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ORIGINAL ARTICLE

Hemophagocytic syndrome in patients living with HIV: a retrospective study

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Abstract

Various infectious diseases can hyper-stimulate the immune system, causing hemophagocytic syndrome (HPS). Little is known regarding the accuracy of diagnostic criteria and epidemiological triggering factors in the acquired immunodeficiency syndrome (AIDS) setting. We investigated the major infectious disease triggers of HPS in patients living with human immunodeficiency virus (HIV)/AIDS and determined the accuracy of bone marrow aspiration (BMA). The inclusion criteria were (i) confirmed HIV diagnosis, (ii) bone marrow aspiration, and (iii) a minimum of four HPS criteria. Patients were further classified into those with four presumed HPS criteria, or ≥ 5 confirmed criteria. The disease triggers, accuracy of bone marrow aspiration, and prognosis markers were examined. Presumed HPS was observed in 15/36 patients (41%), and confirmed HPS in 58% ($n = 21$). The major etiological triggers were infection with *Mycobacterium* (34%), *Cytomegalovirus* (14%), *Cryptococcus neoformans* (11%), and hematological or tumoral disease (11%). BMA demonstrated 93% specificity on screening diagnosis (odds ratio [OR] 12.7, 95% confidence interval [CI] 1.4–115.1, $P = 0.01$). Ferritin > 5000 ng/mL correlated with probability of death in univariate analysis (OR 6.00, 95% CI 1.33–27.05, $P = 0.02$). Ferritin performance as test of death probability presented area under the curve as 0.74 (95% CI 0.56–0.91, $P = 0.016$). However, neither cluster of differentiation for lymphocyte count nor HIV viral load correlated with patient deaths. *Mycobacterium* spp. and *Cytomegalovirus* were the main factors triggering HPS, followed by *Cryptococcus neoformans*, and hematological and tumoral diseases. High ferritin levels were associated with increased death probability. High specificity was noted with BMA.

Keywords AIDS · HIV · Ferritin · Hemophagocytic syndrome

Background

Hemophagocytic syndrome (HPS)—first described in 1939 [1]—is caused by the deregulated activation and proliferation of lymphocytes [2]. Diagnosis is based on clinical and laboratory criteria, including fever, splenomegaly, cytopenias, hypertriglyceridemia or hypofibrinogenemia, positive demonstration of hemophagocytosis process, and elevated cluster of differentiation (CD)25 concentration and natural killer (NK)-cell activity (see Table 1) [3]. HPS is usually classified as either a primary (genetic) or secondary (reactive) syndrome. In adults, the most common cause of HPS includes infection [4].

HPS was first associated with viral infections in 1979 in a report by Risdall et al. [5]. In 2009, human immunodeficiency virus (HIV) itself was demonstrated to be a possible cause of HPS, regardless of the HIV-associated opportunistic infections [6]. The incidence of HPS and its triggers in people living with HIV may be varied depending on their CD4 lymphocyte count, geographic location, and exposure to pathogens. Prior to initiation of highly active antiretroviral therapy (HAART), hemophagocytosis was found in 10% of bone marrow biopsies in HIV-positive patients [7]. In the last decade, *Herpes* viruses and *Mycobacterium* infections have been the most common causes of HPS in HIV-positive patients [4, 6, 8].

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Table 1 Definitions of the criteria considered for the diagnosis of hemophagocytic syndrome

Fever > 38.5 °C
Splenomegaly
Peripheral blood cytopenia, along with at least two of the following
Hemoglobin < 10 g/dL
Absolute neutrophil count < 1000/μL
Platelets < 100,000/μL
Triglyceridemia > 265 mg/dL, or fibrinogen levels < 150 mg/dL
Hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver
Low or absent NK cell activity
Ferritin levels > 500 ng/mL
Elevated soluble CD25 levels

CD cluster of differentiation, *NK* natural killer

However, there is a dearth of information regarding HPS in the HIV setting.

HPS may be classified as either presumed or confirmed, depending on whether patients meet the aforementioned criteria (see Table 1). However, patients do not completely meet the diagnostic criteria during the early stages of the disease, a fact that can often delay diagnosis and increase mortality rates [6]. Recently, Fardet et al. proposed a diagnostic score taking into account underlying immune deficiency, maximal temperature, organomegaly, cytopenias, and hemophagocytic features in bone marrow aspirate, as well as serum triglyceride, ferritin, aspartate aminotransferase (AST), and fibrinogen levels [9].

In this study, we retrospectively analyzed patient records in order to evaluate clinical, laboratory, and etiological data of HPS in a cohort of HIV-positive patients. Additionally, we also evaluated the sensitivity and specificity of HPS detection via bone marrow aspiration.

Methods

In July 2016, we conducted a retrospective study in a South American infectious disease reference hospital—Emilio Ribas Institute of Infectious Disease—in São Paulo, Brazil. We reviewed all bone marrow aspirate biopsies performed between January and December 2015. Additionally, the patient medical records and laboratory results were also reviewed. This study is according to and approved by ethics committee.

Inclusion and exclusion criteria

Patients were included in the study if they (i) had a confirmed HIV diagnosis and (ii) had undergone a bone marrow aspirate biopsy, as well as met ≥ 4 of the HPS criteria: fever (≥ 7 days of high temperature [≥ 38.5 °C {101.3 °F}]), splenomegaly (a palpable spleen > 3 cm below the costal margin, or as determined by radiological examination), cytopenia (≥ 2 of the three hematopoietic lineages; hemoglobin < 90 g/L, platelets < 100×10^a/L, neutrophils < 1.0×10^a/L), low fibrinogen (< 1.5 g/L) or hypertriglyceridemia (> 3.0 mmol/L), hemophagocytosis without evidence of malignancy, low or absent NK cell activity, hyperferritinemia (> 500 ng/mL), and increased soluble CD25 levels (> 2400 U/mL). Data for CD25 levels and NK cell activity were not available in the present study. Patients were excluded if the data and medical records were not clear.

Classification

Patients were classified as having either presumed HPS (four criteria) or confirmed HPS (≥ 5 criteria).

Data and medical records

Baseline demographic, clinical, and laboratory (plasma HIV-1 ribonucleic acid [RNA], CD4 or CD8 lymphocyte counts, leucocyte and platelets counts, as well as hemoglobin, fibrinogen, ferritin, and triglyceride levels) data were collected. All biological parameters were available either on the day of bone marrow aspiration or 3 days prior.

Data on the etiology of HPS and the outcome of the included patients were collected.

Statistical analysis

Chi-squared and Fisher's exact tests were used in the analyses of categorical variables. Mann-Whitney *U* tests were performed for the analyses of continuous variables. Data were fit within a receiver operating characteristic (ROC) curve using the IBM SPSS v.22 statistical software (IBM Corp., Armonk, NY, USA). Significance was set at $P < 0.05$.

Results

General results

A total of 140 medical records were collected from patients who underwent bone marrow aspirate biopsy. Forty-four patients met the ≥ 4 criteria for HPS diagnosis, of which 36 were HIV-positive, none of whom were newly diagnosed. Demographic characteristics of this population are listed in Table 2.

Presumed HPS was observed in 41% ($n = 15$) of the patients, and confirmed HPS in 58% ($n = 21$). Based on the diagnostic criteria, fever and hyperferritinemia were found to be highly prevalent and present in 100% of cases, followed by bicytopenia in 97% ($n = 35$), splenomegaly in 83.3% ($n = 30$), and hypertriglyceridemia in 58% ($n = 21$) of the patients. The remaining markers were present at lower percentages,

Table 2 Demographic characteristics among HIV-positive patients with presumed and confirmed HPS at the Institute of Infectious Disease Emílio Ribas

	Confirmed HPS ($n = 21$)	Presumed HPS ($n = 15$)	P
Male	19	14	0.760
Age (mean (years))	36	38	0.810
Irregular HAART	19	13	0.720
Duration of HIV infection (years) (mean)	7,96	8	0.760
CD4 lymphocyte count (/μL) (mean)	82	85	0.585
Plasma HIV-1 RNA (copies/mL) (mean)	734,163	995,823	0.193
Length of hospital stay (days) (mean)	57	53	0.404

Statistical analysis were performed using chi-squared and Mann-Whitney *U* testing

CD cluster of differentiation, *HAART* highly active antiretroviral therapy, *HIV* human immunodeficiency virus, *HPS* hemophagocytic syndrome, *RNA* ribonucleic acid

including hypofibrinogenemia (33% of patients, $n = 12$) and adenomegaly (36%, $n = 13$). Clinical and laboratory findings are presented in Table 3.

Etiologies

The major etiological triggers of HPS were infection with *Mycobacteria* (34%), *Cytomegalovirus* (14%), and *Cryptococcus neoformans* (11%), as well as the presence of hematological or tumoral disease (11%). The tumoral disease included Kaposi Sarcoma ($n = 4$) and lymphoma (non-Hodgkin [$n = 2$] and Hodgkin lymphoma [$n = 1$]). The etiological triggers are presented in Table 4. Twenty-four (66%) patients presented ≥ 2 possible trigger diagnoses aside from HIV infection, which was diagnosed in 76% and 53% of the patients in the presumed and confirmed groups, respectively. Different diseases combinations in patients who presented more than one possible trigger are demonstrated in Table 5.

Screening tests criteria

Hemophagocytosis was observed in bone marrow aspirates in 30% of the patients ($n = 11$), 90% vs. 10% in the confirmed, and presumed groups, respectively ($P = 0.01$, odds ratio [OR] 12.7, 95% confidence interval [CI] 1.4–115.1). Sensitivity was 47%, and specificity was 93%. Neither triglyceride nor fibrinogen levels displayed acceptable accuracy for diagnosis of HPS. Ferritin level as a diagnostic test demonstrated an area under the curve (AUC) of the ROC of only 0.52, $P = 0.86$. Data on CD25+ lymphocyte and NK cell counts were not available.

Outcomes

Data were collected until either patient death or discharge; thus, outcomes were only evaluated in-hospital. Despite receiving appropriate treatment for HIV and its complications through antibiotic therapy and HAART, the mortality rate of patients was 44%. Only four patients received treatment with intravenous immunoglobulin or high doses of corticosteroids, of whom two subsequently died. Ferritin levels higher than 5000 ng/mL correlated with probability of death in univariate analysis (OR 6.00, 95% CI 1.33–27.05, $P = 0.02$) (see Table 6). CD4 lymphocyte count, HIV viral load, more than one trigger, and length of stay were not significant in univariate analysis. Evaluation of ferritin performance as a test of

Table 3 Clinical and laboratory findings in presumed and confirmed HPS among HIV-positive patients at the Institute of Infectious Disease Emílio Ribas

	Confirmed HPS ($n = 21$)	Presumed HPS ($n = 15$)	P
Fever	21 (100%)	15 (100%)	
Splenomegaly	19 (90%)	11 (73%)	0.174
Hemoglobin (mean (g/dL))	7.3	7.6	0.974
Neutrophils (mean (cells/μL))	2600	2800	0.949
Platelet (mean (/μL))	87,000	110,000	0.070
Ferritin (mean (μg/L))	6472	4671	0.868
Triglycerides (mean (mg/dL))	248	221	0.658
Fibrinogen (mean (mg/dL))	284	328	0.395
Adenomegaly	8 (38%)	4 (26%)	0.473

Statistical analyses were performed using chi-squared and Mann-Whitney *U* testing

HIV human immunodeficiency virus, *HPS* hemophagocytic syndrome

Table 4 Etiological triggers in presumed and confirmed HPS in HIV-positive patients at the Institute of Infectious Disease Emílio Ribas

	Confirmed HPS ($n = 21$)	Presumed HPS ($n = 15$)	P
Mycobacterium spp.	14	8	0.418
Cytomegalovirus	6	3	0.558
Cryptococcus neoformans	5	2	0.434
Hematological or tumoral disease	3	4	
Kaposi's sarcoma	3	1	0.473
Lymphomas	0	3	0.032
Histoplasma spp.	1	2	0.359
Staphylococcus aureus	1	1	0.806
Leishmania spp.	1	1	0.806
Treponema pallidum	0	2	0.085
Candida albicans	2	0	0.219
Herpes simplex	2	0	0.219
Aspergillus spp.	1	0	0.391
Epstein–Barr virus	0	1	0.230
Strongyloides stercoralis	1	0	0.391
Salmonella spp.	1	0	0.391
Autoimmune disease[a]	1	0	0.391
Undetermined	1	0	0.391
Total			
Patients with only one trigger cause	5	7	
Patients with two or more trigger causes	16	8	0.151

Statistical analysis was performed using chi-squared testing

HIV human immunodeficiency virus, *HPS* hemophagocytic syndrome

[a] Cutaneous porphyria

poor prognosis is shown in Fig. 1 and Tables 7 and 8 (AUC 0.74, 95% CI 0.56–0.91, $P = 0.016$).

Table 5 Diseases associations among patients who presented with > 1 HPS possible trigger

Mycobacterium spp. + *CMV*	5
Mycobacterium spp. + Kaposi's sarcoma	4
Mycobacterium spp. + *Cryptococcus neoformans*	2
Mycobacterium spp. + *Histoplasma* spp.	2
Mycobacterium spp. + *Cryptococcus neoformans* + *Strongyloides stercoralis*	1
Mycobacterium spp. + *CMV* + *Candida albicans*	1
Mycobacterium spp. + *Histoplasma* spp. + non-Hodgkin Disease	1
Mycobacterium spp. + *Treponema pallidum*	1
Mycobacterium spp. + *Herpes simplex*	1
Mycobacterium spp. + *Cutaneous porphyria*	1
Cryptococcus neoformans + *Herpes simplex* + *Candida albicans*	1
Cryptococcus neoformans + *Staphylococcus aureus*	1
CMV + *Aspergillus* spp.	1
Non-Hodgkin disease + *Staphylococcus aureus*	1
Leishmania spp. + Hodgkin Disease	1
Total	24

CMV cytomegalovirus, *HPS* hemophagocytic syndrome

Discussion

In our study, we found 21 and 15 cases of confirmed and presumed HPS, respectively. We used one of the largest published studies of an HIV-positive population diagnosed with HPS. The majority of our study population was male (91%), with a median age of 37 years, and with irregular HAART adherence (89%), as shown in Table 2. Similar results were found in studies conducted in different decades, ranging from the pre-HAART to the HAART era [7, 10, 11], even in scenarios where HIV was not present [12], or in the most recent literature review published [4]. There are no specific studies demonstrating the immunological reasons for these similarities. In other studies involving vascular, cerebral, and systemic inflammation, estrogen seemed to have a protective effect against HPS [13–15]. Therefore, possible explanations include the fact that estrogen

Table 6 Variable selected via chi-squared univariate logistic regression

Variable		OR	95% CI	P
Ferritin levels	≤ 5.000 ng/mL > 5.000 ng/mL	6.00	1.33–27.05	0.020

CI confidence interval, *OR* odds ratio

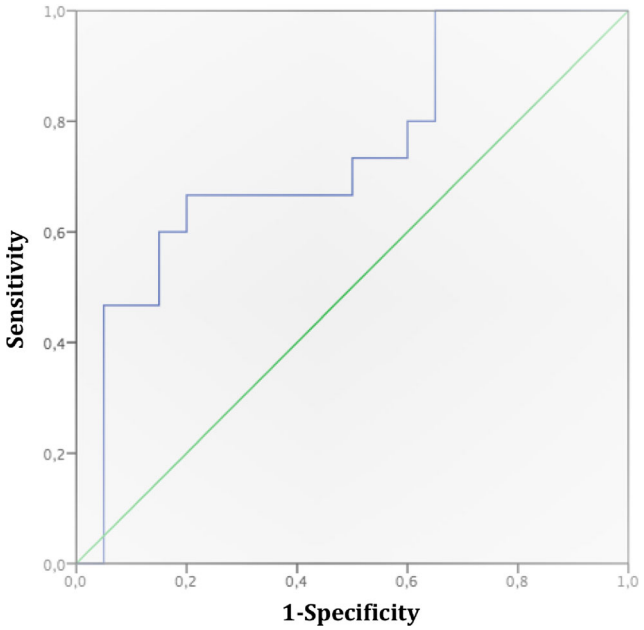

Fig. 1 Area under the receiver operating characteristic curve (AUROC) for ferritin levels

is protective or that the male population experiences greater exposure rates to dangerous pathogens.

The median CD4 lymphocyte count was 35 cells/μL, with an interquartile range (IQR) of 115. Many studies show results that are concordant with our findings. Fardet et al. observed the highest median CD4 count of 101 cell/μL in an HIV-positive population, diagnosed with HPS [11]. Most triggers, infections, or hematological and tumoral diseases are more prevalent in populations with CD4 counts below 200–300 cells/μL. Therefore, a higher HPS prevalence is expected in patients with low CD4 counts, living with HIV/AIDS.

We found infection with *Mycobacterium* spp. (34%) and *Cytomegalovirus* (14%) to be the major etiological triggers of HPS in patients with HIV infection. The prominent triggers of HPS have been noted to vary among different global regions, and between immunocompetent and immunosuppressed populations. In Japan, the main triggers noted in the immunocompetent population were Epstein–Barr virus infection (53%) and lymphoma (19%) [16]. Besides this, *Mycobacterium* sp. infection was shown to be responsible for only 4% of HPS cases in the general population [17]. In Taiwan, again in an immunocompetent population, *Mycobacterium* infection accounted for 23% of HPS cases [18]. In a systematic review, Ramos-Casals et al. found neoplasia to be the main causes of HPS in China, Japan, South-Korea, and Italy [4]. In France, in a study conducted on HIV-positive patients in the pre-HAART era, the main triggers identified were *Toxoplasma gondii* infection, and hematological or tumoral diseases. Unknown triggers were observed in 33% of the population [10]. In another study in France, conducted among HIV-positive patients during the HAART era, neoplastic triggers accounted for 53% of HPS cases, while infectious diseases accounted for 39% thereof; from these, 43% were caused by *Mycobacterium* spp. and 8%, by *Cytomegalovirus* [11]. In contrast, our study found infectious diseases to be the main cause of HPS. It is possible that these differences between global regions may be explained by differential exposure rates to different pathogens. Epidemiological differences between decades may be explained by higher rates of HIV prophylaxis in recent years, and a decrease in the incidence of *Toxoplasma gondii* infection.

Another factor is the significant differences in the molecular technology used as diagnostic tools nowadays. Bone marrow aspirate biopsy demonstrated 93% specificity during screening and diagnosis, with an OR of 12.7 (95% CI 1.4–115.1), $P = 0.01$. Different results were found among published studies, but this non-uniformity might be attributable to the differences in the various methodologies used. Grateau et al. found bone marrow aspirate alteration in 100% of the cases studied. Therefore, it was considered to be an inclusion criterion [10]. Conversely, Fardet et al. found a significant difference between the confirmed and presumed groups—88% and 33%, respectively—demonstrating that specificity was possibly higher than sensitivity [12]. Our results imply that bone marrow aspirate biopsy is an important examination for the confirmation of HPS; however, few studies have been performed to confirm this. Besides traditional criteria, Fardet et al. previously demonstrated a possible diagnostic score (HScore) including known immunosuppressive status, and serum glutamic oxaloacetic transaminase (SGOT) levels (> 30 IU/L), even without CD5 expression levels, or NK cell activity. An HScore higher than 250 was correlated with HPS (probability > 99%) [9]. Therefore, hospitals with limited resources may benefit from these data; however, SGOT levels were not used in this study because these extra factors combined could super estimate HPS, since all

Table 7 Area under the receiver operating characteristic curve (AUROC) for ferritin levels

AUROC	Standard error	*P*	95% confidence interval	
			Lower bound	Upper bound
0.74	0.087	0.016	0.569	0.911

AUROC area under the receiver operating characteristic curve

Table 8 Different cut-off values for ferritin sensitivity and specificity predicting worst outcome

Ferritin (μg/L)	Sensitivity	Specificity
814	100%	5%
3457	74%	50%
5008	60%	85%
10,762	27%	95%

patients had a known immunosuppression, and HAART is known to elevate SGOT levels.

Ferritin was found to be correlated to death in univariate analysis (OR 6.00, 95% CI 1.33–27.05, $P = 0.02$) and a fairly efficient prognostic marker in patients diagnosed with HPS and HIV/AIDS, showing 74% accuracy (AUC 0.74 [95% CI 0.56–0.91], $P = 0.016$). Similar results were found in a study conducted among pediatric patients. Lin et al. found a higher probability of death if ferritin level decreased to less than 50% during treatment [19]. Thus, besides diagnostic criteria, ferritin levels can also be used as a prognostic marker for the monitoring of therapeutic response during treatment for HPS.

Our study had several limitations, the main being its retrospective nature. Besides this, it is possible that many patients were lost during the screening process, because only the patients who underwent bone marrow aspirate biopsy were included, and therefore, we did not have access to data regarding NK cell activity and CD25 counts. Despite these limitations, this was, to our knowledge, the first large study of HPS in a patients living with HIV/AIDS in Latin America, and one of the few similar studies on a global scale. Our results contrast with those from other regions, and show a high prevalence of infectious diseases as triggers for HPS, even during the HAART era.

In conclusion, fever and hyperferritinemia were the most prevalent clinical and laboratory findings. *Mycobacterium* spp. and *Cytomegalovirus* infections were the main triggers of HPS, followed by infection with *Cryptococcus neoformans*, and hematological and tumoral diseases. High levels of ferritin were associated with a higher probability of death, and bone marrow aspirate biopsy presented high specificity, demonstrating an importance to confirm HPS diagnosis. More studies are needed to elucidate the various epidemiological scenarios, and role of each of the screening criteria.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Scott RB, Robb-Smith AH (1939) Histiocytic medullary reticulocytosis. Lancet 2:194–198
2. Verbsky JW, Grossman WJ (2006) Hemophagocytic lymphohistiocytosis: diagnosis, pathophysiology, treatment, and future perspectives. Ann Med 38:20–31
3. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G, for the Histiocyte Society (2007) HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 48:124–131
4. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X (2014) Adult hemophagocytic syndrome. Lancet 383:1503–1516
5. Risdall RJ, McKenna RW, Nesbit ME et al (1979) Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct from malignant histiocytosis. Cancer 44:993–1002
6. Doyle T, Bhagani S, Cwynarski K (2009) Hemophagocytic syndrome and HIV. Curr Opin Infect Dis 22:1–6
7. Sailler L, Duchayne E, Marchou B, Brousset P, Pris J, Massip P, Corberand J, Arlet P (1997) Etiological aspects of reactive hemophagocytoses: retrospective study in 99 patients. Rev Med Interne 18:855–864
8. Lerolle N, Laanani M, Rivière S, Galicier L, Coppo P, Meynard JL, Molina JM, Azoulay E, Aumont C, Marzac C, Fardet L, Lambotte O (2016) Diversity and combinations of infectious agents in 38 adults with an infection-triggered reactive hemophagocytic syndrome: a multicenter study. Clin Microbiol Infect 22:268.e1–268.e8. https://doi.org/10.1016/j.cmi.2015.11.018
9. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, Coppo P, Hejblum G (2014) Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheum 66:2613–2620. https://doi.org/10.1002/art.38690
10. Grateau G, Bachmeyer C, Blanche P et al (1997) Haemophagocytic syndrome in patients infected with the human immunodeficiency virus: nine cases and a review. J Inf Secur 34:219–225
11. Fardet L, Lambotte O, Meynard JL, Kamouh W, Galicier L, Marzac C, de Labarthe A, Cabane J, Lebbe C, Coppo P, Molina JM, Martinez V (2010) Reactive hemophagocytic syndrome in 58 HIV-1-infected patients: clinical features, underlying diseases and prognosis. AIDS 24:1299–1306
12. Schram AM, Comstock P, Campo M, Gorovets D, Mullally A, Bodio K, Arnason J, Berliner N (2016) Haemophagocytic lymphohistiocytosis in adults: a multicentre case series over 7 years. Br J Haematol 172:412–419
13. Sunday L, Tran MM, Krause DN, Duckles SP (2006) Estrogen and progestagens differentially modulate vascular proinflammatory factors. Am J Physiol Endocrinol Metab 291:E261–E267
14. Vegeto E, Benedusi V, Maggi A (2008) Estrogen anti-inflammatory activity in brain: a therapeutic opportunity for menopause and neurodegenerative diseases. Front Neuroendocrinol 29:507–519
15. Hassouna A, Obaia E, Marzouk S, Rateb M, Haidara M (2014) The role of sex hormones in induced-systemic inflammation in female albino rats. Acta Physiol Hung 101:112–127
16. Ishii E, Ohga S, Imashuku S, Yasukawa M, Tsuda H, Miura I, Yamamoto K, Horiuchi H, Takada K, Ohshima K, Nakamura S, Kinukawa N, Oshimi K, Kawa K (2007) Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. Int J Hematol 86:58–65
17. Takahashi N, Chubachi A, Kume M, Hatano Y, Komatsuda A, Kawabata Y, Yanagiya N, Ichikawa Y, Miura AB, Miura I (2001) A clinical analysis of 52 adult patients with hemophagocytic syndrome: the prognostic significance of the underlying diseases. Int J Hematol 74:209–213
18. Tseng YT, Sheng WH, Lin BH, Lin CW, Wang JT, Chen YC, Chang SC (2011) Causes, clinical symptoms, and outcomes of infectious diseases associated with hemophagocytic lymphohistiocytosis in Taiwanese adults. J Microbiol Immunol Infect 44:191–197
19. Lin TF, Ferlic-Stark LL, Allen CE, Kozinetz CA, McClain KL (2011) Rate of decline of ferritin in patients with hemophagocytic lymphohistiocytosis as a prognostic variable for mortality. Pediatr Blood Cancer 56:154–155