Case report

Portal hypertension and reactive hemophagocytosis in pediatric visceral leishmaniasis

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Abstract:
A 10 year old boy suffering from prolonged low grade fever, progressive pallor, one episode of haematemesis and melaena, was found to have hepatosplenomegaly, features of portal hypertension on abdominal ultrasound, and grade II varices in upper gastrointestinal endoscopy. During hospital stay for diagnostic workup, he developed features of hepatic failure and pancytopenia. Bone marrow aspirate revealed hemophagocytosis and plenty of Leishman-Donovan bodies. The child received Injection Sodium Stibogluconate to treat leishmaniasis and received supportive therapy for hepatic failure and pancytopenia. The child responded well to treatment.

Keywords: portal hypertension; chronic liver disease; haemophagocytosis; visceral Leishmaniasis; antimony stibogluconate

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Introduction:

The Leishmaniases are a diverse group of diseases caused by protozoan parasite of genus Leishmania, which are transmitted by phlebotomine sandflies. India is a tropical endemic country for Leishmaniasis where 1-3 lakh cases occur annually [1]. Visceral leishmaniasis (VL) (caused by Leishmania donovani) usually affects older children and young adults in Asia and Africa [2]. The classic clinical features of high fever, marked hepatosplenomegaly, severe cachexia typically develops approximately 6 months after the onset of illness, but a rapid clinical course over 1 month have been reported in 20% of patients. Without specific antileishmanial treatment, the disease is fatal in 90% cases, mainly caused by intercurrent infections and haemorrhages [2,3].

Histiocytic syndromes of childhood [4] result from prominent proliferation or accumulation of cells of the monocyte- macrophage system of bone marrow origin. Class II histiocytosis comprises of 2 variants-

1) Familial hemophagocytic lymphohistiocytosis (FHLH) - The only inherited form of histiocytosis and is autosomal recessive; resulting from mutation of perforin, Munc 13-4 and Syntaxin- 11.

2) Infection associated hemophagocytic syndrome occurring secondary to viral, bacterial, protozoal, mycobacterial and fungal infections.

These two entities are indistinguishable pathologically and characterized by hypercytokinemia, widespread involvement and infiltration of various organ systems with activated phagocytic macrophages and lymphocytes. Rarely the entity may be associated with rheumatologic disorder like systemic lupus erythematosus, Kawasaki disease or a neoplasm like leukemia[4].

This article deals with an unusual case of kala-azar, where the initial presentation was similar to chronic liver disease with portal hypertension. But later he developed infection associated hemophagocytic syndrome.

Case Report:

The index case was a 10- year- old –boy, a migrant child labour, working along with his parents in a brick kiln near Kolkata. Originally they were residents of Purnea district of Bihar, which is an endemic zone for leishmaniasis. He presented with complain of low grade intermittent fever, gradually increasing pallor and progressive abdominal distension over the past 5 months. He had yellow discolouration of eyes and urine over the past 1 month. He had one episode of hematemesis and melena following which he was admitted to the hospital. Examination revealed

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pallor, icterus, hepatomegaly (4 cm below right costal margin), splenomegaly (6 cm along the splenic axis). They were firm in consistency and non-tender. Bleeding manifestations, pedal oedema, clubbing, lymphadenopathy, bony tenderness and shifting dullness were absent. Cardiovascular examination revealed tachycardia with low volume pulse. Respiratory and neurological system examinations were normal. The child was provisionally diagnosed as chronic liver disease with portal hypertension. He was treated with 2 boluses of normal saline (20 ml/kg), one unit of whole blod transfusion, Injection Octreotide (1 microgram/kg bolus followed by 1microgram/Kg/hour infusion), Inj. Ranitidine and Inj. Vitamin K. His gastrointestinal bleed was controlled within 12 hours. Investigations (sent prior to blood transfusion) revealed hemoglobin (Hb)-6 gm%, total Leukocyte count (TLC) -5400/mm^3, neutrophil-36%, lymphocyte-58%, monocyte-6%, eosinophil and basophil-0%, platelet -1.6 lakhs/mm^3, erythrocyte sedimentation rate- 80 mm in first hour, peripheral smear negative for malarial parasite. Liver function test revealed total serum bilirubin (TSB)-4.1 mg/dl (direct bilirubin-3.4 mg/dl and indirect bilirubin-0.7 mg/dl), alanine transaminase (ALT)-100, aspartate transaminase (AST)- 250, alkaline phosphatase (ALP)- 440, albumin- 3.2 grams/dl, globulin-7.4 grams/dl with characteristic polyclonal peak, prothrombin time (PT)- 14.2 seconds (control-11.5 seconds), international normalized ratio (INR)-1.2, and activated partial thromboplastin time (APTT)- 32 seconds (control- 22.6-35 seconds). Renal function test was normal. Abdominal ultrasound with doppler study showed hepatosplenomegaly with diffusely enhanced parenchymal echotexture, normal gall bladder and common bile duct, presence of small amount of free fluid in the abdomen, few collaterals around the portahepatis and splenic hilum with hepatopetal flow in the dilated portal vein (diameter 1.4 cm), velocity being 26 cm/second. Hence he was put on propranolol prophylaxis (1 mg/kg/day). Hemoglobin chromatogram revealed normal pattern. Specific investigations for etiological diagnosis like hepatitis B surface antigen (HBsAg), antibody against hepatitis C virus , autoantibody profile (Anti Smith, Antinuclear antibody, Anti Liver Kidney Microsomal-1 antibody, pANCA, cANCA, Anti soluble Liver antigen), serum ceruloplasmin, 24 hours urinary copper estimation, slit lamp ophthalmological examination for Kayser- Fleischer ring, routine urinalysis, urinary reducing sugars and aminoacidograms, GALT assay (for galactosemia), fructose tolerance test (for hereditary fructose intolerance) were negative. Transcutaneous liver biopsy revealed ballooning degeneration of few hepatocytes, mononuclear cell infiltrate in the portal tracts and lobules, dilated hepatic sinusoids and fibrosis around the portal zone.

The child had deteriorating clinical profile from 6 days after hospital admission. He had febrile peaks ranging from 38□C-40.5□C, his pallor and icterus increased, petechiae and purpura appeared followed by ecchymotic patches. There was increase in the size of the liver and spleen (each by 1.5 cm) and appearance of clinically detectable ascites. However his neurological status remained normal. Hemogram now revealed pancytopenia. Hb- 4 grams/dl, TLC-2700/mm^3, neutrophil-12% (absolute neutrophil count or ANC-324/mm^3), lymphocyte-80%, monocyte-8%, eosinophil and basophil-0, platelet count- 30,000/mm^3, ESR 30 mm in first hour. Liver function test revealed TSB- 7.4 mg/dl (conjugated bilirubin- 6.9 mg/dl and unconjugated bilirubin- 0.5 mg/dl), ALT-220, AST-550, ALP-560, albumin- 2.6 grams/dl, globulin-7.8 grams/dl. Renal function test was again normal. Coagulation profile revealed PT- 134.1 seconds, INR-10.8, APTT-122 seconds. Serologies for Hepatitis A and E virus, Dengue, Leptospira and Human immunodeficiency virus, Widal test, malarial dual antigen, Ig M against viral capsid antigen for Epstein Barr virus, polymerase chain reaction for Herpes simplex virus and Cytomegalovirus, and Rheumatoid factor were negative.

Intensive monitoring of the child's clinical status, maintainence of euglycemia, electrolyte balance, acid- base balance, normoxemia, continuation of enteral feeds with protein intake of 0.8-1 gm/kg/day, and administration of empirical antibiotics (Cefotaxime and Cloxacillin) were done. To treat the anaemia and bleeding manifestations, he received transfusions of concentrated red blood cell, platelet concentrate and fresh frozen plasma. Despite transfusion of blood products, the hemogram and coagulation profile worsened. Platelet count reached a nadir of 17,000/mm^3 and INR increased to 12. Then a bone marrow aspirate was done from the left posterior superior iliac spine, which revealed increased number of plasma cells and macrophages with evidence of hemophagocytosis. There were plenty of extracellular and few intracellular Leishman –Donovan (L-D) bodies. The plasma cells and the macrophages had replaced the other hematopoietic cells. However the erythropoiesis was normoblastic, sequential granulopoiesis and normally functioning

megakaryocytes were seen.Serum triglyceride was 383 mg/dl, ferritin level was 520 ng/ml, and fibrinogen level was 100 mg/dl. The direct agglutination test for Leishmania antibody and immunochromatographic strip (dipstick ELISA) test for Leishmanial anti RK -39 antibody were positive. Thus the diagnosis of visceral leishmaniasis with infection associated hemophagocytosis was established.

The child was treated with intravenous sodium stibogluconate, 20mg/kg/day for 28 days. Monitoring of serum transaminase, amylase, lipase and electrocardiogram were done during the therapy period. The patient received blood products to correct his anaemia and coagulopathy. With therapy of the infection, fever and icterus gradually subsided within 10 days, liver and spleen size started to regress within 2 weeks, ascites disappeared, appetite recovered and body weight increased. At the end of therapy, the hemogram revealed Hb- 10 grams/dl, TLC-6000/mm^3, neutrophil- 40%, lymphocyte-54%, monocyte -4%, eosinophil-2% and basophil-0, platelet- 1.5 lakhs/mm^3, ESR-30 mm in first hour. Liver function revealed TSB- 1.8 mg/dl (conjugated bilirubin- 1.5 mg/dl, unconjugated bilirubin- 0.3 mg/dl), ALT-80, AST-120, ALP-250, Albumin- 3.8 grams/dl, Globulin-4.0 grams/dl. Coagulation profile revealed PT- 14 seconds, INR- 1.1, APTT-28.2 seconds. Repeat bone marrow examination done on day care basis, 1 month after treatment completion, was negative for L-D bodies. 2 months after completion of treatment, USG of abdomen showed normalization of portal venous system and varices had disappeared on endoscopy. The child was discharged 50 days after hospital stay with advice to follow up atleast for 6 months since relapses are common in Indian visceral leishmaniasis.

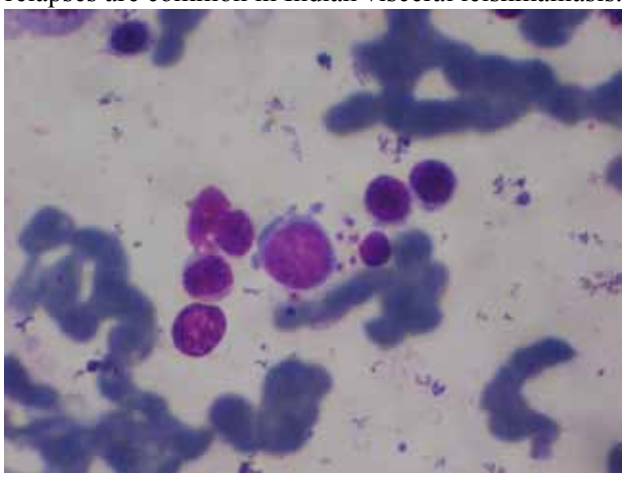

Figure 1- The picture showing extracellular LD bodies (marked with line arrow) and hemophagocytic cells (marked with hollow arrow).

Discussion:

As per the diagnostic criteria[4], this case was diagnosed as infection associated reactive hemophagocytosis because the child had fever >38.5° C lasting for > 7 days, splenomegaly >3 cm, pancytopenia (Hb< 9 gm%, ANC- 1000 neutrophils/μL, Platelet count< 100,000/μL) hypertriglyceridemia>350 mg/dl, hypofibrinogenemia <150mg/dl, presence of hemophagocytosis in bone marrow without evidence of marrow hyperplasia and malignant neoplasm. Associated laboratory findings like elevated hepatic enzymes, coagulopathy and elevated ferritin level were also evident[4]. Infection associated hemophagocytic syndrome caused by Leishmania donovani is very rare and causes diagnostic difficulty since the clinical signs of the two entities coincide[5, 6]. The protective immune response in VL is primarily cell mediated immunity. Activation of T- helper (Th-1) response results in production of Interferon γ and IL-12 and activation of macrophages which phagocytose the promastigotes of the parasite. However activation of Th-2 response results in production of IL-4, failure of effective cell mediated immunity and susceptibility to disseminated disease[1, 2]. The basic pathology in this case seems to be uncontrolled non- malignant proliferation of T lymphocytes and histiocytes with resultant overproduction of cytokines in response to L. donovani infection[5]. Plasmodium vivax and falciparum are other protozoans which have been reported to be associated with reactive hemophagocytosis[7]. There have been very few case reports of hemophagocytic syndrome in pediatric kala-azar, the youngest reported patient being a 1- year- old Swedish boy[8]. Diagnostic distinction between FHLH and secondary hemophagocytosis is necessary because treatment of FHLH includes corticosteroids and cytotoxic therapy, whereas treatment of secondary hemophagocytosis is control of the underlying infection.

The other interesting aspect of this case is the hepatic involvement in kala-azar. This patient had an initial presentation similar to chronic liver disease. Although Aggarwal et al[9] reported that cirrhosis of liver and portal hypertension does not occur in kala-azar, visceral leishmaniasis masquerading as chronic liver disease and portal hypertension have been reported from India by Prakash et al[10], Prasad et al[11] and Dhakal et al[12]. Acute hepatitis like presentation in kala-azar is very rare, occurring in<1% of patients[13]. Histology of the liver reveals that the Kupffer cells are hyperplastic, often laden with parasites. The portal tracts get infiltrated with

lymphocytes, plasma cells, eosinophils. There may be centrilobular hepatocellular necrosis (common in young children), fatty infiltration and fibrin ring granuloma formation. In late stages, the liver becomes increasingly fibrotic, giving the appearance of nodular cirrhosis[14]. Biochemical liver dysfunction is common in kala-azar. In our case, the worsening of liver function during hospital stay could be attributed to hemophagocytic syndrome because portal triaditis and fibriohistiocytic infiltration of the liver is often associated with HPS[15].

Other atypical manifestations of kala-azar are nephropathy due to albuminuria and immune complex deposition, epistaxis, gastrointestinal ulcerations (due to invasion of the mucosa and submucosa of duodenum/jejunum by the parasite) leading to diarrhea and bleeding and nervous system involvement[15]. Ascites is a late sign, often associated with oedema and pleural effusion and considered a bad prognostic indicator. Such unusual signs are common in Indian kala-azar[15]. Although our case responded excellently to sodium stibogluconate, antimony resistance has reached impressive levels in some Indian foci. Alternative treatment includes liposomal amphotericin B, miltefosine, aminosidine, interferon γ and imidazoles (ketakonazole/ itraconazole)[15].

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