

Visceral Leishmaniasis Presenting as Hemophagocytic Lymphohistiocytosis in a Non-endemic Setting: A Case Report

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Abstract

Visceral leishmaniasis (VL) is a protozoal infection that can mimic other systemic inflammatory conditions, particularly in non-endemic regions. Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome that may occur secondary to infections, including leishmaniasis. We present the case of a 26-year-old immunocompetent man in the United Kingdom with fever, cytopenias, and hepatosplenomegaly. Despite broad-spectrum antimicrobial therapy, he remained persistently unwell with worsening laboratory parameters. Clinical features and laboratory findings raised suspicion of HLH, prompting treatment with anakinra; corticosteroids were added after diagnostic sampling. Further investigations confirmed VL through serology, polymerase chain reaction, and histopathology. The patient was treated with liposomal amphotericin B, resulting in rapid clinical improvement. This case illustrates the diagnostic challenge of identifying VL as the underlying trigger of HLH and the value of combining serological, molecular, and histopathological investigations when initial diagnostic findings are inconclusive in patients presenting with HLH features in non-endemic settings.

Categories: Hematology, Internal Medicine, Infectious Disease

Keywords: anakinra, cytopenia, hemophagocytic lymphohistiocytosis, hepatosplenomegaly, hscore, imported tropical disease fever of unknown origin, liposomal amphotericin b, secondary hlh, visceral leishmaniasis

Introduction

Leishmaniasis is a protozoal parasitic disease transmitted by the bite of an infected female phlebotomine sandfly. It manifests in three main clinical forms: cutaneous, mucocutaneous, and visceral [1]. Visceral leishmaniasis (VL) is caused primarily by *Leishmania donovani* and *Leishmania infantum* and remains endemic in parts of East Africa, South Asia, and South America. Historically, approximately 90% of the global VL burden was concentrated in a small number of countries, although the countries accounting for the majority of cases have changed over time [2]. In non-endemic countries, population movement from endemic regions highlights the importance of considering VL in patients with compatible clinical features and relevant travel or migration histories.

VL typically presents with prolonged fever, weight loss, splenomegaly, and, less commonly, hepatomegaly. Laboratory findings frequently include pancytopenia, hypergammaglobulinemia, and varying degrees of immunosuppression. Untreated VL may be complicated by severe systemic manifestations, including hemophagocytic lymphohistiocytosis (HLH), disseminated intravascular coagulation, and acute kidney injury [3].

HLH is a life-threatening hyperinflammatory syndrome that may be triggered by infections, malignancies, or autoimmune and autoinflammatory conditions. Although traditionally classified as primary or secondary, HLH is increasingly conceptualized as a heterogeneous spectrum of immune dysregulation in which genetic predisposition and acquired inflammatory triggers, including infection, may interact to drive disease [4]. In VL, persistent parasitic infection can promote macrophage activation and dysregulated cytokine production, contributing to the hyperinflammatory response characteristic of HLH [5]. The two conditions share clinical and laboratory features, including prolonged fever, hepatosplenomegaly, and pancytopenia. In non-endemic settings, these overlapping features may obscure the underlying infectious trigger and delay diagnosis, particularly when the patient's travel or migration history is not initially linked to the presenting clinical features [5].

This case illustrates the diagnostic challenge of distinguishing VL from other causes of HLH and highlights the importance of targeted parasitological investigations when the underlying trigger of hyperinflammation remains uncertain.

Case Presentation

A 26-year-old immunocompetent man presented with a 12-day history of fever associated with shivering,

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night sweats, marked lethargy, and significantly reduced appetite, with minimal oral intake over the preceding week. This was accompanied by generalized abdominal pain, non-bloody loose stools occurring two to three times daily, and vomiting for the preceding week. He denied respiratory or urinary symptoms, headache, joint pain, or skin rashes. He had migrated from Sudan approximately 15 months previously and denied previous tuberculosis infection or known exposure.

On examination, he was febrile (39.4°C), tachycardic, and hypotensive (blood pressure, 91/60 mmHg). Abdominal examination revealed hepatosplenomegaly with a soft, nontender abdomen. Inguinal lymphadenopathy was also present. Cardiovascular and respiratory examinations were otherwise unremarkable. His National Early Warning Score (NEWS) 2 [6] was 6.

Initial laboratory investigations revealed a hemoglobin level of 80 g/L, a white blood cell count of $4.3 \times 10^9/\text{L}$, and a platelet count of $217 \times 10^9/\text{L}$. C-reactive protein was elevated at 288 mg/L, and serum ferritin was markedly elevated at 24,980 µg/L. Other abnormalities included an alkaline phosphatase level of 499 IU/L, an international normalized ratio of 1.4, and an albumin level of 21 g/L. On hospital day 5, fibrinogen, triglycerides, and aspartate aminotransferase (AST) levels were measured at 3.49 g/L, 3.7 mmol/L, and 38 IU/L, respectively.

The patient was initially managed for presumed sepsis of unknown origin. Blood cultures were negative. Given his clinical presentation and epidemiological history, differential diagnoses included tuberculosis, brucellosis, typhoid fever, viral infections including cytomegalovirus and Epstein-Barr virus, and hematological malignancy. Adult-onset Still's disease was considered less likely in the absence of arthralgia and rash.

Computed tomography of the thorax, abdomen, and pelvis confirmed hepatosplenomegaly, with a liver span of 19 cm and spleen span of 13.5 cm (Figure 1). A left axillary lymph node was identified on CT but was not amenable to biopsy.

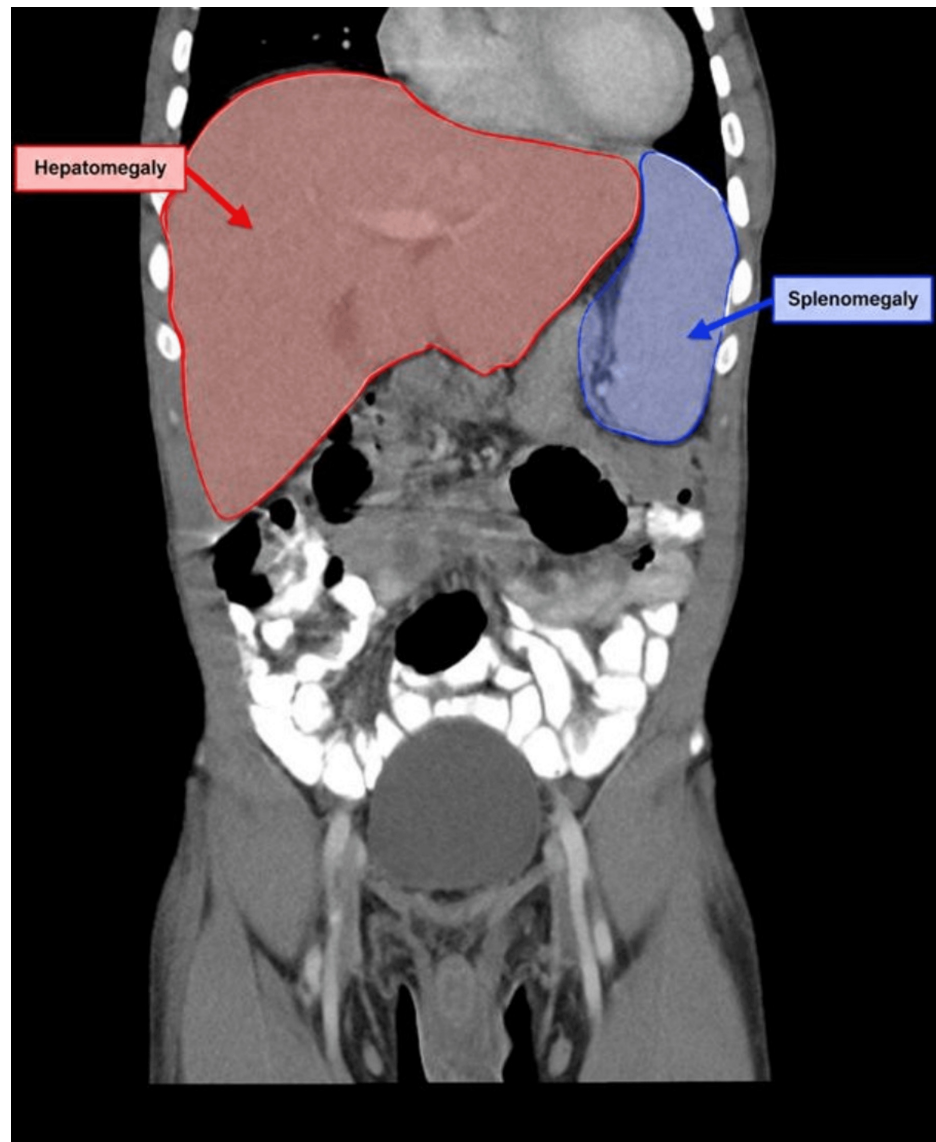


FIGURE 1: Coronal contrast-enhanced computed tomography image demonstrating hepatomegaly and splenomegaly, with the enlarged liver and spleen outlined and labelled.

Given the combination of persistent fever, hepatosplenomegaly, progressive cytopenias, hypertriglyceridemia, and marked hyperferritinemia, HLH was suspected. On hospital day 5, the HScore [7] was calculated as 208 points, indicating a high probability of HLH. The score comprised 33 points for a temperature of 39.4°C, 38 points for hepatosplenomegaly, 24 points for two cytopenic lineages, 50 points for a ferritin level greater than 6,000 µg/L, 44 points for triglycerides of 3.7 mmol/L, and 19 points for an AST level of 38 IU/L. No points were assigned for immunosuppression, hypofibrinogenemia, or hemophagocytosis at the time of assessment.

The HScore is a probabilistic tool used to estimate the likelihood of HLH in adults, whereas the HLH-2004 criteria [8] provide a separate diagnostic framework. In this case, the HScore of 208 indicated a high probability of HLH. The patient initially fulfilled five of the eight HLH-2004 criteria: fever (39.4°C), splenomegaly (spleen span, 13.5 cm), cytopenias affecting at least two peripheral blood cell lineages, hypertriglyceridemia (3.7 mmol/L), and hyperferritinemia (24,980 µg/L). Cytopenias initially manifested as anemia and neutropenia before progressing to pancytopenia. Hypofibrinogenemia was absent (fibrinogen, 3.49 g/L), while soluble CD25 levels and natural killer cell activity were unavailable.

Specialist hematology and rheumatology input was obtained, and subcutaneous anakinra was initiated at 2 mg/kg once daily on hospital day 5, following rheumatology advice. Systemic corticosteroids were initially withheld while infectious causes were investigated and diagnostic sampling was undertaken.

Bone marrow aspirate demonstrated increased megakaryocytes and macrophages, with evidence of hemophagocytosis, fulfilling a sixth HLH-2004 criterion. Bone marrow trephine biopsy demonstrated hypercellular marrow without evidence of granulomatous inflammation (Figure 2). Correlation of the trephine biopsy, bone marrow aspirate, and flow cytometry showed no evidence of infiltrative hematological malignancy or lymphoproliferative disorder.

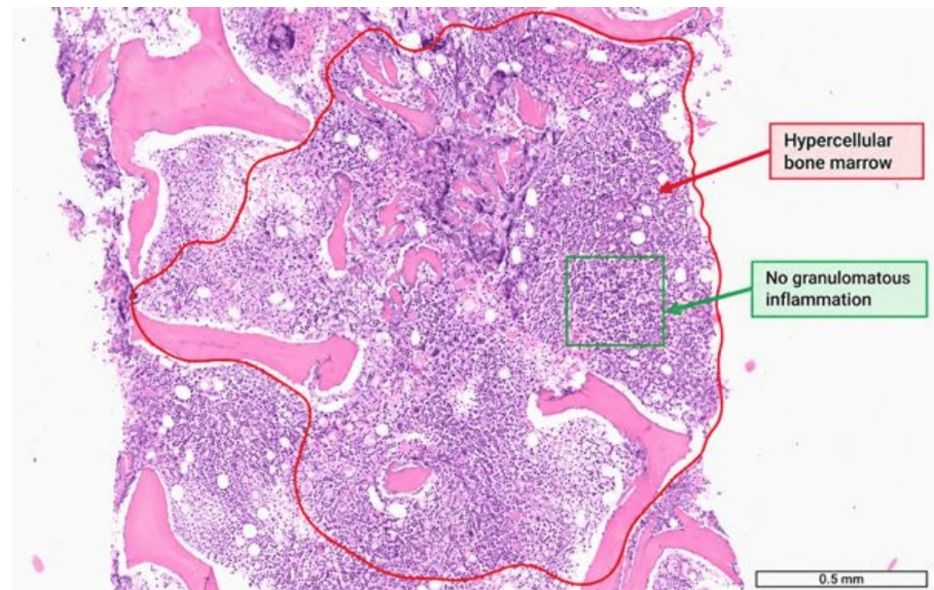


FIGURE 2: Bone marrow trephine biopsy showing hypercellular marrow without granulomatous inflammation (hematoxylin and eosin stain, ×5).

The annotated region highlights the hypercellular marrow; the scale bar indicates 0.5 mm.

Because of persistent hyperferritinemia and lack of clinical improvement, anakinra was subsequently escalated to intravenous administration at 200 mg twice daily on hospital day 9. Following completion of the bone marrow investigations, intravenous methylprednisolone was initiated at 500 mg once daily for five days on hospital day 9, followed by oral prednisolone at 40 mg once daily. Prednisolone was gradually tapered to 10 mg once daily, which was continued until anakinra was discontinued. Thereafter, prednisolone was reduced by 2.5 mg per week until it was fully tapered off.

Given the patient's origin from Sudan, persistent cytopenias, hepatosplenomegaly, and unexplained hyperinflammation, VL was investigated. The leishmaniasis direct agglutination test (DAT) was strongly positive at a titre of 1:409,600, and the rK39 antibody test was positive. Repeat bone marrow sampling, requested by the infectious diseases team following the positive rK39 test, detected *Leishmania* DNA by polymerase chain reaction (PCR), although amastigotes had not been visualized in the initial bone marrow specimen. The reason for the initially negative microscopic examination was not established in this case. Separately, the national HLH multidisciplinary team recommended a liver biopsy to investigate the underlying trigger of HLH. Histopathological examination demonstrated *Leishmania amastigotes* (Figure 3), confirming the diagnosis of VL.

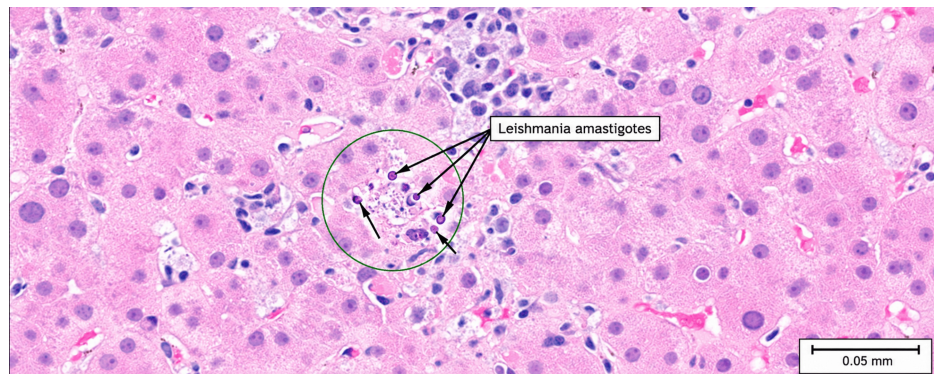


FIGURE 3: Liver biopsy demonstrating intracellular *Leishmania* amastigotes (hematoxylin and eosin stain, $\times 17$).

Arrows identify representative intracellular amastigotes.

Taken together, the clinical and laboratory findings supported HLH, while the patient's epidemiological history and confirmatory parasitological investigations established VL as the underlying trigger.

Once VL was confirmed, liposomal amphotericin B was initiated on hospital day 20 at 4 mg/kg once daily for five consecutive days, followed by additional doses on treatment days 10, 17, 24, 31, and 38, in consultation with the infectious diseases and parasitology teams. Treatment day 1 was defined as the day of the first amphotericin B dose. Although the patient was immunocompetent at presentation, the regimen was selected in view of the high-dose intravenous methylprednisolone (500 mg daily) administered before confirmation of VL, which raised concerns regarding treatment in the context of subsequent immunosuppression. Broad-spectrum antibiotics were continued empirically during the initial phase of investigation.

Following initiation of liposomal amphotericin B, the patient demonstrated clinical and biochemical improvement, with resolution of fever and recovery of blood counts. By hospital day 27, ferritin had decreased to 6,479 $\mu\text{g/L}$, compared with values exceeding 33,511 $\mu\text{g/L}$ on hospital days 5 and 9. At outpatient review 14 days after initiation of amphotericin B, ferritin had decreased further to 3,861 $\mu\text{g/L}$, while triglycerides had fallen to 0.6 mmol/L. These findings indicated substantial improvement, although ferritin remained elevated at the outpatient review.

He was discharged on hospital day 27 after completing the initial five-day course of liposomal amphotericin B, with plans to continue the remaining doses as an outpatient. At discharge, anakinra was transitioned to subcutaneous administration at a dose of 400 mg once daily, with a gradual taper over three weeks. Prednisolone was also gradually tapered.

Serial laboratory parameters demonstrating the evolution of HLH and response to treatment are summarized in Table 1.

Parameter	Reference range	Hospital day 1 (admission)	Hospital day 5 (anakinra initiated)	Hospital day 9 (IV anakinra and methylprednisolone initiated)	Hospital day 27 (discharge)	14 days after amphotericin B initiation (outpatient review)
Hemoglobin (g/L)	130–180	80	81	71	102	112
White cell count (×10 ⁹ /L)	4–11	4.30	2.10	3.10	5.4	7.4
Platelets (×10 ⁹ /L)	150–450	217	181	69	418	396
Ferritin (µg/L)	22–275	24,980	>33,511	>33,511	6,479	3,861
Triglycerides (mmol/L)	0–1.6	Not measured	3.7	4.0	1.4	0.6
Fibrinogen (g/L)	1.5–4.5	Not measured	3.49	1.58	2.68	Not measured

TABLE 1: Serial laboratory parameters during the patient's admission and follow-up.

Hospital day 1 denotes admission; hospital days 5 and 9 correspond to initiation of subcutaneous anakinra and escalation to intravenous anakinra with methylprednisolone, respectively. Liposomal amphotericin B was initiated on hospital day 20. The outpatient measurements were obtained 14 days after amphotericin B initiation and therefore represent a later time point than hospital day 27 discharge. "Not measured" indicates that the investigation was not performed at the specified time point. Ferritin values reported as >33,511 µg/L exceeded the laboratory's upper reporting limit; the exact concentrations at these time points were therefore not available.

The patient completed the planned course of liposomal amphotericin B therapy. Following completion of treatment, his blood counts had improved, and serum ferritin had decreased to 1,102 µg/L. He continued to demonstrate clinical improvement and remained afebrile, with no reported night sweats or unintentional weight loss. He also returned to his usual activities of daily living, indicating favorable functional recovery.

At the three-month follow-up after completion of amphotericin B therapy, repeat laboratory investigations, including a complete blood count and serum ferritin level, were within normal limits, supporting sustained hematological and biochemical recovery. However, radiological resolution of hepatosplenomegaly could not be confirmed because the patient did not attend the scheduled follow-up CT scan. He remains under follow-up with the infectious diseases and hematology teams.

Discussion

This case illustrates the diagnostic and therapeutic challenges of VL-associated HLH, particularly in a non-endemic setting where recognition of the underlying infectious trigger may be delayed [9]. The clinical features of VL - including prolonged fever, hepatosplenomegaly, pancytopenia, and hypergammaglobulinemia - overlap substantially with those of HLH, while infection itself may trigger macrophage activation and dysregulated cytokine responses. This overlap can complicate recognition of both conditions, particularly when VL is not initially considered.

The diagnosis of HLH may be challenging early in the disease course because clinical and laboratory abnormalities are non-specific and may resemble severe infection or sepsis [4,10]. Although the HLH-2004 criteria remain widely used, some components, including natural killer (NK) cell activity and soluble interleukin-2 receptor (sCD25) levels, may not be immediately available, and patients may not fulfil the required number of criteria at presentation [4]. In adults, the HScore provides a complementary approach by incorporating routinely available clinical and laboratory parameters. In this case, an HScore of 208 supported the diagnosis and facilitated early treatment. UK guidance also recommends serial reassessment when clinical suspicion remains high despite an initially non-diagnostic score, thereby supporting recognition of evolving HLH [4].

Current approaches, including those advocated by the North American Consortium for Histiocytosis, increasingly conceptualize HLH as a hyperinflammatory syndrome arising from dysregulated immune responses rather than relying solely on the distinction between primary and secondary disease [4]. Genetic evaluation may be relevant in selected patients because underlying genetic or immune dysregulatory susceptibility can influence prognosis, relapse risk, and treatment strategy, including the risk of recurrence following infection-triggered episodes. The revised HLH-2024 criteria also aim to improve diagnostic

accuracy and no longer include NK-cell activity as a mandatory diagnostic component, which may facilitate their application in centers where this investigation is unavailable [4,11].

Management requires simultaneous control of hyperinflammation and treatment of the underlying trigger. In this case, anakinra was initiated early to control hyperinflammation while diagnostic investigations were ongoing, with subsequent treatment escalation guided by the clinical response [12]. Corticosteroids were commenced after diagnostic samples had been obtained. The identification of VL required complementary serological, molecular, and histopathological investigations, with repeat sampling contributing to the diagnosis when initial testing was inconclusive [13].

Following treatment with liposomal amphotericin B, the patient demonstrated rapid and sustained clinical improvement. Etoposide was not required, reflecting the clinical response to treatment of the underlying infection and control of hyperinflammation. Overall, this case highlights the importance of considering VL as an infectious trigger of HLH in appropriate clinical contexts, using diagnostic scoring tools alongside clinical judgment, and pursuing repeated or complementary investigations when initial testing is inconclusive.

Conclusions

Visceral leishmaniasis should be considered a potential infectious trigger of hemophagocytic lymphohistiocytosis (HLH), particularly in patients with persistent fever, cytopenias, hepatosplenomegaly, and relevant epidemiological exposure, even in non-endemic settings. Early recognition of HLH, prompt identification and treatment of the underlying infection, and multidisciplinary management are important for achieving favorable outcomes. This case also highlights the value of complementary diagnostic investigations when initial findings are inconclusive. Although the patient improved following treatment with liposomal amphotericin B alongside therapy for hyperinflammation, the relative contributions of the individual treatments to his recovery cannot be determined from a single case.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Ishani Attanayake, Pradeep Karunakaran Thozhuthumparambil

Acquisition, analysis, or interpretation of data: Ishani Attanayake, Islam Mohammed

Drafting of the manuscript: Ishani Attanayake, Islam Mohammed

Critical review of the manuscript for important intellectual content: Pradeep Karunakaran Thozhuthumparambil

Supervision: Pradeep Karunakaran Thozhuthumparambil

Disclosures

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Ishani Attanayake and Pradeep Karunakaran Thozhuthumparambil contributed equally to this work and should be considered co-first authors.

References

1. Leishmaniasis. (2023). Accessed: June 29, 2026: <https://www.who.int/en/news-room/fact-sheets/detail/leishmaniasis>.
2. Wamai RG, Kahn J, McGloin J, Ziagbi G: Visceral leishmaniasis: a global overview. *J Glob Health Sci.* 2020, 2:10.35500/jghs.2020.2.e3
3. Scarpini S, Dondi A, Totaro C, et al.: Visceral leishmaniasis: epidemiology, diagnosis, and treatment regimens in different geographical areas with a focus on pediatrics. *Microorganisms.* 2022,

- 10:[10.3390/microorganisms10101887](https://doi.org/10.3390/microorganisms10101887)
4. Jordan MB, Allen CE, Greenberg J, et al.: Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: recommendations from the North American Consortium for Histiocytosis (NACHO). *Pediatr Blood Cancer*. 2019, 66:e27929. [10.1002/pbc.27929](https://doi.org/10.1002/pbc.27929)
5. Cunha BA: The clinical diagnosis of Legionnaires' disease: the diagnostic value of combining non-specific laboratory tests. *J Infect*. 2008, 56:395-7; author reply 397-8. [10.1016/j.jinf.2008.02.009](https://doi.org/10.1016/j.jinf.2008.02.009)
6. National Early Warning Score (NEWS) 2. (2017). Accessed: June 26, 2026: <https://www.rcp.ac.uk/resources/national-early-warning-score-news-2/>.
7. Fardet L, Galicier L, Lambotte O, et al.: Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol*. 2014, 66:2613-20. [10.1002/art.58690](https://doi.org/10.1002/art.58690)
8. Henter JI, Horne A, Aricó M, et al.: HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007, 48:124-31. [10.1002/pbc.21039](https://doi.org/10.1002/pbc.21039)
9. Poloni A, Giacomelli A, Corbellino M, et al.: Delayed diagnosis among patients with visceral leishmaniasis. *Intern Emerg Med*. 2023, 18:2293-300. [10.1007/s11739-023-03430-5](https://doi.org/10.1007/s11739-023-03430-5)
10. Konkol S, Killeen RB, Rai M: Lymphohistiocytosis. StatPearls. StatPearls Publishing, Treasure Island (FL); 2026.
11. Henter JI, Sieni E, Eriksson J, et al.: Diagnostic guidelines for familial hemophagocytic lymphohistiocytosis revisited. *Blood*. 2024, 144:2308-18. [10.1182/blood.2024025077](https://doi.org/10.1182/blood.2024025077)
12. Baverez C, Grall M, Gerfaud-Valentin M, et al.: Anakinra for the treatment of hemophagocytic lymphohistiocytosis: 21 cases. *J Clin Med*. 2022, 11:[10.3390/jcm11195799](https://doi.org/10.3390/jcm11195799)
13. Srivastava P, Dayama A, Mehrotra S, Sundar S: Diagnosis of visceral leishmaniasis. *Trans R Soc Trop Med Hyg*. 2011, 105:1-6. [10.1016/j.trstmh.2010.09.006](https://doi.org/10.1016/j.trstmh.2010.09.006)