SLE associated haemophagocytic lymphohistiocytosis with disseminated histoplasmosis in a HIV seropositive patient

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Abstract

Haemophagocyticlymphohistiocytosis (HLH) is an uncommon, life threating and likely underdiagnosed disease of diverse etiologies caused by a defective NK/T- cell cytotoxic pathway resulting in uncontrolled hypercytokinemialeading 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: Haemophagocyticlymphohistiocytosis, Histoplasmosis, SLE.

Introduction

Haemophagocyticlymphohistiocytosis (HLH) is an uncommon, life threatening hyperinflammatory syndrome caused by hypercytokinemia 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 overactivation of macrophages resulting in haemophagocytosis in various organs. At the same time this disregulated immune system triggered by several factors results in a cytokine storm leading to multiorgan dysfunction[(1)].HLH encompasses two distinct forms, such as; genetic and acquired. Genetic HLH is associated with discrete genetic abnormality and can be divided into two subgroups: Familial HLH (FHL) and those associated with another primary immunodeficiency syndrome. Acquired HLH increasingly reported now-a-days triggered by diverse etiologies including infections (most common), auto-immune/connective tissue disorders (macrophage activation syndrome, MAS) as well as haematologicalmalignancies[(2)].

It has also been reported in patients receiving immunosuppressive therapy after transplant[(3)]or intravessical BCG therapy[(4)].

Disseminated histoplasmosis, an opportunistic fungal infection has been reported to be associated with haemophagocytic syndrome (HPS) in HIV positive and AIDS patients[(5)]. But its association with SLE has been rarely reported[(6)].

The present case who was diagnosed as SLE and was under treatment, suddenly developed MAS associated with disseminated histoplasmosis, also found to be seropositive for HIV which is reported here because of a rare and unique association.

Case Report

A 42 years old female presented with skin rash, photosensitivity and alopecia one and half year back. For this she was under treatment for a prolonged period but had no response and was investigated to rule out any autoimmune disorder. Lupus panel showed positivity for ANA, dsDNA and SmAg. Complement component C3 was65mg/dl (Ref: 90-180) and C4 was 17.2mg/dl (Ref: 10-40). With this a diagnosis of SLE was established and she was started Omnacortil 10mg daily.Gradually she noticed a remarkable clinical improvement with disappearance of rash. After 6 months suddenly she developed low grade fever with an evening rise of temp. Without rigor and chill continuing for 10-12 days. She had mild pallor, liver was 3cm enlarged & spleen not palpable. Hematological investigations revealed pancytopenia, Hb-8.4 gm/dl, TLC-1500/cmm, TPC-17,000/cmm. Diff. WBC count was N-86% L-10%, M-3%, E-1%, B-0%. ESR was 10mm/1st hr. She had ulceration in the mouth and developed bleeding per rectum and was admitted for evaluation of pancytopenia and fever. 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 36mg/dl, S. creatinine 1.0mg/dl. LFT revealed S. bilirubin (D)-0.3mg/dl, (T)-0.8mg/dl, SGOT-128 IU/L, SGPT-82 IU/L, S. Alk. Phosphatase-146 IU/L (<310 Ref), S. Na+ -138meq/l, S. K+ -4.1meq/l. USG of abdomen and pelvis showed hepatomegaly with mild to moderate ascites. Bone marrow examination revealed extremely hypocellular marrow with marked proliferation of macrophages admixed with lymphocytes (Fig.1). Macrophages showed marked haemophagocytosis with ingested erythroid, myeloid precursors and platelets in their cytoplasm and all the macrophages were stuffed with numerous capsulated yeast forms of Histoplasma capsulatum, confirmed by PAS stain (Fig.2). Thus a diagnosis of haemophagocytic syndrome/HLH with disseminated histoplasmosis was made. Immediately inj. Amphotericin B1gm/kg IV 8hrly was started. Serum ferritin, triglyceride and LDH were

24,560mg/dl, 460mg/dl and 840mg/dl respectively confirming HLH.

Since histoplasmosis is an opportunistic infection seen in immuno-compromised patients, she was screened for HIV status which was strongly positive (Elisa). Her CD4 cell count was 11/cmm and viral load came out to be 1 crore copies/ml by RT-PCR.

In spite of IV hemostatic along with antibiotics PR bleeding did not stop. Colonoscopy was advised which showed multiple mucosal ulcerations in the colon with pool of blood. Thinking possibility of DIC further investigations were carried out. PT was 11.7 sec (C), > 1 min (T) and APTT was 27.6 sec (C), >1 min (T). FDP was >40<80µg/ml (N-<4µg/ml).

By this time patient had already received 12 units of BT and 2 units of platelet conc. and was continuing Amphoteresin but PR bleeding continued. Patient was disoriented with mental confusion and developed encephalopathy. She succumbed to her illness on 20th day of hospital admission.

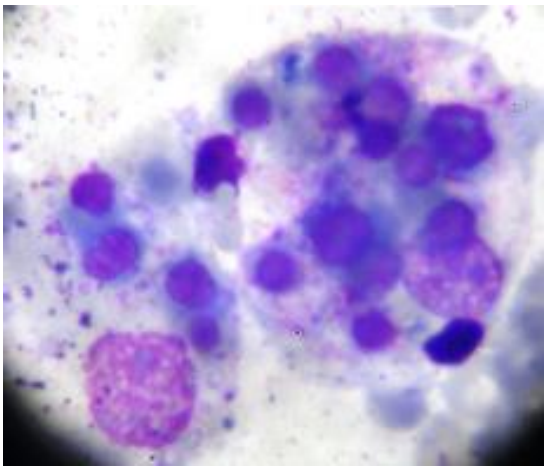

Fig. 1: Marked proliferation of macrophages in the marrow with f/o haemophagocytosis (inset), Leishman, x400.

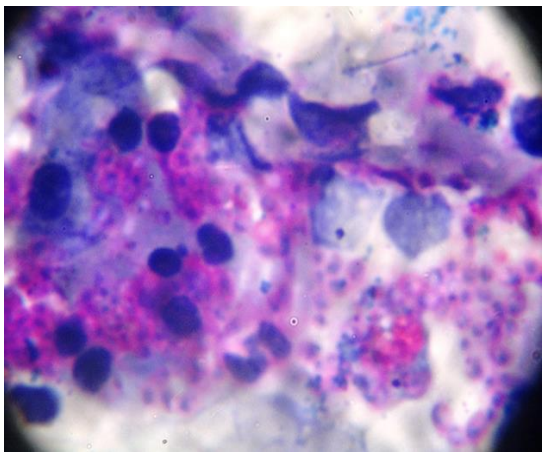

Fig. 2: Yeast forms of Histoplasma capsulatum in the macrophages, PAS, x1000.

Discussion

The first reported case of haemophagocytic lymphohistiocytosis (HLH) was described in 1952 by Farquhar and Claireaux[7] who called the disease familial haemophagocyticreticulosis. HLH is also known as haemophagocytic syndrome (HPS). Genetic HLH most commonly shows a perforin defect. Acquired HLH is commonly infection associated (E.B. virus most common).

The term macrophage activation syndrome (MAS) is often applied to HLH in association with auto-immune diseases in the context of rheumatologic diseases, commonly systemic onset juvenile idiopathic arthritis (SOJIA), adult onset still disease and systemic lupus erythematosus[8]. The estimated prevalence ranges from 7% to 13% of children with SOJIA or still disease[9].

In the present case diagnosis was established basing on HLH-2004 criteria (five out of eight criteria were fulfilled). It was differentiated from other entities like SIRS and LCH. There was no family history and mutation study was not done.

Histoplasmosis, an opportunistic fungal infection commonly seen in patients with AIDS, transmitted by inhalation of fungal spores. It is predominantly reported in areas of North & Central America where histoplasmosis is endemic. Histoplasmosis associated haemophagocytic syndrome occurs in the setting of acute disseminated histoplasmosi swhich occurs in immune-compromised patientsand in HIV infected patients with CD4+ cell count <200/µl (total 18 cases reported) showing a mortality rate of 50% [10]. Histoplasmosis in lupus patients is associated with immune-suppressive drugs use especially azathioprine, cyclophosphamide and rituximab[11]. A recent review reported the association of SLE and histoplasmosis in 14 adult patients. Eight of them had progressive disseminatedhistoplasmosis (PDH)[12].

This patient following corticosteroid therapy for SLE was immunocompromised. HIV infection that was acquired by her was iatrogenic during the course of treatment at different centers.

HLH may be the initial manifestation of HIV infection[13]. Around 10% to 20% of bone marrow biopsy specimens in patients with HIV before initiation of highly active antiretroviral therapy showed haemophagocytosis[14]. The fact that viral infection may interfere with the function of cytotoxic T-cells represents a possible mechanism of infection associated HLH[15].

Alternatively cytokine storm activating macrophages resulted in disseminated haemophagocytosis, peripheral cytopenia and PUO. Persistent fever, DIC, rectal bleeding, liver insufficiency accompanied by encephalopathy all are consequence of MAS with a reported mortality rate of 20 % [16].

Though auto-immune 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 adiagnosis of MAS.

Conclusion

Persistent fever with cytopeniain a SLE patient treated with corticosteroid should raise the suspicion of MAS. If haemophagocytosis is observed in the bone marrow associated with histoplasmosis, screening for HIV status is warranted. HIV induced immune deficiencywith a CD4+ cell count 11/cmm and a viral load of 1 crore copies/ml was the important predisposing factor in this case for disseminated histoplasmosiswhich was responsible for defective cytotoxic functionofNK/T-cell. 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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