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# FROM DIAGNOSIS TO TREATMENT: A SUCCESSFUL CASE OF HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS OF PRESUMED BACTERIAL AETIOLOGY IN AN ADULT

Catarina Pestana Santos, Daniela Cruz, Bruno Gonçalves de Sousa, Tiago Judas

Internal Medicine Department, Hospital Garcia de Orta EPE, Almada, Portugal

**Corresponding author's e-mail:** catarina.pestana.santos@hgo.min-saude.pt

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## ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) affects patients across all age groups and can be classified as either primary HLH (P-HLH) or secondary HLH (S-HLH). The latter is associated with clinical conditions that disrupt normal immunological responses, such as infections, neoplasms or autoimmune diseases. Although HLH can occur sporadically in healthy individuals, it is more frequently observed in patients with haematological malignancies and autoimmune disorders.

The diagnostic process for HLH is often challenging due to its non-specific signs and the absence of pathognomonic findings. The primary objective in treating S-HLH is to eliminate the underlying trigger and control immunological hyperactivation, making the identification and treatment of triggers critically important. Prompt diagnosis and treatment are essential, as the mortality rate remains high. In this context, we present the case of a young woman diagnosed with idiopathic S-HLH, likely triggered by a bacterial infection. The diagnosis was achieved due to a high index of clinical suspicion for S-HLH. The patient exhibited an excellent response to antimicrobial therapy, resulting in the complete resolution of haemophagocytosis. The authors deem it important to present this case to enhance awareness of S-HLH diagnosis, as well as the investigation and management of potential triggers.

## KEYWORDS

Haemophagocytic lymphohistiocytosis, haemophagocytic syndrome, haemophagocytosis, hyperferritinaemia

## LEARNING POINTS

- Haemophagocytic lymphohistiocytosis is characterised as a rare inflammatory syndrome that occurs due to uncontrolled systemic immune activation.
- Timely diagnosis and treatment are essential, as mortality is still high.

## INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH), also known as haemophagocytic syndrome, was first identified in 1939 as a familial genetic syndrome affecting erythrocytes and phagocytic activities, resulting in cytopaenias and clinical features resembling a severe infection[1].

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Currently, HLH is characterised as a rare inflammatory syndrome arising from uncontrolled systemic immune activation[2-8], which manifests clinically and in laboratory findings as intense inflammation. HLH affects patients of all ages and can be classified as primary HLH (P-HLH) or secondary HLH (S-HLH)[1,3].

P-HLH is associated with genetic mutations affecting the cytotoxic functions of T and NK cells and typically presents in children. S-HLH, on the other hand, is linked to clinical conditions that alter the normal immune response such as infections, neoplasms or autoimmune diseases[1,3,4]. Although S-HLH can occur sporadically in healthy individuals, it is more common in patients with haematological malignancies and autoimmune disorders. Other less common aetiologies include medication exposure[1,4], pregnancy and haematopoietic stem cell transplantation[3,4]. Distinguishing between familial and secondary forms can often be challenging. Infections, whether viral or bacterial, are well-known triggers for S-HLH. DNA viruses from the Herpesviridae family are the most common viral agents, with Epstein-Barr virus (EBV) being the most frequently implicated[3,4]. Bacterial agents such as *Staphylococcus aureus*, *Campylobacter spp.*, *Brucella spp.*, *Ehrlichia spp.* and *Borrelia burgdorferi* are less commonly involved. Besides infections, neoplasms are significant triggers for S-HLH, particularly in adults, accounting for approximately 45% of cases[3,4]. Haematological neoplasms are more frequently implicated than solid tumours[3,4], with no clear distinction between lymphoid and myeloid neoplasms.

HLH presents a diagnostic challenge due to the absence of pathognomonic findings and the non-specific nature of its signs[2-4]. Clinical and analytical manifestations of HLH may include fever, hepatosplenomegaly, cytopaenias, hypertriglyceridaemia, hypofibrinogenaemia, liver dysfunction, hyperferritinaemia, elevated serum transaminases, neurological symptoms, lymphadenopathy, skin rashes[1-4] and elevated serum levels of soluble IL-2 receptor (sCD25), a marker of T cell activation[2-4].

In the case of S-HLH, the treatment goals are to eliminate the triggering process and control immunological hyperactivation, making the identification and treatment of triggers critically important[2]. Timely diagnosis and treatment are essential, as the mortality rate remains high[2,5].

## CASE DESCRIPTION

A 50-year-old woman presented with a significant medical history of asthma, hyperthyroidism, two previous spontaneous pneumothoraxes and anxiety. She reported sporadic consumption of alcohol and tobacco, as well as recreational use of smoked and oral drugs. She had home contact with vaccinated dogs and cats and engaged in gardening in a wild garden, without using gloves or any other protection. The patient was admitted to the emergency department with a persistent fever for the past 10 days, peaking at 40°C and showing poor response to antipyretics, accompanied by intense sweating and myalgias. The patient denied pain, shortness of breath, abdominal tenderness, diarrhoea and vomiting.

On physical examination she was febrile (39.1°C) with no altered mental status, with arterial hypotension (80/40 mmHg) and tachycardia (111 bpm), normopneic (fR 20 cpm) and with no supplemental oxygen needed (O2 saturation >94%). Scleral jaundice, dehydration and intense right lumbar pain were also noted (Modified Early Warning Score, 6). No rash, cyanosis, organomegaly or palpable adenomegaly were detected. Initial laboratory tests revealed leukopenia with elevated C-reactive protein (CRP), a pattern of cytocholestasis with marked hyperbilirubinaemia, acute kidney injury and hyponatraemia. The patient subsequently developed thrombocytopaenia and neutrophilia. Thyroid function tests indicated Graves' disease with subclinical hyperthyroidism. Due to hepatic alterations, immediate anti-thyroid medical treatment was not feasible, and she was referred for endocrinology consultation for short-term re-evaluation. Chest radiography, electrocardiogram and arterial blood gas analysis were unremarkable. Given the suspicion of septic shock of abdominal origin, an abdominal ultrasound was performed, but this was also unremarkable. Blood and urine cultures were collected, and empirical antibiotic therapy with ceftriaxone and metronidazole was initiated. Despite haemodynamic stabilisation and autonomous deambulation, the patient continued to exhibit fever and jaundice. Analytical studies showed worsening cytocholestasis and cytopaenias, along with hypertriglyceridemia and hyperferritinaemia. She underwent further investigation for infectious disease as shown in *Table 1*. Based on the clinical and analytical findings, HLH was considered through the calculation of the HScore. Bone marrow biopsy and a myelogram confirmed the presence of haemophagocytosis of multiple neutrophils (2 to 3) by a single reticular-macrophagic cell *(Fig. 1)*. The final diagnosis of secondary HLH (HLH-S), likely triggered by a bacterial infection, was confirmed *(Table 2)*.

Considering the epidemiological history, analytical changes and the lack of a satisfactory response to initial antibiotic therapy, a zoonotic infection (e.g. ehrlichiosis/Anaplasma/leptospirosis) was suspected, leading to the initiation of doxycycline. Plasma serologies and polymerase chain reaction (PCR) tests were all negative. Nonetheless, after starting doxycycline marked clinical and analytical improvement was observed, including apyrexia, regression of jaundice and normalisation of analytical abnormalities, including cytopaenias, hypertriglyceridemia, hyperferritinaemia and cytocholestasis. Progressive decline of inflammatory markers was noted on follow-up.

The patient was clinically discharged after a three-week hospital stay. On clinical re-evaluation three weeks post-discharge, she remained asymptomatic with normalisation of all analytical parameters. She continued regular follow-up with Internal Medicine and Endocrinology consultations and was eventually discharged from Internal Medicine follow-up after two years.

## DISCUSSION

Most cases of secondary haemophagocytic lymphohistiocytosis (HLH-S) are caused by viral infections, though other pathogens such as bacteria, fungi and parasites can also be responsible[2,5]. Neoplastic and autoimmune diseases, particularly lymphoma, must be considered as potential triggers.

In a small percentage of cases, no triggering factor is identified, as observed in this case. Despite an extensive aetiological study, the trigger could not be identified. However, given the clinical and laboratory findings, as well as the patient's excellent response to doxycycline, a bacterial

| Parameters | Result |
|---|---|
| Blood count | Hb 12.3g/dl, platelet 67 x$10^9$/l, leukocyte 2.6 x $10^9$/l, neutrophile 86.4% |
| Stroke volume | 9 |
| Coagulation | Normal |
| Renal function | Cr 1.2 mg/dl, U 58 mg/dl |
| Ionogram | Na 129 mmol/l, K 3.5 mmol/l, Cl 97 mmol/l, P 4.1 mmol/l, Mg 2.4 mmol/l |
| Bilirubin | Total 1.9, direct 1.49 |
| Aspartate aminotransferase | 282 U/l |
| Alanine transaminase | 154 U/l |
| Gamma-glutamyl transpeptidase | 285 U/l |
| Alkaline phosphatase | 278 U/l |
| Lactate dehydrogenase | 1,078 U/l |
| Creatine kinase | 110 U/l |
| Cholesterol | Total 114 mg/dl, HDL 14 mg/dl, LDL 19 mg/dl |
| Triglyceride | 283 mg/dl |
| C-reactive protein | 25.43 mg/dl |
| Procalcitonin | 3.47 ng/ml |
| Total triiodothyronine | 76 ng/dl |
| Free thyroxine | 1.63 ng/dl |
| Thyroid stimulating hormone | 0.03 mU/l |
| Serum iron | 132 U/l |
| Ferritin | 14,121 U/l |
| Transferrin | 95 mg/dl |
| Transferrin saturation | 99.5% |
| Vitamin B12 | >2,000 |
| Folic acid | 5.3 ng/ml |
| VIH 1 e 2 | Negative |
| Ag HBs, Ab anti-HBs, Ab anti-HBc, Ab anti-VHC, Ab anti-VHA | Ac anti-HBs positive only |
| Ab para VIH 1 and 2 | Negative |
| Treponema pallidum | Negative |
| Ab para toxoplasma gondii | Negative |
| Ab CMV | IgG positive, IgM negative |
| Ab anti-HSV 1, Ab anti-HSV 2 | HSV 1: IgG positive, IgM negative |
| HSV 2: negative | |
| Ab anti-EBV | IgG positive, IgM negative |
| Ab parvovírus B19 | IgG positive, IgM negative |
| Ab mycoplasma pneumonia | Negative |
| Ab Coxiella burnetii | Negative |
| Ab Borrelia burgdorferi | Negative |
| Ab Brucella | Negative |
| Ab Rickettsia conorii | Negative |
| Autoimmunity study (ENA, ANA and ANCA) | Negative |
| Arterial blood gas analysis | pH 7.42, $pO_2$ 88.8, $pCO_2$ 30.2, $SO_2$ 97.6%, $HCO_3$ 19.6, lac 1.2 |
| Interleucine-6 | 20.54 pg/ml (<7) |
| Soluble IL-2 receptor (sCD25) | 17,200 pg/ml |
| HFE gene | Heterozygosity for H63D and C282Y mutations |
| Ehrlichia medullary blood PCR | Negative |
| Anaplasma medullary blood PCR | Negative |
| Leptospira | Negative |
| Computed tomography scan of the neck, chest and abdomen | Hepatomegaly |

*Table 1. Aetiological investigation.*

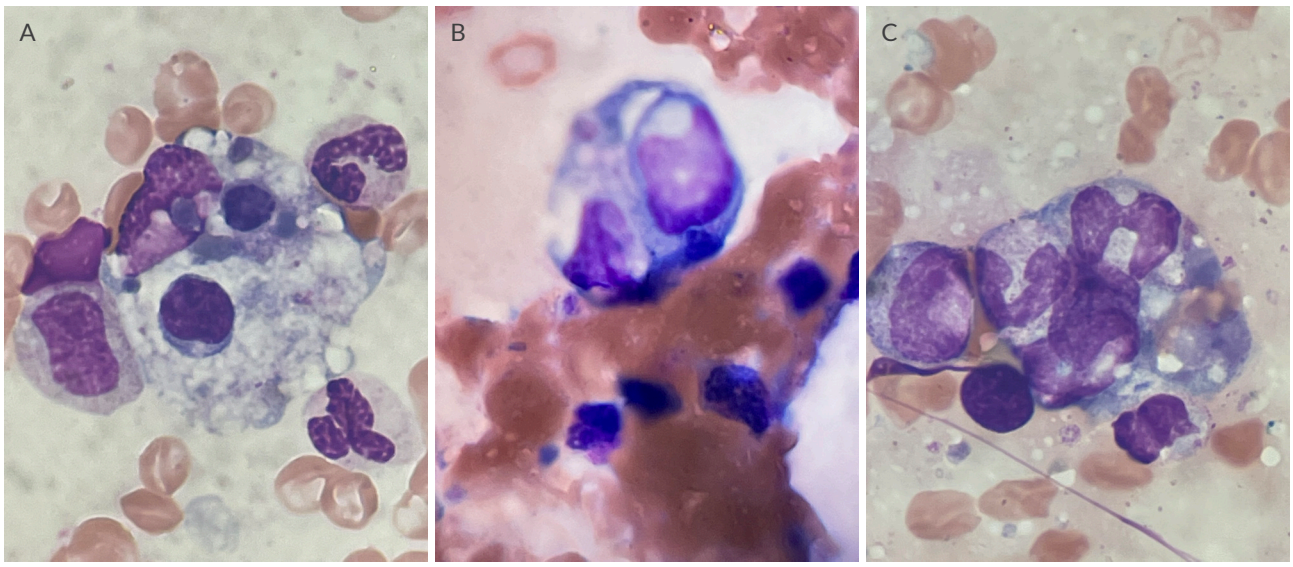


*Figure 1. Findings in bone marrow aspirate. Marked haemophagocytosis. Predominant phagocytosis of A) multiple neutrophils and lymphocytes by the same macrophage cell, B) multiple neutrophils by a single macrophage cell and C) lymphocytes and erythroblasts by a single macrophage cell.*

| HScore parameters | Patient score |
|---|---|
| **Known underlying immunosuppression**<br>No: 0 points<br>Yes: 18 points | 0 |
| **Temperature (°C)**<br><38.4°C: 0 points<br>38.4–39.4°C: 33 points<br>> 39.4°C: 49 points | 33 |
| **Organomegaly**<br>No: 0 points<br>Hepatomegaly or splenomegaly: 23 points<br>Hepatomegaly and splenomegaly: 38 points | 23 |
| **No of cytopaenias**<br>1 lineage: 0 points<br>2 lineages: 24 points<br>3 lineages: 34 points | 24 |
| **Ferritin (ng/ml)**<br><2,000: 0 points<br>2,000–6,000: 35 points<br>>6,000: 50 points | 50 |
| **Triglyceride (mg/dl)**<br>< 132.7: 0 points<br>132.7–354: 44 points<br>>354: 64 points | 44 |
| **Fibrinogen (mg/dl)**<br>>250: 0 points<br><250: 30 points | 0 |
| **AST (U/l)**<br><30: 0 points<br>>30: 19 points | 19 |
| **Haemophagocytosis on bone marrow** aspirate<br>No: 0 points<br>Yes: 35 points | 35 |
| **Total** | 228 |

*Table 2. HScore for this patient.*

infection was presumed to be the trigger for HLH-S. There are two accepted diagnostic scoring systems for HLH: HLH-2004 and the HScore. The latter was developed to estimate the probability of reactive HLH-S[1,5] and includes nine variables[1,4,7], offering an independent system that addresses the main limitations of HLH-2004[7]. Based on this score, our patient had a very high probability of HLH-S.

Haemophagocytosis is defined as the phagocytosis of blood cells by activated macrophages, typically observed in a bone marrow smear. Despite being part of the diagnostic criteria, its presence is neither necessary nor sufficient to diagnose HLH[2,3,7], as haemophagocytosis can occur in various inflammatory conditions such as sepsis, malaria and blood transfusions[2,7,9].

As shown in *Fig. 1*, our patient exhibited haemophagocytosis, including phagocytosis of lymphocytes, erythroblasts and around 2–3 neutrophils by the same macrophage cell, an important criterion for HLH.

The diagnosis of HLH-S was considered after observing a serum ferritin level of 14,121 U/l and a high transferrin saturation of 99.5%. Hyperferritinaemia raised suspicion for HLH, but did not confirm the diagnosis[9]. There is significant overlap in the clinical features of sepsis and HLH-S, both of which involve intense inflammation. Differentiating these conditions is crucial, as HLH treatment aims to suppress the immune response, which could be detrimental in a septic patient. HLH can be triggered or complicated by sepsis, and this possibility should be considered in patients with septic conditions who do not respond to therapy and supportive measures[4]. In our patient's case, persistent analytical abnormalities such as cytopaenias, hepatic cholestasis, hypertriglyceridemia, hyperferritinaemia and hyponatraemia, as well as fever and jaundice, led us to consider HLH as a diagnosis, which was confirmed by elevated IL-2 receptor levels (17,200 pg/ml).

The primary objective in treating HLH-S is to eliminate the triggering process and control immunological

hyperactivation, making it crucial to address the underlying cause[2]. When bacterial infection is the cause, prompt antibiotic treatment is essential. However, in some cases, immunosuppressive therapy, such as systemic corticosteroids and anakinra, may be necessary. Without treatment, the survival rate of HLH is estimated to be less than 10%[10]. In the case described, although the primary infectious agent was not identified, the authors concluded that an intracellular bacterial trigger was most likely. Given the suspicion of zoonosis and the patient's excellent response to doxycycline therapy, immunosuppressive therapy was not initiated. This case underscores the importance of treating the trigger of HLH-S to control hyperinflammation.

## REFERENCES


1. Skinner J, Yankey B, Shelton BK. Hemophagocytic lymphohistiocytosis. *AACN Adv Crit Care* 2019;**30**:151–164.
2. Griffin G, Shenoi S, Hughes GC. Hemophagocytic lymphohistiocytosis: an update on pathogenesis, diagnosis, and therapy. *Best Pract Res Clin Rheumatol* 2020;**34**:101515.
3. Al-Samkari H, Berliner N. (2018). Hemophagocytic lymphohistiocytosis. *Annu Rev Pathol* 2018;**13**:27–49.
4. Ponnatt TS, Lilley CM, Mirza KM. Hemophagocytic lymphohistiocytosis. *Arch Pathol Lab Med* 2022;**146**:507–519.
5. Campo M, Berliner N. Hemophagocytic lymphohistiocytosis in adults. *Hematol Oncol Clin North Am* 2015;**29**:915–925.
6. Pai TS, Stancampiano FF, Rivera C. Hemophagocytic lymphohistiocytosis for the internist and other primary care providers. *J Prim Care Community Health* 2021;**12**:21501327211053756.
7. Machowicz R, Basak, G. How can an internal medicine specialist save a patient with hemophagocytic lymphohistiocytosis (HLH)? *Pol Arch Intern. Med* 2020;**130**:431–437.
8. Naymagon, L. Can we truly diagnose adult secondary hemophagocytic lymphohistiocytosis (HLH)? A critical review of current paradigms. *Pathol Res Pract* 2021;**218**;153321.
9. Kim YR, Kim DY. Current status of the diagnosis and treatment of hemophagocytic lymphohistiocytosis in adults. *Blood res* 2021;**56**:S17–S25.
10. Allen CE, McClain KL. Pathophysiology and epidemiology of hemophagocytic lymphohistiocytosis. *Hematology Am Soc Hematol Educ Program* 2015;**2015**:177–182.