Case Report

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Challenges in diagnosis and management of Langerhans Cell Histiocytosis in a 13-month-old child: a rare case report

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Introduction: Langerhans Cell Histiocytosis is a rare condition characterized by the proliferation of abnormal Langerhans cells in the skin and mucosa. It is mostly seen in children between 1 and 3 years old. Although the skeleton accounts for 80% of infiltration and the skin accounts for 33%, it can affect other organs as well.

Case presentation: The authors report a case of a 13-month-old male with fever, rash, and nontender swelling in the frontal, temporal, and infraorbital regions. Imaging showed diffusion restriction in the frontal, left parietal, right sphenoid, right temporal bones, and right maxillary antrum. Biopsy and immunohistochemistry from the right maxilla confirmed the diagnosis. The patient was treated with vinblastine and prednisolone for 3 months, resulting in reduced swelling and no fever on follow-up.

Discussion: Langerhans Cell Histiocytosis (LCH), formerly Histiocytosis X, has diverse clinical manifestations and is classified as localized or disseminated based on organ involvement. It is associated with viral infections, communication defects, and cytokine processes, with BRAF mutations and the MAPK/ERK pathway implicated. Diagnosis involves clinical, radiological, histological, and immunophenotypic methods, including identifying Birbeck granules in Langerin-positive cells. Treatment varies by disease extent, with vinblastine and prednisolone for children with multisystem disease and tailored approaches for adults.

Conclusion: Despite atypical presentation, thorough evaluation confirmed Langerhans Cell Histiocytosis in a pediatric patient. This highlights the necessity of considering Langerhans Cell Histiocytosis in differential diagnoses for persistent cutaneous lesions and bony swellings. Prompt detection and timely action are essential for successful treatment and better results.

Keywords: dendritic, histiocytosis, Langerhans, lytic, rash

Introduction

Langerhans Cell Histiocytosis (LCH) is an idiopathic condition characterized by the proliferation of abnormal Langerhans cells which are antigen-presenting cells present in skin and mucosa[1]. LCH is a rare condition affecting 1 to 2 newborns per million per year. It generally affects children from 1 to 3 years old, but it has been diagnosed in all age groups[2]. These abnormal reactive cells or neoplastic cells usually infiltrate organs such as the skin, bones, lungs, brain, bone marrow, liver, nervous system, and other organs[3].

Amongst various organs affected, LCH affecting the skeleton and skin accounts for the majority of cases with 80 and 33%, respectively[3]. The clinical manifestation of LCH varies from a single organ to multiorgan involvement and severity varies from milder forms that can spontaneously go into remission to aggressive disease that can lead to death[4].

HIGHLIGHTS

- Langerhans Cell Histiocytosis is a rare disorder typically observed in children aged 1–3 years, characterized by predominant infiltration in the skeleton (80%) and skin (33%).
- It is believed to be triggered by viral infections, issues with cell-to-cell communication, and cytokine-driven processes. Its pathophysiology involves alterations in BRAF genes and the MAPK/ERK signaling pathway.
- Treatment for Langerhans Cell Histiocytosis varies depending on the extent and severity of the disease. In children with multisystem involvement, systemic therapy using vinblastine, and prednisolone is typically administered, while adults may receive tailored treatment approaches based on individual factors.

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The diagnosis of LCH is supported by clinical and imaging features but confirmation of diagnosis is done via histopathological and immunophenotypic examination of multiple biopsy specimens[2,3].

Case presentation

Clinical history

A 13-month-old male presented to the tertiary care center with a rash involving the forehead and swelling over the forehead and right side of the face. On further inquiry of the rash, his parents initially noticed an itchy whitish rash with vesicles in the trunk 6 months back that subsequently involved the scalp and the face. During that time frame, they noticed progressive swelling over the midline of the forehead that gradually involved the right side of the face. Soon, the parents also noticed progressive pallor, decreased feeding, and intermittent fever with temperature maximum recorded of 102 F with no diurnal variation, which was relieved by medication (Paracetamol). His bowel and bladder habits are normal. He had no history of reduced vision, trauma, loss of consciousness, shortness of breath, abnormal body movement, petechiae, joint swelling, and generalized body swelling. He had no family history of malignancy or other tumors.

Physical examination

The patient's general appearance revealed that he was alert, active, and pale. He had stable vital signs. Cutaneous examination revealed a 2×2 cm nontender, hard swelling on the midfrontal, right temporal, and right infraorbital regions, as shown in Figure 1. A whitish, itchy, vesicular rash was also noted on the frontal and right temporal regions, as shown in Figure 1. Bilateral posterior cervical lymphadenopathy was observed. The neurological, respiratory, cardiovascular, and gastrointestinal examinations were completely normal.

Laboratory examination

The laboratory investigations revealed microcytic hypochromic anemia with increased lymphocyte, lactate dehydrogenase, aspartate aminotransferase, and decreased amylase count as shown in Table 1.

Imaging examination

With history and examination in mind, a plain and contrast MRI of the head was done to identify any apparent pathology.

Findings of plain and contrast MRI of the head

Expansile T2/FLAIR heterogeneous high signal intensity lesion measuring $4.3 \times 3.6 \times 1.4$ cm was noted in the midline frontal bone, without separate visualization of the frontal sinus. The corresponding lesion showed T! Mixed intermediate and mild high signal intensity. Patchy diffusion restriction was seen within the lesion. The lesion showed heterogeneous contrast enhancement as well. Erosion of both the outer and inner table of the frontal bone was seen. No obvious intradural extension or extension beyond the aponeurotic layer was seen as shown in Figure 2.

Large similar signal intensity and similar enhancing expansile lesions were also seen in all walls of the right maxillary antrum, right greater wing of the sphenoid, and adjacent right squamous temporal bone as well as right pterygoid plates. Associated obliteration of the right maxillary antrum, as well as the right infratemporal fossa, was seen. No evidence of intradural extension of the right temporal bone lesion as well. A small similar lytic lesion was also seen in the left parietal bone ($12.5 \times 11 \times 4$ mm) as shown in Figure 2.

Histopathological analysis

With history, examination, and radiographic evidence in mind, a biopsy was conducted from the right maxilla for further evaluation. The specimen of five pieces of grey-brown tissues altogether measuring $1.0 \times 0.7 \times 0.4$ cm was sent for immunohistochemistry as well as hematoxylin and eosin staining.

On histopathological examination, the section showed diffuse proliferation of histiocytic cells with abundant pale eosinophilic cytoplasm, round to elongated nuclei, fine chromatin, and inconspicuous nucleoli. Frequent nuclear grooving was seen. Numerous eosinophils, along with a few neutrophils, were identified. Mitotic activity and necrosis were not seen as shown in Figure 3.

Immunohistochemistry (IH 227/80) showed S100 positive and CD1a positive as shown in Figure 4.

The histopathological analysis confirmed the diagnosis as Langerhans cell histiocytosis.

Treatment

The patient was admitted to the pediatric unit. Treatment was started with prednisolone and chemotherapy with vinblastine for 3 months.

Outcome and follow-up

The patient was scheduled for a follow-up after completing 3 months of prednisolone and vinblastine treatment. He showed significant improvement, with no fever and subsided swelling. With the induction phase showing good response, he was planned for the continuation phase of chemotherapy.

Discussion

Langerhans cell histiocytosis is a rare disease and was first described by Paul Langerhans in 1868[5]. LCH was previously termed Histiocytosis X, Letterer-Siwe disease, Hand-Schuller-Christian disease, and diffuse reticuloendotheliosis[4]. Though LCH can present at any age from neonates to old age but the peak incidence is from 1 to 3 years[6]. It affects 1 to 2 newborns per million per year[2].

LCH was previously classified into three groups namely Eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease but currently classified according to the organs involved into two groups: localized (single system with single or multiple sites involvement) and disseminated (multisystem with two or more organ involvement with or without organ dysfunction)[5].

The etiology of Langerhans cell histiocytosis remains unknown, but Langerhans cell proliferation may be induced by a viral infection, a defect in intercellular communication (T cell and

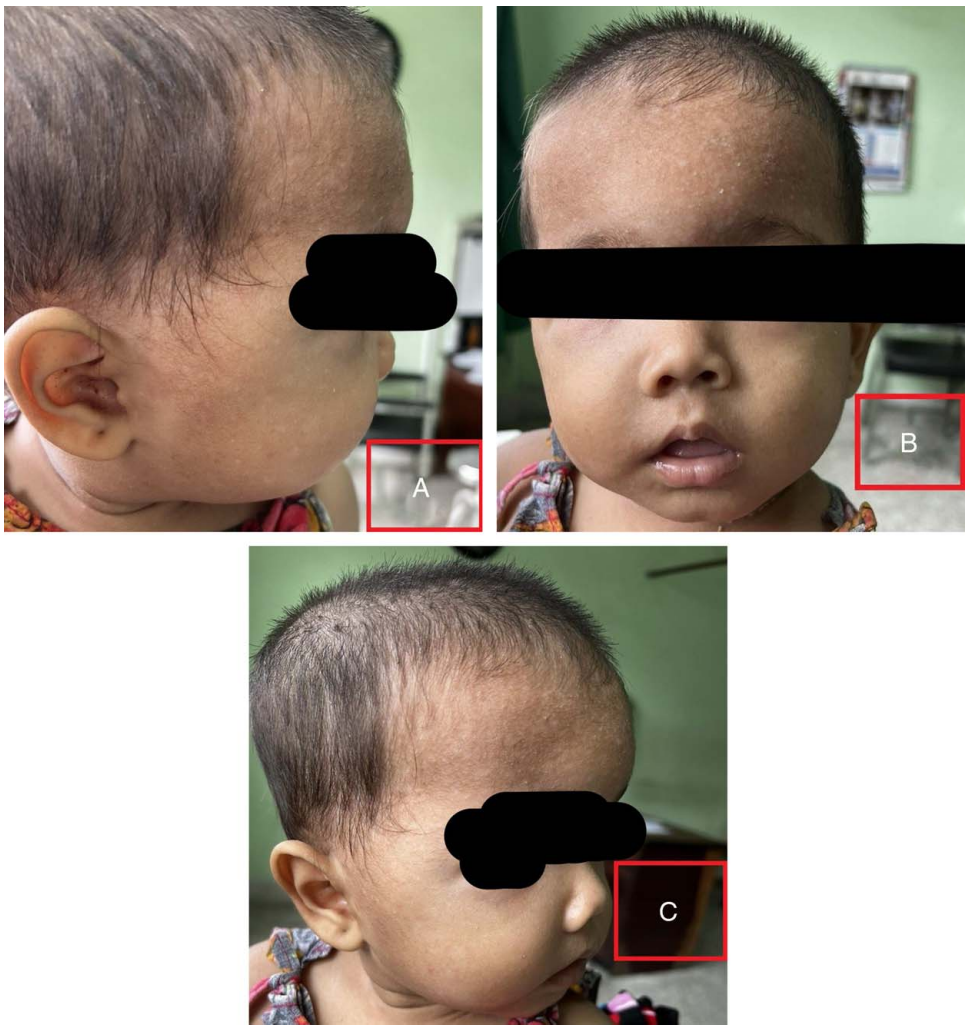

Figure 1. (A, B, C): Swelling on the mid-frontal, right temporal, and right infraorbital regions with whitish, vesicular rash on the frontal and right temporal regions.

macrophage interaction), and/or a cytokine-driven process mediated by Tumor necrosis factor, IL-1, and leukemia inhibitory factor[7]. Pulmonary LCH is caused exclusively in patients aged 20–40 years who smoke cigarettes[8]. The pathophysiology of Langerhans cell histiocytosis remains uncertain but is thought to be caused by activating mutations in BRAF and aberrant MAPK/ERK signaling[2,9].

The clinical presentation of LCH presents from a mild form limited to single organ to multiple organ involvements that progresses quickly. In children, LCH mostly presents as painful lytic bone lesions (77% cases) and rash (39%) along with other nonspecific symptoms such as fever, poor appetite, weight loss, fatigue, etc. whereas pulmonary involvement (50% cases) is more common in adults with LCH and attributed to cigarette smoke[2,10]. The most common skin manifestations are an eczematous rash that resembles candidal infection with brown to purplish papules. LCH involving bones may resemble painful lytic bony lesions with raised, soft, and tender spots. Any bones can be affected but the presentation varies with age. In children, the most commonly affected sites are the skull, femur, rib, vertebra, and humerus, whereas in adults, the most common sites of bony involvement are the jaw, skull, vertebra, extremities, and pelvis. Other symptoms are attributed to other organ involvements such as central nervous system involvement (arginine

Table 1

Laboratory investigations of the patient showing microcytic hypochromic anemia with increased lymphocyte, lactate dehydrogenase, aspartate aminotransferase, and decreased amylase count.

Test	Patient's result	Reference range
Hemoglobin (gm/dl)	7.6	13–18 (Male) 12–16 (Female)
Hematocrit (%)	25.2	35–52
MCV (fl)	66.6	76–100
MCH (pg)	20.2	27–34
MCHC (gm/dl)	30.3	32–35
RDW-CV (%)	30.9	11–17
Total leucocyte count (/cumm)	9210	4000–11 000
Lymphocyte (%)	53	20–45
Lactate dehydrogenase (U/l)	748	135–330 (Children) 135–225 (Adult)
Aspartate aminotransferase (IU/l)	51	< 45
Amylase (IU/l)	16	25–104

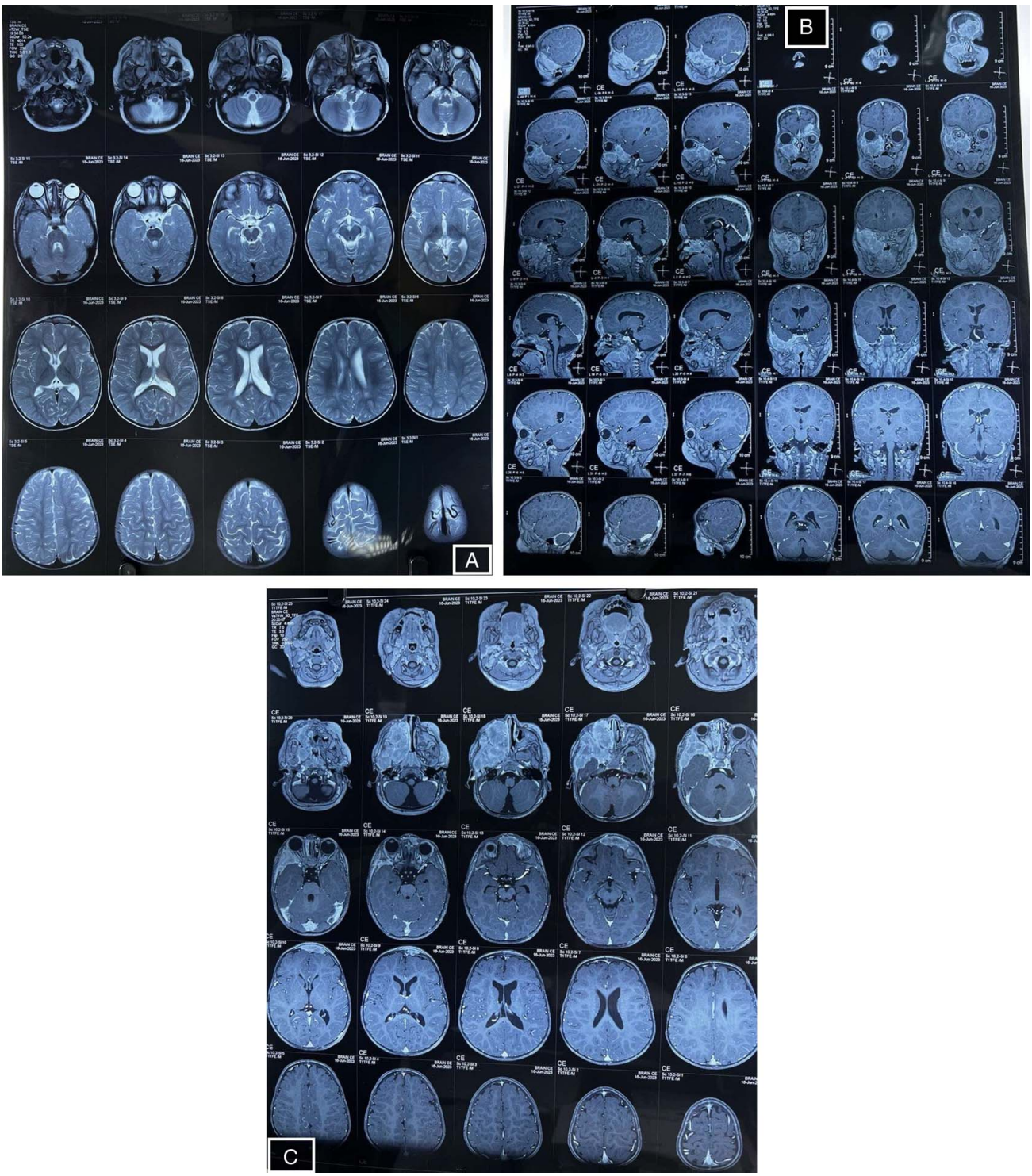

Figure 2. (A, B, C): MRI study of the head (Plain and Contrast), which showed heterogeneously enhancing expansile T2/FLAIR heterogeneous high signal intensity lesions showing diffusion restriction in the frontal bone, left parietal bone, right side of sphenoid bone, right temporal bone and right maxillary antrum. D/D: Metastasis; Langerhans cell Histiocytosis.

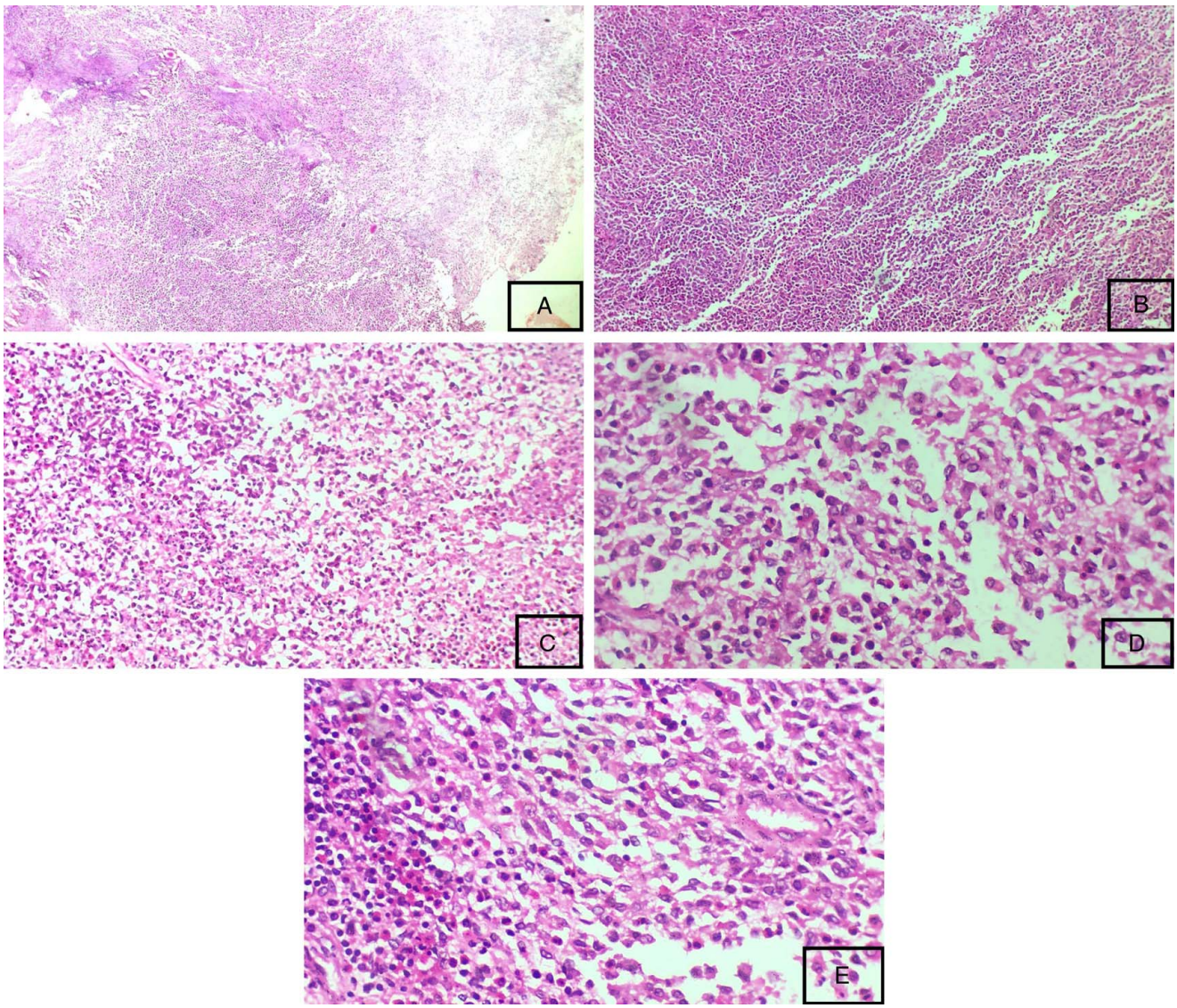

Figure 3. Histopathology of Langerhans cell histiocytosis. (A) Hematoxylin and eosin, H&E X5. (B) Hematoxylin and eosin, H&E X10. (C) Hematoxylin and eosin, H&E X20. (D) Hematoxylin and eosin, H&E X40. (E) Hematoxylin and eosin, HE X40. (A, B, C, D, E) Microscopic examination showing diffuse proliferation of histiocytic cells with abundant pale eosinophilic cytoplasm, round to elongated nuclei, fine chromatin, and inconspicuous nucleoli. Frequent nuclear grooving. Numerous eosinophils along with a few neutrophils. No any Mitotic activity and necrosis.

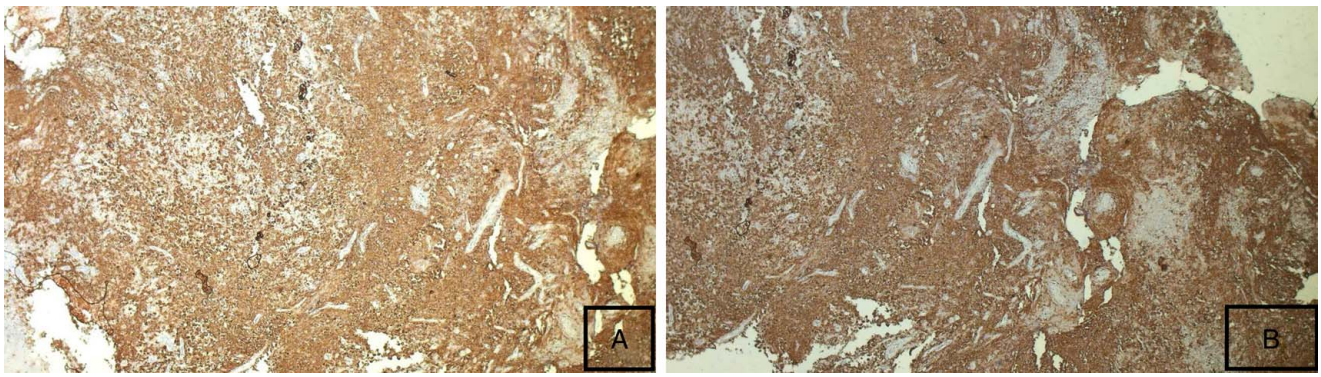

Figure 4. Immunohistochemistry of Langerhans cell histiocytosis. (A) CD1a positive (20X), (B) S100 positive (20X).

vasopressin deficiency and neurodegeneration symptoms such as ataxia and cognitive dysfunction), GI system (diarrhea and malabsorption), spleen (splenomegaly leading to cytopenias), liver (hepatomegaly with increased bilirubin and decreased clotting factors, sclerosing cholangitis), lymph nodes (lymphadenopathy), and bone marrow (increased incidence of AML and lymphoblastic leukemia)[2].

The diagnosis of LCH done by clinical features and radiological imaging, should also involve histological and immunophenotypic examination of lesional tissues from multiple sites[11]. It is characterized histopathologically by neoplastic cells with CD1a+, and CD207+ Langerhans-like cells derived from myeloid dendritic cells[2]. The electron microscopic presence of Birbeck granules in affected Langerin cells suggests LCH[11].

The treatment of LCH depends upon the extent and severity of the disease as well as the system involved. Limited skin involvement responds well with either topical steroid therapy or an oral agent containing methotrexate or lenalidomide. Treatment of a single bony lesion with less than 5 cm involvement or non-CNS risk bone lesion is done by curettage or radiation therapy if the lesion does not respond to curettage or systemic therapy whereas treatment of bony lesion greater than 5 cm or involvement of CNS risk bone (orbit, mastoid, temporal, or sphenoid) requires systemic and/or radiation therapy. Multisystem involvement in children is treated with systemic therapy containing vinblastine and prednisolone divided into induction and continuation phases whereas treatment of multisystem involvement in adults is stratified according to the system affected. Adults with multisystem involvement with no CNS or risk organ (bone marrow, liver, and spleen) involved are treated with cytarabine or cladribine, whereas CNS and risk organ involvement in adults is treated with BRAF inhibitors such as vemurafenib or dabrafenib and associated with poor outcomes[12,13].

Conclusion

Despite the atypical presentation and initial diagnostic challenges, a thorough clinical evaluation and appropriate diagnostic investigations confirmed LCH. This case emphasizes the importance of including LCH in the differential diagnosis for pediatric patients with persistent cutaneous lesions and bony swellings. Early diagnosis and intervention are vital for effective management and improving patient outcomes.

Ethical approval

Ethical approval is not required for case report in this institution.

Consent

Written informed consent was obtained from the patient's parents/legal guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

G.S. and K.K.: conceptualization, data curation, writing – original draft, and writing – review and editing; A.P., P.L.S., and S.P.: writing – original draft and writing – review and editing; S.A.: data curation and writing – review and editing; A.T.: writing – review and editing; A.K.: data curation. All authors approved the final manuscript as submitted.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
2. Unique identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked) : not applicable.

Guarantor

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Data availability statement

All the relevant data have been included in the manuscript itself.

Provenance and peer review

Yes.

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