Pediatric langerhans cell histiocytosis: single center experience over a 17-year period

Dilek İnce[1], Bengü Demirağ[2], Gülcihan Özek[2], Ayşe Erbay[3], Ragıp Ortaç[4], Yeşim Oymak[2], Serra Kamer[5], Yöntem Yaman[2], Selcen Kundak[6], Canan Vergin[2]

[1]Department of Pediatric Oncology, Dokuz Eylül University Institute of Oncology, [2]Pediatric Hematology-Oncology Clinic, and [6]Dermatology Clinic, Dr Behçet Uz Children's Hospital, [4]Department of Pathology, İzmir University Faculty of Medicine, [5]Department of Radiation Oncology, Ege University Faculty of Medicine, İzmir, [3]Division of Pediatric Oncology, Başkent University Faculty of Medicine, Adana, Turkey.
E-mail: dr.dilek.ince@gmail.com
Received: 12th July 2016, Revised: 26th September 2016, Accepted: 31st October 2016

SUMMARY: İnce D, Demirağ B, Özek G, Erbay A, Ortaç R, Oymak Y, Kamer S, Yaman Y, Kundak S, Vergin C. Pediatric langerhans cell histiocytosis: single center experience over a 17-year period. Turk J Pediatr 2016; 58: 349-355.

This study aimed to analyze children with the diagnosis of Langerhans cell histiocytosis (LCH) who were diagnosed and treated between 1998–2015.

Medical records were evaluated retrospectively for clinical and laboratory features, treatment details, and outcome.

There were 20 patients, the median age of diagnosis was 37 months, M/F ratio: 1.5. Nine had single system (SS), 11 had multisystem (MS) LCH. Spontaneous regression occurred in three infants with skin limited LCH. Eight patients had risk organ involvement in MS-LCH group. The curettage alone was performed in only one case. Patients received LCH-II/ LCH-III based chemotherapy schema. Radiotherapy was performed to vertebral disease and residual craniofacial bone disease in four cases.

The regression and relapse rates were 100% and 33% for SS-LCH. The regression and relapse rates were 73%, and 18% for MS-LCH. Two infants with MS-LCH died despite chemotherapy.

Pulmonary and liver involvements affected outcome adversely in MS-LCH. Multidisciplinary treatment approaches are needed.

Key words: Langerhans cell histiocytosis, children, treatment.

The *histiocytoses* represent a group of rare disorders characterized by clonal proliferation and/or accumulation of mononuclear phagocytes[1-3]. The most frequent dendritic cell related histiocytic disorder is Langerhans cell histiocytosis (LCH), and the annual incidence of LCH has been reported 5-6 cases per million[3]. The etiology and pathogenesis of LCH remain unclear. The clinical features of LCH have a broad spectrum. The disease ranges from an isolated lytic bone lesion to fatal multisystemic disease. The definitive diagnosis is based on histopathologic and immunohistologic examination of tumor tissue. The lesional cells demonstrate CD1a and Langerin (CD207) positivity[3,4]. The LCH is classified as unifocal single system, multifocal single system, and multisystem disease. The need for specific treatment depends on the number and type of involved sites. Treatment modalities include performing surgery, administration of combined chemotherapeutic agents, and performing radiotherapy.

In this study, we aimed to analyze clinical characteristics, treatment details and treatment response of children with the diagnosis of LCH who were diagnosed and treated at Dr Behcet Uz Children's Hospital, Pediatric Hematology-Oncology Clinic.

Material and Methods

The medical records of patients with LCH who were diagnosed and treated between 1998 –

Table I. Clinical Classification of Langerhans Cell Histiocytosis (LCH)[3,5].

Categories of LCH	Definitions
Single system LCH (SS-LCH)	One organ / system involved (unifocal or multifocal) Bone (unifocal or multifocal) Skin Lymph node (not the draining lymph node of another LCH lesion) Hypothalamic-pituitary / central nervous system Lungs Other (e.g., thyroid, thymus, ….)
Multisystem LCH (MS-LCH)	Two or more organs / systems involved either with or without involvement of risk organs*

*Risk organs include the hematologic system, the spleen, and the liver. The lung had been considered as a risk organ previously, however its prognostic role has been questioned[6-8].
SS: Single system, MS: multisystem

2015 at our clinic were evaluated retrospectively. In particular, clinical characteristics of patients, main complaints at admission, duration of complaints, positive findings on physical examination, radiologic findings (skeletal survey, chest X-ray, ultrasonography (US), computerized tomography (CT), magnetic resonance imaging (MRI)), laboratory examinations (complete blood count (CBC), biochemical analysis of serum, urine analysis) and histopathologic reports were analyzed retrospectively. Pathology reports were analyzed retrospectively for positive CD1a and S100 immunohistochemical staining. Clinical classification of LCH according to the extent of involvement at diagnosis is summarized in Table I[3,5–8]. Risk organ involvement was defined according to modified Lahey criteria [9]. The involved organs, treatment details, and treatment responses of patients were analyzed retrospectively.

One patient received DAL HX90 protocol as an initial treatment[10]. Two patients received LCH-III, one patient received LCH-IV protocol, and the remaining patients received the LCH-II based chemotherapy schema[11-13]. This LCH-II based chemotherapy schema according to the Histiocyte Society protocols is summarized below:

Induction chemotherapy: Prednisolone, 40 mg/m^2/d P.O., day 1-28, afterwards weekly reduction*;* Vinblastin, 6 mg/m^2 I.V. bolus, day 1, 8, 15, 22, 29, 36.

Continuation chemotherapy: Prednisolone, 40 mg/m^2/d P.O., day 1-5, week 9, 12 15, 18, 21, 24*;* Vinblastin, 6 mg/m^2 I.V. bolus, day 1 of week 9, 12 15, 18, 21, 24*;* 6-Mercaptopurin, 50 mg/m^2/d P.O., week 6 – 24.

Continuation chemotherapy for unresponsive high risk group: Prednisolone, 40 mg/m^2/d P.O., day 1-5, week 9, 12 15, 18, 21, 24*;* Vinblastin, 6 mg/m^2 I.V. bolus, day 1 of week 9, 12 15, 18, 21, 24*;* 6-Mercaptopurin, 50 mg/m^2/d P.O., week 6 – 24*;* Etoposide, 150 mg/m^2 30 min. I.V. infusion, day 1 of week 9, 12 15, 18, 21, 24.

Treatment response was assessed using the criteria employed in the LCH-II and LCH-III trials[11,12]. Reactivation was defined as the reappearance or progression of disease after complete regression (CR). Descriptive analysis was done.

Results

The medical records were analyzed for patients who were diagnosed and treated with LCH at Dr Behcet Uz Children Hospital from Jan 1998 to Dec 2015. There were 21 children with the diagnosis of LCH, and 20 of them were eligible. One patient went to another center at the time of diagnosis. Medical records of 20 cases were analyzed retrospectively. The median duration of complaints was 2.5 months (0.5 – 36) for all patients. The median age of diagnosis was 37 months (5 months – 8 years), M/F ratio was 1.5. There were 9 (45%) patients under 2 years of age at diagnosis. There was no significant difference between ages of SS-LCH and MS-LCH groups. Histopathologic diagnosis was obtained by biopsy in 15 patients, and by primary surgery in 5 patients (3 of them without residue). The CD1a was positive in pathology reports of all patients. Median follow up time was 64 months (1 month – 14 years). Main complaints of patients at admission are summarized in Table II.

Table II. Main Complaints of Patients (n:20) at Admission

	n (%)
Cutaneous rash	7 (35)
Chronic otitis (three of them bilateral)	6 (30)
Periauricular mass	5 (20)
Seborrheic dermatitis	5 (20)
Diaper dermatitis	3 (15)
Periorbital mass lesion	3 (15)
Extremity pain	3 (15)
Back pain	2 (10)
Polypoid mass lesion in outer ear channel	2 (10)
Hearing loss	2 (10)
Parietal mass lesion	1 (5)
Gingival mass lesion	1 (5)
Perianal infected cutaneous lesion	1 (5)
Vertigo, ataxic gait and falling to the ground when trying to walk	1 (5)

Single System LCH (SS-LCH) (n:9): Clinical characteristics of patients are summarized in Table III. There were three infants younger than 6 months-old with isolated skin involvement, one received topical corticosteroid therapy for two weeks. All three infants with skin involvement have been followed up without disease activation. Remaining 6 patients had bone involvement: surgery was the only treatment in one, incomplete surgery + chemotherapy + radiotherapy in one, radiotherapy in one, and chemotherapy in three patients. Regression rate was 100%. Relapse rate was 33%. Relapse without primary bone involvement occurred in two cases at 15 and 46 months and radiotheraphy was performed to them. Disease activation occurred with diabetes insipidus (DI) at 15 months in one case, her family refused further treatment and the patient lost to follow up (LFU). The median follow-up time was 66 months (3 months – 14.4 years), all 8 patients have been followed up without active disease.

Multisystem LCH (MS-LCH) (n:11): Clinical characteristics of patients are summarized in Table III. There were two patients without risk organ involvement. Complete regression was achieved in these two cases by chemotherapy and one of them has been followed up without disease activation. One of them relapsed at the 20th month of diagnosis, she went to another center. We learned that she received 2 chlorodeoxyadenosine (2CdA, cladribine) containing chemotherapy, however she relapsed four times. Now, she has ataxic walking and a speech disorder.

Four patients had multisystem involvement the lung being the only risk organ. All these four cases received chemotherapy. Radiotherapy was performed to cranial bone lesions in two of them. Treatment was changed to prednisolon + vinblastine + methotrexate + cyclophosphamide in one case, because of partial regression at 3rd month by DALHX90 protocol. Complete regression was achieved in three of these four cases. One patient relapsed with pulmonary lesions at the 28th month. Complete regression was achieved by 2CdA containing chemotherapy.

Remaining five patients had multiple risk organ involvement including liver in all. Two infants died within one month due to progression despite receiving chemotherapy. One patient refused chemotheraphy and LFU with active disease at 3rd month of diagnosis. Remaining two patients received chemotherapy, partial regression (PR) was achieved in these two cases. Both of them had chronic liver disease and liver transplantation was offered. Systemic progression and chronic liver disease, sclerozing cholangitis / micronodular cirrhosis occurred in one of them at the 31st month and he went to a university hospital for liver transplantation. The other patient's family refused transplantation,

she has been followed up for 61 months with disease.

In summary for patients with MS-LCH; the median follow-up time was 49 months (1 month – 9.7 years). Regression (CR + PR) rate was 73%. Relapse occurred in two patients (18%). Two patients died with progressive disease within one month. Out of eleven patients, five have been followed up without active disease, and two have been followed up with disease.

Discussion

Langerhans cell histiocytosis is a relatively rare disease. There were only 20 patients who were diagnosed and treated with diagnosis of LCH during a 17-year period in our center. The largest series from Turkey with 217 patients was reported by Yagci B, et al[14]. Langerhans cell histiocytosis can occur at any age, particularly in younger children. Nearly half of our cases were younger than two years of age. During childhood LCH has slightly male predominance. The M/F ratio was 1.5 in our study, and it

Table III. Clinical Characteristics of Patients

	Single system LCH n (%)	Multisystem LCH n (%)
Number of patients	9 (45)	11 (55)
Male / Female ratio	4/5 = 0.8	8/3 = 2.7
Age at diagnosis median (range)	35 months (4months – 8 years)	24 months (6 months – 7.5 years)
Duration of complaints median (range)	1.5 months (0.5 – 12 months)	5 months (1 – 36 months)
Sites of involvement		
Bone,	6 (75%)	8 (73%)
Unifocal	2	1
Multifocal	4	7
Skin	3 (38%)	6 (55%)
Lung	-	7 (64%)
Liver	-	5 (45%)
Spleen	-	2 (18%)
CNS (DI +)	-	3 (27%)
Bone marrow	-	1 (9%)
Lymph nodes	-	1 (9%)
Number of involved organs		
2 organs		4 (36%)
3 organs		4 (36%)
4 organs		2 (18%)
>4 organs		1 (9%)
Patients with risk organ involvement	-	*8 (73%)
Laboratory results		
Hb <10 g/dl	1 (5%)	
WBC <4000 /mm3	1 (5%)	
Platelet < 100.000 /mm3	1 (5%)	
Elevated PT or PTT	1 (5%)	
LDH >500 U/L	1 (5%)	
ESR >20 mm/hour	5 (25%)	
Elevated transaminases	4 (20%)	
Hypoalbuminemia	3 (15%)	

*There were 8 patients with risk organ involved, however additionally one patient with lung involvement was managed according to the LCH-IV protocol and this patient was accepted to have had no risk organ involvement despite having lung disease.

LCH: Langerhans cell histiocytosis; WBC: White blood cell; LDH: Lactate dehydrogenase; ESR: Erythrocyte sedimentation rate; CNS: Central nervous system; DI: Diabetes insipidus.

has been reported between 1.2 to 1.8 in the literature[14-17]. Langerhans cell histiocytosis has a diverse clinical presentation spectrum. Any organ or system can be affected. It can be confused with other common childhood diseases. Kim et al.[18] reported that the most common complaints at the time of diagnosis were local pain and swelling (41%), followed by skin rash (9%), fever (7%), limping gait (6%) and organomegaly (2%). The diagnosis of LCH should be considered particularly in patients who have suggestive clinical manifestations in the skin, ear, bone, lung, liver and CNS.

The clinical presentation of patients with LCH varies depending upon the sites and extent of involvement. In our series; involvement sites were bone (70%) and skin (45%) in all patients with SS- and MS- LCH; lung (64%), liver (45%), central nervous system (CNS) (27%), spleen (18%), and lymph nodes (9%) in MS-LCH group. The most frequently involved organs have been reported as bone (75 – 93%), skin (20 – 38%), lymph nodes (11 – 14%), liver (7 – 15%), spleen (7 – 10%), lung (10 – 14%), hematologic system (2 – 10%) and central nervous system (8 – 21%)[15-18]. As our center is the largest children's state hospital in the western part of Turkey, most of the patients with risk organ involvement were referred to our center. Sometimes multi-institutional management and cooperation with university hospitals have been required for patients with MS-LCH.

The median time for duration of complaints was 2.5 months (0.5 months – 3 years) in our study. In the literature, the median time from first symptom to diagnosis was reported as 1–1.5 months, and variable upper range for duration of complaints was reported as 1.67–5.8 years[18]. As LCH can mimic many of the benign childhood diseases, the diagnosis can be delayed. The longest duration of complaints was 3 years in one of our case, and she had been followed for a long time with the diagnosis of DI and treatment resistant skin lesions. Langerhans cell histiocytosis must be considered in the differential diagnosis of DI. DI and symptoms of neurodegeneration (ataxia, cognitive dysfunction) are the most common manifestations of CNS involvement of LCH. The identification of DI can occur prior to, concomitant with, or after the diagnosis of LCH. Varan et al.[19] reported that 69.8% of patients presenting with central DI had the diagnosis of LCH. Infundibular thickening and absence of posterior pituitary intensity were the most common MRI findings[20,21]. We had three patients with DI at the time of diagnosis of MS LCH. Two of them had multiple cranial bone lesions involving middle ear, mastoids. It has been reported that patients with multisystem disease and craniofacial bone involvement at diagnosis carry a significantly increased risk of developing DI during their course[22,26]. Among patients with LCH, approximately 25% of them may be diagnosed with pituitary involvement within 5-10 years of follow-up[20,23].

Pulmonary LCH is rare during childhood. It has been reported in 22-24% of MS LCH patients[6,7,8]. It is less frequent in children than in adults. We have 7 patients with lung involvement and all of them had MS-LCH. The regression (CR + PR) and relapse rates of our four cases with no more risk organ involvement except for lung were 100% and 25% respectively, and this clinical course was within acceptable limits. The remaining three cases also had liver involvement, and those cases had the worst clinical course among our patients. Two of them died with disease progression within one month while receiving chemotherapy. Even though the lung has been considered as a "risk organ", more recent studies have suggested that it has less effect on prognosis[6,7,8]. Consistently, the results of the clinical course of our patients with pulmonary LCH appear to depend on the presence of other risk organ involvement. The most sensitive diagnostic test is a high-resolution CT scan for pulmonary involvement. Thorax CT had been done in all of our cases with pulmonary LCH. Thorax CT sections revealed cysts and nodules that are characteristics of LCH. Although we did not need invasive approaches, the combination of bronchoalveolar lavage (BAL) and transbronchial lung biopsy has been suggested in patients with nondiagnostic radiographic pattern[5].

Liver involvement had been reported in 7-15% of patients with LCH[15-18]. Liver involvement causes hepatomegaly, tumor-like lesions, and cystic lesions, and is accompanied by hepatic dysfunction, leading to hypoalbuminemia with ascites, hyperbilirubinemia, elevated liver

enzymes, and/or clotting factor deficiencies[23, 24]. We have five patients with liver involvement, and these cases had the worst clinical course. As mentioned before, two of them died with progression. The liver and spleen were both "risk organs" and were related to the worst prognosis. Remaining two patients required liver transplantation due to chronic liver disease, sclerosing cholangitis/micronodular cirrhosis. Sclerosing cholangitis is an uncommon condition in children and is a particularly serious complication of LCH. Liver transplantation has become the treatment of choice for the majority of patients and should be considered early in cases with severe hepatic involvement[23]. Major problems in our cases were delayed admission to hospital, delayed diagnosis of LCH, and also noncompliance of patients.

Langerhans cell histiocytosis can involve any bone of the body. In children, common sites of bone involvement include craniofacial bones, femur, ribs, vertebra, and humerus. Craniofacial bone lesions of LCH are considered as CNS-risk lesions[26]. Bone involvement was present in 70% (n:14) of our patients. Involved bones were craniofacial bones (n:10), iliac bone (n:3), vertebra (n:2), costa (n:2), scapula (n:1), and long bones including femur, tibia, fibula, humerus, radius (n:2). The curettage only was performed in one case with unifocal radius lesion. All remaining cases received systemic chemotherapy. In another case, curettage was performed to scapula lesion and also radiotherapy was performed to T11-12 vertebral bones due to compression fracture. Ten of our cases had craniofacial bone involvement, and three of them required radiotherapy as local treatment.

Skin involvement had been reported in over one third (20-38%) of children with LCH[15,18]. Skin lesions of LCH may present as skin limited disease or a component of MS-LCH. In our series, skin involvement was present in 45% of our cases, and three of them had skin limited disease. Manifestations of our cases were as maculopapular/vesicular-pustular eruptions, seborrheic dermatitis, diaper dermatitis, and infected eroded skin lesions. The most common skin manifestations have been reported as eczema, seborrheic dermatitis and an eczematous rash resembling candidal infection[27]. Biopsy was often delayed as the skin lesions of LCH could easily be confused with common childhood rashes. Our cases with skin only LCH regressed spontaneously, and recurrence did not occur. However non-self-regressive cutaneous LCH can occur during neonate and infancy periods, and it has been reported that skin LCH may progress to MS LCH in varying rates (0 – 60%)[27-29].

Treatment responses of our cases were comparable with the literature. In the most recent Histiocyte Society Trial, LCH-III, patients with low risk disease had nearly 100% overall survival (OS), while patients with high risk disease had 84% 5-years OS[12]. Cladribine, clofarabine, cytarabine were considered as salvage therapy of LCH[30,31]. Cladribine, containing chemotherapy was given as a salvage chemotherapy in two of our cases.

Langerhans cell histiocytosis is a rare disease, and it should be considered in patients with unexplained clinical manifestations of skin, ear, bone, lung, liver and CNS. Treatment of patients depends on the extent of the disease. The number of involved organs and involvement sites are important. Treatment is unnecessary for patients with skin only disease. However, approximately 50% of patients with MS-LCH still have refractory/recurrent disease despite treatment with vinblastine/prednisone based chemotherapy protocols[12]. The prognostic importance of the lung involvement should be questioned. In our series, the worst outcome was observed particularly in patients with liver involvement. Multidisciplinary, optimized therapeutic approaches are needed for better management of these patients.

REFERENCES

1. Willman CL, Busque L, Griffith BB, et al. Langerhans'-cell histiocytosis (histiocytosis X)--a clonal proliferative disease. N Engl J Med 1994; 331: 154-160.
2. Vaiselbuh SR, Bryceson YT, Allen CE, Whitlock JA, Abla O. Updates on histiocytic disorders. Pediatr Blood Cancer 2014; 61:1329-1335.
3. Aricò M., Weitzman S. The histiocytosis. In: Stevens MCG, Caron HN, Biondi A (eds). Cancer in Children: Clinical Management. Oxford, UK: Oxford University Press; 2012: 230-239.
4. Chikwava K, Jaffe R. Langerin (CD207) staining in normal pediatric tissues, reactive lymph nodes, and childhood histiocytic disorders. Pediatr Dev Pathol 2004; 7: 607-614.

5. Haupt R, Minkov M, Astigarraga I, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Pediatr Blood Cancer 2013; 60: 175-184.
6. Braier J, Latella A, Balancini B, et al. Outcome in children with pulmonary Langerhans cell Histiocytosis. Pediatr Blood Cancer 2004; 43: 765-769.
7. Odame I, Li P, Lau L, et al. Pulmonary Langerhans cell histiocytosis: a variable disease in childhood. Pediatr Blood Cancer 2006; 47: 889-893.
8. Ronceray L, Pötschger U, Janka G, Gadner H, Minkov M. Pulmonary involvement in pediatric-onset multisystem Langerhans cell histiocytosis: effect on course and outcome. J Pediatr 2012; 161: 129-133.e1-e3.
9. Lahey ME. Prognostic factors in histiocytosis X. Am J Pediatr Hematol Oncol 1981; 3: 57-60.
10. Minkov M, Grois N, Heitger A, Pötschger U, Westermeier T, Gadner H. Treatment of multisystem Langerhans cell histiocytosis. Results of the DAL-HX 83 and DAL-HX 90 studies. DAL-HX Study Group. Klin Padiatr 2000; 212: 139-144.
11. Gadner H, Grois N, Pötschger U, et al. Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification. Blood 2008; 111: 2556-2562.
12. Gadner H, Minkov M, Grois N, et al. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. Blood 2013; 121: 5006-5014.
13. Minkov M. Multisystem Langerhans cell histiocytosis in children: current treatment and future directions. Paediatr Drugs 2011; 13: 75-86.
14. Yağci B, Varan A, Cağlar M, et al. Langerhans cell histiocytosis: retrospective analysis of 217 cases in a single center. Pediatr Hematol Oncol 2008; 25: 399-408.
15. Guyot-Goubin A, Donadieu J, Barkaoui M, Bellec S, Thomas C, Clavel J. Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000-2004. Pediatr Blood Cancer 2008; 51: 71-75.
16. Braier J, Chantada G, Rosso D, et al. Langerhans cell histiocytosis: retrospective evaluation of 123 patients at a single institution. Pediatr Hematol Oncol 1999; 16: 377-385.
17. Stålemark H, Laurencikas E, Karis J, Gavhed D, Fadeel B, Henter JI. Incidence of Langerhans cell histiocytosis in children: a population-based study. Pediatr Blood Cancer 2008; 51: 76-81.
18. Kim B, Koh K, Suh J et al. Clinical features and treatment outcomes of Langerhans cell histiocytosis: a nationwide survey from Korea histiocytosis working party. J Pediatr Hematol Oncol 2014; 36: 125-133.
19. Varan A, Atas E, Aydın B, et al. Evaluation of patients with intracranial tumors and central diabetes insipidus. Pediatr Hematol Oncol 2013; 30: 668-673.
20. Varan A, Cila A, Akyüz C, Kale G, Kutluk T, Büyükpamukçu M. Radiological evaluation of patients with pituitary langerhans cell histiocytosis at diagnosis and at follow-up. Pediatr Hematol Oncol 2008; 25: 567-574.
21. Robison NJ, Prabhu SP, Sun P, et al. Predictors of neoplastic disease in children with isolated pituitary stalk thickening. Pediatr Blood Cancer 2013; 60: 1630-1635.
22. Grois N, Pötschger U, Prosch H, et al. Risk factors for diabetes insipidus in langerhans cell histiocytosis. Pediatr Blood Cancer 2006; 46: 228-233.
23. Fahrner B, Prosch H, Minkov M, et al. Long-term outcome of hypothalamic pituitary tumors in Langerhans cell histiocytosis. Pediatr Blood Cancer 2012; 58: 606-610.
24. Braier J, Ciocca M, Latella A, de Davila MG, Drajer M, Imventarza O. Cholestasis, sclerosing cholangitis, and liver transplantation in Langerhans cell Histiocytosis. Med Pediatr Oncol 2002; 38: 178-182.
25. 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.
26. Bezdjian A, Alarfaj AA, Varma N, Daniel SJ. Isolated Langerhans Cell Histiocytosis Bone Lesion in Pediatric Patients: Systematic Review and Treatment Algorithm. Otolaryngol Head Neck Surg 2015; 153: 751-757.
27. Battistella M, Fraitag S, Teillac DH, Brousse N, de Prost Y, Bodemer C. Neonatal and early infantile cutaneous langerhans cell histiocytosis: comparison of self-regressive and non-self-regressive forms. Arch Dermatol 2010; 146: 149-156.
28. Titgemeyer C, Grois N, Minkov M, et al. Pattern and course of single system disease in Langerhans cell histiocytosis data from the DAL-HX 83-and 90- study. Med Pediatr Oncol 2001; 37: 108-114.
29. Lau L, Krafchik B, Trebo M, et al. Cutaneous Langerhans cell histiocytosis in children under one year. Pediatr Blood Cancer 2006; 46: 66-71.
30. Weitzman S, Braier J, Donadieu J, et al. 2'-Chlorodeoxyadenosine (2-CdA) as salvage therapy for Langerhans cell histiocytosis (LCH). results of the LCH-S-98 protocol of the Histiocyte Society. Pediatr Blood Cancer 2009; 53: 1271-1276.
31. Rodriguez-Galindo C, Kelly P, Jeng M, Presbury GG, Rieman M, Wang W. Treatment of children with Langerhans cell histiocytosis with 2-chlorodeoxyadenosine. Am J Hematol 2002; 69: 179-184.