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Scrub Typhus Co-infected with Legionella pneumophila Complicated by Acute Arrest of Hematopoiesis and Wernicke Encephalopathy in a Patient with Alcohol Use Disorder: A Case Report and Mini-review

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Case Report

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Scrub Typhus Co-infected with *Legionella pneumophila* Complicated by Acute Arrest of Hematopoiesis and Wernicke Encephalopathy in a Patient with Alcohol Use Disorder: A Case Report and Mini-review

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Abstract

Background: Scrub typhus (ST) presents with nonspecific symptoms, often leading to diagnostic delays. Hematologic complications beyond thrombocytopenia are rare, and concurrent opportunistic infections are challenging to manage, particularly in immunocompromised hosts.

Case Presentation: A 67-year-old male with chronic alcohol use disorder presented with a 10-day history of fever, headache, and abdominal pain. Initial evaluation revealed scrub typhus (eschar + Weil-Felix positive) and severe pancytopenia (WBC 0.91×10^9/L, neutrophil count 0.50×10^9/L, RBC 2.45×10^{12}/L, HGB 81.0g/L, and PLT 1.0×10^9/L). Despite doxycycline therapy, fever persisted. Subsequent workup revealed co-infection with *Legionella pneumophila* (IgM+) and fungal elements on

smear. Bone marrow examination confirmed acute arrest of hematopoiesis (AAH). Neuroimaging demonstrated findings consistent with Wernicke encephalopathy (WE) and acute lacunar infarcts.
Diagnosis and Intervention:The patient was ultimately confirmed to have scrub typhus co-infected with *Legionella pneumophila*, with concurrent acute arrest of hematopoiesis and Wernicke encephalopathy. Remarkably, he achieved rapid recovery after initiation of azithromycin.
Conclusion: This case highlights that AAH can be a complication of ST, potentially triggered by uncontrolled infection. Persistent fever despite first-line therapy should prompt evaluation for co-infections (e.g., *Legionella*) and metabolic encephalopathies (e.g., WE), especially in patients with chronic alcoholism. Azithromycin proved effective against both ST and LD.

Keywords: Scrub typhus, acute arrest of hematopoiesis, Legionnaires' disease, Wernicke encephalopathy, co-infection,case report

Introduction

Scrub typhus (ST) can manifest with diverse clinical presentations due to systemic complications, including encephalitis, interstitial pneumonia, acute renal failure, acute hepatic failure, acute hearing loss, and acute respiratory distress syndrome. The nonspecific signs and symptoms, limited awareness, lack of accessible diagnostic facilities, and low clinical suspicion often pose diagnostic challenges and complicate management.

Pancytopenia is commonly associated with myelodysplastic syndromes, chemotherapy-induced myelosuppression, and aplastic anemia, but is rarely observed in acute arrest of hematopoiesis (AAH). While AAH is seldom reported in scrub typhus, thrombocytopenia represents a relatively common hematologic finding in this infection. Fever and altered mental status are typical clinical features of scrub typhus; however, their persistence despite appropriate first-line antimicrobial therapy is uncommon. Although *Orientia tsutsugamushi* is considered the primary etiologic agent, refractory manifestations may also result from co-infection with other pathogens, such as dengue virus [1], or from concurrent conditions like Wernicke encephalopathy (WE)[2]. Herein, we report a case of scrub typhus co-infected with *Legionella pneumophila*, complicated by AAH and WE, in a patient with a history of chronic alcohol abuse.

Case presentation

A 67-year-old male presented with a 10-day history of fever (maximum temperature 39.1°C), accompanied by chills, headache, and upper abdominal pain. He was initially admitted to a local hospital. Notably, he had a history of nighttime agricultural labor prior to symptom onset. Chest computed tomography (CT) revealed bilateral pulmonary inflammatory changes. The diagnosis of scrub typhus was established at the local facility based on the identification of pathognomonic eschars

on both wrists and a positive Weil-Felix test. The patient was administered doxycycline; however, the full course was not completed. Although defervescence was initially achieved, fever recurred following the continuation of antibiotic therapy.

Due to the development of severe pancytopenia , with the complete blood count (CBC), demonstrating: white blood cell (WBC) count 0.91×10^9/L, neutrophil count 0.43×10^9/L, red blood cell (RBC) count 2.73×10^{12}/L, hemoglobin (HGB) 95.0 g/L, and platelet (PLT) count 1.0×10^9/L, the patient was transferred to our hospital for further management. His past medical history was significant for essential hypertension, alcoholic liver disease, and a previous left ankle fracture. He also reported a prolonged history of alcohol consumption spanning over 40 years.

On admission,physical examination revealed: temperature 36.5°C, blood pressure 135/97 mmHg, heart rate 87 bpm, respiratory rate 20/min, SpO_2 96% on room air. The patient appeared anemic. Scattered spider angiomas were noted on the anterior chest wall. An eschar, approximately 1.5 cm × 1.2 cm and oval-shaped, was observed on each wrist. Cardiopulmonary and abdominal examinations revealed no significant abnormalities. Laboratory investigations revealed as bellow

Hematological and Biochemical Findings

Upon transfer to our facility, laboratory investigations revealed profound pancytopenia: WBC 1.99×10^9/L, neutrophil count 0.50×10^9/L, RBC 2.45×10^{12}/L, HGB 81.0g/L, and platelets 3.0×10^9/L. The reticulocyte count was 3.40×109/L, consistent with bone marrow hypoproliferation. Systemic inflammation was evident with an ESR >140mm/hand CRP 46.3mg/L. Liver function tests indicated synthetic dysfunction (albumin 29.0g/L) and cholestasis (GGT 179U/L, ALP 163U/L), reflective of underlying alcoholic liver disease. A general bacterial smear of the sputum yielded fungi (++), and serology was positive for *Legionella pneumophila* IgM.Table 1 showed the dynamics of blood routine test as bellow.

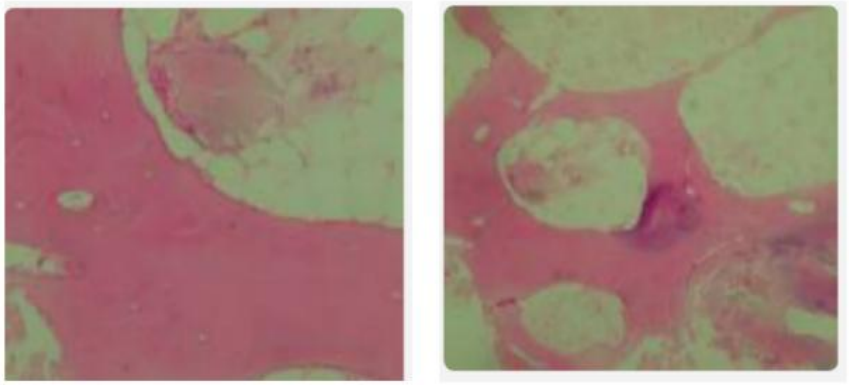
Table 1 the dynamics of blood routine test during hospitalization

items / Date	WBC (×10⁹/L)	HB (g/L)	RBC (×10¹²/L)	PLT (×10⁹/L)	RET (×10⁹/L)
2020/9/14	0.91	95	2.73	1.0	
2020/9/17	1.99	81	2.45	3.0	3.4
2020/9/18	2.23	70	2.09	28	3.1
2020/9/23	2.33	56	1.62	11	4.5
2020/9/25	3.46	49	1.55	16	7.3
2020/9/27	6.09	68	2.05	18	
2020/9/28	3.05	69	2.10	14	
2020/9/30	9.85	69	2.02	56	

Bone Marrow Examination

Bone marrow smear demonstrated marked hypocellularity with dysplastic changes, characterized by granulocytic megaloblastoid maturation and severe

thrombocytopenia. Histopathological analysis of the core biopsy revealed a paucity of hematopoietic cells within the trabecular bone, with a predominance of adipocytes and scattered erythroid precursors. Granulocytic and megakaryocytic lineages were notably absent, confirming the diagnosis of AAH (Figure 1).

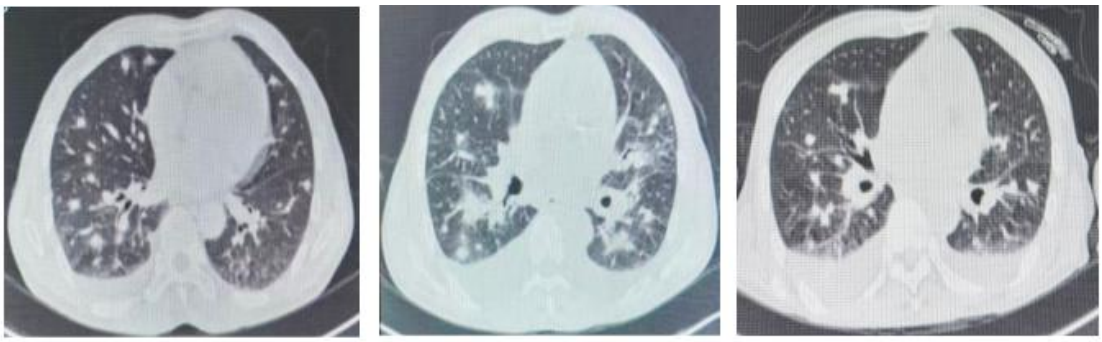


A B

Fig.1 Histopathological analysis of the bone marrow biopsy (A and B)showing scattered erythroid precursors and absence of granulocytic and megakaryocytic lineages (H&E, ×100). These findings are consistent with acute arrest of hematopoiesis (AAH).

Imaging Studies

CT Scans:



C D E

Fig.2 Serial chest CT scans (C,D,E)demonstrating disease progression and response to therapy

September 17, 2020(Fig 2 C): Contrast-enhanced CT of the abdomen and pelvis (with non-contrast chest CT) revealed bilateral pulmonary inflammatory changes suspicious for fungal infection, a small right pleural effusion, hepatomegaly, and a suspected splenic cyst.

□

September 22, 2020(Fig 2 D): Compared to the prior study, there was interval progression of bilateral pulmonary infiltrates. New-onset small left pleural effusion and ascites were noted, in addition to an increase in the right pleural effusion.

□□

September 28, 2020(Fig 2 F): Follow-up chest CT demonstrated slight interval improvement in the bilateral pulmonary infiltrates and pleural effusions. The differential diagnosis was broadened to include Legionella infection versus fungal infection.

Brain MRI (September 22, 2020):

MRI of the brain, including diffusion-weighted imaging (DWI), revealed multiple acute/subacute lacunar infarcts involving the right crus cerebri, bilateral genu of the internal capsules, left corona radiata, and left semioval center. Additionally, white matter hyperintensities corresponding to DWMH Grade I and evidence of age-related brain changes were observed.And extensive high T2 signal appeared in the axial skeleton(Fig 3)

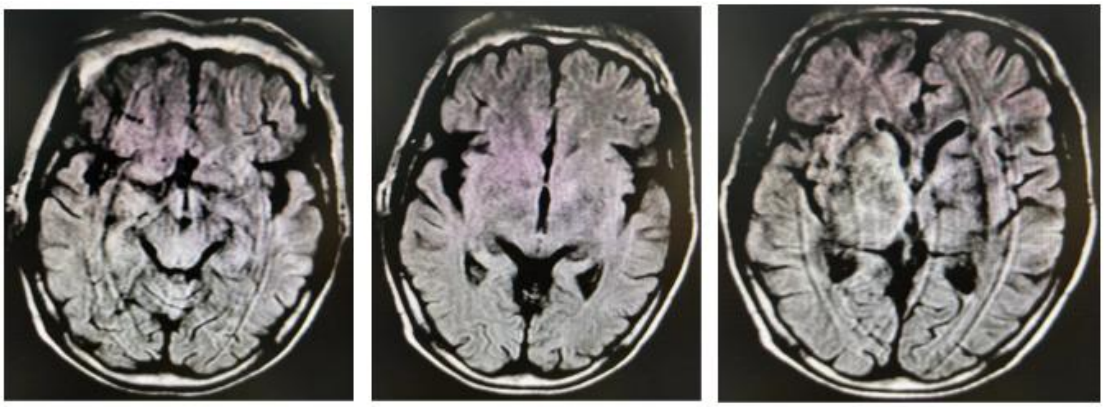


Fig. 3 Brain MRI demonstrated extensive high T2 signal in the axial skeleton on fluid-attenuated inversion recovery (FLAIR) imaging(F,G,H)

Diagnosis and treatment process

Bone marrow examination, integrating histopathological and cytomorphologic assessment, confirmed that the patient's pancytopenia was attributable to an infectious etiology, manifesting as acute arrest of hemopoiesis(AAH) .Initial therapeutic regimen comprised cefoperazone/sulbactam(2g ivgtt q8h)for empiric antibacterial coverage and doxycycline(0.1g po bid) for scrub typhus. Persistence of fever prompted escalation of antifungal therapy with voriconazole(Loading dose:0.4 g IV infusion q12h (for the first 24 hours), then maintenance dose: 0.2 g IV infusion q12h), supported by a fungal smear (++) and radiographic evidence of pulmonary infiltrates(non-contrast chest CT in September 17, 2020 ,figure). However, initiation of voriconazole coincided with acute neuropsychiatric disturbances, including agitation and delirium. Neurology consultation led to the introduction of olanzapine (2.5mg po qn)for symptomatic management, yet neither mental status alterations nor febrile episodes resolved.

Diagnostic reevaluation via cranial MRI and repeat thoracic CT (22 September 2020,) demonstrated progressive bilateral pulmonary infections, suggestive of invasive fungal disease, alongside increased bilateral pleural effusions and new-onset

ascites compared to prior imaging (17 September 2020). In consultation with clinical pharmacy, antibacterial therapy was switched to imipenem(0.5g IV infusion q6h) while continuing voriconazole. Although the patient's temperature initially declined from 38.0 °C to 36.4 °C, a recurrent fever of 38.1 °C was noted on 27 September. Follow-up CT (28 September) indicated slight regression of pulmonary opacities and effusions,with Legionella or fungal infection remaining differential considerations.Subsequent detection of a positive *Legionella pneumophilav* IgM antibody led to infectious disease and intensive care unit consultation, resulting in the addition of azithromycin(0.5g IV infusion qd). This intervention correlated with resolution of fever by 28 September and normalization of peripheral blood counts beginning 30 September. Despite control of the infectious process, neuropsychiatric symptoms persisted. Further neurologic assessment, incorporating a history of chronic alcohol use and characteristic neuroimaging findings(Fig.3)), established a diagnosis of Wernicke Encephalopathy.

Follow-up

The patient was discharged from hospital after achieving rapid recovery following initiation of azithromycin. He remained afebrile thereafter; however, at the time of telephone follow-up with his family post-discharge, he was noted to have persistent cognitive impairment at home.

Discussion

The patient's prominent clinical manifestations were persistent fever and altered mental status. The persistent fever likely reflected ongoing uncontrolled infection, which may have triggered acute arrest of hematopoiesis (AAH). AAH is defined as a transient episode of pure red cell aplasia characterized by reticulocytopenia in peripheral blood, absence of erythroid precursors, and the presence of giant pronormoblasts in bone marrow [3-5]. Prior reports indicate that AAH can be precipitated by infections or drug exposure [6]. While AAH predominantly occurs in patients with hemolytic anemia and is typically self-limiting, with aplasia lasting 5-10 days [4,5], routine blood tests usually reveal anemia and decreased reticulocyte counts; pancytopenia is uncommon, though mild leukopenia and/or thrombocytopenia may occasionally occur [3].

Notably, our patient developed pancytopenia. His bone marrow apiration and histopathology examination confirmed the diagnosis of AAH. The dynamic changes in his complete blood count are shown in Table 1. Following the initiation of azithromycin, his temperature normalized within one day. Moreover, after two days of intravenous azithromycin treatment, his white blood cell count began to recover, and his red blood cell count, hemoglobin level, and platelet count gradually increased.

Although doxycycline is considered first-line treatment for scrub typhus and typically induces rapid defervescence within 48–72 hours [7], it retains preference in severe cases due to its established efficacy compared to alternatives such as azithromycin and rifampin [8]. Previous reports also support doxycycline as the

mainstay therapy, even in patients with severe pulmonary complications [9]. Nevertheless, in the present case, pulmonary infection and radiographic lesions progressed despite a 7-day course of doxycycline combined with imipenem, a broad-spectrum antimicrobial reserved for specific indications. In contrast, marked clinical improvement was observed following the switch to azithromycin: fever resolved within 24 hours, and after two days of intravenous azithromycin, the white blood cell count began to normalize, with gradual increases in red blood cell count, hemoglobin, and platelet levels.One study reported azithromycin is as effective as other anti-rickettsial drugs with higher treatment success rates, lower frequency of adverse effects, and longer time to defervescence (GRADE 2B) [10]. Another study also reported comparable treatment outcomes between patients receiving intravenous azithromycin and those on oral doxycycline, suggesting that intravenous azithromycin may serve as a viable alternative when oral doxycycline is contraindicated[11].The patient's third CT chest without contrast demonstrated: bilateral pulmonary infectious infiltrates,with a differential including legionella vs. fungal pneumonia. Small bilateral pleural effusions were also noted.Clinical correlation is suggested.Given the positive *Legionella pneumophila* IgM, Intensive care unit(ICU) consultation note, and the failure of initial empiric therapy with voriconazole and imipenem(a special-use antibiotic), the regimen was switched to azithromycin.The patient achieved defervescence and eventual control of the infection. The 48- to 72-hour period following treatment initiation may represent a critical window for evaluating therapeutic response and detecting early failure [12,13]. In this case, the initial lack of response to doxycycline was not promptly recognized, partly due to our limited clinical experience with scrub typhus and its management.

Our case further supports the findings of Long J et al., whose study confirmed that antibiotic therapy failure represents a significant clinical challenge in scrub typhus, contributing to prolonged illness duration, increased complication rates, adverse events, and distinct antibiotic-specific failure patterns[14].This experience highlights the importance of considering alternative treatments, such as azithromycin, when first-line doxycycline fails to elicit a clinical response after 72 hours in scrub typhus. In addition, given the frequent occurrence of concurrent infections in immunocompromised patients, other co-infections should be suspected when the clinical course deviates from the expected response to conventional therapy. For instance, one study reported a 27-year-old second-trimester primigravida with Wernicke Encephalopathy (WE) co-infected with leptospirosis and scrub typhus, presenting with altered mental status, fever, and neurological deficits;ophthalmoplegia and confusion were noted on initial examination, and MRI confirmed typical WE findings[2]. Similarly, our patient developed WE in the setting of chronic alcohol use and was concurrently infected with scrub typhus and Legionnaires'disease.

Scrub typhus (ST) can present as severe multilobar pneumonia with pleural effusion, mimicking bacterial pneumonia, which may lead to diagnostic delay and postponed treatment [7]. Legionnaires' disease (LD), caused by the Gram-negative waterborne pathogen *Legionella pneumophila*(Lp), is recognized by the World Health Organization as imposing a high health burden in the European Union[15]. LD can be

acquired in community, travel-associated, or nosocomial settings, with higher susceptibility among males aged ≥ 65 years, especially those with comorbidities, alcohol abuse, smoking history, or immunosuppression[16]. Our patient was a 67-year-old male with a history of chronic alcohol abuse who presented with co-infection by *L. pneumophila* and *Orientia tsutsugamushi*, both Gram-negative intracellular bacteria. Notably, azithromycin is effective against both pathogens, and its administration in this case resulted in defervescence and eventual infection control.

As for the patient's mental disorder, we initially thought it might be the complication of scrub typhus. However, the patient's cranial MRI image(Fig3) demonstrated far more than menigitis.Notably, brain MRI revealed multiple acute/subacute lacunar infarcts in the bilateral internal capsules and right crus cerebri. While DWMH Grade I reflects chronic microangiopathy likely related to chronic alcoholism and aging, the acute lesions suggest an active pathological process. Given the diagnosis of scrub typhus and pancytopenia, these acute infarcts may be attributed to endothelial damage and vasculitis caused by Orientia tsutsugamushi rather than typical atherosclerotic disease.Combined with chronic alcoholism ,MRI of the brain demonstrated extensive high T2 signal in the axial skeleton (Fig 3), showing typical findings of WE ,thus confirming our diagnosis, even in the absence of classic triad of symptoms.

Conclusion

This case illustrates that acute arrest of hematopoiesis (AAH) can occur in scrub typhus (ST) and suggests that persistent fever may reflect uncontrolled infection, potentially triggering AAH. Furthermore, it underscores the diagnostic difficulty in differentiating infectious from metabolic encephalopathy in complex febrile illnesses. The findings also emphasize the importance of considering co-infections and Wernicke Encephalopathy in patients with alcoholism and persistent neuropsychiatric symptoms despite appropriate antimicrobial therapy.

Declarations

Acknowledgements

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Author Contributions

Hairong Shen (H.S.) served as the attending physician for the patient. H.S. performed the bone marrow aspiration and biopsy, authored the manuscript, and prepared the figures. Geng Su was responsible for the pathological analysis. Dadong Wang,Shaoling Yang,Zhiping Lv and Huiqin Wei provided intellectual guidance and oversight throughout the study. All authors participated in reviewing the manuscript and approved the final version.

Ethics Approval and Informed Consent

The authors take full responsibility for all aspects of the work, ensuring that any questions related to the accuracy or integrity of the study are appropriately investigated and resolved. All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and/or national research committee(s) and with the 1964 Helsinki Declaration and its later amendments. And the study protocol was reviewed and approved by the Medical Ethics Committee of Minzu Hospital of Guangxi Medical University（Ethics Approval No.: Guimin Yi Lun Shen Tong Zi (2026) No. 20）. Written informed consent was obtained from the patient's family for the publication of this case report and any accompanying images.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability

The clinical data supporting the conclusions of this case report are included within the article. The mini-review section is based on previously published literature, with full citations provided in the reference list. Raw clinical data are not publicly available to protect patient confidentiality but are available from the corresponding author on reasonable request.

Abbreviations

- Scrub typhus (ST)
- hematopoiesis (AAH)
- Wernicke encephalopathy (WE)
- computed tomography (CT)
- complete blood count (CBC)
- white blood cell (WBC)
- red blood cell (RBC)
- hemoglobin (HGB)
- platelet (PLT)
- Erythrocyte Sedimentation Rate（ESR）
- C-Reactive Protein（CRP）
- Reticulocyte（RET）
- Gamma-Glutamyl Transferase(GGT)
- Alkaline Phosphatase(ALP)

- immunoglobulin M (IgM)
- hematoxylin and eosin (H&E)
- Magnetic Resonance Imaging(MRI)
- diffusion-weighted imaging (DWI)
- Deep White Matter Hyperintensities(DWMH)
- Intensive care unit(ICU)
- Legionnaires' disease (LD)

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