Langerhans Cell Histiocytosis: Clinical, Histopathological and Radiological Case Series Study: An Institutional Experience

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Authors’ contributions

This work was carried out in collaboration among all authors. Author MEG designed the study, wrote the protocol, collected the literature and wrote the draft. Author AEH shared in writing the draft and she prepared the images. All the rest of authors shared in collecting the literature and writing the draft. All authors read and approved the final manuscript.

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ABSTRACT

Background: Langerhans cells histiocytosis (LCH) is a rare disease characterized by the uncontrolled proliferation of Langerhans cells (LCs). This study aimed to explore the clinic-epidemiological and pathological data of that disease in our population.

Methods: Sixteen patients were referred to the Dermatology and the Clinical Oncology & Nuclear Medicine Departments of our university during the 6 years from 2007 to 2012. Records data were retrospectively analyzed. Pathologic specimens and radiologic films were reassessed by consultants.

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**Results:** Pediatric age and male sex predominated. The multifocal uni system (MUS) was the commonest presentation (50% of cases) while the multifocal multisystem (MMS) was found in 37.5% of cases including a case of Letterer-Siwe disease. Microscopic examination revealed dense infiltrate mainly of LCs with characteristic features and positive immunostaining for S100, CD1a and CD68. The treatment was heterogeneous. The follow-up time was well documented for 12 cases (mean=5 years). The prognosis was variable. Limitation of this study was the retrospective nature.

**Conclusions:** This case series showed the predominance of males, pediatric age, bone involvement and good treatment response. Diversity of system involvement necessitates a multidisciplinary approach. This diversity also could be a cause of underdiagnosis.

**Keywords:** LCH; Histiocytosis-x; skull infiltrative disease; hand schuller cristian disease.

1. INTRODUCTION

Langerhans cells (LCs) are histiocytes of dendritic cell lineage originating in the bone marrow and constitute 2-4% of normal epidermal cells. Langerhans cells histiocytosis (LCH) shows uncontrolled proliferation of Langerhans cells (LCs) [1,2] which commonly involve bone, skin, spleen, and bone marrow [3,4]. Most investigators consider LCH an immune defect [5-8].

LCH was classified into Letterer-Siwe disease (acute disseminated multifocal multisystem LCH that affects the skin, internal organs and bone marrow), Hand-Schuler-Christian syndrome (chronic multifocal multisystem LCH) and eosinophilic granuloma (uni system with single or multiple lesions) [1,5,7,9]. The unifocal form is usually of benign course, while the multi-focal and multisystem forms are more serious [8,10-12]. Letterer-Siwe disease has the worst prognosis especially in the first 2 years of life 1,3.

LCs stained with Hematoxylin and Eosin (Hx&E) appear as clear cells in the epidermis and the epithelium of mucous membranes. Yet, the diagnostic gold standard is the detection of the tennis-racket-shaped intracytoplasmic Birbeck granules, with the electron microscope (EM). The definitive diagnosis of LCH is based on the immunophenotypic expression of proteins like S-100, CD1a and CD68 [1,13,14].

The present work aimed to retrospectively analyze the clinical manifestations, histopathological and radiological features of LCH cases presented to the Dermatology and the Clinical Oncology & Nuclear Medicine Departments of our University Hospital.

2. CASE PRESENTATION AND DESIGN

This retrospective study analysed data of LCH patients in both the Dermatology and the Clinical Oncology & Nuclear Medicine Departments during the 6 years from 2007-2012.

Exclusion criteria included missing pathology specimen and the existence of major comorbidities.

The following data were collected: age, sex, symptoms, signs, lesions description, radiology, treatment is given, response, follow up and outcome. Tth diseased tissue and healthy specimens were processed and stained with Hx & E. Also, immunostaining for S100 protein (rabbit polyclonal anti-S100 antibody; Sigma Bioscience, St Louis, Mo, dilution 1:800), CD1a (mouse monoclonal anti-CD1a antibody; Novocastra, dilution 1:200) and CD68 (monoclonal antibody MA1-80133; Thermo Scientific, dilution 1:50) was done. Tissue processing techniques were according to published guidelines [15,16]. Pathologic diagnosis was confirmed by transmission EM.

Radiologic films were reviewed by the radiology consultant.

2.1 Statistical Analysis

Mean and median were calculated for continuous variables as age while categorical variables as sex were expressed as numbers and percentages. Follow up was calculated from the end of treatment till the date of the last visit or death while overall survival was calculated from the date of diagnosis till the date of last visit or death.

3. RESULTS

This case series study included 16 patients with LCH; 12 males & 4 females (ratio 3:1) showing an age range from 13 months to 50 years old.
Lesions were unifocal unisystem (UUS) [2 patients (12.5%)], multifocal-unisystem (MUS) [8 patients (50%)] and multifocal-multisystem (MMS) [6 patients (38%)] (Tables 1-5) and (Figs. 1, 5 and 8).

UUS lesions were in bones while MUS were in bones in 6 patients and other tissues like skin and lymph nodes in 2 patients. Lastly, MMS affected different tissues like bone, skin, lymph nodes (LN), genital system, spleen, bone marrow and brain.

Bone was the commonest system affected in the present study [6 patients (37.5%)].

Pathological features of skin and lymph nodes in comparison to the normal histology were illustrated in Figs. (2,3,4,6 and 7). These figures illustrated the abnormal marked cellular infiltration, the large LCH with the coffee beans-like nucleus, the EM image of intracytoplasmic Birbeck granules and the different immunostaining.

Fig. 1. A case of Letterer-Siwe disease (13 months old female): (A) purpuric papules over the back (B) Seborrhea like lesions and skin atrophy in the flexures (C) Crusted lesions and bacterial super infection over the scalp (D) Onycholysis, paronychia and palmoplantar keratoderma of both hands (Clinical details in Table 5; case No1)

Fig. 2. Microscopic examination of normal skin: (A) The epidermis (E) with normal dermal papillae and the dermis (D) with few cells in the papillary and reticular layers. (Hx & E X 400). (B) An electron micrograph of a normal epidermal LC between suprabasal KCs (k). LC shows large folded nucleus (N) and characteristic intracytoplasmic Birbeck granules (b) "tennis racquet appearance" (X 23000, Inset X 6000)
Different management plans were applied according to the extent of disease. Two patients underwent surgical treatment (13%), 12 patients received chemotherapy (75%) while 7 patients (44%) received radiotherapy. One case (6%) was treated by cautery and laser. The chemotherapy regimens were based on vinblastine and prednisolone. Follow up ranged from 2.5 months - 10 years (mean=5 years). Nine patients (56.25%) showed a satisfactory response. On the other hand, 3 cases showed progression. Overall survival ranged from (4 months – 10 years). Lastly, four patients (25%) had undocumented or irregular follow up.

4. DISCUSSION

Although LCH is usually curable, it can cause sequelae affecting various tissues involved [3]. Some may be present at diagnosis, while others manifest decades later.

The majority of our patients were males of pediatric ages suffering from bone lesions. These findings are in harmony with literature [4-7,12,17-21]. However, equality in the incidence of the disease between both sexes was reported as well [8].

Morren et al. [10] published an interesting retrospective study about different cutaneous presentations in a cohort of 32 children. He reported that none of the cutaneous lesions was predictive for the outcome. Thus, even skin-limited LCH needs strict follow up. Skin lesions were found in 4 of our cases (25%), a rate similar to that reported by Sun et al. [17] but less than what was reported by Haupt et al. [4] and Rautenbach & Stones [2] who reported skin involvement in 33% and 40% respectively. The riskiest of our cases with skin lesions was the case of Letterer-Siwe disease (Table 5; case No.1). She was similar to the case described by
Das et al. [3] who reported diffuse cutaneous eruption resistant to traditional treatment in an 11-months male who developed later organomegaly and lung infiltration and died due to respiratory failure. Similarly, Plotski et al. [1] reported skin lesions in a newborn together with lung and lymph node infiltration as proved by autopsy after death due to respiratory failure.

Fig. 4. A - 6 year-old female with multiple, firm, dome shaped, umbilicated skin colored papules MUS LCH in: upper limbs [A], lower limbs [B] and back [C](Clinical details in Table 4; case 2). [D] A lesional skin biopsy showing a dense upper dermal cellular infiltrate and thickening of the overlying epidermis (Hx&E x 100). [E] Positive S100 immune reaction in dermal cellular infiltrate and some epidermal cells (S100 x 100). [F] CD 68 +ve immune reaction in the dermal infiltrate (CD 68 x 100)
Fig. 5. A - 44 year-old female with Multifocal Multisystem LCH: Intraoral view after extraction of all teeth showing: Generalized alveolar bone loss with multiple ulcers surrounded by a halo of erythema observed on the right side [A]. An alveolar mass on the left side [B]. Multiple genital ulcerations over the vulva and perineum with underlying skin hyperplasia [C] (Clinical details in Table 5; case 3)

Fig. 6. Skin biopsy of the genital ulcer: [A] Pseudoepitheliomatous hyperplasia of the epidermis (asterisk), ulcerated epidermis (arrow), and nodular aggregates of histiocytes & eosinophils in the dermis (H&E x40). [B] A higher magnification showing cellular infiltrate of LCs (arrow heads) and inflammatory cells including eosinophils (arrow) (H&E x400). [C] Dense dermal infiltrate rich in cells with +ve S100 immune reaction, (S100 X40). [D] Positive CD1a immune reaction especially in the deep dermis (CD1a X40). [E] Positive CD68 immune reaction all over the dermis (CD68 X40)
Oral and vulval involvement in LCH has miscellaneous patterns [8,14,17]. We presented a 44-year female diagnosed 7 years ago with mastoid bone LCH and presented to us with recurrent oral & genital ulcerations (Table 5; case No.3 & Fig. 5). An initial biopsy of a gingival lesion 6 years ago was misinterpreted as squamous cell carcinoma that necessitated the extraction of all teeth. Similarly, Hegemann & Schreml reported of a 77-year-old male who presented with plaques and ulcerations in the groin with multiple oral & mandibular lesions, hearing deficiency, otorrhea and enlarged lymph nodes. They explained loosing of teeth by the gingival and alveolar bone infiltration and discouraged extraction of teeth in these cases [12]. However, tooth extraction in our case was due to the initial misdiagnosis. Lajolo & his colleagues [18] reported a similar case with MMS- LCH in a 77-year-old female with genital and oral ulcers, bilateral parotid lesions and diabetes insipidus. Batra et al and Tiwari had reported similar lesions as well [5,20]. Indeed, radiologists and ENT specialists have to be minded by LCH. On the other hand, oral –only lesions were reported by Shooriabi et al. [8] and Altay et al. [14] highlighting the importance of dentists perception of the disease.

LCH could present by lymphadenopathy [22]. Lymphadenopathy was encountered in 4 cases (25%) of our series. This per cent is more than that reported by the interesting review of Haupt et al. [4] (5-10%). Isolated LN involvement could be managed by close follow up [23,24], however, this was not our institutional policy.

Two of our cases who died from progressive disease had splenic involvement. Spleen is considered in literature as one of the high-risk organs in LCH [25].
CNS involvement may cause neuroendocrine deficits [13,26]. The triad of Hand-Schuller-Christian (exophthalmos, diabetes insipidus and skull lytic lesions) exists in no more than one-third of cases [27]. We presented one Hand-Schullers-Christian case (Table 5; Case No. 2), who presented with skull masses, intra-cranial lesions and diabetes insipidus with no exophthalmos. Bonifazi and Milano [13] reported a higher percentage of the triad in their respective review (20-25%).

Since the first LCH Classification in 1987, several molecular findings have been detected. The new classification system consists of 5 groups of diseases: (1) Langerhans-related, (2) cutaneous and mucocutaneous, (3) malignant histiocytoses (4) Rosai-Dorfman disease (5) Hemophagocytic lymphohistiocytosis and macrophage activation syndrome [28]. LCH is characterised by immature LC plus variable inflammatory cells [1,18]. LCs appeared large acidophilic nearly rounded cells which differs from LCs of normal epidermis which have clear cytoplasm and dendritic shape as described in literature by Sauget et al. [29] and Shooriabi et al. [8]. Birbeck’s granules must be detected by electronic microscopy. Moreover,

Fig. 8. MRI of case of MUS LCH: 5-year old male child with right proptosis (Table2, case no.1). Non-contrast (A and B) and post-contrast (C and D) axial T1 MRI of the brain reveal destructive enhanced bony lesions of right orbital roof & both parietal bones with right proptosis. Pathologically proved LCH.
### Table 1. Unifocal–Unisys stem LCH group (n=2)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Presentation</th>
<th>Investigations</th>
<th>Treatment &amp; fate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-</td>
<td>Male</td>
<td>4.5 years</td>
<td>Recurrent mandibular swelling after 3 years from a previous excision of a similar lesion in another tertiary oncology center.</td>
<td>-Bone survey: free apart from the mandibular osteolytic lesion (recurrence). Biopsy:LCH</td>
<td>Chemotherapy: one year course of Triple therapy. Radiotherapy: 600 cGy/3 sittings. Follow up: response was satisfactory.</td>
</tr>
</tbody>
</table>

### Table 2. Multifocal-Unisystem LCH in the skull bones (n=4)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Presentation</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Male</td>
<td>5 years</td>
<td>Gradually developing skull lesions and proptosis of 1 year duration.</td>
<td>MRI: destructive enhanced bony lesions of right orbital roof &amp; both parietal bones with right proptosis (Fig 8: A-D). Biopsy:LCH</td>
<td>Chemotherapy: one year course of Triple therapy. Follow up: response was satisfactory.</td>
</tr>
<tr>
<td>2.</td>
<td>Female</td>
<td>2.5 years</td>
<td>Hard, non-tender Skull swellings of 3 months duration with gradual onset and progressive course.</td>
<td>X-ray skull: osteolytic lesions of right frontal and parietal bones. Biopsy:LCH</td>
<td>Unknown (lost follow up).</td>
</tr>
<tr>
<td>3.</td>
<td>Male</td>
<td>7 years</td>
<td>Multiple skull lesions 4 years after previous excision of solitary parietal bone lesion in another center.</td>
<td>Bone survey and CT scan characterized the skull lesions. Biopsy:LCH</td>
<td>Chemotherapy: one year course of Triple therapy. Radiotherapy: 1000 cGy/5 sittings. Follow up: response was satisfactory.</td>
</tr>
<tr>
<td>4.</td>
<td>Male</td>
<td>8 years</td>
<td>Two years history of gradually developing parietal bone lesions.</td>
<td>Bone survey and CT scan characterized the skull lesions. Biopsy:LCH</td>
<td>Chemotherapy: one year course of Triple therapy. Radiotherapy: 1000 cGy/5 sittings. Follow up: response was satisfactory.</td>
</tr>
</tbody>
</table>
Table 3. Multifocal-Unisystem LCH in the skull bones and/or other bones (n=2)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Presentation</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Male</td>
<td>2 years</td>
<td>Limping of 3 months duration.</td>
<td>X-ray: osteolytic lesions of skull, left radius, vertebrae and left femur neck. Biopsy:LCH</td>
<td>Chemotherapy: six months course of Triple therapy. Follow up: response was satisfactory</td>
</tr>
</tbody>
</table>

Table 4. Multifocal-Unisystem LCH in the lymphatic system and skin (n=2)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Presentation</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Male</td>
<td>11 years</td>
<td>Cervical and hilar lymphadenopathy of 3 months duration.</td>
<td>Lymph node biopsies revealed marked LCS and eosinophil cell infiltration (Fig. 7: A-D)</td>
<td>Chemotherapy: Triple therapy for 1 year. Followup: satisfactory response.</td>
</tr>
<tr>
<td>2.</td>
<td>Female</td>
<td>6 years</td>
<td>Multiple, firm, dome shaped, umbilicated skin colored papules all over the body of gradual onset and progressive course over 2 years (Fig. 4: A-C).</td>
<td>-Bone survey, brain CT, chest X-ray, abdominal US: free. -Skin biopsy revealed LCH (Fig. 4: D-F).</td>
<td>-Cautery and laser Follow up: No response.</td>
</tr>
</tbody>
</table>

Table 5. Multifocal-Multisystem LCH group (n=6)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Presentation</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Female</td>
<td>13 months</td>
<td>&quot;Letterer-Siwe disease&quot;</td>
<td>-Scaly erythematos papules on the back, abdomen, and proximal extremities. There is super infection over the scalp and hands (onycholysis and paronychia) (Fig. 1; C, D). -Seborrhea-like lesions and skin atrophy in the flexures (Fig. 1; A, B).</td>
<td>-Abdominal US: HSM &amp; LN enlargement. -Chest x-ray: chest infection. -Skin biopsies revealed LCH (Fig. 3). -LN biopsy was positive for LCH. -BM was not infiltrated by histiocytes.</td>
</tr>
<tr>
<td>Patient</td>
<td>Sex</td>
<td>Age</td>
<td>Presentation</td>
<td>Investigations</td>
<td>Treatment</td>
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<tr>
<td>3.</td>
<td>Female</td>
<td>44 years</td>
<td>Right auricular pain, discharge and appearance of right mastoid mass 7 years ago. Toothache, floating teeth, oral ulcers, gingival ulcers, gingival hyperplasia (Fig. 5). Recurring and resistant genital ulcers along 2 years duration.</td>
<td>Mastoid mass biopsy: LCH. Biopsy of skin &amp; genital ulcers revealed LCH (Fig. 6: A-E).</td>
<td>Surgery: Right mastoidectomy since 7 years. Chemotherapy: Triple therapy. Follow up: Progression</td>
</tr>
<tr>
<td>4.</td>
<td>Male</td>
<td>50 years</td>
<td>Recurrent rigors and stitching pain in left hypochondria with large spleen and a hard mass of left clavicle of 7 months duration.</td>
<td>Abdominal US: marked enlargement of spleen with hypoechoic sub capsular masses plus isoechoic LNs at splenic hilum.</td>
<td>Chemotherapy: Four months course of double therapy + Palliative radiotherapy on clavicular mass (1500 cGy in 1.5 week in 7 sittings). Progression was reported.</td>
</tr>
<tr>
<td>5.</td>
<td>Male</td>
<td>16 years</td>
<td>Gradual enlargement of axillary &amp; inguinal LNs over 4 months with ulceration of overlying skin.</td>
<td>LN &amp; skin biopsies: marked LC and eosinophil infiltration.</td>
<td>Chemotherapy: One year course of triple therapy. Satisfactory response.</td>
</tr>
<tr>
<td>6.</td>
<td>Male</td>
<td>24 years</td>
<td>Pain all over left lower limb of 3 months duration.</td>
<td>X-ray: Osteolytic lesion of left greater trochanter. Biopsy: LCH Bone marrow aspiration: LCH.</td>
<td>Chemotherapy: One year course of triple therapy. Radiotherapy 1000 cGy/5 sittings. Follow up: Response was satisfactory.</td>
</tr>
</tbody>
</table>

HSM = hepatosplenomegaly. BM = Bone marrow. Triple therapy = vinblastine, methotrexate and prednisolone. Double therapy = vinblastine and prednisolone. LN = Lymph node. VAP protocol = vinblastine 1.5 mg/m2, Arachidonic acid 100 mg/m2 and prednisone 40 mg/m2.
CD1 antibodies, S-100 protein and CD68 must be found to be positive [4,6,13,14]. S100 proteins are localized in the cytoplasm and the nucleus of a wide range of cells including LCs and macrophages. They are involved in regulation of cellular processes such as cell growth, differentiation, cell cycle, transcription, structural organization of membranes and dynamics of cytoskeleton constituents [30]. Regarding CD1a, it is an antigen on the surface of LCs which is used in presenting lipid antigens to T cells [31]. Lastly, CD68 is a transmembrane glycoprotein that is expressed in cells of the mononuclear phagocyte lineage [32]. It is classified as a member of the scavenger receptor family, whose functions include clearance of cellular debris [33].

Combined chemotherapy for multisystem lesions and surgical operation or radiotherapy for unifocal lesions was the general adopted treatment policy in literature [34] and for our cases as well. The International Histiocyte Society have conducted several studies on multisystem LCH since the early 1990s. The standard protocol in those trials consisted of 6-12 weeks of initial therapy (daily oral steroids and weekly vinblastine injections), followed by pulses of prednisolone/vinblastine every 3 weeks, for a total treatment duration of 12 months [35]. Ongoing studies aim at tailoring treatment intensity depending on expected risk [36].

Three of our MMS cases responded poorly to treatment, rapidly progressed and died (Table 5; cases No.1,3,4). The correlation between multiple organ infiltration and non durability of response were documented in literature [11,25].

Enviromental factors could play a role in pathogenesis of LCH. Pulmonary LCH was proved to be associated with smoking [37]. However, we were not able to define LCH-related environmental factors in our series.

This series can not be indicative of the real incidence of the disease in our locality as the variable disease presentations suggest that their might be undiagnosed cases.

5. CONCLUSION

Our LCH case series showed predominance of male sex, pediatric age and bony affection with favourable outcome in most cases. Diversity of system involvement necessitates a multidisciplinary approach for management. Dentists and radiologists should be aware about the different presentations of the disease.

6. LIMITATIONS OF THIS STUDY

Limitations of this study include the retrospective nature with missing follow up data and the small number of patients.

CONSENT AND ETHICAL APPROVAL

The study protocol was approved by our institutional Ethical Committee. Patient's families gave informed consent.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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