Hemophagocytic Lympho-Histiocytosis Secondary to Rickettsial Infection: A Case Report

Shriya Sharma[1], Aakriti Adhikari[2], Nirmal Ghimire[3], Gaurab Mainali[1], Sumit Yadav[4], Prasamsa Pudasaini[2], and Shashank Neupane[2]

[1]Nepalese Army Institute of Health Sciences College of Medicine
[2]Nepalese Army Institute of Health Sciences
[3]Nepal Police Hospital
[4]Birendra Sainik Aspatal

February 22, 2024

Abstract

Hemophagocytic Lympho-histiocytosis (HLH) is a rare life-threatening condition characterized by widespread activation of the immune system leading to tissue damage all over the body.

Hemophagocytic Lympho-Histiocytosis Secondary to Rickettsial Infection: A Case Report

Shriya Sharma[1], Aakriti Adhikari[1], Nirmal Ghimire[2], Gaurab Mainali[1], Sumit Kumar Yadav[3], Prasamsa Pudasaini[1], Shashank Neupane[1]

[1]Nepalese Army Institute of Health Sciences, Kathmandu, Nepal

[2]Department of Internal Medicine, Nepal Police Hospital, Kathmandu, Nepal

[3]Department of Internal Medicine, Shree Birendra Hospital, Kathmandu, Nepal

Corresponding author

Shriya Sharma

Nepalese Army Institute of Health Sciences, Kathmandu, Nepal

Email:shriya.sharma@naihs.edu.np

Abstract

Hemophagocytic Lympho-histiocytosis (HLH) is a rare life-threatening condition characterized by widespread activation of the immune system leading to tissue damage all over the body. It is divided into Primary HLH due to inborn error in lymphocytes, T cells, and macrophages and Secondary HLH which is mostly due to infections, systemic connective tissue diseases, and lymphoid malignancies. Here we report, a 34-year-old man with a history of high-grade fever, chills, and rigor, eschar, splenomegaly with the laboratory findings of thrombocytopenia, hypochromic RBCs with anisocytosis and basophilic stippling, elevated transaminases, and a positive Weil Felix test along with positive PCR results for Orientia tsutsugamushi and the presence of IgG and IgM antibodies. A detailed workup was done to rule out other etiology for fever. Diagnosis of HLH secondary to Rickettsia infection was made with a thorough history, clinical evaluation, and a variety of investigations. The patient was treated with Doxycycline, Ciprofloxacin, Etoposide, and Dexamethasone but unfortunately, the patient expired during treatment due to multiorgan failure. Patients with scrub typhus

typically respond well to therapy, therefore early detection and antibiotic treatment can help avoid serious complications. Scrub typhus with the hemophagocytic syndrome can result in DIC and multiorgan failure. Despite its rarity, scrub typhus may be lethal; as a result, practitioners must be aware of the necessity of detecting and treating suspected cases as soon as possible. We learned that a systematic diagnostic approach, use of diagnostic criteria, and prompt treatment are very crucial in this disease.

Keywords : scrub typhus, *Orientia tsutsugamushi* , hemophagocytosis, hemophagocytic lymphohistiocytosis

1 | Introduction

Hemophagocytic lymphohistiocytosis is an aggressive and life-threatening condition with excessive activation of cytotoxic T lymphocytes, natural killer (NK) cells, and macrophages resulting in hypercytokinemia and immune-mediated damage to multiple organ systems. Primary (driven via underlying genetic mutations or secondary (driven from a malignant, infectious, or autoimmune stimulus without an identifiable underlying genetic trigger).(1) Progress has been made regarding the pathophysiology of HLH over the past decade. However, diagnosis of HLH remains with many dilemmas because of the heterogeneous nature of the disease.(2)

The guidelines for hemophagocytic lymphohistiocytosis describe the various symptoms that can be considered for a clinical diagnosis. If five of the following eight symptoms are present, then a clinical diagnosis can be made. These eight symptoms are fever; an abnormally large spleen (splenomegaly); low red cell, white cell, or platelet levels (cytopenias); abnormally high levels of a type of fat called a triglyceride in the blood (hypertriglyceridemia) or low levels of a specific blood-clotting protein (hypofibrinogenemia); destruction of blood cells by macrophages (hemophagocytosis) in the bone marrow; low or absent natural killer cell activity; abnormally high levels in the blood of a protein that binds to iron (ferritinemia); and elevated soluble interleukin-2 receptor (sCD25), a specialized protein that builds up in the blood when the immune system is stimulated.

Excessive monocyte activation in HLH could be caused by high amounts of activating cytokines. High levels of interferon (IFN), soluble interleukin-2 receptor, tumor necrosis factor (TNF), interleukin-1, and interleukin-6 have been found, implying that T-helper cells are elaborating activating cytokines or that poorly regulated or inappropriate Th1 responses to intracellular pathogens are to blame. Although the details of immunological protective mechanisms against rickettsial infections, such as cytokine activation, are unknown, macrophages and T-cells are thought to play a key role in rickettsial infection protection and the emergence of HLH. HLH is caused by a variety of viruses, including CMV, Epstein-Barr virus (EBV), and human herpesvirus-6, as well as collagen-vascular disorders and malignancies, including T-cell lymphomas.(3)

2 | Case report

A 34 years old male presented to the emergency department with a history of high-grade intermittent fever, associated with chills and rigor along with a frontal headache with no rash or bleeding diathesis. There is no history of cough, sore throat, pain abdomen, burning micturition, earache/discharge, nausea, vomiting. There was the presence of two similar dark scab-like lesions with erythematous bases around 1 cm in diameter on the abdomen (Figure 1). He was later admitted for further evaluation and a definitive diagnosis. In view of thrombocytopenia (platelet count – 97600/cmm, raised transaminases (AST – 164 IU/dl and ALT – 156 IU/L), LDH (i.e2780 IU/L), CRP (i.e1474 mg/L) with no other localizing signs, and a positive Weil Felix Test he was treated as a case of Rickettsia fever with Doxycycline and Ciprofloxacin tablets. He was hemodynamically stable but continued to have fever(101-102°F) with chills and rigors which was intermittent. The patient was receiving supportive care, including IV fluids and paracetamol for fever. The fever began to fade during his stay, but it was predicted to last for around a month, according to the infectious diseases specialist.

He was evaluated in the line of infective, inflammatory, autoimmune, neoplastic possibilities for the fever. To rule out infectious processes as a cause for fever; PPD tests and malarial blood smear were done for Tuberculosis and Malaria which were negative. Similarly, workup was done to rule out EBV, CMV, Hepatitis

A, Hepatitis B, Hepatitis C, HIV 1 and 2, Dengue fever, Salmonella, and Brucella infections which were negative.

Then, a Peripheral blood smear was done where Hypochromic RBC with Anisocytosis and basophilic stippling along with-it Leukopenia and giant platelets were seen. For further evaluation, a Bone marrow biopsy was done which showed Dys-erythropoietic features with erythrophagocytic cells (Figure 2). In the line of investigation to rule out malignancy; a CT scan of the Chest, Abdomen, and pelvis was done. An Abdomen CT scan showed a spleen with an upper limit size measuring 14 cm. Whole Body FDG PET/CT was done which showed mildly enlarged spleen measuring up to 13 cm in length, demonstrating mild diffuse hypermetabolism of liver activity. The remaining low-attenuation splenic lesions were not appreciated with certainty on the current unenhanced CT, without focal abnormal FDG uptake. However, few small upper abdominal lymph nodes are seen demonstrating faint FDG uptake just above background liver activity, including at the gastrohepatic ligament, periportal, and right superior diaphragmatic regions, such as a 12 x 8 mm gastrohepatic ligament lymph node. There is normal FDG activity throughout the remainder of the abdomen and pelvis.

After this extensive Work-up, a diagnosis of Hemophagocytic lymphohistiocytosis secondary to Rickettsial infection was made with the following findings:Triglyceride: 267 mg/dl, Ferritin: >2000 mcg/dl, Fibrinogen: 98mg/dl, Bone marrow aspiration and biopsy: Hyperactive macrophages with erythrophagocytosis, LDH: 2780 U/L, Bi-cytopenia: Hb:10.9g/dl TLC: 3800/microliter

He was started on dexamethasone 10 mg/m^2 after which the patient started getting better. Further treatment were dexamethasone 10 mg/m^2 once daily for 2 weeks followed by tapering to 4-5 mg/ m^2, Etoposide 150 mg/m^2twice weekly for 6 weeks followed by once weekly and reassessment accordingly. The patient then developed abdominal pain in the right and left upper quadrant along with petechial spots in the abdomen. He also developed a high-grade fever of 103 F along with features suggestive of septic shock. He was shifted to ICU due to his deteriorating condition and deranged hematological panel. During his stay in ICU the patient died because of MODS.

3 | Discussion

O. tsutsugamushi being a mite-borne bacterium poses the risk of a serious disease called Scrub Typhus. Rodents function as animal reservoirs for O. tsutsugamushi, however, the microorganism also can be maintained among mite colonies through transovarial transmission.(4) Studies show scrub typhus is an evolving public health problem with numerous outbreaks since 2015 in Nepal. Scrub typhus is a neglected tropical disease, is one of the important causes of undifferentiated treatable fever in Asia.(5)

Scrub typhus is associated with the eschar, which is a pathognomonic lesion. It's the first lesion that appears after being bitten by a chigger (Leptotrombidium mite). Because eschar is where O. tsutsugamushi is multiplying and a huge number of organisms are found there, it has been demonstrated to be a superior sample for PCR test than blood.(6) Scrub typhus is defined by small vessel vasculitis, which affects the lungs, heart, brain, and kidneys in particular. Scrub typhus has non-specific clinical signs, and patients frequently report to the physician with a generalized fever of uncertain etiology. Severe symptoms of MOF, ARDS, shock, and DIC, on the other hand, may develop.(7)

Primary HLH occurs due to hereditary immune conditions, while on the contrary secondary HLH occurs in settings such as infection, malignancy, autoimmune disease, post-allogeneic hematopoietic stem cell transplantation, and drug hypersensitivity.(5) Interconnection between HLH and infection is vital as both familial and sporadic cases are commonly provoked by infectious diseases. HLH imitates infectious diseases concealing the identification of a causative agent leading to serious health problems.(8)

Patients with HLH die because of bleeding in visceral organs, opportunistic infection secondary to neutropenia, or Multiple organ failure within 2 months which accounts for more than 10% of cases.(4)

With an increasing number of cases documented in the last ten years, HLH is a potentially serious consequence of scrub typhus. However, the majority of instances recorded thus far have been single cases or case series

with limited sample size. As a result, the clinical symptoms and prognosis of individuals with HLH linked with scrub typhus are mostly unknown.(2)

In the present case, the patient had a high-grade intermittent fever with eschar which was not responding to broad-spectrum antibiotics. During the initial work, the patient was diagnosed with a case of Scrub typhus not responding to Doxycycline and Ciprofloxacin. For this reason, an extensive workup was carried out to rule out other etiologies of fever which failed to establish the cause. Bi-cytopenia and Hyperactive macrophages with erythrophagocytosis in bone marrow biopsy suggested the possibility of HLH. Similarly, in line with HLH, biochemical parameters met the criteria for diagnosis of HLH. The patient initially responded well to the treatment but eventually, his condition deteriorated due to multi-organ failure leading to death.

4 | Conclusion

Hemophagocytic Lympho-histiocytosis (HLH) is a rare life-threatening condition. Scrub typhus with the hemophagocytic syndrome can result in DIC and multiorgan failure. Despite its rarity, scrub typhus may be lethal; as a result, practitioners must be aware of the necessity of detecting and treating suspected cases as soon as possible

CONFLICT OF INTEREST:

The authors declare that they have no competing interest

ACKNOWLEDGMENTS:

None

AUTHOR CONTRIBUTIONS:

All the authors were involved in the drafting and/or revision of the article and approved the final version to be published.

CONSENT:

The authors confirm that the patient has provided written informed consent to the submission of this case report, in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT:

Data available on request from the authors The data that support the findings of this study are available from the corresponding author upon reasonable request

References

1. Al-Samkari H, Berliner N. Hemophagocytic Lymphohistiocytosis. Annu Rev Pathol. 2018 Jan;13:27–49.

Crossref Pubmed

2. Naoi T, Morita M, Kawakami T, Fujimoto S. Hemophagocytic Lymphohistiocytosis Associated with Scrub Typhus: Systematic Review and Comparison between Pediatric and Adult Cases. Trop Med Infect Dis [Internet]. 2018 Feb 14;3(1):19. Available from: https://pubmed.ncbi.nlm.nih.gov/30274417

Crossref Pubmed

3. Valsalan R, Kosaraju K, Sohanlal T, Prem Kumar P. Hemophagocytosis in scrub typhus. J Postgrad Med [Internet]. 2010 Oct 1;56(4):301–2. Available from: https://www.jpgmonline.com/article.asp?issn=0022-3859

Crossref

4. Salje J. Orientia tsutsugamushi: A neglected but fascinating obligate intracellular bacterial pathogen. PLoS Pathog. 2017;13(12):1–6.

Crossref Pubmed

5. Dhimal M, Dumre SP, Sharma GN, Khanal P, Ranabhat K, Shah LP, et al. An outbreak investigation of scrub typhus in Nepal: confirmation of local transmission. BMC Infect Dis [Internet]. 2021;21(1):193. Available from: https://doi.org/10.1186/s12879-021-05866-6

Crossref Pubmed

6. Biswal M, Zaman K, Suri V, Rao H, Kumar A, Kapur G, et al. Use of eschar for the molecular diagnosis and genotypic characterisation of Orientia tsutsugamushi causing scrub typhus. Indian J Med Microbiol. 2018;36(3):422–5.

Crossref Pubmed

7. Jin Y, Huang L, Fan H, Lu G, Xu Y, Wu Z. Scrub typhus associated with hemophagocytic lymphohistiocytosis: A report of six pediatric patients. Exp Ther Med [Internet]. 2016/09/06. 2016 Oct;12(4):2729–34. Available from: https://pubmed.ncbi.nlm.nih.gov/27698778

Crossref Pubmed

8. Fisman DN. Hemophagocytic syndromes and infection. Emerg Infect Dis. 2000;6(6):601–8.

Crossref Pubmed