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VISCERAL LEISHMANIASIS UNVEILING AS HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND PORTAL HYPERTENSION- A CAPTIVATING CASE REPORT.

General Medicine

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ABSTRACT

Tropical infection visceral leishmaniasis is caused by intracellular protozoa leishmania. Transmission occurs via sandfly bites carrying promastigote forms. It affects reticuloendothelial systems and present as febrile illness with splenomegaly. Rarely it can cause Hemophagocytic Lymphohistiocytosis (HLH) is a potentially life-threatening syndrome linked to abnormal immune system activation. This case report presents the clinical journey of 36-year-old gentlemen from Pauri Garhwal, Uttarakhand, who presented with chronic high-grade fever and substantial weight loss over a six-month period. He had massive splenomegaly and pancytopenia. The primary differential diagnosis focused tropical infections and hematological malignancies. A comprehensive tropical fever workup, including bone marrow aspiration biopsy, ultimately led to a diagnosis of Visceral Leishmaniasis. Initial investigations revealed pancytopenia, elevated inflammatory markers- ferritin, and low fibrinogen. He had high H-score (214) and he was classified as hemophagocytic Lymphocytic Histiocytosis as per 2014 HLH criteria. Patient HLH was secondary to visceral leishmaniasis and it improved with treatment of Kala azar. However, patient had persistent splenomegaly and signs of portal hypertensions, which could not be attributed to any other etiology. Proliferation and swelling of Kupffer cells can lead to Increase in sinusoidal and post sinusoidal resistance which was the cause of portal hypertension. This case highlights the complexity of presentations of Kala-azar as secondary HLH and portal hypertension, thus underscores the need for further research to unravel the precise pathogenesis of portal hypertension in such cases. HLH syndrome carries high mortality if left untreated. Accurate diagnosis and timely intervention are paramount for managing rare manifestations of tropical diseases effectively.

KEYWORDS

INTRODUCTION:

Visceral leishmaniasis, commonly known as Kala Azar, is prevalent in developing tropical nations. As per WHO departmental new 2021, the major hotspots for this disease, which account for 90% of the global burden, include India, Bangladesh, Sudan, Ethiopia, and Brazil. This condition is caused by intracellular protozoa belonging to the Leishmania genus and predominantly affects the reticuloendothelial system. Humans contract the infection through the bites of sandflies that carry promastigote forms in their bloodstream. Typically, it manifests as a high-grade fever accompanied by chills, rigor, and significant splenomegaly. It may also lead to pancytopenia and, in some cases, progress to disseminated intravascular coagulation. A successful response to treatment is assessed by monitoring improvements in hematological parameters and a reduction in spleen size.

Hemophagocytic Lymphohistiocytosis (HLH) is a potentially life-threatening syndrome resulting from abnormal immune system activation. It can occur as a primary syndrome due to genetic factors or secondary to various conditions, including malignancies, autoimmune diseases, and infections. Among bacterial infections, it can be triggered by agents like rickettsia, Q fever, Leptospira, brucella, mycobacteria; viral infections such as H1N1, SARS Coronavirus, EBV; fungal infections like cryptococcus, Histoplasma; and protozoan infections such as visceral leishmaniasis, plasmodium, and babesia. (1)(3) In this case, we present a patient with secondary HLH and portal hypertension linked to visceral leishmaniasis.

SUMMARY:

A 36-year-old unmarried male, laborer by occupation, without any history of substance abuse, resident of sapuli malli, Pauri Garhwal, Uttarakhand with no known comorbidities presented to Emergency with chronic high grade, intermittent fever associated with chills, rigor, myalgia, and no diurnal variation for last 6 months. The fever documented a maximum up to 104 F. He was initially having 1-2 spike per week which progressed in last 2 months with daily fever spike. There was no history of abdomen pain, vomiting, loose stools, jaundice, melena, hematuria, burning micturition, epistaxis, shortness of breath, seizures, joint pain, rash. He was also complaining of gradual onset dry cough last 3 months which was non-progressive, not associated with hemoptysis, and no diurnal or postural variations. He also had a progressive fatigue; loss of appetite and significant weight loss (14 kg in the last 5 months) and he had received 2 units of PRBC transfusion in last 7 days. There was no history of travel and TB contact in last few years. His bowel, bladder habits were normal. There was no history of similar complaints in other family members. On examination, he was febrile with regular pulse rate of 110/min. he had pallor, bilateral symmetric, painless, pitting pedal edema present. Multiple nonpalpable purpuras present on limbs and trunk. Per abdomen was soft, non-tender and spleen was palpable below the umbilicus. Rest systemic examination was unremarkable.

Differential Diagnosis:

Fever with massive splenomegaly. Tropical fever was kept as first differential diagnosis. Infections: kala Azar, chronic or complicated malaria, Enteric fever, Tuberculosis, hematological malignancy like non-Hodgkin's lymphomas, CML.

Investigations

Initially, he had pancytopenia with Hb of 6.5gm/dl, platelets of 10000/ml, and TLC of 310/ml. There was A: G reversal; a ratio of 0.34. ferritin, ESR, CRPH and other inflammatory markers were raised. His H-score was 214 which indicate 93-96% of HLH. Other clinical and laboratory parameters were suggestive of Hemophagocytic lymphocytic histiocytosis. A tropical fever workup for malaria, scrub typhus, enteric fever, genxpert for mycobacterium was negative. As there was high suspicion of kala azar, RK 39 Antibody sent, it came negative. Bone marrow aspiration biopsy revealed prominent macrophages with numerous intracellular and extracellular LD bodies diagnostic of Visceral Leishmaniasis. His urine culture was sterile, while blood culture was positive for staphylococcus hemolytic us. Injection Amphotericin B was given for 15 days along with culture sensitive antibiotics. His symptoms resolved and his counts improved. Despite of full course of amphotericin B, there was no change in the spleen size which is unusual for an isolated case of kala-azar. USG abdomen and portal vein doppler revealed dilated portal vein and splenic vein of diameter 14.7 mm and 11.3 cm respectively with hepatoportal flow suggestive of portal hypertension. There was no

obstruction in the portal vein and Fibro scan revealed features of liver fibrosis. His viral markers (HbsAg and IgM antiHCV) were negative.

Investigations	12/7/22	13/7/22	17/7/22	18/07/22	20/07/22	23/07/22	24/07/22	25/07/22	29/07/22	20/8/22
Hb	6.5	6.723	6.301	6.9	8.3	6.9	7.964	7.8	6.6	7.3
TLC	310	0.5993	0.3486	0.57	0.78	0.65	1.015	1.07	2.33	4.840
Platelets	10	11.67	<20	14	15	21	31.28	27	44	224
Bilirubin(T)		1.33		3.43				2.06	1.43	
Bilirubin (D)		0.63		1.89				1.24	0.76	
SGPT		78		69				164	87	
SGOT		220		151				156	84	
ALP		1361		1130				1966	866	
GGT		155		196				291	96	
S. Protein		4.3		4.3				5.9	6.1	
S. Albumin		1.1		1.2				1.5	1.4	3.7
S. Globulin		3.2		3.1				4.4	4.7	
Blood Urea		31	27	29	30	22	21	19	22	
S. Creatinine		0.48	0.43	0.37	0.48	0.4	0.33	0.37	0.44	
S. Na+		120	120	123	122	125	125	130	125	
S. K+		2.8	3.21	3.4	4.12	3.23	2.99	2.7	3.02	
S. Cl-		94	92	94	95	95	97	99	98	
S. calcium		6	6.34	6.3	7	6.5	6.5	7.3	6.1	
S. uric acid		2.7	2.4	2.7	3.2	2.9	3.1	3.1	2.3	
S phosphorus		2.1	3.2	3.7	4.5	3.3	2.8	3.5	3.9	
S Magnesium				1.47			2.08			

- Tropical fever workup:

Malaria Ag: -ve, Dengue NS1 Ag and IgG negative, Typhi dot: negative, scrub ICT: negative
Peripheral smear: negative for malaria parasite
LEISHMANIA (KALA AZAR) rK-39 ANTIBODY (17/07/22) – NEGATIVE

- Aerobic Blood Culture – Staphylococcus haemolyticus – isolated
- Urine culture: negative
- USG ABDOMEN (14/07/22)- Mild hepatomegaly and massive splenomegaly, Moderate ascites
- HRCT CHEST (17/07/22)- Bilateral gross pleural effusion, Mild pericardial effusion
- USG ABDOMEN (22/07/22)- Features of Portal hypertension, Grade 2 fatty liver
- CE-MRCP (23/07/22)- Massive splenomegaly, No IHBRD, CBD diameter normal, no stone.
- FIBROSCAN: LSM: 11.7-kpa, IQR: 14.1, CAP: 257

ESR WESTGREN – 45 mm/hr
FIBRINOGEN – 34 mg/dl
APTT – 58.1 sec
D-DIMER - >5.50 mg/dl
FERRITIN - >1650 ng/ml
FOLATE, SERUM – 5.90 ng/dl
Total Cholesterol – 79 mg/dl
Serum Triglyceride – 180 mg/dl
LDL cholesterol – 44 mg/dl
Vitamin D – 13.92 ng/dl
Procalcitonin: 2.8 (at day of admission)
Viral Marker: HbsAg, Anti-HCV, Anti-HIV: negative

Bone marrow aspiration- Shows numerous intracellular and extracellular LD bodies
Bone marrow shows leishmaniasis

HLH criteria: 5/8 criteria fulfilled.

For diagnosis of haemophagocytic lymphohistiocytosis (HLH), either one or both of the following criteria should be met.
A. Molecular diagnosis compatible with HLH: pathological mutations of *STX11, PRF1, UNC13D, Rab27a, BIRC4, STX11, Munc18-2* or *SH2D1A*.
B. Five of the following eight diagnostic criteria
1. Fever
2. Splenomegaly
3. Cytopaenias (at least 2 of the following lineages)
   - Haemoglobin <9 g/dL
   - Neutrophils <1×103/mL
   - Platelets <100×103/mL
4. Hypofibrinogenaemia (<150 mg/dL) and/or hypertriglyceridaemia (fasting, >265 mg/dL).
5. Haemophagocytosis found in bone marrow, lymph nodes, liver or spleen.
6. Ferritin levels >500 ng/mL.
7. Decreased or non-existent natural killer cell activity.
8. Increased levels of soluble CD25>2400 U/mL.

H score: 214: 93-96% probability of HLH

An H-score cutoff of 168 revealed a sensitivity of 100% and a specificity of 94.1%, thereby providing slightly superior diagnostic accuracy compared to HLH-2004 criteria. Both HLH-2004 criteria and score proved to be of good diagnostic accuracy and consequently might be used for HLH diagnosis in critically ill patients. (2)

Treatment:

The patient presented with pancytopenia with Neutropenic fever. As patient blood culture grow streptococcus organism, culture sensitive antibiotics with antipseudomonal coverage was given. As diagnosis of kala azar established, Inj Amphotericin B 50 mg/per day was given to him for period of 14 days. Daily Sr creatinine and Sr k level was monitored. Patient appetite improved day 10 of admission, fever subsided by day 14, neutropenia resolved by day 17 and counts was on improving trend. During Follow up visit after 3 weeks, his pancytopenia resolved with TLC of 4840 cell/cc, platelets: 2.4 lakhs

cell/cc, Sr albumin: 3.7. However, splenomegaly was persistent. LFT derangements like enzymes and hypoalbuminemia improved during follow-up visits.

DISCUSSION:

Hemophagocytic Lymphohistiocytosis (HLH) encompasses a wide array of disorders, which can be categorized as either primary (genetic) or secondary, often arising in the context of infections, malignancies, or autoimmune conditions. This condition results from dysregulated immune responses, leading to an uncontrollable hyperinflammatory reaction. Consequently, there is an uncontrolled proliferation of histocytes, accompanied by excessive hemophagocytosis and the overproduction of cytokines. Clinically, the syndrome is characterized by symptoms such as fever, hepatosplenomegaly, cytopenia, liver dysfunction, and elevated levels of ferritin. (3) It poses significant challenges in both diagnosis and treatment, requiring the fulfillment of at least five out of nine criteria for a conclusive diagnosis. The HLH-2004 criteria, when met by five or more criteria, have demonstrated a specificity of 93%, sensitivity of 91%, and a positive predictive value of 90%. (2) The presence of hemophagocytes in tissue, while observed in some cases, lacks both sensitivity and specificity as a definitive diagnostic marker.(4) HLH is a rapidly progressing and life-threatening condition if not promptly treated. Primary cases often necessitate systemic steroids as part of the treatment regimen. (5) In instances where HLH is secondary to visceral leishmaniasis, it has shown a favourable response to antiprotozoal therapy.

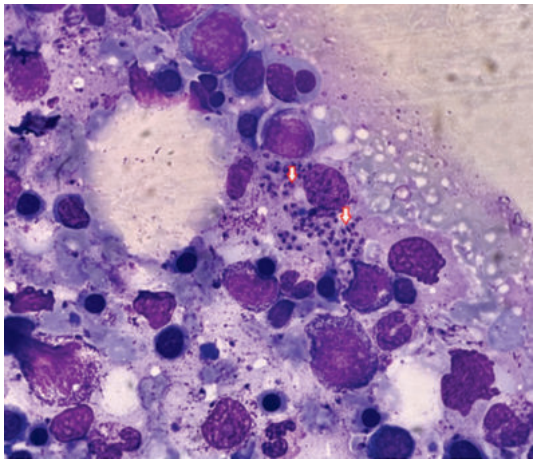

Figure 1: Bone marrow aspirate showing LD body infestation consistent with Visceral Leishmaniasis

Visceral leishmaniasis/ kala azar is caused by protozoa leishmania donovani which affects reticuloendothelial system. The organism preset in distinct 2 forms: extracellular promastigote form in sandfly vector and intracellular non flagellate from as amastigotes in the vertebral host. Definitive diagnosis is established by the identification of amastigotes, within the vertebral hosts. In immunocompetent patients with kala azar, the RK 39 rapid diagnostic test has exhibited over 95% sensitivity and 90% specificity. (6) This test was negative in our case, could be due to underlying immune dysregulation due to HLH. However, as there was high suspicion, bone marrow aspiration and biopsy were done which clinched the diagnosis. In patient with Kala Azar, response to treatment was assessed by improvement in symptoms, hematological parameters and reduction in spleen size. Despite of improvement in clinical and other hematological lab parameters, splenomegaly was persistent at follow up visit in our case. Liver involvement is not unusual in kala-azar, presentation as chronic liver disease, cirrhosis, and portal hypertension is rare. The exact etiopathogenesis of portal hypertension occurring with kala-azar is unknown. (7) Portal hypertension categorizes in to three different groups depending on pathogenesis. Prehepatic, Post-hepatic, Hepatic-presinusoidal, sinusoidal, post sinusoidal. Schistosomiasis, infiltrative disorders- sarcoidosis, NCPF are the different causes. (8) Parasitic infections like Schistosoma and malaria are well-known causes of presinusoidal hypertension. However, its association with visceral leishmaniasis was unrecognized. A case series of 3 patients described in literature of Kala-azar found that there was persistently elevated intrasplenic pressure with splenomegaly during the follow-up period despite of adequate treatment. (8) Liver biopsy showed granuloma with kuffar cell hyperplasia without evidence of fibrosis. Another study, conducted at tertiary hospital of Bihar between July 2004 to 2008 studied 88 cases of pediatric leishmaniasis. They have identified 8 cases of portal hypertension, as indicated by enlarged diameter of both the portal and splenic veins, along with development of splenic and periportal collateral vessels. There was no cirrhotic change on liver biopsy among these cases. (9)The chronicity and low-grade persistent nature of the disease causes sinusoidal dilatation with an increase in intrasinusoidal pressure.(8) Increase in sinusoidal and post sinusoidal resistance is likely secondary to marked proliferation and swelling of Kupffer cells. Our patient denied for liver biopsy. However, USG revealed grade 2 fatty liver without any cirrhotic changes. Our patient is nonalcoholic, non-diabetic, and nonreactive for HCV and HbsAg. Portal hypertension could not be explained by any other etiology so we attribute it to Kala-azar infection. Further study are needed to identify exact pathogenesis of portal hypertension in patient with Kala-azar.

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