Multisystem Langerhans cell histiocytosis in an infant: A case report and review of literature

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disease of childhood which originates from marrow-derived immature myeloid dendritic cells of skin and visceral organs with incompletely understood etiopathogenesis. An 11-month-old infant presented with fever, pallor, multiple erythematous, crusted, scaly hypopigmented macules, and shiny colored papules over scalp, forehead, and trunk along with hepatosplenomegaly. Persistent pancytopenia, punched out lesion on a brain scan, and multinucleated giant cells with eosinophilic cytoplasm admixture with eosinophils and lymphocytes on skin biopsy were seen. Immunohistochemistry was positive for CD1a and S100. The patient was treated with vinblastine and steroid, but unfortunately parents did not complete the therapy. A high index of suspicion is necessary to make timely diagnosis and therapy to minimize the frustration felt by parents/patients.

Key words: *Dendritic cells, Infant, Langerhans cell histiocytosis*

Langerhans cell histiocytosis (LCH) is a spectrum of clinicopathological condition caused by the reactive proliferation of marrow-derived immature myeloid dendritic cells of the skin and visceral organs. The annual incidence in the pediatric population (in <15 years) is 4–5 cases per million per year, and more than 50% of cases are diagnosed in the first 3 years of life with male predominance [1]. Although exact etiology of LCH is yet to be completely understood, environmental factors, viral infections, and smoking in adult trigger this reactive disease, and loss of heterozygosity and instability of chromosome and elevated oncogene products are more persuasive evidence of neoplasia [2]. Clinical presentation varies from self-healing lesions to life-threatening disseminated disease. It may affect any organ, but bone (80%), skin (33%), and the pituitary gland (25%) are most commonly affected in children [3]. Diagnosis of LCH is based on synthetic analysis of clinical manifestation, imaging, and histopathological features. Prognosis depends on age of onset, risk organ involvement, and the rate of progression [4]. Here, we have described a case of multisystem multifocal LCH.

CASE REPORT

An 11-month-old female infant born of non-consanguineous parents presented with moderate- to high-grade fever, pallor, and skin lesion over the abdomen and scalp. On further inquiry, she had a history of failure to thrive and bilateral ear discharge but no bleeding manifestation, respiratory, or urinary complaint. She had an uneventful birth history with appropriate birth weight. She was developmentally normal and immunized as per age. Family history was not significant. On physical examination, her vitals were stable except she was febrile and had severe pallor (Hemoglobin [Hb]-3.9 g%). She had multiple erythematous, crusted, scaly hypopigmented macules, and shiny colored papules over the scalp, forehead, and trunk between multiple petechial spots over the trunk and perineal region (Fig. 1a and b). Nails were distally erythematous and she had no signs of vitamin deficiency or bony tenderness and swelling. No ocular abnormalities were found. The liver was palpable 4 cm and spleen 2 cm below costal margin.

Laboratory investigation revealed persistent pancytopenia (Hb-3.9 g%, total leukocyte count-4500/cumm, and platelet 39,000/cumm) on multiple occasions with normal coagulation profile. Liver function, renal function, and electrolytes were within the normal limit. Dengue antigen test, tuberculin test, and solubility test were negative, and malarial parasites were not detected on peripheral smear. Chest radiograph and ultrasound abdomen were within normal limits except hepatosplenomegaly, whereas bone marrow examination and serum ferritin were within normal limits. Computed tomography of the brain reveals calvarial intradiploic soft tissue density lesion predominantly hypodense of average HU 25, of average size 19.5 mm×7.7 mm noted in the right high parietal region causing underlying bony defect (punched out lesion) (Fig. 2a and b). Skeletal survey, including whole bone scan, did not reveal any abnormality.

A biopsy from skin lesion showed focal thinning of the epidermis with crust formation. Superficial dermis showed

dilatation of capillaries with the extravasation of red blood cells and infiltration by large abnormal cells with moderate amount of eosinophilic cytoplasm and multilobulated tumor cells, occasional admixture with eosinophils and lymphocytes that suggested LCH (Fig. 3). On immunohistochemistry, the cells were found to be CD1a and S-100 positive. Based on the clinicopathological, radiological, and immunohistochemistry, the diagnosis of multifocal multisystem LCH was done. The infant was treated with vinblastine and prednisolone. In addition, antipyretics, antibiotics, blood, and platelet transfusions were prescribed. In spite of proper counseling and appropriate therapy, the parents were not willing for further treatment and the patient was discharged against medical advice.

DISCUSSION

The old terminology "Liechtenstein's histiocytosis X" is now replaced by LCH. It is a rare clonal proliferation disorder of antigen presenting cells which could be present at any age right from the neonate to old age, but most often it is diagnosed in the first 3 years of life. The annual incidence in children <15 years is 4–5 cases per million per year with male predominance [1,5,6]. Historically, it was described as eosinophilic granuloma characterized by the presence of one or more lytic bone lesion; Hand–Schuller–Christian disease, comprising the clinical triad of bone defects, exophthalmos, and polyuria; and Letterer–Siwe disease which is a disseminated disorder marked by hepatosplenomegaly, lymphadenopathy, skin rash, bone lesion, and hematological compromise.

Recently, stratification system was adopted by Histiocytosis Society and classified it into single system disease (SS-LCH), which occurs in about two-third of pediatric age group, and can be further subdivided into single site and multiple site forms and multisystem (MS-LCH), in which more than two organ system are involved at the time of diagnosis. Multisystem LCH is subdivided into low- and high-risk forms. In high-risk forms, multiples organs are involved such as bone marrow, liver, spleen, and lung [1,7]. The present case had liver, spleen, bone, and hematopoietic system involvement and thus classified as multisystem high-risk form.

The etiology of LCH has been debatable till date whether it is a neoplastic or of reactive nature. It has been described as neoplastic process due to monoclonal proliferation, loss of heterozygosity and instability of chromosome, elevated level of oncogene product, and recent report of BRAF V600E oncogenic mutation. However, the hypothesis of reactive inflammatory disorder resulting from dysregulation of immune system by various trigger like environmental factors, viruses (cytomegalovirus and herpes virus), and smoking in adult lung LCH are supportive as LCH is known to release a number of inflammatory chemokine receptors, ligands, macrophages, inflammatory proteins, monocytes chemoattractant proteins, and interleukins. These chemokines are playing an important role for the recruitment of circulating immature dendritic cell as well as other immune cells, and this "cytokine storm" stimulates the autocrine and paracrine cascade

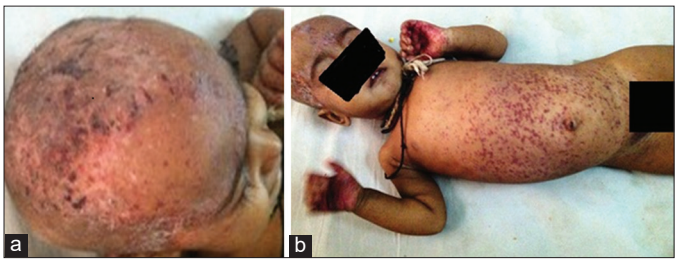

Figure 1: (a and b) Seborrheic dermatitis of scalp and infant with skin lesion

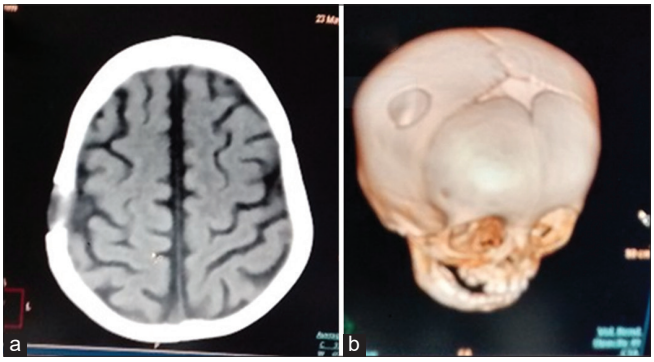

Figure 2: (a and b) Bony defect of parietal scalp bone and punched out lesion on CT brain

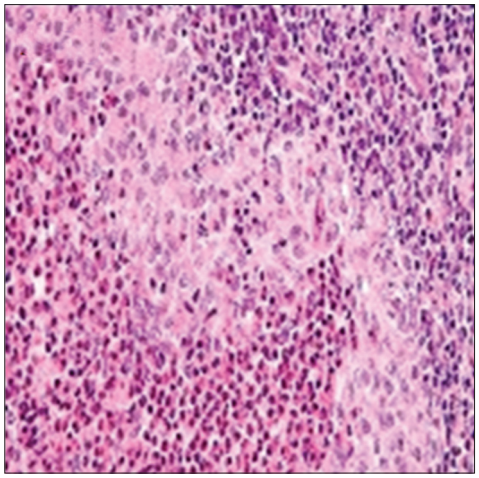

Figure 3: Histopathological finding on skin biopsy

and explains a number of clinical symptoms including fever and failure to thrive [1,4,7].

The diagnosis of LCH is based on clinical presentation, imaging, and histopathological findings. Pathologically, LCH is a granulomatous lesion containing multinucleated Langerhans cells, eosinophils, macrophages, and histiocytes. The pentilaminal, "racquet-shaped" cytoplasmic granules (Birbeck granules) is a gold standard for the diagnosis on electron microscopic examination. However, cell surface markers such as CD1a, S100, and CD207 support the diagnosis on immunohistochemistry of biopsy specimen [8,9]. Nowadays, highly specific and sensitive monoclonal antibody against CD207 (Langerhans), which is important for the formation of Birbeck granules, has become commercially available. We confirmed the diagnosis of LCH on histopathological observation and immunohistochemistry staining with CD1a and S100.

Management of multisystem LCH is a challenge as mortality is high in young children with involvement of risk organs and bouts of reactivation of disease. Several international protocols have been designed for MS-LCH, but the most popular regimen is vinblastine or etoposide and steroid. Other options include cladribine and cytarabine or hematopoietic stem cell transplantation [9]. The use of radiation therapy is controversial. The patient was treated with vinblastine and steroid, but unfortunately, parents did not complete the regimen, and we could not assess the effectiveness.

CONCLUSION

Due to extreme clinical heterogeneity, LCH can present with varied presentation, and thus, high index of suspicion is necessary to make timely diagnosis and treatment to minimize the frustration felt by parents/patients. Proper and effective counseling paired with family support is of paramount importance to adhere to the treatment plan.

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