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Research Article

Adult Onset Langerhans Cell Histiocytosis: A Single Center Experience

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Abstract

Aim: Langerhans cell histiocytosis (LCH) is a proliferative disease caused by the abnormal proliferation of histiocytes in the bone marrow dendritic cell structure. LCH is very rare in adults and its incidence is 1-2 cases per million. Therefore, there is still no clear management plan for adults. It was aimed to evaluate the very rare adult LCH patients.

Materials and Methods: Ten LCH patients who were followed up at Erciyes University Hematology Department between January 2010 and January 2020 were included.

Results: Eight (80%) of them were male and 2 (20%) were female. The median age of the patients was 34.5±8.4 (23-52) years. Although the most common involvement at the time of diagnosis was bone in 7 patients (70%) and lung in 3 patients (30%); pituitary, tympanic membrane, liver, and brain involvement were also observed. Three (30%) patients had single system involvement and 7 (70%) had multisystem. Four (40%) patients had relapsed and all had multisystemic involvement. The BRAF V600E mutation could be performed in 3 patients. It was negative in two patients and positive in 1 patient. All patients still have remission.

Conclusion: Unlike children, LCH has a better course in adults. The most important approach is to determine single or multisystem involvement. In our patients with single system involvement, we obtained response with corticosteroid and surgery alone. We have observed that vinblastin plus methylprednisolone treatment is a good option for multisystemic involvement. In relapsed patients, we obtained a significant response with clofarabine.

Keywords: Adult, BRAF V600E mutation, clofarabin, histiocytosis, langerhans cell, radiotherapy, treatment, vinblastin plus methylprednisolone

INTRODUCTION

Langerhans Cell Histiocytosis (LCH) is an idiopathic group of diseases that cause damage due to local or diffuse accumulation of various tissues such as bone, lymph nodes, skin, lung, liver, and spleen (1). LCH is diagnosed most frequently in children under 3 years old but it can be seen at any age. LCH is very rare in adults and its incidence is 1-2 cases per million (2).

The diagnosis is made by biopsy taken from the involved tissue. After diagnosis, the most important factor is to evaluate whether the disease is single-system or multisystemic. In single-system LCH, curettage of bone lesions, topical treatment for skin, and prednisone are sufficient for treatment, while multisystemic LCH requires chemotherapeutic agents (3,4).

There is still no clear approach in the treatment of multisystemic LCH in adults. Vinblastin-methylprednisolone (VB+MP), cladribine, cytarabine, clofarabine, and vincristine are the most preferred treatments (5-7). In addition, vemurafenib is used by identifying BRAF V600E mutations in LCH patients (8).

LCH is an extremely rare disease in adults, whose diagnosis,

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treatment and clinical course are still unclear. Therefore, in order to increase the awareness of LCH and to evaluate this disease better, we retrospectively evaluated the data of 10 patients who were followed up in our clinic for the last 10 years.

MATERIAL AND METHOD

Ten LCH patients who were followed up at Erciyes University Hematology Department between January 2010 and January 2020 were included in this study. All patients received the diagnosis of LCH by histopathological examination of the samples from the involved tissue. All information about patients was recorded retrospectively from patient files and the hospital automation system.

Age, gender, laboratory features, follow-up time, symptoms at diagnosis, biopsy region, BRAF mutation, bone marrow biopsy, treatments, and response status were evaluated. Also, relapse status, relapse location and post-relapse treatments were evaluated. Patients with and without relapse were compared. All patients were screened with Positron Emission Tomography/Computed Tomography (PET/CT). Pituitary Magnetic Resonance Imaging (MRI) was performed in patients who were considered or diagnosed with diabetes insipidus (DI).

Kolmogorov Smirnov test was used for the normal distribution of the data. Mann Whitney U test was used to compare nonparametric data; Student t-test was used to compare parametric data. Chi-square or Fisher's Exact test was used to compare categorical data. The data were analyzed by using Statistical Package for the Social Sciences (SPSS) for Windows computer program (release 25.0; SPSS Inc., Chicago, IL, USA). $p<0.05$ was considered significant in all tests.

RESULTS

Ten patients with LCH were included in our study. Eight (80%) of them were male and 2 (20%) were female. The median age of the patients was 34.5±8.4 (23-52) years. The first symptoms at the time of diagnosis were headache in 3 patients (30%), bone pain in 2 patients (20%), otalgia in 1 patient (10%), stomachache in 1 patient (10%), polyuria in 1 patient (10%), lymphadenopathy in 1 patient (10%) and swelling of the vulva in 1 patient (10%) (Table 1).

Table 1. Demographic Data of Patients with Langerhans Cell Histiocytosis

Case no	Age at the diagnosis	Gender	Comorbidities	Smoke p/y	Symptom at the time of diagnosis	Biopsy location	PET/CT İnvolvements areas	Pituitary MRI	Bone marrow biopsy	BRAF V600E mutation
1	26	Male	-	4	Bone pain	Symphysis pubis	Bone	N/A	N/A	N/A
2	37	Female	DI	15	Swelling of the vulva	Vulva	Vulva, Lung, pituitary gland	Involvement+	N/A	N/A
3	23	Male	-	-	Headache	Temporal lobe	Brain, Bone, Lung	N/A	N/A	N/A
4	52	Female	DI	-	Polyuria	Jaw	Bone	Involvement+	N/A	N/A
5	33	Male	-	-	Lymphadenomegaly	Left 5. Rib	Lymph node, Bone	Normal	N/A	N/A
6	27	Male	-	10	Bone pain	Left spina scapula	Bone, Lung	N/A	N/A	N/A
7	39	Male	DM, Bipolar disorder	15	Stomach ache	Liver	Liver	N/A	Normocellular	N/A
8	36	Male		15	Headache	Occipital bone	Bone, Lymph node	N/A	Normocellular	negative
9	39	Male	HT	-	Otalgia	Right tympanic membrane	Tympanic membrane	Normal	N/A	positive
10	30	Male	-	-	Headache	Temporal bone	Bone	N/A	N/A	negative

DI: Diabetes insipidus, DM: Diabetes mellitus, HT: hypertension, p/y:pockets/year, MRI: Magnetic resonance imaging, N/A: not applicable, PET/CT: Positron Emission Tomography/Computed Tomography

Organ involvement at the time of diagnosis, bone in 7 patients (70%), lung in 3 patients (30%), pituitary and DI in 1 patient (10%), lymph node in 1 patient (10%), liver in 1 patient (10%), brain in 1 patient (10%) and 1 patient (10%) tympanic membrane involvements were developed. Bone involvements were observed in skull 3 (42.8%), rib 1 (14.3%), scapula 1 (14.3%), jaw 1 (14.3%) and symphysis pubis 1 (14.3%). The BRAF V600E mutation could be performed in 3 patients. It was negative in two patients and positive in 1 patient.

Three (30%) patients had single system involvement and 7 (70%) had multisystem. Patients with osteolytic lesions were given monthly zoledronic acid. One of the patients with single system involvement only had bone involvement and was treated with surgical curettage. The other patient with single system involvement only had tympanic membrane involvement and only received methylprednisolone therapy. In our third patient with single system involvement, only temporal bone involvement was present, but VB +MP treatment was given because of the high risk for the central nervous system (CNS) disease. All of these 3 patients are still in remission.

All patients with multisystemic involvement received systemic chemotherapy. Radiotherapy was given to 2 patients. As an initial treatment, 1 patient (14.3%) received cytarabine and the other 6 patients (85.7%) received VB+MP (Table-2). The patient who received cytarabine as an initial treatment relapsed after 3 years. VB+MP were given after relapse but the patient had again relapse and clofarabine was started and and still treatment is ongoing. Complete response was obtained in 3 of 6 patients who started VB+MP as an initial treatment. The other 3 patients had relapse. Clofarabine treatment was given to 2 of 3 recurrent patients. Cytarabine was started in the other patient, but relapsed again and clofarabine was given. All of the recurrent patients are now in remission.

Four (40%) patients had relapsed but 6 (60%) did not have. The symptoms and location of involvement in all recurrent patients were pain and bone. Patients with and without relapse were compared. The median age of the patients with relapse was 37.5±11.9 years and 1 (25%) was female. The median age of the patients without relapse was 32±5.3 years, and 1 (16.6%) was female (p values 0.34 and 1.00 respectively). Treatments and laboratory values are provided in Table-3. The median hemoglobin level was 13.7±2.1 g/dL in patients with relapse, 15.6±1.6 g/dL in patients without relapse (p=0.13). The median alkaline phosphatase level was 113.7±37.9 g/dL in patients with relapse, 71.6±23.4 g/dL in patients without relapse (p=0.60). While 3(100%) patients with single system involvement didn't have relapse, 3 (42,8%) patients with systemic involvement didn't have relapse (p=0.20). Four (66.6%) patients without relapse received VB+MP treatment and 4 (100%) patients with relapse received VB+MP treatment (p=0.47).

The median overall survival (OS) was 34.4±11.2 months (95% CI, 12.6 to 56.3). All of our patients are still alive.

Table 2. Treatments. outcomes. and clinical course of patients

Case no	Treatment type	Treatment Time	RT	Relapse and time	Symptom at the relapse	Relapsed areas	Treatment after relapse	Final situation
1	Curettage		-	-	-			Remission
2	VB+MP	25 Weeks	-	-	-		-	Remission
3	VB+MP	39 Weeks	-	+: 9 Months	Headache	Bone. Lung	Clofarabine (6 cures)	Remission
4	VB+MP	25 Weeks	+: Cranium	+:12 Months	Bone pain	Bone	Cytarabine (6 cures) Clofarabine (3 cures) Cytarabine+Clofarabine (3 cures)	Remission
5	VB+MP	25 Weeks	-	-	-		-	Remission
6	VB+MP	25 Weeks	-	-	-		-	Remission
7	VB+MP	25 Weeks	+: Shoulder	+: 9 months	Headache		Clofarabine (6 cures)	Remission
8	Cytarabine	6 Months	-	+:3 years	Headache	Bone	Vinblastine (9 cures) Clofarabine (6 cures)	Remission
9	MP	5 Weeks	-	-	-	-	-	Remission
10	VB + MP	25 Weeks	-	-	-	-	-	Remission

VB: Vinblastine, MP: Methylprednisolone

Table 3. Data of LCH patients with and without relapse

	Patients without Relapse	Patients with Relapse	p
Gender	K: 1. E: 5	K: 1. E: 3	1.0[c]
Treatment			
VB+MP	4.66.6%	4.100%	0.47[c]
Cytarabine	0	2.50%	0.13[cc]
Methylprednisolone	5.83.3%	4.100%	1.00[c]
Excision	2.33.3%	0	0.47[c]
Radiotherapy	1.16.6%	1.25%	1.00[c]
Clofarabine	1.16.6%	3.75%	0.20
Disease Involvement			
Single system	3.50%	0	0.52[c]
Multisystemic	3.50%	4.100%	
Age	32±5.3	37.5±11.9	0.34[t]
WBC (103/µL)	8.9±2.8	6.6±1.1	0.16[t]
Hb (g/dL)	15.6±1.6	13.7±2.1	0.13[t]
PLT (103/µL)	312.3±110.6	212.5±71.3	0.30[t]
Creatinin (mg/dL)	0.72±0.12	0.76±0.07	0.57[t]
Albumin (g/dL)	4.76±2.5	4.64±0.33	0.68[t]
LDH (u/L)	208±41.5	175.5±15.2	0.18[t]
ALP (u/L)	71.0±234	113.7±37.9	0.60[t]
Uric Acid (mg/dL)	5.17±0.6	6±2.2	0.76[m]

cChi-square, M: Mann-Whitney u Test, T: Independent Sample t Test
ALP: alkaline phosphatase, Hb: hemoglobulin, PLT: platelet, LDH: lactate dehydrogenase, MP: methylprednisolone, VB: vinblastine, WBC: white blood cell

DISCUSSION

LCH is a disease with unknown etiology caused by the abnormal proliferation of histiocytes in dendritic cells derived from bone marrow with a variable number of leukocytes, neutrophils, eosinophils, lymphocytes, and giant multinucleated cells causing tissue damage. Langerhans type cells express CDla, langerin and S100 protein, and have Birbeck granules. This disease was previously called histiocytosis-X, diffuse reticuloendotheliosis, Hashimoto-Pritzker syndrome, Letterer-Siwe disease, Hand-Schüller-Christian disease, and eosinophilic granuloma but is now called LCH.

LCH is diagnosed more frequently between the ages of 1 to 3 and is clinically severe in this age group but very rare in adults, and the clinical course is milder. There is an approximately 2-3 times male predominance (9) but some demonstrated female predominance. In our study, the female/male ratio was 1/4.

LCH involvement can occur almost anywhere at the time of diagnosis. In a prospective study involving 1741 patients, 77% bone, 39% skin, 19% lymph nodes, 16% liver, 10% lung and 6% CNS involvement were observed (10). In our study, 70% bone, 30% lung, 10% lymph nodes, 10% liver and 10% CNS involvement were present at the time of diagnosis. Although many studies show that skulls are the most common bone involvement, one study has been shown to be jaw. DI was detected in 1 patient at the time of diagnosis and in 1 patient during follow-up. In other studies, DI was the most common endocrinological disorder in LCH, with a frequency of 4% before diagnosis, and 18% during or after diagnosis (11,12).

According to the Histiocyte Society, the most important approach after diagnosing LCH is to determine whether the disease is a single system or multisystem disease. Single system disease treatment includes prednisone, curettage of bone lesions and topical therapy. Topical nitrogen mustard and topical corticosteroids are effective in patients with single skin involvement (13). It was also demonstrated that oral thalidomide and oral methotrexate treatments were effective in the same group of patients (14). Orbital, mastoid, ethmoid, sphenoid or temporal bone involvement should be treated as a multisystemic disease, since the involvement is a risk factor for CNS even if it is only a single system disease.

Multisystemic disease should be treated with systemic chemotherapy. VB +MP, cytarabine, clofarabine, cladribine,

vindesine, vincristine, cyclophosphamide and etoposide are used in multisystemic disease (5,7,15,16). In our patients with multisystemic LCH, VB+MP treatment was given to 6 (85.7%) of them and cytarabine was given to 1 (14.3%). Complete response was observed in all our patients, but 4 patients had relapsed. Our relapsed patients had lower hemoglobulin levels and higher alkaline phosphatase levels. However, since the number of our patients was low, a statistically significant difference was probably not observed. All of our relapsed patients had multisystemic involvement. Also in other studies, relapse frequently developed especially in multisystemic disease.

Single-agent and combination therapies are recommended in the treatment of relapse. Combination treatments include adding oral methotrexate and mercaptopurine to VB+MP (17), and adding vincristine and prednisone to cytarabine. VB + MP, cytarabine, clofarabine, and cladribine are used as the single agent treatment (4,7). In our study, VB+MP was given to 1 (%25), cytarabine was given to 1 (%25) and clofarabine was given to 4 (100%) patients with relapsed. The response was received from all relapsed patients after clofarabine. In other studies, a 90% survival rate was obtained in patients with relapsed /refractory LCH after clofarabine (7,18).

Radiotherapy (RT) is a highly effective treatment for LCH bone lesions. LCH has been reported to be more than 70% effective in adults in the treatment of bone involvement and pain (19). Two patients with bone relapse were treated with RT and their pain decreased and also received remission. Bisphosphonate therapy is effective in reducing pain in bone lesions and improving functional conditions (20). Bone involvement was 70% at the time of diagnosis and 100% at the relapsed of our patients and zoledronic acid was given to all of them.

The BRAF V600E mutation is increasingly reported in LCH and has often been associated with poor prognosis (21). Therefore, BRAF inhibitors such as vemurafenib, dabrafenib and trametinib are taking more place in the treatment of LCH (22,23). In addition, some studies have reported that MEK inhibitors are effective (24). BRAF V600E mutation was performed in our 3 patients. Only one of them was positive. This patient had a single bone lesion and was treated with only curettage and is still in remission.

CONCLUSION

The most important factor in LCH is to identify single or multiple system involvement. In our patients with single system involvement, we obtained response with corticosteroid and surgery alone. We have observed that VB+MP treatment is a good option for multisystemic involvement. In relapsed patients, we obtained a significant response with clofarabine. Our results are very promising however, since our study has a single center experience and the number of patients is low, they have limitations, and further large-scale multicenter studies are needed.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *The study was carried out with the permission of Clinical Research Ethics Committee of Erciyes University. (date: 29.01.2020, Decision No: 2020/63)*

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