International Journal of Contemporary Pediatrics
Virk A et al. Int J Contemp Pediatr. 2024 Feb;11(2):232-234
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20240003

Case Report

Hemophagocytic lymphohistiocytosis-a rare life threatening association with scrub typhus: case report

Arashdeep Virk[1], Mohit Singla[1], Pranay Trivedi[1], Prasun Bhattacharjee[1]*, Abhinav Tiwari[2]

[1]Department of Paediatrics, Ananta Institute of Medical Sciences, Rajsamand, Rajasthan, India
[2]Department of Paediatrics, AIIMS, Raipur, Chhattisgarh, India

Received: 12 December 2023
Revised: 29 December 2023
Accepted: 30 December 2023

***Correspondence:**
Dr. Prasun Bhattacharjee,
E-mail: prasunpedia@gmail.com

ABSTRACT

Scrub typhus is an important cause of acute febrile illness and one of the re-emerging infectious diseases in India particularly in southern Rajasthan. Hemophagocytic lympho-histiocytosis (HLH) results from an uncontrolled and ineffective hyperinflammatory response to a variety of triggers. HLH is further subdivided into primary and secondary type. We present a case of Scrub typhus which presented with multiple organ dysfunction syndrome (MODS) and secondary HLH which is a rare entity. A 9-month-old male child presented with high grade fever with encephalopathy. Examination showed hepatosplenomegaly, cervical Lymph adenopathy with eschar mark visible on abdomen. Scrub typhus was suspected on clinical grounds and further investigations were done. Serological diagnosis was strongly positive for scrub typhus. Initially, child did not respond to doxycycline, so further investigations were done to rule out HLH which fits into criteria of secondary HLH as per the revised HLH 2004 protocol. In view of secondary HLH and MODS methylprednisolone was added to treatment. Child responded to steroids and there was complete recovery. Scrub typhus patient with progressive MODS, in spite of appropriate antimicrobial therapy should raise the suspicion of secondary HLH which is rare but life-threatening condition and steroids plays an important role in the management of this condition.

Keywords: Scrub typhus, HLH, MODS, Steroids

INTRODUCTION

Scrub typhus is a bacterial infection caused by the bacterium *Orientia tsutsugamushi*. It is transmitted to humans through the bites of infected larval mites, specifically of the genus *Leptotrombidium*, commonly known as Chiggers.[1] The disease is characterized by symptoms such as sudden onset of fever, headache, muscle aches, and the presence of a distinctive eschar or skin lesion at the site of the chigger bite. The infection is prevalent in South and East Asia and parts of the Pacific Rim.[2] The two main categories of vertebrates that carry chiggers are the "maintaining hosts," which include rodents, shrews, and ground-dwelling birds, and the "incidental hosts," comprising other birds and larger mammals, such as humans.[3]

The incidence of scrub typhus has been on the rise in recent years, with an estimated one million cases annually.[4] Hospitalization is required for about a third of cases due to the involvement of multiple organs, and the disease is associated with high fatality rates.[5] In India, a study revealed that 24.4% of patients with unexplained fever, with or without multi-system involvement, had scrub typhus. Additionally, 53.1% of those with scrub typhus experienced acute kidney injury.[6] If left untreated, scrub typhus has a mortality rate of around 6%, but this rate can rise to 13% when appropriate antibiotics are not used. Complications further contribute to higher mortality

rates, with central nervous system infection and multiple organ involvement leading to rates of 14% and 20%, respectively. Common complications associated with scrub typhus include hepatitis (40.5%), thrombocytopenia (28.4%), acute respiratory distress syndrome (ARDS) (20.5%), acute kidney injury (19.2%), meningitis (16.4%), shock (16.2%), and myocarditis (15.5%).[7]

HLH is a syndrome characterized by an uncontrolled and ineffective hyperinflammatory response. This condition can be triggered by various factors, including infections, malignancies, and autoimmune disorders. HLH is further classified into primary and secondary types based on its underlying causes. Primary HLH is primarily due to genetic mutations affecting immune system regulation. Inherited genetic abnormalities disrupt the normal function of immune cells, leading to an exaggerated immune response. Secondary HLH occurs as a result of various triggers, such as infections, malignancies, or autoimmune disorders. In response to these triggers, the immune system becomes over-activated and releases an excessive amount of inflammatory cytokines, leading to widespread inflammation and tissue damage.

Scrub typhus is considered an important cause of acute febrile illness, particularly in certain regions of India. Southern Rajasthan is highlighted as an area where scrub typhus is a re-emerging infectious disease. This resurgence could be due to various factors, including changes in environmental conditions, human behaviour, and microbial factors. In the case of scrub typhus, factors such as climate, land-use changes, and human movement may contribute to its resurgence. The combination of scrub typhus and HLH in the presented case indicates a complex interplay between an infectious disease and the immune system. In this scenario, the infection with *Orientia tsutsugamushi* likely served as the trigger for the development of secondary HLH in the affected individual. The immune system's response, intended to eliminate the infectious agent, becomes dysregulated and causes harm to the body's own tissues.

CASE REPORT

A 9-month-old male child presented with high grade fever with encephalopathy. Examination showed hepatosplenomegaly (splenomegaly more than hepatomegaly), cervical lymphadenopathy with eschar mark visible on abdomen. In view of suspected scrub typhus further investigations were done.

Management and outcome

A panel of complete blood count, liver function tests (LFT), coagulation profile, lipid levels, inflammatory markers and antibody titres. Serological diagnosis was strongly positive for scrub typhus. Hemogram showed anaemia and thrombocytopenia and LFT was deranged. Coagulation studies showed prolonged prothrombin time (PT) with very high d dimer. Serum ferritin and triglyceride was raised which fits into criteria of secondary HLH as per the revised HLH 2004 protocol. Doxycycline, an antibiotic effective against scrub typhus, was started as per IAP protocol but child did not respond and condition of the patient worsened. He developed ARDS and need to be placed on ventilator. In view of secondary HLH and MODS, methylprednisolone was added to treatment. There was dramatic response to steroids followed by complete recovery.

Table 1: Diagnostic criteria for HLH in index case.

2004 diagnostic criteria for HLH	Criteria fulfilled in index case
Clinical criteria	
Fever	Yes
Splenomegaly	Yes
Laboratory criteria	
Cytopenia (≥2 of 3 cell lines)	Yes
Hemoglobin <9 gm/dl	Yes
Platelets <1,00,000 per dl	Yes
Neutrophil <1,000 per dl	No
Fibrinogen <1.5 gm/l and/or	Yes
Hypertriglyceridemia	Yes
Histopathologic criteria	
Hematophagocytosis in bone marrow or spleen or lymph nodes	No
No evidence of malignancy	Yes
Additional criteria	
Low or absent NK activity	Not done
Ferritin >500 mcg/l	Yes
Soluble CD 25 2,400 U/ml	Not done

DISCUSSION

This case highlights the challenges in managing severe cases of scrub typhus, especially when complicated by conditions like secondary HLH and MODS. The decision to add methylprednisolone suggests a consideration of the hyperinflammatory state associated with HLH, and the positive response indicates the potential effectiveness of immunomodulatory therapy in such cases. Basu et al found that over a period of 1 year, there were 58 children with scrub typhus infection at their institute with 18 cases of HLH. All patients presented with anemia, thrombocytopenia and hyperferritinemia.[8] The complicated presentation is more likely in adults, but paediatric population also requires proper attention.[9] developments of ARDS underscores the systemic impact of scrub typhus, as respiratory complications can arise from widespread inflammation and organ dysfunction. A study by Jin et al covered 16 children with scrub typhus-associated HLH, meeting HLH-2004 criteria. All had fever, multisystem damage, elevated hepatic transaminases, and abnormal blood tests. Treatments included 5-day intravenous azithromycin (6 cases), 7-10 days of intravenous chloramphenicol (10 cases), intravenous albumin (5 cases), intravenous immunoglobulin (3 cases), and dexamethasone (2 severe

cases).[10] The multidisciplinary approach, including antibiotic therapy, supportive care, and immunomodulation, reflects the complexity of managing severe infectious diseases with systemic involvement.

It's crucial to note that each case is unique, and individual responses to treatment can vary. The successful outcome in this case underscores the importance of prompt recognition, a comprehensive diagnostic approach, and tailored interventions based on the evolving clinical picture. This scrub typhus patient with progressive MODS, in spite of appropriate antimicrobial therapy should raise the suspicion of secondary HLH which is a rare but life-threatening condition and steroids plays an important role in the management of this condition.

CONCLUSION

This case shows that severe cases of scrub typhus need to be handled carefully, with a high index of suspicion and awareness of potential complications based on the endemic diseases prevalent in the area.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. El Sayed I, Liu Q, Wee I, Hine P. Antibiotics for treating scrub typhus. Cochrane Database Systematic Rev. 2018;9(9):CD002150.
2. Xu G, Walker DH, Jupiter D, Melby PC, Arcari CM. A review of the global epidemiology of Scrub typhus. PLoS Neglected Trop Dis. 2017;11(11):e0006062.
3. Traub R, Wisseman Jr CL. The ecology of Chigger-borne rickettsiosis (Scrub typhus). J Med Entomol. 1974;11(3):237-303.
4. Lu D, Wang T, Luo Z, Ye F, Qian J, Zhang J, et al. Evaluation of the Therapeutic Effect of Antibiotics on Scrub Typhus: A Systematic Review and Network Meta-Analysis. Frontiers Publ Heal. 2022;10:883945.
5. Elliott I, Pearson I, Dahal P, Thomas NV, Roberts T, Newton PN. Scrub typhus ecology: a systematic review of *Orientia* in vectors and hosts. Parasites Vectors. 2019;12(1):1-36.
6. Kumar V, Kumar V, Yadav AK, Iyengar S, Bhalla A, Sharma N, et al. Scrub typhus is an under-recognized cause of acute febrile illness with acute kidney injury in India. PLoS Neglected Trop Dise. 2014;8(1):e2605.
7. Devasagayam E, Dayanand D, Kundu D, Kamath MS, Kirubakaran R, Varghese GM. The burden of Scrub typhus in India: A systematic review. PLoS Neglected Trop Dise. 2021;15(7):e0009619.
8. Basu A, Chowdhoury SR, Sarkar M, Khemka A, Mondal R, Datta K, et al. Scrub typhus-associated hemophagocytic lymphohistiocytosis: Not a rare entity in pediatric age group. J Trop Pediatr. 2021;67(1):fmab001.
9. Suganthan N, Mahakumara M, Sooriyakumar T. Hemophagocytic lymphohistiocytosis: an unusual presentation of Scrub typhus. Cureus. 2020;12(7).
10. Jin YM, Liang DS, Huang AR, Zhou AH. Clinical characteristics and effective treatments of scrub typhus-associated hemo-phagocytic lympho-histiocytosis in children. J Adv Res. 2019;15:111-6.

Cite this article as: Virk A, Singla M, Trivedi P, Bhattacharjee P, Tiwari A. Hemophagocytic lymphohistiocytosis-a rare life threatening association with scrub typhus: case report. Int J Contemp Pediatr 2024;11:232-4.