PORTUGUESE JOURNAL OF PEDIATRICS

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CASE REPORT

Rickettsial infection complicated by suspected hemophagocytic lymphohistiocytosis in a pediatric patient: a case report

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Abstract

Introduction: Rickettsial infections are vector-borne zoonoses that often present with nonspecific symptoms, making early diagnosis challenging, particularly in pediatric populations. **Case report:** A previously healthy six-year-old boy presented with a high-grade, persistent fever, generalized rash, abdominal pain, non-bloody diarrhea and lower limb myalgias. Initial laboratory tests revealed elevated liver enzymes and inflammatory markers. Despite empiric azithromycin therapy, he developed hepatosplenomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia and polyserositis, raising suspicion for evolving hemophagocytic lymphohistiocytosis (HLH). Blood and stool cultures were negative, and a Rickettsia PCR assay later confirmed *Rickettsia conorii* infection, with serology showing positive IgM and negative IgG. The patient improved progressively with doxycycline and ceftriaxone, without the need for *immunomodulatory therapy*. **Discussion:** This case highlights the potential trigger of rickettsial infections for HLH-like hyperinflammatory syndromes and the importance of early empiric antibiotic therapy.

Keywords: Rickettsia infections. Hemophagocytic lymphohistiocytosis. Pediatrics.

Rickettsiose complicada por suspeita de Linfohistiocitose Hemofagocítica numa criança: relato de caso

Resumo

Introdução: As rickettsioses são zoonoses transmitidas por vetores que frequentemente se manifestam por sintomas inespecíficos, o que dificulta o diagnóstico precoce, sobretudo em idade pediátrica. **Caso clínico:** Rapaz de 6 anos, previamente saudável, iniciou febre alta persistente, exantema generalizado, dor abdominal, diarreia não sanguinolenta e mialgias nos membros inferiores. A avaliação laboratorial inicial revelou elevação das enzimas hepáticas e dos parâmetros inflamatórios. Apesar de ter iniciado terapêutica empírica com azitromicina, desenvolveu hepatoesplenomegalia, citopenias, hiperferritinemia, hipertrigliceridemia e polisserosite, quadro sugestivo de linfohistiocitose hemofagocítica (HLH). As culturas foram negativas, a PCR para *Rickettsia* foi positiva para *Rickettsia conorii*, e as serologias foram IgM positiva e IgG negativa. Iniciou doxiciclina e ceftriaxone com evolução favorável, sem necessidade de imunomodulação. **Discussão:** Este caso alerta para o potencial das infeções por *Rickettsia* como desencadeadoras de síndromes hiperinflamatórias tipo HLH e reforça a importância do início precoce da antibioterapia empírica.

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Received: 24-09-2025
Accepted: 14-06-2026
https://pjp.spp.pt

Available online: 10-07-2026
Port J Pediatr. (Ahead of print)
DOI: 10.24875/PJP.25000072

Key points

What is known

- Rickettsial infections often present with nonspecific symptoms, delaying diagnosis in children.
- Hemophagocytic lymphohistiocytosis (HLH) may be triggered by infectious agents, including *rickettsiae*.
- Early doxycycline initiation is critical to improve prognosis in suspected rickettsial disease.

What is added

- Rickettsial infections may evolve with HLH-like features without meeting full HLH diagnostic criteria.
- Infection-triggered hyperinflammation may resolve with targeted antimicrobial therapy alone.
- Recognition of "incipient HLH" may guide management and avoid premature immunosuppression.

Introduction

Rickettsial infections are vector-borne zoonoses caused by obligate intracellular Gram-negative bacteria of the genus Rickettsia, transmitted globally and responsible for a spectrum of acute febrile illnesses.[1,2] Clinically, these infections often present with nonspecific symptoms such as fever, headache, rash and gastrointestinal disturbances. The presence of a tick eschar, although suggestive, is frequently absent or overlooked.[2,3,4] Diagnosis is often challenging due to the non-specific nature of early symptoms, the lack of a clear exposure history, the limited sensitivity of early serological tests and limited availability of PCR testing.[1,2,3] While Mediterranean spotted fever (MSF) caused by *Rickettsia conorii* is endemic in Southern Europe, it may present atypically, particularly in the pediatric population.[2]

A rare but life-threatening complication of infectious diseases, including rickettsioses, is hemophagocytic lymphohistiocytosis (HLH).[2,5] HLH is a hyperinflammatory syndrome caused by the uncontrolled activation of T lymphocytes and macrophages, leading to a cytokine storm and potential multiorgan failure.[6,7,8] Secondary HLH can be triggered by various infections, malignancies or autoimmune disorders and its recognition in the context of rickettsial infections is difficult given overlapping clinical features.[5,6,9]

Here, we describe a pediatric case of rickettsial infection complicated by features suggestive of evolving HLH, highlighting diagnostic challenges, a biphasic course and the importance of maintaining a high index of suspicion even in the absence of confirmatory tests.

Case report

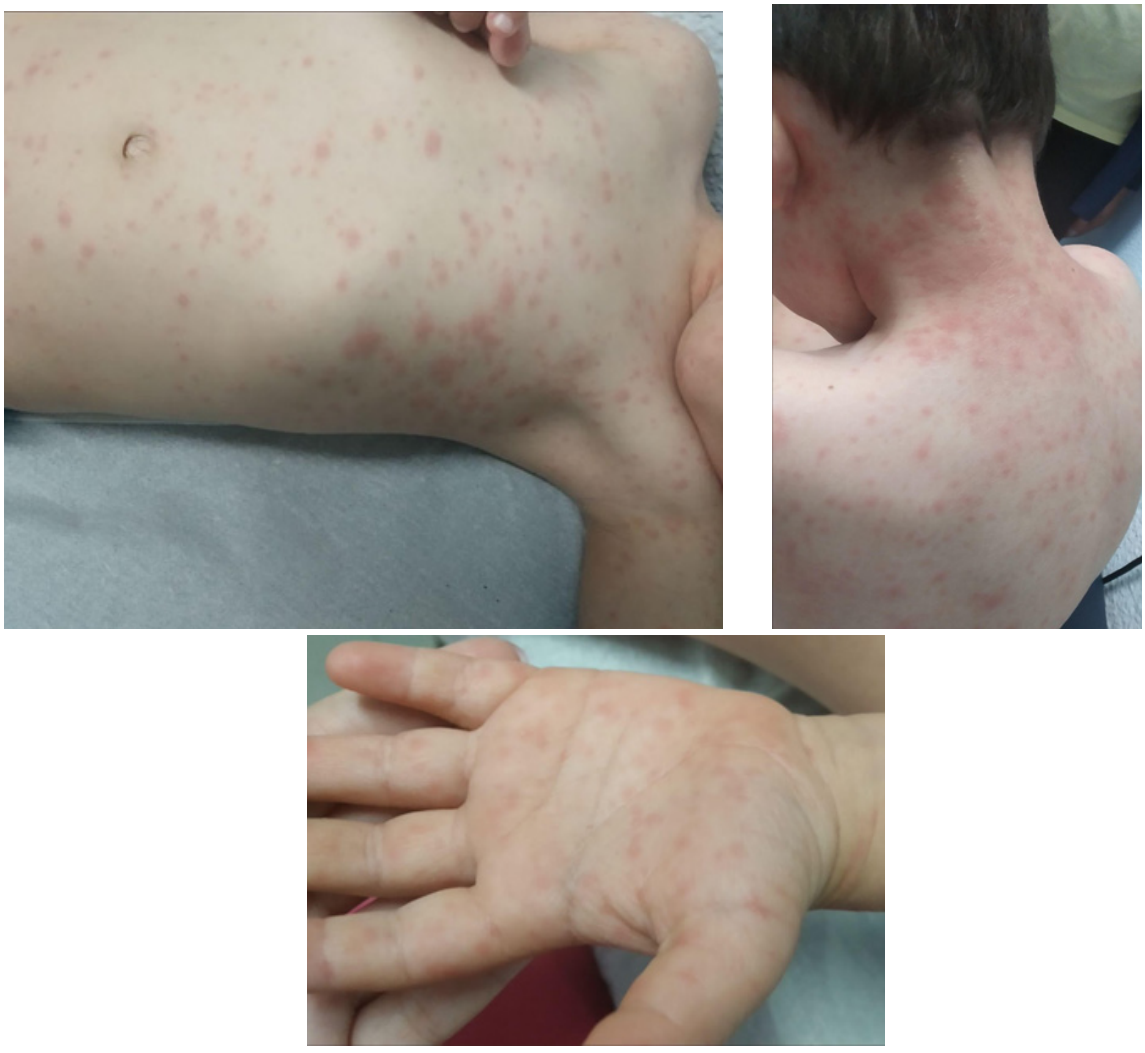
A previously healthy and fully immunized six-year-old boy presented to the Emergency Department with a five-day history of a high-grade persistent fever, abdominal pain, non-bloody diarrhea, sore throat, mild cough and a generalized rash involving the palms of the hands and soles of the feet. The rash developed on the second day of fever, first appearing on the upper limbs and rapidly becoming generalized, involving the entire body. It was non-pruritic, non-vesicular, non-tender and showed no desquamation.

The patient lived in a rural area, with regular exposure to domestic animals (a vaccinated and dewormed dog) and frequent contact with livestock (sheep and pigs) at his grandparents' farm. He had also visited a zoo three weeks prior. There was no recent travel, known exposure to unwell individuals or history of tick bites or eschar.

On examination, the child was afebrile and hemodynamically stable. He appeared pale, without jaundice. A blanchable erythematous maculopapular rash was noted, including on the palms of the hands and soles of the feet (Figs. 1-3). There were no oral changes (no lip erythema, pharyngeal hyperemia or strawberry tongue) or conjunctival injection. On deep abdominal palpation, diffuse tenderness was noted across all quadrants, with no hepatosplenomegaly. Cardiovascular examination revealed a grade II/VI systolic murmur, while pulmonary auscultation was unremarkable. Neurologically, he was irritable but showed no meningeal signs. No tick bite or black eschar were identified, and there were no musculoskeletal abnormalities.

Initial laboratory testing revealed increased liver enzymes, elevated C-reactive protein and mild hyponatremia (Table 1). He was admitted for investigation, clinical monitoring and intravenous hydration. On the second day of hospitalization, a presumptive diagnosis of Mediterranean spotted fever was considered, and oral azithromycin therapy was initiated. A pediatric cardiology evaluation, including echocardiography, revealed no abnormalities.

By day four of hospitalization, the patient showed clinical deterioration, with persistent fever, lower limb myalgias, worsening abdominal pain, vomiting and peripheral edema, with no diarrhea or jaundice. Subsequent laboratory evaluation revealed anemia, thrombocytopenia, worsening cholestatic hepatitis, hypoalbuminemia, hypofibrinogenemia and elevated D-dimers (Table 1).



Figures 1. Erythematous maculopapular rash in the six-year old boy of the described clinical case.

Due to the unavailability of abdominal ultrasound at our center, a chest-abdomen-pelvis computed tomography scan was performed, revealing hepatosplenomegaly, periportal edema and polyserositis (small bilateral pleural effusions, minimal pericardial effusion and mild ascites).

After consulting pediatric infectious disease specialists, antibiotic therapy was escalated to doxycycline (4 mg/kg/day on day one, then 2 mg/kg/day) and ceftriaxone 100 mg/kg/day.

By day six, the patient's condition worsened further with evolving purpuric skin lesions, conjunctival injection, bilateral calf tenderness, bilateral ankle edema and abdominal distension with palpable hepatomegaly 3 cm below the right costal margin. Laboratory testing at this time revealed elevated ferritin and hypertriglyceridemia (Table 1), raising suspicion for hemophagocytic lymphohistiocytosis (HLH).

The patient completed five days of antibiotic therapy with doxycycline and ceftriaxone, showing progressive clinical improvement, resolution of the rash and defervescence from day seven. Hepatomegaly was no longer palpable by day nine of hospitalization.

Blood and stool cultures were negative. Serologies and PCR testing for HIV, hepatitis A, B and C, parvovirus B19, Epstein–Barr virus (EBV), cytomegalovirus (CMV), leptospirosis, *Borrelia* and *Brucella* were all negative. A peripheral blood smear revealed hypochromic red cells, anisocytosis, moderate pleomorphism of mononuclear cells and reactive lymphocytes.

The patient was discharged feeling generally well, having completed two additional days of doxycycline at home, for a total of seven days of treatment.

Table 1. Blood test results from admission to D9

Test (units)	Admission	D2	D4	D6	D7	D9	Reference range
Hemoglobin (g/dL)	11.7	10.7	9.8	9.4	9.8	9.7	12.0-15.0
Hematocrit (%)	33.5	32.1	28.8				35-45
WBC count (n/mm3)	7.1	8.8	9.0	17.7	20.7	13.8	5-13
Platelet count (n/mm3)	181	137	115	182	256	329	150-350
C-reactive protein (mg/dL)	4.8	6.3		3.2	2.0	0.6	< 0.5
Potassium (mEq/L)	3.9		4.3		5	4.8	3.5-5.1
Sodium (mEq/L)	132		136		136	135	136-146
Lactate dehydrogenase (U/L)	773				960	721	125-230
Albumin (g/dL)	3.4	2.7	2.2		3.4	4.1	3.8-5.4
Urea (mg/dL)	14		15	15	12	32	15-36
Creatinine (mg/dL)	0.51		0.41	0.49	0.48	0.52	0.70-1.25
CPK (U/L)	126			188	142	59	30-200
Total bilirubin (mg/dL)	0.64		2		0.64	0.58	< 1.2
Gamma-glutamyl transferase (U/L)	103	174		454	557	397	12-64
Glutamic pyruvic transaminase (U/L)	152	131	125	119	128	85	< 55
Glutamic oxaloacetic transaminase (U/L)	332	167	163	159	144	54	5-34
Alkaline phosphatase (U/L)	186		375	753	802	558	< 500
Fibrinogen (U/L)			1.7		2.3	2.4	2.0-4.0
Prothrombin time (seconds)		13.8	12.0	10.8	10.9	11.3	10.0-14.6
Activated partial thromboplastin time (seconds)		31.7	31.7	26.7	29.6	32.9	26.9-38.7
D-dimer (ng/mL)		27434	20221	7119	1820	604	60-567
Ferritin (ng/mL)				878	553	281	21.8-275
Triglycerides (mg/dL)				361	449	389	< 150

Subsequently, a *Rickettsia* blood PCR assay was reported positive for *Rickettsia conorii*, and the serology was consistent with acute infection, showing positive IgM and negative IgG. The case was notified to public health authorities, as it is a notifiable disease.

Discussion

Rickettsial infections in children present significant diagnostic challenges due to their nonspecific presentations, variable clinical evolution and often absent history of tick exposure or characteristic eschar.

In this case, the initial symptoms mimicked a common viral illness, but the persistence of a high fever, rash involving the palms of the hands and soles of the feet, abdominal symptoms and signs of systemic inflammation prompted the early suspicion of a rickettsial etiology. Empiric treatment for suspected rickettsiosis was initiated on the second day of hospitalization (day seven of the disease).

The clinical evolution with hepatosplenomegaly along with laboratory findings of hyperferritinemia, hypertriglyceridemia, cytopenias and elevated transaminases raised the possibility of hemophagocytic lymphohistiocytosis (HLH). HLH is a life-threatening hyperinflammatory syndrome characterized by an uncontrolled immune activation and a cytokine storm leading to multiorgan dysfunction.[8,9] While HLH secondary to tick-borne infections is rare, it carries considerable morbidity and mortality when not promptly recognized and treated.[9]

Based on the HLH-2004 diagnostic criteria, the patient fulfilled at least four out of eight criteria

(persistent fever exceeding seven days, elevated ferritin, hypertriglyceridemia and hepatosplenomegaly), with borderline cytopenias suggesting a fifth. Although hemophagocytosis was not demonstrated and immunological studies were unavailable, the clinical picture was compatible with incipient or evolving HLH, a concept increasingly acknowledged in pediatric infectious disease.[5,7,10] Although the degree of cytopenias did not quantitatively meet the established thresholds, the observed values were borderline and, when considered alongside the broader clinical picture, supported a presumptive diagnosis of evolving HLH. The absence of advanced immunological testing —including soluble IL-2 receptor (sCD25), NK cell activity and evidence of hemophagocytosis in the bone marrow, lymph nodes, liver or spleen— due to resource limitations, precluded definitive confirmation. Nevertheless, such incomplete or evolving presentations, often referred to as "incipient" or "subclinical" HLH, are increasingly recognized as clinically relevant and warrant close monitoring and early therapeutic intervention.[7,10]

Multiple causes have been described to trigger HLH. Infections remain one of the most common causes of secondary HLH, most frequently associated with intracellular pathogens, with viral agents such as EBV, CMV and herpes simplex virus (HSV) most frequently implicated. However, other intracellular pathogens, including bacterial and tick-borne infections like *Rickettsia*, as well as parasitic infections such as leishmaniasis, have also been reported as triggers.[2,5,7]

The diagnostic overlap between severe rickettsiosis and HLH creates a therapeutic dilemma regarding the use of immunomodulating therapy.[9]

Current expert consensus recommends antibiotic monotherapy in infection-associated HLH, particularly in mild cases, whereas moderate-to-severe presentations may benefit from adjunctive HLH-directed therapies. However, there are no established guidelines for the management of rickettsial HLH, and treatment decisions often rely on clinical judgment and disease severity.[3]

In our case, despite the delayed confirmatory serology and PCR assay due to difficulties in sample processing, the patient presented with a clinical picture suggestive of MSF and subsequently showed progressive improvement with antimicrobial therapy alone. This clinical course strongly supports rickettsial infection as the underlying infectious trigger of the HLH-like syndrome.

Mortality associated with HLH secondary to tick-borne infections is estimated at approximately 16% — lower than that observed in primary HLH, but notably higher than for rickettsiosis alone. Delayed or inappropriate empiric antibiotic therapy has been associated with worse outcomes.[9] Therefore, early clinical recognition of both the suspected rickettsial etiology and the accompanying hyperinflammatory state is critical. The prompt initiation of empirical antibiotic treatment (preferably with doxycycline), even in the absence of serological confirmation, is essential to improve prognosis and reduce mortality.[7] Doxycycline is considered safe in pediatric patients and should not be withheld when clinical suspicion is high. Careful clinical assessment and supportive management are equally important while treatment of the underlying cause takes effect.

This case underscores the need for heightened clinical suspicion for HLH in pediatric rickettsial infections with systemic involvement. Early recognition, timely initiation of doxycycline and multidisciplinary management are essential to prevent the progression to full-blown HLH and to improve outcomes. Further studies are warranted to better define the immunopathology of rickettsial-induced HLH and to establish evidence-based management protocols for these rare but severe cases.

Author contributions

R. dos Santos-Carvalho: conception and design of the case report; acquisition of data from both the patient and literature; data analysis and interpretation. A. Afonso and R. dos Santos Carvalho: methodology; drafting of the article; critical review of the article for important intellectual content; final approval of the version to be published. Elsa Lima Teixeira: supervision; validation; critical review of the article for important intellectual content; final approval of the version to be published.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's

confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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