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RESEARCH ARTICLE

Retrospective analysis of seven patients with adult-onset langerhans cell histiocytosis syndromes: A single center experience

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ABSTRACT

Langerhans cell histiocytosis syndromes have been described as encompassing a range of disorders, such as eosinophilic granuloma, Letterer-Siwe syndrome and Hand-Schüller-Christian disease. These disorders have been mainly diagnosed at early ages of life and are relatively rare entities in adult age groups. In this study, we aimed to retrospectively evaluate the patients with Langerhans cell histiocytosis followed-up in our hospital.

Seven patients were treated between 1995 and 2005. Median age of patients was 27.5 (18-40) years. Main complaints were classified as bone pain in multiple sites (100%), polydipsia (28%), lung infiltration (14%), oral mucosal infiltration (14%), and cranial nerve infiltration (14%). Two patients were diagnosed as Hand-Schüller-Christian disease, and the others were accepted as eosinophilic granuloma. There was no bone marrow or any other organ infiltration except lung infiltration in one patient. Bone infiltration was the prominent sign in all patients with a minimum of one to maximum of seven different sites.

All patients were alive during the follow-up period. All patients were treated with radiotherapy except one patient treated with chemotherapy regimen started with vincristine plus dexamethasone and continued with cladribine. Three of seven patients were treated with combined modality, one patient with only chemotherapy and the others with only radiotherapy. There was no grade 3-4 hematological or systemic side effects of treatment. Relapses were detected in only two patients as new bone infiltrations which responded completely to radiotherapy.

Langerhans cell histiocytosis syndromes have a relatively benign course in adult patients and can be treated with either radiotherapy or chemo-radiotherapy successfully.

Key Words: Langerhans cell histiocytosis, adult onset

ÖZET

Erişkin langerhans hücreli histiositoz sendromlu hastaların retrospektif incelenmesi

Langerhans cell histiocytosis sendromları geniş spektrumlu bir hastalık grubu olarak tanımlanır ve bu grupta Eosionophilic Granuloma, Letterer-Siewe syndrome ve Hand-Schuller-Christian Disease gibi hastalıklar bulunur. Bu hastalıklar genelde erken yaşta görülme eğilimindedir ve erişkin yaşta nadirdirler. Erişkin hastalar için standart bir tedavileri olmamakla birlikte 2-chlorodeoxyadenosine (Cladribine)'nin tedavide etkin olduğu bildirilmektedir. Bu çalışmada hastanemizde tanı alan ve takip edilen Langerhans cell histiocytosis hastaları geriye dönük olarak değerlendirilmiştir.

Yedi hasta (4 erkek, 3 kadın) 1995–2005 yılları arasında merkezimizde takip edilmiştir. Ortalama yaş 27.5 (18–40) yıl olarak hesaplanmıştır. Başlıca şikâyetler; çoklu alanlarda kemik ağrısı (%100), polidipsi (%28), akciğer infiltrasyonu (%14), oral mukozal infiltrasyon (%14), ve kranial sinir tutulumu (%14) olarak kaydedilmiştir. İki hasta Hand-Schuller-Christian Disease, diğerleri Eosinophilic Granuloma olarak kabul edilmiştir. Hiçbir hastada kemik iliği ve akciğer dışı organ tutulumu saptanmamıştır. Kemik tutulumu, alan sayısı 1'den 7'ye kadar değişmekle beraber, en sık klinik bulgu olmuştur.

Tüm hastalar halen yaşamaktadır. Bir hasta dışında tüm hastalar radyoterapi almış ve bir hasta vincristine ve dexamethasone ile tedavi edilmeye başlanmış ve tedavisi cladribine ile tamamlanmıştır. Yedi hastanın 2'si radyoterapi ve kemoterapi ile kombine tedavi edilmiştir. Kalan 4 hasta ise sadece radyoterapi ile tedavi edilmiştir. Tedavi sonrası tüm hastalar asemptomatik hale gelmiştir. Hiçbir hastada grade 3-4 hematolojik ve diğer sistem toksisiteleri gelişmemiştir İki hastada yeni kemik tutulumu tarzında reaktivasyon saptanmış ve bunlar radyoterapiye iyi yanıt vermiştir.

Erişkin yaş grubunda Langerhans cell histiocytosis sendromları nispeten benin bir gidişat izlemekte ve radyoterapi ya da kemoterapi ile başarılı şekilde tedavi edilebilmektedir.

Anahtar Sözcükler: Langerhans hücreli histiyositoz, erişkin baslangıçlı

INTRODUCTION

Langerhans cell histiocytosis (LCH) encompasses a disparate group of diseases and distinct clinical syndromes such as eosinophilic granuloma (EG), Letterer-Siwe syndrome (LSS), Hand-Schüller-Christian disease (HSCD), Hashimoto Pritzker syndrome, self-healing histiocytosis, and pure cutaneous histiocytosis [1]. LCH is characterized by the proliferation of abnormal dendritic antigen-presenting histiocytes known as Langerhans cells. The disease can be presented as a localized or disseminated form. The most common sites of involvement are skin, bone, lymph nodes, lungs, liver and central nervous system. These disorders have been diagnosed mostly at early ages of life and are rare entities in adult age groups. The median age at diagnosis is two to three years. Males are affected more frequently than females [2].

The patterns of the organ involvement determine the form of the clinical syndrome. EG is characterized by local involvement and mostly seen in young adults. The most common involved tissue is bone and lesions can be presented as a single or multiple bone lesion(s). The calvariae bones are the most frequently involved sites both in children and adults. When the lesions are disseminated in skin, bone, bone marrow, lung, liver, spleen, lymph nodes, thymus, and pituitary gland, the disorder is called LSS. LSS is mainly diagnosed during infancy and has poor prognosis. The triad of multiple bone lesions, exophthalmia and diabetes insipidus (DI) constitutes HSCD [3].

The prognosis of LCH depends on the number of involved organs and the organ dysfunction. Systemic disease with organ failure can be fatal. Treatment decision should be based on the number of systems involved and disability resulting from the lesions. Unifocal bone lesions may require no therapy or curettage performed for diagnosis may be sufficient. Progressive and recurrent lesions can be treated with low dose radiotherapy. Systemic therapy is generally required for soft tissue disease and multi-focal skeletal lesions. However, there is no standardized treatment modality for these diseases at adult onset [3-4]. In this study, we aimed to retrospectively evaluate the patients with LCH followed-up in our hospital.

MATERIALS and METHODS

We evaluated retrospectively the patients with LCH who were treated at our center. Seven patients (4 male, 3 female) were entered into this study between 1995 and 2005. All patients were screened using total bone survey by X-ray and scintigraphy, abdominal ultrasonography, chest computerized tomography (CT) and cranial magnetic resonance imaging (MRI) and additional specific tests if required. Bone marrow aspiration and biopsy were performed in all patients to demonstrate the possible bone marrow infiltration. All diagnoses were confirmed by histopathological examination of the samples obtained from the infiltrated sites.

RESULTS

Seven patients were treated at our center between 1995 and 2005. Mean age of patients was 27.5 (18-40) years. The main complaints were classified as bone pain in multiple sites (100%), polydipsia (28%), lung infiltration (14%), oral mucosal infiltration (14%), and cranial nerve infiltration (14%). Two patients were diagnosed as Hand-Schüller-Christian disease, and the others were accepted as EG. There was no bone marrow or any other organ infiltration except lung infiltration in one patient. Bone infiltration was the prominent sign in all patients with a minimum of one to maximum of seven different sites (Table 1).

All patients were alive during the follow-up period. All patients were treated with radiotherapy except one patient treated with chemotherapy regimen started with vincristine plus dexamethasone and continued with cladribine. Three of seven patients were treated with combined modality of radiotherapy and chemotherapy, one patient with only chemotherapy and the others with only radiotherapy. After treatment, all patients became asymptomatic compared to diagnostic stage. There was no grade 3-4 hematological or systemic side effects of treatment. Relapses were detected in only two patients as new bone infiltrations which responded completely to radiotherapy (Table 2). Figure 1 represents the infiltration of different skeletal sites, while Figure 2 represents the histopathological documentation of LCH from the biopsy specimen.

The following contains a summary of the disease course in each patient.

Case 1 was a 31-year-old male patient. His main complaint was toothache. Before tooth extraction, mandible radiography was performed and two suspicious lesions were seen. Histopathological examination from mandibular

Table 1. Clinical characteristics of all patients

Patients	*Age*	*Sex*	*Initial symptoms*	*Number of bone lesions [figure]**	*Involvement of other sites*
1. O.O	31	M	Toothache	2	
2. A.A.	18	M	Shoulder pain	1	
3. Y.E.	22	F	Mandibular pain, polydipsia	1	Hypophysis, lung
4. B.K.	34	F	Sternal pain	>3	Hypophysis
5. G.C.	18	M	Headache	3	Cranial nerve
6. M.A.	40	F	Hip pain	>3	
7. E.A.	30	M	Mandibular pain	>3	Oral mucosa

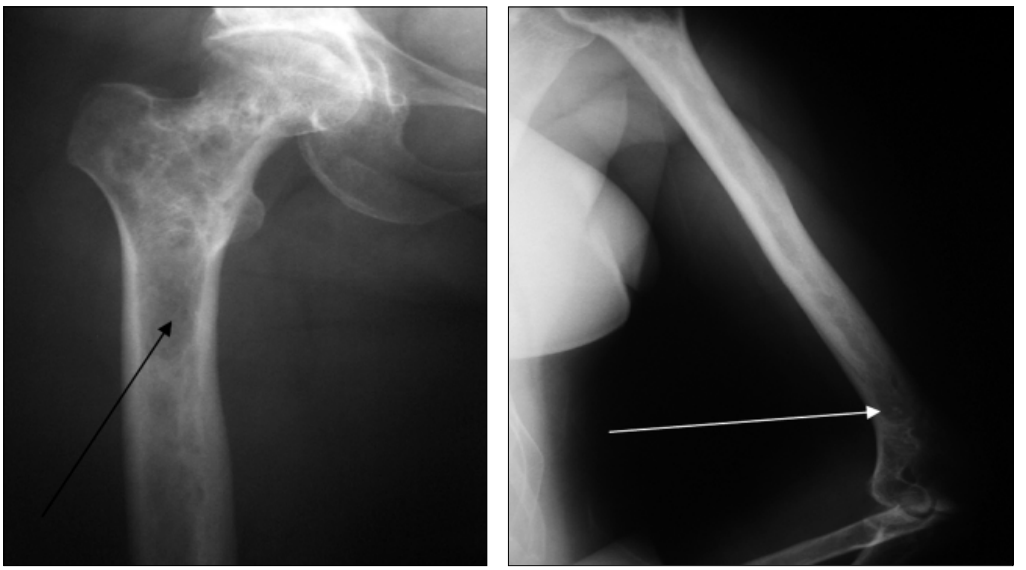

Figure 1. Typical skeletal infiltration of LCH by plain X-rays.

lesions revealed LCH. There was no bone marrow or any other organ involvement. He was treated only with dose of 10800 cG external radiotherapy. His follow-up period was nine months and no relapses were seen during this period.

Case 2 was an 18-year-old male patient referred from a local hospital with a complaint of right shoulder pain. The pathologic examination of a lytic lesion detected by MR, from distal localization in right clavicle, was concluded as EG. There was no systemic involvement. He was treated with only radiotherapy. He has been regularly followed-up without any problem for five months.

Case 3 was a 22-year-old female patient with Hand-Schüller-Christian disease who complained of mandibular pain and polydipsia. There was a left mandibular nonexpansive lytic lesion in maxillo-facial CT. MRI showed evidence of an infiltrating pituitary lesion. She also had lung involvement. She was treated with desmopressin and dexamethasone in addition to radiotherapy. She relapsed during the follow-up period and was treated with radiotherapy and followed-up for 19 months.

Case 4 was a 34-year-old female patient admitted with the complaint of sternal pain and left mandibular lesion. In bone scintigraphy, an activity increase was observed in left clavicula. LCH was detected through fine-needle aspiration biopsy of mandibular lesion. There was a lesion in the pituitary gland region detected by MRI. She was treated with radiotherapy and chemotherapy. She relapsed four times during the 118-month follow-up period and each relapse occurred at a different site

Table 2. Treatment outcomes and clinical course of patients

Patients	*Radiotherapy field*	*Dose of RT [cG]*	*Additional therapy*	*Duration of follow up [month]*	*Number of relapses*
1.	Mandible	10800	-	9	-
2.	Clavicula	12000	-	5	-
3.	Mandible + Hypophysis	10800	Desmopressin + Dexamethasone	19	1
4.	Mandible + Hypophysis	16000	Vinblastine	118	4
5.	Cranial	12600	-	65	-
6.	Iliac bone	None	Vincristine + Dexamethasone / Cladribine	10	-
7.	Mandible	10800	Cladribine	76	-

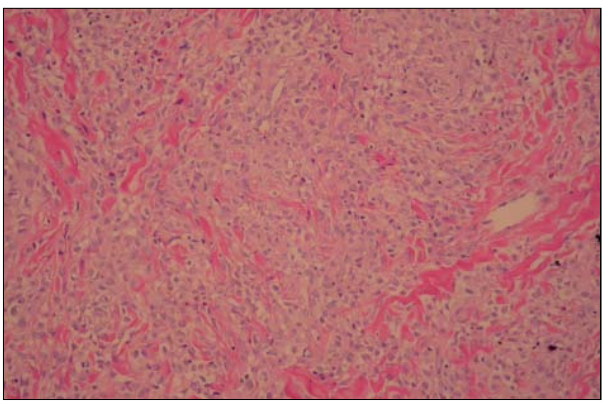

Figure 2. Typical Langerhans cells in biopsy specimen by hematoxylin and eosin (HE) x20.

of the skeletal system and was treated with radiotherapy.

Case 5, an 18-year-old male patient, presented with the main complaint of headache. Destructive lesions in right occipital and temporal bone were detected with both CT and MRI. Surgery was performed and pathologic examination revealed the diagnosis of EG. He was treated with radiotherapy and has been followed-up for 65 months.

Case 6 was a 40-year-old female patient. X-ray was performed because of right hip pain and a sclerotic lesion in iliac bone was seen. Iliac bone biopsy showed LCH. Multiple bone lesions were seen both in X-ray and MRI. There was no systemic involvement. She was treated with chemotherapy initially with vincristine and dexamethasone and continued with cladribine and followed up for 10 months.

Case 7, a 30-year-old male patient, presented with the main complaint of mandibular pain. A biopsy from the oral mucosa revealed the diagnosis of EG without any other organ involvement. He was treated with radiotherapy and chemotherapy containing cladribine and has been followed up for 76 months without any relapse.

DISCUSSION

Langerhans cell histiocytosis is thought to be a pediatric disease and a rare entity in adult age groups. In a retrospective review of 541 patients with LCH, Islinger *et al.* [5] reported 211 (39%) cases in adults at the age of 21 years or older. In 1995, a Mayo Clinic study described 91 (35%) adult patients aged 17 years or older and in 1996 Malpas [6] described 47 patients with LCH with a female predominance [4-5]. There are differing reports on gender distribution in LCH. Patients in our study were 18 years or older and the male/female ratio was 4:3.

Three main forms of LCH have been described previously as EG (localized LCH), HSCD, and Letterer-Siwe syndrome (disseminated LCH). Two patients were diagnosed as HSCD, and the others were accepted as EG in our study. Pulmonary involvement with LCH can be observed in patients of any age [7]. There was only one patient with lung infiltration detected by high resolution computed tomography (HRCT) in our study. Arico *et al.* [8] reported that lung involvement was determined at the ratio of 58.4% in the adult age group, which is significantly higher compared to other internal organs.

Most studies containing large number patient series have reported similar anatomic distributions of lesions of LCH in bone. The skull is the most common site in all age groups [6]. In our study there were calvariae bone lesions in four patients. Clavicle and iliac bones have been determined as the other commonly involved sites. DI has been found to be the most common endocrinological disorder associated with LCH, which is caused by infiltration of the posterior pituitary by Langerhans cells. Incidence of DI ranges from 5 to 50% [9]. Two patients in our study had complained of polydipsia, and pituitary lesions were detected in MRI and both required therapy with desmopressin.

Since there have not been many controlled and randomized studies, treatment of LCH remains uncertain. Many cases could possibly demonstrate favorable natural history without treatment. Solitary bone lesions can be treated with surgical curettage. Local radiation therapy or local radiation therapy after surgical excision has also been reported as a successful modality for the treatment of solitary bone lesions. Although there has been a general consensus that biopsy and local curettage is usually sufficient for the diagnosis and treatment of an isolated bone lesion, there is divergence on the treatment decision of acute refractory and progressive disease, chronic relapsing disease, and chronic and progressive multi-system disease with involvement of the lung, liver, and central nervous system. Single agent chemotherapy has been widely used for treatment of these conditions. Various agents including carboplatin, chlorambucil, cyclophosphamide, cytosine arabinoside (Ara-C), daunomycin, etoposide, mercaptopurine, methotrexate, mechlorethamine, procarbazine, vinblastine, vincristine, and vindesine have been widely used [2-10]. In addition, in recent years, new agents have been established with more efficient and promising results. 2-chlorodeoxyadenosine (2-Cda) has been reported as effective in adults with refractory or relapsed disease [11]. Despite the good response rates with 2-Cda as a single agent, in refractory disease and disseminated LCH with organ dysfunction, combination therapy with Ara-C would be more effective [12]. We used 2-Cda as a single agent and in combination chemotherapy. Despite treatment, approximately 20% of patients with LCH with multisystem disease do not respond and have a poor prognosis with high mortality. There were two relapsed patients during the follow-up period in our study and they were treated successfully.

In conclusion, LCH syndromes have a relatively benign course in adult patients and could be treated with either radiotherapy or chemoradiotherapy successfully. Nevertheless, further studies with more patients are still needed to clarify the underlying mechanisms of occurrence of this disease in the adult age group and establish effective curative treatment modalities and for sufficient practice in the management of the disease.

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