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Case Series

Paediatrics Section

Langerhans Cell Histiocytosis in Children: A Case Series

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ABSTRACT

Langerhans Cell Histiocytosis (LCH) is a rare haematological disorder with prominent proliferation or accumulation of cells of macrophages, dendritic cells and their haematopoietic precursors. Early diagnosis by the common histologic finding of Birbeck granules on electron microscopy is essential for optimal outcomes. A series of eight LCH cases who presented with skin, skeletal, lymph node involvement, hepatosplenomegaly are reported here. The age of the patients ranged from four months to twelve years. Two patients presented with skin involvement, two patients had disseminated lymphadenopathy, four patients had skeletal involvement. Tissue biopsy and immunohistochemistry of either the skin or bone lesions was done for confirmation of the diagnosis. It is challenging to diagnose LCH in children as it mimics common disorders in children. Diagnosis is mainly clinical. Evaluation of a child with persistent dermatitis for LCH is necessary to prevent delay in diagnosis till systemic involvement occurs.

Keywords: Haematopoietic precursors, Histopathology, Immunohistochemistry

INTRODUCTION

The LCH is a rare haematological disorder with prominent proliferation or accumulation of cells of macrophages, dendritic cells and their haematopoietic precursors. It can occur at any age with a peak incidence between one to three years of age with a slight male predominance. Children of Hispanic ethnicity are more often affected, suggesting racial predisposition [1]. These disorders are variable in their clinical expression like skeletal, skin, ocular or multisystem involvement. Early diagnosis is essential for optimal outcomes. The histiocytic disorders share the common histologic finding of Birbeck granule, a tennis racket shaped bilamellar granule in the cytoplasm of the Langerhans cell on electron microscopy [2]. Somatic clonal mutation of BRAFV600E gene was identified in fifty percent of patients with LCH. Activating Mitogen Activated Protein Kinase (MAPK) pathway gene mutations were identified in most of the patients with LCH. LCH is also considered as a disorder of immune regulation [3-5]. It is now recognised as a myeloid neoplasm due to the identification of clonal haematopoietic precursors by activating MAPK pathway somatic gene mutations which created a paradigm shift in the understanding of the disease. Clinically, LCH is divided into single lesion, multifocal low-risk or multifocal high-risk [6]. Low-risk or high-risk indicates risk of death associated with LCH lesions in liver, spleen, bone marrow. The distinction of risk organs liver, spleen, haematopoietic system and lung involvement is important for deciding the intensity of treatment approach and has been incorporated into standard treatment approaches for LCH, as delineated in histiocyte society protocols. This is an observational study of all cases presenting to the hospital diagnosed with LCH over a period of two years.

Here, eight cases of patients with LCH seen over a period of two years from September 2020 to August 2022 have been discussed. A thorough clinical and laboratory evaluation was undertaken in all patients. This included: complete blood cell count, liver function tests, coagulation studies, skeletal survey, chest radiograph and measurement of urine osmolality. Additionally, detailed evaluations of any organ system shown to be involved by physical examination or appropriate investigations were performed to establish the extent of disease, before initiation of treatment. Tissue biopsy and immunohistochemistry of either the skin or bone lesions was done for confirmation of the diagnosis. Summary of all the eight cases have been presented in [Table/Fig-1].

CASE SERIES

Case 1

A four-month-old female child was admitted with progressive distension of the abdomen, intermittent fever, decreased activity since three months and rash all over body since two months which was not responding to treatment. She had no significant antenatal history. It was a term gestation with no Neonatal Intensive Care Unit (NICU) admission. On examination she had SpO_2 of 90% in room air, pallor, tachypnoea with subcostal retractions, hypopigmented patches over chest and abdomen, seborrheic dermatitis of scalp, massive hepatosplenomegaly [Table/Fig-2]. Her reports revealed anaemia, thrombocytopaenia, elevated direct bilirubin and liver enzymes, normal High Performance Liquid Chromatography (HPLC), normal bone marrow, ultrasound abdomen showed dilated portal vein with periportal cuffing and ascites. Scalp skin biopsy revealed atypical infiltrating cells showing strong positivity with S100 and CD1a consistent with LCH [Table/Fig-3].

Case 2

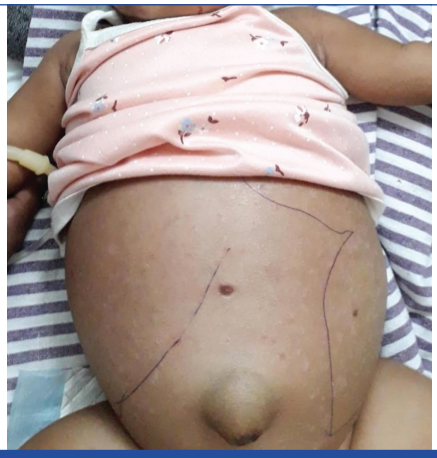
A one-year-old female child came with fever, rash with scaly lesions on forehead, hands and feet [Table/Fig-4-7], jaundice, clay-coloured stools, progressive abdominal distension since two months. The skin rash was resistant to treatment. Evaluation revealed hepatosplenomegaly, anaemia, thrombocytopaenia, elevated liver enzymes, conjugated hyperbilirubinaemia. Hepatitis viral markers and work up for inborn errors of metabolism were negative. Blood culture and bone marrow biopsy were normal. Skin biopsy showed atypical papillary dermal infiltrate and liver biopsy [Table/Fig-8] was strongly positive for S100 protein and CD1a on immunohistochemistry consistent with involvement by LCH.

Case 3

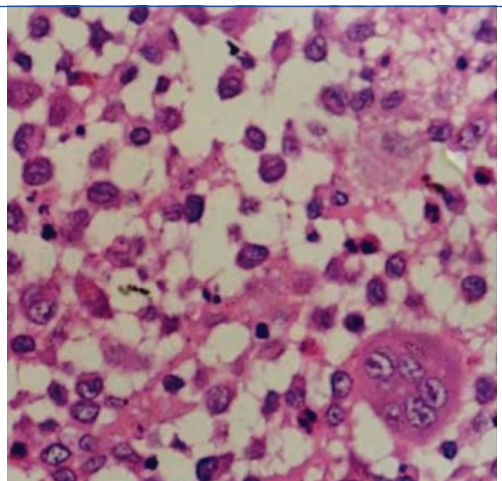
A two-year-old male child presented with swelling over the left submandibular region and cervical lymphadenopathy noticed since one week [Table/Fig-9]. Ultrasound of neck revealed bilateral cervical and submandibular lymphadenopathy. Bone marrow

Variables	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age/gender	4 months/ female	1year/female	2 years/male	18 months/male	4 years/ male	11 years/male	3 years /male	12 years/male
Clinical presentation	Skin rash, abdominal distension	Skin rash, jaundice, clay coloured stools	Left submandibular swelling	Increased thrist, increased frequency of micturition,lack of weight gain	Noisy breathing	Swelling in the left occiput	Swelling in the left eye	Swelling on both sides of neck
Skin involvement	Yes	Yes	Nil	Nil	Nil	Nil	Nil	Nil
Skeletal involvement	Nil	Nil	Nil	Yes	Nil	Yes	Yes	Yes
Lymphadenopathy	Nil	Nil	Yes	Nil	Nil	Nil	Nil	Yes
Hepatosplenomegaly/ jaundice	Yes	Yes	Yes	Yes	Nil	Nil	Nil	Nil
Fever, weight loss	Yes	Yes	Yes	Yes	Nil	Nil	Nil	Nil
Other tests			CT abdomen: multiple enlarged para aortic,para iliac, inguinal lymph nodes	CT brain: thick pituitary stalk CT abdomen: non enhancing lesion in both lobes with periportal lymphadenopathy	CT PNS: Irregular lytic lesion in the clivus		MRI of the orbits: mass lesion in the extra conal superomedial left orbit	Bone scan revealed hot spot in frontal bone suggestive of metastases.MRI brain and pituitary showed evidence of pituitary lesion on contrast study.
Histopathology and Immunohistochemistry	Skin biopsy: infiltrating cells positive for S100 and CD1a	Skin biopsy: atypical papillary dermal infiltrate positive for S100and CD1a	Lymph node excision biopsy positive	Skull bone biopsy: positive for CD1a and S100	Nasopharyngeal mass biopsy positive for S100	Biopsy of occipital swelling: eosinophilic granuloma positive for S100and CD68	Incision biopsy: eosinophilic granuloma positive for S100 and CD68	Lymph node excision biopsy: positive stain with CD1a,CD68,PAX5

[Table/Fig-1]: Summary of the presented cases.
CT: Computerised tomography; MRI: Magnetic resonance imaging; PNS: Paranasal sinuses

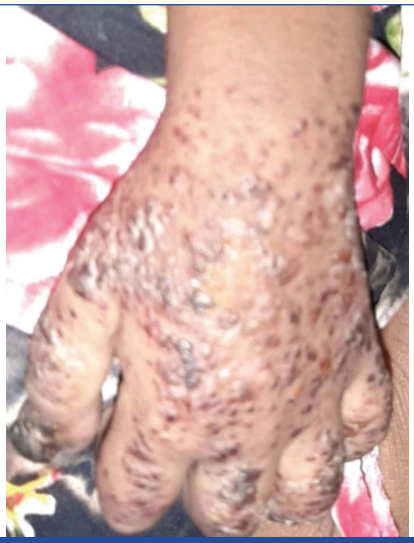


[Table/Fig-2]: Above image shows abdominal distension, hepatosplenomegaly, hypopigmented patches on abdomen in LCH.

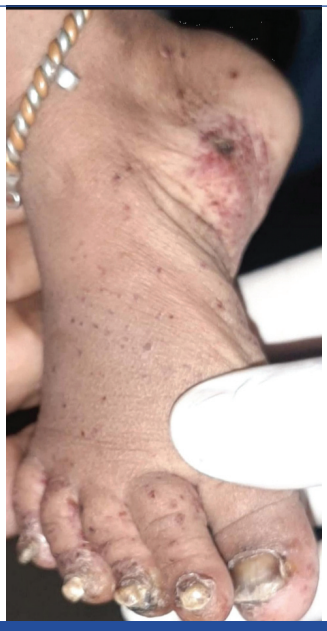


[Table/Fig-3]: Skin biopsy suggestive of LCH (H&E, 400× magnification).

aspiration was normal. A Computed Tomography (CT) scan of the abdomen showed multiple enlarged para aortic, para-iliac, inguinal lymph nodes. A bone scan did not show any evidence of active skeletal lesions. Cervical lymph node excisional biopsy [Table/Fig-10] showed positivity for S100 protein and CD1a which was in favour of LCH or eosinophilic granuloma.

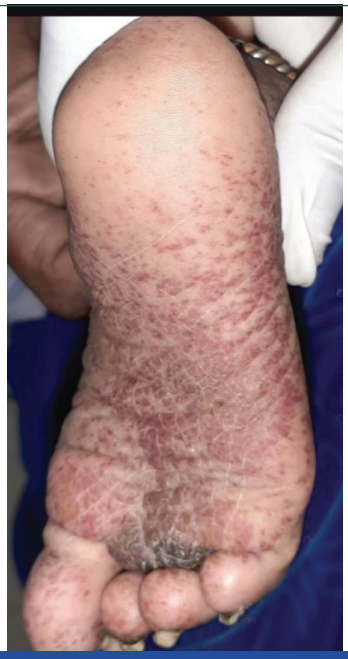


[Table/Fig-4]: Scaly lesions on the skin of hands deformities in a one-year-old child.

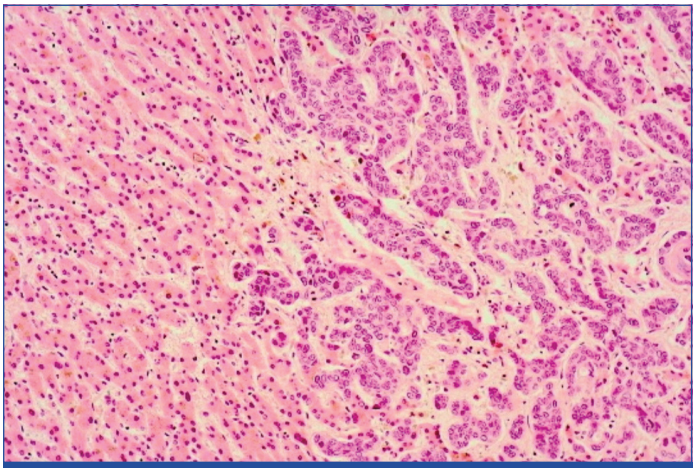


[Table/Fig-5]: Scaly lesions on the skin of feet deformities in a one-year-old child.

[Table/Fig-6]: Scaly lesions on the skin of forehead deformities in a one-year-old child.



[Table/Fig-7]: Scaly lesions on the skin of soles and nail deformities in a one-year-old child.

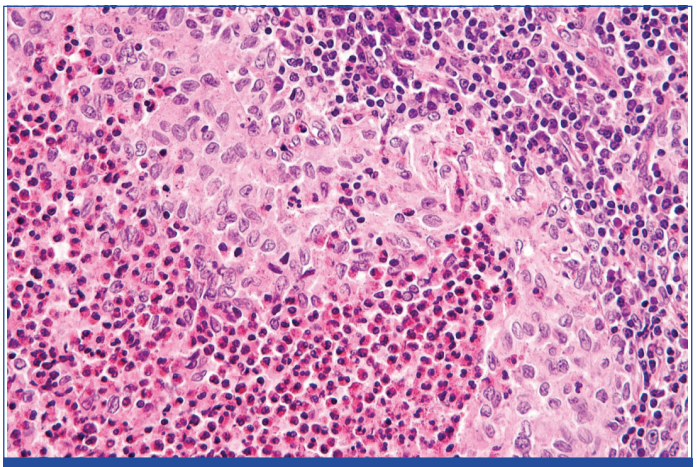


[Table/Fig-8]: Liver biopsy in LCH, H&E, 400×.

Case 4

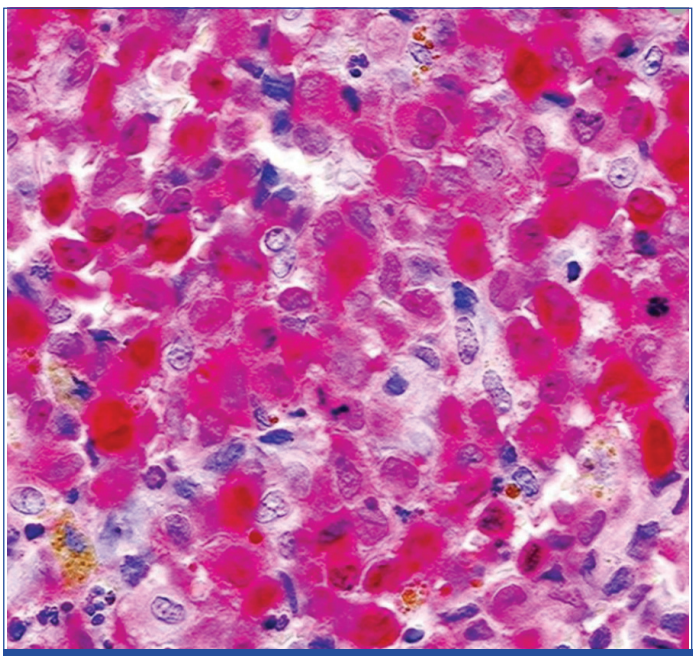
An 18-month-old male child was admitted with complaints of lack of weight gain, increased thirst and increased frequency of micturition, jaundice, ear discharge for one month. Examinations showed pallor, icterus, hepatosplenomegaly, weight for height less than first percentile. Investigations revealed anaemia, leukocytosis, normal platelet count, elevated direct bilirubin, high alkaline phosphatase, mildly elevated liver enzymes, decreased urine specific gravity. X-ray skull showed lytic lesions. A Contrast-Enhanced Computed

[Table/Fig-9]: Left submandibular swelling in a two-year-old child.



[Table/Fig-10]: Lymph node excision biopsy in LCH, H&E 400×.

Tomography (CECT) of the brain showed a thick pituitary stalk. A CECT of the abdomen was suggestive of few small non-enhancing lesions in both lobes of liver and periportal lymphadenopathy. Biopsy of the skull bones [Table/Fig-11] was CD1a and S100 positive consistent with LCH.

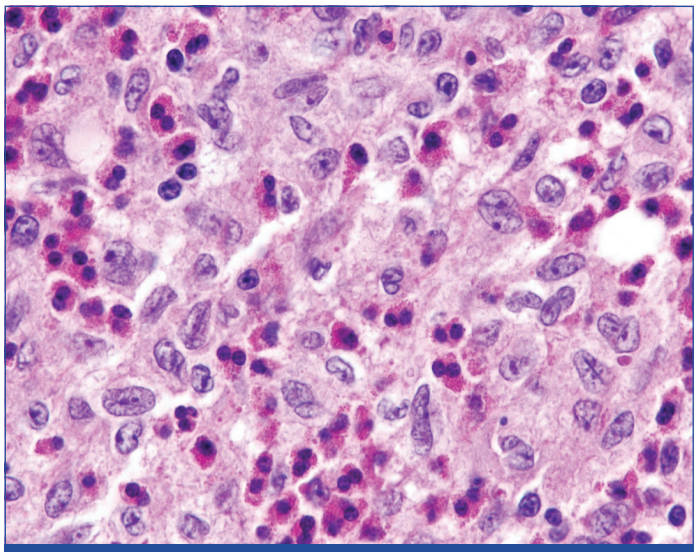


[Table/Fig-11]: Skull biopsy with immunohistochemistry marker staining of LCH cells positive for S100, H&E, 400×.

Case 5

A four-year-old male child presented with noisy breathing for one month. Nasopharyngeal examination revealed a smooth, lobulated, single pale mass in the nasopharynx. A CT scan of para nasal sinuses showed irregular lytic lesion in the clivus with adjacent prevertebral

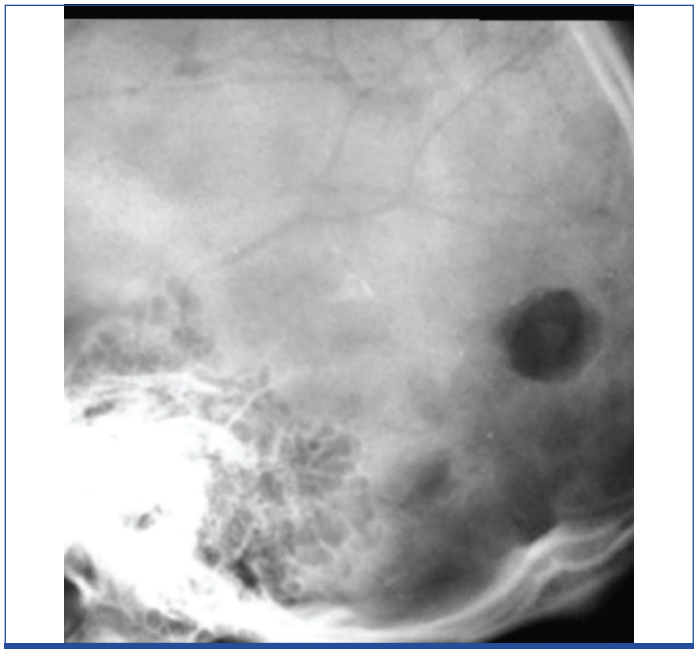
soft-tissue projecting into and compromising the nasopharynx and oropharynx extending from sphenoid bone to C2 level. His Complete Blood Picture (CBP), LFT and bone marrow aspiration were normal. Histopathology of the nasopharyngeal mass [Table/Fig-12] was suggestive of lymphoid follicular hyperplasia with germinal centres, adenoid tissue, well-formed mantle zones, macrophages and histiocytic cells positive for S100 suggestive of LCH.



[Table/Fig-12]: Nasopharyngeal mass biopsy in LCH, H&E 400×.

Case 6

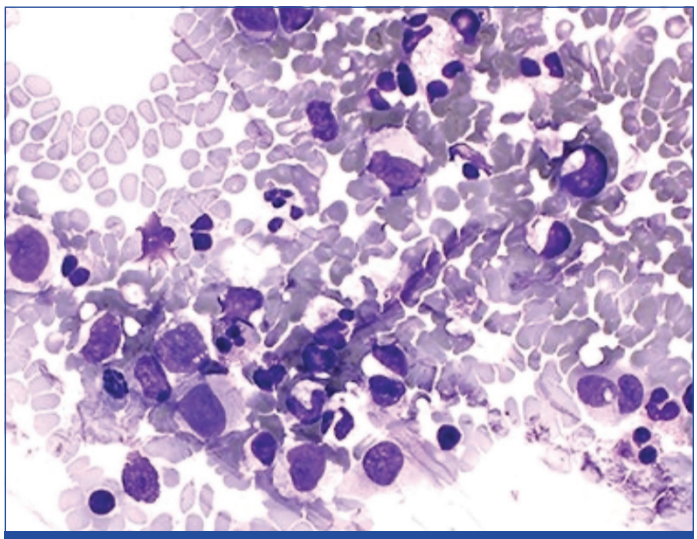
An 11-year-old male child presented with a left occipital swelling noticed since one week. He had ear discharge since two months. His CBP, LFT, bone marrow aspiration and biopsy, X-ray of the skull [Table/Fig-13] showed eosinophilic granuloma appearing as rounded lucent lesion in the left occipital bone. CT scan of the chest and abdomen and bone scan were normal. Histopathological examination of a biopsy from the occipital region was suggestive of eosinophilic granuloma which was positive for S100 and CD 68.



[Table/Fig-13]: X-ray of skull with eosinophilic granuloma appearing as a rounded lucent lesion at the left occipital bone.

Case 7

A three-year-old male child admitted with swelling in the left eye noticed since fifteen days and ear discharge since one month. A Magnetic Resonance Imaging (MRI) of the orbits revealed a mass lesion in the extraconal superomedial left orbit with extension to ipsilateral ethmoids and nasal cavity with minimal intracranial extension. CT guided core needle biopsy of retro orbital region [Table/Fig-14] showed eosinophilic granuloma positive for S100 and CD68 Bone scan report revealed hot spot in frontal bone suggestive of metastases. He had no liver, skin or other bone involvement.



[Table/Fig-14]: Bone biopsy suggestive of LCH H&E, 400×.

Case 8

A 12-year-old male child presented with a 2-month history of progressive swellings on both sides of the neck and ear discharge. He had fever, weight loss and loss of appetite for one month. There were multiple matted nodes in the posterior triangle and along jugular region. His CBP and bone marrow were normal. A CECT of the neck showed a lytic lesion in the basiocciput. Bone scan showed a hot spot in the vertex and occipital bone. A CT scan of the chest revealed osteopenia of the vertebral bodies. MRI brain and pituitary showed evidence of a pituitary lesion on contrast study. An excision biopsy of the neck node stained positively with CD1a, CD68 and PAX5 suggestive of LCH.

DISCUSSION

The presentation of LCH in this series was variable. Cases 1 and 2 had red scaly papules with seborrheic dermatitis like appearance with no improvement after months of treatment and referred to higher centres after onset of systemic symptoms like abdominal distension and cholestatic jaundice. In children less than one year skin involvement is more common than other organs [7]. Retrospective case series by Dhar S et al., concluded that cutaneous LCH without systemic involvement has a good prognosis [8]. In other studies, progression of skin lesions to multi system LCH was seen [9,10]. Case 3 presented with neck swelling and further investigation revealed disseminated lymphadenopathy involving the mediastinum and abdominal lymph nodes. Approximately, twenty percent of patients present with lymphadenopathy most frequently affecting cervical lymph nodes. Involvement of mediastinal lymph nodes and thymus can also occur. As the physiologic Langerhans cells and CD 207+ dermal dendritic cells move from skin to the lymph nodes as part of immune response, cases with isolated lymph node involvement must be confirmed by experienced pathologist [11].

Cases 4, 6, 7, 8 presented with bone lesions which involved the pituitary, base of skull, scalp and orbital swelling with clinical features of polyuria, nasopharyngeal mass, scalp swelling and proptosis. Bone involvement is seen in seventy-five percent of patients of LCH. Radiographs revealed osteolytic expansive bone defects. Orbital bone disease was typically unilateral presenting as proptosis which may be confused with infections and rhabdomyosarcoma. One of the most severe complications of LCH is LCH associated Neuro Degeneration (LCH-ND) which may develop with the onset of LCH or several years after the patient is in remission. Patients who have CNS risk lesions (orbit, mastoid, temporal, maxilla, ethmoid, sphenoid, clivus) appear to have a greater risk of developing LCH-ND even years after apparent remission [1].

More recent studies have supported clonal origin of microglia like mononuclear cells at sites of neurodegeneration with BRAFV600E mutation with systemic LCH lesions [12-14]. Infiltration of the pituitary is seen in ten to twenty percent of cases resulting in diabetes insipidus due to deficient production of ADH by the posterior pituitary. Anterior pituitary hormone deficiency can also occur [15]. Case 4 and case 8 presented with polyuria and polydipsia and failure to thrive. CECT brain showed thick pituitary stalk. Cases 4,6,7,8 had chronic otitis media. Case 5 who had noisy breathing had a nasopharyngeal mass on a CT scan and diagnosed by biopsy. Case 1 and 2 had anaemia and thrombocytopaenia. Elevated liver enzymes were seen in three cases. X-ray skull showed multiple lytic lesions in three patients with an eleven-year-old presenting with left occipital region swelling. Maria Postini A et al., in their 40-year experience on LCH concluded single system multifocal bone involvement as the most common presentation over two years of age [16]. Systemic or organ involvement may occur in some cases over a period and requires long-term follow-up. Bone scan had hot spots in frontal, vertex and occipital regions in cases 7 and 8. Immunohistochemistry was diagnostic in all cases.

CONCLUSION(S)

It is challenging to diagnose LCH in children as it mimics common disorders in children. Diagnosis is mainly clinical. It needs to be confirmed by histopathology and immunohistochemistry. Evaluation of a child with persistent dermatitis for LCH is necessary to prevent delay in diagnosis till systemic involvement occurs.

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