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Case Report

A Case Series of Four Children with Langerhans Cell Histiocytosis

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Abstract

Langerhans Cell Histiocytosis (LCH) is a rare pediatric disorder characterized by abnormal proliferation of Langerhans cells originating from the bone marrow. This case series highlights four pediatric presentations of LCH, emphasizing its clinical diversity and diagnostic challenges. The cases describe varied manifestations, including bony swellings, skull deformities, scalp lesions and systemic symptoms, which were often misdiagnosed due to non-specific clinical features. Histopathological analysis, including CD1a positivity and immunohistochemistry, played a pivotal role in confirming LCH diagnosis, supported by imaging modalities such as X-rays, CT and MRI.

The treatment approach primarily involved systemic chemotherapy, with protocols including vinblastine and prednisolone, following the HISTSOC-LCH-III guidelines. Surgical interventions, such as curettage and biopsy, were also employed for lesion management. Outcomes varied, with most patients showing significant clinical improvement and remission following comprehensive treatment. However, challenges remain, particularly in cases complicated by late-onset neurodegenerative syndromes or loss to follow-up.

This case series underscores the importance of considering LCH in differential diagnosis for pediatric head and neck swellings, given its rarity and lack of distinctive clinical features. Timely diagnosis, multidisciplinary intervention and adherence to treatment protocols are crucial for favorable outcomes. Further research is warranted to address unresolved issues, including the management of progressive neurodegenerative complications. This series highlights the need for broader awareness of LCH among clinicians to ensure accurate diagnosis and effective treatment strategies.

Keywords: Langerhans Cell Histiocytosis; Head and Neck Swellings; Diagnosis; Neurodegenerative Syndromes

Introduction

Langerhans Cell Histiocytosis (LCH), previously called histiocytosis X, is a rare blood disorder marked by abnormal growth and spread of Langerhans cells originating from the bone marrow [1]. It most commonly affects children aged 1 to 5 years. The childhood histiocytes constitute a diverse group of disorders that are frequently severe in their clinical expression. These disorders are individually rare and are grouped together because they have in common a prominent proliferation or accumulation of cells of the monocyte-macrophage system of Bone marrow (myeloid) origin. Three classes of childhood histiocytes are defined, based on histopathologic findings. The best known is Langerhans Cell Histiocytosis (LCH), LCH includes the clinical entities of bone or skin limited disease, eosinophilic granuloma, Hand-Schuller-Christian disease and Letterer-siwe disease.

The exact causes of this condition are not fully elucidated [2]. However, the hallmark of LCH in all forms is the presence of a clonal proliferation of cells of the monocyte-dendritic cell lineage containing the characteristic electron microscopic findings of a Langerhans cell. The Birbeck granule. The birbeck granule expresses a newly characterized antigen, Langerin (CD207). This

expression becomes an additional diagnostic marker. The definitive diagnosis of LCH is established by demonstrating CD1a positivity of lesioned cells. Importantly an activating somatic mutation of the BRAF gene(V600E) has been identified [3].

Case Report

Case 1

A 5-month-old male child from Arunachal Pradesh presented to us with complaints of two painful swellings over the left supra-orbital region and the right maxillary region for 6 months. Total counts were slightly elevated. Contrast-Enhanced Computed Tomography (CECT) of the head and para-nasal sinuses suggested lymphoma/leukemia. Abdominal ultrasound did not reveal any signs of Langerhans Cell Histiocytosis (LCH) in any other organ. Incisional biopsy and curettage of the lesions were performed under general anesthesia and specimens were sent for Histopathological Examination (HPE). Reports revealed a case of eosinophilic granuloma/Langerhans cell histiocytosis. The patient underwent chemotherapy, receiving weekly injection of Vinblastine 6 mg/m^2 for 7 weeks, following the HISTSOC-LCH-III (NCT00276757) study, along with daily oral prednisolone 40 mg/m^2 for 4 weeks, tapered over 2 weeks. Subsequently, prednisolone was given for 5 days at 40 mg/m^2 every 3 weeks with vinblastine injection. Chemotherapy was administered for a total of 12 months as per the protocol, resulting in regression of the lesions. Follow-up every 3 months included a repeat CECT at 3 months, which showed near-total regression of the previous soft tissue density mass lesions in the facio-maxillary regions compared to the previous CT. Residual bony erosions in the left supraorbital, right inferior lateral orbital wall and right zygoma subsided after one year of complete chemotherapy. The patient was followed up and showed no signs of recurrence at 3 years of age (Fig. 1).

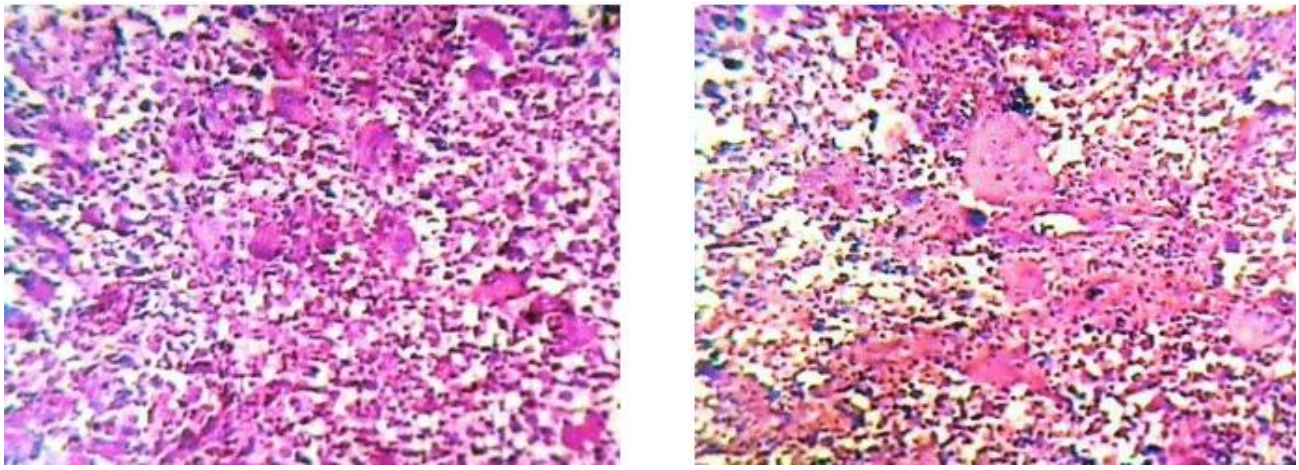


Figure 1: Histopathology of Case 1.

Case 2

A 3-year-old male child from Arunachal Pradesh presented with bony swelling and deformity across the entire skull. No other lesions were observed in the orbit or maxilla. The patient reported no pain, fever or other complaints besides the swelling. Blood parameters were within normal ranges. X-ray revealed multiple lytic lesions of the skull and MRI confirmed multiple eroded lesions over the entire skull bone. The patient underwent surgery, curettage was performed and the specimen was sent for histopathological examination, revealing a case of Langerhans Cell Histiocytosis (LCH).

Immunohistochemistry reported S-100 negative. The patient received chemotherapy for a total of 12 months, involving weekly Vinblastine injections at 6 mg/m^2 for 7 weeks and daily oral prednisolone at 40 mg/m^2 for 4 weeks, tapered over 2 weeks. This was followed by oral prednisolone at 40 mg/m^2 for 5 days every 3 weeks with Vinblastine injections. The patient was followed up for 2 years and showed no signs of disease recurrence (Fig. 2,3).

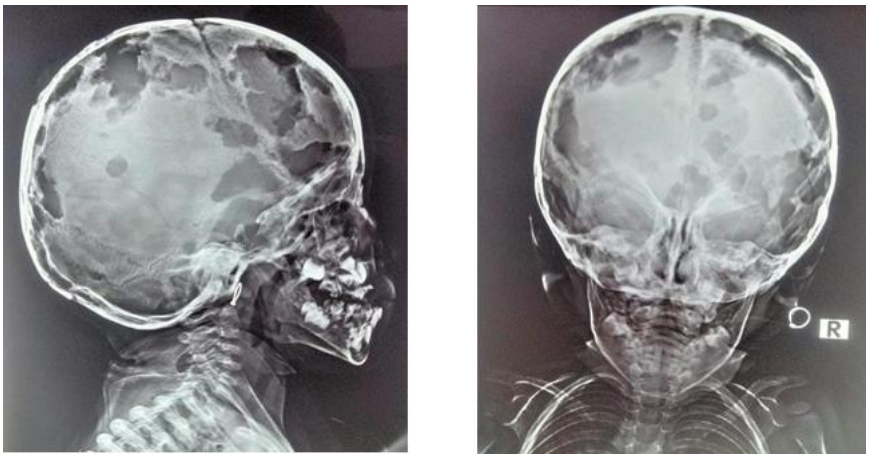


Figure 2: Pre-treatment imaging of Case 2.

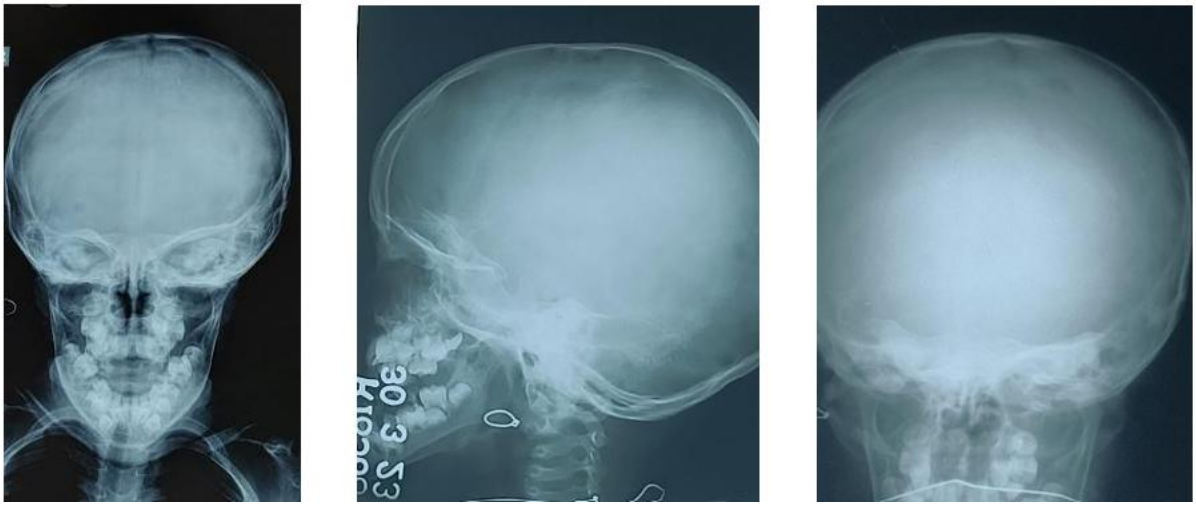


Figure 3: Post-treatment imaging of Case 2.

Case 3

A 7-year-old male child from Assam presented with extensive multiple neck swellings for 2 months. A biopsy was performed and sections from the tissue revealed fibrous tissue infiltrated with eosinophils, neutrophils and atypical cells displaying a mild degree of nuclear atypia. Some cells exhibited folding and elongated nuclei with longitudinal grooves, while sections from the bony tissue showed lamellar bone with fibrosis, all consistent with Langerhans Cell Histiocytosis (LCH). Unfortunately, the patient did not return for treatment and was lost to follow-up.

Case 4

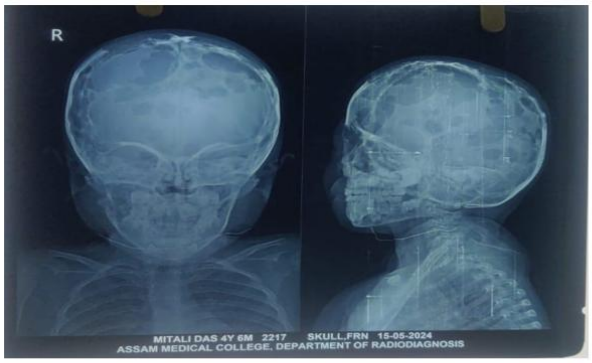
A 4 years old female presented with increased itching in the scalp from the past 2-3 months , the followed by protrusion of eyeballs for 2-3 months and history of increased frequency of micturition and history of increased intake of water from the past 1 months and with multiple soft swelling on the scalp region ,there is history of extensive flaky scalp skin(seborrhea) since birth for which they consulted local physicians multiple times ,Institutional delivered child with 2.6 kg of birth weight with no history of NICU admission with normal developmental milestones attained as per peers group. On evaluation vitals were normal, soft cystic lesion noted over the scalp with active scalp skin lesion were seen with cradle cup appearance with easily pluckable hairs, Bilateral proptosis was noted on clinical examination.

On investigations it was seen that

- CBC, PBS, RFT, LFT, S Electrolytes, Thyroid profile, uric acid, LDH, iron profile, coagulation profile were within normal limit ,ESR and CRP were raised
- X-ray skull suggestive of multiple lytic lesions, X ray of other long bones were within normal

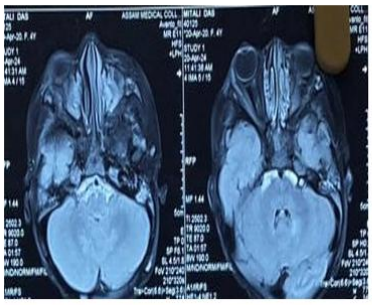
- USG B scan suggestive of Bilateral thickened optic nerve
- MRI Brain reveals T1 weighted imaging showing hyperintensities in the diploic space in bilateral fronto-parieto-occipital bones. T2/FLAIR imaging hyperintensities are noted involving dentate nucleus, MRI orbit reveals bilateral proptosis is noted with normal signal intensity in bilateral optic nerve
- Punch biopsy of the skull bone tissue shows a tumour consisting of sheets of polygonal cells with oval nuclei with nuclear grooving with plenty of inflammatory cells of eosinophils and scattered foreign body giant cells are seen S/o Langerhans cell histiocytosis. Sections from the lymph nodes show reactive changes with sinus histiocytosis Biopsy sample from skull bone tissue was positive for CD1a cells

The patient received chemotherapy for a total of 12 months, involving weekly Vinblastine injections at 6 mg/m² for 7 weeks and daily oral prednisolone at 40 mg/m² for 4 weeks, tapered over 2 weeks. This was followed by oral prednisolone at 40 mg/m² for 5 days every 3 weeks with Vinblastine injections (Fig. 4).

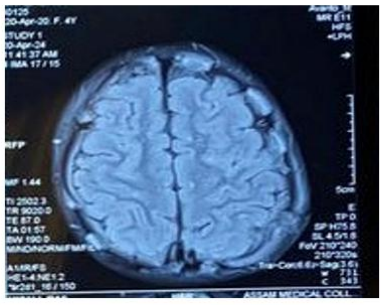


X- ray skull showing multiple lytic lesion .

T2/FLAIR HYPERINTENSITIES IN THE DENTATE NUCLEUS



SHOWING MULTIPLE EOSINOPHILIC GRANULOMA



Punch biopsy of the skull lesion and lymph node -

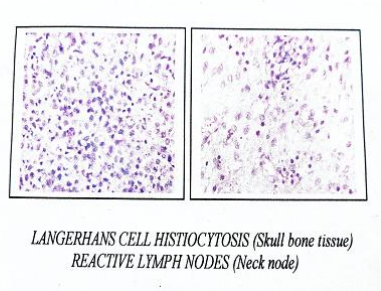


Figure 4: Biopsy details of the skull lesion and lymph node.

Discussion

Langerhans Cell Histiocytosis (LCH), formerly known as histiocytosis X, encompasses a range of clinicopathological conditions characterized by histologically evident monoclonal proliferation of histiocyte-like cells, accompanied by varying eosinophils, lymphocytes, plasma cells and multinucleate giant cells. These histiocytes are identified as Langerhans cells, normally present in the epidermis, mucosa, lymph nodes and bone marrow, with their usual function being antigen processing and presentation to T- lymphocytes. In LCH, the literature suggests a monoclonal proliferation of these cells, leading to the destruction of both hard and soft tissues. Traditionally considered a reactive immune regulation disorder, recent evidence points to a neoplastic nature with the monoclonal proliferation of lesional cells. Langerhans Cell Histiocytosis (LCH) is a rare disease, with an incidence of 1 in 560,000. It exhibits a higher prevalence in males compared to females, with reported ratios ranging from 1.1:1 to 4:1 [4]. The most frequent clinical presentations involve solitary or multiple bone lesions, commonly affecting the skull, jaws, ribs and vertebrae. Langerhans cell histiocytosis has an extremely variable presentation. The skeleton is involved in 80% of patients, approximately 50% patients have skin involvement. Localized or disseminated lymphadenopathy seen approximately in 33% patients and 20% of patients have Hepatosplenomegaly,10-15% of patients have pulmonary infiltrates [5].

The disease is broadly classified into three disorders based on age and clinical presentation. These variants are (a) Eosinophilic granuloma, a chronic localized form with skeletal involvement (single or multiple), typically observed in adults; (b) Letterer-Siwe disease, an acute disseminated form with multiple system involvement, most commonly in infants; (c) Hand-Schuller-Christian disease, a chronic disseminated form with both skeletal and extra-skeletal lesions [5]. Additionally, a congenital self-resolving form known as Hashimoto- Pritzker disease has been reported. Each of these variants is then clinically staged according to the Greenberg, et al., clinical staging system.

Since there are no distinctive clinical or radiographic features of Langerhans Cell Histiocytosis (LCH), the diagnosis relies on histopathological examination. Radiological features are evident due to the bone destruction caused by Langerhans cells, a common characteristic across all three forms of LCH.

The treatment approach for Langerhans Cell Histiocytosis (LCH) depends on factors such as the disease's pathogenesis, the patient's age and the extent of lesion dissemination. Localized accessible lesions, like those in the maxilla and mandible, may be managed with surgical curettage or excision. Radiation, although posing a malignancy risk in younger patients is considered for less accessible lesions. Intralesional corticosteroids, such as prednisolone can be effective for some patients with localized lesions. Systemic chemotherapy is required for multisystemic disease, commonly involving combinations of corticosteroids, vinblastine, etoposide, cytarabine, methotrexate and others. A combination of vincristine and prednisone is used to reduce recurrence risk. The HISTSOC-LCH-III trial recommends 12 months of treatment with weekly vinblastine and prednisone for good responders [6].

Prognostic criteria for Langerhans Cell Histiocytosis (LCH) encompass (1) age, with children under 2 years generally indicating disseminated disease and a poorer prognosis; (2) the number of sites involved, where multisystem disease is associated with a poorer prognosis and (3) the presence of organ dysfunction, contributing to an unfavorable prognosis if present.

Conclusion

This case series emphasizes the significance of including Langerhans Cell Histiocytosis (LCH) in the differential diagnosis for pediatric head and neck swellings, given its frequent misdiagnosis due to the lack of characteristic clinical features. Langerhans cell histiocytosis is a subset of group of disorder which are individually rare and grouped together. This group of disorder are difficult to distinguish clinically, accurate diagnosis is essential for specific treatment progress and needs comprehensive evaluation of biopsy specimen.

- Single system involvement LCH and low risk multiorgan involvement LCH when treated with proper chemotherapy have been found to be very effective
- An unresolved problem is treatment of (usually late onset) severe, progressive and intractable LCH associated neurodegenerative syndrome

Timely diagnosis, coupled with surgical intervention and additional therapies, is crucial for achieving better outcomes.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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