A 10-year single center survey of pediatric patients with histiocytic disorders in Iran

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Childhood histiocytosis is a rare and diverse group of proliferative disorders, characterized by accumulation and infiltration of antigen-presenting cells or antigen- processing cells, which can affect any tissue or organ. This study was performed in order to investigate the clinical characteristics of Iranian children with different types of histiocytic disorders.

Thirty-five patients, with a median age of 3.5 years, who were referred and diagnosed with histiocytic disorders in a referral Children's Hospital in Iran from 1997-2006, were investigated in this study.

According to the World Health Organization classification, 27 patients were in class 1, followed by 6 patients in class 2, and 1 patient in class 3. Moreover, 1 patient was diagnosed with sinus histiocytosis with massive lymphadenopathy.

Bone lesions were the most common manifestation, which were detected in 15 cases, followed by skin lesions (11 cases) and fever (10 cases). Nonspecific findings like hepatomegaly and splenomegaly were found in 15 cases. Different types of treatment protocols were used according to the diverse groups of histiocytic disorders and different stages of disease, including surgical excision, radiotherapy, chemotherapy, and stem cell transplantation. Twelve patients did not respond well to the treatment and subsequently died due to complications of their disease.

Although histiocytosis is considered a rare condition, it can be problematic for pediatric hematologists because of the unknown etiologies and pathogenesis, variable classifications and subtypes, diagnostic difficulties, poor therapeutic responses with high mortality, and some complications after different therapeutic protocols.

Key words: proliferative disorder, histiocytosis, hemophagocytosis, stem cell transplantation.

Histiocytic proliferative diseases are rare disorders, characterized by accumulation and infiltration of antigen-presenting cells (APCs), including follicular dendritic reticular cells, interdigitating reticular cells, and Langerhans cells (LC), or of phagocyte cells, which can affect all tissues and organs[1,2]. The primary clinical manifestation can range from limited involvement to being life-threatening. This disorder may occur at any age, most commonly below 15 years[3-8]. Although histiocytic disorders are relatively rare,[1,3,9,10], they have presented great challenges for pediatric pathologists and hematologists/oncologists, because of unknown etiologies and pathogenesis, the clonality theory, variable classifications and subtypes, diagnostic difficulties, spontaneous remission

to chronic active courses, poor therapeutic responses with high mortality, recurrences, and some poorly understood complications after different types of therapies[1,8,11,12]. According to the World Health Organization (WHO) classification, histiocytic disorders are classified into three major groups, characterized by the central role occupation of one cell type[1,9,13]: LCs in Langerhans cell histiocytosis (LCH), as class 1; hemophagocytic lymphohistiocytosis (HLH), including infection-associated hemophagocytic lymphohistiocytosis (IAHL) and familial hemophagocytic lymphohistiocytosis (FHL), as class 2; and malignant histiocytosis, as class 3. A few histiocytic disorders, such as sinus histiocytosis with massive lymphadenopathy (SHML), were also reported[1]. In addition, some types of immunodeficiency syndromes such as Griscelli syndrome have a presentation similar to that of HLH.

This study was performed to investigate for the first time in this region the clinical features, laboratory and histopathological findings, therapeutic protocols and results, and complications of Iranian children with different types of histiocytic disorders.

Material and Methods

This was a cross-sectional study based on descriptive and analytic adjustment. Thirty-five patients less than 15 years of age were enrolled. All patients were diagnosed with histiocytic disorders in Mofid Children's Hospital, a main referral center in Tehran, Iran, from 1997-2006. A two-page questionnaire was designed to complete the clinical and laboratory data of the patients, which was approved by the local ethics committee of the hospital. Diagnosis of histiocytic disorders was made based on histopathological reports. The diagnosis of LCH was also confirmed by detection of CD1a and S100 protein (9,14). The classification of patients with histiocytosis was made according to the WHO Committee on Histiocytic/Reticulum Cell Proliferations and the Working Group of the Histiocyte Society: LCH - class 1; HLH (IAHL and FHL) - class 2; and malignant histiocytosis - class 3[1,9,13,15].

Results

Patient Characteristics

Thirty-five patients (20 male, 15 female), with a median age of 3.5 years (age range: 2 months to 15 years), were diagnosed as histiocytic disorder during a 10-year period. According to WHO classification, 27 patients (77.1%) were in class 1 (16 male, 11 female), 6 patients (17.1%) in class 2 (3 male, 3 female), and 1 patient (2.9%) in class 3. Moreover, 1 patient (2.9%) was diagnosed with SHML. There was no significant difference in sex and age between classes 1 and 2.

Consanguinity was detected in 66.7% of the parents of patients in class 2, which was significantly higher than the 14.8% rate among parents of patients in class 1 (p-value=0.02).

Clinical Manifestations

Bone lesions were the most common manifestation in class 1, which were detected in 15 cases (55.5%), followed by skin lesions in 10 (37%), hepatomegaly in 8 (29.6%), and splenomegaly in 9 (33.3%). In this group, 2 patients had single system involvement (only bone lesions) and 25 patients had two or more sites of involvement, such as liver, lung and bone marrow. Based on bone involvement, 6 patients had single lytic lesions and 9 cases had multiple bone involvement. Fever (100%), splenomegaly (83.3%) and hepatomegaly (83.3%) were the most common clinical signs and symptoms of the patients in class 2. We had 1 patient in class 3 and 1 with SHML, who presented fever, hepatosplenomegaly and lymphadenopathy (Table I).

Imaging

Chest X-ray (CXR) of the histiocytic patients showed lung parenchymal involvement such as reticular infiltration or honeycomb appearance in 3 patients in class 1. Lung hilar lymphadenopathy was also detected in 2 cases of this group, and 2 patients had recurrent pneumothorax.

Abdominal and pelvic ultrasonography confirmed hepatomegaly and splenomegaly in 15 cases, while ascites and para-aortic lymphadenopathy were reported in 3 cases and 1 case, respectively.

Computed tomography (CT) was also performed, which confirmed the findings in CXR and ultrasound. Brain CT scan showed 2 cases in class 2 with diffuse white matter hypodense changes.

Table 1. Classification of Different Types of Histiocytosis

Class	Class 1	Class 2	—Class 3	SHML
Sex (F/M)	11/16	3/3	0/1	1/0
Mean age in years (SD)	(2 mo - 15 y) mean: 3.6 (4.4)	(2 mo - 12 y) mean: 3.4 (4.7)	4	7
Clinical manifestations	Skin lesions 10 (37%) Splenomegaly 9 (33.3%) Hepatomegaly 8 (29.6%) Bone lesions 15 (55.5%)	Fever 6 (100%) Hepatomegaly 5 (83.3%) Splenomegaly 5 (83.3%)	Fever Hepatomegaly Splenomegaly Lymphadenopathy Skin rash	Fever Generalized lymphadenopathy Hepatomegaly Splenomegaly
Laboratory data: WBC (/mm^3) PMN (%) Lymphocyte (%) Monocyte (%)	7,550	7,130	12,000 30 60 10	13,000 60 35 5
Hb (g/dl)	10.9	9.3	7	9
Plt (/mm^3)	283,000	59,000	160,000	170,000
TG (mg/dl)	Normal	159-750 Mean: 408±287	Normal	Normal
Cholesterol (mg/dl)	Normal	166	Normal	Normal
Bone involvement:	15 (55.5%)	Normal	Normal	Normal
Single lytic lesion	6 (40%)			
Multiple lytic lesions	9 (60%)			
Relation of parents	First cousins: 14.8%	First cousins: 66.7%	-	-
BMA	Normal	Erythroid hyperplasia: 2 (5.7%) Hemophagocytosis: 5 (14.5%)	Normal	Normal
Treatment	Single bone lesion: 1-Curettage 2-Curettage +Vinblastine + Corticosteroid	Chemotherapy: Prednisone Cyclosporine IVIG VP16	Chemotherapy: Prednisone Adriamycin Vincristine Cyclophosphamide	Chemotherapy: Prednisone Cyclosporine
Maintenance therapy	Multi system lesions: Chemotherapy: Prednisone Vinblastine Adriamycin Cyclosporine VP16 Vincristine Cyclophosphamide 2-CDA + Cytosar Lung involvement in 2 patients: Bleomycin (intra pleural) 6MP, Methotrexate 27 (100%) Corticosteroid 27 (77.1%) Vinblastine 23 (65.7%) Radiotherapy SCT (1 patient, Allogeneic SCT)	SCT in 3 (50%)		
Response to Treatment Death Complete response Under treatment	8 (29.6%) 10 (37%) 9 (33.3%)	3 (50%) 1 (16.7%) 2 (33.4%)	1	
Undetermined response (Unknown)				1
Complications	Diabetes insipidus: 3 (8.6%) Diabetes mellitus: 1 (2.9%) Facial palsy: 1 (2.9%)	Progressed to acute lymphoblastic leukemia (T cell-ALL): 1 (2.9%)	-	-

WBC: White blood cells. PMN: Polymorphonuclear neutrophils. Hb: Hemoglobin. Plt: Platelets. TG: Triglycerides. BMA: Bone marrow aspiration. IVIG: Intravenous immunoglobulin. SCT: Stem cell transplantation. 2-CDA: 2-Chlorodeoxyadenosine .

The bone lytic lesions were detected in 15 cases (6 with single and 9 with multifocal lesions) through the bone survey; all belonged to class 1 (LCH).

Laboratory Findings

Diagnosis was based on histopathology report of different sites of involvement, including bone marrow aspiration (BMA)/biopsy (10 cases), skin (10 cases), cervical lymph nodes (6 cases), liver (3 cases), lung (2 cases), and axillary lymph nodes (1 case). Histopathology report of other sites was also compatible with the diagnosis in 10 cases. The results of immunohistochemistry (IHC) study, including S100 protein and CD1a, were also positive in the patients in class 1.

There was no significant difference in white blood cell (WBC) or hemoglobin (Hb) level between classes 1 and 2 (median WBC 7550/mm^3 in class 1 *vs.* 7130/mm^3 in class 2; and median Hb 10.9 g/dl in class 1 *vs.* 9.3 g/dl in class 2). However, the median platelet count of class 2 patients was significantly lower than of class 1 patients (59000/mm^3 *vs.* 283000/mm^3, p=0.002).

The lipid profile of the patients in class 2 revealed a high median triglyceride level of 408 mg/dl (range: 159-750 mg/dl) and high median cholesterol level of 166 mg/dl (range: 70-328 mg/dl).

The serologic laboratory tests and polymerase chain reaction (PCR) results for Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis (B and C), human immunodeficiency virus (HIV), tuberculosis, and collagen vascular tests in evaluations were all negative.

In the patients in class 2, BMA revealed hemophagocytosis in 5 cases (14.5%) and erythroid hyperplasia in 2 cases (5.7%). BMA assessment of the other patients was normal (Table I).

Therapeutic Protocols

Different protocols were used according to the types and different stages of disease over these 10 years, and included surgical excision, radiotherapy, chemotherapy, and stem cell transplantation (SCT). Patients with single system lesions in class 1 were treated with curettage in 1 and curettage with vinblastine and corticosteroid in another patient. Treatment of patients with multiple system lesions included reduction therapy based on corticosteroid and vinblastine. The chemotherapy regimen was modified based on the patient's response to treatment. The most utilized therapeutic drugs were corticosteroid (27 patients, 77.8%) and vinblastine (23 patients, 66.7%). Cyclophosphamide, adriamycin, cytosar, etoposide, and 2-CDA (2-chlorodeoxyadenosine) were used if the primary therapy was not effective. Maintenance therapy included methotrexate, 6-mercaptopurine and cyclosporine. Allogeneic SCT using bone marrow stem cells of a HLA-matched sibling was performed only in a seven-year-old male in class 1 with generalized skeletal involvement who was unresponsive to chemotherapy. The patient did not show any significant complication or disease during a four-year period after transplantation.

Chemotherapy was started for class 2, but the definite treatment for these patients was SCT. The patients in class 2 were mainly treated by corticosteroid, etoposide (vp16) and cyclosporine. Intravenous immunoglobulin was also administered in this group of patients, and 3 patients were also treated with SCT.

The patient in class 3 and the SHML patient received chemotherapy; however, they did not have good response to treatment (Table I).

Therapeutic Responses and Complications

Twenty-two cases had good response to treatment and are still under treatment and follow-up, while the only patient in the SHML group did not refer to our center for further follow-up.

Twelve patients did not respond well to the treatment and subsequently died due to complication of their diseases (40%). The 2 patients in class 1 with single system disease had a very good prognosis following local treatment and chemotherapy. Mortality rate in class 1 was 8 (29.6%), who were all suffering from multiple system involvement. Patients died because of multiple organ problems, especially lung and liver involvement, and unmanageable treatment. SCT was not possible. In class 2, the mortality rate was 3 (50%); 2 patients developed sepsis and disseminated intravascular coagulation (DIC), and 1 patient

Fig. 1. Skin lesions in a patient in class 2 histiocytosis with hemophagocytosis.

had central nervous system (CNS) involvement. In the end, patients did not have an HLA-matched donor, and chemotherapy was not very effective in the absence of SCT. The only patient with malignant histiocytosis (class 3) was a five-year-old boy, who died after failed treatment.

Complications included diabetes insipidus in 3 patients in class 1, which was treated by desmopressin (DDAVP), diabetes mellitus in 1 patient (class 1), facial nerve paralysis in 1 patient (class 1), and transformation to acute lymphoblastic leukemia (ALL) in 1 patient (class 2) (Table I).

Interesting Cases

Case 1. A 16-month-old boy was referred with hepatosplenomegaly, icterus and rash on his head and hand during the disease course (Fig. 1), leukocytosis, thrombocytosis, anemia, and increased levels of liver function tests, triglyceride, cholesterol, and erythrocyte sedimentation rate (ESR). No infectious disease was found in the patient. Histopathology report of the liver indicated histiocytosis. Hemophagocytic cells were observed in the BMA (Fig. 2). Immunosuppressive drugs and supportive care were started. The patient died three months later, as a result of multiple organ failure.

Case 2. A six-month-old girl was referred due to pneumonia. Reticular infiltration was detected in CXR (Fig. 3) and the chest CT scan showed cystic lesions. LCH was diagnosed by biopsy of humerus lytic lesions. The patient was treated with immunosuppressive drugs, chemical pleurodesis and supportive care, but the therapeutic protocols were not successful and the patient died due to severe respiratory distress one year after diagnosis and treatment.

Case 3. A five-month-old girl, with silvery grayish hair (Fig. 4), eyebrows and eyelashes was referred to our center. She also had fever, hepatosplenomegaly and pancytopenia. The patient's parents were first cousins. No giant cytoplasmic granule was observed in leukocytes of peripheral blood smear or BMA. Serum levels of triglyceride and cholesterol were increased, but serum level of fibrinogen was decreased. BMA and bone marrow biopsy demonstrated only hemophagocytosis without any evidence of a malignant process. Assessment of the hair showed irregular pigment agglomeration in the hair shaft (Fig. 5). The whole presentation suggested the Griscelli syndrome in this patient.

Case 4. A 14-year-old girl (second child of first cousins with history of death of previous child) with class 2 histiocytosis progressed to ALL (T cell type) about two years after the appropriate response to chemotherapy and splenectomy. The patient died because of disease relapse, sepsis and DIC three years later. She did not

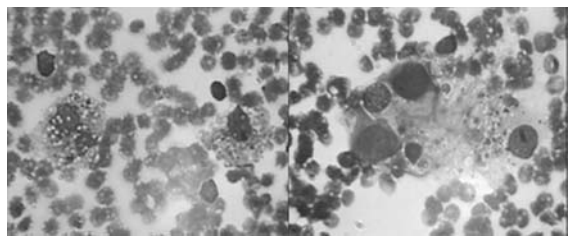

Fig. 2. Hemophagocytic cells observed in bone marrow of a patient with class 2 histiocytosis.

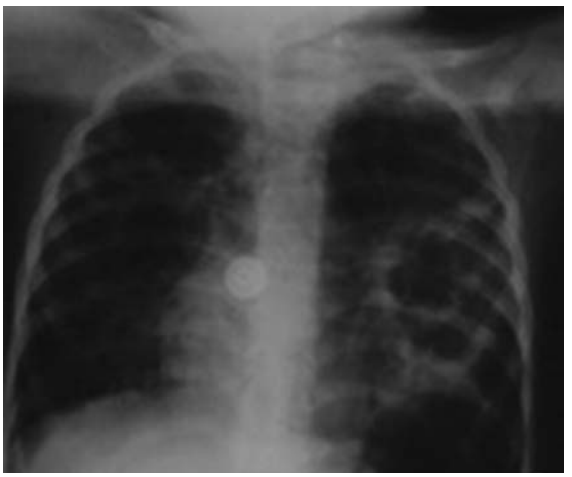

Fig. 3. Chest X-ray showing lung reticular infiltration in the patient with Langerhans cell histiocytosis.

have a matched stem cell donor.

Case 5. A six-year-old girl was diagnosed as SHML, also known as Rosai-Dorfman syndrome, according to the histopathologic report of cervical node biopsy. The clinical features were fever, generalized lymphadenopathy and hepatosplenomegaly. The patient had good response to chemotherapy and is now on follow-up.

Discussion

Although the histiocytic disorders are considered rare conditions, they can cause many challenges for pediatricians[1,3,9,10]. The etiology and pathogenesis of such diseases are not fully understood; they have different clinical manifestations, which complicates diagnosis of the disease. Poor therapeutic responses and resultant complications can lead to a high mortality rate in the affected cases[1, 8,11,12].

In this study, the clinical characteristics and therapeutic responses of 35 Iranian cases with different types of histiocytic disorders were investigated. More than 75% of the cases belonged to class 1, while there were 6 cases in class 2 and only 1 case in class 3, which is uncommon in childhood[16]. In our patients, there was also a rare case of immunodeficiency syndrome associated with HLH, Griscelli syndrome, based on her findings such as clinical presentation, parental consanguinity and the characteristics of her hair on light microscopy study.

This classification showed a frequency of the histiocytosis subgroups similar to the previous studies[1, 3,17,18]. While the median age of patients in class 1 was 3.6 years, similar to some previous studies[2,3], it was much lower than 5 years in Hungarian patients[17] and much higher than 2 years in the English study[11]. Although none of our patients was diagnosed during the neonatal period, similar to the previous study in England[11], the Austrian/German/Swiss/ Dutch LCH Study Group (GPOH) reported that 2% of their LCH cases were diagnosed in the neonatal period, before the age of 28 days[11,19]. Thus, increasing the awareness of medical professionals on such conditions is necessary, and could lead to the early diagnosis of patients and decrease diagnostic delay. The high parental consanguinity rate among our patients could show the important role of consanguineous marriages, especially in FHL groups of class 2 histiocytosis, which was similar to the previous reports[20-22]. This rate is significantly higher than the rate of consanguineous marriages in the normal population of the country and similar to the rate of other diseases with autosomal inheritance pattern[23]. Since consanguinity is common in our country, there is an urgent need for public education programs and provision of the facilities for genetic counseling and

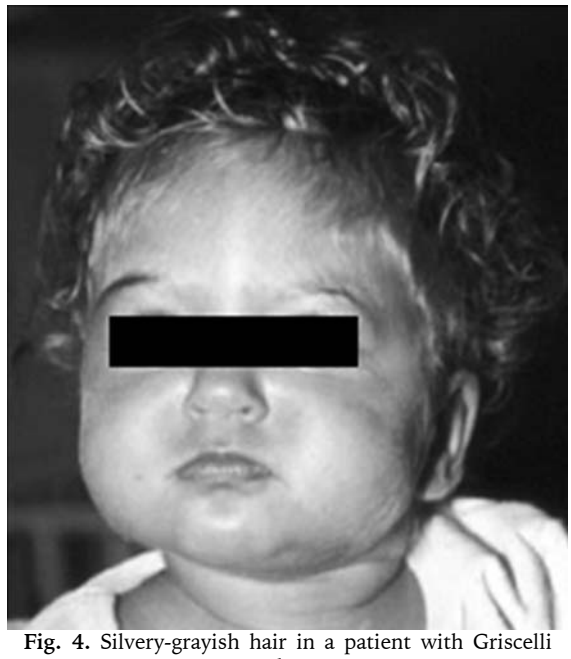

Fig. 4. Silvery-grayish hair in a patient with Griscelli syndrome.

Fig. 5. Irregular pigmentation of the hair shaft in the patient with Griscelli syndrome.

reproductive risk assessment for patients in the FHL group[23].

Regarding the clinical manifestations of the patients, the high frequency of hepatosplenomegaly at the time of diagnosis in our patients was considerable. More than 40% of the patients had such nonspecific findings, which was significantly higher than in other previous reports[2,3,11,17]. In contrast, while bone lytic lesions were the most frequent clinical manifestation in class 1 (55.5%), the rate was much lower than reported in other studies (2,3,11). The frequency of the skin lesions was similar to the previous studies[2,3,11,17]. Fingernail and toenail involvement was reported in 1 patient with LCH, which is distinctly uncommon[23,24]. The nail changes in LCH could have a bad prognostic role[24-27] and should be treated mainly by cotrimoxazole[24-26]. LCH should be considered as an etiology of lung cystic disease, which can be treated with early diagnosis and therapy of LCH[28]. Two patients with LCH in our study were referred with continuous pneumothorax. LCH is one of the most common diseases among the systemic underlying disorders that may cause central diabetes insipidus[29]. Diabetes insipidus was reported in 3 cases in class 1 as a complication of the therapeutic protocols; such complication was reported in 25% of the patients in California[30] and 6% of Hungarian patients at the time of diagnosis[17]. The population-based study of LCH in France also reported the pituitary site and diabetes insipidus in 18 patients with LCH[2].

Different therapeutic protocols are used all over the world, based on the types and stages of disease, including combination of steroids and vinblastine, etoposide, cyclosporine, and other drugs[17,31-34]. The most common therapeutic protocol in our center was corticosteroid and vinblastine in patients of class 1, and prednisone, cyclosporine, etoposide, and intravenous immunoglobulin for those in class 2.

In our study, 12 cases (44%) died, which was significantly higher than in other studies[2,11,12,17]. This difference could be due to delay in diagnosis, different types of histiocytic disorders, severe stages of disease in our study, and poor compliance of patients/family to long-term treatment. Involvement of the hematopoietic system such as leukopenia and thrombocytopenia, CNS involvement, and multiple system involvement were associated with poor prognosis in patients in the different histiocytosis groups. Mortality rate in class 1 was 30%, and all patients suffered from multiple organ failure, ineffective chemotherapy, and absence of HLA-matched donor for SCT. In class 2, 3 patients (50%) died due to unmanageable treatment, CNS involvement, sepsis and DIC. Moreover, the high mortality rate for class 2 may be due to the low number of patients in this group.

In conclusion, primary clinical features should be considered for further evaluation of such diseases, while early diagnosis and treatment can prevent the complications and even death in the affected cases. Further studies on SCT and other favorable therapeutic protocols should be performed to increase the survival rate of the patients with histiocytic disorders, especially patients in the FHL group (35-39).

REFERENCES

1. Savaşan S. An enigmatic disease: childhood Langerhans cell histiocytosis in 2005. Int J Dermatol 2006; 45: 182-188.
2. Guyot-Goubin A, Donadieu J, Barkaoui M, et al. Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000-2004. Pediatr Blood Cancer 2008; 51: 71-75.

3. Stålemark H, Laurencikas E, Karis J, et al. Incidence of Langerhans cell histiocytosis in children: a population-based study. Pediatr Blood Cancer 2008; 51: 76-81.
4. Egeler RM, D'Angio GJ. Langerhans cell histiocytosis. J Pediatr 1995; 127: 1-11.
5. Aricò M, Egeler RM. Clinical aspects of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998; 12: 247-258.
6. Arceci RJ. The histiocytoses: the fall of the Tower of Babel. Eur J Cancer 1999; 35: 747-767.
7. Henter JI, Tondini C, Prichard J. Histiocyte disorders. Crit Rev Oncol Hematol 2004; 50: 157-174.
8. Mittheisz E, Seidl R, Prayer D, et al. Central nervous system-related permanent consequences in patients with Langerhans cell histiocytosis. Pediatr Blood Cancer 2007; 48: 50-56.
9. 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 Oncol 1997; 29: 157-166.
10. Narula G, Bhagwat R, Arora B, et al. Clinico-biologic profile of Langerhans cell histiocytosis: a single institutional study. Indian J Cancer 2007; 44: 93-98.
11. Alston RD, Tatevossian RG, McNally RJ, et al. Incidence and survival of childhood Langerhans cell histiocytosis in Northwest England from 1954 to 1998. Pediatr Blood Cancer 2007; 48: 555-560.
12. Morimoto A, Ikushima S, Kinugawa N, et al; Japan Langerhans Cell Histiocytosis Study Group. Improved outcome in the treatment of pediatric multifocal Langerhans cell histiocytosis: results from the Japan Langerhans Cell Histiocytosis Study Group-96 protocol study. Cancer 2006; 107: 613-619.
13. Chu T, D'Angio GJ, Favara BE, et al. Histiocytosis syndromes in children. Lancet 1987; 2: 41-42.
14. Nezelof C, Basset F. Langerhans cell histiocytosis research. Past, present, and future. Hematol Oncol Clin North Am 1998; 12: 385-406.
15. 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.
16. Risdall RJ, Brunning RD, Sibley RK, et al. Malignant histiocytosis: a light- and electron-microscopic and histochemical study. Am J Surg Pathol 1980; 4: 439-450.
17. Müller J, Garami M, Hauser P, et al; Hungarian Pediatric Oncology Network. Hungarian experience with Langerhans cell histiocytosis in childhood. Pediatr Hematol Oncol 2006; 23: 135-142.
18. [No authors listed]. A multicenter retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983-1993. The French Langerhans' Cell Histiocytosis Study Group. Arch Dis Child 1996; 75: 17-24.
19. Gadner H, Heitger A, Grois N, et al. Treatment strategy for disseminated Langerhans cell histiocytosis. DAL HX-83 Study Group. Med Pediatr Oncol 1994; 23: 72-80.
20. Mizumoto H, Hata D, Yamamoto K, et al. Familial hemophagocytic lymphohistiocytosis with the MUNC13-4 mutation: a case report. Eur J Pediatr 2006; 165: 384-388.
21. Janka G, Zur Stadt U. Familial and acquired hemophagocytic lymphohistiocytosis. Hematology Am Soc Hematol Educ Program 2005: 82-88.
22. Shahla A, Parvaneh V, Hossein HD. Langerhans cells histiocytosis in one family. Pediatr Hematol Oncol 2004; 21: 313-320.
23. Rezaei N, Pourpak Z, Aghamohammadi A, et al. Consanguinity in primary immunodeficiency disorders; the report from Iranian Primary Immunodeficiency Registry. Am J Reprod Immunol 2006; 56: 145-151.
24. Jain S, Sehgal VN, Bajaj P. Nail changes in Langerhans cell histiocytosis. J Eur Acad Dermatol Venereol 2000; 14: 212-215.
25. de Berker D, Lever LR, Windebank K. Nail features in Langerhans cell histiocytosis. Br J Dermatol 1994; 130: 523-527.
26. Tzortzatou-Stathopoulou F, Xaidara A, Mikraki V, et al. Effect of trimethoprim-sulphamethoxazole in Langerhans' cell histiocytosis: preliminary observations. Med Pediatr Oncol 1995; 25: 74-78.
27. Timpatanapong P, Hathirat P, Isarangkura P. Nail involvement in histiocytosis X. A 12-year retrospective study. Arch Dermatol 1984; 120: 1052-1056.
28. Schulze J, Kitz R, Grüttner HP, et al. Severe isolated pulmonary Langerhans cell histiocytosis in a 6-year-old girl. Eur J Pediatr 2004; 163: 320-322.
29. Prosch H, Grois N, Prayer D, et al. Central diabetes insipidus as presenting symptom of Langerhans cell histiocytosis. Pediatr Blood Cancer 2004; 43: 594-599.
30. Willis B, Ablin A, Weinberg V, et al. Disease course and late sequelae of Langerhans' cell histiocytosis: 25-year experience at the University of California, San Francisco. J Clin Oncol 1996; 14: 2073-2082.
31. Gadner H, Grois N, Arico M, et al; Histiocyte Society. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. J Pediatr 2001; 138: 728-734.
32. Ladisch S. Langerhans cell histiocytosis. Curr Opin Hematol 1998; 5: 54-58.
33. 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.
34. Gadner H, Grois N, Pötschger U, et al.; for the Histiocyte Society. Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification. Blood 2008; 111: 2556-2562.
35. Llano OG, Perez JC, Rodriguez OC, et al. Allogeneic hematopoietic stem cell transplantation using a reduced-intensity conditioning regimen in infants: experience at a single institution in Mexico. Pediatr Hematol Oncol 2008; 25: 39-47.

36. Cesaro S, Gazzola MV, Marson P, et al. Successful engraftment and stable full donor chimerism after myeloablation with thiotepa, fludarabine, and melphalan and CD34-selected peripheral allogeneic stem cell transplantation in hemophagocytic lymphohistiocytosis. Am J Hematol 2003; 72: 143-146.

37. Lai CC, Huang WC, Cheng SN. Successful treatment of refractory Langerhans cell histiocytosis by allogeneic peripheral blood stem cell transplantation. Pediatr Transplant 2008; 12: 99-104.

38. Stoll M, Freund M, Schmid H, et al. Allogeneic bone marrow transplantation for Langerhans' cell histiocytosis. Cancer 1990; 66: 284-288.

39. Imashuku S, Shioda Y, Kobayashi R, et al.; the Japan LCH Study Group (JLSG). Neurodegenerative central nervous system disease as late sequelae of Langerhans cell histiocytosis. Report from the Japan LCH Study Group. Haematologica 2008; 93: 615-618.