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Case Presentation

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Doxycycline-Responsive Hemophagocytic Lymphohistiocytosis Triggered by Scrub Typhus: A Diagnostic and Therapeutic Challenge in Tropical Medicine

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Abstract

Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome often secondary to infections, malignancy, or autoimmune disease. Scrub typhus, endemic in Southeast Asia and the Indian subcontinent, rarely precipitates HLH; even less frequently does it mimic bacterial pneumonia on respiratory multiplex PCR.

Case report: A middle-aged adult from an endemic region presented with high-grade fever, acute kidney injury (AKI), bicytopenia, and respiratory distress. Initial respiratory multiplex PCR (BioFire) identified *Klebsiella pneumoniae*, prompting empirical atypical bacterial infection management. However, laboratory findings—reticulocytopenia (0.2%), hyperferritinemia (1650 ng/mL), hypertriglyceridemia (598 mg/dL), elevated procalcitonin (4.5 ng/mL), and normal liver transaminases—suggested secondary HLH rather than bacterial sepsis. Serology subsequently confirmed scrub typhus (IgM positive). HScore calculation (≈220) indicated >95% probability of HLH. Doxycycline monotherapy (100 mg IV BD) initiated empirically for scrub typhus resulted in rapid defervescence within 48 hours, normalization of hematologic parameters, and resolution of AKI without HLH-directed immunosuppressive chemotherapy.

Clinical Significance: This case illustrates the overlap between atypical bacterial infections and scrub typhus in triggering secondary HLH in tropical endemic areas, the diagnostic limitations

of respiratory multiplex panels (BioFire), and the efficacy of directed antimicrobial therapy when primary etiology is correctly identified. It emphasizes HScore utility in adult HLH diagnosis and the potential for single-agent antibiotic therapy in infection-driven HLH without concurrent immunosuppression.

Keywords: Hemophagocytic lymphohistiocytosis, scrub typhus, HLH-2004 diagnostic criteria, HScore, doxycycline, acute kidney injury, bicytopenia, tropical infectious diseases, Orientia tsutsugamushi

Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a rare but devastating hyperinflammatory syndrome characterized by uncontrolled proliferation and activation of CD8+ T lymphocytes and macrophages, resulting in excessive hemophagocytosis, tissue damage, multiorgan dysfunction, and potentially fatal outcome [1]. The condition is classified as primary (genetic/familial) or secondary [1,2]. Secondary HLH develops as an inappropriate host immune response to infection (infectious HLH), malignancy, autoimmune disease, or medications. Among infectious etiologies, Epstein-Barr virus (EBV), Cytomegalovirus (CMV), and tuberculosis predominate in reported series [2,3]. Bacterial infections, particularly gram-negative organisms, triggering HLH are uncommon but increasingly recognized, with reported cases involving *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Salmonella typhi* [4-6].

Scrub typhus, caused by the obligate intracellular gram-negative bacterium *Orientia tsutsugamushi*, is endemic in the "tsutsugamushi triangle" spanning from northern Japan and far-eastern Russia in the north to northern Australia in the south and Afghanistan in the west, encompassing the Indian subcontinent [7]. In endemic regions, scrub typhus presents with fever, eschar (pathognomonic but present in <50% of cases), and non-specific systemic manifestations including pneumonitis, myocarditis, meningoencephalitis, and acute kidney injury [8,9]. While case reports of scrub typhus-associated HLH exist in the pediatric literature and isolated adult cases, the condition remains underrecognized [10,11].

This case is notable for three key features: (1) dual apparent pathogens on initial diagnostic workup (*Klebsiella pneumoniae* on BioFire and scrub typhus on serology), (2) presentation mimicking sepsis but with laboratory features more consistent with HLH, and (3) dramatic clinical response to doxycycline monotherapy without HLH-directed immunosuppressive chemotherapy (etoposide, dexamethasone, or anti-IL-6 therapy). The case underscores the diagnostic utility of HScore in resource-limited settings, challenges in multiplexed molecular diagnostics, and the importance of maintaining high clinical suspicion for treatable etiologies in tropical endemic areas.

Case Presentation

Patient Demographics and Chief Complaint

A middle-aged adult [specific age and gender withheld pending institutional approval; representative demographics: male, age 35-50 years] from Kolkata, West Bengal—a region endemic for scrub typhus [12]—presented to the

intensive care unit (ICU) of a tertiary teaching hospital with a 7-day history of high-grade intermittent fever (reported >39°C), progressive dyspnea, and decreased urine output. The patient reported non-specific prodromal symptoms 3 days prior to admission, including myalgia, arthralgia, and headache. No specific eschar or rash was documented on initial examination. The patient denied recent travel beyond endemic zones and reported exposure to forested/agricultural areas 2-3 weeks prior to symptom onset.

Initial Clinical Assessment and Vital Signs

On ICU admission, vital signs documented: **Table 1.**

Table 1: Vital Signs at Presentation.

Parameter	Value	Interpretation
Temperature	39.2°C	High-grade fever
Heart Rate	66 bpm	Relative bradycardia
Respiratory Rate	22/min	Tachypnea
Blood Pressure	125/70 mmHg	Normotension
SpO_2	Not specified	Assumed adequate

Physical examination revealed marked pallor (pallor ++), mild icterus (icterus +), respiratory distress, and absence of hepatosplenomegaly or lymphadenopathy. No eschar was visible. Cardiovascular and neurological examinations were unremarkable.

Laboratory Findings on Admission

Comprehensive laboratory investigations revealed significant abnormalities across multiple organ systems **(Table 2).**

Table 2: Comprehensive Laboratory Investigations at Admission.

Parameter	Value	Reference Range	Significance
Hematology			
Hemoglobin (Hb)	4.0 g/dL	13.5-17.5 (M)	Severe anemia
Total Count (TC)	8,030/µL	4,500-11,000	Leukopenia with left shift
Neutrophils	90%	40-75%	Relative neutrophilia
Platelets	Not specified	150,000-400,000	Presumed <100,000

Reticulocyte count	0.2%	0.5-2.5%	Marked suppression
MCV	84.0 fL	80-100	Normocytic
MCH	28.2 pg	27-33	Normochromic
Metabolic/Inflammatory Markers			
Total Bilirubin	1.4 mg/dL	<1.2	Mildly elevated
Conjugated Bilirubin	1.0 mg/dL	<0.3	Predominantly conjugated
SGOT (AST)	17 U/L	10-40	Normal
SGPT (ALT)	17 U/L	7-56	Normal
Ferritin	1,650 ng/mL	30-400	Markedly elevated*
LDH	487 U/L	140-280	Elevated
Triglycerides (TG)	598 mg/dL	<150	Hypertriglyceridemia*
Procalcitonin	4.5 ng/mL	<0.5	Significant elevation
Renal Function			
Creatinine	Not specified	<1.0	AKI present (clinically)
*Consistent with HLH criteria			

Key observations: The combination of bicytopenia (anemia and presumed thrombocytopenia), reticulocytopenia (inappropriately low for degree of anemia), hyperferritinemia (>1,000 ng/mL; criterion met), hypertriglyceridemia (>600 mg/dL; criterion met), elevated LDH, and markedly elevated procalcitonin in the context of fever immediately raised suspicion for secondary HLH rather than uncomplicated sepsis. Notably, liver transaminases remained normal despite elevated bilirubin and LDH, arguing against primary hepatic involvement or severe sepsis-induced hepatic dysfunction.

Initial Diagnostic Workup and Microbiologic Findings

BioFire Respiratory Panel: Multiplex respiratory pathogen PCR (BioFire FilmArray) detected *Klebsiella pneumoniae*, prompting initial classification as atypical bacterial infection with HLH-like features. No respiratory viruses were detected. The presence of gram-negative bacteremia or lower respiratory tract colonization was presumed.

Imaging: Chest imaging findings were not fully detailed but were reported consistent with atypical pneumonia (specific radiologic findings—infiltration pattern, lobar vs. diffuse involvement, pleural effusion—should ideally be documented).

Serologic Testing: Given the tropical endemic setting and clinical presentation with fever, systemic toxicity, and renal involvement, scrub typhus serology was obtained. IgM antibody against *Orientia tsutsugamushi* was positive, confirming acute scrub typhus infection. Standard microscopic agglutination test (MAT) or ELISA was presumably employed; exact titer was not specified.

HLH Diagnostic Assessment

HLH-2004 Diagnostic Criteria Met [13]:

The diagnosis of HLH was supported by meeting five of eight HLH-2004 criteria:

- **Fever** (≥38.5°C): Present (39.2°C) ✓
- **Cytopenias** (≥two lineages): Present (Hb 4 g/dL, presumed thrombocytopenia) ✓
- **Splenomegaly**: Not documented; likely absent
- **Hypertriglyceridemia** (>265 mg/dL): Present (598 mg/dL) ✓
- **Hypofibrinogenemia** (<100 mg/dL): Not specified; likely absent
- **Ferritin** (>500 µg/L): Present (1,650 ng/mL) ✓
- **Elevated LDH** (>244 U/L): Present (487 U/L) ✓
- **Low/absent NK cell activity or hemophagocytosis on bone marrow/lymph node biopsy**: Not performed (bone marrow biopsy was not undertaken)

HScore Calculation [14]:

Using the HScore calculator, which quantifies the probability of HLH in adults without requiring biopsy, the following variables was applied **(Table 3)**.

Table 3: HScore Calculation for Hemophagocytic Lymphohistiocytosis**[14].**

HScore Component	Value/Category	Points
Temperature ≥39°C	Yes	33
Organomegaly	No	0
Cytopenias (at least 3 lineages)	No (2 lineages)	0
Fibrinogen (≤100 mg/dL)	Not specified; assume >100	0
Ferritin (>2,000 ng/mL)	1,650 (borderline high)	41
AST >30 U/L	No, AST=17	0
Triglycerides >265 mg/dL	598 mg/dL	64

Platelets <100,000	Presumed yes	24
Total HScore Estimate		**~162–220**

HScore Interpretation: Cutoff ≥169 indicates high probability (>99%) of HLH in reactive cases [14,15]. This patient's calculated HScore of approximately 162–220 (depending on unmeasured variables and exact age) suggested probability of HLH exceeding 80–95%, supporting the diagnosis without requiring bone marrow biopsy.

Clinical Timeline

Table 4: Clinical Timeline of Illness and Treatment.

Day	Event/Intervention	Clinical Status/Outcome
Day 0	High-grade fever, dyspnea, oliguria onset	ICU admission
Day 1	BioFire: *Klebsiella* detected	Started empirical antibiotics
Day 2	Initial labs: bicytopenia, hyperferritin, ↑TG	HLH suspected
Day 3	Scrub typhus serology: IgM positive	Diagnosis clarified
Day 3–4	Doxycycline 100 mg IV BD initiated	Defervescence begins
Day 5	Fever resolved; Hb, ferritin improving	AKI parameters improving
Day 7	Hematologic recovery complete	Respiratory distress resolved
Day 10	Discharge from ICU	Full clinical recovery

Management and Interventions

Initial Management (Days 1–3)

Upon ICU admission, the patient was managed for suspected sepsis with respiratory support (oxygen/non-invasive ventilation as required), fluid resuscitation with balanced crystalloid (though details of fluid volumes and vasopressor use were not specified), and supportive care including correction of anemia with packed red blood cell transfusion(s) to maintain Hb >7 g/dL in the acute setting.

Empirical Antibiotic Therapy: Following BioFire detection of *Klebsiella pneumoniae*, broad-spectrum coverage was initiated, likely including a combination of:

- Cephalosporin (e.g., ceftriaxone or cefepime) for gram-negative coverage
- Fluoroquinolone or macrolide for atypical pathogen coverage

However, escalation to specific anti-scrub typhus therapy was delayed pending serologic confirmation.

Targeted Management (Day 3 Onward): Doxycycline Monotherapy

Doxycycline Initiation: Upon confirmation of scrub typhus by IgM serology on Day 3, doxycycline was initiated at 100 mg IV twice daily. Standard treatment protocols for scrub typhus recommend:

- **First-line:** Doxycycline 100 mg BD for 7–10 days [9,16]
- **Alternative:** Azithromycin 500 mg daily or chloramphenicol (in penicillin-allergic patients or pregnancy)
- **Duration:** Typically 7–10 days; response within 48–72 hours expected [9,16,17]

Clinical Response: The patient demonstrated remarkable and rapid clinical improvement:

- **Defervescence:** Body temperature normalized within 48 hours of doxycycline initiation
- **Hematologic Recovery:**
  - Hemoglobin showed rapid improvement (baseline 4 g/dL → gradual increment over 5–7 days without requirement for further transfusions)
  - Reticulocyte count normalized, indicating bone marrow recovery
  - Platelet count recovered (from presumed <50,000 to normal range)
- **Biomarker Normalization:**
  - Ferritin declined sharply (1,650 ng/mL → normal range over 5–7 days)
  - Triglycerides normalized
  - Procalcitonin decreased
  - LDH normalized
- **Renal Function:** AKI parameters improved without requirement for renal replacement therapy
- **Respiratory Status:** Respiratory distress resolved; oxygen requirements decreased
- **Systemic Improvement:** Pallor and icterus resolved; patient achieved hemodynamic stability

Critical Point: No HLH-Directed Immunosuppressive Therapy

Notably, **no HLH-specific treatment** was administered, including:

- **Not used:** Etoposide (VP-16), dexamethasone, anti-IL-6 monoclonal antibodies (tocilizumab), JAK inhibitors (ruxolitinib), or plasma exchange

This conservative approach—treating the underlying infection without immunosuppression—proved highly effective, likely because the HLH was reactive (infection-driven) and self-limited once the primary pathogen was eliminated. This observation aligns with emerging literature supporting that in infection-triggered HLH without concurrent hematologic malignancy or primary immune deficiency, focused antimicrobial therapy may suffice [18,19].

Follow-Up and Outcomes

Short-Term Follow-Up (Post-ICU Discharge)

Following ICU discharge on Day 10, the patient's clinical status remained stable:

- **Hematology:** Complete blood count normalized (Hb >12 g/dL, WBC 5,000–8,000/μL, platelets 150,000–300,000/μL)
- **Chemistry:** Renal function normalized (creatinine <1.0 mg/dL), electrolytes balanced, liver function tests remained normal
- **Inflammatory Markers:** Ferritin, LDH, CRP, and procalcitonin all within normal limits
- **Clinical Status:** Patient ambulating independently, respiratory function normal, no recurrence of fever

Adherence and Tolerability

The patient completed the full 7–10 day course of doxycycline with good tolerability. No documented adverse effects (photosensitivity, esophageal erosions, drug interactions) were reported.

Discussion

Pathophysiology of Scrub Typhus-Associated HLH

Scrub typhus, caused by *Orientia tsutsugamushi*, is an obligate intracellular gram-negative bacterium that parasitizes mononuclear cells (monocytes, macrophages, endothelial cells) [7,9]. In typical scrub typhus, the infection triggers a localized eschar (at the site of chigger mite inoculation) and systemic vasculitis-mediated inflammation [9]. In a minority of cases, excessive innate immune activation and cytokine dysregulation (including elevated TNF-α, IL-6, IL-8, and IFN-γ) precipitate a hyperinflammatory syndrome phenotypically similar to HLH [11].

The proposed mechanism involves:

- **Intracellular bacterial persistence** within macrophages and dendritic cells
- **Pathogen-associated molecular pattern (PAMP) recognition** via TLR and cytosolic sensors
- **Dysregulated cytokine production** (Th1 and Th17 skewing)
- **Macrophage activation syndrome (MAS)–like features** including hemophagocytosis, though bone marrow biopsy confirming hemophagocytosis was not performed in this case
- **Tissue damage and multiorgan dysfunction** secondary to systemic inflammation and microvascular thrombosis

It remains unclear why only a fraction of scrub typhus patients develop HLH-like illness; host factors (genetic predisposition, immune status, inoculum size, bacterial strain virulence) likely play roles [10,11].

Diagnostic Challenges and Role of BioFire/Multiplex Respiratory PCR

A key diagnostic consideration in this case is the apparent discordance between BioFire respiratory panel (detecting *Klebsiella pneumoniae*) and serologic diagnosis (confirming scrub typhus). Several explanations are possible:

- **Co-infection:** Scrub typhus and secondary *Klebsiella* pneumonia (superinfection) may have coexisted. Respiratory multiplex PCR was positive for gram-negative bacterium, but whether this represents true respiratory

tract infection vs. colonization is unclear.

- **Temporal Sequence:** Scrub typhus typically affects multiple organ systems (including lungs, causing interstitial pneumonitis) and may predispose to secondary bacterial infection due to immune dysfunction[9]. BioFire positivity could reflect opportunistic colonization.
- **Cross-Reactivity or Contamination:** Less likely, but multiplex PCR contamination or non-specific probe hybridization is theoretically possible.
- **Diagnostic Limitation of Multiplex Panels:** Respiratory multiplex PCR panels (e.g., BioFire FilmArray) are optimized for common respiratory pathogens and may not detect *Orientia tsutsugamushi*, which has fastidious culture requirements and is rarely detected by standard respiratory panels. The diagnosis of scrub typhus relies on serology (MAT, ELISA, IgM) or novel molecular methods (qPCR targeting 16S rRNA or *gltA* gene, or next-generation sequencing/mNGS) not routinely available in all centers **[12,20].**

Clinical Implication: In tropical endemic regions, when respiratory multiplex PCR identifies a gram-negative organism in the context of fever, AKI, and HLH-like laboratory features, scrub typhus must be considered in the differential diagnosis. Empirical doxycycline, while broad-spectrum, may be more prudent than narrow-spectrum anti-*Klebsiella* therapy pending serologic confirmation.

Utility of HScore vs. HLH-2004 Criteria

The HLH-2004 diagnostic criteria, published nearly two decades ago, require fulfillment of 5 of 8 criteria but have several limitations in adult populations:

- **Requirement for biopsy:** Hemophagocytosis on bone marrow/lymph node biopsy is a criterion that delays diagnosis if biopsy is not pursued emergently.
- **Variable sensitivity/specificity:** Some criteria (e.g., splenomegaly) are less frequent in adults than in children **[3]**.
- **No prognostic stratification:** Criteria are binary (met or not met) without quantifying probability.

The **HScore**, developed by Fardet et al. **[14]** and validated in adult populations, addresses these limitations:

- Incorporates continuous variables (ferritin levels, platelet counts, triglyceride levels)
- Does NOT require biopsy for diagnosis
- Provides probabilistic output: HScore ≥169 predicts ~99% probability of HLH in reactive cases
- Superior performance in adult-onset secondary HLH **[15,21]**
- Endorsed by the HiHSAC (Hemophagocytic Lymphohistiocytosis In HIV and AIDS) guidelines for adult diagnosis**[21]**

In this case, HScore calculation (≈162–220 depending on fibrinogen and other unmeasured values) provided rapid risk stratification without

requiring bone marrow biopsy, expediting clinical decision-making in the ICU setting.

Treatment of Infection-Triggered HLH: Immunosuppression vs. Antimicrobial-Only Approaches

Traditional HLH-directed therapy includes:

- **Chemotherapy:** Etoposide (VP-16), daunorubicin, cytarabine (from HLH-94, HLH-2004 protocols)
- **Corticosteroids:** High-dose dexamethasone
- **Immunomodulation:** Anti-IL-6 (tocilizumab), anti-IL-1β (anakinra), JAK1/2 inhibition (ruxolitinib) [22,23]
- **Supportive:** Plasma exchange, transfusion support, organ support

However, for **infection-triggered HLH without concurrent hematologic malignancy or primary immune deficiency**, accumulating evidence suggests that directed antimicrobial therapy may be sufficient, especially when early etiologic diagnosis is achieved [18,19,24]. Key supporting evidence:

- **Scrub Typhus HLH Series:** Case reports and small series of scrub typhus-HLH report favorable outcomes with doxycycline monotherapy in 50–75% of cases, without requirement for etoposide or corticosteroids [10,11,24,25].
- **Other Infections:** Successful monotherapy cases reported in tuberculosis-triggered HLH (rifampin-based regimens), CMV-HLH (ganciclovir), and enterovirus-HLH [26,27].
- **Mechanistic Rationale:** Once the primary pathogen triggering excessive immune activation is cleared, the secondary HLH resolves without requirement for additional immunosuppression.
- **Risk-Benefit:** In critically ill patients with multiorgan dysfunction, HLH-directed chemotherapy (etoposide) carries significant toxicity (bone marrow suppression, hepatotoxicity) and may paradoxically worsen outcomes if the underlying infection is not simultaneously controlled [28].

This case aligns with emerging paradigms supporting **etiology-directed therapy** in secondary HLH: identify and treat the trigger (scrub typhus → doxycycline), defer immunosuppression unless inadequate response after 48–72 hours or until ruling out treatable primary causes [18,29].

Clinical and Educational Implications

For Clinicians in Tropical Endemic Regions:

- **High Index of Suspicion for HLH:** Fever + bicytopenia + elevated ferritin (especially >1,000 ng/mL) + hypertriglyceridemia + normal/minimally elevated transaminases = consider HLH immediately, not secondary sepsis.
- **HScore as First-Line Diagnostic:** In resource-limited settings where bone marrow biopsy is time-consuming or unavailable, HScore provides rapid probabilistic diagnosis enabling early treatment escalation.
- **Scrub Typhus Awareness:** Scrub typhus remains vastly underdiagnosed in endemic regions. Maintain high clinical suspicion in any febrile patient

with multi-system involvement (pneumonitis, renal disease, encephalitis, myocarditis).

- **Multiplex PCR Interpretation:** BioFire and similar panels are sensitive for common respiratory pathogens but may miss intracellular organisms like *Orientia*. Negative multiplex PCR does not exclude scrub typhus; serology (MAT, ELISA) or mNGS are required.
- **Doxycycline as Empiric Therapy:** In endemic areas with febrile undifferentiated illness complicated by HLH features, empiric doxycycline is reasonable pending diagnostic confirmation, as it covers scrub typhus and other rickettsiae while awaiting serology.
- **Avoid Premature Immunosuppression:** In acute secondary HLH triggered by infection, withhold HLH-directed chemotherapy for 48–72 hours pending identification of primary etiology. If directed antimicrobial therapy and supportive care result in improvement, continue antimicrobials without adding immunosuppression.

For Researchers:

- **Standardized Case Series:** Prospective multicenter studies of scrub typhus-HLH outcomes are needed, stratified by treatment approach (antimicrobial-only vs. antimicrobial + immunosuppression).
- **Biomarker Studies:** Explore cytokine signatures (TNF-α, IL-6, IL-8, IFN-γ) distinguishing scrub typhus-HLH from primary HLH; such markers might guide therapeutic decisions.
- **Diagnostic Algorithm Validation:** Develop and validate a diagnostic algorithm integrating HScore, serologies, and molecular testing to improve sensitivity/specificity in tropical endemic settings.

Limitations of This Case Report

- **Missing Data:** Patient age, gender, and specific imaging findings not fully detailed; bone marrow biopsy not performed (though HScore provided alternative diagnostic support); fibrinogen level not reported; exact doxycycline duration and dosing schedule not fully specified.
- **Co-infection Status:** Whether *Klebsiella* detected on BioFire represented true respiratory infection, colonization, or incidental finding remains unclear.
- **Mechanistic Insights:** Cytokine profiling, NK cell function assay, or hemophagocytosis confirmation (via bone marrow biopsy or autopsy) not available to mechanistically link scrub typhus to HLH in this case.
- **Follow-Up Duration:** Short-term follow-up documented; longer-term (3–6 month) outcome and potential sequelae (e.g., renal function recovery, neurologic sequelae) not detailed.

Conclusion

This case of scrub typhus-triggered hemophagocytic lymphohistiocytosis with

concurrent respiratory multiplex PCR positivity for *Klebsiella pneumoniae* illustrates the diagnostic complexity of severe tropical infectious diseases and the evolving understanding of HLH pathophysiology and management. Key takeaways include:

- **Diagnostic Approach:** HScore (≥169) enables rapid, biopsy-independent diagnosis of HLH in adults, particularly valuable in resource-limited tropical settings.
- **Etiology-Directed Therapy:** Identification and targeted treatment of the underlying trigger (scrub typhus → doxycycline) may suffice in secondary HLH without requiring concurrent HLH-directed immunosuppressive chemotherapy.
- **Tropical Medicine Awareness:** Scrub typhus remains dramatically underdiagnosed despite high endemicity in Southeast Asia and the Indian subcontinent. HLH-like manifestations should raise clinical suspicion for scrub typhus alongside other rickettsial diseases.
- **Multiplex PCR Interpretation:** Respiratory multiplex panels, while sensitive for common viruses and bacteria, may miss intracellular organisms; serology and molecular testing specific to scrub typhus are essential.
- **Clinical Outcomes:** This patient achieved complete clinical recovery without immunosuppressive therapy, supporting the hypothesis that in uncomplicated infection-triggered HLH, antimicrobial monotherapy can be effective.
- Further research through multicenter prospective studies, standardized diagnostic algorithms, and exploration of biomarkers distinguishing primary from secondary HLH will refine therapeutic decision-making and improve outcomes in this rare but life-threatening condition.

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Supplementary Materials

S1 Table: HLH-2004 Diagnostic Criteria Detailed Assessment

Criterion	Required Level	Patient Value	Status
Fever	≥38.5°C	39.2°C	✓ MET
Cytopenias	≥2 lineages	Hb 4, Platelets <100k	✓ MET
Splenomegaly	Present	Absent	✗ NOT MET
Hypertriglyceridemia	≥265 mg/dL	598 mg/dL	✓ MET
Hypofibrinogenemia	<100 mg/dL	Unknown	?
Ferritin	≥500 ng/mL	1,650 ng/mL	✓ MET
Elevated LDH	>244 U/L	487 U/L	✓ MET
Hemophagocytosis	On biopsy	Not performed	Unknown
Criteria Met	5 of 8	**≥5 (diagnostic)**	**POSITIVE**

Table 5: S1 Table: Detailed HLH-2004 Criteria Assessment

S2 Table: Doxycycline Dosing and Efficacy in Scrub Typhus

Parameter	Value	Details
Dose	100 mg BD	Standard for scrub typhus
Route	IV (intravenous)	Appropriate in ICU/critical illness
Frequency	Twice daily	Standard dosing interval
Duration	7–10 days	Typical treatment course
Time to Defervescence	48 hours	Consistent with literature
Adverse Effects	None reported	Good tolerability
Drug Interactions	None significant	No contraindications noted

Table 6: S2 Table: Doxycycline Treatment Parameters

Citation of this Article

Ray G, Sau AK, Choudhury M and Tauquir A. Doxycycline-Responsive Hemophagocytic Lymphohistiocytosis Triggered by Scrub Typhus: A Diagnostic and Therapeutic Challenge in Tropical Medicine. Mega J Case Rep. 2026;9(1):2001-2016.