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A Diagnostic Challenge in Severe Scrub Typhus: Secondary Hemophagocytic Lymphohistiocytosis With Multiorgan Dysfunction Syndrome

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Abstract

Scrub typhus-associated secondary hemophagocytic lymphohistiocytosis (HLH) is an uncommon but potentially fatal complication, particularly when accompanied by severe systemic inflammation and multiorgan dysfunction. Although it has been reported in endemic regions within the tsutsugamushi triangle, early recognition remains challenging because its clinical features may overlap with those of severe scrub typhus itself. We report the case of a 32-year-old male who presented with high-grade fever, jaundice, and altered sensorium. He was positive on IgM ELISA for scrub typhus and had elevated ferritin levels, hypofibrinogenemia, hypertriglyceridemia, and significant hepatic and renal dysfunction. Ultrasonography (USG) showed mild hepatomegaly and moderate splenomegaly. The HScore was 254, indicating a high probability of secondary HLH; on this basis, a clinical diagnosis of multiorgan dysfunction syndrome (MODS) with secondary HLH due to scrub typhus was made. The patient was treated with appropriate antibiotics and supportive care and followed up regularly for four weeks. This case report highlights the importance of early diagnosis of secondary HLH in patients with scrub typhus and the need for prompt initiation of appropriate treatment.

Categories: Hematology, Internal Medicine, Infectious Disease
Keywords: hscore, multiorgan dysfunction syndrome, orienta tsutsugamushi, scrub typhus, secondary hemophagocytic lymphohistiocytosis (hlh)

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially life-threatening hyperinflammatory disorder characterized by uncontrolled activation of T lymphocytes and macrophages, which leads to excessive cytokine production and immune-mediated tissue damage. It may occur as a primary disorder due to inherited genetic defects or as secondary HLH triggered by infections, malignancies, autoimmune diseases, drug hypersensitivity, or hematopoietic stem cell transplantation (HSCT) [1]. The underlying immunopathogenesis involves impaired cytotoxic activity of natural killer (NK) cells and cytotoxic T lymphocytes, which results in persistent immune activation and a dysregulated inflammatory response.

The clinical manifestations of HLH include persistent high-grade fever, hepatosplenomegaly, cytopenias, and variable degrees of hepatic and multiorgan dysfunction syndrome (MODS). Characteristic laboratory abnormalities include hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, elevated soluble interleukin-2 receptor (sCD25) levels, and impaired NK-cell activity. According to the HLH-2004 diagnostic criteria, the diagnosis can be established by either a compatible molecular diagnosis or the presence of at least five of eight specified clinical and laboratory criteria, including fever, splenomegaly, cytopenias, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, reduced NK-cell activity, elevated ferritin, and increased sCD25 [2].

Among the infectious triggers of secondary HLH, scrub typhus is an important consideration in endemic regions. Scrub typhus is a mite-borne zoonotic infection caused by the obligate intracellular bacterium Orientia tsutsugamushi, which is prevalent in the geographical region known as the Tsutsugamushi triangle, extending from northern Japan and eastern Russia to northern Australia and Pakistan. Although the infection commonly presents with acute febrile illness, severe cases may be complicated by hepatitis, acute kidney injury, acute respiratory distress syndrome, and MODS. The development of secondary HLH represents an uncommon but potentially serious complication of scrub typhus.

The diagnosis of HLH in patients with severe scrub typhus can be challenging because of considerable clinical and laboratory overlap between the two conditions. Persistent fever, hepatosplenomegaly, cytopenias, hepatic dysfunction, and elevated inflammatory markers may occur in both, which can delay recognition of the underlying hyperinflammatory syndrome. A systematic review by Naoi et al. identified 30 reported cases of scrub typhus-associated HLH, with an overall mortality of 6.7%, underscoring the clinical

significance of this association [3]. Earlier reports have also demonstrated that prompt recognition and appropriate treatment of the underlying infection are essential for favorable outcomes [4].

Although scrub typhus-associated HLH has been described in previous case reports and case series, its rarity and diagnostic complexity warrant continued clinical attention. We report the case of a 32-year-old male who presented with high-grade fever, jaundice, and altered sensorium, tested positive for scrub typhus-specific IgM antibodies by ELISA, and was subsequently diagnosed with secondary HLH. This case highlights the importance of considering HLH in patients with severe scrub typhus presenting with hepatic and neurological dysfunction, particularly when the clinical course suggests a systemic hyperinflammatory response.

Case Presentation

A 32-year-old man, a farmer by occupation, presented with high-grade fever for 11 days, associated with yellowish discoloration of the eyes and dark-colored urine for five days. He had also developed altered sensorium, right upper quadrant abdominal pain, myalgia, and headache for two days before presentation. There was no history of chills or rigors, bleeding manifestations, seizures, or previous hospitalization for fever. On examination, he had pallor, icterus, and grade 1 bilateral pitting pedal edema (left > right). No eschar was seen. The abdomen was soft and distended, with diffuse tenderness, predominantly over the epigastrium and right hypochondrium. Cardiovascular, respiratory, and neurological examinations were unremarkable.

Serial investigations (Table *1*) showed progressive cytopenias, with hemoglobin decreasing from 16.1 g/dL on day one to 6.3 g/dL on day seven (which can be attributed to hemolysis occurring during severe inflammation) and platelet count decreasing from 63,000/µL to 50,000/µL. The peripheral smear showed giant platelets. Liver indices, including total and direct bilirubin, AST, ALT, and ALP, were elevated, with marked worsening by day five (indicating acute liver injury). Serum ferritin levels progressively increased from 1,964 ng/mL (day one) to 8,205 ng/mL (day seven). Renal function deteriorated by day six, with a serum creatinine of 4.8 mg/dL and a urea of 207.3 mg/dL (indicating acute kidney injury).

Lab parameter	Normal range	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Hb (g/dL)	13-17	16.1	13.1	12.4	12.6	10.2	6.7	6.3
Platelet (/µL)	150,000-450,000	63,000	72,000	69,000	54,000	63,000	55,000	50,000
Total leukocyte count (/µL)	4,000-11,000	11,000	8,300	6,500	4,900	7,400	5,200	5,300
Total bilirubin (mg/dL)	0.3-1.2	9.2	13.4	15.8	18.3	19.5	29	25.4
Direct bilirubin (mg/dL)	0.1-0.3	3.6	5.1	5.5	5.9	6.7	13.7	19.6
AST/ALT (IU/L)	10-40/10-60	20/30	42/32	68/34	43/29	40/20	85/22	95/25
ALP (IU/L)	40-130	154	190	221	249	214	224	150
Ferritin (ng/mL)	30-400	1,964	3,465	4,540	5,780	6,443	7,321	8,205
Urea (mg/dL)	15-40	32	40	89	125	168	207.3	210
Creatinine (mg/dL)	0.6-1.2	0.9	1.2	1.4	2.1	3.2	4.8	4.7
Triglycerides (mmol/L)	0.5-1.7	0.62	1.81	2.21	2.64	3.48	3.87	3.92

TABLE 1: Serial hematological parameters from day 1 to day 7

Hb: hemoglobin; AST: aspartate aminotransferase; ALT: alanine transaminase; ALP: alkaline phosphatase

Scrub typhus IgM was positive, while dengue NS1 antigen, the macroscopic slide agglutination test (MSAT) for leptospirosis, QBC testing for malaria, and the Widal test were negative. Ultrasonography (USG) revealed borderline hepatomegaly, moderate splenomegaly, and altered bilateral renal and pancreatic echoes. CT of the chest and abdomen demonstrated bilateral mild pleural effusion, minimal ascites, and mild perinephric stranding (Figures *1A*, *1B*).

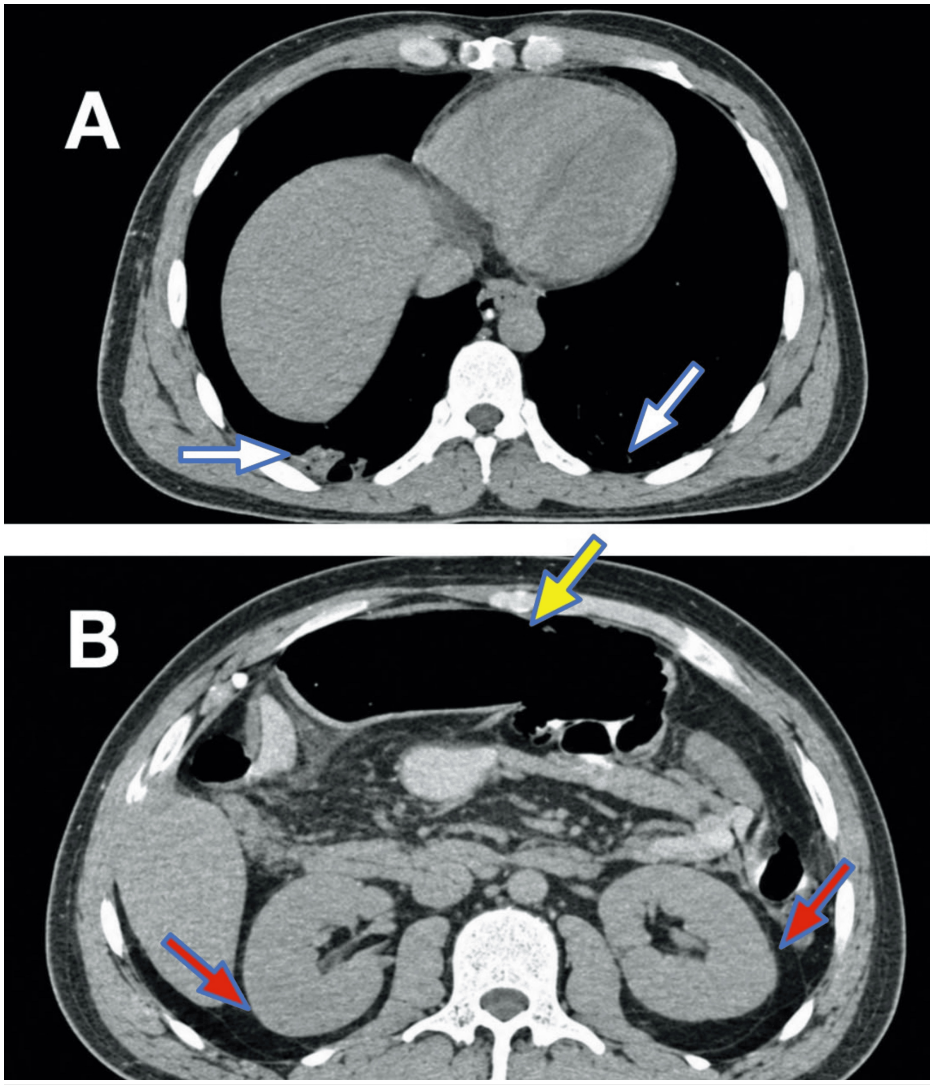


FIGURE 1: CT chest and abdomen

CT chest (A) revealing mild pleural effusion (white arrows) and CT abdomen (B) showing mild ascites (yellow arrows) and mild perinephric stranding (red arrows)

CT: computed tomography

In light of the progressive cytopenias, hypofibrinogenemia, elevated ferritin, and multiorgan involvement, secondary HLH was suspected. The HScore was 254, indicating a very high probability of HLH. The calculation of HScore is presented in Table *2*.

Parameter	Reference values	Finding	Points
Known immunosuppression	No: 0, yes: 18	No	0
Temperature (°C)	< 38.4: 0, 38.4-39.4: 33, > 39.4: 49	40	49
Organomegaly	No: 0, hepatomegaly/splenomegaly: 23, hepatomegaly + splenomegaly: 38	Hepatomegaly + splenomegaly	38
Cytopenias	1 lineage: 0, 2 lineage: 24, 3 lineage: 34	2 lineage	24
Ferritin (ng/mL)	< 2 000: 0, 2 000-6 000: 35, > 6 000: 50	8,205	50
Triglycerides (mmol/L)	< 1.5 mmol/L: 0, 1.5-4: 44, > 4: 64	3.87	44
Fibrinogen (g/L)	> 2.5: 0, ≤ 2.5: 30	< 2.5	30
AST (IU/L)	< 30: 0, ≥ 30: 19	40	19
Hemophagocytosis seen on bone marrow aspirate	No: 0, yes: 35	No	0
Total score	254		

TABLE 2: Calculation of HScore

AST: aspartate aminotransferase

Based on the clinical, laboratory, and microbiological findings, a final diagnosis of MODS with secondary HLH associated with scrub typhus was made. The patient was initially treated with broad-spectrum antibiotics, dexamethasone, N-acetylcysteine, and supportive care. Following confirmation of scrub typhus, oral doxycycline 100 mg twice daily was initiated. The patient showed progressive clinical improvement and was discharged on day 14, with follow-up for four weeks.

Discussion

HLH is a rare hyperinflammatory syndrome arising from impaired regulation of cytotoxic T lymphocytes, NK cells, and macrophages. This uncontrolled immune activation leads to excessive cytokine release and subsequent immune-mediated damage involving multiple organ systems. HLH has traditionally been classified as primary or secondary. Primary HLH, or familial HLH, has a genetic basis, whereas secondary or acquired HLH is due to various factors such as infection, malignancy, autoimmune diseases, post-HSCT status, and drug hypersensitivity.

The most common infectious cause of secondary HLH is Epstein-Barr virus (EBV) [1], but the etiology of secondary HLH varies and depends on local epidemiological patterns, patient demographics, and underlying immune status. In India and other low- and middle-income settings, endemic infections such as scrub typhus, dengue, enteric fever, malaria, visceral leishmaniasis, and tuberculosis remain the main precipitants [2]. The burden of secondary HLH associated with scrub typhus in India is illustrated by Selvam et al., who reported secondary HLH in 28 (18.7%) of 150 patients with laboratory-confirmed scrub typhus diagnosed by IgM ELISA, blood PCR, or eschar tissue PCR [3].

Secondary HLH presents more commonly in adults and is a heterogeneous disorder, converging on a common pathway of widespread systemic inflammation, and manifests clinically as high-grade fevers, mild to severe organomegaly, cytopenias, and rapid development of multiorgan dysfunction [4]. The diagnosis of HLH is aided by the HScore. The score consists of nine variables, with the maximum points per variable ranging from 18 to 64. Unlike the HLH-2004 criteria (older criteria), which were derived from a pediatric population, the HScore was developed in an adult cohort including patients aged ⩾ 18 years, making it more appropriate in our case [5]. Our patient had an HScore of 254 (Table *2*), which is well above the threshold of 169, indicating a high probability of HLH.

MODS refers to the development of acute dysfunction in two or more organ systems following a severe physiological insult, with the potential for recovery [6]. Our patient developed acute kidney injury (serum creatinine: 4.8 mg/dL, serum urea: 207.3 mg/dL) on the sixth day and acute liver injury (markedly elevated liver function test parameters) on the fifth day, thus fulfilling the criteria for MODS. Nevertheless, the contribution of HLH to the observed hepatic and renal dysfunction cannot be definitively distinguished from the direct systemic effects of scrub typhus. This overlap highlights the importance of considering secondary HLH in patients with severe scrub typhus who develop progressive hyperinflammatory features.

A similar case was reported by Basheer et al., in which a 64-year-old man presented with sepsis that progressed to MODS and secondary HLH, with a positive scrub typhus IgM ELISA. As in our case, the patient became asymptomatic after treatment of the underlying scrub typhus infection with doxycycline [7]. Diwan et al. reported a case in which the patient progressed to a severe form of HLH, macrophage activation syndrome (MAS) [8]. This was not observed in our patient, which may be attributed to early intervention in our patient, differences in socioeconomic status, and genetic background, among other factors.

Our patient made a full recovery without any neurological deficits. This contrasts with the case reported by Han et al., in which, despite appropriate antirickettsial therapy and treatment for HLH, the patient's neurological dysfunction progressively deteriorated without evidence of clinical recovery. That report was the first case of severe neurological impairment resulting from the association of HLH with scrub typhus [9]. Therefore, in endemic areas, a high index of suspicion for secondary HLH is needed in patients presenting with scrub typhus.

Recent changes in therapeutic modalities have improved the outcomes of patients with secondary HLH. According to a study by Hua et al., a combination of doxycycline, IVIG, and dexamethasone resulted in fever resolution within 72 hours, and the patient showed complete recovery [10]. In 2026, Dong et al. reported the use of JAK1/2 inhibitor therapy for scrub typhus-associated HLH, raising the possibility that combining ruxolitinib with azithromycin may facilitate rapid disease control while maintaining good tolerability [11].

Conclusions

Scrub typhus-associated HLH is a rare, potentially life-threatening hyperinflammatory complication that can progress rapidly to multiorgan dysfunction and death. The considerable clinical and laboratory overlap between severe scrub typhus and secondary HLH poses a diagnostic challenge, particularly in patients presenting with progressive cytopenias, hyperferritinemia, and organ dysfunction. This report highlights the importance of considering secondary HLH in patients with severe scrub typhus and a progressive hyperinflammatory clinical course. Early recognition, appropriate evaluation, and timely management of both the underlying infection and associated hyperinflammation may be important in optimizing clinical outcomes. However, the contribution of HLH to individual organ dysfunction and the impact of early treatment on long-term outcomes cannot be definitively established from a single case report.

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.

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Disclosures

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