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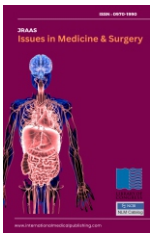

Case Report

Section: Pathology

Langerhans Cell Histiocytosis Presenting Primarily as Cervical Lymphadenopathy: A Diagnostic Challenge in Tuberculosis-Endemic Regions

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HIGHLIGHTS

- Rare cervical presentation
- FNAC enables early diagnosis
- Immunohistochemistry confirms LCH
- Skull lesions detected
- Early diagnosis improves outcomes

Key Words:

Langerhans cell histiocytosis
Cervical lymphadenopathy
Fine needle aspiration cytology
Immunohistochemistry
Diagnostic challenge
Pediatric pathology

ABSTRACT

Introduction: Langerhans Cell Histiocytosis (LCH) is an uncommon clonal proliferative disorder of antigen-presenting dendritic cells, predominantly affecting children. It presents with a wide clinical spectrum, ranging from localized bone or skin involvement to disseminated multisystem disease. Cervical lymphadenopathy is unusual and often mimics infectious or lymphoproliferative conditions, making diagnosis challenging. **Aim & Objective:** To highlight an unusual presentation of LCH as bilateral cervical lymphadenopathy with skull lesions, and to emphasize the diagnostic utility of fine needle aspiration cytology (FNAC) with cell block immunohistochemistry in distinguishing it from mimickers. **Case Presentation:** A one-and-a-half-year-old girl presented with bilateral cervical lymphadenopathy and intermittent fever for four months. Clinical and radiological evaluation was performed. FNAC from cervical lymph nodes with cell block preparation and immunohistochemistry was undertaken. **Results:** Cytological smears showed numerous atypical histiocytes with vesicular nuclei, nuclear grooves, and abundant pale cytoplasm, accompanied by eosinophils, lymphocytes, and multinucleated giant cells. Immunohistochemistry revealed positivity for S100 and CD68, supporting the diagnosis of LCH. Radiological imaging demonstrated lytic lesions in the frontal and parietal skull bones. Based on cytomorphology, immunohistochemistry, and radiological correlation, a final diagnosis of LCH was made. **Conclusion:** This case highlights the diagnostic challenge posed by LCH with unusual lymph node involvement. Its clinical resemblance to tuberculosis, lymphoma, or Rosai-Dorfman disease often leads to misdiagnosis. FNAC, aided by immunohistochemistry, plays a pivotal role in early recognition. Early diagnosis is crucial as clinical behavior ranges from self-limiting lesions to aggressive multisystem disease requiring chemotherapy. Awareness of atypical presentations prevents diagnostic delays and improves patient outcomes.

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INTRODUCTION

Langerhans Cell Histiocytosis (LCH) is a rare clonal proliferative disorder characterized by the accumulation of Langerhans cells, which are specialized dendritic cells of bone marrow origin involved in antigen presentation. The condition has historically been known by various terms, including eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease, which are now recognized as part of the LCH spectrum. The incidence is estimated at 2–5 cases per million children annually, making it an uncommon pediatric entity with diverse clinical presentations [1,2].

LCH may present as localized disease involving a single system (such as bone or skin) or as a multisystem disorder with potentially life threatening organ involvement. The most affected sites are bone (particularly the skull, ribs, and long bones) and skin, while lymph node, liver, spleen, and lung involvement occurs less frequently. The biological behavior of the disease is unpredictable, ranging from indolent self-limited lesions to aggressive disseminated disease requiring systemic chemotherapy [3].

The pathogenesis of LCH is still not fully understood. Earlier theories suggested a reactive disorder, but accumulating evidence supports its neoplastic nature, with identification of activating mutations in the MAPK pathway, especially BRAF V600E mutations, in a substantial subset of patients. These findings provide further insight into its clonal nature and potential therapeutic targets [4].

Clinically, the diagnosis of LCH can be delayed or obscured when its protean manifestations are overshadowed by prominent, distracting symptoms. In endemic regions, striking cervical lymphadenopathy is reflexively attributed to tubercular lymphadenitis. Similarly, Rosai-Dorfman disease and malignant lymphomas enter the differential diagnosis due to overlapping clinical features. When lymph node enlargement is the most visually prominent and concerning symptom for the parents, it can clinically mask the presence of more classic LCH signs, such as localized bone swellings. [5,6].

This clinical diversion poses a significant diagnostic challenge. While fine needle aspiration cytology (FNAC) serves as a rapid, frontline diagnostic tool for evaluating cervical lymphadenopathy in children, cytological findings of LCH can overlap with other histiocytic or lymphoproliferative disorders. Recognition of the classical cytological features particularly the presence of cells with nuclear grooves and a “coffee-bean” appearance combined with immunohistochemical markers on cell block preparations, becomes essential to redirect the diagnosis. The case presented herein involves a young child where prominent bilateral cervical lymphadenopathy initially diverted clinical suspicion toward tuberculosis, masking the underlying classic skull lesions of LCH [7].

The case presented herein involves a young child with bilateral cervical lymphadenopathy and associated skull swellings, initially raising suspicion for tuberculosis or lymphoma. FNAC smears revealed characteristic features of LCH, which were

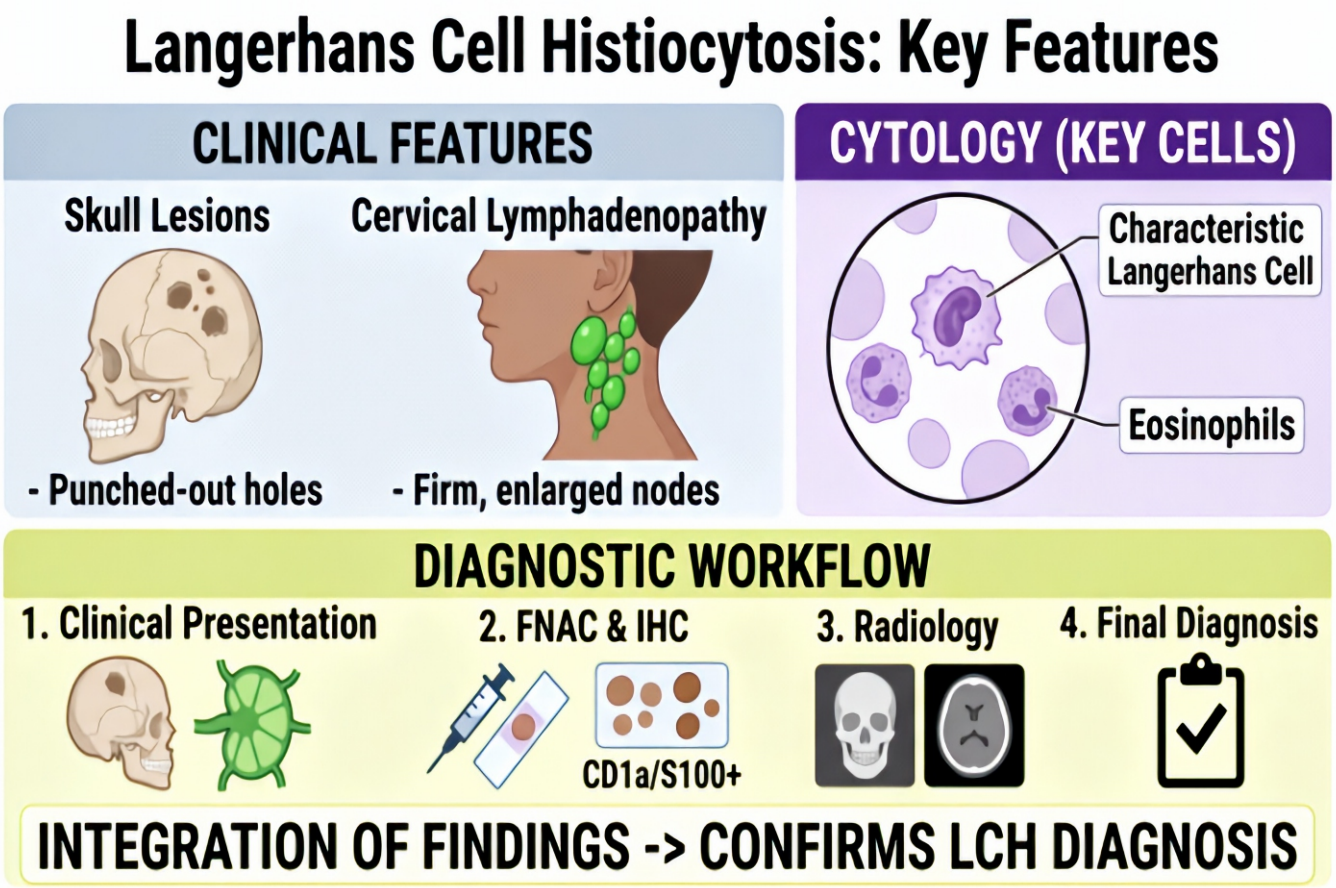

Figure 1: Clinical, radiological, and cytopathological features of Langerhans cell histiocytosis (LCH) in a child.

confirmed by immunohistochemistry and radiology. This unusual presentation emphasizes the importance of considering LCH in the differential diagnosis of pediatric lymphadenopathy, particularly when accompanied by bony lesions. Early diagnosis has significant prognostic implications, as localized disease may require minimal intervention, while multisystem disease necessitates aggressive therapy [8]. **Figure 1.** Schematic illustration of pediatric Langerhans cell histiocytosis (LCH) showing osteolytic skull lesions, cervical lymphadenopathy, characteristic Langerhans cells with coffee-bean nuclei on FNAC, and the diagnostic workflow including cytology, IHC confirmation, and radiological correlation.

This case underscores the role of cytology and ancillary techniques in overcoming diagnostic pitfalls and highlights the need for heightened clinical suspicion in atypical presentations of LCH.

CASE PRESENTATION

A one-and-a-half-year-old girl presented with a history of bilateral cervical swellings and intermittent fever persisting for four months. The parents reported gradual enlargement of cervical lymph nodes, accompanied by occasional irritability and poor appetite. There was no history of weight loss, night sweats, or cough. On clinical examination, multiple bilateral cervical lymph nodes were palpable as shown in **Figure 2.** These nodes were firm, tender, slightly mobile, and the largest measured approximately 2.5 × 1.5 cm. In addition, multiple ill-defined soft tissue swellings were noted over the frontal and parietal regions of the skull. Hepatosplenomegaly was absent. Laboratory investigations revealed microcytic hypochromic anemia on peripheral smear. White blood cell count and differential count were within normal limits.

No atypical cells were observed. FNAC was performed from the cervical lymph nodes, and smears were prepared using Hematoxylin and Eosin (H&E) and Leishman stains.

As shown in **Figures 3a** and **3b**, the smears were highly cellular, showing numerous atypical histiocytes as the predominant cell type. These cells appeared singly and in loose clusters, intermixed with eosinophils, neutrophils, lymphocytes, plasma cells, foamy histiocytes, and multinucleated giant cells.

As shown in **Figure 4**, the atypical histiocytes were large, with moderate to abundant pale blue cytoplasm and eccentric to central round-to-oval vesicular nuclei. Nuclear indentations and grooves imparting a “coffee-bean” appearance were conspicuous. Nucleoli were absent. Marked pleomorphism was noted, with some cells being mononuclear and others binucleate or multinucleated. Multinucleated reactive histiocytic giant cells were also present but could be distinguished morphologically.

As shown in **Figures 5 & 6**, cell block preparation was performed, and immunohistochemistry revealed positivity for S100 and CD68, supporting the diagnosis of LCH. CD1a, a specific marker for Langerhans cells, could not be performed due to technical limitations.

As shown in **Figures 7a & 7b**, radiological evaluation included a plain X-ray of the skull, which revealed lytic lesions corresponding to the frontal and parietal swellingsComputed tomography (CT) confirmed “punched-out” lytic lesions with associated homogenous soft tissue swelling of the scalp but no dural involvement. No additional systemic lesions were detected. Based on the integration of clinical presentation, cytomorphological features, immunohistochemi-stry, and radiological findings, a final diagnosis of Langerhans Cell Histiocytosis presenting with bilateral cervical lymphadenopathy and skull involvement was made.

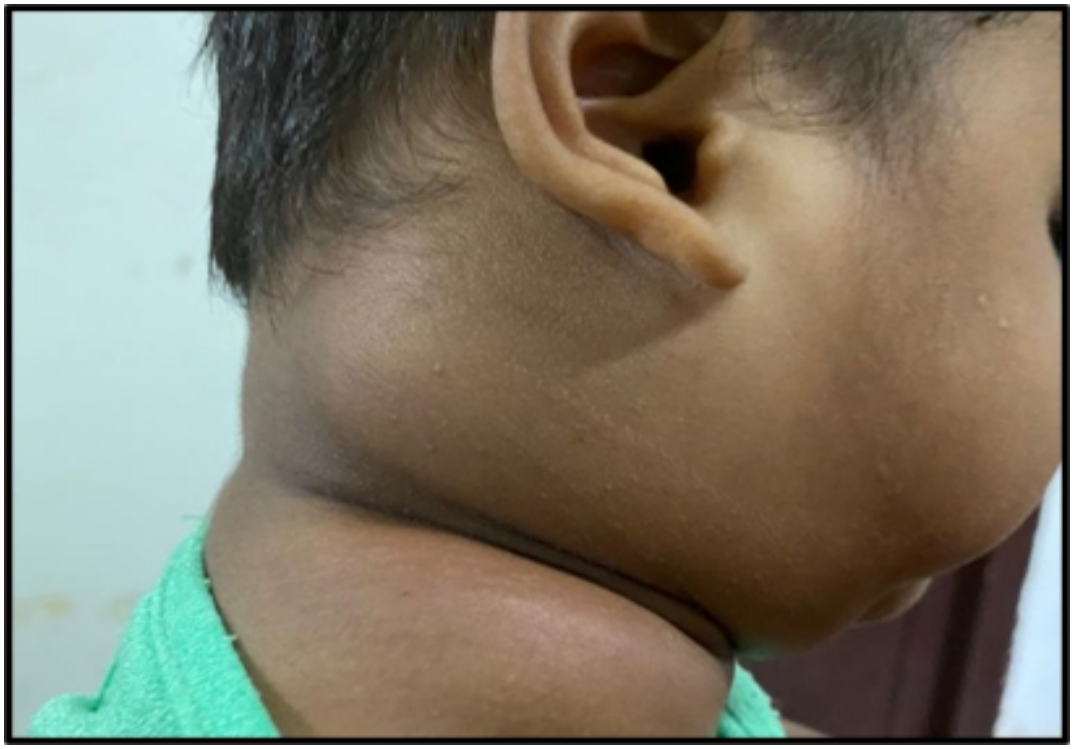

Figure 2: Bilateral cervical lymphadenopathy in a child with Langerhans Cell Histiocytosis

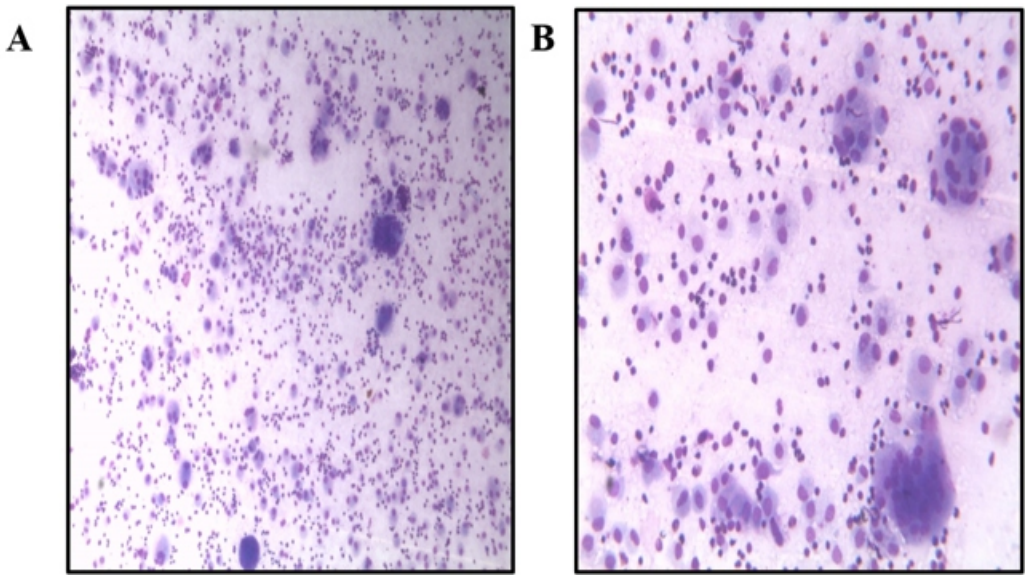

Figure 3: (A) FNA smear from right cervical lymph nodes (Leishman stain 4x); (B) FNA smear from left cervical lymph nodes (Leishman stain 10x)

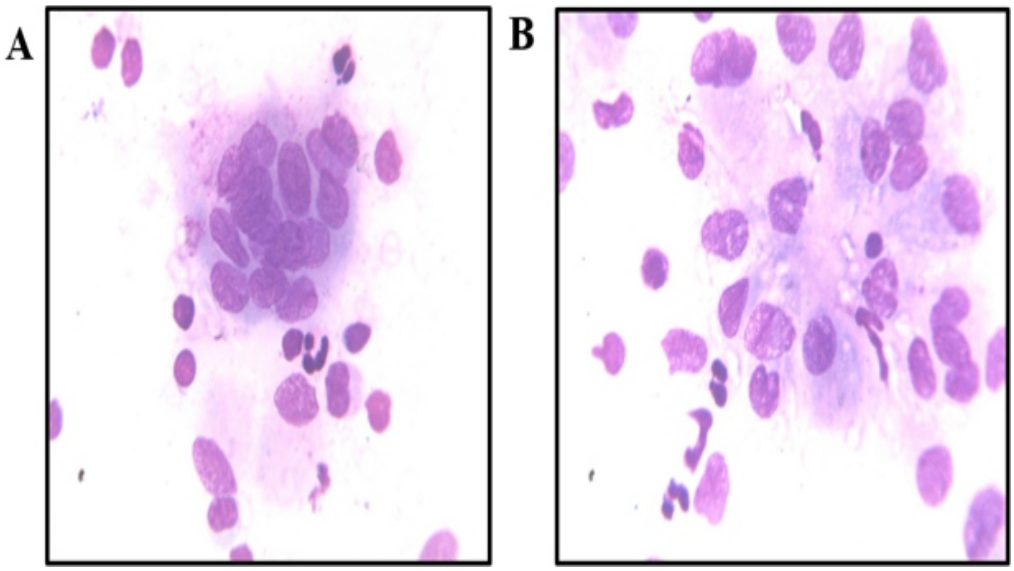

Figure 4: FNAC smears show nuclear grooving and indentations (Leishman stain 40x)

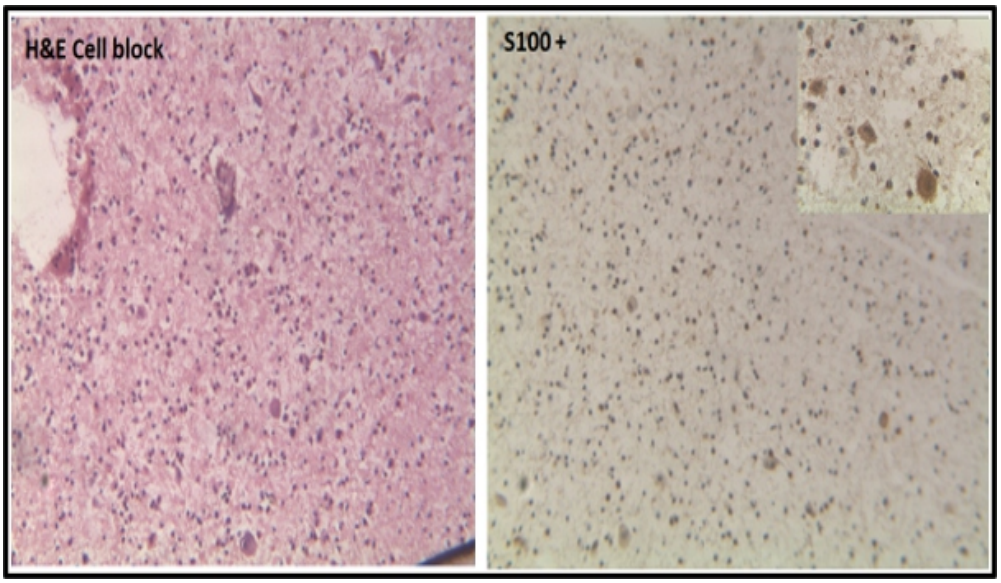

Figure 5: Immunohistochemistry on Cell Block

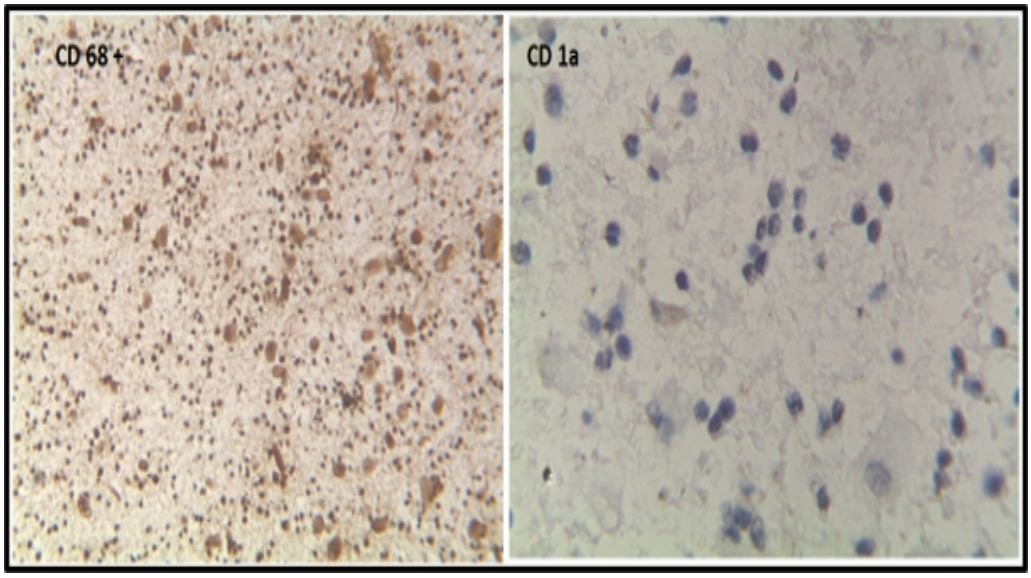

Figure 6: Immunohistochemistry On Cell Block

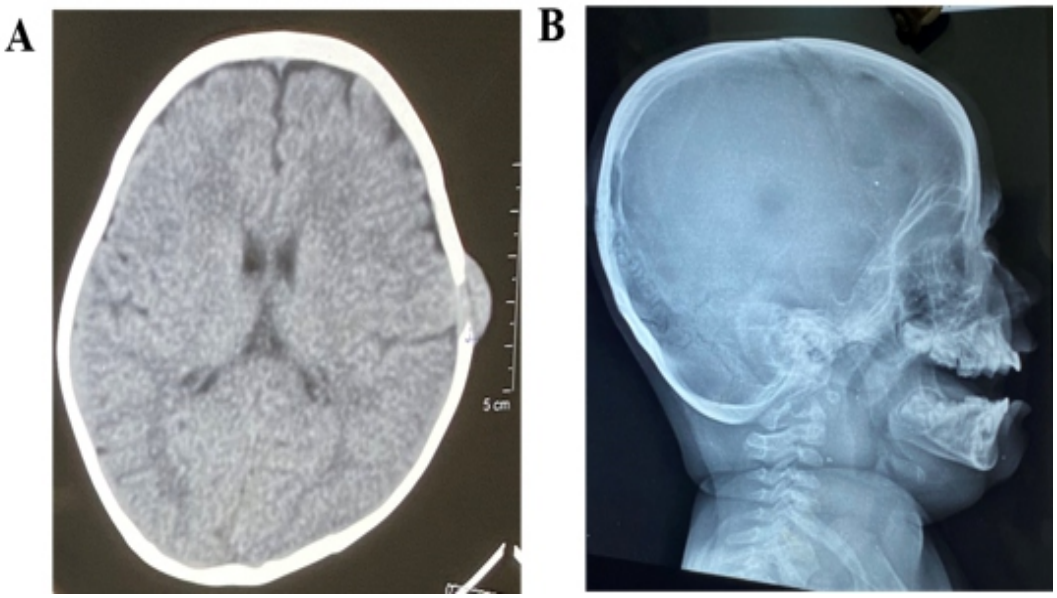

Figure 7: (A) CT scan of the head showing punched-out lytic lesion in the parietal bone with associated soft tissue swelling in Langerhans Cell Histiocytosis; (B) Lateral skull X-ray showing multiple punched-out lytic lesions in the calvarium consistent with Langerhans Cell Histiocytosis

RESULTS

A one-and-a-half-year-old girl presented with bilateral cervical lymphadenopathy and intermittent fever of four months' duration. Clinical examination revealed multiple bilateral cervical lymph nodes that were firm, tender, slightly mobile, with the largest measuring 2.5 × 1.5 cm, along with multiple ill-defined soft tissue swellings over the frontal and parietal regions of the skull; hepatosplenomegaly was absent. Hematological evaluation showed microcytic hypochromic anemia, while total and differential leukocyte counts were within normal limits with no atypical cells. Fine-needle aspiration cytology (FNAC) of the cervical lymph nodes demonstrated highly cellular smears composed predominantly of atypical histiocytes arranged singly and in loose clusters, admixed with eosinophils, neutrophils, lymphocytes, plasma cells, foamy histiocytes, and multinucleated giant cells. The atypical histiocytes exhibited moderate to abundant pale blue cytoplasm and round-to-oval vesicular nuclei with characteristic nuclear grooves and indentations, imparting a "coffee-bean" appearance, with occasional binucleate and multinucleated forms. Cell block immunohistochemistry showed positivity for **S100** and **CD68**, supporting the diagnosis of Langerhans Cell Histiocytosis, although **CD1a** staining could not be performed due to technical limitations. Radiological evaluation revealed characteristic frontal and parietal "punched-out" osteolytic skull lesions with associated homogeneous scalp soft tissue swelling and no dural involvement or additional systemic lesions. Based on the concordant clinical, cytomorphological, immuno-histochemical, and radiological findings, a final diagnosis of Langerhans Cell Histiocytosis with cervical lymph node and skull involvement was established.

DISCUSSION

Langerhans Cell Histiocytosis is a rare hematopoietic neoplasm with variable clinical behaviour. Its etiology remains incompletely understood, but evidence of clonal proliferation and MAPK pathway mutations has led to its classification as a neoplastic disorder rather than a reactive condition [9].

The clinical spectrum of LCH is broad, with unifocal bone lesions and cutaneous involvement being the most common presentations. While involvement of lymph nodes occurs, it rarely dominates the initial clinical picture. In the present case, the sheer prominence of the bilateral cervical lymphadenopathy acted as a clinical distractor. In tuberculosis-endemic areas, such striking lymph node enlargement strongly biases initial clinical suspicion toward tubercular lymphadenitis, inadvertently diverting attention from the associated, albeit less conspicuous, soft tissue swellings over the skull. However, the absence of granulomas, caseous necrosis, and epithelioid cells on cytology successfully argued against tuberculosis. Lymphoma was similarly excluded due to the lack of a monomorphic lymphoid population or Reed-Sternberg cells. Rosai-Dorfman disease was also ruled out by the absence of emperipolesis and prominent nucleoli, and the distinct presence of characteristically grooved nuclei. Ultimately, the cytological findings prompted a re-evaluation of the skull swellings, which radiological imaging confirmed as "punched out" lytic lesions, a classic hallmark of LCH [10,11]. The hallmark cytological features of LCH include large atypical histiocytes with abundant cytoplasm and vesicular nuclei showing prominent indentations and grooves (“coffee-bean nuclei”). A mixed inflammatory background rich in eosinophils further supports the diagnosis. Ancillary tests, especially immunohistochemistry, are crucial. The co-expression of CD1a, S100, and Langerin is diagnostic. In this case, positivity for S100 and CD68, along with morphology, sufficed for confirmation, although CD1a could not be tested [12,13]. Radiological correlation strengthens the diagnosis. The presence of lytic skull lesions alongside lymphadenopathy reinforced the suspicion of LCH. Such lesions are frequently described as “punched-out” and are characteristic of the disease [14]. Management of LCH depends on the disease extent. Localized lesions may regress spontaneously or require minimal therapy, such as curettage or steroids. Systemic involvement, however, necessitates chemotherapy, often using vinblastine and corticosteroids as first-line agents. Prognosis is favourable in localized disease but guarded in multisystem involvement, particularly with liver, lung, or bone marrow infiltration [15].

This case emphasized the importance of considering LCH in the differential diagnosis of persistent paediatric lymphadenopathy. Early recognition through FNAC and immunohistochemistry enables prompt initiation of therapy, potentially preventing progression to multisystem disease [16].

CONCLUSION

Langerhans Cell Histiocytosis is a rare paediatric disorder with a wide clinical spectrum. Its unusual presentation as bilateral cervical lymphadenopathy with skull lesions poses a significant diagnostic challenge, often mimicking infectious or lymphoproliferative disorders. FNAC, coupled with immunohistochemistry and radiological evaluation, plays a pivotal role in establishing the diagnosis. Early recognition is crucial, as clinical outcomes vary depending on disease extent. This case highlights the importance of considering LCH in differential diagnoses of paediatric lymphadenopathy, particularly in endemic regions, to ensure timely diagnosis and appropriate management, thereby improving prognosis and preventing disease progression.

LIMITATIONS & FUTURE PERSPECTIVES

Despite the classical cytomorphological and radiological findings, we acknowledge certain limitations in the diagnostic workup of this case. The definitive immunohistochemical markers for Langerhans cells, namely CD1a and Langerin (CD207), could not be performed due to technical and resource limitations. Furthermore, while recent advances highlight the neoplastic nature of LCH driven by MAPK pathway mutations (such as BRAF V600E), molecular profiling was unavailable. Nevertheless, the diagnosis was robustly established by correlating the striking cytomorphology specifically the hallmark "coffee-bean" nuclei and the positivity for S100 and CD68 on the cell block, with the classic "punched-out" lytic skull lesions observed radiologically. This demonstrates that in resource-constrained scenarios, careful integration of cytological, available immunohistochemical, and radiological data can confidently overcome diagnostic limitations. Future studies should incorporate multicentre designs with larger populations to enhance validity, assess long-term outcomes, and investigate advanced diagnostic & management approaches. Such efforts will improve overall patient care & help minimize complications.

CLINICAL SIGNIFICANCE

This case underscored the diagnostic challenge posed by Langerhans Cell Histiocytosis when it presents with unusual features such as cervical lymphadenopathy. In tuberculosis-endemic areas, such a presentation is easily mistaken for tubercular lymphadenitis, leading to misdiagnosis and inappropriate therapy. Similarly, overlapping features with Rosai-Dorfman disease and lymphoma can complicate diagnosis. Fine needle aspiration cytology, though minimally invasive, provides critical clues by demonstrating atypical histiocytes with characteristic nuclear grooves. The addition of immunohistochemistry on cell block preparations (S100, CD1a, Langerin) significantly enhances diagnostic accuracy. Radiological correlation with lytic lesions further supports the diagnosis. Early and accurate recognition of LCH is clinically significant as it directly influences management decisions. Localized disease may be self-limiting, whereas multisystem involvement requires aggressive chemotherapy. Awareness of such unusual presentations among clinicians and pathologists is essential for timely diagnosis and optimal patient outcomes.

ABBREVIATIONS

LCH: Langerhans Cell Histiocytosis
FNAC: Fine Needle Aspiration Cytology
IHC: Immunohistochemistry
CD: Cluster of Differentiation
MRI: Magnetic Resonance Imaging

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AUTHOR CONTRIBUTIONS

All authors significantly contributed to the study conception and design, data acquisition, or data analysis and interpretation. They participated in drafting the manuscript or critically revising it for important intellectual content, consented to its submission to the current journal, provided final approval for the version to be published, and accepted responsibility for all aspects of the work. Additionally, all authors meet the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE) guidelines.

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

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All data generated and analyzed are included within this research article. The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon a re-asonable request.

USE OF ARTIFICIAL INTELLIGENCE (AI) & LARGE LANGUAGE MODEL (LLM)

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