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Case Report

Internal Medicine Section

Disseminated Histoplasmosis with Haemophagocytic Lymphohistiocytosis in an Immunocompetent Host

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ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) is a devastating syndrome due to uninhibited immune activation. Disseminated histoplasmosis is a rare cause of HLH. There have been few case reports and series demonstrating a relation between the two disease entities in immunosuppressed hosts. HLH secondary to disseminated histoplasmosis is even rarer in an immunocompetant host. We report a rare case of HLH triggered by disseminated histoplasmosis in an immunocompetant patient.

Keywords: Clinical infectious disease, Haemophagocytosis, Invasive fungal infections

CASE REPORT

A 43-year-old lady presented to the Department of Gastroenterology with complaints of intermittent high grade fever with chills since seven months. She had a negative workup for malaria, dengue and typhoid fever and her blood culture did not grow any pathogenic organism. She also complained of loss of weight and appetite alongwith generalized fatigability. Six months back, she was diagnosed with pulmonary tuberculosis (TB) {sputum Acid Fast Bacillus (AFB) positive, chest radiograph suggestive of bilateral upper zone infiltrative shadows} and received treatment under Directly Observed Treatment, Short-course (DOTS). Her sputum AFB was negative at three months, five months and end of treatment. However, she continued to lose weight (five kilograms over six months) and complained of generalized weakness and persistent loss of appetite. Since, two months prior to presentation, she complained of gradually progressive abdominal distension and dull, dragging, continuous, non-radiating, bilateral hypochondriac pain. She had early satiety, joint pains and continued to have fever with chills. She developed swelling over both legs and a nonproductive cough. She had no major medical and surgical co-morbidities other than recently treated TB. She was a homemaker and had two healthy children. On examination, she had mild fever (99° Fahrenheit), pallor, bilateral pitting pedal oedema and gross hepatosplenomegaly. Both the liver and spleen were firm, nontender and had a smooth surface and rounded margins. The liver span was 20 cm and the spleen had enlarged upto the umbilicus with a palpable splenic notch.

Laboratory Parameter	Month Prior to Admission	At Admission	One week after completion of treatment	Two weeks after completion of treatment	At Discharge
Hb (g/dl)	7.6	7.8	7.0	9.2	10.4
Packed Cell Volume (%)	23.2	24.3	22.4	29	31
Mean Corpuscular Volume (cu-microns)	71.38	73.86	77.6	81.3	83.4
Total Leucocyte Count (cu-microns)	3600	2800	2600	2700	5400
Red Cell Diameter Width (%)	19.5	19.2	22.4	22.2	20.6
Platelet Count (/mm^3)	116000	54000	91000	121000	163000

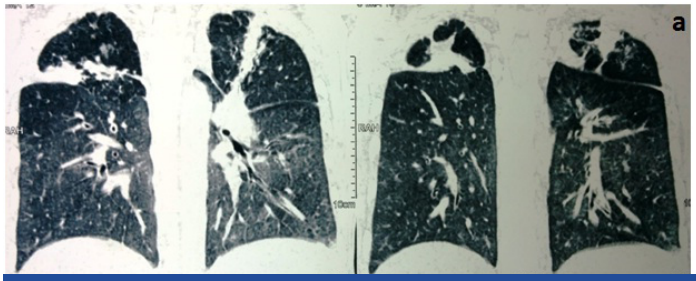
[Table/Fig-1]: Serial complete blood counts.

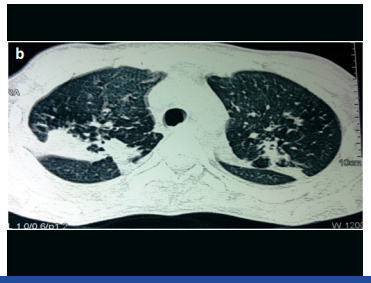
Laboratory evaluation revealed pancytopenia, low serum albumin with albumin-globulin ratio reversal, raised serum lactate dehydrogenase and serum alkaline phosphatase levels [Table/Fig-1,2]. She underwent an ultrasound of the abdomen that revealed moderate hepatomegaly with altered echotexture without any biliary obstructive changes, gross splenomegaly, no ascites and few small peripancreatic lymph nodes. A Computerized Tomogram (CT) of the chest was performed for new onset dry cough which

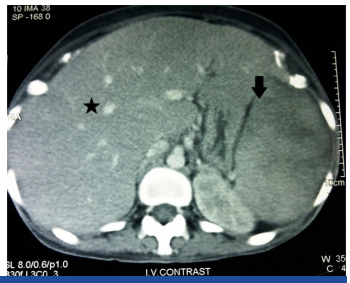
Laboratory parameter	Value	Reference Range
Bilirubin (Total)	0.5 mg%	(0.0 mg% -1.0 mg%)
Bilirubin (Direct)	0.2 mg%	(0.0 mg% -0.3 mg%)
Total Proteins	5.6 g%	(6.4 g% - 8.2 g%)
Serum Albumin	1.6 g%	(3.4 g% - 5.0 g%)
Serum Globulin	4.0 g%	(2.8 g% - 3.6 g%)
Serum Cholesterol	67 mg%	(125 mg% - 200 mg%)
ALT	23 mU/ml	(15 mU/ml – 63 mU/ml)
AST	28 mU/ml	(15 mU/ml – 37 mU/ml)
Alkaline Phosphatase	277 mU/ml	(50 mU/ml – 136 mU/ml)
GGTP	69 mU/ml	(5mU/ml – 85 mU/ml)
Serum Ferritin	891.7 ng/ml	(13 ng/ml – 150 ng/ml)
Serum Creatinine	0.9 mg%	(0.6 mg% - 1.3 mg%)
Serum Triglycerides	89 mg%	(30 mg% - 200 mg%)
Serum Fibrinogen	53 mg/dl	(180 mg/dl – 350 mg/dl)
Serum Lactate Dehydrogenase	296 mU/ml	(81 mU/ml – 234 mU/ml)
Thyroid Stimulating Hormone	3.68 uIU/ml	(0.2 uIU/ml – 6 uIU/ml)
Fasting Blood Sugar	109 mg/dl	(70 mg/dl – 120 mg/dl)
Erythrocyte Sedimentation Rate	19 mm/hr	(0 mm/hr - 20 mm/hr)

[Table/Fig-2]: Other laboratory parameters.

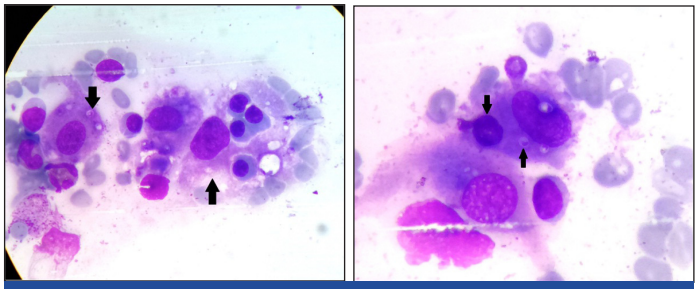
revealed lesions in bilateral upper lung lobes representing resolving tuberculous infection and hepatosplenomegaly [Table/Fig-3a,b,4]. Sputum for AFB smear (2 samples) was negative and TB Gene Xpert did not detect *Mycobacterium Tuberculosis*. Antinuclear antibody test by immunofluorescence technique was negative. Tests for Human Immunodeficiency virus (HIV), antibody to Hepatitis C virus (Anti-HCV) and Hepatitis B virus surface antigen (HBsAg) were non reactive. In view of persistent pancytopenia, gross splenomegaly and continual fever despite adequate TB treatment, a bone marrow examination was performed. It revealed a mildly hypercellular marrow showing panmyelosis, histiocytes showing presence of







[Table/Fig-3a,b]: A CT image of chest (coronal and sagittal) suggestive of fibrotic strands in bilateral upper lobes demonstrating healed pulmonary tuberculosis
[Table/Fig-4]: A CT image of Abdomen suggesting Hepatomegaly (Star) and Splenomegaly (Down Arrow)



[Table/Fig-5]: A Haematoxylin-Eosin photomicrograph of bone marrow aspirate revealing an erythrophagocytic cell devouring a red cell (Up Arrow) and multiple intracytoplasmic Histoplasma capsulatum (Down Arrow)
[Table/Fig-6]: A Haematoxylin-Eosin photomicrograph of bone marrow aspirate revealing an erythrophagocytic cell devouring multiple red blood cells (Down Arrow) and multiple intracytoplasmic Histoplasma capsulatum (Up Arrow)

Histoplasma capsulatum and occasional erythrophagocytosis [Table/Fig-5,6]. Methanamine Silver staining revealed few small round to oval, occasionally budding, yeast forms of *Histoplasma capsulatum*. She received Amphotericin B deoxycholate for 14 days followed by Itraconazole therapy. At the end of 14 days, the liver and spleen had regressed in size and she was asymptomatic. At one month follow-up, she was completely symptom-free and was tolerating Itraconazole well.

DISCUSSION

Haemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease characterized by fever, jaundice, splenomegaly and the pathologic finding of haemophagocytosis (destruction of erythrocytes, leukocytes, platelets and their precursors by macrophages) in bone marrow and other tissues. A "cytokine storm" caused by uncontrolled proliferation of activated lymphocytes and macrophages results in severe inflammation. Primary HLH, seen mostly in children, is triggered by primary genetic disorders and is a heterogeneous autosomal recessive disorder. The underlying defect in cytotoxic functioning of natural killer (NK) and T lymphocytes results in secretion of large quantities of cytokines. In adults, hematologic malignancies, autoimmune diseases, bacterial, fungal and viral infections can trigger "secondary HLH" [1,2]. Common laboratory anomalies seen in HLH are anaemia, thrombocytopenia, neutropenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and hyperbilirubinemia.

Temporary acquired immune-suppressant states also cause NK cell defects leading to secondary HLH. Organisms causing intracellular infection can hence trigger HLH and these include viruses (Epstein-Barr virus (EBV), Cytomegalovirus, Human Immunodeficiency Virus, Parvovirus B19, Dengue, Varicella-Zoster, Herpes Simplex Virus), parasites (*Malaria* sp., *Babesia* sp. *Leishmania* sp., *Toxoplasma gondii),* mycobacteria, fungi *(Cryptococcus neoformans, Histoplasma Capsulatum, Aspergillus, Penicillium marneffei) and* bacteria *(Salmonella sp., Rickettsia sp*., *Leptospira sp*., *Brucella* sp., *Borrelia* sp., *Bartonella* sp., *Listeria* sp., *Coxiella*). A "double hit" of ineffective clearance of infection and a hyper immune response causes extensive tissue damage. One study looked at HLH triggered by tropical infections from the Indian sub-continent, among adults. The most common tropical infectious diseases triggering more than 50% of the cases of HLH were visceral leishmaniasis; rickettsial infection; malaria; histoplasmosis; enteric fever and tuberculosis. Viral agents triggered another 30% (most often EBV and Parvovirus B19) [3].

Four types of infection caused by histoplasmosis have been described in literature: primary pulmonary histoplasmosis, primary cutaneous histoplasmosis, progressive disseminated histoplasmosis and African histoplasmosis [4]. Progressive disseminated histoplasmosis, especially seen in an immunocompromised host is an uncommon disease in India. Inhalation of soil mixed with bird and bat droppings is the most common source of infection. Diagnosis is established by demonstrating the organism in an extrapulmonary location. Thirty eight cases of Histoplasmosis associated HLH have been reported worldwide, including the largest case series (11 cases) published recently [5]. Eight cases of disseminated histoplasmosis with HLH have been reported from India largely in immunosuppressed hosts [6-11]. Four of them had a fulminant disease and died, one had underlying HIV infection and another three was treated successfully with antifungal therapy. Only two patients were immunocompetant. This is thus a rare case of HLH complicating disseminated histoplasmosis in an immunocompetant

Author	Year of Publication	Co-morbidities/Immune Status	Survival
Gil-Brusola [12]	2007	HIV	Died
Wang [13]	2007	Chronic Hepatitis C, Cryoglobulinemia, Chronic Kidney Disease and Fungal endocarditis	Died
Guiot [14]	2007	HIV	Survived
Sanchez [15]	2007	HIV	Survived
Phillips [16]	2008	Sarcoidosis on chronic steroids	Survived
De Lavaissiere [17]	2009	HIV	Survived
Van Koeveringe [18]	2010	Chronic Lymphocytic Leukemia	Survived
Lo [19]	2010	Renal transplant	Survived
Vaid [7]	2011	HIV	Died
Chandra [8]	2012	HIV	Survived
Nieto-Rivers [20]	2012	Renal Transplant	Survived
Nieto-Rivers [20]	2012	Renal Transplant	Died
Telfer M [21]	2012	HIV	Died
Alina M Huang [22]	2014	HIV	Survived
Ashish Rajput [23]	2015	Scleroderma, Monoclonal Gammopathy of Undetermined Significance	Survived
M Kashif [24]	2015	Sickle cell anaemia	Died
A Subedee [25]	2015	HIV	Died
T Mukherjee [10]	2015	Chronic Obstructive Pulmonary Disease, Erythema Nodosum	Died
De [11]	2015	Healthy	Survived (Patient 1)
De [11]	2015	Healthy	Survived (Patient 2)
A Sonavane (Present Report)	2015	Healthy	Survived

[Table/Fig-7]: The table enlists prominent cases of disseminated histoplasmosis with HLH published in literature over the last 10 years

host reported from India. All cases of disseminated histoplasmosis with HLH reported in literature over the last 10 years with their clinical outcome have been summarized in a tabulated form [Table/Fig-7] [12-25].

Clinical Practice Guidelines [26] for the management of patients with histoplasmosis (2007) by the Infectious Diseases Society of America recommends liposomal Amphotericin B (3.0 mg/kg daily) for 1–2 weeks, followed by oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months) for moderately severe to severe disease. The deoxycholate formulation of Amphotericin B (0.7–1.0 mg/kg daily) is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity. For mild-to-moderate disease, itraconazole (200 mg 3 times daily for 3 days and then twice daily for at least 12 months) is recommended. Lifelong therapy with itraconazole (200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed and in patients who relapse despite receiving appropriate antifungal therapy.

CONCLUSION

Our patient satisfied both the HLH-2004 criteria for diagnosis of HLH and Infectious Diseases Society of America Guidelines for diagnosis of histoplasmosis. Disseminated Histoplasmosis as a cause of haemophagocytic syndrome is a very rare syndrome that has been described in only a handful of cases in the literature and most of them had an underlying immunosuppressed host. However, HLH with histoplasmosis is extremely rare in an immunocompetant individual. The patient was treated adequately for pulmonary tuberculosis as the initial clinical picture was consistent and she had sputum AFB positivity. However, as fever and hepatosplenomegaly did not revert with adequate TB treatment, search for a possible second infection or malignancy prompted a bone marrow examination that uncovered histoplasmosis. She was adequately treated with the recommended antifungals and had a favourable outcome. Well-timed diagnosis and timely treatment is the cornerstone of management as the disease, if left untreated can prove fatal.

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