

Review began 12/04/2024
Review ended 12/10/2024
Published 12/12/2024

© Copyright 2024
Henriques et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.75598

Peripheral Axonal Neuropathy in Hemophagocytic Lymphohistiocytosis Secondary to *Rickettsia conorii* Infection

Adriana Henriques¹, Mariana Guerra¹, Ana Rita Ramalho¹, Ana Coimbra¹, Jandira Lima¹

1. Internal Medicine, Centro Hospitalar e Universitário de Coimbra, Coimbra, PRT

Corresponding author: Adriana Henriques, adriana.henriques0@gmail.com

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal hyperinflammatory syndrome characterized by dysregulated immune activation and systemic inflammation. Secondary HLH is often triggered by infections, with *Rickettsia conorii* being an infrequently reported cause. Peripheral axonal neuropathy is a rare and poorly understood complication of HLH. We present the case of a 58-year-old male who presented with fever, diarrhea, a maculopapular rash involving the palms and soles, and progressive lower limb weakness. Laboratory findings revealed pancytopenia, hyperferritinemia, elevated soluble CD25, liver cytolysis, hypofibrinogenemia, and raised inflammatory markers. Serological testing confirmed *Rickettsia conorii* infection. The patient fulfilled six of the eight HLH-2004 diagnostic criteria, establishing the diagnosis of secondary HLH. Treatment was initiated with intravenous dexamethasone and doxycycline. During hospitalization, the patient developed severe hypoxemic respiratory failure, paraplegia, and acute sensory loss. The neurological evaluation confirmed peripheral axonal neuropathy linked to *Rickettsia conorii* infection, which preceded the development of HLH. After 21 days of doxycycline therapy, the patient was discharged to a rehabilitation facility with full neurological recovery. This case underscores the rarity of *Rickettsia conorii* as a trigger for HLH and highlights the exceptional occurrence of peripheral axonal neuropathy as a complication. The singularity of this case reinforces the importance of a correct and early diagnosis of HLH, which can have atypical and severe complications but also a successful outcome.

Categories: Internal Medicine, Infectious Disease, Hematology

Keywords: adrenal cortex hormones, hemophagocytic lymphohistiocytosis, hemophagocytic syndrome infection-associated, polyneuropathy, rickettsia conorii

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal disease characterized by an acute, rapidly progressive systemic hyperinflammatory response [1]. This condition results from excessive activation of cytotoxic T lymphocytes and histiocytes and generalized activation of macrophages that phagocytize healthy hematopoietic cells. This mechanism triggers a failure in the inhibitory control of cytotoxic T lymphocytes, leading to overproduction of pro-inflammatory cytokines and systemic accumulation of activated T cells and macrophages, perpetuating a hyperinflammatory state [1,2].

Although predominantly a pediatric condition, HLH can occur at any age [2]. It can be hereditary or acquired, being, in this case, triggered by infections, malignant tumors, autoimmune diseases, or immunosuppression [3].

Among infectious causes, viral infections are most common in adults, particularly Epstein-Barr virus. Nevertheless, bacterial agents, such as *Rickettsia conorii*, can also be precursors. The spectrum of clinical manifestations is broad, including persistent fever, hepatosplenomegaly, pancytopenia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia (>500 mcg/L), elevated soluble CD25, and absence or reduced activity of natural killer (NK) cells.

Despite being a pathognomonic finding for the diagnosis of HLH, the presence of hemophagocytosis in bone marrow, liver, or lymph node samples is not essential for the assumption of the disease. Diagnostic criteria such as those established in the HLH-2004 protocol remain widely used in clinical practice [4,5].

Neurological involvement is known to be present in up to 30% of published cases, including encephalitis, seizures, ataxia, and behavioral changes [6]. Peripheral axonal neuropathy, as documented in this case, is an extremely rare complication, possibly resulting from macrophage-mediated destruction of the myelin sheath, leading to significant motor and/or sensory sequelae [7].

In this context, we report a case of HLH secondary to infection with *Rickettsia* spp., presenting with peripheral axonal neuropathy, contributing to the limited literature on neurological and systemic complications of this rare condition.

How to cite this article

Henriques A, Guerra M, Ramalho A, et al. (December 12, 2024) Peripheral Axonal Neuropathy in Hemophagocytic Lymphohistiocytosis Secondary to *Rickettsia conorii* Infection. Cureus 16(12): e75598. DOI 10.7759/cureus.75598

Case Presentation

We present the case of a 58-year-old male admitted with a one-day history of diarrhea, fever, and a generalized maculopapular rash involving the palms and soles. The patient also reported progressive muscle weakness in the lower limbs that had started 10 days before admission. He denied other complaints. His medical history included type 1 diabetes mellitus, medicated with human isophane insulin (8 units for breakfast and 6 units for dinner), with poor compliance to treatment and poor metabolic control of the disease. He also had an alcohol use disorder, lived in a rural area, and had a dog as his only pet.

On initial physical examination, the patient was disoriented, hypotensive (BP 70/40 mmHg), tachycardic (HR 101 bpm), and febrile (39°C). A maculopapular rash with scattered petechiae was noted on the trunk, limbs, palms, and soles without signs of inoculation lesions ("tache noire"). Neurological examination revealed isochoric and reactive pupils, no deficits in ocular movements or visual fields, no facial asymmetry or dysmetria, normal language function, tongue midline alignment, and no motor strength deficits in the upper and lower limbs. Sensory, coordination, and gait assessments were unremarkable.

Initial laboratory tests (Table 1) showed elevated inflammatory markers (C-reactive protein (CRP) 8.52 mg/dL, procalcitonin 2.39 ng/mL), liver cytolysis (alanine aminotransferase (AST) 985 U/L, alanine aminotransferase (ALT) 175 U/L), elevated cholestatic enzymes (gamma-glutamyl transferase (GGT) 344 U/L, ALP 165 U/L), pancytopenia (leukocytes 2.7x10⁹/L, hemoglobin 10.7 g/dL, platelets 67x10⁹/L), hypofibrinogenemia (39 mg/dL), hyperferritinemia (65,865 ng/mL), and elevated soluble CD25 (3,124 U/mL). Arterial blood gas analysis identified hyperlactatemia (2.6 mmol/L).

Serum Analysis	Emergency Department	Reference Values
LDH	670 U/L	<248 U/L
AST	985 U/L	<31 U/L
ALT	175 U/L	<34 U/L
GGT	344 U/L	<38 U/L
Alkaline phosphatase	165 U/L	30-120 U/L
Total bilirubin	1.7 mg/dL	0.2-1.2 mg/dL
Direct bilirubin	1.3 mg/dL	<0.5 mg/dL
Albumin	2.3 g/dL	3.5-5.2 g/dL
C-reactive protein	8.52 mg/dL	<0.5 mg/dL
Procalcitonin	2.39 ng/mL	0-0.5 ng/mL
Leukocytes	2.7x10 ⁹ /L	4.0-10.0x10 ⁹ /L
Hemoglobin	10.7 g/dL	12-15.6 g/dL
MCV	107 fL	80-99 fL
Platelets	67.0x10 ⁹ /L	150-400x10 ⁹ /L
Prothrombin time	57%	70-120%
Fibrinogen	39 mg/dL	200-500 mg/dL
Ferritin	65,865 ng/mL	30-300 ng/mL
Triglycerides	277 mg/dL	43.8-195.1 mg/dL
Soluble CD25	3,124 U/mL	-

TABLE 1: Analytical results at admission
LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; MCV: mean corpuscular volume

An abdominal ultrasound revealed hepatomegaly (17.2 cm) (Figure 1) with a hyperechoic structure

suggestive of steatosis. The spleen was of normal size and homogeneous.



FIGURE 1: Hepatomegaly detected on abdominal ultrasound

Septic screening, including blood and urine cultures, was negative. Infectious serologies were collected, but results were pending. Empirical treatment with ceftriaxone (2 g/day) and intravenous dexamethasone (10 mg/m²/day) was initiated based on suspected HLH secondary to an undetermined infectious process.

On the third day of hospitalization, the patient experienced a sudden worsening of consciousness and new-onset hypoxemic respiratory failure (PaO₂/FiO₂ ratio 80), requiring invasive mechanical ventilation.

The chest X-ray showed no consolidations (Figure 2), while the cranial computed tomography (CT) revealed marked generalized parenchymal atrophy and mild periventricular arteriopathic leukoencephalopathy without acute vascular lesions or sequelae (Figure 3).



FIGURE 2: Chest X-ray without significant alterations



FIGURE 3: Cranial computed tomography showing generalized parenchymal atrophy and mild periventricular leukoencephalopathy

The lumbar puncture revealed elevated cerebrospinal fluid protein (157 mg/dL) without pleocytosis (Table 2).

Cerebrospinal Fluid Biochemistry	Result	Reference Values
Proteins	157 mg/dL	15-40 mg/dL
Glucose	132 mg/dL	40-70 mg/dL
Leukocytes	<3/mm ³	<3/mm ³

TABLE 2: Cytological analysis of cerebrospinal fluid

In this context, the patient was transferred to the intensive care unit (ICU) for closer monitoring and advanced care. Subsequently, infectious serologies returned positive for *Coxiella burnetii* IgG (1:1280) and *Rickettsia conorii* IgM (1:1280). Given the cross-reactivity of *Coxiella burnetii*, phase I and II antibodies were tested and found negative. Thus, HLH secondary to *Rickettsia conorii* infection was confirmed, and doxycycline was added to the treatment regimen, maintaining the previously initiated dexamethasone.

After 17 days in the ICU, the patient was transferred back to the internal medicine ward, where paraplegia and hypoesthesia in the L1-S4 dermatomes were noted. Electromyography (Figure 4) confirmed peripheral sensorimotor axonal polyneuropathy, attributed to HLH.

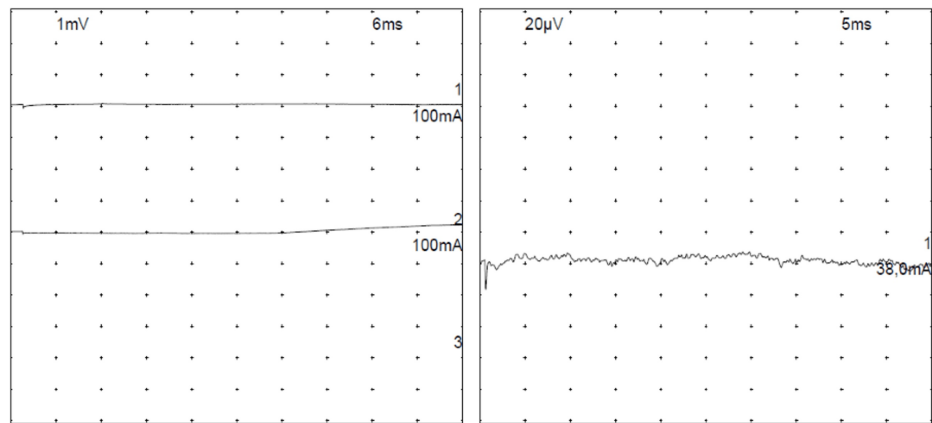


FIGURE 4: Electromyogram showing sensory-motor axonal polyneuropathy, with loss of voluntary muscle activation

Additional workup included dorsolumbar magnetic resonance imaging (MRI), which identified diffuse signal changes in the vertebrae of the dorsal and lumbosacral segments. No pathologic contrast enhancements, abnormal tissue masses, or degenerative changes compromising canal or foraminal dimensions were observed. Metabolic, nutritional, and other causes of HLH were excluded.

The patient completed 21 days of doxycycline therapy and, on the 41st day of hospitalization, was discharged to a rehabilitation center. He stayed there for one month and showed complete recovery of neurological deficits.

Discussion

HLH is a rare and potentially fatal condition characterized by uncontrolled immune hyperactivation. When untreated, it is associated with high mortality rates, making early recognition and immediate intervention crucial for a successful treatment. The broad spectrum of clinical manifestations, nonspecific clinical and laboratory findings, and the rarity of this syndrome contribute to diagnostic delays [8].

In this case, clinical findings such as fever, a maculopapular rash, and pancytopenia led to the diagnosis of spotted fever, consistent with positivity for *Rickettsia conorii* and *Coxiella burnetii*. The positivity for *Coxiella burnetii* was attributed to cross-reactivity. However, the rapid clinical deterioration, accompanied by marked hyperferritinemia, elevated soluble CD25, and hypofibrinogenemia, indicated a hyperinflammatory syndrome, leading to an early diagnosis of secondary HLH.

Diagnosing HLH is challenging due to overlapping manifestations with other clinical conditions [2]. Despite the limited data available, the HLH-2004 diagnostic criteria remain widely used for secondary causes of HLH in adults. At least five of the eight criteria are required to establish a diagnosis. In the presented case, the patient met five of the eight criteria (fever, pancytopenia, hypofibrinogenemia/hypertriglyceridemia, hyperferritinemia, and elevated soluble CD25), supporting the diagnostic hypothesis [4].

Nonetheless, the rarity of the association between *Rickettsia* spp. and HLH increases the risk of diagnostic delay. A review published in February 2024 included 69 articles (totaling 98 patients) and identified only 14 cases (14.3%) of HLH complicated by *Rickettsia* spp. infection [9].

This case emphasizes the importance of considering HLH in the differential diagnosis of patients with *Rickettsia* spp. infections and laboratory findings suggestive of immune hyperactivation.

Neurological manifestations are an important yet often underappreciated component of HLH. They vary and, when present, typically occur 14 to 21 days after infection. They include seizures, gait ataxia, dysmetria, dysarthria, and changes in consciousness and/or behavior, as observed in this patient. These findings may dominate the clinical picture or occur alongside other signs or symptoms [10].

The central nervous system (CNS) is the most affected site (in 10% of cases), significantly worsening the prognosis and potentially causing permanent sequelae. CNS involvement results from activated macrophage infiltration, producing symptoms like encephalitis. Brain MRI findings include hypodense areas or necrosis, and cerebrospinal fluid alterations are present in 50% of cases, typically showing mononuclear pleocytosis (lymphocytic meningitis) or albuminocytologic dissociation [11].

Peripheral axonal neuropathy due to *Rickettsia conorii* infections is rare, typically presenting as subacute,

often asymmetrical, and involving mixed sensory and motor fibers [12]. The pathophysiology remains unclear but likely involves a multifactorial process, including vascular invasion by the pathogen and an immune response contributing to neuronal degeneration [12].

Three cases of peripheral polyneuropathy associated with *Rickettsia conorii* infection have been documented, all serologically confirmed as in the present case. In the first case, a 78-year-old woman developed sensory ataxic neuropathy 17 days post-infection, treated with doxycycline but with only partial deficit improvement [13]. Another case involved a 63-year-old woman who developed acute demyelinating motor-sensory neuropathy, consistent with Guillain-Barré syndrome, treated with doxycycline, ceftriaxone, and immunoglobulin, but progressed to chronic inflammatory demyelinating polyneuropathy [14]. Finally, a 76-year-old man experienced acute facial paralysis followed by flaccid tetraparesis one week after infection, treated with two weeks of doxycycline with complete recovery [12].

It is essential to exclude neoplasms, rheumatic diseases, immunodeficiencies, or infections, as these conditions are common in HLH patients, especially adults. Treatment aims to suppress inflammation as early as possible [15].

The EULAR 2022 guidelines recommend early empirical immunomodulatory therapy for HLH, alongside supportive care and targeted antimicrobial/antifungal/antiviral or antiparasitic therapy based on the suspected microorganism. High-dose corticosteroids (oral prednisone or IV methylprednisolone, 1–2 mg/kg/day or IV dexamethasone, 10 mg/m²/day), immunoglobulins (1 g/kg/day for the first two days, then 0.4–1 g/kg/day for two to five days), or anakinra (5–10 mg/kg/day), an interleukin-1 blocker, are suggested for severe infections with persistent symptoms and/or multiorgan dysfunction [16].

The NHS England recommends anakinra for patients who do not respond to or have contraindications for conventional immunosuppressive therapy, as it has shown efficacy in reducing mortality and improving inflammatory parameters [17]. Thus, the choice of immunosuppressant should always be individualized to the patient's clinical condition [16,17]. In 2004, these guidelines were updated, combining etoposide, dexamethasone, and cyclosporine as initial therapy (one to eight weeks) for patients with HLH regardless of genetic or familial evidence [4].

Conclusions

HLH is a rare, potentially fatal condition that presents significant challenges in clinical practice, particularly due to the nonspecific nature of its early signs and symptoms. This case underscores the importance of early recognition, especially in the presence of persistent fever, pancytopenia, and significant inflammatory alterations such as hyperferritinemia. A multidisciplinary approach was essential in managing both systemic and neurological complications, including the rare manifestation of peripheral axonal neuropathy associated with *Rickettsia* spp. infections but potentially reversible with timely diagnosis and treatment.

The favorable outcome in this case highlights the positive impact of early, tailored, and targeted interventions in reducing morbidity and mortality and ensuring complete functional recovery. Furthermore, the case contributes to raising awareness of the rare manifestations of HLH, particularly in adults, when associated with *Rickettsia* spp. infections. Early detection and integrated management were critical in modifying the clinical course of this syndrome, preventing severe complications and offering the patient the possibility of a full recovery and improved quality of life.

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: Adriana Henriques, Ana Coimbra, Mariana Guerra, Ana Rita Ramalho, Jandira Lima

Acquisition, analysis, or interpretation of data: Adriana Henriques

Drafting of the manuscript: Adriana Henriques

Critical review of the manuscript for important intellectual content: Ana Coimbra, Mariana Guerra, Ana Rita Ramalho, Jandira Lima

Disclosures

Human subjects: Consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support

was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Al-Samkari H, Berliner N: Annual review of pathology: mechanisms of disease hemophagocytic lymphohistiocytosis. *Annu Rev Pathol Mech Dis*. 2018, 13:27-49.
2. Griffin G, Shenoi S, Hughes GC: Hemophagocytic lymphohistiocytosis: an update on pathogenesis, diagnosis, and therapy. *Best Pract Res Clin Rheumatol*. 2020, 34:101515. [10.1016/j.berh.2020.101515](https://doi.org/10.1016/j.berh.2020.101515)
3. Ponnatt TS, Lilley CM, Mirza KM: Hemophagocytic lymphohistiocytosis. *Arch Pathol Lab Med*. 2022, 146:507-19. [10.5858/arpa.2020-0802-RA](https://doi.org/10.5858/arpa.2020-0802-RA)
4. Henter JL, 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)
5. Naymagon L: Can we truly diagnose adult secondary hemophagocytic lymphohistiocytosis (HLH)? A critical review of current paradigms. *Pathol Res Pract*. 2021, 218:153321. [10.1016/j.prp.2020.153321](https://doi.org/10.1016/j.prp.2020.153321)
6. Sivaramalingam G, Vlk A, Raghavan B, Govindaraj J: Imaging spectrum of neurological manifestations of hemophagocytic lymphohistiocytosis in pediatrics: a case series. *Indian J Radiol Imaging*. 2023, 33:548-54. [10.1055/s-0043-1772495](https://doi.org/10.1055/s-0043-1772495)
7. Jovanovic A, Kuzmanovic M, Kravljanc R, Micic D, Jovic M, Gazikalovic S, Pasic S: Central nervous system involvement in hemophagocytic lymphohistiocytosis: a single-center experience. *Pediatr Neurol*. 2014, 50:233-7. [10.1016/j.pediatrneurol.2013.10.014](https://doi.org/10.1016/j.pediatrneurol.2013.10.014)
8. Rosée P La, Rosée R, Horne A, et al.: Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood*. 2019, 133:2465-77. [10.1182/blood.2018894618](https://doi.org/10.1182/blood.2018894618)
9. Jevtic D, da Silva MD, Haylock AB, et al.: Hemophagocytic lymphohistiocytosis (HLH) in patients with tick-borne illness: a scoping review of 98 cases. *Infect Dis Rep*. 2024, 16:154-69. [10.3390/idr16020012](https://doi.org/10.3390/idr16020012)
10. Kamila ŻW, Teresa R, Patrycja MG, Andrzej S: Neurological presentation of hemophagocytic lymphohistiocytosis. *Neurol Neurochir Pol*. 2015, 49:329-31. [10.1016/j.pjnns.2015.07.001](https://doi.org/10.1016/j.pjnns.2015.07.001)
11. Fohle E, Afriyie F, Dekowski SS: Central nervous system involvement in adult-onset hemophagocytic lymphohistiocytosis. *Cureus*. 2021, 13:e14792. [10.7759/cureus.14792](https://doi.org/10.7759/cureus.14792)
12. Spengos K, Stouraitis G, Voumvourakis K, Zambelis T, Karandreas N: Motor and sensory polyneuritis with distal conduction failure as uncommon complication of an acute Rickettsia conorii infection. *J Neurol Sci*. 2005, 234:113-6. [10.1016/j.jns.2005.03.045](https://doi.org/10.1016/j.jns.2005.03.045)
13. Verbiest HBC, van Woerkom TCAM, Dumas AM, Bots GTAM, Endtz LJ: Subacute progressive sensory ataxic neuropathy after Rickettsia conorii infection. *Clin Neurol Neurosurg*. 1990, 92:81-5. [10.1016/0303-8467\(90\)90013-U](https://doi.org/10.1016/0303-8467(90)90013-U)
14. Tzanetakos D, Papadopoulou M, Kanellopoulos D, Mamali M, Safarikas M, Katsianos D, Zisimopoulou V: Chronic inflammatory demyelinating polyneuropathy associated with Rickettsia conorii: first case report. *J Neurol Sci*. 2016, 371:60-1. [10.1016/j.jns.2016.10.015](https://doi.org/10.1016/j.jns.2016.10.015)
15. Hines MR, von Bahr Greenwood T, Beutel G, et al.: Consensus-based guidelines for the recognition, diagnosis, and management of hemophagocytic lymphohistiocytosis in critically ill children and adults. *Crit Care Med*. 2022, 50:860-72. [10.1097/CCM.0000000000005361](https://doi.org/10.1097/CCM.0000000000005361)
16. Shakoory B, Geerlinks A, Wilejto M, et al.: The 2022 EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). *Ann Rheum Dis*. 2023, 82:1271-85. [10.1136/ard-2023-224123](https://doi.org/10.1136/ard-2023-224123)
17. NHS England: Clinical Commissioning Policy: Anakinra for Haemophagocytic Lymphohistiocytosis (HLH) for Adults and Children in All Ages [210701P] (1924). NHS England, Leeds, England; 2021.