Case Report

Hemophagocytic Lymphohistiocytosis in Erythema Nodosum Leprosum: Case Report of an Unusual Conundrum

Abstract

Hemophagocytic lymphohistiocytosis (HLH) and erythema nodosum leprosum (ENL) result from a complex agent–host interaction and form a continuum of the same spectrum. A 30-year-old multi-gravida presented at 36 weeks gestation with fever and erythematous raised lesions over the face and upper and lower limbs after defaulting treatment for borderline lepromatous leprosy. Skin biopsy confirmed ENL, hence multi-drug therapy (MDT) and oral steroids were restarted. However, her condition worsened and she developed icterus, periorbital puffiness, pleural effusion, ascites and splenomegaly. Laboratory investigations showed pancytopenia, conjugated hyperbilirubinemia, transaminitis, elevated lactate dehydrogenase, hypertriglyceridemia, hyperferritinemia and hypofibrinogenemia. Dapsone was stopped on the suspicion of dapsone hypersensitivity but hyperbilirubinemia progressed. Diagnosis of HLH was clinched after bone marrow aspirate showed florid hemophagocytosis and subsequently, intravenous immunoglobulin (2 g/kg) over 5 days and dexamethasone were administered. The patient improved gradually with normalization of laboratory parameters and restarted MDT. This case depicts a rare and potentially catastrophic complication of ENL and emphasizes a vigil for HLH syndrome in such cases.

Keywords: *Erythema nodosum leprosum, hemophagocytic lymphohistiocytic syndrome, leprosy*

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) and erythema nodosum leprosum (ENL) result from a complex agent–host interaction and form a continuum of the same spectrum.[1] The macrophages laden with lepra bacilli present antigens to Th1 cells leading to increased production of chemokines, pro-inflammatory cytokines (tumour necrosis factor-alpha and interferon-gamma), activation of T-cells, neutrophils and macrophages and production of immune complexes which cause further amplification of immune response leading to ENL and tissue damage.[2] The persistence and proliferation of lepra antigens can cause uncontrolled cytokine storm and activation of macrophages leading to a defective T-cell and NK-cell function, thus causing HLH.[3-5] Despite similar pathophysiology, the prevalence of HLH in ENL is very rare, and to the best of our knowledge, there are only three case reports to date in this regard.[1,3,4] We present here a case of a 30-year-old female with ENL who progressed to HLH. Informed consent of the patient was duly taken.

Case Report

A 30-year-old multi-gravida was diagnosed with borderline lepromatous leprosy (BL) with ENL at 28 weeks of pregnancy and started on multi-drug therapy multi-bacillary (MDT-MB) and tapering dose of oral steroids. She responded well to chemotherapy; however, she discontinued treatment on her own and presented again at 36 weeks of gestation with fever and fresh crops of erythematous raised lesions over the face, and upper and lower limbs suggestive of ENL [Figure 1]. Skin biopsy showed leucocytoclastic vasculitis and perineural infiltration by acid-fast bacilli laden foamy cells [Figure 2]. The Bacteriological Index of the patient was 5. She was restarted on MDT and oral steroids; however, her condition worsened and hence early induction of labour was done at 35 weeks. The patient had an uneventful normal vaginal delivery and thalidomide was added post-partum. However, the patient

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developed high-grade fever, anorexia, jaundice, periorbital puffiness and pedal oedema. Her laboratory investigations are summarized in Table 1. Contrast-enhanced computerized tomography chest and abdomen revealed gross ascites, bilateral pleural effusion and splenomegaly. The patient was suspected to develop dapsone hypersensitivity syndrome (DHS), hence dapsone was stopped. She was administered broad-spectrum antibiotics and supportive therapy. However, the patient continued to be febrile with worsening hyperbilirubinemia (serum bilirubin – 3.8 → 7.6 → 16.4 → 25.6 mg/dL). In view of pancytopenia, splenomegaly, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and hemophagocytosis on bone marrow aspirate (as shown in Figure 2), the patient was diagnosed with HLH. She was started on intravenous immunoglobulin (2 g/kg) over 5 days along with intravenous dexamethasone, and rifampicin and thalidomide were stopped. There was gradual improvement in her condition over one month, including the normalization of hematological and biochemical parameters. She was restarted on oral prednisolone and placed on second-line MDT (ofloxacin 400 mg OD, clarithromycin 500 mg OD and clofazimine 100 mg A/D) as there was an earlier clinical suspicion of DHS along with HLH. The patient is currently tolerating the treatment well without any recurrence of ENL.

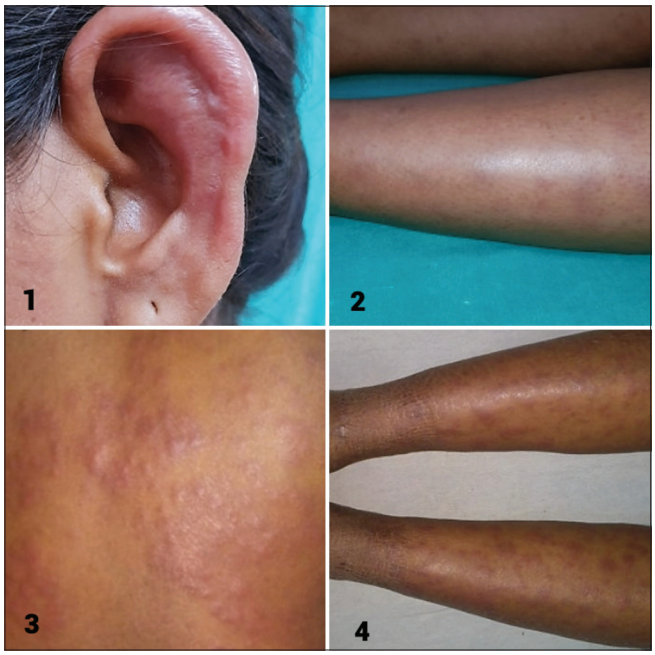

Figure 1: Photographs of skin lesions of the patient. Tender erythematous plaques over left pinna (1) and tender subcutaneous nodules over both legs (2) at initial presentation. Multiple erythematous tender papules and plaques over back (3) and multiple discrete to coalescent warm tender nodules and plaques on both lower limbs (4) when presented with HLH

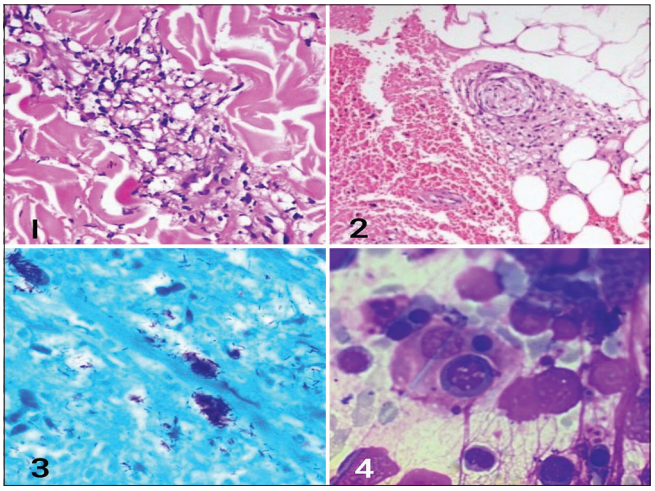

Figure 2: Photomicrographs of skin biopsy and bone marrow aspirate of the patient. Skin biopsy (H&E, 40×) – The dermal capillaries are lined by plump endothelial cells and are associated with perivascular aggregates of foamy cells and karyorrhectic debris (1), the dermal nerve twig being surrounded by foamy cells (2), numerous acid-fast bacilli in foamy cells, modified Fite-Faraco, 100× (3), bone marrow aspirate (LG, 100×) hemophagocytosis (4)

Table 1: Laboratory abnormalities of the patient at admission and during hospitalization

Parameters	Normal range	At admission	Day 7	Day 14	Day 30 (post-IvIg)
CBC*					
Hb† (g/dL)	12-14	9.2	7.6	6.8	11.4
ANC‡ (/µL)	1500-	1200	800	600	4400
Platelets (/µL)	150-450×10^3	70000	10000	10000	150000
Liver function tests					
Serum BR§ (mg/dL)	0.3-1	3.8	7.6	25.6	2
Conjugated BR§ (mg/dL)	0.1-0.3	2.7	5.8	22.4	0.9
ALT‖ (IU/L)	7-55	307	820	1510	45
AST¶ (IU/L)	8-48	764	1362	3447	67
Serum ferritin (ng/mL)	12–150	1027	5200	10120	365
Serum triglycerides (mg/dL)	<150	292	296	312	90
Plasma fibrinogen (mg/dL)	200-400	120	100	100	265
LDH** (U/L)	150-250	624	724	812	240

*Complete blood count, † Hemoglobin, ‡ Absolute neutrophil count, §Bilirubin, ‖ Alanine transaminase, ¶ Aspartate transaminase, ** Lactate dehydrogenase

Discussion

ENL is a type II lepra reaction seen in approximately 60% of lepromatous leprosy and 10% of borderline lepromatous leprosy patients. Pregnancy and lactation are major precipitating factors; however, few studies have found stress, puberty, intercurrent infections, vaccination, anti-tubercular therapy, HIV and malaria as potential triggers.[2] Our patient presented initially at 28 weeks of pregnancy when she was diagnosed as BL with ENL; however, despite her initial response, she reported back with fresh crops after discontinuation of therapy on her own. She developed high-grade fever, periorbital puffiness, pedal oedema, splenomegaly, progressive hyperbilirubinemia, gross ascites and bilateral pleural effusion after restarting MDT in post-partum period raising suspicion of DHS. DHS is a multi-system potentially fatal disorder characterized by a triad of fever, skin rashes and internal organ involvement, more commonly hepato-pulmonary, seen several weeks to six months after starting dapsone in 0.5–3.6% of patients.[6] However, our patient had pancytopenia, hypofibrinogenemia, hyperferritinemia and hypertriglyceridemia in addition to splenomegaly. Hence HLH was a more plausible diagnosis and bone marrow aspirate subsequently confirmed the diagnosis. The H-score of our patient was 234, which suggested a 98–99% probability of HLH syndrome.

ENL and HLH are progressive ramifications of agent–host interaction seen in leprosy.[7,8] While ENL is an immune-mediated type III hypersensitivity reaction, HLH is triggered by defective NK-cell and cytotoxic T-cell response leading to persistence and proliferation of the lepra bacilli, uncontrolled cytokine storm and activation of macrophages.[7-9] The HLH 2004 criteria required five of eight criteria for secondary HLH, which included (i) fever >38.5°C for a minimum of seven days, (ii) splenomegaly, (iii) cytopenia of two or more lineages (hemoglobin <10 g/dL, absolute neutrophil count <1000/μL, platelets <100000/μL), (iv) hypertriglyceridemia (>265 mg/dL) or hypofibrinogenemia (<150 g/L), (v) serum ferritin >500 ng/mL, (vi) elevated soluble CD25/IL2R levels >2400 IU/mL, (vii) decreased or absent NK-cell activity and (viii) hemophagocytosis in bone marrow, spleen or lymph node. The supportive criteria include neurological manifestations, hyperbilirubinemia, elevated liver transaminases, hyponatremia, coagulopathy and raised lactate dehydrogenase levels.[5] The revised proposed HLH 2009 criteria required (i) the presence of three of four features, fever, splenomegaly, bicytopenia and hepatitis, and at least one of four which include (i) hemophagocytosis, (ii) hyperferritinemia, (iii) decreased or absence of NK-cell activity and (iv) elevated soluble CD25/IL2R levels.[9] The paucity of routine availability of assays for NK-cell function and soluble CD25 levels in equivocal situations can be overcome by using an online calculator-based H-score.[10] Our patient fulfilled HLH 2004, HLH 2009 and H score criteria for HLH.

Conclusion

This case depicts a rare and potentially fatal complication of ENL seen in leprosy, which is a common tropical infection. A vigil for HLH syndrome is vital for promptly halting the unabated cytokine storm that can lead to catastrophic sequelae.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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