EJCRIM
European Journal of Case Reports in Internal Medicine

ENVENOMATION-INDUCED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH): FIRST REPORTED ADULT CASE FOLLOWING A SPIDER BITE

Justin Baik[1], Faizan Khajar[1], Neil Hughes[1], Muhammad Usman[2]

[1] Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, USA
[2] Bronson Methodist Hospital Hematology, Medical Oncology, Kalamazoo, USA

Corresponding author's e-mail: justinbaikmd@gmail.com

Received: 04/06/2026
Accepted: 22/06/2026
Published: 24/08/2026

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained.
This article is licensed under a CC Attribution-NonCommercial-NoDerivatives 4.0 License

How to cite this article: Baik J, Khajar F, Hughes N, Usman M. Envenomation-induced hemophagocytic lymphohistiocytosis (HLH): first reported adult case following a spider bite. EJCRIM 2026;13:doi:10.12890/2026_007013

ABSTRACT

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome driven by dysregulated activation of cytotoxic T lymphocytes and macrophages. While infections and malignancies represent the most frequently identified triggers, HLH precipitated by arthropod envenomation is exceptionally rare, with prior reports confined predominantly to paediatric populations.

Case description: A 65-year-old male with multiple comorbidities developed progressive fever, cytopenias, extreme hyperferritinaemia (>8,000 ng/ml), and multiorgan dysfunction following a suspected spider bite to the inner left thigh. Evaluation revealed markedly elevated soluble interleukin-2 receptor (sCD25 >4,000 pg/ml) and CXCL9 (35,623 pg/ml; 55-fold above the upper limit of normal), along with reduced natural killer (NK) cell counts. Bone marrow biopsy confirmed haemophagocytosis. The patient fulfilled 6 of 8 HLH-2004 diagnostic criteria, with an HScore of approximately 197, corresponding to a >90-95% probability of HLH. Treatment with high-dose corticosteroids, ruxolitinib, and anakinra resulted in rapid suppression of inflammatory markers. The course was complicated by acute kidney injury requiring temporary haemodialysis. By early 2026, the patient achieved normalization of all laboratory parameters and returned to near-baseline functional status.

Conclusion: This case illustrates an exceptionally rare adult presentation of envenomation-associated secondary HLH. Clinicians should consider HLH in patients with persistent fever, cytopenias, and extreme hyperferritinaemia following arthropod exposure. Early immunomodulatory therapy, including cytokine-directed agents such as ruxolitinib and anakinra, may avert irreversible organ damage in the absence of cytotoxic etoposide-based therapy.

KEYWORDS

Hemophagocytic lymphohistiocytosis, hyperinflammatory syndrome, spider envenomation

LEARNING POINTS

- First documented adult case of spider bite-associated HLH, expanding awareness of a rare but fatal presentation.
- Guides internists to consider HLH when fever, cytopenias, and extreme hyperferritinaemia persist after envenomation.
- Emphasizes that early immunomodulatory therapy can prevent irreversible organ damage.

EFIM European Federation of Internal Medicine

Publisher smc media srl

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a severe, potentially fatal hyperinflammatory syndrome characterized by uncontrolled activation and proliferation of cytotoxic T lymphocytes and macrophages, culminating in a cytokine storm and progressive multiorgan dysfunction[1]. HLH is broadly classified as primary (familial), arising from inherited defects in cytolytic pathways, most commonly mutations in PRF1, UNC13D, and STX11, or as secondary (acquired), precipitated by infections, malignancies, autoimmune conditions, or, rarely, other inflammatory stimuli[2].

The diagnostic framework for HLH rests on the HLH-2004 criteria, which require ≥5 of 8 features: fever (≥38.5°C), splenomegaly, cytopenias in ≥2 cell lineages, hypertriglyceridemia and/or hypofibrinogenemia, haemophagocytosis on bone marrow, lymph node, or spleen biopsy, low or absent natural killer (NK) cell activity, hyperferritinaemia (≥5 µg/ml), and elevated soluble CD25 (sCD25 ≥2,400 U/ml)[3]. Complementarily, the HScore provides a validated probability estimate for HLH diagnosis based on clinical, biological, and histological parameters[4].

While infectious triggers, particularly Epstein-Barr virus (EBV), cytomegalovirus (CMV), and other herpesviruses, account for the majority of secondary HLH cases, arthropod envenomation represents an exceedingly rare precipitant. The proposed pathophysiology involves toxin-mediated innate immune dysregulation, wherein venom components act as potent activators of the mononuclear phagocyte system, driving excessive secretion of interferon-gamma (IFN-γ), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α)[5]. Published cases of envenomation-associated HLH have been largely limited to children; adult presentations are nearly absent from the literature[6,7].

We report a case of severe secondary HLH in a 65-year-old man arising after a suspected spider bite, with emphasis on diagnostic challenges, the role of IFN-γ pathway biomarkers, and the therapeutic utility of a cytokine-directed, etoposide-sparing immunomodulatory regimen.

CASE DESCRIPTION

A 65-year-old male with a history of atrial fibrillation, compensated systolic heart failure, chronic kidney disease (CKD) stage IIIa (baseline creatinine ~1.3 mg/dl), hypertension, and benign prostatic hyperplasia presented in August 2025 following a suspected spider bite to the inner left thigh. He reported an erythematous puncture wound with localized oedema, accompanied by fever, nausea, vomiting, diarrhoea, and dark urine within 24-48 hours of the presumed envenomation. No spider was identified or captured. The patient denied any prior hematologic conditions, recent travel, sick contacts, or immunosuppressive therapy.

Over the ensuing 10 days, the patient developed progressive thigh induration with marked swelling (estimated softball size) and persistent febrile episodes exceeding 40°C despite antipyretics and supportive measures. He presented to the emergency department with new-onset thrombocytopenia (platelet count 68 $\times 10^9$/l), lactic acidosis (lactate 4.2 mmol/l), and acute-on-chronic kidney injury (serum creatinine 2.4 mg/dl; baseline ~1.3 mg/dl). Blood pressure was 98/62 mmHg with orthostatic changes. Physical examination was notable for a warm, indurated left medial thigh without fluctuance, mild splenomegaly, and scleral icterus.

Comprehensive laboratory evaluation demonstrated the following:

- Ferritin >8,000 ng/ml (reference: <300 ng/ml)
- C-reactive protein (CRP) 287 mg/l
- Triglycerides 184 mg/dl
- Fibrinogen 576 mg/dl (elevated; consistent with acute-phase reactivity)
- NK cells count 70/µl (reference: 103-498/µl)
- Soluble CD25 (sCD25) >4,000 pg/ml
- CXCL9 35,623 pg/ml (upper limit of normal <647 pg/ml; 55-fold elevation)
- Liver transaminases mildly elevated: AST 78 U/L, ALT 64 U/l
- Platelet count 68×10^9/l, haemoglobin 9.4 g/dl, white blood cell count 2.8 $\times 10^9$/l

A comprehensive autoimmune panel (antinuclear antibody, anti-double-stranded DNA, antineutrophil cytoplasmic antibody, rheumatoid factor) was unremarkable. Infectious workup including blood cultures, viral serologies (EBV, CMV, HIV, hepatitis B and C), and respiratory pathogen panel were all negative. Peripheral blood smear showed no schistocytes or evidence of thrombotic microangiopathy (TMA).

Computed tomography (CT) of the chest, abdomen, and pelvis revealed mild splenomegaly without lymphadenopathy, hepatomegaly, abscess, or evidence of occult malignancy. Soft tissue imaging of the thigh demonstrated subcutaneous oedema without drainable collection.

Bone marrow biopsy performed on hospital day 3 demonstrated normocellular marrow with trilineage haematopoiesis and unequivocal haemophagocytosis, with activated macrophages engulfing erythroid and myeloid precursors. Genetic testing for primary HLH mutations (PRF1, UNC13D, STX11, RAB27A) was sent and returned negative. Renal biopsy on hospital day 7 demonstrated acute tubular necrosis (ATN) without features of TMA, immune-complex deposition, or crescentic injury.

Based on these findings, the patient fulfilled 6 of 8 HLH-2004 criteria: fever, splenomegaly, cytopenias (≥2 lineages), hyperferritinaemia, haemophagocytosis on biopsy, and elevated sCD25. The HScore was calculated at approximately 197, corresponding to a >90-95% probability of HLH. The absence of classic hypofibrinogenemia was attributed to the early acute-phase elevation of fibrinogen, a recognized diagnostic pitfall in HLH.

Given the rapidly progressive multiorgan involvement and high HLH probability, directed immunomodulatory therapy was initiated on hospital day 5. Etoposide-based therapy was deferred in consideration of the patient's advanced age, significant renal and cardiac comorbidities, and the presumed non-malignant, toxin-driven etiology. The following regimen was initiated:

- Prednisone 80 mg daily (~1 mg/kg/day)
- Ruxolitinib 10 mg twice daily (JAK1/2 inhibitor; dose-adjusted for renal function)
- Anakinra 100 mg subcutaneously daily (IL-1 receptor antagonist)

Inflammatory markers improved significantly within 48-72 hours of therapy initiation, with ferritin trending downward and CRP normalizing. Despite this, renal function continued to deteriorate, consistent with the established ATN, necessitating initiation of temporary haemodialysis via tunnelled catheter on hospital day 10. Additional complications during admission included anaemia of chronic inflammation (nadir haemoglobin 7.8 g/dl, requiring two units of packed red blood cells), mild transaminitis, orthostatic hypotension treated with midodrine, and significant unintentional weight loss. The patient was discharged in improved condition on hospital day 16.

Outpatient haemodialysis was successfully discontinued by November 2025 as renal function recovered. Corticosteroids and anakinra were tapered and discontinued in December 2025. Ruxolitinib was gradually tapered through early 2026. By February 2026, all laboratory parameters had normalized and the patient had returned to near-baseline functional status with independent ambulation and restoration of activities of daily living.

DISCUSSION

This case represents one of very few documented adult cases of secondary HLH arising in the context of suspected arachnid envenomation. While sporadic paediatric reports have described spider bite-associated HLH[6,7], adult presentations are nearly absent from the published literature, underscoring the diagnostic challenge this condition poses in routine clinical practice. Additionally, a rare case of HLH following wasp venom immunotherapy has been reported, suggesting that venom-related immune stimulation may serve as a trigger for HLH beyond arthropod envenomation alone[8].

Spider venoms contain complex arrays of proteases, phospholipases, hyaluronidases, and cytotoxic peptides capable of inducing local tissue necrosis and systemic inflammation[9]. In susceptible individuals, these venom constituents may act as immune activators, functionally analogous to superantigens or pathogen-associated molecular patterns (PAMPs), driving macrophage hyperactivation and triggering a cytokine storm indistinguishable from macrophage activation syndrome (MAS)[5,9]. The resulting IFN-γ-dominated cytokine milieu promotes macrophage-mediated phagocytosis of hematopoietic precursors, the histological hallmark of HLH[10].

The markedly elevated CXCL9 in this case (35,623 pg/ml; 55-fold above the upper limit of normal) is particularly instructive. CXCL9 is a downstream chemokine induced by IFN-γ signalling and serves as a sensitive and specific biomarker of IFN-γ pathway activation in HLH[11]. Its dramatic elevation here confirms robust IFN-γ pathway engagement and may serve as a marker of treatment response, a utility increasingly recognized in HLH management.

A central diagnostic challenge in this case was the clinical overlap between HLH and severe sepsis, both of which can present with fever, cytopenias, coagulopathy, and multiorgan dysfunction. Key distinguishing features of HLH include disproportionate hyperferritinaemia (particularly >5,000-10,000 ng/ml), markedly elevated sCD25, extreme CXCL9 elevation, and bone marrow haemophagocytosis on biopsy[3]. Prompt calculation of the HScore at initial presentation provides a quantitative diagnostic probability estimate and should be incorporated into standard workup for all patients with unexplained fever, cytopenias, and hyperferritinaemia[4].

A notable diagnostic nuance was the atypically elevated fibrinogen (576 mg/dl). In classical HLH, hypofibrinogenemia (≤1.5 g/l) reflects consumptive coagulopathy driven by macrophage-mediated fibrinolysis. The elevated fibrinogen observed here is consistent with its role as an acute-phase reactant early in the inflammatory cascade, a recognized pitfall that may cause failure to fulfil the HLH-2004 fibrinogen criterion, potentially resulting in underdiagnosis. Clinicians should be cautious not to exclude HLH on this basis alone in the early phases of illness.

The differential diagnosis in this case also included disseminated intravascular coagulation (DIC), thrombotic microangiopathy (TMA), toxin-mediated systemic inflammatory response syndrome, and malignancy-associated HLH. The negative infectious and autoimmune workup, absent schistocytosis, non-malignant bone marrow morphology, renal biopsy showing ATN without TMA features, and clinical context of envenomation collectively supported a diagnosis of toxin-triggered secondary HLH.

Standard HLH management, as per the HLH-94 and HLH-2004 protocols, consists of dexamethasone and etoposide, with or without cyclosporine, followed by allogeneic hematopoietic stem cell transplantation in primary or refractory disease[3]. However, in secondary HLH with an identifiable and potentially transient inflammatory trigger, cytokine-directed therapies offer a compelling alternative, particularly for patients with significant comorbidities for whom cytotoxic agents pose unacceptable risk[12].

Ruxolitinib, a JAK1/2 inhibitor, suppresses signalling from multiple proinflammatory cytokines including IFN-γ, IL-6, and IL-2 via blockade of the JAK-STAT pathway[13].

Preclinical and clinical data support its efficacy in refractory and secondary HLH[14]. Anakinra, a recombinant IL-1 receptor antagonist, provides complementary immunomodulation particularly relevant in MAS-associated hyperinflammatory states and has been used as a steroid-sparing strategy in HLH[14]. The combination of ruxolitinib, anakinra, and corticosteroids achieved rapid and sustained remission in this patient, avoiding the hematologic and immunologic toxicities associated with etoposide, a particularly important consideration given the patient's baseline CKD and cardiac disease.

This case carries several important clinical implications. First, HLH should be considered in any patient with persistent, unexplained fever and extreme hyperferritinaemia following arthropod exposure, even in the absence of a confirmed diagnosis or identified spider species. Second, IFN-γ pathway biomarkers, specifically CXCL9 and sCD25, can serve as powerful diagnostic adjuncts and should be obtained early in the workup. Third, the HScore should be calculated routinely as a complement to HLH-2004 criteria. Fourth, in selected patients with secondary HLH and identifiable triggers, etoposide-sparing cytokine-directed regimens may offer effective and less toxic therapeutic options.

CONCLUSION

HLH following suspected arthropod envenomation is an exceptionally rare but life-threatening condition in adults. This case highlights the value of extreme hyperferritinaemia, markedly elevated CXCL9, and bone marrow haemophagocytosis as diagnostic anchors distinguishing HLH from sepsis in the setting of envenomation. A cytokine-directed, etoposide-sparing combination regimen incorporating ruxolitinib, anakinra, and corticosteroids produced durable remission, supporting its consideration in non-malignant secondary HLH, particularly in patients for whom etoposide poses excess risk. Continued case reporting and collaborative registry efforts are needed to delineate optimal therapeutic algorithms and long-term outcomes in this rare presentation.

REFERENCES

1. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. The Lancet 2014;383:1503–1516. doi: 10.1016/S0140-6736(13)61048-X
2. Stepp SE, Dufourcq-Lagelouse R, Le Deist F, Bhawan S, Certain S, Mathew PA, et al. Perforin gene defects in familial hemophagocytic lymphohistiocytosis. Science 1999;286:1957–1959. doi: 10.1126/SCIENCE.286.5446.1957
3. Henter JI, Horne AC, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–131. doi: 10.1002/PBC.21039
4. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol 2014;66:2613-2620. doi: 10.1002/art.38690
5. Rosée P La, Horne AC, Hines M, Greenwood TVB, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465–2477. doi: 10.1182/BLOOD.2018894618
6. Dandoy C, Grimley M. Secondary hemophagocytic lymphohistiocytosis (HLH) from a presumed brown recluse spider bite. J Clin Immunol 2014;34:544–547. doi: 10.1007/s10875-014-0036-1
7. Erat T, Yahşi A, Çanakçı C, Korkmaz A, Karahan C, İleri T, et al. A rare cause of secondary hemophagocytic lymphohistiocytosis: systemic loxoscelism. Turk J Pediatr 2020;62:641–646. doi: 10.24953/turkjped.2020.04.014
8. Nittner-Marszalska M, Kosińska M, Suchnicki K, Rzeszutko M. Hemophagocytic Lymphohistiocytosis (HLH) Triggered by Wasp Venom Immunotherapy Is Rare but Noteworthy. J Investig Allergol Clin Immunol 2019;29:49–51. doi: 10.18176/jiaci.0322
9. Isbister GK, Fan HW. Spider bite. The Lancet 2011;378:2039–20 47. doi:10.1016/S0140-6736(10)62230-1
10. Crayne CB, Albeituni S, Nichols KE, Cron RQ. The Immunology of Macrophage Activation Syndrome. Front Immunol 2019;10. doi: 10.3389/FIMMU.2019.00119
11. Weiss ES, Girard-Guyonvarc'h C, Holzinger D, De Jesus AA, Tariq Z, Picarsic J, et al. Interleukin-18 diagnostically distinguishes and pathogenically promotes human and murine macrophage activation syndrome. Blood 2018;131:1442–1455. doi: 10.1182/BLOOD-2017-12-820852
12. Daver N, McClain K, Allen CE, Parikh SA, Otrock Z, Rojas-Hernandez C, et al. A Consensus Review on Malignancy-Associated Hemophagocytic Lymphohistiocytosis in Adults. Cancer 2017;123:3229. doi: 10.1002/CNCR.30826
13. Maschalidi S, Sepulveda FE, Garrigue A, Fischer A, De Saint Basile G. Therapeutic effect of JAK1/2 blockade on the manifestations of hemophagocytic lymphohistiocytosis in mice. Blood 2016;128:60–71. doi: 10.1182/BLOOD-2016-02-700013
14. Broglie L, Pommert L, Rao S, Thakar M, Phelan R, Margolis D, et al. Ruxolitinib for treatment of refractory hemophagocytic lymphohistiocytosis. Blood Adv 2017;1:1533–1536. doi: 10.1182/BLOODADVANCES.2017007526