Langerhans Cell Histiocytosis: A Case Report

Om Shankar Chaurasiya¹, Ravi Ambey², Tarun Chandra¹
¹Department of Pediatrics, Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh, India, ²Department of Pediatrics, Gajra Raja Medical College, Gwalior, Madhya Pradesh, India

ABSTRACT
Langerhans cell histiocytosis (LCH) is a rare proliferative disorder in which pathological LC accumulate in a variety of organs. Historically the nomenclature regarding LCH has been confusing because the disease had been subcategorized simply based on different clinical manifestations. Herein, we report a child with classic finding of disseminated LCH, categorize and stratify on current recommendations of histiocyte society and discuss its treatment and prognosis.

Keywords: Dendritic cells, Langerhans cells, Langerhans cell histiocytosis

INTRODUCTION
Langerhans cell histiocytosis (LCH) refers to a group of diseases whose primary pathogenesis is an abnormal polyclonal proliferation of LCs. LCs, which are macrophages that are normally present only in the dermis, are the characteristics of this disease. LCH is divided into three subtypes: Eosinophilic granuloma, Hand-Schuller-Christian disease (HSC) and Letterer-Siwe disease (LS).

The incidence of LCH is approximately 5.4/million. It is a rare disease with a mile. It mainly affects children of age between 1 and 4 years. The clinical presentation of LCH depends upon the site of involvement. It can range from a multifocal to a solitary lesion. It usually affects the head and neck, mainly the skull base, in 60% of cases. The temporal bone is involved in 19-25% of cases and the involvement is bilateral in a third of all cases. This disease has an unpredictable natural history varying from a rapidly, fatal progressive disease to spontaneous resolution. Herein we report a child with disseminated LCH, who presented with fever, Breathlessness, extensive skin rashes, osteolytic bony lesions, and oral ulceration. Though this case, we summarize the current recommendations of the histiocyte society regarding classification, stratification, evaluation and treatment of LCH.

CASE REPORT
A 3-years-old boy, born to non-consanguineous marriage admitted to Maharani Laxmi Bai Medical College, Jhansi for 8 months fever, insidious, mild to moderate grade, intermittent. 5 months back child was diagnosed as pulmonary Koch’s and prescribed anti-tubercular treatment, from last 4 months patient developed red color maculopapular rash, which started from scalp and gradually covered neck and trunk region, rashes were red initially but later became hypopigmented. Rashes were non-scaly 2 months back patient developed nodular eruption over the scalp, which were initially pinhead in size and later increased in size and gradually multiple areas of scalp depressions, 2-3 cm size were noticed. There is a history of purulent ear discharge 1-year back and gum swelling 2 months back.

On examination, there were multiple depressions on palpation (Figure 1), which on Skiagram revealed multiple punched out lesions in frontal, and parietal bone (Figure 2), which was also confirmed by computed tomography (CT)
skull (Figure 3). The patient has one oral ulcer over hard palate (Figure 4). The patient has hypopigmented maculopapular rashes over back chest and abdomen (Figure 5). There was no crusting over rashes, the child was tachypneic with a respiratory rate of 38/min. Heptomegaly with a liver span of 12.5 cm and splenomegaly of 7 cm size was appreciated. Laboratory testing revealed hemoglobin $10.99 \text{ g\%}$, platelet count $506 \times 10^9/L$, total leucocyte count $11.1 \times 10^9/L$, liver function test was within the normal limit, urine specific gravity was 1.017.

Skull X-ray shows multiple irregular osteolytic lesions (Figure 2). These findings were confirmed by CT scan (Figure 3). X-ray chest posterior-anterior view shows multiple cavitory lesions (Figure 6). CT scan revealed honeycomb of lung parenchyma (Figure 7), which involved up to 60% of lung parenchyma (Figure 8). Histologic...
examination of a punch biopsy obtained from a lesion on the back revealed (Figure 9).

The patient was diagnosed with LCH with multiorgan involvement and organ failure as multisystem LCH with involvement of risk organs according to histiocytosis society (2009).6

**DISCUSSION**

Clinically and histologically the histiocytosis comprise a diverse group of proliferative disorders characterized by infiltration and accumulation of histiocytes and other effector cells of the immune system within various tissues. The generic term “histiocyte” refers to several types of cells including monocytes/macrophages, dermal/interstitial dendrite cells and LCs. LCs are dendrite bone marrow cells situated suprabasally in most stratified squamous epithelia.

In the past, there had been a great deal of confusion as to how to classify the histiocytoses since the exact ontogeny was not completely understood. However, with the advent of immunohistochemical stains, the histiocyte society proposed reclassification of these disorders based on predominant cell type in the infiltrate. The initial classification system included: Langerhans histiocytosis (Class I), non-LCH (Class II), and malignant histiocytosis (Class III).7 As more information has become available, a revised classification scheme was proposed and includes dendritic cell disorders, macrophage related disorders, and lastly, malignant histiocytic disorders.

The incidence of LCH ranges from 0.5 to 5.4 cases per million persons per year, depending upon the age of population investigated.8,10 Although the disease can present at any age, it usually presents within the first few years of life and has a slight male predominance. The clinical presentation can range from localized disease, which may spontaneously resolve, to widely disseminated disease with organ failure and death.

Included in this category, are conditions that were previously designated as eosinophilic granuloma, HSC...
disease, LS disease, histiocytosis X, pure coetaneous histiocytosis, congenital self healing reticulohistiocytosis, Hashimoto and Pritzker disease, LC granulomatosis, Type II histiocytosis, and the generic term non-lipid reticuloendotheliosis.\textsuperscript{7,11}

Several large retrospective studies consisting of neonates and children under the age of 4 year have shown that 51-71\% of children with LCH present with multiorgan disease.\textsuperscript{8,12-15}

There is an ongoing debate as to whether LCH represents an abnormal immune response as to an unidentified antigen or whether it is truly a neoplastic process.\textsuperscript{16} As the microscopic features which are presented in LCH, an inflammatory etiology has been proposed.\textsuperscript{17} A bacteriological origin has also been suggested although no specific causative microorganism has been identified in histiocytosis lesions.\textsuperscript{17,18} Although no clear etiology has been identified, the general consensus is that patients with LCH have a dysregulated immune response with failed transition from “innate” to “adaptive” immunity.\textsuperscript{12,19} The LCs in LCH manifest an activated immunophenotype, resulting in their increased proliferation and migration. Aberrant or uncontrolled cytokine production by these inflammatory cells likely results not only in further proliferation of LCs, but also contributes to the pathological sequelae of LCH, including fever, fibrosis, bone resorption and necrosis.\textsuperscript{20,21}

The histiocyte society had established a set of guidelines to assist in the diagnosis and study of LCH.\textsuperscript{22} The initial evaluation consists of a complete physical examination, inclusive of height, weight, in addition to laboratory studies including hematological assays and coagulation studies, liver function tests, and urine osmolality. Although some authorities advocate bone marrow examination in every baseline examination, it is not required unless symptoms or blood tests suggest involvement. Finally the patient must have a complete skeletal radiographic survey and chest radiography patients with identified abnormalities require more specific studies, such as pulmonary function tests and lung biopsy, small bowel series, liver biopsy, panoramic dental films, CT or magnetic resonance imaging of the brain with particular attention paid to the hypothalamic-pituitary axis, endocrine evaluation and otolaryngology consultation with audiogram. Since patients with LCH often have chronic and recurrent disease, follow-up studies are required every month to 6 months, depending upon organ system involvement and the degree of organ dysfunction.\textsuperscript{22}

To aptly determine a patient’s prognosis and treatment protocol, it is currently recommended that patients are risk stratified based on the number of organs involved and degree of organ dysfunction.\textsuperscript{22-26} Patients diagnosed with organ dysfunction are further stratified based upon which organ system is involved. Patients with involvement the spleen, lung liver or hematopoietic system often have worse prognosis.\textsuperscript{16,24,26,27}

Within the last 20 years, several multicenter, randomized therapeutic trials have contributed to a more uniform treatment approach. Patients with the limited cutaneous disease typically require no therapy. If therapy is needed topical steroids may be tried as a first line treatment.\textsuperscript{15,28,29} Patients who have localized bone lesions, curettage is generally sufficient for diagnosis as well as therapy, although some cases may require intralesional steroids or low dose radiation.\textsuperscript{30} Treatment of multiorgan disease is controversial, with some advocating high-dose prednisone as the first line therapy, whereas others suggesting use of single agent chemotherapy.\textsuperscript{28,31,32}

Currently, the LCH III treatment protocol is probably the most common therapeutic strategy used in children with multiorgan involvement. In the future, monoclonal antibodies that target CD1a or CD207 or specific cytokine inhibitors may be employed.\textsuperscript{28,29}

As a result of recent therapeutic trials, it has been shown that the single best prognostic indicator is a patient’s response to chemotherapy during the 6 weeks induction phase.\textsuperscript{26,33,38} Patients who respond to chemotherapy during the 1-6th week of therapy have 88-91\% survival rate, but survival rates drop to 17-34\% in patients who fail to respond. It had been advocated that non responders be identified early so that more aggressive therapy may be employed.\textsuperscript{26,29,33,38}

CONCLUSION

The clinical course of LCH is variable. Patients with unifocal disease generally have an excellent prognosis. After initial bone scanning and radiographic survey to assess the extent of the disease, follow-up studies after treatment should be performed at 6-month intervals for 3 years. If no additional lesions are present at 1-year, the development of subsequent lesions is unlikely. A full recovery is also expected in cases of solitary lymph node involvement or isolated skin disease. Multifocal LCH has a variable prognosis, especially in patients at the extremes of age with pulmonary involvement. The prognosis is worse than in patients with unifocal disease but better than those with disseminated disease. 60\% of patients with multifocal disease have a chronic course, 30\% of patients undergo complete remission, and 10\% of patients with multifocal LCH die from the disease. Response to chemotherapy in
the first 6 weeks (induction therapy) is among the most important prognostic indicators for multifocal LCH. A good response to chemotherapy during this period is associated with significantly improved survival. Conversely, hematologic involvement or involvement of organs such as the lungs, spleen, and liver is associated with worse long-term outcomes. Letterer-Siwe disease (disseminated) has a high mortality rate. The prognosis in these patients depends on the patient's age, the extent of disease, and the degree of organ dysfunction. The mortality rate is 50% or higher. The congenital form of histiocytosis tends to resolve spontaneously within weeks to months. Although the absence of systemic disease at presentation and the tendency of resolution of the disease are favorable, long-term follow-up care to detect evidence of relapse or progression in these patients is suggested. Relapse in these patients has been reported up to 5 years after the initial disappearance of the disease. Cutaneous lesions usually disappear by 3 months, leaving residual hypopigmentation.

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