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Severe leptospirosis and secondary hemophagocytic syndrome: A rare case from Indian subcontinent

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CASE STUDY

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ABSTRACT

Hemophagocytic syndrome (HPS) is a rare clinicopathological condition resulting from dysregulation of the immune system. This unusual clinical syndrome is characterized by fever, cytopenia, liver dysfunction, increased ferritin level and hemophagocytosis of bone marrow. We report a case of a 40-year-old male with severe leptospirosis and secondary hemophagocytosis who presented to us with high grade fever and jaundice and later was complicated by multi organ dysfunction and death despite aggressive management. Our case highlights leptospirosis as a rare cause of HPS. A high index of clinical suspicion and prompt treatment for HPS in patients with severe leptospirosis with progressive multi-organ dysfunction despite antimicrobial therapy, is very important as the condition otherwise carries a very high mortality.

Key Words
Leptospirosis, infection, hemophagocytic syndrome

Implications for Practice:

1. What is known about this subject?
Hemophagocytic syndrome is a potentially fatal hyperinflammatory condition occurring as a primary condition due to genetic mutation and also secondary to many infectious and non-infectious diseases.

2. What new information is offered in this case study?
Leptospirosis is a rare precipitant of hemophagocytic syndrome. A high index of clinical suspicion and prompt treatment of this severe clinicopathological condition is very important which otherwise carries a very high mortality rate.

3. What are the implications for research, policy, or practice?
This case study highlights that though rare, HPS should be kept in mind during the treatment of leptospirosis with progressive multi organ dysfunction despite proper antimicrobial therapy. Early detection of leptospira in the host, prompt treatment as well as creating awareness in the public are the steps that could be taken to reduce the extent of the problem.

Background

Hemophagocytic syndrome (HPS) is a rare but potentially fatal inflammatory disorder resulting from a highly stimulated but ineffective immune system.[1] First described by Scott and Robb-Smith in 1939 as histiocytic medullary reticulosis, this disorder occurs primarily due to some genetic mutation or secondary to various infectious, rheumatologic, malignant and metabolic diseases.[2] Clinical manifestations included prolonged fever, jaundice, bleeding, CNS dysfunction, skin rash, hepatosplenomegally and laboratory parameters of pancytopenia, hyperferritenemia, hypofibrinogenemia, transaminitis, coagulopathy and bone marrow hyperphagocytosis. HPS has been described in association with many infectious diseases like tuberculosis, typhoid fever, leishmaniasis, malaria, dengue fever, scrub typhus, Epstein- Barr virus and sepsis.[3]

There are few case reports of leptospira associated HPS and all these cases are of severe leptospirosis with multiorgan dysfunction. Although leptospirosis is known to be endemic in India, most of the outbreak was from the coastal region of the Indian peninsula and the Andaman Islands with few case series and reports from northeast India. We present a first case report of severe leptospirosis with secondary hemophagocytosis from northeast India.

Case details

A 40-year-old male, was an agro pastoralist from a rural area of Arunachal Pradesh (North East India), and presented to the emergency department with complaint of high grade continuous fever for 10 days followed by yellowish discolouration of eyes and urine for four days and redness of eyes and recurrent epistaxis for two days. On examination he appeared acutely ill. The temperature was 39.8°C, the blood pressure 90/60mmHg, the pulse rate 122 per minute, respiratory rate 26 per minute and oxygen saturation 92 per cent with room air. There was conjunctival suffusion and haemorrhage, jaundice and bilateral leg edema. The abdomen was soft with mild hepatosplenomegaly. Other systemic examinations were normal. Lymph nodes were not palpable.

His initial blood parameters revealed severe pancytopenia and serology tests for malaria, dengue, scrub typhus, enteric fever, chickungunia were negative. Blood biochemistry reports showed mild renal dysfunction and hepatitis (Table 1). Serology for hepatitis A, B and C were also negative and HIV status was negative. Autoimmune workup including ANA, RA factor and Coomb's test were negative. Results of chest radiography, electrocardiography and echocardiography were normal.

He was initially started with intravenous ceftriaxone (1gm twice daily) with other supportive measures like packed cells, platelet and fresh frozen plasma (FFP) transfusion. Blood sample for leptospira was sent on day two because of persistent fever, jaundice, renal dysfunction and conjunctival haemorrhage. Leptospira immunoglobulin M (IgM) was positive in blood by enzyme linked immunosorbent assay (ELISA). Tablet doxycycline 100mg twice daily was added to ceftriaxone. His condition remained the same for the next couple of days.

Because of persistent fever despite antimicrobial therapy, a bone marrow examination was done on day five and serum ferritin and lipid profile was arranged. Ferritin level was very high and triglyceride level was grossly elevated. Bone marrow picture was suggestive of hemophagocytosis (Figure 1A and B). Injection methylprednisolone as pulse therapy of 1gm/day for three days was added and antibiotics were continued as before. Patient was responding to the above treatment, fever disappeared and pancytopenia improved. But later during the course of his hospital stay his clinical condition was complicated by persistent high grade fever, progressive dyspnoea, and recurrent episodes of fluid responsive hypotension and pancytopenia. He was put on mechanical ventilation for progressive hypoxemia and escalating doses of ionotropic agents. His conditions rapidly deteriorated and on day 12 he suffered a cardiac arrest from which he could not be resuscitated.

Discussion

HPS, also known as hemophagocytic lymphohistiocytosis (HLH) is a clinical diagnosis that is based on eight diagnostic criteria. These criteria were developed for the diagnosis of HLH in children and may be less useful in adults. At least five of the following eight criteria must be present for a diagnosis to be established: fever; splenomegaly; cytopenia (affecting at least two of three lineages in the peripheral blood); fasting triglyceride levels ≥3mmol/litre (i.e., ≥265mg/dl) and/or fibrinogen level ≤1.5g/litre; ferritin level ≥500ng/ml; soluble CD25 level ≥2400U/ml; decreased or absent natural killer(NK) cell activity (according to local laboratory reference); or hemophagocytosis in bone marrow, spleen, or lymph nodes.[4] Although severe leptospirosis itself can cause multi organ dysfunction, our patient did meet 5/8 HLH criteria and he was not responding to antimicrobial therapy.

Though the actual pathogenesis that caused this rare form of disease is not known, it is postulated to be due to an impairment of the cytolytic activity of T cells and natural killer cells and leads to uncontrolled T-cell activation and increased secretion of cytokines. There is marked elevation of tumour necrosis factor-alpha (TNF-alpha), soluble interleukin-2 receptor (sIL-2R), interferon gamma (IFN-γ), IL-6, IL-10 and IL-18 especially during the active phase of the disease. These hypercytokinemia ultimately lead to activation of the macrophage.[5] Proliferation and activation of benign macrophages is associated with phagocytosis of hematopoietic elements throughout the reticuloendothelial system. Activated macrophages also secrete ferritin, leading to hyperferritinemia.

HPS can be classified into two groups: primary (familial/genetic) and secondary (acquired). Secondary causes include severe infections, malignancies, rheumatologic disorders and some metabolic diseases.[6]

HPS due to secondary infection has been categorized as a separate entity. Most of the cases have been described in association with EBV followed by dengue, herpes, cytomegalovirus (CMV), and human immunodeficiency virus (HIV). Of the bacterial infections, most were found secondary to tuberculosis followed by case series and case reports of enteric fever, scrub typhus, leishmeniasis, malaria, toxoplasmosis and many others.[2] The possible pathophysiologic mechanism for infection associated HPS includes excessive stimulation of Th1 mediated immune response resulting in overproduction of tumour necrosis factor alpha, interleukin 1 or interleukin 6 and gamma interferon. Leptospirosis is a zoonotic disease in tropical and subtropical regions of the world with various animal species acting as carriers including sheep, goats, cattle, dogs, and horses Rats are the major known host of leptospira species. The diseases can be transmitted to humans through consumption of infected meat and drinking contaminated water or urine.[7]

Leptospirosis is characterized by a broad spectrum of clinical manifestations varying from mild in apparent infection to fulminant, fatal disease. There are few case reports of leptospirosis - associated HPS. In all these case reports leptospirosis patients were in a severe state with multi organ dysfunction. There are two case reports of leptospira- associated HPS from Taiwan, both of them presenting with acute renal failure and one died on day 12 due to multi organ failure and the other recovered after 80 days of treatment.[8] Another case report was from South India of a young male who presented with fever, oliguria and reactive hemophagocytosis and who responded to corticosteroid and standard antimicrobial treatment.[9]

Conclusion

Association of leptospirosis and HPS is a very rare and potentially fatal clinicopathological condition. A high index of suspicion and prompt treatment for HPS, based on clinical and investigational findings for a patient with leptospirosis and progressive multi organ dysfunction despite antimicrobial therapy, is a matter of the greatest urgency.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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PATIENT CONSENT

The authors, *Barman B, Lynrah KG, Tiewsoh I, Jitani A, Ete T* declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.

Figure 1: (A) Histiocyte phagocyting myeloid and erythroid precursor cells, nucleus of the histiocyte is pushed to the periphery; (B) Histiocyte phagocyting RBC can be seen. (Leishman stain; x1000)

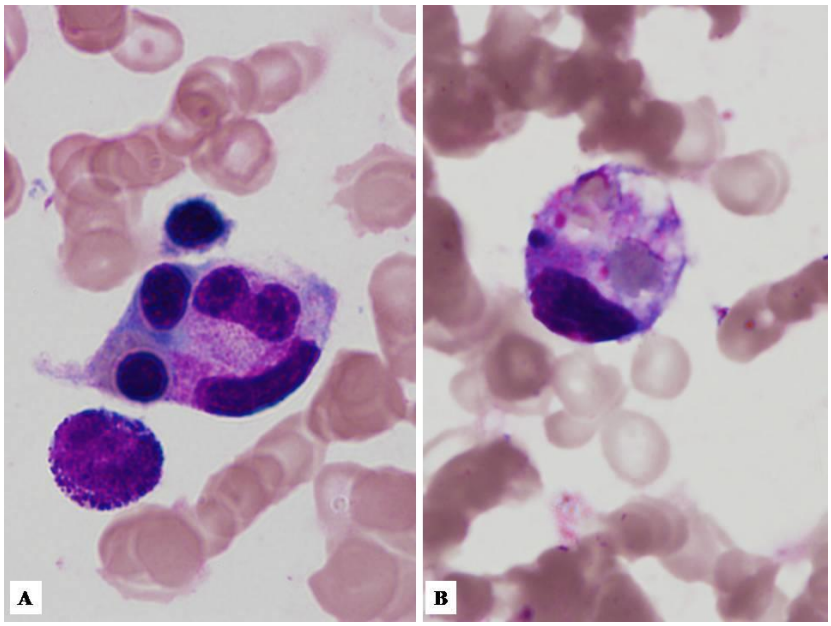

Table 1: Showing changes in haematological parameters during admission

Laboratory parameters (Units)	Reports					Reference values
	26/5/16 (Date of admission)	29/5/16 (Day 4)	31/5/16 (Day 6)	2/6/16 (Day 8)	5/6/16 (Day 11)	
Haemoglobin (gm/dl)	9.5	8.3	7.8	7.6	6.5	12-18
Total count ($\times10^3/mm^3$)	1500	1000	1000	2000	1500	4.0 – 11.0
Differential leukocyte count (%)						
Neutrophil	55	69	76	56	60	40-75
Lymphocyte	40	28	20	34	35	20-45
Eosinophil	3	8	6	6	4	2-10
Monocyte	2	4	0	4	1	1-6
Basophil	0	1	0	0	0	≤1
Platelet count($\times10^3/mm^3$)	40	30	35	120	65	150- 400
Erythrocyte Sedimentation rate (mm/h)	02	05	16	18	12	0-20
Blood Urea (mg/dl)	83	61	65	71	75	10-50
Serum Creatinine (mg/dl)	2	2.8	1.9	1.9	1.6	0.5 – 0.9
Total Billirubin (Direct) (mg/dl)	5.9 (4)	9.2(5.5)	4.3(2.5)	3.7(1.9)	3.5(1.6)	0.3 – 1.3 (0.1 – 0.4)
ALT (IU/L)	1013	475	173	312	175	7 – 41
AST (IU/L)	250	202	105	107	98	12 – 38
Alkaline phosphatase (IU/L)	590	531	614	719	650	30-120
Total protein (g/dl)	5.0	4.7	5.0	4.3	4.8	6.3-8.2
Serum Albumin (g/dl)	2.5	2.5	2.3	2.0	2.2	3.5-5.0
PT(INR)	1.45	1.30	1.40	1.2	1.2	1.34
Serum Ferritin (ng/ml)		1400		456		
Serum Tryglyceride (mg/dl)		525		235		53-150
HBsAg/Anti HCV	Negative					
HIV I, II	Nonreactive					
ANA, RA factor	Negative					
Dengue, Malaria, Chikunguinya, Scrub typhus	Negative					
Leptospira serology	Positive					
Urine and Blood Culture and sensitivity		Sterile				

ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; INR = International Normalised Ratio