SLE ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS WITH DISSEMINATED HISTOPLASMOSIS IN A HIV SEROPOSITIVE PATIENT

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ABSTRACT

BACKGROUND

Hemophagocytic Lymphohistiocytosis (HLH) is an uncommon, life-threatening and likely underdiagnosed disease of diverse aetiologies caused by a defective NK/T - cell cytotoxic pathway resulting in uncontrolled hypercytokinaemia leading to end organ damage carrying a high mortality rate. Here, we report HLH complicating SLE in a 42 years old female associated with disseminated histoplasmosis and accidentally detected as seropositive for HIV. This is extremely rare in the world literature.

KEYWORDS

Hemophagocytic lymphohistiocytosis, histoplasmosis, SLE.

HOW TO CITE THIS ARTICLE: Mohanty P, Bhuyan P, Kar A, et al. SLE associated hemophagocytic lymphohistiocytosis with disseminated histoplasmosis in a HIV seropositive patient. J. Evid. Based Med. Healthc. 2016; 3(80), 4374-4376.
DOI: 10.18410/jebmh/2016/930

INTRODUCTION: Hemophagocytic Lymphohistiocytosis (HLH) is an uncommon life-threatening hyperinflammatory syndrome caused by hypercytokinaemia due to a highly stimulated, but ineffective immune process. The underlying pathogenic mechanism being a defect in the NK/T-cell cytotoxic pathway leading to over activation of macrophages resulting in hemophagocytosis in various organs. At the same time, this dysregulated immune system triggered by several factors results in a cytokine storm leading to multiorgan dysfunction.[1] HLH has been traditionally divided into a primary form, which typically manifests in children with documented genetic abnormalities of the cytotoxic function of NK/T cell and a secondary form that tends to occur at older ages in the setting of an associated condition such as infection and malignancy without an identifiable genetic abnormality.[2]

Disseminated histoplasmosis, an opportunistic fungal infection has been reported to be associated with Hemophagocytic Syndrome (HPS) in HIV positive and AIDS patients.[3] But, its association with SLE has been rarely reported.[4] The present case who was under treatment for SLE suddenly developed MAS with disseminated histoplasmosis found to be seropositive for HIV, which is reported here because of a rare and unique association.

Financial or Other, Competing Interest: None.
Submission 12-09-2016, Peer Review 17-09-2016,
Acceptance 30-09-2016, Published 06-10-2016.
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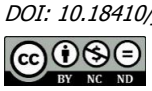
DOI: 10.18410/jebmh/2016/930



CASE REPORT: A 42 years old female presented with skin rash, photosensitivity and alopecia one and a half years back. Lupus panel showed positivity for ANA, dsDNA and SmAg with complement C3-65 mg/dL (Ref: 90-180) and C4-17.2 mg/dL (Ref: 10-40). She was diagnosed as SLE and started Omnacortil 10 mg daily with clinical improvement. After 6 months, she developed low-grade fever with an evening rise of temperature for 10-12 days. She had mild pallor, liver 3 cm enlarged and spleen not palpable. Haematological investigations revealed pancytopenia (Hb-8.4 gm/dL, TLC-1,500/cmm, TPC-17,000/cmm), DC: N-86%, L-10%, M-3%, E-1%, B-0% and ESR 10 mm/1st hr. She had ulceration in the mouth and developed bleeding per rectum. Viral serology for dengue, hepatitis B and C were all negative. ICT for malaria and Widal test were also negative. Biochemical investigations revealed blood urea 36 mg/dL, S. creatinine 1.0 mg/dL, S. bilirubin (D)-0.3 mg/dL, (T)-0.8 mg/dL, SGOT-128 IU/L, SGPT-82 IU/L, S. Alk. Phosphatase-146 IU/L (<310 Ref), S. Na+-138 mEq/L, S. K+-4.1 mEq/L. Bone marrow examination revealed extremely hypocellular marrow with marked proliferation of macrophages (Fig. 1) showing prominent hemophagocytosis (Fig. 2), also stuffed with numerous capsulated yeast forms of Histoplasma capsulatum confirmed by PAS stain (Fig. 3). Serum ferritin, triglyceride and LDH were 24,560 mg/dL, 460 mg/dL and 840 mg/dL, respectively. Thus, a diagnosis of hemophagocytic syndrome/HLH with disseminated histoplasmosis was made. Immediately Inj. Amphotericin B 1 gm/kg IV 8 hrly. was started. She was detected strongly positive for HIV with CD4 cell count of 11/cmm and viral load of 1 crore copies/mL.

In spite of IV haemostatics and antibiotics PR bleeding did not stop. Colonoscopy showed multiple mucosal ulcerations with pool of blood. Further investigations revealed PT-11.7 secs. (C), >1 min. (T), APTT-27.6 secs.

(C), >1 min. (T), FDP >40 <80 µg/mL (N <4 µg/mL), thus confirming DIC.

By this time, she had already received 12 units of BT and 2 units of platelet conc. Patient was disoriented, developed encephalopathy and succumbed on 20th day of hospitalisation.

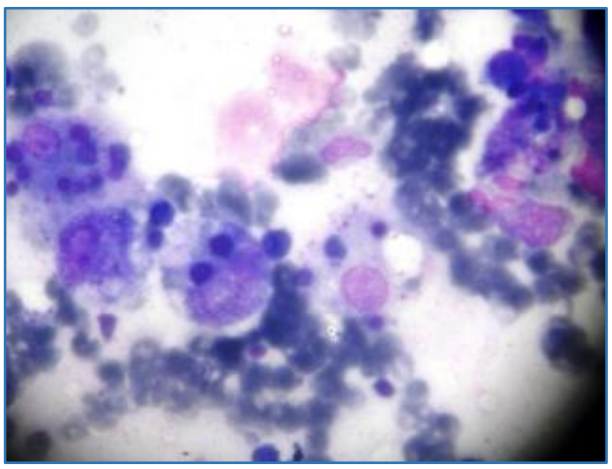


Fig. 1: Proliferation of Macrophages in the Marrow, Leishman x 400

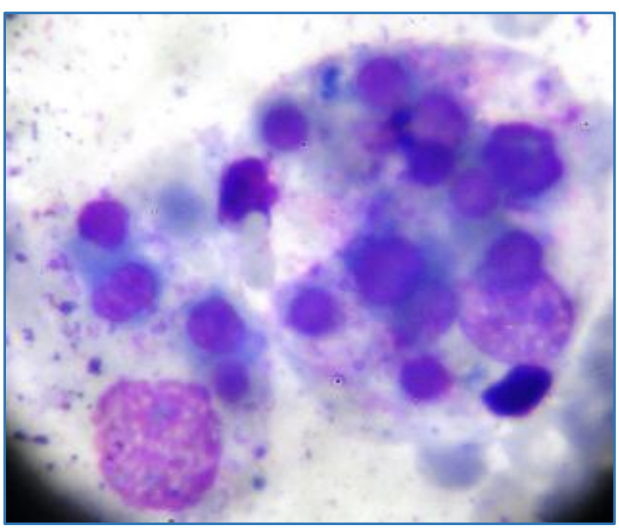


Fig. 2: Macrophages showing Hemophagocytosis, Leishman x 1000

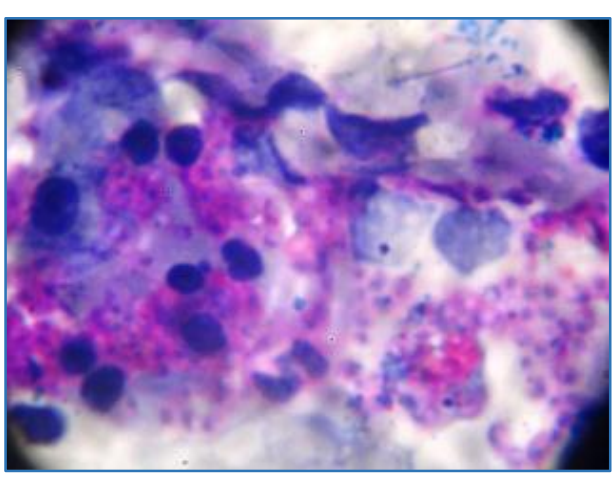


Fig. 3: Yeast Forms of Histoplasma Capsulatum in the Macrophages, PAS x 1000

DISCUSSION: HLH was first described in 1952 by Farquhar and Claireaux who termed it familial hemophagocytic reticulosis.[5] The exact incidence of HLH is not known; it may range from 0.8%-4% among critically ill patients presenting with cytopenias.[6] Primary HLH maybe familial with known genetic defects (Perforin, syntaxin, UNC13D) or maybe associated with immunodeficiency syndromes (Chediak-Higashi syndrome, Griscelli syndrome type 2, X-linked immunoproliferative syndrome) seen in babies and young children.[7] Whereas secondary HLH are acquired usually associated with infection, autoimmune diseases, malignancies and immune suppression/organ transplantation encountered in adults.[8] A number of infectious agents can trigger HLH. Viral infection like Epstein-Barr (commonest), HIV, cytomegalo, herpes simplex are frequently reported. Bacterial infection-like tuberculosis, Brucella, various gram-negative bacteria and rickettsia spp.; parasites-like Leishmania, malaria, toxoplasmosis and fungal infection that are associated with HLH are histoplasmosis, candida, Cryptococcus, pneumocystis and Aspergillus.[9] HLH can develop in the setting of autoimmune diseases like systemic juvenile rheumatoid arthritis, SLE, adult-onset still disease where it is termed as Macrophage Activation Syndrome (MAS).[10] Various hematolymphoid neoplasms like NK/T cell lymphoma, anaplastic large cell lymphoma and ALL; immunosuppressive states like post chemotherapy and following organ transplant are documented showing an association with HLH.[8]

The present case was differentiated from other entities like SIRS and LCH. Diagnosis was established as per HLH-2004 criteria (5 out of 8 criteria were fulfilled). There was no family history and mutation study could not be done. The proposed HLH-2009 criteria is an updated one showing little modification like - in the absence of molecular diagnosis, HLH requires at least 3 of 4 features (Fever, Splenomegaly, Bicytopenia, Hepatitis) and minimum one of 4 parameters (hemophagocytosis, increased ferritin, absent/decreased NK cell activity, increased soluble IL2Rα) for diagnosis. Other features supportive of HLH diagnosis include hypertriglyceridemia, hypofibrinogenemia and hyponatraemia.[11] The present case also fulfilled HLH-2009 criteria.

Lupus patients treated with immunosuppressive drugs especially azathioprine, cyclophosphamide and rituximab are more prone to develop histoplasmosis. A recent review reported the association of SLE and histoplasmosis in 14 adult patients; eight of them had Progressive Disseminated Histoplasmosis (PDH).[12] HIV infected patients with CD4+ cell count <200/µL show a greater association with acute disseminated histoplasmosis and HLH (Total 18 cases reported) showing a mortality rate of 50%.[13]

HIV-induced immunodeficiency with a CD4+ cell count 11/cmm and a viral load of 1 crore copies/mL was the predisposing factor in this case for disseminated histoplasmosis contributing towards impairment of cytotoxic function of NK/T-cell. Alternatively, cytokine storm activating macrophages resulted in disseminated hemophagocytosis, peripheral cytopenia and PUO.

Persistent fever, liver insufficiency, DIC accompanied by encephalopathy all are consequence of MAS with a reported mortality rate of 20%.[14] Though autoimmune cytopenia is a common feature of SLE and there are overlapping features between SOJIA flare and HLH, it is the extreme hyperferritinemia and LDH elevation that points to a diagnosis of MAS.

CONCLUSION: Persistent fever with cytopenia in a SLE patient treated with corticosteroid should raise the suspicion of MAS. If hemophagocytosis is observed in the bone marrow associated with histoplasmosis, screening for HIV status is warranted. Since, thorough literature searching revealed very few cases of SLE associated HLH (MAS) with disseminated histoplasmosis in AIDS, this case is worth reporting.

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