

Hemophagocytic lymphohistiocytosis (HLH) associated with scrub typhus: Report of 2 cases

Apoorva Gomber¹, Vijay Kumar², Shashikant Singh³, Manjari Kishore⁴, Sadhna Marwah²

From ¹Postgraduate, ²Professor, ³Postgraduate Student, ⁴Senior Resident, Department of Pathology, PGIMER, Dr. Ram Manohar Lohia Hospital, Delhi, New Delhi, India.

Correspondence to: Dr. Manjari Kishore, Department of Pathology, Room No 310, 3rd Floor, OPD Building, Dr RML Hospital, Baba Kharak Singh Maarg, New Delhi - 110001, Delhi, India. E-mail: drmanjarik@gmail.com

Received - 26 September 2019

Initial Review - 12 October 2019

Accepted - 18 October 2019

ABSTRACT

Hemophagocytic Lymphohistiocytosis (HLH) is a fatal hyperinflammatory syndrome characterized by histiocytic proliferation along with hemophagocytosis. HLH can be primary (inherited) or secondary, to any severe infection, malignancy or rheumatological disease. HLH, though rare, has also been noted in association with scrub typhus which is an acute febrile illness resulting from the bite of infected larval form of mite (also known as chigger). We hereby describe two cases of HLH associated with rickettsial infection (*Oriental tsutsugamushi*) in a 36-year-old male and in a 10-year-old male child. The former presented with high-grade fever and pruritic macular rash over abdomen. While the latter was presented with fever and decreased urinary output at the time of admission.

Keywords: Bone marrow examination, Eschar, HLH, Pancytopenia, Rash, Scrub typhus.

Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome (HPS) is a rare hematological phenomenon resulting from prolonged and excessive activation of antigen presenting cells and CD8⁺ T cells [1-3]. It may be inherited or occur secondarily to infections/malignancy at any age.¹ The diagnosis is established by the **Proposed HLH diagnostic criteria, 2009**. Scrub typhus infection is an important etiology of acute undifferentiated fever in India. It is a rickettsial illness caused by *Oriental tsutsugamushi*, transmitted by the bite of trombiculid mite. The infection is characterized by flu-like symptoms of fever, headache and myalgia lasting for over a week. However, in some cases the illness turns fatal involving multi organ dysfunction and ultimately causing death [3-4].

Table 1: Complete hemogram in the first and second patient

Parameters	Value	
	Case 1	Case 2
Haemoglobin	8.7 gm/dl	6.9 gm/dl
Total leukocyte count	9400 cells/cu mm	5900 cells/ cu mm
Differential leukocyte count	P 60%, L 34%, E 02%, M 02%, Metamyelocytes 02%	P 84%, L 13%, E 2%, M 01%
MCV	80.7 fl	70.3 fl
MCH	25.2 pg	24.4 pg
MCHC	31.2 gm/dl	34.8 gm/dl
RBC	3.44x 10 ⁶ cells/ cu mm	3.76 x 10 ⁶ cells cu mm
Platelet count	80,000 cu mm	90,000 cu mm
Reticulocyte count (corrected)	1.5%	2%
Peripheral smear	RBC- Predominantly normocytic normochromic; WBC- Mild shift to left; Platelets- adequate	RBC- Predominantly normocytic normochromic with few microcytes; WBC- relative neutrophilic prominence (no toxic granules); Platelets- reduced

We describe two cases of HLH secondary to scrub typhus; in a 36-year-old male and a 10-year-old child, respectively.

CASE REPORT

CASE 1

A 36-year-old male presented with history of high-grade fever (100-102°F) associated with a pruritic macular rash on the abdomen which had developed on 3rd day of fever. The patient also had difficulty in breathing, swelling over limbs and yellowish discoloration of whole body for last five days. There was no history of diabetes, tuberculosis, hypertension or any other chronic illness.

Table 2: Biochemical and serological parameters in Case 1 and Case 2

Biochemical parameters with result value		Serological markers/ culture	
Case 1	Case 2	Case 1	Case 2
LFT- Bilirubin increased [Direct>Indirect]	LFT- within normal limits	Rickettsial serology: ELISA IgM and IgG- +ve for scrub typhus	Rickettsial serology: OX19 titres positive
SGOT/SGPT/ALP increased	SGOT, SGPT and total proteins- Normal	Dengue ELISA NS-1 rapid Ag-Negative	Dengue ELISA NS-1 rapid Ag-Negative
Lipid profile: Cholesterol increased, Triglycerides increased (811 mg/dl), HDL decreased	Triglyceride- 500 mg/dl	Viral serology- Negative	Viral serology- Negative
Blood sugar and KFT- within normal limit	KFT deranged urea -111.4 & Creatinine - 4.9 mg/dl	HIV/ HCV/HBsAg- Negative	HIV/HCV/HBsAg- Negative
S. ferritin- 13624.7 mg/dl (markedly increased)	S. ferritin- 1700 ng/ml	Blood C/S- Sterile	Blood C/S- Sterile
Cardiac profile (LDH)- increased	Cardiac profile (LDH) increased: 690 U/L	Urine C/S- Sterile	Urine C/S- Sterile
Persistent hyponatremia- Na<125mmol/l	--	--	--
Hypoalbuminemia: 2.1 gm/dl	Urine- RBCs and pus cells	--	--
S. fibrinogen- decreased	--	--	--

The detailed investigations including the complete hemogram and peripheral smear [Table 1], biochemical and serological [Table 2] are highlighted along with bone marrow aspiration and biopsy in both cases.

Ultrasound abdomen showed hepatosplenomegaly with grade 2 fatty liver and mild free fluid in the peritoneum. Two-dimensional echocardiography showed mild pericardial effusion with left ventricular ejection fraction of 60%.

Bone marrow aspiration (BMA) smears were cellular and showed erythroid hyperplasia with myeloid and erythroid ratio of 1:1. The erythroid series cells were predominantly normoblastic and few megaloblasts were seen with features of dyserythropoiesis. Myeloid series cells were seen in all stages of maturation. Prominence of plasma cells- 6-8% of all nucleated cells was seen. Scattered histiocytes were found with occasional histiocytes showing hemophagocytosis (Fig. 1a-b). Bone marrow biopsy revealed similar findings as BMA. Megakaryocyte was adequate and functioning (Fig. 1c-d). Few scattered histiocytes were seen with evidence of hemophagocytosis.

Our patient fulfilled the essential diagnostic criteria (2009) for HLH with fever, splenomegaly, cytopenia and hepatitis along with hyperferritinemia and hypertriglyceridemia. Haemophagocytosis was seen on bone marrow aspiration studies secondary to rickettsial infection. The patient was successfully treated with a course of antibiotic and supportive measures.

CASE 2

A 10 years old male presented to paediatric department with complaints of fever and decreased urine output for last five days. Fever was of intermittent grade, (102°F), continuous and relieved on medication. The patient had three episodes of non-projectile vomiting while there was no significant past history.

On general examination, pallor and puffiness on the face was noted. There was no palpable peripheral lymphadenopathy. Per-abdominal examination revealed hepatomegaly, 4cm below the costal margin; however, no splenomegaly was present. The complete hemogram along with the peripheral smear have been depicted in table 1 and the complete biochemical and serological findings are enumerated in table 2.

Ultrasonography abdomen showed hepatomegaly along with 100 cc of free fluid collection. CECT abdomen showed few sub-centimetric non-necrotic lymph nodes in mesentery. The patient underwent bone marrow aspiration. BMA smears examined were cellular and showed many scattered histiocytes, a significant number of which showed hemophagocytosis (Fig. 1b). In view of clinical profile, laboratory parameters, peripheral blood and bone marrow aspiration smears findings, a diagnosis of hemophagocytic lymphohistiocytosis was considered in this patient of scrub typhus.

Both the patients were given a course of antibiotic; Tab Doxycycline 100 mg BD for 7 days. Additionally, the second patient was given Intravenous immunoglobulin as an immunomodulatory therapy. Both the patients were doing well on the last follow up.

DISCUSSION

Hemophagocytosis Syndrome or HLH is a rare hematological disorder characterized by febrile illness, cytopenia, lymphadenopathy, hepatosplenomegaly and hyperferritinemia [1-3]. Phagocytosis of blood cells and their precursors is a hallmark of HPS. Hemophagocytosis is achieved mostly by monocytes and macrophages. Nitroblue tetrazolium reduction by monocytes from patients with HPS is approximately six times that of control monocytes [2-4].

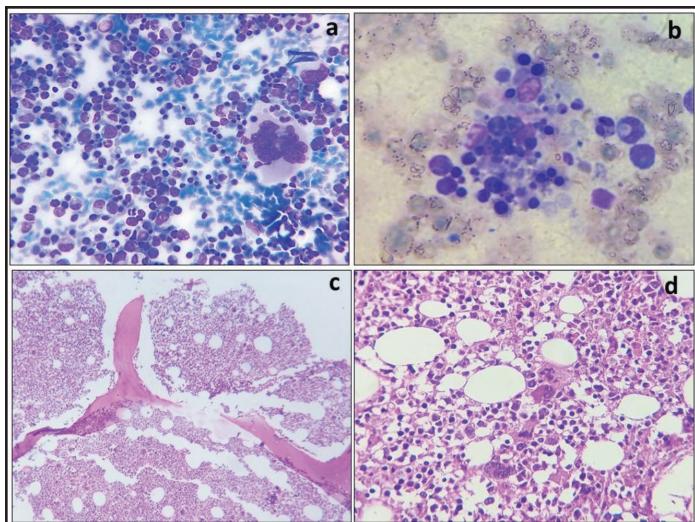


Figure 1a-d: 1a: Low power view of bone marrow aspiration smears showing erythroid hyperplasia and megakaryocytes with myeloid series in all stages of maturation (Giems, 400X). 1b: View of hemophagocytosis in BMA (Giems, 400X). 1c: Bone marrow biopsy showing a cellular marrow (HandE, 100X). 1d: High power view showing erythroid hyperplasia with megakaryocytes and occasional hemophagocytosis (HandE, 400X).

Excessive activation of monocytes in HLH may be due to stimulation by high levels of activating cytokines. High levels of interferon- γ (IFN γ), soluble interleukin-2 receptor, Tumor necrosis factor-A (TNF α), interleukin-1, and interleukin-6 have been demonstrated to be involved in HPS, suggesting the elaboration of activating cytokines by T-helper cells [2-5]. It can also result from poorly regulated or inappropriate Th-1 responses to intracellular pathogens. HPS is caused by number of viruses, including Cytomegalovirus (CMV), Epstein Barr Virus (EBV), human herpes virus-6 as well as malignancies like T-cell lymphomas and collagen vascular diseases [3-6]. Hemophagocytosis causing pancytopenia is a medical emergency and may be fatal despite aggressive treatment.

Scrub typhus is usually endemic in South East Asia, northern Australia and pacific islands. In India, it has been reported from Himalayan regions, Haryana and southern India [3-6]. Furthermore, Scrub typhus has been frequently been reported from North East India and associated with major clinical complications. Scrub typhus is an acute febrile illness which results from the bite of infected larval form of mite, called chigger, in endemic areas. Following, an incubation period of 7 to 10 days, the nonspecific prodrome of pyrexia, skin rash, myalgia, gastrointestinal disturbances, and lymphadenopathy starts.

Although not consistently seen, the most pathognomonic sign of scrub typhus is an eschar that develops at the site of mite bite [4-6]. During human infection, *O. tsutsugamushi*, being a rickettsial organism, selectively targets the vascular endothelial cells of the small to medium-sized blood vessels. However, it can also invade underlying tissues leading to widespread vasculitis or perivasculitis and Multiorgan Dysfunction Syndrome (MODS) in patients with severe infection [5-7].

One of our patients was diagnosed to have scrub typhus with positive immunochromatographic card test for detection of IgM

antibodies to *O. tsutsugamushi*. The clinical profile of our patient along with serological evidence of scrub typhus and evidence of haemophagocytosis enabled us to make the diagnosis of haemophagocytosis associated with scrub typhus infection.

The initial clinical symptoms of scrub typhus are nonspecific, and patients often present to the physician with appearance of common fever of unknown origin. Primary HLH appears to have a genetic etiology, whereas secondary HLH may occur together with a variety of underlying diseases. In the literature, there are only a few cases of HLH associated with scrub typhus in adults, whereas similar reports for children are extremely rare. Few recent studies have been published on secondary HLH due to rickettsial infections especially in pediatric populations with presenting symptoms consistent with our case [9-10]. A characteristic eschar was signalled in 50% patients and some had severe complications like acute renal failure and MODS [7-11]. These all findings were consistent with our patient.

Serological diagnosis of scrub typhus is usually possible after 5-10 days following onset of symptoms. Poor sensitivity and specificity of Weil-Felix is well established. Recently IgM ELISA and IgM capture ELISA techniques have shown better predictive value as diagnostic test. Once the diagnosis is established, patients should be started on antibiotics to treat scrub typhus along with additional therapies. Antibiotics such as doxycycline, minocycline, chloramphenicol, azithromycin and clarithromycin can be started [8-12]. The additional therapies for HLH include dexamethasone therapy, etoposide chemotherapy, cyclosporine, intrathecal methotrexate and intravenous immunoglobulin (IVIG) [9-12].

HPS though rare, should be considered in severe cases of scrub typhus especially if associated with cytopenias, liver dysfunction, and coagulation abnormalities especially in endemic areas like India [3-12]. Furthermore, wherever possible, a diagnosis of primary HPS should always be excluded in these cases by appropriate mutation analysis studies. However, it is always beneficial to start anti-rickettsial medication empirically in these patients in places where diagnostic facilities are not readily available.

CONCLUSION

HLH should be considered in all cases of rickettsial diseases, including the severe cases. The patients with scrub typhus usually have an excellent response to treatment, therefore early diagnosis and prompt treatment can prevent serious complications.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Gomber A, Kumar V, Singh S, Kishore M, Marwah S. Hemophagocytic lymphohistiocytosis (hlh) associated with scrub typhus: report of 2 cases. *Indian J Case Reports.* 2019;5(6):520-523.

Doi: 10.32677/IJCR.2019.v05.i06.005