

# Langerhans cell histiocytosis

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## ABSTRACT

Langerhans cell histiocytosis is a disease caused by the monoclonal proliferation of Langerhans cells. Langerhans cell histiocytosis may involve bone, skin, lymph nodes, liver and spleen, with haematologic changes, and cause fever, malaise and failure to thrive. Up to 50% of patients with either single or multi-organ manifestation of Langerhans cell histiocytosis initially present with cutaneous symptoms. Cutaneous Langerhans cell histiocytosis is heterogeneous in its clinical features and therefore prone to misdiagnosis. We report here a case of Langerhans cell histiocytosis in a child who presented with multiple scalp lesions, in whom a presumptive diagnosis of Langerhans cell histiocytosis is made when characteristic histomorphological features are identified on biopsy tissue, and the definitive diagnosis is established by immunohistochemical examination with appropriate antibodies.

**Keywords:** Langerhans cell histiocytosis, cutaneous lesions, immunohistochemistry

## INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disease. It is a proliferative disorder of the Langerhans cells (LC) and antigen-presenting cell of the dendritic cell line. The trigger factor leading to this proliferation is not yet known. However, it has been proposed that altered environments may lead to immune dysregulation and activate cytokines such as Granulo-Monocyte Colony Stimulating Factor (GM-CSF) and Tumour Necrosis Factor (TNF) alpha, which in turn will cause a monoclonal proliferation of the Langerhans cells.

The clinical presentation can range from localised self-healing lesions to a multi-system involvement with organ dysfunction. LCH is found mostly in children, with an estimated incidence between 0.2 and 2.0 cases per 100,000 children under 15 years of age, and a peak incidence of ages 2–4.<sup>1</sup> We report herein one such rare case with cutaneous lesions and hepatosplenomegaly.

## CASE REPORT

A five-year-old boy presented with multiple raised lesions over the right temporal region for the past three months. This was associated with intermittent bilateral ear discharge and cough in the previous three weeks before presentation. There was no history of fever, chills or vomiting. On examination, a single 2

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x 2cm well defined, firm lobulated nodule with multiple erythematous pustules were seen. The clinical diagnosis of infected sebaceous cyst was given.

Complete blood count and erythrocyte sedimentation rate (ESR) were within normal limits. Liver function tests were abnormal. Total bilirubin was 1.2 mg/dL (range 0.2 to 1.0 mg/dL) and conjugated bilirubin was 0.6 mg/dL (range 0 to 0.3 mg/dL). Alanine aminotransferase was 131 IU/L (range 0 to 40 IU/L) and alkaline phosphatase was 168 IU/L (range 15 to 112 IU/L). Ultrasound scan (USS) revealed a well-defined 1.5 x 1.2cm hypoechoic region over scalp in subcutaneous tissue. USS of abdomen showed hepatosplenomegaly. Skull and chest radiography were normal.

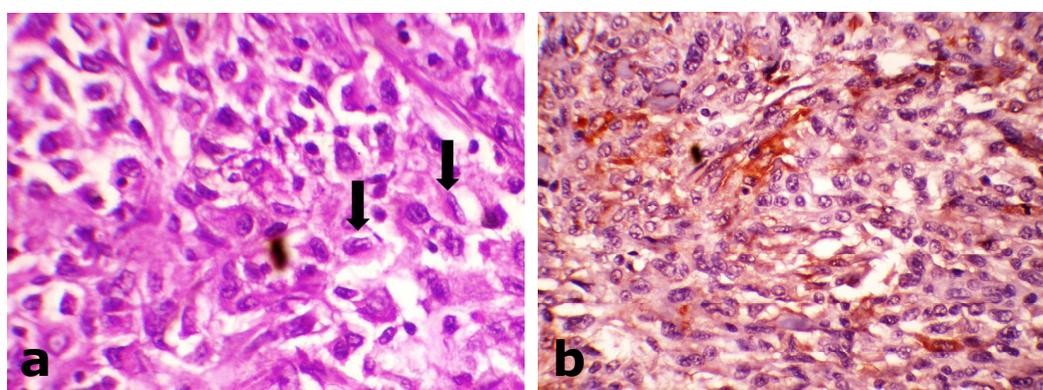
Excision of the swelling was done and tissue biopsy was sent for histopathology examination. Section studied showed skin with epidermis and dermis. The epidermis was keratinised with foci of papillary hyperplasia and irregular rete ridges. The dermis showed diffuse sheets of histiocytes extending to deep dermis. These cells had pink granular and at places vacuolated cytoplasm, irregular, hy-

perchromatic nuclei. Some of these cells showed typical nuclear grooves (Figure 1a). There was focal ulceration and infiltration by these histiocytes. The deeper dermis showed spindloid cells intermingled with fibrocollagenous tissue and histiocytes. Multinucleated giant cells and moderate aggregates of lymphocytes and eosinophils were also seen. A presumptive diagnosis of LCH was established on the basis of characteristic histopathological features. Immunohistochemical stains revealed positivity for S100 protein, CD1 antibody, and was negative for HMB45, confirming the histomorphological diagnosis of LCH (Figures 2 and 3). Electron microscopic examination was not done.

## DISCUSSION

LCH is a rare proliferative disorder of the Langerhans cells. The term encompasses the formerly known entities of Histiocytosis X which included Letterer-Siwe disease, Hand Schuller Christian disease and eosinophilic granuloma. It occurs mostly in children and young adults, with males being affected more frequently than females.<sup>2</sup>

Histiocytes are mononuclear phagocytes found within the epidermis, and are



**Figs. 1:** a) Mononuclear Langerhans cells showing prominent nuclear grooves and folds indicated by arrows (H&E stain, x400), and b) Immunohistochemical stain showing macrophages positivity to antibodies against S100 protein; (x400).

scattered in other organs of the body, where they function normally as tissue macrophages as part of a healthy reticuloendothelial system. The diagnosis of LCH lies mainly in the histopathological identification of the unique histiocyte, the LC, within the diseased tissue.<sup>3</sup> The LC themselves are described as being either elongated or rounded and containing pink or clear cytoplasm. Most notably, the nucleus, crucially, is indented by a central sulcus or groove, giving it the appearance of a 'coffee-bean' shape. This specifically differentiates the LC from the normal histiocyte.<sup>3</sup> The diagnosis of LCH has been based on a histopathological pattern in biopsy specimens showing mono- or multi-nucleated LCs, histiocytes, and eosinophils and further confirmed by immunohistochemical evaluation using S100 protein and CD1 antibody as in the present case.<sup>4</sup>

Although electron microscopy is the 'gold standard' for identification of the pathognomonic Birbeck granules in tissues, this technique has its limitations in terms of availability and cost. It is reported that Langerin (CD207) is a new monoclonal marker specific for LC.<sup>3</sup>

LCH most commonly presents as unifocal involvement as Eosinophilic granuloma or a solitary bone lesion in patients usually 5–15 years old. Hand-Schüller-Christian disease is characterised by multifocal bone lesions and extraskeletal involvement of the reticuloendothelial system (RES) and pituitary gland, usually seen in children 1–5 years old.<sup>5</sup> In 10% of cases, a classic 'Christian triad' of symptoms has been described of diabetes insipidus, cranial bony lesions and exophthalmoses.<sup>3</sup> In Letterer-Siwe disease, there is

disseminated involvement of the RES with a fulminant clinical course in children less than two years old. It shows systemic involvement characterised by extensive skin eruptions, erosive osteolytic lesions, pulmonary infiltrations and hepatosplenomegaly.<sup>3, 5</sup> This disease has preponderance in males, sometimes as high as 60–70%, and is more common in Caucasians of northern European descent.<sup>6</sup> The most common presentation is unifocal (about 65%) and the bone is the most frequently affected tissue making up 90% of such cases. The most common site involved is the skull and accounts for more than 50% of cases. The location of lesions is similar in unifocal and in multifocal disease (about 35% of presentations), with 60% affecting only bone, 25% affecting bone and soft tissue, and 15% affecting only soft tissue.<sup>1</sup> Our case presented with cutaneous lesions, and hepatosplenomegaly without bone involvement.

The key diagnostic feature in any biopsy for histological study is the pathognomonic evidence of LCs, which shows positive immunostaining for CD1a and S-100 markers. The diagnostic gold standard is the identification of characteristic ultrastructural features designated as Birbeck granules, which are 34 nm wide tubular or tennis-racket-shaped intracytoplasmic pentalaminar structures with a zipper-like central core.<sup>4, 7, 8</sup>

Due to the relative paucity of patients with LCH, there is no current standard treatment regime and management is usually individualised. Treatment options include surgery, chemotherapy and radiotherapy, either individually or in combination, according to the system involved, extent and severity of

the disease. All patients with LCH require long-term follow-up to identify disease recurrence and late-stage complications.

In conclusion, we wish to emphasize the important role of the biopsy of the lesion in a child with multiple scalp lesions. A definitive diagnosis of LCH can be made by thorough morphological examination of the characteristic LCs in tissue sections, and immunohistochemical demonstration of antigenic markers that react with CD1 glycoprotein and the S100 protein. The clinical and histomorphological findings coupled with awareness of the condition are crucial in establishing a definitive diagnosis.

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