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Case Report

A Rare and Challenging Case of Haemophagocytic Lymphohistiocytosis in a Patient of Leprosy with Recurrent Erythema Nodosum Leprosum

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Leprosy is one of the oldest diseases known to mankind with chronic and unpredictable course having distinct clinical, histopathological features based upon individual immunity. Recurrent type 2 lepra reaction in lepromatous pole is difficult to treat at times. Development of haemophagocyticlymphohistiocytosis (HLH) makes it more challenging and life threatening. HLH is a dysregulated activation and proliferation of macrophages, leading to uncontrolled hemophagocytosis, cytokine storm, and ineffective immune response characterized by fever, lymphadenopathy, hepatosplenomegaly, cytopenias, liver dysfunction, and hyperferritinemia. The disorder is classified into primary or genetic HLH syndrome and secondary or reactive HLH syndrome with underlying infection, autoimmune or rheumatologic, malignant, or metabolic conditions. There are only two case reported till now, and in this study we report a middle aged lady in late postpartum phase on regular therapy for Hansen's disease with type 2 lepra reaction who developed features of HLH syndrome. She was successfully managed by systemic steroids and addition of intravenous immunoglobulins along with multidrug therapy in intensive care setting. This case aims to highlights that having high index of suspicion, awareness of clinical and laboratory parameters by practicing dermatologist and multispecialty consultations are keys in the management of HLH.

Key words : Hansen's Disease, Type 2 Reaction, Haemophagocytic lymphohistiocytosis

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a dysregulated activation and proliferation of macrophages, leading to uncontrolled hemophagocytosis, cytokine storm, and ineffective immune response characterized by

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fever, lymphadenopathy, hepatosplenomegaly, cytopenias, liver dysfunction, and hyperferritinemia (Ramos-Casals et al 2014). The disorder is classified into primary or genetic HLH syndrome and secondary or reactive HLH syndrome. Primary HLH refers to an underlying genetic abnormality causing the disorder, whereas secondary HLH indicates that the disorder is secondary to underlying infection, autoimmune or rheumatologic, malignant, or metabolic conditions (Janka 2007). There are multiple case reports of many infective agents including viral, bacterial, fungal parasites etc leading to HLH (Rouphael et al 2007). The condition carries high morbidity and mortality. If left untreated, the dysregulated inflammatory response causes severe neutropenia, and patients often die from bacterial or fungal infections leading to sepsis or multi-organ failure. Therefore, early and prompt diagnosis is very essential to prevent the fatality (Ramos-Casals et al 2014). HLH in the context of leprosy is very rare. Till now only two cases have been reported so far (Saidi et al 2015, Panda et al 2017). Our patient was a middle aged lady in late postpartum phase on regular therapy for Hansen's disease who developed features of HLH syndrome. The case is being reported for its rarity and challenges faced in the management.

Case Report

31 year old lady, a resident of Mathura, Uttar Pradesh, India in her third trimester of pregnancy (33 weeks) presented to a tertiary care Govt hospital with numbness over her hands and feet for one year duration and recurrent, red raised, tender skin lesions on upper extremities, chest from last 2 months. The fresh episodes of red raised tender lesions were present since for last 7days. She had moderate grade of fever with temperature of 101^{0}F with malaise; however, there was no epistaxis, redness of eyes, nasal stuffiness, pain abdomen or shooting pain down the limb. On examination, she had multiple, discrete as well as confluent, tender, dusky, nodules as well as plaques over her both forearm, and upper trunk. There was infiltration of both the pinna. She had patchy glove and stocking kind of hypoaesthesia to superficial sensation of touch, temperature and pain. Both the ulnar and common peroneal nerves were thickened but nontender. Skin biopsy done from the nodules revealed features of erythema nodosum leprosum (ENL) along with Ziehl Neelsen stain showing lepra bacilli with bacillary index (BI) of 5 plus (Figs. 1a, 1b). She was clinically, histopathologically and bacteriologically diagnosed as a case of Hansen's disease borderline lepromatous with type 2 lepra reaction. She was started on three drugs MDT (cap rifampicin 600 mg/month, tab dapsone 100 mg OD, cap clofazimine 50 mg OD and 300 mg monthly) and oral prednisolone. Considering her pregnancy, thalidomide the drug of choice for type 2 reaction could not be administered. After three weeks of therapy, she underwent an elective caesarean section and delivered a healthy male baby. Post-partum period was totally uneventful. She was started on cap thalidomide considering her recurrent ENL and tab prednisolone and MDT were continued. Six weeks following child birth, she developed high grade fever which was continuous, associated with chills & rigors. She started passing high coloured urine and developed facial swelling. On examination she had a temperature of 103^{0}F, pulse of 110/ min, respiratory rate of RR-22/min. She had icterus, bilateral pitting pedal edema, generalised lymphadenopathy and splenomegaly. Cutaneous examination revealed her having multiple discrete as well as confluent, erythematous to dusky nodules and plaques over the both the forearm and trunk. There was

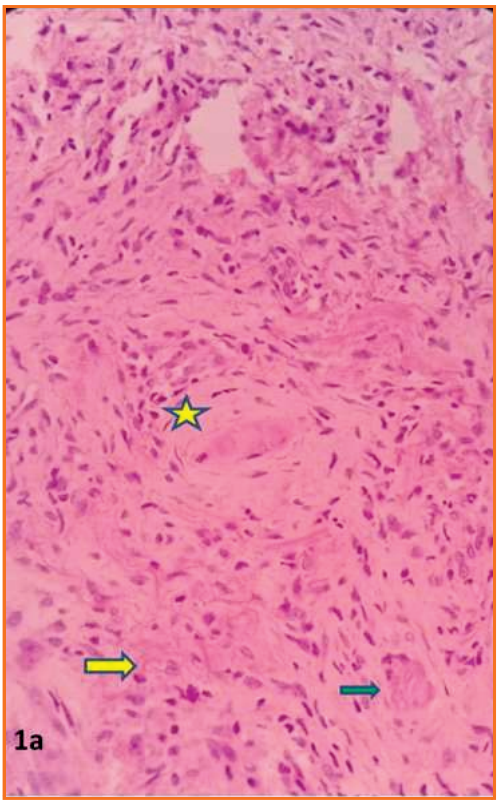


Fig. 1a : Histopathological examination : (haematoxylin-eosin staining with magnification X 400) shows periadnexal (Yellow star) and dermal infiltration by numerous foamy macrophages (yellow arrow), scattered Langhans giant cell (green arrow) and lypmphoplasmocytic cells, some of which formed ill defined granulomas.

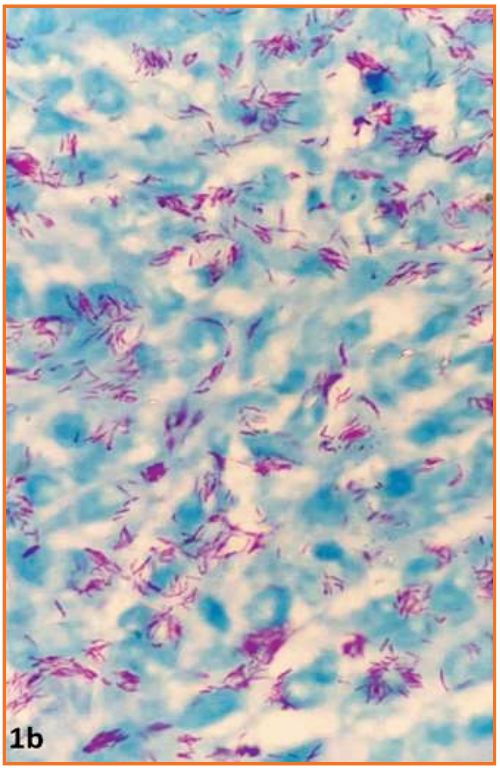


Fig.1b : Histopathology examination : Acid-fast staining of a skin biopsy specimen by Zeihl Neelsen showing acid-fast bacilli inside foamy macrophages; bacterial index: 5+ (acid-fast staining, original magnification-1000).

erythematous, indurated infiltration of both the pinna along with erythematous plaque on the left side of face (Figs. 2a, 2b and 2c). She continued to have gloves and stocking anaesthesia. Investigation revealed total leukocyte count-2600/mm^3, platelets- 95000 /mm^3, haemoglobin 8.1gm/dl, C-reactive protein (CRP) of 8 mg/dl, ESR was raised with 72 mm fall in 1 hr serum bilirubin 9 mg/dl, SGOT/SGPT- 327 IU/246 IU, serum

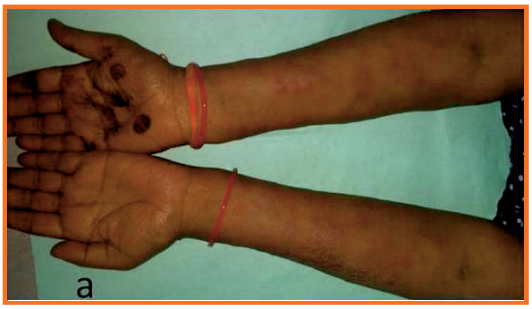
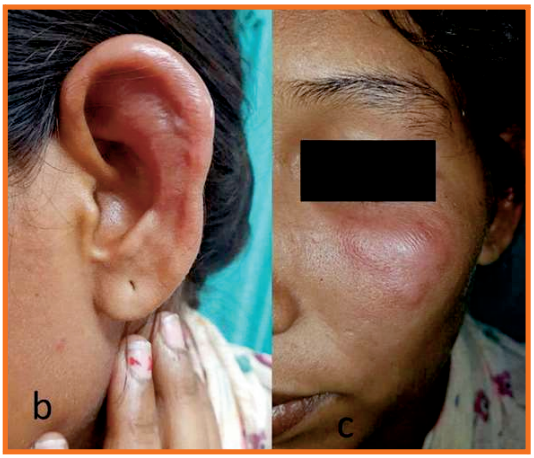


Fig. 2 : Clinical images of lady showing
2a. Multiple, erythematous to dusky, discrete as well as confluent nodules and plaques on both the forearm.



2b. Erythematous and indurated infiltration of left pinna.
2c. An erythematous indurated plaque on the left side of the face.

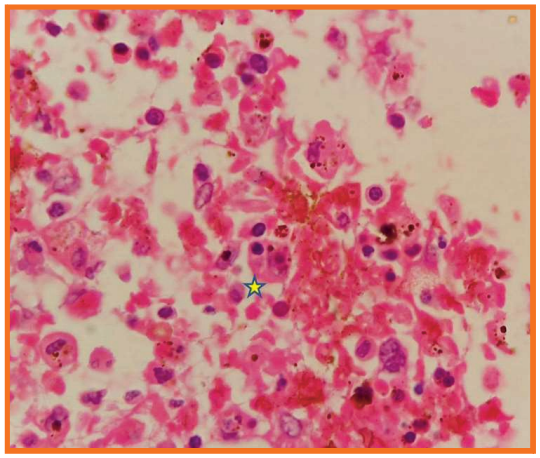


Fig.3 : Bone marrow biopsy showing phagocytic cell with engulfed hematopoietic elements (myeloid cells) indicated by yellow star (H&E stain; X400 magnification)

triglyceride 425mg/dl, serum ferritin 1200 ng/dl and d-dimer of 1121/16 ng/dl. RA factor, ANA test were negative. CSF examination was unremarkable. USG Abdomen showed bilateral mild pleural effusion with mild ascitis even CECT chest and abdomen revealed the same. Viral markers including (HBs Ag, Anti HCV Ab, HIV Ab, dengue serology, TORCH serology and EBV), malarial parasites, leptospira antigen and scrub typhus serological tests were negative. Blood, urine & stool culture did not show any growth. A bone marrow biopsy revealed aerythroid hyperplasia with haemophagocytic lymphohistiocytes (Fig. 3).

Considering the clinical picture and laboratory parameters the patient was diagnosed as a case of HLH in the back ground of Hansen's disease borderline lepromatous. She was admitted in the intensive care unit and started on IV fluids & antipyretics. Tab Dapsone, thalidomide, and clofazimine were stopped immediately. She was started on injection dexamethasone 4 mg 8 hourly along with broad spectrum intravenous antibiotic meropenem. On fourth day of admission she continued to have high grade fever with gross icterus. Her haemoglobin dropped to 7.8g/dl and LFT further deranged with serum bilirubin of 17 g/dl, SGOT/SGPT 756/535 IU/l. Considering deterioration in clinical conditions patient was started on intravenous immunoglobulins (IVIG) at the dose of 0.5g/kg which was given over 5 days along with injection dexamethasone and injection meropenem administered empirically. She showed significant improvement both clinically and in lab parameters. Her dexamethasone was replaced with tab prednisolone. She became afebrile on the 7th day post admission with progressive fall in serumbilirubin levels and liver enzymes level. Her lab parameters gradually normalized over next 04 weeks. She was discharged from hospital after 35 days on tab prednisolone 30 mg, and second line MDT consisting of tab ofloxacin 400 mg OD, cap minocycline 100 mg OD, along with alternate day

dose of clofazimine 100 mg. During follow up she kept on developing ENL for which she was started on thalidomide 100 mg TDS and dose of clofazimine increased to 100 mg BD. Presently, after three months of discharge from the hospital she is stable tolerating second line MDT well. Her follow-up lab parameters are within normal limits.

Discussion

Leprosy is one of the oldest diseases known to mankind. Classically it has distinct spectrum of clinical, histopathological features based upon immunity of affected individual. High bacillary load in lepromatous leprosy tilts the balance from low cell-mediated immunity of Th1 to humoral Th2 response (Modlin 1994). Defective cytotoxic T cells and NK cells produce disordered and inadequately regulated immune response that may result in the survival and proliferation of bacteria with ongoing immunological stimulation. Furthermore, the NK cells may be unable to regulate the immune response by effectively destroying the proliferating immune cells. This probably results in a cytokine storm with uncontrolled macrophage proliferation manifesting as a variety of clinical and laboratory abnormalities (Schmid et al 2010, Osugi et al 1997). In the backdrop of already dysregulated immune status, massive activation of macrophages and cytotoxic T cells due to HLH creates a life-threatening situation.

Diagnosis was based upon the presence of molecular parameters consistent with HLH and/or at least five of eight HLH-2004 criteria, which include: (i) fever (≥38 °C) persisting for at least one week; (ii) splenomegaly; (iii) unexplained progressive peripheral blood cytopenias involving at least two cell lines; (iv) fasting hypertriglyceridemia and/or hypofibrinogenemia; (v) hyperferritinemia (≥500 lg/l); (vi) evidence of histiocytic hemophagocytosis in the examination of bone marrow, spleen, liver, or lymphnodes; (vii) low or absent natural killer (NK) cell activity; and (viii) high levels of soluble interleukin (IL)-2 receptor (Henter et al 2007). These criteria have been further modified in the proposed HLH-2009 criteria. As per this updated criteria, the diagnosis of HLH requires at least three of four features (fever, splenomegaly, bicytopenia, hepatitis) and a minimum of one of four parameters (hemophagocytosis, increased ferritin, absent/decreased NK cell activity, increased soluble IL-2 receptor (Filipovich 2009). Our patient fulfilled both the proposed criteria of HLH. However in our case NK cell activity and IL-2 receptor level measurement could not be done due to financial constrain. Varied clinical and abnormalities in laboratory parameters can be explained by the pathophysiology of HLH. Fever, splenomegaly, cytopenia, high triglycerides, elevated ferritin can all be explained due to high interleukin levels, infiltration by lymphocytes and macrophages, high concentrations of TNF-α & IFN-γ , direct hemophagocytosis, decreased lipoprotein lipase activity and macrophage scavenging of heme via the CD163 receptor respectively (Janka 2006). Most reported cases of hemophagocytic syndrome in patients with mycobacterial infections have been associated with *Mycobacterium tuberculosis* (Brastianos et al 2006, Claessens et al 2006, Aggarwal et al 2012). Published literature of management of HLH in the backdrop of leprosy is very limited 9 (Saidi et al 2015, Panda et al 2017). One case of leprosy with haemophagocytosis even misdiagnosed as HLH (Zeng et al 2014). Pregnancy and post partum association of HLH is not uncommon. In one such

series of HLH in post partum period usual onset was within three to four days post pregnancy (Tumian et al 2015, Samra et al 2015, Song et al 2019). Our case was unique in the sense it has developed features of HLH after 06 weeks of post delivery. Unlike the above series underlying leprosy with high bacillary load was the trigger in our case.

Management of HLH involves admission in ICU set up with close monitoring and multispecialty care. Broadly, treatment options of HLH are immune-suppressive (corticosteroid, cyclosporine, methotrexate), immune modulatory agents (IVIG), anticancer (etoposide), bio¬logical response modifiers (biologics, colony stimulating factors, IL2 or INF alfa etc.) treatment of the underlying illness if secondary, and subsequent stem-cell transplantation (Henter et al 2007, La Rosée et al 2019).

Our patient was already on a steroid which was prescribed for type 2 reaction during pregnancy. She did not respond to high dosage of dexamethasone, we decided to add intravenous immunoglobulins (IVIG) and continue the oral steroid for long period along with second line MDT. Management of recurrent ENL is as such difficult, co-existence of HLH due to underlying leprosy make it more complicated and challenging. This case highlights that high index of suspicion, awareness of clinical and laboratory parameters by practicing dermatologist and multispecialty consultation are keys in the management of HLH.

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