EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 5
01-07
Year: 2016

INFANTILE LANGERHANS CELL HISTIOCYTOSIS, FROM DIAGNOSIS TO TREATMENT, A CASE REPORT

Rawya Awada MD[1], Hassan Khalifeh MD[2], Ali Zaitoun MD[3], Bassem Abou Merhi MD*[1], Imad Chokr MD[1], Nawfal Nawfal MD[1] and Youmna Mourad MD[4]

[1]Department of Pediatric, Lebanese University, Faculty of Medical Sciences.
[2]Department of Pediatric Hematology and Oncology, Lebanese University, Faculty of Medical Sciences.
[3]Department of Pediatric, Bahman Hospital, Lebanon.
[4]Clinical Pathologist, Zahraa University Hospital.

***Corresponding Author: Dr. Bassem Abou Merhi MD**
Department of Pediatric, Lebanese University, Faculty of Medical Sciences.

Article Received on 24/02/2016 **Article Revised on 15/03/2016** **Article Accepted on 05/04/2016**

ABSTRACT
Langerhans Cell Histiocytosis (LCH) is a rare disease of unknown origin with a heterogeneous clinical presentation, varying from benign and self-limited to lethal. It is classified as single or multisystem, according to the number of organs involved (one or at least two, respectively). Diagnosis can be challenging and is based on the histological and immune-phenotypic examination of affected tissues. This proliferative disorder consists in an accumulation and infiltration of monocytes, macrophages, and dendritic cells in the affected tissues. Herein, we report a 2-months old infant with findings of LCH and summarize the classification, manifestations, pathology, prognosis and treatment.

KEYWORDS: Langerhans Cell Histiocytosis (LCH), 6-Mercaptopurine (6MP), World Health Organization (WHO), Mononuclear Phagocyte System (MPS).

INTRODUCTION
Historically, several nomenclatures were used to describe histiocytic disorders such as Histiocytosis X, Eosinophilic Granuloma, but due to the development of new ultra structural and immunohistochemical techniques, "Langerhans cell Histiocytosis" was known to be the preferred nomenclature. Langerhans cell Histiocytosis (LCH) is a proliferative disease of histiocyte-like cells, with a wide range of clinical presentations that vary from a solitary lesion to more severe multifocal or disseminated lesions in any body organ including osteolysis, ulcerations of the skin and soft tissues, and occasionally visceral involvement. The most frequent sites of a visceral manifestation are the lungs, followed by the skin and the lymph nodes.[2-5] The disease is rare with estimated annual incidence ranging from 0.5-5.4 cases per million persons, per year,[15] with male predominance[7,8] and higher prevalence among whites.[4]

It can affect any age group; however, the peak incidence rate is in infants aged between 1 and 3 years-old. The incidence appears to be three to five cases per million children, which is the same as pediatric Hodgkin lymphoma, and one to two cases per million adults.[6,7]

An epidemiologic study from the United States suggested a connection between solvent exposure in parents, as well as perinatal infections, and no increased incidence after viral epidemics.[9] Herein we report a two months old girl infant with LCH who presented with continuous crying and irritability, bloody diarrhea and osteolytic bony lesions. Through this rare case, we summarize the clinical manifestations, pathology, diagnosis and treatment of LCH.

CASE REPORT
A 2- months-old baby girl, full term, born by normal vaginal delivery, with no neonatal intensive care admission at birth, to a non consanguineous parents, admitted to Bahman Hospital for History which goes back **to 1 month** prior to presentation when the baby started to have bloody stools (more than 4 episodes/day), associated with fever sometimes reaching 39 degree. She was admitted to another hospital one month prior to this admission where investigations showed Amebiasis (in stool) for which she was discharged on Metronidazole. Past surgical history was negative.

On physical examination, the child was pale and irritable; she had hardness in the soft tissue of the right thigh. No abnormal or dysmorphic features, neither

palpable goiter, nor heart murmur or hepatosplenomegaly.

Family history was negative of malignancies and Histiocytosis. Laboratory data upon admission revealed hemoglobin of 9.27 (low) with white blood cell count of 11.000 (67% neutrophils and 20% lymphocytes) and platelet count of 651000 (elevated). Clotting time, bleeding time and prothrombin time were normal. Blood film inspection showed: hypochromic, anisocytosis tending to microcytosis, few schistocytes/ Normal WBC/ thrombocytosis with large platelets. Electrolytes and creatinine level were normal as well as bilirubin, thyroid function studies, calcium, phosphorus PTH level and vitamin D level. CRP was 125 mg/L (normal: 0-5mg/L). Alkaline phosphatase 425 U/L (normal: 30-120U/L) and LDH 276 U/L (normal: 140-271U/L). EBV and CMV serology were negative. Fourth day of admission the baby became pale started to have bloody stools and turbid urine with hematuria? So CBCD was repeated to show hemoglobin of 5.5. Also developed periorbital and facial edema, total serum protein showed albumin=24 G/L (normal: 38-51G/L), so she was transfused with fresh packed cell.

Skull X-ray showed multiple irregular osteolytic lesions (Fig.1). A complete skeletal survey also revealed disseminated osteolytic lesions mainly left tibia (Fig.2 and Fig.3). On MRI brain and spine, bilateral periosteal reaction and subperiosteal edema at the diaphysis of both femurs and to a lesser extent at both tibias, also multiple areas of abnormal signal at both femurs, with loss of weight of the vertebral bodies T12, L1 and L2 with H shaped vertebra were noted (Fig.4). While the images of the brain, abdomen and pelvis were unremarkable. This appearance orients toward Histiocytosis X.

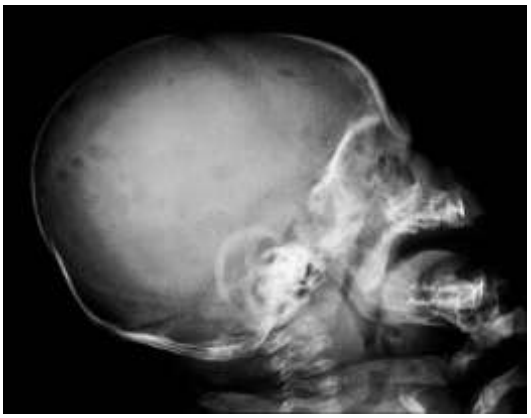

Figure 1: Osteolytic skull lesions on lateral view of skull X-ray

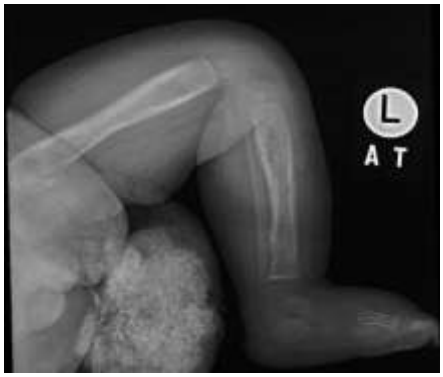

Figure 2: Left tibia revealed osteolytic lesions by skeletal survey

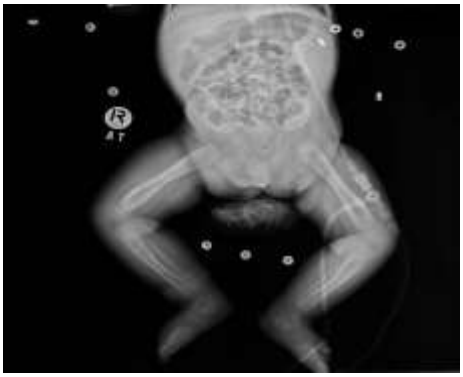

Figure 3: Skeletal survey showing disseminated osteolytic lesions

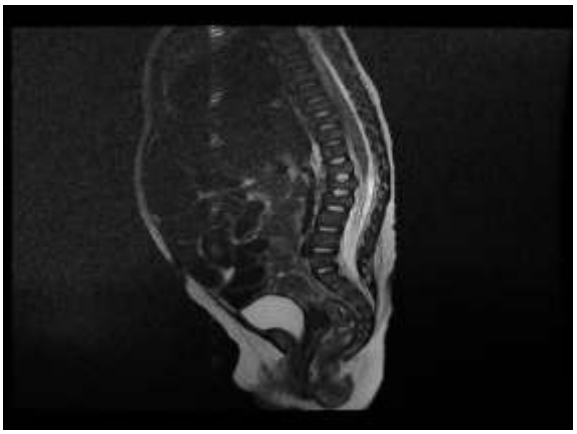

Figure 4: MRI spine showing loss of weight of the vertebral bodies T12, L1 and L2 with H shaped vertebra

A percutaneous needle biopsy of bone (left tibia) was performed under ultrasound guidance, and showed features compatible with LCH. Histological examination of the biopsy showed a bony tissue with morphology and phenotype suitable for Langerhans Cell Histiocytosis X. The medullar spaces demonstrated increased cellularity with an increase of macrophages and eosinophils, while immunohistochemical technique showed a mild positivity with CD1a and S100 protein. No signs of malignancy have been showed.

Day six of admission she developed periorbital and facial edema, Total Serum Protein showed albumin=24 g/l (normal: 38-51g/l) so she was given albumin once and had improvement of her edema. Day ten of her hospitalization she started to have bad smell urine and

analysis showed to numerous WBC and positive leucocyte esterase and positive Nitrites so UTI that was suspected and treated with Cefotaxime (Claforan for 7 days) inspite of negative culture.

At the day of discharge, after 15 consecutive days of hospitalization, a polysite catheter was inserted and the baby was planned to be started on chemotherapy within 1 week according to protocol consisting of Prednisone, Vinblastine and 6-Mercaptopurine because treatment of multiorgan disease is controversial, with some advocating high dose prednisone as the first line therapy, whereas others suggesting use of single agent chemotherapy.

DISCUSSION

The Histiocytoses are a diverse group of hematologic disorders defined by the pathologic infiltration of normal tissues by cells of the Mononuclear Phagocyte System (MPS). The heterogeneity of this family of disorders, a direct result of the biologic variability of the cells of the MPS and the tissues they inhabit, makes the study of these diseases one of the most intriguing yet complex areas of modern hematology.

Advances in basic hematology and immunology over the last two decades have significantly enhanced our understanding of the Histiocytic disorders. It is now accepted that the pathogenic cells central to the development of the Histiocytoses arise from a common hematopoietic progenitor. More specifically, the ability to molecularly identify the hematopoietic cells has enabled us to classify the Histiocytoses based on the cellular basis of the disease and to define the natural history of these disorders.[1,2]

In the past, there had been a great deal of confusion as to how to classify the Histiocytoses since the exact ontogeny was not well understood. However, with the advent of immunohistochemical techniques, the Histiocyte Society proposed reclassification of these disorders based upon the predominant cell type in the infiltrate. This initial classification system included: Langerhans Histiocytosis (Class I), Non-Langerhans Cell Histiocytosis (Class II) and malignant Histiocytosis (Class III) [3] (table 1). As more information has become available, a revised classification of hematopoietic and lymphoid tumors done by the World Health Organization (WHO) divides disorders of these cells into the following three categories: dendritic cell disorders, macrophage-related disorders, and malignant Histiocytic disorders.[4]

One of the most common Histiocytosis is LCH which is considered a rare proliferative disorder that primarily affects children. Langerhans cells has the potential to accumulate in a number of different sites and organs, including the bone, lungs, liver, spleen and lymph nodes ultimately leading to a disease process.[5]

The genetics of LCH have not been well elucidated. There is no evidence that relatives of patients with LCH are at increased risk of developing LCH. Very rarely are twins or singleton siblings concordantly affected, despite a few reported cases with early disease presentation and similar organs affected in presumed monozygotic twins.[10] One report described three cases with skin and bone involvement in one Iranian family.[11] Another study noted an association with a family history of thyroid disease, but the meaning of this finding is not understood.[12]

Rarely, LCH has been described in patients with other concomitant Histiocytic disorders, such as Erdheim-Chester Disease and Rosai Dorfman Disease.[13,14]

Concerning pathogenesis, LCH is so named because of a presumed derivation from the morphologically similar Langerhans cells, which are specialized dendritic cells found in the skin and mucosa. However gene expression array data have shown that the skin Langerhans cell is not the cell of origin for LCH. Rather, it is a myeloid dendritic cell that expresses the same antigens (CD1a, CD 207) as the skin Langerhans cell. Peripheral monocytes found in normal blood can differentiate into macrophages and interstitial dendritic cells that may travel through lymphatics to draining lymph nodes. There are probably two populations of circulating myeloid dendritic cells that can differentiate into committed dendritic cells. Expression array results support the notion that one of these could become the pathologic dendritic cell in LCH.[16]

Although a few studies have purported to show evidence of viruses in LCH lesions, the weight of evidence does not support a viral etiology of LCH.[17,18]

The debate regarding whether the disorder is reactive or neoplastic is now clearly tilted to an inflammatory myeloid neoplasia because of two mutations found in up to 75 percent of all LCH biopsies.[19] Some, but not all, cases of LCH are clonal. The Langerhans cells in biopsies of children with single system or multisystem disease are caused by proliferation of a single clone. Although clonal proliferation is a hallmark of neoplastic conditions, it can also be consistent with a reactive process. Further study is needed to elucidate the pathogenesis of LCH.

Table 1: Classification of Histiocytosis

	Diseases	Cellular Characteristics of the Lesions
Class I	Langerhans cell histiocytosis	Langerhans cells (CD1a positive) with Birbeck granules
Class II	Familial erythrophagocytic lymphohistiocytosis	Morphologically normal reactive macrophages with prominent erythrophagocytosis
	Infection-associated hemophagocytic syndrome	
Class III	Malignant histiocytosis	Neoplastic proliferation of cells with characteristics of monocytes/ macrophages or their precursors
	Acute monocytic leukemia	

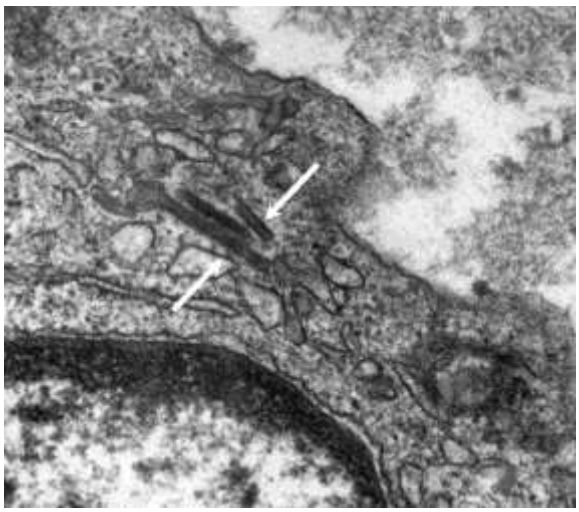

Figure 5: Electron Microscopy demonstrating ultrastructural Birbeck granules (Cluster between two arrows)

The clinical manifestations of patients with LCH vary depending upon the sites and extent of involvement. The disease is limited to one organ system (bone) in approximately 55% of patients, while the remainder presents with multisystem disease.[20] More than half the patients younger than 2 years with disseminated LCH and organ dysfunction die of the disease, whereas unifocal LCH and most cases of congenital self-healing Histiocytosis are self-limited.

In order of decreasing frequency, the following areas are involved at the time of diagnosis: bone (77 %), skin (39%), lymph nodes (19%), liver (16%), spleen (13%), oral mucosa (13%), lungs (10%), and central nervous system (6%). Disseminated multisystem disease is most commonly seen in children less than 3 years of age while a more indolent disease involving a single organ is more common in older children and adults.

Bone involvement occurs in the majority of patients with LCH. Although some lesions are asymptomatic, the patient may complain of pain in a localized area of bone; Examination usually reveals a raised, soft, tender spot. Radiologic studies typically demonstrate a lytic, "punched out" appearance, sometimes with an accompanying soft tissue mass. LCH can involve any bone of the body, and the most common sited differ depending upon the patient's age. In children, the most frequent sites of involvement are the skull (40%), femur, rib, vertebra and humerus.[21] The digits are involved only in the most diffuse cases. Spine lesions in children are most often located in the cervical vertebrae and are frequently associated with other bone lesions.[22]

Skin involvement is seen in approximately 40 % of patients. The most common skin manifestations are brown to purplish papules referred to as congenital self-healing reticulohistiocytosis and an eczematous rash resembling a candidal infection. Other skin lesions may be pustular, purpuric, petechial, vesicular, or papulo-nodular.[22]

LCH can manifest in children and adults as a red papular rash that occurs in the groin, abdomen, back, or chest and resembles a diffuse candida diaper rash. The most common oral manifestations of LCH are intraoral mass, gingivitis, mucosal ulcers, and loose teeth. Pain and mass effects can derive from lesions of the bones or soft tissues.

Lymphadenopathy is seen in approximately 20 percent of patients. Cervical nodes are most commonly involved. On physical examination, involved nodes are usually soft and matted. An enlarged thymus or mediastinal nodes can mimic lymphoma or an infection and may cause asthma-like symptoms due to compression of local structures.

The liver and spleen are both "risk organs" and involvement denotes a worse prognosis. Hepatic involvement can include tumor-like or cystic lesions, or overall hepatomegaly, and can be accompanied by elevated liver enzymes, hepatic dysfunction, leading to hypoalbuminemia with ascites, hyperbilirubinemia,

and/or clotting factor deficiencies.[23] Lung involvement is seen in approximately 10% of cases. It is less frequent in children than in adults, in whom smoking is a key etiologic factor. Children with uncontrolled LCH may develop chronic respiratory failure, presenting with cysts or bullae.

LCH involves the central nervous system (CNS) in approximately 6% of patients at the time of diagnosis.[20] MRI is the imaging modality of choice to visualize CNS involvement. Posterior pituitary involvement: Diabetes Insipidus is the most frequent endocrine abnormality in LCH manifesting with polyuria, nocturia and/or polydipsia. Other endocrinopathies can also occur: hypogonadism, growth failure abnormalities of glucose metabolism (Diabetes Mellitus), enlarged thyroid gland.

Gastrointestinal system involvement of LCH is uncommon. Approximately 2 percent of patients present with diarrhea or malabsorption.

LCH is diagnosed based upon biopsy with the pathologic evaluation of involved tissue interpreted within the clinical context. A biopsy of an osteolytic bone lesion or skin lesion is generally preferred. LCH can be difficult to diagnose since it is an uncommon disease that can affect many organ systems. LCH in bone, Lymph nodes, thymus, liver or spleen can be confused with lymphomas, solid tumors, or primary CNS tumors including Germinoma and Meningioma. The Histiocyte Society has established a set of guidelines to assist in the diagnosis and study of LCH [24]. The initial evaluation consists of a complete physical examination, inclusive of height and weight measurements, in addition to laboratory studies including hematological assays and coagulation studies, liver function tests, and urine osmolality. Although some authorities advocate bone marrow examination in every baseline examination, it is not required unless symptoms or blood tests suggest involvement. Lastly, the patient must have a complete skeletal radiographic survey and chest radiography. Patients with identified abnormalities require more specific studies, such as pulmonary function tests and lung biopsy, small bowel series, liver biopsy, panoramic dental films, CT or MRI of the brain with particular attention paid to the hypothalamic-pituitary axis, endocrine evaluation and otolaryngology consultation with audiogram. Since patients with LCH often have chronic and recurrent disease, follow-up studies are required every month to 6-months, depending upon organ system involvement and the degree of organ dysfunction.[24]

To aptly determine a patient's prognosis and treatment protocol, it is currently recommended that patients are risk-stratified based upon the number of organs involved and degree of organ dysfunction.[24,25,26,27,28]

Patients diagnosed with organ dysfunction are further stratified based upon which organ system is involved. Patients with involvement of the spleen, lung, liver or hematopoietic system often have a worse prognosis.[26,28] Although some studies found that the younger the patient is at the time of diagnosis, the worse the prognosis, this only holds true when multiorgan involvement is present, because neonates who present with isolated cutaneous lesions do exceptionally well.[28]

In the past, treatment for LCH was anecdotal and without consensus. However, within the last 20 years several multi-centers, randomized therapeutic trials have contributed to a more uniform treatment approach. Patients with limited cutaneous disease typically require no therapy. If therapy is required, topical steroids may be tried as a first line treatment. Patients, who are non-responsive to steroids, can utilize topical nitrogen mustard or PUVA therapy as viable second-line options.[29-30]

For patients who have localized bone lesions, curettage is generally sufficient for diagnosis as well as therapy, although some cases may require intralesional steroids or low dose radiation.[31] Treatment of multiorgan disease is controversial, with some advocating high dose prednisone as the first line therapy, whereas others suggesting use of single agent chemotherapy.[29-32-33]

More recently, several large cooperative studies have shown that multi-agent chemotherapy that is sustained over a longer duration results in a greater response with fewer reoccurrences.[30] Currently, the LCH III treatment protocol is probably the most common therapeutic strategy used in children with multiorgan involvement. In the future, monoclonal antibodies that target CD1a or CD207 or specific cytokine inhibitors maybe employed.[29,30]

As a result of recent therapeutic trials, it has been shown that the single best prognostic indicator is a patient's response to chemotherapy during the 6-week induction phase.[28] Patients who respond to chemotherapy during the first 6 weeks of therapy have an 88-91 % survival rate, but survival rates drop to 17-34 %t in patients who fail to respond. It has been advocated that non-responders be identified early so that more aggressive therapy may be employed.[28,30]

Disease activity may be assessed utilizing criteria established by the Histiocyte Society. Under this system, patients are placed into one of four subcategories: non-active disease, evidence of disease with regression, stable disease, and progressive disease. Although this system appears simple, a more objective assessment of disease activity has been recently proposed.[34] The later methodology is based upon obtaining a score derived from three primary parameters including: clinical examination, laboratory evaluation, and radiological findings. Patients with more abnormal findings receive a higher score, and therefore are at greater risk for disease progression and demise.

Despite adequate treatment, it has been shown that survivors of LCH have long term squealae, some of which may not become apparent until many years later.[35] One retrospective study analyzed patients who had been treated for multi-organ system LCH and found that 75 % had detectable long term sequalae, such as hypothalamic-pituitary dysfunction (50%), cognitive dysfunction (20%), and cerebellar involvement (17.5%).[36] Some sequalae are multifactorial. For example, growth retardation can occur as a result of gastrointestinal involvement by LCH thereby resulting in malabsorption or due to deficiencies in growth hormone from anterior pituitary lesions, or from the residua of chemotherapy. Furthermore, long term complications are not limited to patients with multi-organ system disease and approximately 25% of patients with single system disease experience permanent sequalae.[37] Even patients diagnosed with congenital self-healing LCH have been shown to have late relapses and/or progression to systemic disease. Consequently, all patients with LCH require long term follow up to identify disease recurrence or late-stage complications. Lastly, caregivers should be cognizant that patients with LCH are at risk for second malignancies, including solid tumors and hematopoietic conditions.

CONCLUSION

LCH is a rare proliferative disease of Histiocyte -like cells associated with a wide spectrum of presenting symptoms and variable clinical behavior and prognosis.

It most commonly affects individuals in childhood 1-3 years old and is limited to one organ (example, bone) in approximately half of patients.

Diagnosis of LCH should be based on the synthetical analysis of clinical presentations, in addition to features of imaging and histopathology.

A definitive diagnosis of LCH can be made by obtaining a biopsy that yields cells morphologically and immunohistochemically compatible with LCs.

The reported case showed a LCH with bone and visceral involvemnent, treated with a Vinblastine and Prednisone based regimen. The patient was shown to progress well and continues to undergo close follow-up to assess for signs of recurrence.

Proposals by the Histocyte Society have assisted in the unification of LCH into one disease category and has allowed for more efficient treatment protocols to be designed via risk stratification.

The prognosis depends chiefly upon the involvement of multiple organ systems, organ dysfunction and the patient's response to chemotherapy during the initial 6 weeks of treatment.

REFERENCES

1. Favara BE, Feller AC, Pauli M et al. Contemporary classification of histiocytic disorders. The WHO Committee on Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. Med Pediatr Onco, 1997; 29: 157–66.
2. Chu T, D'Angio GJ , Favara B , Ladisch S, Nesbit M, Pritchard J. Histiocytosis syndromes in Children. Writing Group of the Histiocyte Society. Lancet, 1987; 2(8549): 41-42.
3. Jaffe R, Weiss LM, Facchetti F. Tumours derived from Langerhans cells. In: World Health Organization Classification of Tumours of Hematopoietic and Lymphoid Tissues, Swerdlow SH, Campo E, Harris NL, et al (Eds), IARC Press, Lyon, 2008; 358.
4. Jan E. Drutz, Histiocytosis. Pediatrics in Review, 2011; 32; 218. DOI: 10.1542/pir.32-5-218.
5. Carstensen H, Ornvold K. The epidemiology of LCH in children in Denmark, 1975-89. Med Pediatr Oncol, 1993; 21: 387.
6. Baumgartner I, von Hochstetter A, Baumert B, et al. Langerhans'-cell histiocytosis in adults. Med Pediatr Oncol, 1997; 28: 9.
7. Aricò M, Girschikofsky M, Généreau T, et al. Langerhans cell histiocytosis in adults. Report from the International Registry of the Histiocyte Society. Eur J Cancer, 2003; 39: 2341.
8. Nicholson HS, Egeler RM, Nesbit ME. The epidemiology of Langerhans cell histiocytosis.Hematol Oncol North Am, 1998; 12: 379.
9. Aricò M, Nichols K, Whitlock JA, et al. Familial clustering of Langerhans cell histiocytosis. Br J Haematol, 1999; 107: 883.
10. Shahla A, Parvaneh V, Hossein HD. Langerhans cells histiocytosis in one family. Pediatr Hematol Oncol, 2004; 21: 313.
11. Bhatia S, Nesbit ME Jr, Egeler RM, et al. Epidemiologic study of Langerhans cell histiocytosis in children. J Pediatr, 1997; 130: 774.
12. Pineles SL, Liu GT, Acebes X, et al. Presence of Erdheim-Chester disease and Langerhans cell histiocytosis in the same patient: a report of 2 cases. J Neuroophtalmol, 2011; 31: 217.
13. Wang KH, Cheng CJ, Hu CH, Lee WR. Coexistence of localized Langerhans cell histiocytosis and cutaneous Rosai-Dorfman disease. Br J Dermatol, 2002; 147: 770.
14. Alston RD, Tatevossian RG, McNAlly RJ, Kelsey A, Birch JM, Eden TO. Incidence and survival of childhood Langerhans cell histiocytosis in Northwest England from 1954 to 1988.Pediatr Blood Cancer, 2007; 48(5): 555-560.
15. Allen CE, Li L, Peters TL, et al. Cell-specific gene expression in Langerhans cell histiocytosis lesions reveals a distinct profile compared with epidermal Langerhans cells. J Immunol, 2010; 184: 4557.

16. McClain K, Jin H, Gresik V, Favara B. Langerhans cell histiocytosis: lack of a viral etiology. Am J Hematol, 1994; 47: 16.
17. Jeziorski E, Senechal B, Molina TJ, et al. Herpes-virus infection in patients with Langerhans cell histiocytosis: a case-controlled sero-epidemiological study, and in situ analysis. PLoS One, 2008; 3: e3262.
18. Berres ML, Allen CE, Merad M. Pathological consequence of misguided dendritic cell differentiation in histiocytic diseases.Adv Immunol, 2013; 120: 127.
19. Grois N, Pötschger U, Prosch H, et al. Risk factors for diabetes insipidus in Langerhans cell histiocytosis. Pediatr Blood Cancer, 2006; 46: 228.
20. Slater JM, Swarm OJ. Eosinophilic granuloma of bone. Med Pediatr Oncol, 1980; 8: 151.
21. Garg S, Mehta S, Dormans JP. Langerhans cell histiocytosis of the spine in children. Long-term follow-up. J Bone Joint Surg Am, 2004; 86-A: 1740.
22. Newman B, Hu W, Nigro K, Gilliam AC. Aggressive histiocytic disorders that can involve the skin. J Am Acad Dermatol, 2007; 56: 302.
23. Braier JL, Rosso D, Latella A, et al. Importance of multi-lineage hematologic involvement and hypoalbuminemia at diagnosis in patients with "risk-organ" multi-system Langerhans cell histiocytosis. J Pediatr Hematol Oncol, 2010; 32: e122.
24. Broadbent V, Gadner H, Komp DM, Ladisch S: Histiocytosis syndromes in children: II. Approach to the clinical and laboratory evaluation of children with Langerhans cell histiocytosis. Clinical Writing Group of the Histiocyte Society. Med Pediatr Oncol, 1989; 17(6): 492-5.
25. Hicks J, Fliatz M. Langerhans cell histiocytosis: Current insights in a molecular age with emphasis on clinical oral and maxillofacial pathology practice. Oral Surg Oral Med Oral Pathol Pral Radiol Endod, 2005; 100(2): S42-S66.
26. Lahey E. Histiocytosis-X: an analysis of prognostic factors. J Pediatr, 1975; 87(2): 184-189.
27. Arceci RJ, Brenner MK, Pritchard J. Controversies and new approaches to treatment of Langerhans cell histiocytosis. Hematol Oncol Clin North Am, 1998; 12(2): 339-357.
28. Gadner H, Grois N, Arico M, Broadbent V, Ceci A, Jakobson A, Komp D, Nicholson S, Potschger U, Pritchard J, Ladisch S; Histiocyte Society. A randomized trial of treatment for multisystem Langerhans cell histiocytosis. J Pediatr, 2001; 138 (5): 728-734.
29. Arico M, Egeler RM. Clinical aspects of Langerhans cell histiocytosis. Hematol Oncol Clin North Am, 1998; 12(2): 247-259.
30. Broadbent V, Gadner H. Current therapy for Langerhans cell histiocytosis. Hematol Oncol Clin North Am, 1998; 12(2): 327-338.
31. Kilpatrick SE, Wenger DE, Gilchrist GS, Shives TC, Wollan PC, Unni KK. Langerhans cell histiocytosis (Histiocytosis X) of bone. A clinicopathologic analysis of 263 pediatric and adult cases. Cancer, 1995; 76(12): 2471-2484.
32. Howarth DM, Gilchrist GS, Mullan BP, Wiseman GA, Edmonson JH, Schomberg PJ. Langerhans cell histiocytosis: diagnosis, natural history, management, and outcome. Cancer, 1999; 85(10): 2278-90.
33. McLelland J, Broadbent V, Yeomans E, Malone, Pritchard J. Langerhans cell histiocytosis: the case for conservative treatment. Arch of Disease Child, 1990; 65(3): 301-303.
34. Donadieu J, Piguet C, Bernard F, Barkaoui M, Ouache M, Bertrand Y, Ibrahim H, Emile JF, Hermine O, Tazi A, Genereau T, Thomas C. A new clinical score for disease activity in Langerhans cell histiocytosis. Pediatric Blood & Cancer, 2004; 43(7): 770-776.
35. Haupt R, Naduri V, Calevo MG, Bernstrand C, Braier JL, Broadbent V, Rey G, McClain KL, Janka-Schaub G, Egeler RM. Permanent Consequences in Langerhans cell histiocytosis patients: A pilot study from the Histiocyte society-Late effects study group. Pediatr Blood Cancer, 2004; 42(5): 438-444.
36. Nanduri VR, Pritchard J, Levitt G, Glaser AW. Long-term morbidity and health related quality of life after multi-system Langerhans cell histiocytosis. Eur J Cancer, 2006; 42(15): 2563-2569.
37. Titigemeyer C, Grois N, Minkov M, Flucher-Wolfram B, Gatterer-Menz I, Gadner. Pattern and course of single system disease in Langerhans cell histiocytosis data from the DAL-HX83 and 90 studies. Med Pediatr Oncol, 2001; 37(2): 108-14.