalizations with follow-up by the Hematology Service. Family history with no relevant findings relevant to the case. When questioning the psychobiological habits, he refers to an occasional alcoholic, abandoned in the last 8 months, he denies smoking. Occupation: transportation of dairy products. 2 sexual partners. The review of apparatus and systems: refers to weight loss > 10 kg in 8 months; occasional headache, of an oppressive nature, of mild to moderate intensity; Bristol 4 daily evacuation pattern; dark urine and decreased urinary volume in the last 6 days.

The physical examination at admission reports Blood Pressure: 80/40 mmHg, Mean Blood Pressure: 53 mmHg, Heart Rate: 89 bpm, Respiratory Rate: 18 bpm, Temperature: 39°C, Weight: 60 kg, Height: 1,70 cm, Mass Index Corporal: 17. Patient in poor clinical condition, feverish, dehydrated, earthy appearance, with marked mucous skin pallor, pale conjunctiva, white sclera, isochoric pupils normoreactive to light, normal eye movements, thin, dehydrated lips, thick saliva, without lesions on oral mucosa, in the neck examination, multiple bilateral, non-painful, mobile lymph nodes are palpated, not adherent to deep planes greater than 1 cm in diameter, in addition, bilateral lymph nodes in the inguinal region are palpated with the same characteristics previously described. Symmetric normoexpandable chest, normal vocal thrill, normoresonant, audible vesicular murmur in both hemithorax without aggregates. Rhythmic heart sounds without murmur, point of maximum impulse in 5th left intercostal space, midclavicular line. Depressible soft abdomen, not painful on superficial or deep palpation, hepatomegaly is palpable 3 times below the costal margin, blunt border, without masses, grade II splenomegaly, 3-minute air-fluid noises. Neurological examination: conscious, coherent language, oriented in time, space and person, isochoric pupils normoreactive to light, undamaged cranial nerves, global V / V muscle strength, normoreflexic, bilateral plantar flexor skin, without neck stiffness, gait and cerebellar tests without alterations. Patient is approached by the Internal Medicine Service of the institution, who administers hydric rescue obtaining improvement of the hemodynamic state and requests laboratories.

Presents laboratories performed 2 days prior to admission that report leukocytes 3.000 mm³, segmented 65,1%, lymphocytes 25%, hemoglobin 7,3 gr/dl, hematocrit 22,1%, platelets 138.000 mm³; at the time of admission, a new hemogram of leukocytes 2.000 mm³ is performed, segmented 60%, lymphocytes 40%, hemoglobin 7,0 gr/dl hematocrit 23,40%, platelets 182.000 mm³. (Table 3). In relation to blood chemistry 2 days prior to admission, random glycemia 128 mg/dl, creatinine 2,4 mg/dl, urea 110 mg/dl, uric acid 6,4 mg/dl, aspartate aminotransferase (AST) 98 U/L, alanine aminotransferase (ALT) 86 U/L, total bilirubin 1,9 mg/dl,

direct bilirubin 0,06 mg/dl bilirubin indirect 1,03 mg/dl, cholesterol 248 mg/dl, triglycerides 285 mg/dl. Upon admission, he presented random glycemia 120 mg/dl, creatinine 5,7 mg/dl, AST 141 U/L, ALT 130 U/L, total bilirubin 1,30 mg/dl, direct bilirubin 0,80 mg/dl, indirect bilirubin 0,50 mg/dl. (Table 4). Presents uroanalysis of days prior to admission that reports pH 6, density 1.015, proteins (++) , negative glucose, negative ketone bodies, negative bilirubin, negative nitrites, leukocytes 6-8 xc, scarce bacteria. Subsequently, he presents urinalysis pH 6, density 1.025, albumin (+), bilirubin (+), bile pigments (+), bile salts (+), hemoglobin (+), leukocytes 1-3 xc, red blood cells 2-4xc, rare bacteria, sparse epithelial cells. Chest X-ray without parenchymal pathological infiltrates, with a cardiothoracic index of 0.5. (Figure 1). An Echocardiogram was performed that reports Ejection Fraction of 67%, slight increase in the left atrium, mild concentric hypertrophy of the left ventricle, mitral valve prolapse with mild reflux, without evidence of vegetations. Abdominal ultrasound reports nonspecific diffuse hepatosplenomegaly (liver diffuse and homogeneous enlargement, regular contours, right hepatic lobe measuring 18,9 cm; diffuse and homogeneous enlarged spleen, measuring 18,5 cm), gallbladder with changes typical of systemic disease (gallbladder, normal size, discrete thickening of the walls, with changes typical of systemic disease (hypoproteinemia), without images inside) and bilateral renal lithiasis. Two blood cultures were performed: urine culture, stool culture, thick film, direct Coombs, Widall reaction (febrile agglutinins), serology for Toxoplasma Immunoglobulin (Ig) M and IgG and Hepatitis Viruses A, B and C, all obtaining negative. The serology for Epstein-Barr Virus is IgM Negative and IgG Positive, which means that he had a past infection, Cytomegalovirus (CMV) IgM Positive, IgG Positive, (previous medical history is reviewed where serology for CMV IgM Negative and IgG Positive is reviewed), suggesting a reactivation of the CMV infection.



Figure 1. Chest X-ray.

During its in-hospital evolution, marked jaundice, manifestations of petechiae-type bleeding and ecchymosis, in addition to generalized edema, were evidenced. The Hematology Service who performs follow-up with Peripheral Blood Smear (PBS) where bicytopenia is initially evidenced (anemia with marked hypochromia and anisocytosis and leukopenia), later marrow failure due to marked pancytopenia is evidenced. (Table 3). Serum iron is requested 66 mcg/dl (Normal value (NV) 60-160 mcg/dl), total iron

binding capacity to transferritin (TIBC) 140 mcg/dl (NV 300-360 mcg/dl), % of transferritin saturation 47,10 (NV 30-50%), ferritin 2.340 ng/ml (NV 15- 300 ng/ml). A bone marrow biopsy is performed, which reports a small cylindrical fragment of spongy bone tissue containing a total of four good-size bone marrow particles. All the particles are slightly or moderately hypercellular with 80-85% cells and the rest made up of adipose tissue. In all the particles, cells that belong to the three normal myeloid series are observed intermixed with a moderate amount of Hyperplastic Histiocytes that present good differentiation and many of them with a clear cytoplasm. However, there is no evidence of hemophagocytosis in these histiocytes, but neither can we rule it out absolutely. This hyperplasia is most likely associated with hemophagocytosis. All three normal myeloid series are diminished. Granulopoiesis is deviated to the left with a predominance of intermediate forms such as

myelocytes and metamyelocytes without an increase in myeloblasts. Erythropoiesis is depressed and is normoblastic in nature. Few megakaryocytes are seen.

The diagnosis of HPS is established by the following criteria presented by the patient: Fever, Splenomegaly, Cytopenias (with involvement of the 3 peripheral blood lines), Hypertriglyceridemia, Hemophagocytosis is not evidenced in the bone marrow fragments, but proliferation of histiocytes, no evidence of malignancy, Ferritin > 500 ng/ml (2.340 ng/ml), other clinical or laboratory findings consistent with the diagnosis are: lymphadenopathy, jaundice, edema, alteration in liver enzymes, hypoproteinemia, hyponatremia; these among other diagnostic criteria are those proposed by the Histiocyte Society in 2004 [11]. During his in-hospital evolution, transfusion support is administered, likewise corticosteroids, Ganciclovir, Antiretroviral Treatment, however, he presents torpid evolution and reaches death.

Table 3. Comparative table of the hemogram during the intra-hospital evolution.

Lab	2 days before	Adm.	Intra-hospital evolution day								
			3rd	6th	11th	15 th	18 th	21st	22nd	24 th	25th
Leuc (mm ³)	3.000	2.000	2.300	2.000	800	900	500	600	400	500	400
Seg (%)	65,1	60	50	65	-	-	-	-	-	-	-
Lymph (%)	25	40	45	35	-	-	-	-	-	-	-
Mon (%)			3								
MM (%)			2								
Hb (gr/dl)	7,3	7,0	5,2	6,1	5,1	6,8	6,5	4,7	4,6	5,1	5,1
Hto (%)	22,1	23,40	16,9	19	16	21,7	21,1	15	14,8	16	17,1
MCV (fl)			97,3		96,7	96,2	96,4		95,5		97,0
MCH (fl)			29,8		30,7	30,0	29,6		29,4		29,8
MCHC (fl)			30,7		31,8	31,3	30,8		31		28,8
RBC (mm ³)			1.740.000		1.660.000	2.260.000	2.190.000		1.560.000		1.770.00
Plat (mm ³)	138.000	182.000	210.000	160.000	166.000	182.000	120.000	50.000	60.000	25.000	24.000
PBS report			Good plat. count, marked hypochromic, anisocytosis		Plat. 8-3 xc, marked hypochromic, anisocytosis	Plat. 9-1 xc, marked hypochromic, anisocytosis with predominance of microcytosis	Plat. 6 xc, marked hypochromic, anisocytosis		Plat. 3 xc, marked hypochromic, anisocytosis		Plat. 3 xc, marked hypochromic, anisocytosis

Lab: Laboratory. Adm: Admission. Leuc: Leukocytes. Seg: Segmented. Lymph: Lymphocytes. Mon: monocytes. MM: Myelomonocytes. Hb: Hemoglobin. Hto: Hematocrit. MCV: Mean Corpuscular Volume. MCH: Mean Corpuscular Hemoglobin. MCHC: Mean Corpuscular Hemoglobin Concentration. RBC: Red Blood Cell Series. Plat: platelets. PBS: Peripheral Blood Smear.

Table 4. Comparative table of Blood Chemistry during Intra-hospital Evolution.

Lab	2 days before	Adm.	Intra-hospital evolution day							
			1st	2nd	5th	6th	11th	18th	19th	26th
Glycemia (mg/dl)	128	120	120	125		100			100	
Creat. (mg/dl)	2,4	5,7	1,4	0,8		0,6			0,8	
Urea (mg/dl)	110									
Ac. Uric (mg/dl)	6,4									
AST (U/L)	98	141			159		59			
ALT (U/L)	86	130			96		32			
TB (mg/dl)	1,09	1,30			2,30		4,70	7,52		
DB (mg/dl)	0,06	0,80			1,30		2,50	4,01		
IB (mg/dl)	1,03	0,50			1,00		2,20	3,50		
LDH (U/L)					320		258			
AP (U/L)					1.326		1.938			
GGT (U/L)					490		698			
TP (g/dl)					5,90					
Alb (mg/dl)					2,70					
Glob (mg/dl)					3,20					
Alb/glob Rat (mg/dl)					0,84					

Lab	2 days before	Adm.	Intra-hospital evolution day							
			1st	2nd	5th	6th	11th	18th	19th	26th
Cholest (mg/dl)	248							332		
HDL (mg/dl)								46		
LDL (mg/dl)								239		
VLDL (mg/dl)								46,20		
TG (mg/dl)	285							231		
Na (mEq/L)										126
Osm										265
K (mEq/L)										5,22
Cl (mEq/L)										104

Lab. Laboratory. Adm: Admission. Creat: Creatinine. AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. BT: Total Bilirubin. BD: Direct Bilirubin. BI: Indirect Bilirubin. LDH: Lactate Dehydrogenase. AP: Alkaline Phosphatase. GGT: Gamma Glutamyl transpeptidase. TP: Total Proteins. Alb: Albumin. Glob: Globulin. Alb/glob Rat: Albumin/Globulin ratio. Cholest: Cholesterol. HDL: high-density lipoprotein. LDL: low-density lipoprotein. VLDL: very low density lipoproteins. TG: triglycerides Na: plasma sodium. Osm: Plasma osmolarity. K: Plasma potassium. Cl: Plasma chlorine.

3. Discussion

The case of an HIV patient with reactivation of CMV infection is presented, who meets the diagnostic criteria proposed by the Histiocyte Society for Hemophagocytic Syndrome; I present the following criteria: Fever, Splenomegaly, Cytopenias (with involvement of the 3 peripheral blood lines), Hypertriglyceridemia, hemophagocytosis is not evidenced in bone marrow fragments, but proliferation of histiocytes was observed, no evidence of malignancy, Ferritin > 500 ng / ml (2340 ng / ml), other clinical or laboratory findings consistent with the diagnosis are: lymphadenopathy, jaundice, edema, alteration in liver enzymes, hypoproteinemia and hyponatremia. Unfortunately I present torpid and unfavorable evolution. Guijarro [13] reported a similar case of HPS in a newly diagnosed HIV patient (1 month prior to admission) with CMV infection, like this case presented a fatal outcome despite the treatment instituted. Dos Santos et al [14] reported a case of HPS in an HIV patient who evolved favorably to the instituted treatment, far from this case as he did not present an associated CMV infection. Parikh et al [12] reported 62 cases of HPS of these 21 were secondary to infection, 3 cases were associated with CMV; similar data showed Li et al [10] in their analysis of 103 adult patients with HPS, 24 cases presented a disease underlying infectious disease, of which 6 were due to CMV. Rivière et al [15] reported 162 cases with HPS, of these 73 cases had an underlying immunosuppression, of which 61 were HIV, 40 cases were secondary to infections, 10 due to viruses and of these 6 were due to CMV, around 30% of the patients with HPS did not show any hemophagocytic characteristics in their bone marrow aspirate, this is similar to what was observed in this case, where a proliferation of histiocytes was observed without evidence of hemophagocytosis, which highlights the importance of knowing the established diagnostic criteria for HPS and thus establish adequate and timely treatment.

4. Conclusion

Based on the clinical picture, evolution and outcome of the case described, it is concluded that the diagnosis of HPS is complex, a diagnostic challenge, since it is usually

overlapped by the underlying diseases, such is the reported case, HIV patient with fever and constitutional symptoms, in addition, systemic compromise, where there are various diagnostic possibilities, given by HIV itself, as well as by the state of immunosuppression that makes it prone to opportunistic infections such as CMV, both viruses by themselves are related to HPS; What is necessary is knowledge of the criteria proposed by the Histiocyte Society to make an early diagnosis and establish timely treatment, thus increasing survival and reducing mortality from HPS.

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