LANGERHANS CELL HISTIOCYTOSIS IN CHILDREN

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Summary

Background: Langerhans cell histiocytosis (LCH) is a rare proliferative disorder of histiocytes encompasses a wide clinical spectrum, ranging from a benign localized disease to acute generalized disease with fatal outcome.

Objectives: to retrospectively evaluate clinical characteristics at diagnosis and outcome of patients with Langerhans cell histiocytosis.

Patients and methods: A retrospective analysis of data on 21 children with Langerhans cell histiocytosis followed at Oncology unit, Children Welfare Teaching Hospital, Medical City, Baghdad, between 1999 and 2006.

Results : The age at time of diagnosis of LCH ranged from 3 months to 9 years, with a median of 22 months, and male to female ratio was 1:1.1. The duration of the onset of the disease before diagnosis ranged from 1month to1 year. Bone lesions, skin lesions and LAP were the common presenting features. Skull was the major site of lytic lesions 10(47.6%) patients. Tissue biopsy and/or aspiration were the main diagnostic procedures. Twenty patients treated by different combinations of chemotherapy. Ten patients survived (50%), and the mean time of follow up was 28 months.

Conclusion : The study showed a relatively high incidence of advanced (III and IV) stages of disease 12 patients (57.1 %) with subsequent poor outcome and survival.

Recommendation : Long term follow-up by a multidisciplinary care team is required

Keyword : Langerhans Cell Histiocytosis, children

Introduction :

Langerhan' cell histiocytosis is a disease complex that includes the syndromes originally described as Hand-Schüller-Christian syndrome, Letterer-Siwe disease, and eosinophilic granuloma. Lichtenstein recognized the overlapping pathologic features of these entities and, in 1953, unified them, using the histiocytosis X. with the recognition that the characteristic mononuclear cells present in histiocytosis X have the properties of Langerhans cells, the term Langerhans cell histiocytosis (LCH) has been adopted for these disorders.

The morphologic impression that a lesion represents LCH should be confirmed by proving that the mononuclear cells have the ultrastructural, enzymatic, or, more often, immunophenotypic characteristics of Langerhans cells. The most common and useful diagnostic test is the demonstration of S-100 and CD1a with immunoperoxidase techniques on paraffin-embedded biopsies. Electron microscopic studies can be used to demonstrate the pentilaminar organelle, usually referred to as Birbeck granule.(1)

LCH can affect virtually any tissue and organ. Most commonly involved are the skeletal system and skin but it may also affect parenchymal organs, lymph nodes, and the central nervous system (CNS).

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LCH can manifest as a single system (SS) disease, involving only one organ system, or multisystem (MS) disease involving two or more organ systems. LCH may develop at any age but young children are most commonly affected. (2-5)

In children, SS disease has a 3-year survival of almost 100%, whereas in MS disease, in contrast, the 3-year-survival is only around 80%. (6-9)

Almost all children that die have involvement of the so-called risk organs; the liver, the spleen, the lungs, and the hematopoietic system. (7)

Patients and methods:

A retrospective study was conducted over seven year period from Jan. 1st 1999 to Dec. 31st 2006, including 21 patients consecutively diagnosed and treated as Langerhans cell histiocytosis at the Hemato-Oncology Unit in Children Welfare Teaching Hospital, Medical City/Baghdad.

The presumptive diagnosis of LCH was established based on conventional histologic finding showing multinucleated Langerhans cells, histiocytes, and eosinophils.

Immunohistochemical staining and electron microscopy that required for the definitive diagnosis were not available.

Clinical staging system for LCH (table 1) was based on (age, number of organs involved, and presence of organ dysfunction). (10) which required a thorough clinical and laboratory evaluation

(complete blood cell count, liver function test, coagulation studies, renal function test, urine for specific gravity, skeletal survey, chest radiograph, abdominal ultrasound, bone marrow aspirate/ biopsy) and in selected cases CT scan and/or MRI scan.

Table (1) Clinical staging system for LCH

Variable	*Points*
Age at presentation	
>2 years	*0*
<2 years	*1*
Number of organs involved	
< 4	*0*
≥4	*1*
Presence of organ dysfunction*	
No	*0*
yes	*1*
Stage	*Total points*
I	*0*
II	*1*
III	*2*
IV	*3*

*Hepatic, pulmonary, or hematopoietic

The criteria of Lahey (11) were used to assess organ dysfunction:
-pulmonary dysfunction: tachypnea, dyspnea, cough, cyanosis, pneumothorax, or pleural effusion attributable to LCH is present.
-Liver dysfunction: hypoproteinemia (<5.5 g/dL total protein and < 2.5 g/dL albumin or both), edema, ascites, and hyperbilirubinemia (> 1.5mg/dL total and not attributed to hemolysis).
-Hematopoietic involvement: when the hemoglobin level is less than 10 g/dL, the neutrophil count is less than 1500/mm^3, the white blood cell count is less than 4000/mm^3, or the platelet count is less than 100,000/mm^3. The presence of an increased number of histiocytes is not considered to be evidence of marrow dysfunction.

Treatment:
Steroid alone or in combination with chemotherapy had been used according to the protocols (10,12) chosen on the basis of the extent of the disease, and sometimes according to the availability of drugs. Patients were followed up at the Outpatient Clinic of the Hemato-Oncology department in Children Welfare Teaching Hospital for a period ranging from 9 months to 6 years.
The healing of lytic lesions, reduction in the size of lymph nodes, resolution of visceromegaly, absence of fever, healing of skin lesions, and normalization of laboratory parameters were regarded as signs of therapeutic response. The patients were categorized into three groups according to responses (7):
-"Better" response: total resolution or continuous remission of the disease;
-Intermediate response: stable disease and patients with remission of the disease at some sites, with development of lesions at other sites;
-Lack of response: disease progression

Relapse of the disease was defined as the development of new lesions or organ dysfunction after a 3-month stable course.
The better response patients were continued treatment as per protocol, while non- responding and relapsing cases were treated by further different combinations of chemotherapy. All irreversible clinical conditions occurring at any time during the course of the disease were regarded as sequelae.

Results:

Age at time of presentation ranged from 3 months to 9 years with a median of 22 months. Thirteen patients (61.9%) presented between 1and 3 years. Male to female ratio was (1:1.1) as shown in Table 2.

The duration of the onset of the disease before diagnosis was in the range of 1 month to 1 year. Bone lesions were the most frequent features in 13 patients (61.9%), followed by skin lesions, LAP, and fever as shown in Table 3.

On skeletal survey, thirteen patients (61.9%) had lytic lesions; Skull was the major site of the lytic lesions in 10 patients (47.6%), followed by ribs and long bones. Some patients had more than one site of lytic lesions as shown in Table 4.

Chest radiograph showed infiltration in 6 patients (28.6%). One patient (4.76%) had pneumothorax, and also 1 patient (4.76%) had pleural effusion. On abdominal ultrasound 6 patients (28.5%) had hepatosplenomegaly. Anemia was found in 11 patients (52.4%). Elevated liver enzymes seen in 3 patients (14.3%), and 1 patient (4.76%) had elevated blood urea and serum creatinine.

Tissue biopsy was the main diagnostic procedure. The most frequent site was skin in 5 patients (23.8%), bone marrow in 5 patients (23.8%), followed by lymph node in 3 patients (14.3%), and gingiva in 2 patients (9.5%). Two patients (9.5%) were diagnosed by fine needle aspirate from scalp masses as shown in Table 5.

Only 4 patients (19%) have single system involvement (bony lesions) while the rest of patients have more than one organ involvement. Advanced stages of disease (III and IV) were seen in 12 patients (57.1%) as shown in table 6.

Treatment:- table 7

One patient died before starting therapy, other 20 patients treated by a combination of steroids and chemotherapy.

Initial treatment phase:-

During the first six weeks of treatment, 3/20 patients were discharged on parent's responsibility, 3/20 died of progressive disease, 7/20 patients showed a better response, 2/20 showed an intermediate response and 5/20 showed lack of response to initial treatment.

Higher percentage of better response was noted in stage I (4 patients) and stage II (2 patients), compared with stage IV (1 patient) and none in stage III. All patients who died during initial treatment were from stage IV.

Post Initial treatment phase:

From 7 patients with Intermediate and lack of response; 5 patients got remission after receiving more intensive chemotherapy, one patient died and one lost to follow up while in progressive disease.

Five patients relapsed after variable period and all of them got remission after receiving more intensive chemotherapy.

Outcome: table 8

The follow-up period ranged from 9 month to 6 years. The mean time of follow-up was 28 months, and median time was 20 months.

From 20 patients analysis, ten patients (50%) remained alive in remission, five patients (25%) died during the follow up period, and five patients (25%) were lost to follow-up (4 with active disease and 1 during remission).

The median time of survival for those who died was 37 days and ranged from 3-108 days.

The presumptive causes of death were respiratory failure in 3patients (50%), followed by progressive disease in 2 patients (33.3%), and one patient (16.7%) died with CNS involvement as shown in table 9.

Sequela:

Diabetes insipidus was the only sequela recorded, and it was detected in two patients who presented with polyuria and polydipsia as a sign of relapse state.

Table (2) Age and Sex distribution

Age (yr.)	Male		Female		Total
	No.	%	No.	%	No. (%)
< 1	0		4	19	4 (19)
≥ 1-3	7	33.3	6	28.6	13 (61.9)
≥ 3-6	1	4.76	0		1 (4.76)
≥ 6-9	2	9.52	1	4.76	3 (14.28)
Total	10	47.6	11	52.4	21 (100)

Table (3) Clinical manifestations at time of presentation*

Manifestations	No.	%
Bone lesions	13	61.9
Skin lesions	11	52.38
Enlarged lymph nodes	7	33.3
Fever	7	33.3
Hepatomegaly and/or splenomegaly	6	28.5
Pallor	6	28.5
Scalp masses	6	28.5
Dyspnea	5	23.8
Ear discharge	4	19
Jaundice	4	19
Oral mucous membrane lesions	4	19
Cough	3	14.3
Ascitis	2	9.5
Cheek swelling	2	9.5
Convulsion	2	9.5
Loose teeth	2	9.5
Orbital proptosis	2	9.5
Cranial nerve palsy	1	4.76
Loss of vision	1	4.76
Pneumothorax	1	4.76
Pleural effusion	1	4.76
Scrotal swelling	1	4.76
Thyroid nodule	1	4.76

*Some patients may have more than one clinical finding

Table (4) Sites of lytic lesions*

Site	No.	%
Skull	10	47.6
Ribs	3	14.3
Femur	2	9.5
Humerus	2	9.5
Mandible	1	4.76
Clavicle	1	4.76

*Some patients may have more than one bone involvement

Table (5) Diagnostic procedures for patients with LCH

Diagnostic procedure	No.	%
Biopsy	14	66.67
Skin	5	23.8
Lymph node	3	14.3
Gingiva	2	9.5
Bone	1	4.76
Palate	1	4.76
Periorbital swelling	1	4.76
Thigh soft tissue mass	1	4.76
BMA/BMB	5	23.8
FNA from scalp mass	2	9.5
Total	21	100

BMA: Bone Marrow Aspirate, BMB: Bone Marrow Biopsy, FNA: Fine Needle Aspirate

Table (6) Staging of LCH according to Lahey criteria

Stage	No.	%
I	5	23.8
II	4	19
III	7	33.3
IV	5	23.8
Total	21	100

Table (7) Clinical response of 20 patients within 6 weeks of treatment*

Stage	No.	Outcome				
		Better response	Intermediate response	Lack of response	Died	Discontinued
I	5	4	1	0	0	0
II	4	2	0	2	0	0
III	7	0	1	2	1	3
IV	5	1	0	1	3	0
Total	20	7	2	5	4	3

*One patient stage III died before starting treatment

Table (8) Outcome of 20 patients with LCH who received treatment

Outcome	No.	%
Alive (free of disease)	10	50
Death	5	25
Lost to follow-up during remission	1	5
Lost to follow-up with active disease	4	20
Total	20	100

Table (9) Causes of death in 21 patients

Cause	No.	%
Respiratory failure	3	50
Progressive disease	2	33.3
CNS involvement	1	16.7
Total	6	100

Discussion:

The age of the patients at the time of diagnosis ranged from 2 months to 9 years .The median age was 22 months, which is lower than 2.5 years reported by Campos study 2007. (13)

The distribution between genders was similar; most studies describe ratios from 1.1 to 2 boys to every girl. (7,14-17)

Extensive diseases with advanced stages (III & IV) forming 57.1%. Campos (13) reported extensive disease in 48% while it was 69% in Howarth (18) study. This is probably due to delay in diagnosis or referral of children with less severe form of disease.

In all cases, the diagnosis was presumptive because we lack facilities for immunophenotyping and electron microscope which points out to the difficulty in establishing the diagnosis in our setting.

Osteolytic lesions were the major initial radiological findings of the disease, which is consistent with literature data. (2,3,19-21)

Plain x-ray was the main examination available for the diagnosis and follow-up of most osteolytic lesions as there was limitation in CT scanning and unavailability of schintigraphy which might be of help in cases that cannot be defined by radiographic examination and for anatomically complex regions.

The most common site of lytic lesion was the skull 10 patients (47.6%) higher than that reported by Howarth (30%) and Campos (38.3%). (18,13)

Lymph node involvement was the second most frequent clinical manifestation at diagnosis, it was observed in 33.3% in this study. Lymph node enlargement is described in less than 10% of children at the time of diagnosis. (3) In these cases, the definitive diagnosis would be important to confirm the disease, since the frequency observed was much higher than that described in the literature. (19)

Skin lesions were the second most frequent clinical manifestations at diagnosis, and was observed in 11 cases (52.38%) which is similar to (50%) reported by Munn (22) but higher than that reported by Campos (33.3%).

Skin lesions are often the first manifestation of LCH. (2) Of the 11 children of this study who had skin lesions, nine were in advanced stages (III & IV) which might reflect a delay in diagnosis. The possible delay in the diagnosis of skin disease, due to its similarity to other diseases, has been reported. (3)

Optimal treatment of LCH has not been established. The aim of therapy in histiocytosis is to relieve the clinical symptoms and prevent complications of the disease. (23)

Due to the observational study design and to the small number of patients, it was not possible to assess the relative efficacy of the different treatment used.

Chemotherapy was the main stay of treatment in our study, there was no role for surgery or radiotherapy due lack of multidisciplinary care team in our country, in addition to long waiting list and old generation machines in radiotherapy institute.

Five patients relapsed after remission but all of them went into a second remission after more intensive treatment. This might show that recurrence after total resolution is not a predictive factor for worse results regarding mortality. (6)

High percentage of remission was noted in stage I & II in comparison with stage III & IV.

The case fatality rate was 5/20 patients (25%) which is higher than that reported by Howarth (8.9 %), and by Campos (14%), due to higher incidence of advanced stages of disease, in addition to delay in referral of some cases and lack of facilities in others.

Respiratory failure was the major cause of death in 3 patients (50 %), followed by progressive disease in 2 patients (33.3 %), and CNS involvement in 1 patient (16.7 %). In Howarth study, (18) the major cause of death was respiratory failure (32 %) followed by second malignancy (18%). The median time of survival for those who died was 37 days and ranged from 3-108 days.

The number of sequelae found in the present study was smaller than that observed by Haupt et al.(25) who assessed 182 patients with single-system and multisystem disease and detected sequelae in 52% of them. This difference can be explained by the small number of patients and by the fact that the sequelae were not systematically investigated in the present study. The length of follow-up does not seem to have hindered the analysis of sequelae in a significant way, since most of the sequelae appear within the first years after diagnosis. Diabetes insipidus was the most frequent sequelae, which is consistent with most reports. (24,25)

The study concluded high mortality and low survival rate due to high incidence of advanced stages of disease and high rate of patients lost to follow up.

Long term follow up by a multidisciplinary care team with knowledge of LCH is recommended.

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