Artículo de revisión

Hemophagocytic lymphohistiocytosis associated with visceral leishmaniasis. Review of cases reported

Linfohistiocitosis hemofagocítica asociada con leishmaniasis visceral. Revisión de casos reportados

David Garrido[1*] https://orcid.org/0000-0002-7384-1236
Michelle Fuseau[1] https://orcid.org/0000-0002-5435-8572
Santiago Garrido[2] https://orcid.org/0000-0002-8130-588X
Santiago Celi[3] https://orcid.org/0000-0003-2091-9295

[1]Universidad de la República. Montevideo, Uruguay.
[2]Hospital General del IESS. Ibarra, Ecuador.
[3]Ministerio de Salud Pública del Ecuador. Esmeraldas, Ecuador.

[*]Corresponding author: david_labinmuno@hotmail.com

ABSTRACT

Introduction: Leishmaniasis is a tropical and subtropical disease highly reported in Southeast Asia, East Africa, Latin America, and the Mediterranean basin, with an incidence of two million new cases by year and 500,000 cases of visceral leishmaniasis. One of the more severe and rare complications of visceral leishmaniasis is hemophagocytic lymphohistiocytosis.

Objective: To describe the clinical characteristics of hemophagocytic lymphohistiocytosis associated with visceral leishmaniasis

Methods: We performed a literature review based on the case reports indexed in MEDLINE/PubMed.

Results: Twenty-five cases were included; 52 % under two years of age. All cases presented splenomegaly and 84% hepatomegaly. Cytopenias were described in all patients: 100% thrombocytopenia, 96% anemia, and 84% leukopenia or neutropenia. Hypertriglyceridemia and hypofibrinogenemia were found in 68% and 32%, respectively, and hyperferritinemia in 80%. Additionally, hemophagocytosis was documented in 84%, with *Leishmania*

detection in 92%. All patients were treated against Leishmania: 80% with liposomal amphotericin B. regarding the treatment for hemophagocytic lymphohistiocytosis; corticosteroid were used in 36%, endovenous immunoglobulin in 28%, cyclosporine in 28% and etoposide in 16%

The complications reported included gastrointestinal hemorrhage (8%), disseminated intravascular coagulation (8%), autoimmune hemolytic anemia (12%), multiple-organ dysfunction/septic shock (12%), petechial rash (16%), and four patients deceased. Variables such as fever (p=0.031), hemoglobin level (p=0.031), platelet count (p=0.0048), and ferritin (p=0.0072) were associated with mortality

Conclusions: During visceral leishmaniasis, the hemophagocytic syndrome is a rare condition that mainly affects pediatric patients, but with excellent outcomes using liposomal amphotericin B. However, there is a lack of strong evidence to make a recommendation.

Keywords: Leishmaniasis; hemophagocytic lymphohistiocytosis; amphotericin B; pediatrics.

RESUMEN

Introducción: La leishmaniasis es una enfermedad tropical y subtropical con una elevada incidencia, dos millones de casos nuevos por año y 500 000 de leishmaniasis visceral. La linfohistiocitosis hemofagocítica es una complicación grave y rara de la leishmaniasis visceral.

Objetivo: Describir las características clínicas de la linfohistiocitosis hemofagocítica asociada con leishmaniasis visceral.

Métodos: Se realizó una revisión bibliográfica basada en los informes de casos indexados en MEDLINE/PubMed. Se identificaron 34 publicaciones; después de analizarlas en función de los criterios de inclusión se trabajó con 22 trabajos.

Resultados: En los trabajos incluidos se informaron 25 casos; el 52 % fueron pacientes menores de 2 años. Todos presentaron esplenomegalia y 84 % hepatomegalia. Se describieron citopenias en todos los pacientes: 100 % trombocitopenia, 96 % anemia y 84 % leucopenia o neutropenia. Se encontró hipertrigliceridemia e hipofibrinogenemia en 68 % y 32 %, respectivamente, e hiperferritinemia en 80 %. Todos los pacientes fueron tratados contra leishmania, 80 % con anfotericina B liposomal. Las complicaciones incluyeron: hemorragia gastrointestinal, coagulación intravascular diseminada, anemia hemolítica autoinmune, falla multiorgánica/*shock* séptico, erupción petequial y cuatro pacientes fallecieron.

Conclusiones: En la leishmaniasis visceral, el síndrome hemofagocítico es una afección poco frecuente que afecta principalmente a pacientes pediátricos. Para el tratamiento, usando la anfotericina B liposomal se obtienen excelentes resultados; sin embargo, la evidencia es insuficiente para hacer una recomendación.

Palabras clave: leishmaniasis; linfohistiocitosis hemofagocítica; anfotericina B; pediatría.

Recibido: 25/12/2019

Aceptado: 14/06/2020

Introduction

Visceral leishmaniasis (VL) is a tropical and subtropical disease caused by the infection of phagocytic cells within the reticuloendothelial system (RES) in the liver, spleen and bone marrow, by intracellular *Leishmania* species. This parasite is transmitted to humans by the bite of a female sandfly, mainly Phlebotomus and Lutzomyia. The disease is clinically characterized by a febrile infectious illness, with a prolonged incubation period which ranges from 3 to 8 months often associated to hepatosplenomegaly and bone marrow suppression.[1]

Leishmaniasis has a broad global distribution, particularly affecting Southeast Asia, East Africa, Latin America, and the Mediterranean basin. In these populated areas it is estimated that there are 14 million people infected, with an incidence of 2 million new cases yearly, of which 500 000 cases are visceral leishmaniasis (VL) caused by *L. donovani, L. infantum*, and *L. chagasi*.[2] According to the World Health Organization (WHO) reports, in 2017, 20 792 out of 22 145 (94%) new cases occurred in Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan (Fig.).[3]

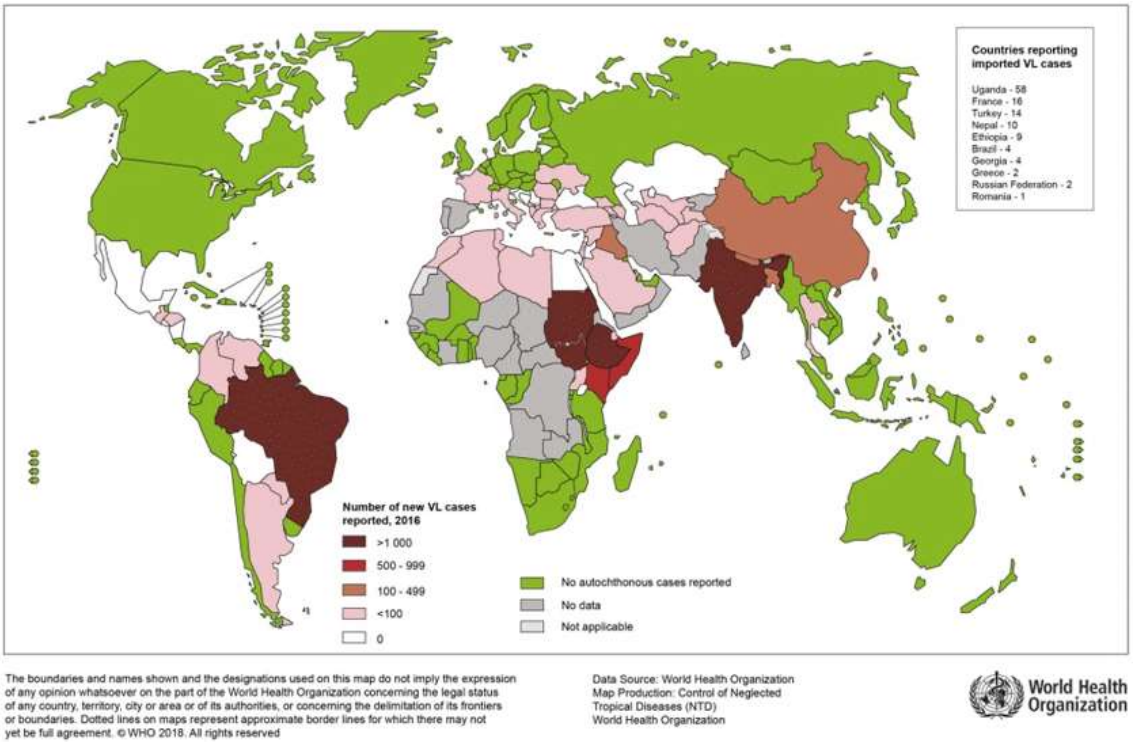

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Fig - World Health Organization report regarding the status of endemicity of visceral leishmaniasis worldwide, 2018.

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome with high mortality even with appropriate treatment, caused by excessive activation of macrophages, lymphocytes, high levels of inflammatory cytokines, and phagocytosis of hematopoietic cells by activated macrophages.[4] The diagnosis of HLH can be established if there is a molecular finding consistent with HLH or if at least 5 of the 8 diagnostic criteria are met, which includes; 1) fever, 2) splenomegaly, 3) cytopenias affecting two or three lineages in the peripheral blood (hemoglobin <9 g/dl, in infants under four weeks of age hemoglobin <10 g/dL, platelets 100000/ml, neutrophils < 1000/mL), 4) hypertriglyceridemia (≥ 265 mg/dL) and/or hypofibrinogenemia (≤ 1.5 g/L), 5) hemophagocytosis in bone marrow, spleen or lymph nodes, 6) low or absent NK-cell activity, 7) ferritin ≥ 500 ug/L, y 8) CD25 soluble ≥ 2400 U/mL . HLH is a condition that could be triggered by a wide range of infectious pathogens, within which the most common are Epstein Barr Virus (EBV) and *Leishmania*.[5] Secondary HLH may be a potentially fatal condition without prompt identification and treatment. Morimoto et al. described hemophagocytosis physiopathology elements using a mouse model study. They found that amastigotes infected 100% of hemophagocytes and 50.2% of splenic macrophages. Additionally, hemophagocytosis was observed more often in heavily infected macrophages, especially those with more than 20 amastigotes/per cell (66.5 ± 6.2%). These findings suggest that hemophagocytosis is

triggered by the macrophages infection and cytokine release such as IL-4 and IFN gamma.[6] However, this phenomenon has not been described in humans.

Leishmaniasis is a neglected disease that may course with HLH, and even when many scientific reviews of *Leishmania* or leishmaniasis have been published in the last decade, the HLH syndrome has been scarcely explored or not mentioned. Therefore, this review aims to present the main characteristics reported in HLH associated with VL, and highlight current recommendations regarding this pathology.

Methods

This is a review of the published cases reports regarding HLH associated with VL conducted between May and June 2019.

We searched in PubMed, using the combination of words "Hemophagocytic lymphohistiocytosis leishmania" and restricting the results only to case reports. With this strategy, thirty-four publications were identified. After analyzing the fulfillment of the inclusion criteria, 12 papers were excluded.

The inclusion criteria were: 1) manuscripts in all languages with English abstracts and full text online available, 2) manuscripts detailing the methodology used for the diagnosis of HLH and Leishmania, and 3) papers which includes the follow up of the patient

The frequency of clinical manifestations was described as a percentage, whereas, the continuous variables were presented as average with standard deviation.

For tabulation and data analysis we used SPSS v.23 software.

Results

In the 22 papers included, 25 cases were reported. The possible country of *Leishmania* infection and the country were each case was reported, are presented in table 1.

Table 1 - Probable country of contagion, country of repor, year of publication

Case reports	Age	Probable country of contagion	Country where the case was reported	Year of publication
Case 1[7]	27	India	India	2019
Case 2[8]	19 m	Italy	Italy	2018
Case 3[9]	32 y	Portugal	Portugal	2018
Case 4 [10]	18 m	Italy	Switzerland	2018
Case 5 [10]	27 m	Italy	Switzerland	2018
Case 6 [11]	73 y	Spain	España	2018
Case 7[12]	27 y	Yemen	Oman	2016
Case 8[13]	2 y	Siria	Turkey	2015
Case 9[14]	27 y	Colombia	España	2016
Case 10[15]	20 m	Spain	Spain	2015
Case 11[16]	22 m	Spain	Spain	2015
Case 12[17]	73 y	Spain	USA	2014
Case 13[18]	3 m	France	France	2013
Case 14[18]	10 y	France	France	2013
Case 15[19]	21 m	Croatina	Canada	2013
Case 16[20]	4 m	Turkey	Turkey	2012
Case 17[21]	18 m	Tunisia	Tunisia	2010
Case 18[21]	22 m	Tunisia	Tunisia	2010
Case 19[22]	46 y	Israel	Israel	2009
Case 20[23]	9 m	Cyprus	Cyprus	2008
Case 21[24]	15 y	Turkey	Turkey	2007
Case22[25]	2y	Turkey	Turkey	2007
Case 23[26]	34 y	Tunisia	Tunisia	2006
Case 24[27]	5y	Turkey	Turkey	2005
Case 25[28]	2 y	Israel	Israel	2001

Clinical characteristics of HLH associated with Leishmania infection

The most frequently affected patients, by age and sex respectively, were those under 2 years (52%); and men (64%).

Fever was present in all cases, starting 7 to 180 days before diagnosis. Similarly, organomegaly was reported in all patients; all of them at least presented splenomegaly, 84% hepatomegaly and 20% adenopathies. Other common clinical manifestations found in our review were fatigue or asthenia, weight loss, and pallor, reported in approximately 40% of patients (Table 2).

Table 2 - Characteristics of the patients included

Case reports	Age	Gender	F	A	S	L/N	T	HP	LD	H	HF	HT	sCD25/NK
Case 1[7]	27	Male	+	+	+	+	+	+	+	+	+	-	-
Case 2[8]	19 m	Male	+	+	+	+	+	+	+	-	-	+	-
Case 3[9]	32 y	Female	+	+	+	+	+	+	+	-	+	+	-
Case 4 [10]	18 m	Female	+	+	+	+	+	+	+	-	+	-	+
Case 5 [10]	27 m	Female	+	+	+	-	+	-	+*	-	-	-	-
Case 6 [11]	73 y	Male	+	-	+	+	+	+	+	-	+	-	-
Case 7[12]	27 y	Male	+	+	+	+	+	+	+	-	+	+	-
Case 8[13]	2 y	Male	+	+	+	+	+	+	+	+	-	-	-
Case 9[14]	27 y	Female	+	+	+	+	+	+	+	-	+	-	-
Case 10[15]	20 m	Male	+	+	+	-	+	-	+	-	+	+	-
Case 11[16]	22 m	Female	+	+	+	-	+	+	+	-	+	+	+
Case 12[17]	73 y	Male	+	+	+	+	+	+	+	+	+	-	+
Case 13[18]	3 m	Male	+	+	+	+	+	+	+	+	+	+	-
Case 14[18]	10 y	Male	+	+	+	+	+	+	+	-	+	+	-
Case 15[19]	21 m	Male	+	+	+	+	+	+	+	-	-	+	+
Case 16[20]	4 m	Male	+	+	+	+	+	+	+**	-	+	+	-
Case 17[21]	18 m	nr	+	+	+	+	+	+	+	+	+	+	-
Case 18[21]	22 m	nr	+	+	+	+	+	-	+	+	+	-	-
Case 19[22]	46 y	Female	+	+	+	+	+	+	+	+	+	+	+
Case 20[23]	9 m	Female	+	+	+	-	+	-	+	-	+	+	-
Case 21[24]	15 y	Male	+	+	+	+	+	+	+	+	+	+	-
Case22[25]	2y	Male	+	+	+	+	+	+	+	-	+	+	-
Case 23[26]	34 y	Male	+	+	+	+	+	+	+	-	-	+	-
Case 24[27]	5y	Male	+	+	+	+	+	+	+	-	+	+	-
Case 25[28]	2 y	Male	+	+	+	+	+	+	+	-	+	+	+

F: Fever; A: Anemia; S: Splenomegaly; L/N: Leukopenia/Neutropenia; T: Thrombocytopenia; HP: Hemophagocytosis; LD: Leishmania diagnóstic; H: Hypofibrinogenemia; HF: Hyperferritinemia; H: Hypertrigliceridemia; sCD25/NK: High levels of CD25 soluble and/or low natural killer activity; y: years; m: months; +: reported; -: not reported.
*Polymerase chain reaction (PCR); **Immunofluorescence antibody test (IFAT).

Laboratory findings of HLH associated with Leishmania infection

Cytopenias were described in all patients: 100% presented with thrombocytopenia 96% anemia and 84% leukopenia or neutropenia. Regarding the severity of cytopenias, hemoglobin ≤ 7 g/dL was found in 44% patients, platelets < 50 000/uL in 28%, and leukocytes < 2000/mL in 28%. The nadir for hemoglobin, platelets, leukocytes, and neutrophils was; 4 g/dL, 10 000/uL 900/uL, and 360/mL, respectively. Of all patients, 32% required transfusion of one or more blood products. These results are presented in table 1.

Hypertriglyceridemia and hypofibrinogenemia were found in 17 (68%) and 8 (32%) of the patients, respectively. Hyperferritinemia was present in 80%. Additionally, the evidence of hemophagocytosis was documented in 21 patients (84%). Regarding the detection of *Leishmania* infection, the pathogen was visualized in 23 (92%) of cases, and in two cases was detected by indirect methods. In this context, *Leishmania infantum* was the most frequent (36%); however, the *Leishmania* species was not specified in 52% of cases.

High levels of soluble CD 25 were reported in 24% of patients, and a reduced NK activity was reported in 4% of cases.

Laboratory findings non-diagnostic criteria for HLH

Inflammatory markers, including C reactive protein and/or erythrosedimentation rate, were increased in 64% of the reports. Moreover, elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) were observed in 52% of cases. ANA positive test was found in one patient at a titer of 1/1280, and Coombs positive test in 12% of patients.

PET was included in the evaluation of only two patients, in which there was reported splenic metabolic activity

Coinfectous microorganisms were reported in six cases; EBV (20%), Influenza A virus subtype H1N1 (4%), *Klebsiella pneumoniae* (4%), *Staphylococcus aureus* (4%), *Staphylococcus haemolyticus* (4%), and *Escherichia coli* (4%).

Treatment

All patients received treatment against Leishmania: 80% received liposomal amphotericin B; 1 amphotericin B without specifying formulation, and glucantime was used in three (12%) cases. Additionally, one patient died before receiving treatment against Leishmania. Treatment directed to manage HLH included corticosteroid use in 36% (Dexametasone 16%, hidrocortisone 8%, prednisone 4%, not specified 8%), endovenous immunoglobulin in 28%, cyclosporine in 28%, etoposide in 16%, and only one case received rituximab, one received tocilizumab, one received mycophenolate and one undergo splenectomy.

Complications

Complications reported included infectious panniculitis (4%), gastrointestinal hemorrhage (8%), disseminated intravascular coagulation (8%), and hemolytic immune anemia by Coombs+ (12%), multiple-organic dysfunction and/or septic shock (12%) and petechial rash (16%).

Mortality

Four patients died. When compared with the group of patients that survived, we found significant differences in variables such as, number of days with fever (p=0.031), level of hemoglobin (p=0.031), platelet count (p=0.0048), and ferritin levels (p=0.0072). Additionally, patients who died presented transfusional requirement (1/4), lymphadenopathy (2/4), Leishmania infantum infection (2/4), pallor (3/4), male (3/4), mucocutaneous bleeding (3/4), multiple-organ dysfunction (3/4), splenomegaly and hepatomegaly (4/4). Regarding Leishmania treatment, two patients received glucantime as first-line treatment, in one case, liposomal amphotericin b was used as first-line therapy, and one patient died before receiving any drug against Leishmania infection. Regarding HLH treatment, corticoid was used in 2 cases, and one patient received endovenous immunoglobulin.

Regarding concurrent infections, in 2 patients Escherichia coli and Staphylococcus aureus infection were detected.

Discussion

VL is a clinical manifestation of *Leishmania* infection which has a widespread distribution, but especially in tropical and subtropical areas. In our review, we found the countries considered as a possible source of infection belong to the group of countries with the highest prevalence reported by the WHO.[3] In this context, the main types of *Leishmania* were *infantum* and *donovani*, finding that was predicted as the majority of cases in our review came from the Mediterranean region and Asia.

Secondary HLH has been associated with infectious conditions as was presented in a descriptive study in which a cohort of 250 adult patients treated at Mayo Clinic in Rochester, Minnesota. Among them, 34% were associated with an infectious cause.[29] A similar finding was reported in a study conducted in France including 162 adult patients among which infections were associated with HLH in 24.4%.[30]

As reviewed by Grzybowski B and Vishwanath VA, with regards to the clinical manifestations, it is frequent the prolonged fever, hepatosplenomegaly, and the high serum ferritin levels.[31] Additionally, common laboratory alterations are pancytopenia, elevated liver function tests, elevated D-dimer, hypertriglyceridemia, and hypofibrinogenemia. Also, respiratory distress and altered coagulation are reported complications of HLH.[31] We evidenced all those clinical manifestations, laboratory findings, as well as the complications presented. Additionally, there was reduced use of CD25 soluble and natural killer activity.

As reviewed by George MR, non-viral infections account for 20% of all the causes associated with secondary HLH. Among these, protozoan infection is an important cause, especially in endemic countries. In this context, in spite of protozoarian diseases are not a frequent infectious cause of HLH, the more relevant protozoarian involved in hemophagocytic syndrome are *Leishmania* sp, *Plasmodium* sp, and *Toxoplasma Gondii*.[32]

According to the study presented by *Shu* et al. in 2010 at the Xijing Hospital, in a series of 28 patients diagnosed with Hemophagocytic syndrome, two cases were associated with *Leishmania* infection.[33] Concerning HLH associated with *Leishmania* infection, in the systematic review conducted by Rajagopala S and Singh N in the Indian subcontinent, VL was the trigger of hemophagocytic syndrome in 40,6% of adult cases with infection-related HLH.[34] In the report performed in Germany by Bode SFN et al., in 2014, there were included 13 patients diagnosed with HLH secondary to *Leishmania*, all of them imported, mainly from Spain. Similarly to our findings, among the cases reported in this paper, thrombocytopenia, hemophagocytosis, fever, and splenomegaly were present in the 100%,

hemoglobin under 9 g/dL was evidenced in 85%, neutrophils under 1000/mL in 62%, ferritin in 87%, hypofibrinogenemia 45%, and hypertriglyceridemia 60%. Additionally, they reported as first-line treatment against leishmania amphotericin B in 12 patients and one sodium stibogluconate, from them, five patients received L-AmB without previous or concomitant immunosuppression. L-AmB led to the cure of visceral leishmaniasis in 11 cases. In 9 patients (75%), a standard protocol with less than ten days was enough to achieve resolution of VL. Regarding the use of HLH directed therapy, four patients received etoposide, corticosteroid, and cyclosporine A, 2 of whom were given full HLH-2004 induction regimen, and one had a hematopoietic stem cell transplantation. To conclude, in this German study, it was denoted that if therapy directed to HLH is started without treating VL, a more prolonged remission cannot be reached.[35]

To overcome VL, liposomal Amphotericin B has been recommended as first-line therapy.[36] This strategy was observed in the majority of cases included in our study. However, in spite of two of the four patients who deceased received glucantime as first-line therapy, we cannot conclude the superiority of liposomal Amphotericin B when HLH is present. Regarding the use of specific therapy to control HLH, our results reflect that a group of patients overcame the disease when the underlying cause was treated with or without the concomitant use of corticoids, immunoglobulin, cyclosporin A, or etoposide. This phenomenon was previously suggested in the revision made by *Jordan et al.*[37] Although, it is essential to highlight that in the patients included in our study, who didn't receive immunosuppressive therapy, they were promptly treated against Leishmania.

Similarly to our findings, in a study conducted in Brazil, the mortality in pediatric VL has been associated with mucosal bleeding (OR 4.1, 95% CI 1.3-13.4), jaundice (OR 4.4, 95% CI1.7-11.2), dyspnea (OR 2.8, 95% CI 1.2-6.1), suspected or confirmed bacterial infections (OR 2.7, 95% CI1.2-6.1), neutrophil count < 500/mm^3 (OR 3.1, 95% CI1.4-6.9) and platelet count < 50 000/mm^3 (OR 11.7, 95% CI 5.4-25.1).[38] Also, a study conducted in Central Tunisia demonstrated as risk factors for in-hospital death; bleeding at admission (OR= 25.5, 95% CI: 2.26-287.4; p= 0.009), white cell count less than 4000/mm^3 (OR= 5.66, 95% CI: 1.16-27.6; p= 0.032), cytolysis (OR= 28.13, 95% CI: 4.55-173.6; p< 0.001), and delay between onset of symptoms and admission ≥ 15 days (OR= 11, 95% CI: 1.68-72; p= 0.012).[39] Regarding a late in hospital admission, we found that the higher the number of days with fever the higher the mortality.

In another study, including adult patients diagnosed with VL, in the group of deceased patients was significant the lower number of red cells (p= 0.014), but in contrast to our

findings, they found a higher percentage of segmented neutrophils (p= 0.002). Also, in this report, the main risk factors associated with death were secondary bacterial infection (OR 42.86, 95% CI 5.05-363.85), relapse (OR 12.17, 95% CI 2.06-71.99), edema (OR 7.74, 95% CI 1.33-45.05) and HIV/AIDS co-infection (OR 7.33, 95% CI 1.22-43.98).[40] In the case of concomitant bacterial infections, in our review half of deceased patients were positive to a bacterial infection. However we cannot establish a statistical conclusion as the number of patients included is reduced.

Limitations

The main limitation of this review is the fact that we only had access to the information published in each case report included. Also, as the number of patients included in this review is small, we cannot make conclusions regarding the best therapeutic option or the main predictor factors to estimate the risk of death in HLH patients

Conclusions

Secondary HLH associated with VL infection is a rare disease that mainly affects pediatric patients and often presents thrombocytopenia, anemia, splenomegaly, leukopenia, hyperferritinemia, and hemophagocytosis, along with the evidence of Leishmania infection through visual detection of the parasite in the bone marrow. Additionally, we found potential risk factors associated with death; prolonged time with fever, lower levels of hemoglobin and platelets, and higher levels of ferritin. to add, recurrent clinical signs in deceased patients were mucocutaneous bleeding, hepatomegaly, splenomegaly, and the main complication in this group was multi organic dysfunction

The experience in many case reports, as well as case series, presents liposomal amphotericin B as the preferred option.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors support

David Garrido: The conception, design, and analysis, interpretation of the data; elaboration or critical revision.

Michelle Fuseau: The conception, design, and analysis, interpretation of the data; elaboration or critical revision.

Santiago Garrido: The conception, design, and analysis, interpretation of the data; elaboration or critical revision.

Santiago Celi: The conception, design, and analysis, interpretation of the data; elaboration or critical revision.