

The Enigmatic Langerhan Cell Histiocytosis A Study of Nine Pediatric Cases

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ABSTRACT

INTRODUCTION: Langerhan Cell Histiocytosis is a rare disease that is found mostly in children, with an estimated incidence between 0.2 and 2.0 cases per 100,000 children under 15 years of age and a peak incidence between ages of 2-4 years. The disease has preponderance in males, sometimes as high as 60-70% and is more common in whites of north European descent. The disease encompasses three disorders Eosinophilic Granuloma, Hand Schuler Christian Disease and Letterer Siwe Syndrome according to clinical and pathological features.

AIMS AND OBJECTIVES: Were to establish the clinical spectrum, radiological findings and frequency of bone marrow infiltration in Langerhan Cell Histiocytosis in pediatric population.

PATIENTS AND METHODS: This study included nine children diagnosed with Langerhan Cell Histiocytosis over 15 month period from Feb 2011 to Jun 2012 in Children Hospital /ICH Lahore and were referred for bone marrow examination.

RESULTS: All cases presented in the first decade of life with male preponderance (2:1), and mean age being 3.1 years. There were 3 cases of Eosinophilic Granuloma, 2 cases of Hand Schuler Christian Disease and 2 cases of Letterer Siwe disease and 2 cases presented with lymph node involvement only. Anemia was present in all cases, bicytopenia in two and pancytopenia in only one case diagnosed with Letterer-siwe disease. Bone Marrow infiltration was found in only one case diagnosed with Letterer Siwe Disease both on aspirate and trephine biopsy. Radiological examination in 7 out of 9 (77.7%) patients in this study revealed lytic lesions in skull, 2 of which had involvement of other bony sites as well. Two cases presented with nodal involvement only.

CONCLUSION: LCH can present in a multitude of ways, The difficulty in diagnosis and the historically complex nomenclature have, as expected made the true prevalence and incidence of these disorders difficult to ascertain therefore it must remain on the differential when a patient presents with osteolytic lesions

INTRODUCTION

Langerhan Cell histiocytosis (LCH) is a rare disease often present in childhood with a continuum of clinical entities ranging from a localized lytic lesion to a fatal disseminated myeloid-like leukemia and is associated with fibrosis and osteolysis, which lead to organ dysfunction¹. LCH is a clonal disease in which the majority of cases carry an activating allele of an authentic oncogene indicates that it is a neoplasm. While some of its clinical manifestations may be related to an accompanying inflammatory state, it is possible that some of its behavior may be exacerbated by inflammatory stimuli. The pathogenesis of a majority of LCH cases lies firmly within the paradigm of a cell-autonomous

proliferative disorder that arises from a somatic mutation of a cell proliferation gene². Recent studies on global gene expression patterns in LCH support the notion that the disease may arise from early myeloid precursors rather than mature Langerhan cells themselves³.

The clinical presentation of LCH is highly variable and historically, three distinct clinical syndromes have been described. Eosinophilic Granuloma characterized by the presence of one or more lytic bone lesions in which the proliferating histiocytes are accompanied by prominent infiltrate of eosinophils, Hand-Schuller-Christian disease, comprising the clinical triad of bone defects, exophthalmos, and polyuria and Letterer-Siwe disease, a fulminant disorder marked by

hepatosplenomegaly, lymphadenopathy, skin rash, bone lesions and hematological compromise^{4,5}. Eosinophilic granuloma is the most common subtype, accounting for about 70% of LCH cases⁶. Approximately two-thirds of children with LCH have single-system disease that most commonly affects bone, but that can also involve skin, lymph nodes or the central nervous system(CNS).The remaining children have multisystem disease,which tends to be present in younger children.Even within the multisystem group, the involvement of the so called risk organs portends a worse outcome. These risk organs are bone marrow, liver and lungs⁷.

The typical histologic appearance of LCH varies with the age of the lesion examined.The langerhan cell is the prominent diagnostic feature in the histology of Langerhan cell histiocytosis⁸.The Langerhan cell is 15 to 25 m in diameter, with a central to slightly eccentric oval uniform –shaped nucleus with a delicate chromatin network and inconspicuous nucleoli. A indentation or groove across the face of the nucleus is a feature of many cells⁹.Together with LCH cells, other cell types have been shown to be present in LCH lesions, including lymphocytes, macrophages, eosinophils and multinucleated giant cells¹⁰.

Histiocytes in LCH express CD207,also known as Langerin, which is a C –type lectin with binding specificity for mannose-containing sugars¹¹. However Langerin can also be expressed by so called Langerin- positive DCs¹², indicating that it is not solely an LC marker. A definitive diagnosis of LCH relies on the immunohistochemical identification of the presence of langerhan cells by cell surface CD1a, or by the presence of Birbeck's granules by electron microscopy¹³. CD1a has become the gold standard for LCH diagnostics^{14,15,16}.

Aim of the present study was to determine the clinical spectrum and radiological findings of this disorder in pediatric population and determine the frequency of marrow infiltration.

PATIENTS AND METHODS

This study included all patients diagnosed with Langerhan cell histiocytosis and referred to hematology department of Childrens Hospital /Institute of Child Health for bone marrow examination, over fifteen month period from february 2011 to may 2012 in childrens hospital/ICH, Lahore. Cases were diagnosed on

tissue biopsy eg lymph node or bony mass. Routine H&E stain histopathology was followed by immunohistochemical staining for CD1a in all cases. Investigations performed included complete blood count, bone marrow aspiration and trephine biopsy, skeletal survey and in some cases CT scans and Bone scans.

RESULTS

The salient clinical features of the cases studied are presented in table1. All cases presented in the first decade of life, with an average age of 3.1yrs.

There was a preponderance of male patients with male:female of 2:1. There were three cases (33.3%) of eosinophilic granuloma and two had only monoostotic involvement while polyostotic involvement was present in the third case. There were two cases of Hand schuler Christian disease and two cases of Letterer-siwe disease and in two cases lymph nodes were the only sites involved. Tissue biopsies in all cases had the suggestive morphology and immunohistochemistry confirmed presence of CD1a positive langerhan cells.

Complete blood counts revealed anemia in all cases, bicytopenia in two cases (cases#6&7),and pancytopenia in only one case diagnosed with Letterer-Siwe disease(case #1).

Radiological examination revealed well defined lytic lesions without sclerosis in skull in both cases with monoostotic Eosinophilic Granuloma, and in polyostotic Eosinophilic Granuloma such lesions were present in skull, ribs, spine and limbs and scapulae(fig.1,fig.2). In two cases with Hand Schuller Christian Disease similar lesions were found in skull in addition to exophthalmos and diuresis. In one case with Letterer Siwe Disease lytic lesions were present in skull and in the other case they were present both in skull and whole of spine. Overall lytic lesions on X-ray were present in seven cases. Bone scan ^{99m}Tc-MDP performed in one case with Letterer-siwe disease revealed in homogenous tracer uptake and CT Scan of a case with Hand Schuller Christian disease revealed diffuse mass involving both orbits and temporal fossa with intracranial extension and erosion of bone. Bone marrow aspiration and trephine biopsies were performed in all cases and marrow infiltration with typical langerhans cells was present in only one case(fig:3,fig:4) both on aspirate and trephine biopsy and immunohistochemistry for CD1a was positive. In three cases though the marrow was not involved yet both hemophagocytosing and non hemophagocytosing macrophages were prominent.

Table No.1: Age, Sex & Clinical/Hematological Characteristics of Patients

| | Age & sex | Clinical features | HB | TL C | PL T | LN | Hepato megalay | Spleno megalay | Bone Marrow | X-Ray | CT-Bone ScAN |
|-------------------------|------------------|---|-----|------|------|--|----------------|----------------|---|--|--|
| #1 .LS D | 5 yrs Female | Neck swelling | 3.9 | 2.9 | 54 | +VE cervical axillary Abdominal | +VE | +VE | Infiltrated with CD1a+ve langerhan cells | Lytic lesions skull/ spine | Tc99Mmdp In Homogenous Tracer up take |
| #2 .E G | 1.6 yrs Male | Forehead Swelling | 9.3 | 11 | 768 | -VE | -VE | -VE | -ve | Lytic lesions skull | |
| #3 .H S C D | 5 yrs Male | Forehead swelling /excessive urination/ exophthalmos | 9.0 | 10 | 485 | -VE | -VE | -VE | -ve | Lytic lesions skull | |
| #4 .LS D | 2.6 yrs Male | Fever, Neck Swelling Skin Rash, Ear discharge | 9.2 | 8 | 400 | +VE | -VE | -VE | -ve Hemophagocytosis +ve | Lytic lesions skull | |
| #5 .H S C D | 6 yrs Male | Forehead Swelling /Exophthalmos | 10 | 16 | 797 | -VE | -VE | -VE | -ve | Lytic lesions skull | Diffuse mass involving both orbits & r temporal fossa with intracranial extension & bone erosion |
| #6 .N od al | 1.6yrs Female | Neck & Inguinal swelling | 10 | 14 | 45 | +VE | -VE | -VE | -ve | | |
| #7 .N od al | 8 months Male | Fever, loose motion Developmental delay Neck Swelling | 7 | 5.2 | 139 | +VE | -VE | -VE | -ve Hemophagocytosis +ve | | |
| #8 .E G | 3yrs Male | Fever, Fracture | 6.4 | 16 | 853 | +VE | -VE | -VE | -ve | Lytic lesions skull/spine/ limbs/ ribs | |
| #9 .E G | 3yrs Female | Scalp swelling / Ear Discharge | 8 | 9 | 315 | -VE | +VE | -VE | -ve Hemophagocytosis + | Lytic lesions skull | |



Figure 1. X-ray Skull Lateral view showing multiple well defined punched out lytic lesions without sclerotic margins (case no 8).

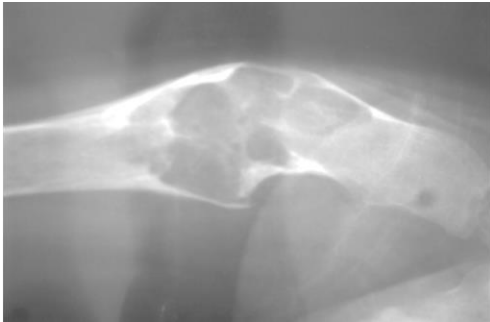


Figure 2. X-Ray AP View of Lower limb showing multiple lytic lesions (case no 8)

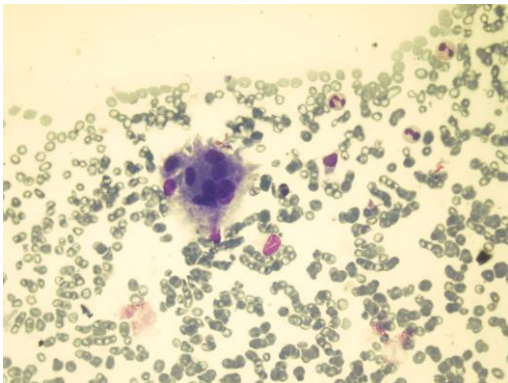


Figure 3 : Bone marrow aspirate showing infiltration with Langerhan cells (Hematoxylin and eosin stain)x 400.

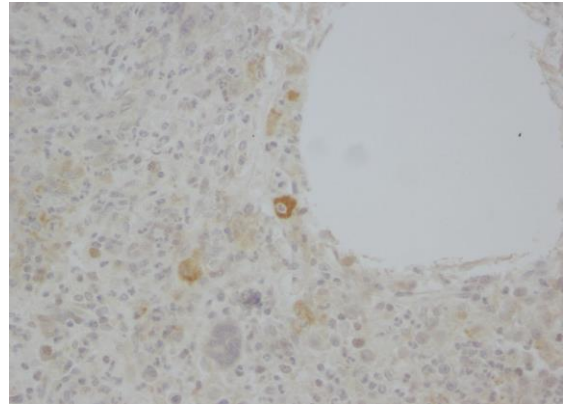


Figure 4 : Langerhan cells with positive staining.(CD1a) x400

DISCUSSION

Langerhan Cell Histiocytosis is a proliferative disease of cells that share phenotypic characteristics with Langerhan cells(LCs),the primary antigen presenting cells of the epidermis. Although usually thought of as an extremely rare disease of childhood, its incidence of 2-5 per million children per year in Western Europe is comparable to that of Hodgkins lymphoma in a similar population^{17,18}. Patient age ranges from 5-15 years in about 90% of the cases and males are slightly predominant ¹⁹. In the present study all the cases were in the first decade of life, with eight cases being in children of 5 years or younger and only a single case in which the child was older and male predominance was observed, similar observations were made by D Ambrosio etal ²⁰ who reported a peak incidence of disease between ages of 2-4 years.

Approximately 2/3 children with LCH have single system disease that most commonly affects bone, but can also involve skin, lymph nodes or central nervous system,The remaining children have multisystem disease.which tends to be present in younger children⁷.

The signs and symptoms of LCH vary considerably,depending on which organs are infiltrated by the Langerhan cells and accompanying immunoreactive cells.Bone, skin, teeth, gingival tissue, ear,endocrine organs, lungs, liver ,spleen ,lymph nodes and bone marrow can all become involved and exhibit dysfunction secondary to cellular infiltration²¹. Although patients rarely fall into discrete categories defined by the classic designations of Eosinophilic Granuloma ,Hand-Schuller-Christian disease,and

Abt-Letterer-Siwe disease, this nomenclature remains valuable, if only to catalog the clinical manifestations of LCH. In addition these eponyms preserve the historic perspective of this enigmatic group of disorders. However the difficulty in diagnosis and the historically complex nomenclature have, as expected, made the true prevalence and incidence of these disorders difficult to ascertain²². In the present study three cases of Eosinophilic Granuloma were diagnosed two having monoostotic skull involvement, radiographically, the lesions were multiple sharply marginated, round or oval with well defined lytic lesions without sclerosis. Patients (case 2 & case 9) were aged 18 months and 3 year respectively, while the third case, a 3 years old male (case 8) had polyostotic involvement. According to Mickelson and Bonfiglio, Eosinophilic granulomas are found predominantly in older children, as well as in young adults, usually within the first 3 decades of life with the incidence peaking between 5 and 10 years of age²³. Hand-schuller-Christian disease was diagnosed in two cases, both males, aged 5 and 6 years respectively, (cases 3 and 5) presenting with exophthalmos, polyuria and lytic lesions in skull. According to Arceci²⁴ Hand-Schuller-Christian disease (multisystem disease) is most common in younger children between 2 and 5 years of age and represents 15- 40% of such patients. Bony defects with exophthalmos are due to tumor mass in the orbital cavity, This usually occurs from involvement of the roof and lateral wall of the orbital bones²⁵.

The rarest (10% of patients) and most severe form of LCH is Abt-Letterer-Siwe disease²³. Typically, patients are younger than 2 years of age, and present with a scaly, seborrheic, eczematoid sometimes purpuric rash involving the scalp, ear canals, abdomen and intertriginous areas of the neck and face. The rash may be maculopapular or nodulopapular. Draining ears, lymphadenopathy, hepatosplenomegaly and in severe instances hepatic dysfunction can occur. In this study two cases of Letterer-Siwe disease were diagnosed aged 5 years and 2 and a half years old, with extensive eczematoid skin involvement in one of the cases along with discharging ears and lymphadenopathy, while the other case had hepatosplenomegaly and generalized lymphadenopathy.

One of the most significant areas of involvement is the hematopoietic system, with the

potential to result in pancytopenia.² In this study all 9 cases (100%) had anemia and two cases (22%) (cases 6 & 7) had bicytopenia. One (11.1%) case of Letterer-Siwe disease had pancytopenia. Thrombocytopenia most frequently portends a poor outcome²⁶. In a study by Galluzzo et al monocytopenia, bicytopenia and pancytopenia was present in 41%, 32% & 9% case respectively while 18% cases had no hematological dysfunction.

Patients with systemic involvement frequently have bone lesions in addition to other manifestations of disease²¹. In the present study bony lesions were present in seven out of nine cases (77.7%) They presented with well defined lytic skull lesions, and two cases had polyostotic involvement (cases 1 & 8).

Luscent defect in lung were present in one case while CT lung of another case revealed interstitial lung changes. The chest radiograph may vary from a diffuse infiltrate consistent with bilateral interstitial pneumonia to a honey comb lung appearance due to pulmonary fibrosis, such findings have been reported in other studies^{27,28}.

LCH can have a strictly nodal presentation, characterized by significant enlargement of multiple lymph node groups, with little or no other signs of disease²⁹. In this study two cases presented with solely nodal involvement.

Bone Marrow involvement was identified in only one case (11%) and it revealed on aspirate smears, clusters of histiocytes with few showing hemophagocytosis, The nuclei of some of these abnormal cells revealed the coffee bean groove characteristic of LCH cells. Trephine biopsy revealed replacement of 90% marrow space by histiocytic infiltrate, which were CD1a+. Marrow involvement in 3 out of 22 cases (13.6%) and 14 out of 41 cases (34%) has been reported in diagnosed cases of langerhan cell histiocytosis^{30,31}. The combination of conventional aspiration cytology with CD1a staining appears to be the most reliable tool for bone marrow assessment in LCH³¹. Increased histiocytes and hemophagocytosis was reported in 41% patients with multisystem LCH³⁰ and in another study all patients had increased mononuclear phagocytes in the marrow³². In the present study hemophagocytosis was found in 4 out of 9 LCH cases (44.4%) including the case with marrow infiltration with langerhan cells. Bone marrow involvement at diagnosis maybe associated with more extensive and potentially fatal disease³³. Multinucleated giant cells (MGCs) were

also found interspersed among langerhan cells in the marrow involved with LCH, The presence of osteoclast-like multinucleate giant cells may be explained by the production of osteoclast-inducing cytokines such as receptor activator of nuclear factor kB ligand and macrophage colony stimulating factor by both CD1a+ LCH cells and T cells in these lesions. In three different lesional tissues, bone, skin, and lymph nodes the MGCs are reported to express the characteristic osteoclast markers, tartrate-resistant acid phosphatase and vitronectin receptor as well as the enzyme cathepsin k and matrix metalloproteinase-9. The expression of typical osteoclast markers as well as characteristic osteoclast-secreted enzymes by the multinucleated giant cells in LCH lesions confirms that these cells are osteoclast-like multinucleated giant cells and excessive bone destruction found in LCH is likely to be mediated by osteoclast-like giant cells³⁴. LCH lesions frequently regress either spontaneously or after local treatment^{17,35,36}. Langerhan Cell Histiocytosis is a rare disease with varied manifestations, it is difficult to diagnose, lytic lesions on X-rays are frequently detected, In this study they were present in a majority (77.7%) of patients. Langerhan Cell Histiocytosis must remain on the differential in a patient who presents with osteolytic lesions. .

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