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Original Research Article

A 5 Years Retrospective Study of Various Presentation of Langerhans Cell Histiocytosis in Children : In A Tertiary Care Hospital

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Abstract

Background: Langerhans cell histiocytosis (LCH) a rare disease with various clinical presentations characterized by the accumulation of CD1a-positive immature dendritic cells. This study was done with the aim of documenting the various clinical presentations of LCH occurring in Indian population. *Methods:* All histopathologically proven cases of LCH were retrieved retrospectively over a period of 5 years (January 2013- December 2017) at Institute of Child Health and included in our study. *Results:* Out of 14 cases observed as LCH, 11 cases (78.57%) were between 0-3 years of age, with male predominance. Bone involvement was the commonest presentation seen in 10 cases (71.43%), of which skull was commonly involved in 8 cases (80%). Isolated skin involvement was seen in 3 cases (21.43%), next to bone involvement. 1 case (7.14%) presented with pure lymph node involvement. *Conclusion:* Lesions presenting as isolated skin involvement is not very rare which can be seen in children upto 3 years of age and in our study, it was observed in 3 cases (21.43%) which is higher than the previous observations [15,16]. Other unusual presentations like sternum, mandible (alveolus) involvement, pure lymph node involvement can also occur. Skin involvement being the second commonest of the presentations next to bone lesions and hence warrants a skin biopsy in susceptible age group (0-3 years) with chronic skin lesion and an associated skeletal survey, so that it offers the clinician a road to the diagnosis and proper treatment is initiated to the patient at the earliest. Follow up of cases is needed to rule out relapse.

Keywords: Langerhans cell histiocytosis; Various presentations; Skin involvement.

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Introduction

Langerhans cell histiocytosis a rare and challenging disease, has a spectrum of clinical presentations ranging from multisystem life threatening disorder to a spontaneously regressing solitary lesion of bone. It is characterized as infiltration by Langerhans cells which are the cells of the accessory immune system. The incidence of Langerhans cell histiocytosis in children ranges

from 2-9 cases/1000 000/year, and is slightly predominant in males (M/F = 1.2-1.4) [1,2,3,4,5]. Herein we are reporting a case series, focusing on the various clinical presentations of Langerhans cell histiocytosis that were observed during a period of 5 years in our Institute.

Materials and Methods

A 5 year retrospective study was done from January 2013 to December 2017 at Institute of Child Health, Chennai and clinicopathological details of cases which were histologically confirmed as Langerhans cell histiocytosis was compiled from medical section records of department of pathology. 14 cases of Langerhans cell histiocytosis was identified which was histologically and immunohistochemistry wise proven. The Haematoxylin and Eosin sections and immunohistochemistry slides available were re-examined.

Case Series

The details are as follows:

Table 1: Various clinical presentations of LCH

S. No	Age	Sex	Suspected Clinical Diagnosis	Clinical Presentations	Investi Gations	Histo Pathology Diagnosis	IHC Markers
1.	6Y	M	Eosino philic granuloma	Swelling right parietal region	X-ray: Single osteolytic lesion parietal bone	Eosinophilic granuloma	CD1a and S100 strong +ve.
2.	12Y	M	LCH	Occipital lytic lesion.	X-ray skull: Lytic lesion present. (Bone biopsy was performed)	LCH	CD1a +ve.
3.	3Y	F	Hyper IgE	Purpuric rash.	X-ray skull: Lytic lesion. (Skin biopsy was performed)	LCH	CD1a +ve.
4.	11m	M	Skin rash	Skin rash	Skin biopsy was performed.	Eosinophilic granuloma	CD1a +ve.
5.	7m	M	LCH	Anaemia, hepatosplenomegaly, Seborrheic dermatitis, ear discharge, lytic lesion over skull.	X-RAY: Lytic lesion. (Skin biopsy was performed)	LCH	CD1a +ve.
6.	6m	M	Post auricular hemangioma	Osteolytic lesion in scalp and hyperpigmented skin lesions.	X-ray skull: Osteolytic lesion. (Skin biopsy was performed)	LCH	CD1a strong +ve.
7.	2Y	M	LCH	Seborrheic dermatitis like lesion and bilateral otitis media, hepatosplenomegaly	X-ray: Lytic lesion. (Skin biopsy was performed)	LCH	CD1a +ve.
8.	7Y	F	-	Right cervical lymphadenopathy.	CT brain: Soft tissue swelling in right parietal region with bony erosion of inner and outer table. (Lymph node biopsy was performed)	Eosinophilic granuloma	CD 1a +ve.
9.	2.5Y	M	Suspected LCH	Sternal mass	Bone biopsy was performed.	LCH	CD1a +ve.
10.	11m	M	Bone pain	Right scalp swelling (Temporal region)	X-ray skull: Osteolytic lesion. (Bone biopsy was performed)	Eosinophilic granuloma	CD1a +ve.
11.	1.5Y	M	Left side lateral neck swelling Lymphoma Neuro-blastoma	Left cervical swelling	USG neck/ CT neck: 6*4*4 cm large lobulated solid mass with encasement of left carotid artery and compression of IJV. (Node biopsy was performed)	Eosinophilic granuloma	CD1a +ve.

12.	3Y	F	LCH (Recurrence)	Mandibular swelling (Alveolar mass)	Known case of LCH (Previous Biopsy proven – Bone marrow biopsy showed histiocytosis) At present bone biopsy was done.	LCH	CD1a +ve.
13.	3Y	M	LCH completed chemotherapy ? relapse	Skin pigmentation in the scalp	Skin biopsy was done.	Recurrent LCH	CD1a +ve.
14.	2Y	F	Histiocytosis	Skin biopsy from scalp	Skin biopsy was done.	Eosinophilic granuloma	CD1a +ve.

M=Male, F=Female, m=months, Y=years, LCH=Langerhans Cell Histiocytosis, +ve=positive, IHC=Immunohistochemistry.

Results

In our study, among 14 patients diagnosed as LCH, 4 cases (28.57%) were infants, 7 cases (50%) were between 1-3 years of age and 3 cases (21.43%) between 3-12 years of age. Almost 11 cases (78.57%) diagnosed between 0-3 years of age. Of which 10 cases (71.4%) were male and 4 cases (28.6%) were female. M/F = 2.5(Male predominance present). Systems affected: Bone: Among 14 cases, 10 cases (71.43%) had bone involvement. Among the bone involvement, skull involvement was common and observed in 8 cases (80%), followed by sternal and mandibular involvement seen in 1 case each (10% each). Bone involvement alone was seen in 5 cases (35.71%), of which 3 cases (60%) involved the skull, 1 involved the sternum (20%) and 1 case (20%) involved the mandible. Skin: Isolated skin involvement was seen in 3 cases (21.43%), the presentation was like that of a skin rash in all the three cases. Of which 1 case 33.33% was an infant and 2 cases 66.66% were children more than 1 year of age (one case was 2 years old and another case was 3 year old) unlike that of previous studies. Out of 3 cases, 2 were males (66.66%). 2 cases (14.29%) had bone and skin involvement. Lymph node: 1 case (7.14%) which presented with pure lymph node involvement which was clinically suspected as neuroblastoma. The cervical lymph node was involved. 1 case (7.14%) presented with both bone and lymph node involvement. Multisystem involvement: was seen in 2 cases (14.29%), of which one case was an infant and one case was 2 year old child. 2 cases were relapse of LCH of which primary site of involvement in both cases were bone and one case had relapse in mandible and other case the relapse site was skin.

Histopathological and immunohistochemistry pictures of a Langerhans cell histiocytosis case is shown in Fig. 1 and 2.

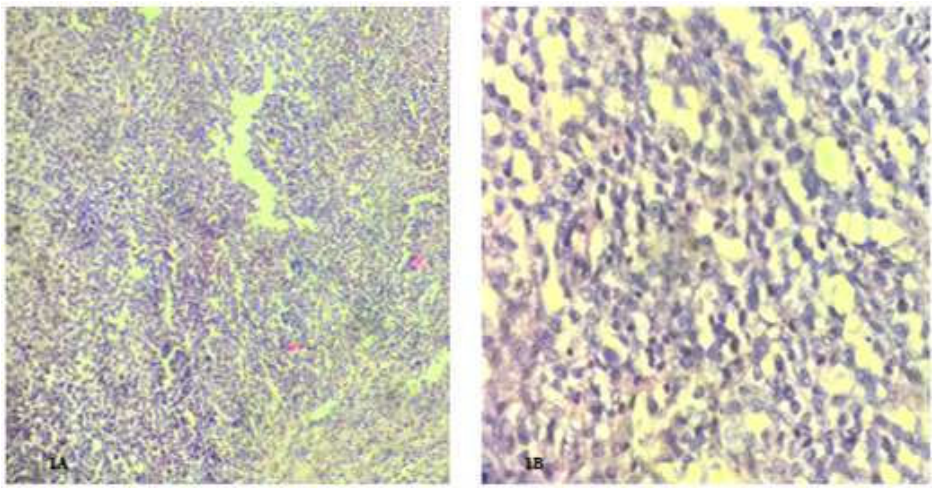

Fig. 1A: Langerhans cell histiocytosis (H and E, X10). **1B:** Lagerhans cell histiocytes showing Langerhans cell with lingitudinal grooving resembling coffee bean appearance (H and E, X40)

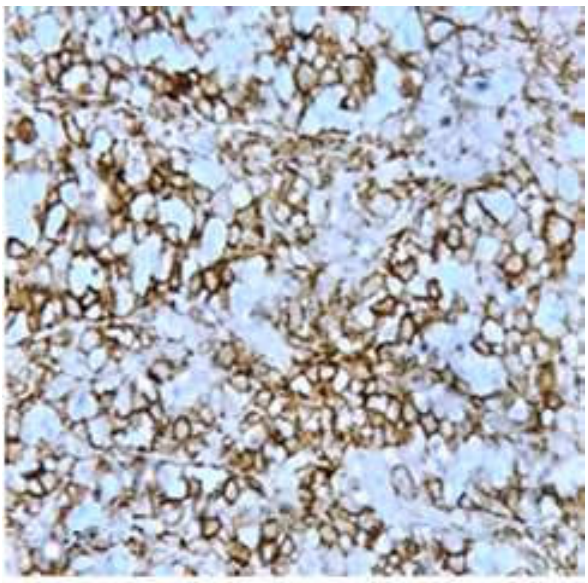

Fig. 2: Diffuse strong positivity of CD1 a in Langerhans cell histiocytes (X 40)

Discussion

As Lichtenstein proposed that the disease entities known as Eosinophilic granuloma, Hand – Schuller Christian disease and Letterer – Siwe diseases all share common pathological appearance [6] and that they all come under one roof. This view was challenged by Liberman *et al.* [7] they suggested that Letterer-Siwe disease is not a specific entity but may involve several pathologic process. Many evidence suggest however that atleast some of the disseminated diseases with features of Letterer-Siwe disease are actually LCH. Studies have shown clonality in LCH, suggesting a neoplastic origin [8,9].

Langerhans cell histiocytosisis a rare clonal disease of the monocyte-macrophage system characterized by uncontrolled proliferation and accumulation of CD1a positive/ CD207 positive dendritic cells as a result of continuous immune stimulation [10]. It is characterized by infiltration of Langerhans cell. Langerhans cell histologically has oval nuclei, which is often lobulated/ indented, sometimes with longitudinal groove, resulting in "coffee-bean appearance", acidophilic cytoplasm, with specific intracytoplasmic organelle known as Langerhans or Birbeck granules. It is accompanied by admixture of eosinophils, giant cells, neutrophils, foamy cells and areas of fibrosis. Mitotic figures including atypical mitotic figures are not uncommon. The diagnostic IHC markers are S100 protein, CDIa and Langerin (CD207). CD1a and Langerin are more specific markers. On basis of type and organ involvement, LCH of bone is divided into 3 major categories:

1. *Solitary Bone Involvement*: which is the most common variety, known as "Eosinophilic granuloma". Most common sites are cranial vault, jaw, humerus, ribs and femur. They present as osteolytic lesion with excellent prognosis.
2. *Multiple Bone Involvement:* (with or without skin involvement) known as "Hand –Schuller Christian disease" presenting as proptosis, diabetes insipidus, chronic otitis media or a combination of these with favourable outcome in most cases.
3. *Multiple Organ Involvement*: like bone, liver, spleen and others which is known as Letterer-Siwe disease. These patients have poor prognosis.

Langerhans cell histiocytosis can occur at any age. However, peak occurrence is between 1 and 4 years of age. There is slight predominance in males (M/F = 1.2-1.4) [1-5]. In our study, among 14 patients diagnosed as LCH, almost 11 cases (78.57%) were diagnosed between 0-3 years of age. Of which 10 cases (71.4%) were male and M/F = 2.5 (Male predominance present).

LCH has varied presentations of which bone involvement is seen in about 80% of cases with LCH [11]. In pediatric age group patients, skull is most often affected location followed by spine, extremities, pelvic bone and ribs [12]. In our study, among 14 cases, 10 cases (71.43%) had bone involvement. Among the bone involvement, skull was involved in 8 cases (80%), followed by sternal and mandibular involvement seen in 1 case each (10% each). Bone involvement alone was seen in 5 cases (35.71%), of which 3 cases (60%) involved the skull, 1 involved the sternum (20%) and 1 case (20%) involved the mandible. Therefore apart from the usual sites of bone involvement like skull, sternum and mandible (alveolus) involvement was also seen in our study.

Skin lesions are the second most-common clinical manifestations of LCH (30-60%) [13], which is particularly frequent in infants [13]. However, an isolated cutaneous form of disease is rare (the number of described cases does not exceed 12% of all patients with LCH), typically concerns only male infants [15,16]. In our study, isolated skin involvement was seen in 3 cases (21.43%) which is higher than that of above said observation. The presentation was like that of a skin rash in all the three cases. Of which 1 case 33.33% was an infant

and 2 cases 66.66% were children more than 1 year of age (one case was 2 years old and another case was 3 year old) unlike that of previous studies. Out of 3 cases, 2 were males (66.66%). 2 cases (14.29%) had bone and skin involvement. Therefore isolated skin involvement is not very rare and it is seen even in children upto 3 years of age. Other presentations like lymph node involvement was also seen.

Multisystem involvement was seen in 2 cases (14.29%), of which one case was an infant and one case was 2 year old child. They had various presentations like anaemia, hepatosplenomegaly, seborrheic dermatitis like lesion, ear discharge (due to bilateral otitis media) and lytic lesions over skull. 2 cases were relapse of LCH of which primary site of involvement in both cases were bone and one case had relapse in mandible and other case the relapse site was skin. Therefore follow up of cases is necessary to rule out relapse.

Treatment depends on the form of LCH. Systemic therapy is indicated for all patients with single system multisite and multisystem LCH as well as for special localizations. A standard two-drug regimen with vinblastine and prednisolone consisting of an initial intensive phase for 6-12 weeks, followed by maintenance therapy for a total treatment duration of atleast 12 months, is recommended [17]. Patients with single system disease limited to skin may be observed. If the skin lesions do not spontaneously resolve, variety of methods may be used, including topical steroids, oral methotrexate or thalidomide, topical nitrogen mustard, or psoralens with UV light [18]. A single bone lesion involving the frontal, parietal, occipital bones and any other bones may be treated by curettage only or curettage with a local injection of methylprednisolone [19].

Conclusion

LCH the diagnosis of which is challenging as pediatric patients has various presentations. The most common presentation being isolated bone involvement. Next to bone involvement, isolated skin involvement was seen. Lesions presenting as isolated skin involvement is not very rare, can be seen in children upto 3 years of age and in our study, it was seen in 3 cases (21.43%) which is higher than the previous observations [15,16]. Other unusual presentations like sternum, mandible (alveolus) involvement, pure lymph node involvement can also occur. Skin biopsy is hence warranted in all suspicious skin lesions in susceptible paediatric age group of 0 to 3 years of age. Once diagnosis of LCH is established, radiological evaluation is necessary to rule out associated bone involvement which is the commonest site of involvement in pediatric age group. Next step is, multisystem involvement has to be ruled out as treatment varies in each group of patients depending on whether there is single system unisite or multisite involvement or multisystem involvement. Follow up of cases are required to rule out relapse.

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