RESEARCH ARTICLE

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# Pathology, Classification, Clinical Manifestations and Prognosis of Langerhan's Cell Histiocytosis: A Single Center Experience

**ABSTRACT**

**Objective:** The aim of the study is to raise awareness about clinical features, histopathological and radiological analyzes and treatment details of this rare disease.

**Methods:** A total of 55 Langerhans cell histiocytosis patients, diagnosed between the year 2006 and October 2020 in our department were included in the study. The patients were evaluated in terms of age, gender, tumor localization, risk groups, treatment modalities, recurrence, and outcome of the disease.

**Results:** Twenty-three out of 55 patients were children and 32 were adults. The ages of the patients were between 7 months and 72 years. Thirty-seven of the cases were male and 18 were female. The most common clinical complaint in both groups was pain and swelling. The duration between the onset of the patient complaints and admission to the hospital varies between 7 days-12 months in children, and 10 days-23 years in adults. Forty-three of the cases had single organ involvement and 12 had multiorgan involvement. The most frequently affected organ in both groups was bone. Forty of the 55 patients had follow-up data and the treatment modalities are as follows: Nine patients radiotherapy, 8 patients chemotherapy+steroid, 7 patients chemotherapy, 2 patients chemotherapy+radiotherapy+steroid, 1 patient steroid, 2 patients chemotherapy+radiotherapy. Eleven patients were followed up without additional treatment after surgery. Median follow-up from the time of biopsy was 45.9 months in children and 41.9 months in adults.

**Conclusions:** As a result, diagnosis requires a high degree of suspicion and final diagnosis is based on the histological examination of the lesions and biopsies.

**Keywords:** Langerhans Cell Histiocytosis, Adult, Pathology, Children, Prognosis.

# Langerhans Hücreli Histiyositozun Patolojisi, Sınıflandırılması, Klinik Belirtileri ve Prognozu: Tek Merkez Deneyimi

**ÖZET**

**Amaç:** Çalışmanın amacı, nadir görülen bu hastalığın; klinik özellikler, histopatolojik, radyolojik analizler ve tedavi detayları hakkında farkındalığı arttırmaktır.

**Gereç ve Yöntem:** 2006 Ocak-2020 Ekim tarihleri arasında anabilim dalımızda tanı konan 55 Langerhans hücre histiyositozu hastası çalışmaya dahil edildi. Hastalar yaş, cinsiyet, lokalizasyon, risk grupları, tıbbi tedavi, nüks ve hastalığın sonuçları açısından değerlendirildi.

**Bulgular:** 55 hastanın 23'ü çocuk, 32'si yetişkindi. Hastaların yaşları 7 ay ile 72 yıl arasında değişmektedir. Olguların 37'si erkek, 18'i kadındı. Her iki gruptada en sık şikâyet ağrı ve şişlikti. Hasta şikâyeti ile hastaneye başvuru süresi çocuklarda 7 gün ile 12 ay arasında değişirken, erişkinlerde 10 gün ile 23 yıl arasında değişmektedir. Olguların 43'ünde tek organ tutulumu, 12'sinde multiorgan tutulumu vardı. Yetişkinlerde ve çocuklarda en sık etkilenen organ kemikti. Takipli hastalar tedavi açısından incelendiğinde: 9 olgu radyoterapi, 8 olgu kemoterapi + steroid, 7 olgu kemoterapi, 2 olgu kemoterapi + radyoterapi + steroid, 1 olgu sadece steroid, 2 olgu kemoterapi + radyoterapi ve onbir olgu ise cerrahi sonrası ek tedavi gerekmeksizin takip edildi. Biyopsiden sonra medyan takip süresi çocuklarda 45.9 ay ve erişkinlerde 41.2 ay idi..

**Sonuç:** Sonuç olarak tanı için yüksek derecede şüphe gerektiren hastalıkta, kesin tanı lezyonların ve biyopsilerin histolojik incelemesine dayanmaktadır.

**Anahtar Kelimeler:** Langerhans Hücre Histiyositozu, Erişkin, Patoloji, Çocuk, Prognoz.

## INTRODUCTION

Langerhans cell histiocytosis (LCH) is a quite rare and heterogeneous disease that is characterized by the accumulation of Langerhans-type cells in various tissues (1-6). Although the disease is most commonly encountered at patients 20 years of age or under, it can be seen at any age (3,5). The etiology is not fully understood, it is still not determined whether LCH is mediated by an immunological or a neoplastic mechanism (3,5). Viral, bacteriological and genetic studies have been performed for etiology, and some forms were thought to have an infectious origin since they recover spontaneously (5). However, it is recently identified as a clonal disorder due to a mutation found on the BRAF gene (3,7,8). The discoveries led to a newer classification of histiocytic disorders and started an era of targeted therapy in LCH (7). In the study Özer et al; in 2019, that opened the door to targeted treatment studies in LCH two results were obtained (7). First, while 60% of LCH samples have the BRAF V 600E mutation, secondly LCHs demonstrated universal immunostaining of phospho - MEK and phospho-ERK regardless of BRAF status (7).

LCH frequently affects the bone, skin, bone marrow, lungs, lymph nodes, spleen, liver and pituitary gland (9-15). The clinical features of LCH have a wide spectrum. The spectrum of the disease ranges from an isolated lytic bone lesion to a fatal multisystemic disease. The definitive diagnosis is based on histopathologic and immunohistochemical examination of the tumor tissue. Langerhans cells are immunohistochemically positive for CD1a, Langerin and S100 (3,6). Histopathologically, the lesion may contain Langerhans cells with kidney-shaped nuclei, clear eosinophilic cytoplasm, irregular contours as well as eosinophils, lymphocytes, neutrophils, and plasma cells. Treatment modalities include performing surgery, chemotherapeutic agents and radiotherapy (3,4,6).

We analyzed our single center experience of patients with LCH. The aim of the study is to rise the awareness about clinical features, histopathological and radiological analyzes and treatment details of this rare disease.

## MATERIAL AND METHODS

A total of 55 LCH patients diagnosed between years January 2006 and May 2020 in our department were included in the study. A 14-year electronic diagnostic data search was performed in the hospital medical data management system using the keywords ‘’ Langerhans cell histiocytosis ‘ and ‘’Eosinophilic granuloma ‘’ in the diagnostic line. As a result of screening, 55 patients diagnosed with Langerhans cell histiocytosis ' and 'Eosinophilic granuloma' were included in the study.

Medical records of patients with LCH were based on patient’s clinical records and retrospective clinical data collection. The patients were evaluated in terms of age, gender, localization, risk groups, medical treatment, recurrence and outcome of the disease. In addition to morphology, CD1a and S100 were administered immunohistochemically for all patients and clinical findings were evaluated together. Descriptive statistics for the continuous variables were presented as mean and standard deviation, while count and percentages for categorical variables.

SPSS version 21 (Chicago , IL, USA) statistical program was used for all statistical computations.

## RESULTS

Twenty-three out of 55 patients (41.2 %) were children (under 16 years old) and 32 (58.2 %) were adults ( 18 years and above ). The ages of the patients ranged from 7 months to 72 years. In the childhood group, there were 12 patients under the age of 5 years, 5 patients between the ages of 6-10 years and six patients aged 11 and over. In the adult group, there were 26 patients between the ages of 18 and 40, and 6 people over the age of 41. Median age at the diagnosis was $6.7 \pm 4.5$ in children and $35.6 \pm 11.9$ in adults. Thirty-seven (67.3%) of the cases were male and 18 (32.7%) were female. Male – female distribution specific to childhood and adult groups are as follows: 15 of the children were male and 8 were female, 22 of the adults were male and 10 were female.

Patient complaints vary according to the organs involved. Patients with pulmonary involvement admitted to the hospital with dry cough, shortness of breath, chest pain, patients with bone involvement swelling, pain and fracture, patients with skin involvement itching and wounds that do not heal, patients with sternum involvement with chest pain. Headache was the main complaint in patients with cranial bone involvement while low back pain was common in patients with vertebral involvement. Loose memory, polyuria, and polydipsia were the most commmon complaints in patients with hypothalamic involvement. The most common complaint in both groups was pain and swelling. While the duration of admission to the hospital from the onset of patient complaints varies between 7 days and 12 months in children (2 months on average) , it varies between 10 days to 23 years in adults (4 months on average, in case the patient who has had an itching for 23 years is excluded).

Five of our patients had obesity, 4 had diabetes mellitus, one had Familial Mediterranean Fever (FMF), one had a neurodegenerative disease, and one patient had additional cervical cancer (Patient characteristics are summarized in Table 1).

**Table 1**. Clinical characteristics of patients a child and adult

| | Child | Adult | | Child | Adult |
|---|---|---|---|---|---|
| **Number of patients** | 23 | 32 | **SS-LCH** | 19 | 24 |
| | | | Bone | 18 | 16 |
| **Male/female ratio** | 15/8 (1.9) | 22/10 (2.2) | Skin | 1 | 4 |
| | | | LN | | 2 |
| **Age at diagnosis median** | 7 M-16Y(6.91) | 18-72 (35.6) | Lung | | 1 |
| 0-5 years old | 12 | | Hypothalamus | | 1 |
| 6-10 years old | 5 | | **MS-LCH** | 4 | 8 |
| 11 years and above | 6 | | Lung+bone | 1 | 2 |
| 18-40 years old | | 26 | Lung+skin | 1 | 1 |
| 40 years and above | | 6 | Lung+LN | 1 | |
| | | | Lung+bone+spleen | 1 | |
| **Duration of complaints** | 7 D-12 M | 10 D-23Y | Thymus+sinus | | 1 |
| | | | Thyroid+skin | | 1 |
| **Relaps** | 2 | 6 | Lung+hypothalamus | | 1 |
| | | | Liver+bone | | 1 |
| **Follow of time** | 12-119 M | 2-196 M | Liver+skin+BM | | 1 |
| | **Child** | **Adult** | | **Child** | **Adult** |
| **Complaint** | | | **Treatment** | 19 | 21 |
| Swelling | 13 | 6 | RT | 4 | 5 |
| Pain | 7 | 15 | CT | 4 | 3 |
| Cough | 1 | 2 | CT+RT | 1 | 1 |
| Fever+rash | 2 | | CT+Steroid | 4 | 4 |
| Rash | | 5 | CT+RT+Steroid | | 2 |
| Itching | | 3 | Steroid | 1 | |
| DI finding | | 1 | Follow | 5 | 6 |
| | | | Without follow | 4 | 11 |

CT: Chemotherapy; RT: Radiotherapy; DI: Diabetes insipidus; LN: Lymph node; SS: Single system; MS: Multisystem; D: Day; M: Month; Y: Years

**Table 2.** Clinical classification of langerhans cell histiocytosis (LCH)

| Categories of LCH | Definitions |
|---|---|
| Single system LCH (SS-LCH) | One organ/system involved (unifocal or multifocal) |
| | -Bone (unifocal or multifocal) |
| | -Lymph node |
| | -Skin |
| | -Lungs |
| | -other (eg, thyroid, thymus, …..) |
| Multisystem LCH (MS-LCH) | *Two or more organs/systems |
| | İnvolved either with or without |
| | involvement of **high** risk organs |

* high-risk organs include the hematologic system, the spleen and the liver LCH: Langerhans cell histiocytosis

Criteria for histological diagnosis were based on the recommendations of the Histiocyte Society (Table 2) (4,6). Forty-three of the cases had single organ involvement and 12 had multiorgan involvement (Table 3). While 19 (82.6%) of 23 patients in childhood group had single organ involvement, 4 (17.4%) patients had multiorgan involvement, 24 (75%) of 32 patients in the adult group had single organ involvement while 8 (25%) adult patients had multiorgan involvement.

**Table 3.** Organs involvement as single and multisystem

| Held Organ | N(%) | Held Organ | N(%) |
|---|---|---|---|
| MS-LCH | 12 (21.8 %) | SS-LCH | 43 (78.2 %) |
| Lung + Bone | 3 (5.5 %) | Bone | 34 (61.8 %) |
| Lung + Skin | 2 (3.7 %) | Skin | 5 (9.1 %) |
| Liver + Bone | 1 (1.8 %) | LN | 2 (3.7 %) |
| Lung + LN | 1 (1.8 %) | Lung | 1 (1.8 %) |
| Lung + Hypothalamus | 1 (1.8 %) | Hypothalamus | 1 (1.8 %) |
| Thyroid + Skin | 1 (1.8 %) | | |
| Thymus + Sinus | 1 (1.8 %) | | |
| Lung +Spleen +Bone | 1 (1.8 %) | Total | 55 (100 %) |
| Liver+Skin+Bone morrow | 1 (1.8 %) | | |

MS-LCH: Multi system langerhans cell histiocytosis SS-LCH: Single system langerhans cell histiocytosis LN: Lymph node

In childhood group three of the patients with single organ involvement had multifocal bone involvement. In adults five of the cases with single organ involvement were also multifocal. In three patients multifocally involved organs were skin and in the remaining two were lymph nodes. The organ

most frequently affected organ both in adults and children was the bone. The most frequently involved bones were cranial bones. The numbers of organs involved in our series are summarized in Table 4. Of the 55 cases, 54 ( 98.2%) were alive, 1 ( 1.8%) were dead. All patients except one were still in complete remission at the time of the study review.

**Table 4**. The numbers of organs held in our series

| Involvement organs | N | Involvement organs | N |
|---|---|---|---|
| Bone | 39 | Skin | 9 |
| Head bone | 19 | Lung | 8 |
| Vertebrae | 8 | Lymph node | 3 |
| Humerus | 4 | Liver | 2 |
| Sternum | 3 | Hypothalamus | 2 |
| Femur | 2 | Thymus | 1 |
| Scapula | 1 | Spleen | 1 |
| Clavicula | 1 | Thyroid | 1 |
| Radius | 1 | Bone morrow | 1 |

Nineteen (82.6%) of 23 child patients, and 21 (65.6%) of 32 adult patients had follow-up data. Out of the 15 cases without follow-up data, 8 were consultation cases that admitted to our hospital for pathologic diagnosis confirmation, 5 cases did not re-admitted to our hospital after the diagnosis and two cases were lost from the follow-up after 3 and 5 months, respectively.

The treatment modalities of the 40 patients who had follow-up data are as follows: Nine patients radiotherapy (RT), 8 patients chemotherapy (CT) + steroid, 7 patients CT, 2 patients CT + RT + steroid, 1 patient steroid, 2 patients CT + RT. Eleven patients were followed up without additional treatment after surgery.

Median follow up from of biopsy was 45.9 ± 30.2 months (range= 12-119 months) in children and 41.9 ± 52.6 months (range= 2-176 months) in adults.

Recurrence was observed in 8 patients. Two of the recurrent cases were children and 6 were adults. Recurrences in children both occurred after 1 year, while recurrences occurred after 7 months, 1, 3, 7, 8, and 10 years respectively in adults. The characteristics of patients with recurrent diseases are summarized in the table (Table 5). The first recurrence of our case (176 months), which we followed for the longest period in adults, is 7 years later. The patient then repeated three more times but is now being followed in remission. The patient with died was 35 years old male and had multiorgan (liver + skin + bone marrow) involvement. The patient was diagnosed as ready paraffin blocks (liver + bone marrow) and then was out of follow-up.

**Table 5.** Features of our recurrence cases

| Case | Age | Gender | Localization | Multifocal | Recurrence |
|---|---|---|---|---|---|
| 1 | 2 | Female | Lung+bone+spleen | No | 1 year |
| 2 | 3 | Male | Bone (Cranium) | No | 1 year |
| 3 | 25 | Female | Lung +skin | No | 10 year |
| 4 | 32 | Female | Lymph node | Yes | 8 year |
| 5 | 35 | Male | Bone (Cranium) | No | 7 month |
| 6 | 27 | Male | Thyroid + skin | No | 7 year |
| 7 | 27 | Male | Lymph node | Yes | 1 year |
| 8 | 33 | Female | Skin | No | 3 year |

## DISCUSSION

Although LCH previously thought as a reactive process in which the Langerhans-type cell accumulate in various tissues and cause damage , it is now classified as a true neoplasm due to BRAF V600 mutations recently defined in these lesions (5,11). LCH is a rare disease and can occur at any age, particularly in younger children. The majority of reported cases (60-70%) are under 20 years old. The most common age range is between 5-10 years old. Adult pateints are predominant in our series; 32 (58.2%) of our cases were adults and 23 (41.2%) were children. About half of our pediatric patients were between 0-5 years old. LCH is slightly more common in men than in women (55%) (5,14). In our series there were male predominance in both age groups. The M / F ratio was 15/8 (1.9) in children, and 22/10 (2.2) in adults.

Although the disease was previously called with 4 different names; Hashimoto Pritzker disease, Eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease, representing the 4 different clinical presentations, these diseases are now all called as LCH due to their common immunological properties (2,5,13,16).

Etiology of the disease is still not determined whether it is mediated by on immunological or a neoplastic mechanism. It is however recognized as a clonal disorder and a mutation of the BRAF gene (BRAF V600) has been lately identified present in more than half of the patients, favoring the hypothesis of a neoplastic origin (1,3,7,8,14).

The disease has no specific symptoms, physical examination, or laboratory findings. The diagnosis of the disease is made by clinical, histopathological and immunohistochemical analysis. It should be considered in patients with unexplained clinical manifestations of skin, bone, ear, lymph node, lung, liver and CNS. LCH can be asymptomatic or it can manifest with different signs or symptoms according to the organ involved. The most common symptoms are pain, bone swelling, cutaneous rash, and lymphadenopathy, followed by respiratory insufficiency, hepatomegaly, splenomegaly, neutropenia, anemia (5,17). The most common complaints in our series were pain and bone

swelling. The median time for the start of the complaints and admission to the hospital was 2 months (7 days-12 months) in children and 4 months (10 days-23 years) in adults, in our series. In the literature, the median time from the first symptom to diagnosis was reported as 1-1.5 months (6). The reason for the high prevalence of adult patients in our series may be that patients are asymptomatic and undiagnosed for a longer period of time.

The diagnosis of LCH is often difficult and delayed (9). Due to the complaints of swelling and pain in bone involvement, the duration of diagnosis is shorter as the time to admission to the hospital is shorter. In skin involvement and/or other organ involvements, if the disease is suspected and a biopsy is taken, the diagnosis time may be shortened.

Radiological imaging methods are also used in diagnosis. In particular, findings in bone involvement imitate many bone tumors radiologically (such as Ewing sarcoma, aneurysmal bone cyst, osteomyelitis, osteosarcoma, metastatic bone tumor). In our series, Ewing sarcoma and osteomyelitis are frequently considered in the radiological differential diagnosis of the bone lesions. The definitive diagnosis is based on the histopathologic and immunohistochemical examination of tumor tissue (6,17). Diagnosis was established for all of our patients by demonstrating pathologic Langerhans cells which are stained immunohistochemically with CD1a and S100 as well as typical clinical findings (6,10,11). Histopathologically, eosinophils, neutrophils, lymphocytes and plasma cells can also accompany Langerhans cell proliferation (Figure 1). In all of our cases, S100 (Figure 2) and CD1a (Figure 3) were positive in langerhans cells.

In the classification made by the LCH study group according to organ involvement, the disease is examined in two main groups: single system (SS) involvement and multisystem (MS) involvement (4,6). While single organ involvement (monofocal or monostatic type) of the disease constitutes 65% of cases, 35% of cases show multiorgan involvement (5). In our series, 43 (78.2%) cases, ( 19 in children and 24 in adults) showed single organ involvement. Four of the 12 patient (22.8%) with multiorgan involvement were children and eight were adults. A disease that starts as the monostatic type can then turn into the polistatic type.

Bone involvement with or without other associated sites are the most common manifestation of LCH and has been observed in 80-100% of cases based on a review of the literature (9). The single organ involved is most commonly the bone, which is followed by skin (11). The organ involvement pattern (bone being the most common, and skin the second) in our series is consistent with this literature. LCH can involve any bone of the body. The most commonly involved bones in our cases are cranium and vertebrae and it is also compatible with the literature. Unusual sites of bone involvement includes zygomatic bone, scapula, clavicula and sternum.

In children common sites of bone involvement include craniofasial bones, femur, ribs, vertebrae and humerus (4,6). Bone involvement was present in 39 (70.9%) of our patients. Involved bones were craniofacial bones 19 ( 34.6%), vertebrae 8 (14.5%), sternum 3 (5.5%) , scapula 1 (1.8%), clavicule 1 (1.8%), and long bones including femur, humerus, radius 7 (12.7% ).

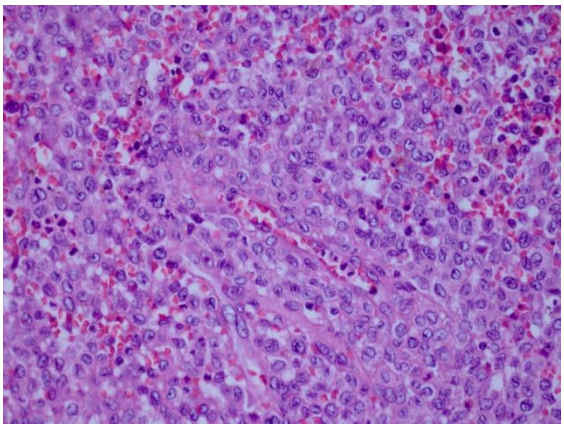

**Figure 1.** Close-up view of langerhans cells with irregular contours, some with kidney-shaped nuclei, clear-eosinophilic cytoplasm (HEx200)

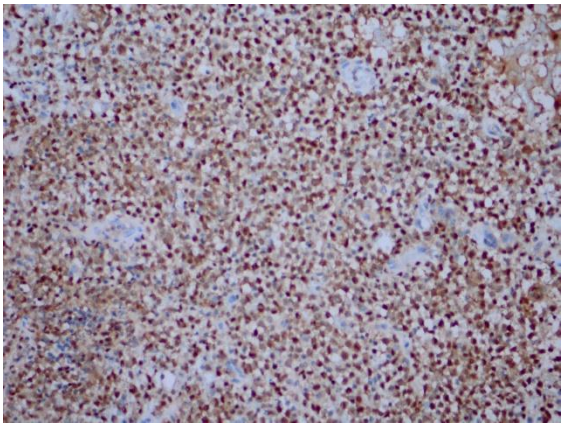

**Figure 2.** Diffuse positivity of Langerhans cells with S100 (IHKx200)

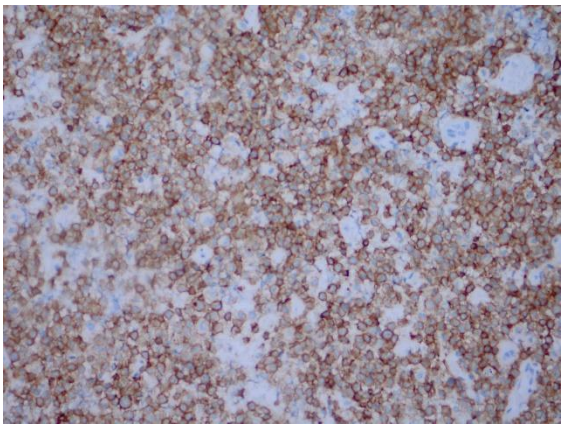

**Figure 3.** Diffuse positivity of langerhans cells with CD1a (IHKx200)

In considering patients of all ages, skin is the second most frequently involved organ system after bone (18). Skin involvement had been reported in over one third (20-38%) of children with LCH (6). Skin involvement can be a limited disease or a component of MS-LCH. Isolated cutaneous disease has only been observed in 2% of the total LCH (20). Skin involvement was present in 9 ( 16.4% ) of our cases, and 5 of them had skin limited disease. Skin involvement was present in 2 children (1 SS-LCH, 1 MS-LCH) and 7 adults (4 SS-LCH, 3 MS-LCH). Especially in infants, a seborrheic dermatitis-like rash often causes LCH to be misdiagnosed as seborrheic dermatitis, while groin involvement can present as treatment-resistant, recurring diaper dermatitis (18). In our series, three cases were followed up with seborrheic dermatitis and were subsequently diagnosed as a result of a biopsy. In two of our cases (7 months and 1 year old), LCH was diagnosed as a result of biopsies taken for persistent lesions in the perianal region.

Pulmonary involvement is observed in 3-5% of patients with LCH. While in adult LCH, pulmonary involvement is as high as 50-60% compared to other organs, unlike the pulmonary LCH where pulmonary involvement is rare (6). In our series, there was a total of 8 patients have pulmonary involvement, which of 3 are children and 5 are adults. Isolated type pulmonary disease occurs predominantly in adults, whereas this is rare in children (19). In our series, there was no case with isolated pulmonary in children, and all 3 pediatric patients pulmonary involvement was a component of systemic disease. In adults, isolated pulmonary disease is observed in 1 patient, and lung involvement in remaining 4 patients was observed as a component of multiorgan involvement. Five of the patients with lung involvement were male and 3 were female. In our series, lung involvement is observed less frequently than in the literature. The rate of lung involvement in 14.5% in our series, while it is 22-24 % in the literature (6). Cigarette smoking is reported in an overwhelming majority of adult patients with pulmonary involvement (10,19,20). Ten of our patients were smokers, and four of them had lung involvement. The reason for the low lung involvement rate in our series may be due to the low rate of smoking among our patients.

Central nervous system (CNS) involvement usually occurs by contiguity of the skull lesions into the brain tissue. Most commonly involved sites are the cerebellum, hypothalamic nuclei and pituitary gland, producing diabetes insipidus (3). Diabetes insipitus (DI) is the most common endocrinopathy in LCH (16). DI prevalence has a very broad range in various studies, changing between 5-50% pointing out the risk of progressive disease (2). Two of our patients had hypothalamic involvement and presented DI findings. One of these patients was a child and the other one was an adult. Thyroid involvement is quite rare, with only 75 cases reported in the literature and may present with nodular or diffuse enlargement (18,21). Patients are typically euthyroid or hypothyroid (18). In our series, Thyroid + skin involvement was present in one case. Our patient had subclinical hypothyroidism and the LCH lesion in the thyroid was growing nodularly.

Liver involvement is especially seen in patients with MS-LCH (18,22). Patients may present with hepatomegaly, jaundice or sclerosing cholangitis (18). There was liver involvement in two cases with multisystem involvement in our series. While one of the cases presented with the complaint of pain and multiple liver masses, the other admitted to the clinic with the complaint of itching and jaundice lasting for about 20 months. In the histopathological evaluation of the biopsy performed to enlighten the etiology of itching and jaundice in this patients, langerhans cell infiltration, as well as grade 4-5 fibrosis were observed. In long-term and resistant itching and patients with unexplained jaundice, LCH should be considered and biopsy should be performed for differential diagnosis.

Thymus involvement is mostly seen in patients with MS-LCH. Isolated LCH of the thymus gland is quite rare (23,24). There was thymus involvement in one case with multisystem involvement in our series.

Addition of skin and mucousal lesions to the bone lesions, relapse of bone lesions after treatment, involvement of three or more bones, patients age under 5 years, and two or more system involvements accompanying to bone lesions are signs of poor prognosis (5). Previous studies on LCH have shown that children do worse than adults (2). In our series, 1 case died and 8 cases had relapsed. Our patient who died was a 35 years old male and had MS-LCH (Liver + bone marrow + skin). Two of our recurrent patients were children and 6 were adults. One of the relapsed children had multiorgan involvement (Bone + lung + spleen) and the other case had multiple bone involvement. Both patients were under 5 years old. Two of the 6 patients who relapsed in adult age group were MS-LCH and 4 were SS-LCH. Two of the patients with SS-LCH had multifocal involvement. In our patients with died and recurrence were present organs involvement which were risk groups (bone morrow, spleen, and liver).

The course of the disease varies from spontaneous resolution to a progressive multisystem disorder with organ dysfunction and potentially life-threatening complications (9). In the treatment of LCH, if the lesion does not show any symptoms, it should only be monitored, even if it is massive. However, if there are findings such as pain, deformity, risk of pathological fracture, neurological deficit, it should be treated.

Differential diagnosis includes indeterminate dendritic cell tumor (IDCT) and Langerhans cell sarcoma (LCS). IDCTs are Langerin negative, while LCS and LCH are positive. IDCT usually shows

aggressive histological features (such as central necrosis and a high Ki67 proliferation index ). In addition, Birbeck granules are not observed in electron microscopy (25,26). Cytologically LCS can be differentiated from LCH as it displays malignant features ( such as cellular atypia, increased mitotic activity, and necrosis) (27).

In treatment, steroid application into the lesion as well as curettage and bone graft, CT, low dose RT, combined therapies, and bone marrow transplantation can be applied (3,5). In localized disease, namely in unifocal bone lesions, surgical curettage should be considered as a first-line therapeutic option, as well as intralesional steroids or focal RT. Chemotherapy is indicated in multisystem disease or high-risk organ involvement (3). The treatment method is determined by the age of the patient, the localization of the lesion, the number of bone and lesions retained, the size of the lesion, and its natural course. Patients with a multisystem disease or multifocal bone lesions are usually treated with systemic CT (1). When we look at the treatment protocols of our 40 patients who had follow-up data in our series: 11 were followed, 9 were treated with RT, 8 were treated with CT + steroid, 7 were treated with CT, 2 were treated with CT + RT + steroid, and 1 had only steroid treatment. Since the RT dose used in the treatment of LCH is low and effective, side effects can be well tolerated (2). In our series, no secondary cancers or treatment related serious late effects were developed so far. Evaluations were done with 3-6 months of intervals during treatment and until 3-5 years after the end of treatment, and whenever patients complained of systems relevant to LCH. In our series, while the follow-up of pediatric patients was more regular, follow-up intervals were remarkably longer in the adult age group. The reason for the relapse rate in children (10.1%) to be lower than adults (28.5%) may be due to their regular follow-up.

The limitation of our study is that it is retrospective and not supported molecularly (such as BRAF). Our study should be supported by prospective studies.

Consequently; Diagnosis of LCH requires a clinically high degree of suspicion and the final diagnosis is usually based on the histopathological examination of the lesions. LCH disease should be considered in the differential diagnosis in patients presenting with bone pain, prolonged and resistant itching, prolonged cough, or unexplained jaundice. Multidisciplinary optimized therapeutic approaches are needed for better management of these patients. Identification of patients with high-risk organ involvement is essential because these patients usually need more aggressive treatment. We believe that correct and early diagnosis is a factor prognostically as important as multisystem involvement. We wanted to draw attention to the fact that this disease, which has a good prognosis with correct diagnosis, proper management and regular follow up, may well be seen in adults , not only in children, and should be kept in mind in the differantial diagnosis.

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