Case Report

Scrub typhus with secondary haemophagocytic lymphohistiocytosis

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ABSTRACT

A male agricultural worker, aged 50 years was admitted with fever of 60 days. He had generalized weakness and headache. He was febrile. Anaemia (haemoglobin 11.7g/dL) and thrombocytopenia (platelet count 80,000/mm^3) were evident. He also developed hepatocellular hepatopathy. Other salient laboratory abnormalities included low serum fibrinogen (55 mg/dL), elevated serum creatinine (5.1 mg/dL) suggestive of disseminated intravascular coagulation (DIC). Serum procalcitonin was elevated (15.6 ng/mL). Ultrasonography abdomen showed mild hepatosplenomegaly. Weil-Felix test for scrub typhus was positive in 1:640 dilutions. Serological testing to detect scrub typhus immunoglobulin M antibodies tested positive.

During the hospital course of 10 days, he developed pancytopenia (haemoglobin 8.4g/dL, total leucocyte count 3,400/mm^3 and platelet count 50,000/mm^3), fulminant hepatic failure, acute kidney injury, acute respiratory distress syndrome and DIC. Bone marrow study revealed haemophagocytosis.

Patient was managed with intravenous antibodies and supportive management. But the patient died on the 10th day of hospitalization. The patient was diagnosed to have (IgM) scrub typhus with secondary haemophagocytic lymphohistiocytosis complicated by DIC and multiple organ dysfunction syndrome.

Key words: *Scrub typhus lymphohistiocytosis hemophagocytic*

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INTRODUCTION

Scrub typhus is a rickettsial disease caused by small Gram-negative obligate intracellular bacteria, *Orientia tsutsugamushi*, transmitted to humans by arthropod bite of larval mites (chiggers) of *Leptotrombidium deliense*. Macrophage activation syndrome is a part of group of disorders collectively known as Haemophagocytic Lymphohistiocytosis (HLH).

HLH is an unusual syndrome characterized by fever, splenomegaly and the pathologic finding of haemophagocytosis (phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors) in bone marrow and other tissues.[1] HLH may be associated with malignant, genetic, autoimmune diseases or Epstein-Barr (EBV) virus infection. It was also associated with other viral, bacterial, fungal, and parasitic infections.

Tropical HLH may be triggered by tuberculosis, salmonella, plasmodium, dengue or parvovirus B19.[2] HLH associated with rickettsial diseases was reported in 2011 by Antonio Cascio et al.[3] HLH is a rare but potentially fatal clinical syndrome resulting from dysregulated activation and proliferation of lymphocytes. Infections are important triggers for haemophagocytosis. Few case reports of scrub typhus associated HLH in children are reported from a hospital in Northern India.[4] A seasonal

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pattern was suggested as cases occur more often in the summer.[5] Among adults with HLH, age >30 years appears to be associated with high mortality.[6]

We present an uncommon complication of Scrub typhus captured retrospectively from medical registry and is being reported.

CASE REPORT

A 50-year-old male agricultural worker and Shepherd, was admitted with low grade fever of two months duration. Initially the fever was low grade, 7 days before admission, he developed high grade fever. He had generalized weakness and headache.

He was febrile and anaemic. There was no evidence of organ dysfunction. During hospital stay he developed jaundice.

Serial haemogram reports are shown in Table 1. Urine examination was normal. Hepatic transaminase enzymes were elevated to three times upper limit of normal, serum lactate dehydrogenase (LDH) (11304 U/L) and serum triglycerides (243 mg/dL) were elevated. Serum fibrinogen (55 mg/dL) levels were low and serum ferritin (116.8 µg/dL) levels were normal. He developed deranged renal function (blood urea 110 mg/dL and creatinine 5.1mg/dL), disseminated intravascular coagulation (DIC). Serum procalcitonin was elevated (15.6 ng/ml).

Ultrasonography of abdomen showed mild hepatosplenomegaly. Laboratory testing including smear for malarial parasite, rapid diagnostic test for malaria, Widal test and blood culture were negative. Serological testing for leptospirosis, brucellosis, dengue fever and human immunodeficiency virus infection and Anti-nuclear antibody tested negative. Weil-Felix test (Progen OX K Weil Felix reagent Tulip Diagnostics, India) for scrub typhus tested positive in 1:640 dilutions. Immunocromato-graphy test (ICT) (Standard Diagnostics, Seoul, South Korea) and ELISA (Scrub Typhus Detect IgM ELISA InBios International, Seattle, U.S.A) to *Orientia tsutsugamushi* (IgM) were positive.

The patient was diagnosed to have scrub typhus with secondary haemophagocytic lymphohistio - cytosis (HLH) (Table 2)[7] complicated by DIC and MODS.

Oral doxycycline was started empirically. However, fever did not subside. The infection was clinically thought to be resistant to doxycycline, hence started on macrolides, after laboratory confirmation of the diagnosis of scrub typhus became available. In the hospital course he developed pancytopenia. Bone marrow aspiration study revealed marked prominence of histiocytes with phagocytic activity (Figure 1). Patient also developed acute respiratory distress syndrome (ARDS), fulminent hepatic failure, acute kidney injury (AKI) and DIC during hospital stay.

Patient was managed with antimicrobial drugs, blood components and organ support along with supportive care. The patient died.

DISCUSSION

As per the revised diagnostic criteria for HLH by Histiocytosis Society 2004, either 1 or 2 of the criteria (Table 2) should be fullfilled. Our case satisfied 5 out of 8 diagnostic criteria (like fever, splenomegaly, cytopenias, hypofibrino-

Table 1: Serial laboratory reports

	Day 1	Day 2	Day 5	Day 7	Day 8
Haemoglobin (g/dL)	11.7	11.6	9.1	10.4	8.4
Absolute neutrophil Count (cells/mm^3)		6,300	3,360		
Platelets (/mm^3)	80.000	90.000	40,000	80,000	50,000

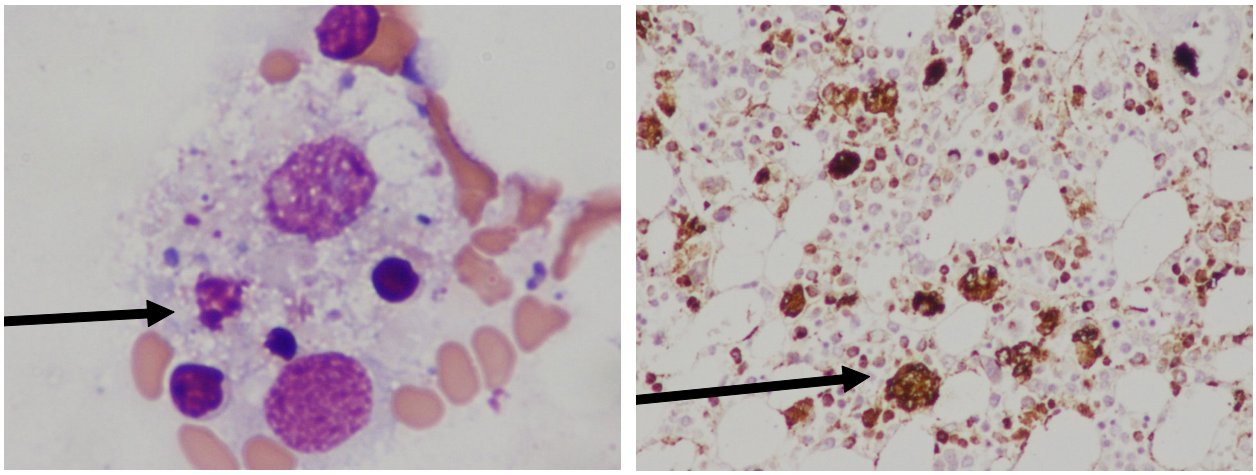

Figure 1: Bone marrow aspirate **(A)** showing histiocytes with haemophagocytosis and biopsy with immunohistochemistry CD68 **(B)** showing positivity indicating histiocytes

genaemia and haemophagocytosis in bone marrow.

In an earlier report[8] on the outbreak of scrub typhus from our institute in 2014, the clinical profile of 176 cases was discussed along with the complications. But occurrence of HLH was not noted in that series. This is our first experience documenting the occurrence of secondary HLH in scrub typhus.[8]

In another study[4] from Chandigarh, three of the four children with scrub typhus were diagnosed to have HLH; one of these children had died.

In another report[9] the profile of a woman aged 34 years who presented with MODS, one week history of fever and abdominal pain was reported. Laboratory testing showed cytopenias, splenomegaly, hyperferritinaemia and hypofibrinogenaemia. Bone marrow examination revealed haemophagocytosis. Diagnosis of scrub typhus was confirmed by Weil-Felix test (titer of 1:80), positive IgG and IgM antibodies and PCR for *Orientia tsutsugamushi*. The patient developed intracranial haemorrhage and expired. Our case also had similar course of events and succumbed to illness.

As HLH is associated with immunologic, neoplastic, genetic and infectious disorders, clinicians should work closely with pathologists

Table 2: The revised diagnostic criteria for HLH by Histiocytic Society 2004[7]

A molecular diagnosis consistent with HLH	
or	
At least 5 out of 8 to be fullfilled	
(i)	Fever
(ii)	Splenomegaly
(iii)	Cytopenias affecting ≥ 2 of 3 lineages in peripheral blood with haemoglobin < 10 g/dL, platelets < 1L/μL and polymorphs < 1,000/μL
(iv)	Hypertriglyceridemia (>265mg/dL) and/ or hypofibrinogenaemia (≤1.5 g/dl)
(v)	Haemophagocytosis in bone marrow or spleen or lymph node
(vi)	Low or absent NK cell activity
(vii)	Ferritin ≥500μg/dL
(viii)	Soluble CD25 (soluble interlukin-2 receptor) ≥2400 U/mL

HLH = haemophagocytic lymphohistiocytosis

and microbiologists to clearly define precipitating or underlying illnesses.[1] HLH if left untreated may result in a high mortality.[10]

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