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ORIGINAL STUDY

Adult Langerhans cell histiocytosis of bones : A rare cancer network study

Banu ATALAR, Robert C. MILLER, Fazilet Oner DINCBAS, Jan Henning GEISMAR, Oliver MICKE, Serap AKYUREK, Enis OZYAR

From the Rare Cancer Network (RCN)

Langerhans Cell Histiocytosis (LCH) is an uncommon benign bone tumour typically seen in children. LCH of bones in adults has been reported as solitary cases. The aim of the current study is to analyze different treatment approaches and the role of radiotherapy (RT) in adult LCH.

Thirty patients from five Rare Network Cancer centers were included in this retrospective study. Median age was 30 years. The localization of tumours was skull bones in 12 (40%), lower extremity in 6 (20%), thoracic bones in 4 (13.3%), spine in 3 (10%), pelvis in 2 (6.7%) and multiple sites in 3 (10%) patients. Primary treatment was surgery in 1 (3.3%), surgery+ radiotherapy (RT) in 15 (50%), RT in 12 (40%), RT + CHT in 1 (3.3%) and corticosteroids in 1 (3.3%) patient.

Median follow-up was 58 months. Complete remission was obtained in 21 (70%), partial remission in 4 (13.3%) ; 2 lesions were stable (6.7%) and progression was noted in 2 (6.7%) of the patients. Nine patients (30%) had recurrent disease. Recurrence rates were significantly lower in patients who were treated with surgery and RT ($p < 0.003$).

Surgery plays a major role in the treatment of adult LCH of bones ; radiotherapy should be considered in the adjuvant setting and palliation.

Keywords : Langerhans Cell Histiocytosis ; bone

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare tumour-like benign condition, affecting primarily pediatric patients, but also occurring in adults in a minority of cases (*12*). LCH is characterized by a proliferation of Langerhans cells derived from pluripotent stem cells and maturate from proliferating monoblasts and promonocytes (in bone mar-

■ Banu Atalar, MD, Consultant
Department of Radiation Oncology, Acibadem University, Faculty of Medicine, Istanbul, Turkey
■ Enis. Ozyar, MD, Professor
Department of Radiation Oncology, Acibadem University, Faculty of Medicine, Istanbul, Turkey
■ Robert C..C. Miller, MD, Professor
Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota, USA
■ Fazilet O. Dincbas, MD, Professor,
Department of Radiation Oncology, Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey
■ Jan Henning Geismar, MD, Consultant
Department of Radiation Oncology, Kantonsspital St. Gallen, Switzerland
■ Oliver Micke, MD, Consultant
Department of Radiation Oncology, Franziskus Hospital, Bielefeld, Germany
■ Serap Akyurek, MD, Associate Professor
Department of Radiation Oncology, Ankara University Faculty of Medicine, Ankara, Turkey

Correspondence : Banu Atalar, MD, Acibadem Maslak Hospital, Department of Radiation Oncology, Buyukdere Caddesi, Istanbul, Turkey

Email : banu.atalar@asg.com.tr

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row) to nonproliferating monocytes in the blood and various peripheral tissues.

LCH is divided into three major categories according to the type and extent of organ involvement : (*1*) solitary bone involvement (eosinophilic granuloma or EG) which represents 60-80% of LCH ; (*2*) multifocal, single organ system involvement that typically occurs in bone (Hand-Schüller-Christian disease) which may cause proptosis, diabetes insipidus, chronic otitis media or a combination of symptoms ; (*3*) multiple organ involvement such as bone, liver, spleen, and other organs (Letterer-Siwe disease) which may present with hepatosplenomegaly, anemia or thrombocytopenia, polyostotic bone involvement and hemorrhagic skin lesions (*12,16,17*). However, due to the different presentation of these syndromes, it is not always possible to differentiate one category from another with sharp boundaries.

EG is the most common form of the LCH. Cranial vault, jaw, humerus, ribs and femur are most commonly involved sites. Lytic lesions may go together with periosteal new bone proliferation or pathologic fracture. These lesions may regress spontaneously and are highly radiosensitive. Only 10% of the cases progress into multisystem disease (*16,17*). Symptoms differ according to the involved bones but mostly bone lesions lead to local pain and/or swelling. Plain radiography plays a major role in diagnostic imaging and reveals lytic bony lesions with or without sclerosis. Advanced lesions of the spine presents as collapse of vertebral bodies and so called 'vertebra plana'. Computed tomography (CT) and magnetic resonance imaging (MRI) provide detailed information when there is soft tissue involvement and/or in complex areas. Bone scintigraphy detects skeletal lesions even before visible radiographic defects occur and is useful in follow-up (*8,12*).

Different forms of treatment methods including observation, steroids, surgery, radiotherapy (RT) and chemotherapy have been reported previously (*4,6,7,14,18*). Even though the age group affected by LCH is wide, the majority of patients are under 15 years old at diagnosis. To the best of our knowledge the role of radiotherapy in adult LCH has not been discussed outside of the context of anecdotal case reports and studies with a very limited number of patients. In this study, we aimed to analyze different treatment approaches and the role of radiotherapy in adult LCH of bones. For this purpose we have evaluated 30 adult LCH patients with bone involvement only.

MATERIALS AND METHODS

Participants in this study collected multinational, multicenter retrospective data from 5 participating Rare Cancer Network (RCN) member institutions. The medical records of 30 patients with adult LCH sequentially diagnosed between 1980 and 2006 were reviewed for patient and tumour characteristics, treatment details and follow-up information.

Adult patients were defined as 17 years and older, median age was 30 years (*17-67*). Seventeen (56.7%) out of 30 patients were male. The localization of the tumour was skull bones in 12 (40%), lower extremity in 6 (20%), thoracic bones in 4 (13.3%), spine in 3 (10%), pelvis in 2 (6.7%) and multiple bones in 3 (10%) patients. Involvement of bones was single in 24 (80%) and multiple bones in 6 (20%) patients. Pain was the most common symptom at diagnosis in 27 patients (90%), another 3 patients reported diabetes insipidus, had a tumour in the clivus, paraparesia and a visible tumour mass in the right frontal bone. Seventeen patients had more than one diagnostic method. Plain radiography was used for diagnosis in 63.4% of patients ; other methods were computerized tomography in 59.9%, bone scintigraphy in 39.9% and MRI in 13.3% of patients. PET CT was used only in 1 patient. Lytic bone lesions of involved bones were reported in the plain radiographs and CT, no soft tissue involvement was seen in MRI.

Pathologic diagnosis was typically performed through an excisional biopsy, in 19 of 30 (63.3%) patients, and by needle biopsy in 7 (23.3%) patients. The patient with clivus involvement was diagnosed with cerebrospinal fluid cytology. Primary treatment method was surgery in 1 (3.3%), surgery + radiotherapy (RT) in 15 (50%), RT in 12 (40%), RT + chemotherapy (CHT) in 1 (3.3%) and corticosteroid in 1(3.3%) patient. Types of

surgery were curettage in 9 (30%), total excision in 5 (16.7%) and biopsy in 2 (6.7%) patients. RT was used as salvage treatment for 4 patients after recurrence, other salvage methods were surgical curettage and CHT. Patient characteristics were detailed in table I.

Radiotherapy treatments were delivered with linear accelerators or Co60 teletherapy units. Although the irradiated volume varies for each center, it typically encompasses the bony lesion with a clinical target volume encompassing the bone surrounding the radiographically evident lesion. RT dose range was between 1000-3600 cGy (median 1200 cGy) and fraction size was between 150-400 cGy (median 200 cGy) in 3 to 20 fractions.

Statistical analyses were done by Kaplan Meier method and Chi square tests.

RESULTS

Median follow-up was 58 months (1-204 months). Complete remission was obtained in 21 (70%), partial remission in 4 (13.3%), stabilization in 2 (6.7%) and progression in 2 (6.7%) patients. Palliation of symptoms was achieved in 90% of patients. Nine patients (30%) subsequently developed recurrent disease, 5 in the same bone, and 4 in different bones. Median time to recurrence was 11 months (1-36 months). Recurrence was statistically lower in patients who were treated with combined surgery and RT ($p < 0.003$). In this group only one patient (1/15) recurred and it was on a different site. Patients who were treated with radiotherapy alone had a recurrence rate of 50% (6/12 patients). The other 3 recurrent patients were treated with steroids alone, surgery plus RT, and RT plus chemotherapy. In the univariate analyses, involvement of multiple bones was statistically significant for disease recurrence ($p < 0.0001$). Six of 9 recurrent patients had multiple site involvement at the time of diagnosis. Nine recurrent patients' characteristics and treatments were detailed in table II.

At the last follow-up 22 patients were alive with no evidence of disease, 6 alive with disease and 2 died with disease. One-year and 3-year survival was 96.3% and 90%, respectively. The correlation between death and type of treatment was statistically significant ($p < 0.004$), surgery plus RT was superior when compared with other treatments. Age, gender number of sites involved, recurrence and recurrence site did not have a statistically significant effect on overall survival.

DISCUSSION

The clinical, radiological and pathological features of pediatric LCH have been well defined by previous studies. However, optimal treatment is still controversial (*4,6-8,12,14,16-18*). EG is a rare tumour, it is usually diagnosed in children and is limited to single or few bones. This localized form of LCH is the least aggressive form and clinical manifestations are related to the affected bones. Due to its favorable prognosis, minimal invasive treatment is preferred. Most of the series reported in literature to date have been paediatric LCH and some of these lesions can heal spontaneously during the time from childhood to adulthood. There are few reports of adult LCH of bones cases and only two prior studies with sufficient numbers of patients (*2-5,11,15*). There is no consensus on the treatment of adult LCH and it is conventionally treated with surgery, radiotherapy, chemotherapy, steroids or with a combination of these.

One of the largest series in the literature with adult Langerhans Cell Histiocytosis of bone was reported by Kilpatrick *et al* (*4*). The authors evaluated 263 patients, of which 91 were adults. Data was collected from a large group of patients, who were treated in an 80-year period. As expected, treatment was not uniformly applied over the period of analysis. Diabetes insipidus (DI) was the most commonly observed manifestation of extraskeletal involvement by LCH, occurring in 30% of the patients. A correlation was noted between DI and skeletal recurrence and/or new bone lesions, which was statistically significant for children, but not for adults. In our study, only one patient (3.3%) had diabetes insipidus with involvement of the clivus. In the Kilpatrick study, the rate of recurrence skeletal lesions treated with RT was not examined, but the authors mentioned that low-dose RT did not appear to reverse the need for vasopressin replacement therapy. They concluded

Table I. — Patient characteristics

	Median (min-max)	N	%
Age	30.5 (17-67)		
≤30 years		15	50
>30 years		15	50
Gender			
Male		17	56,7
Female		13	43,3
Symptoms			
Pain		27	90.0
Other		3	10.0
(DI, paraparesia, visible tumour mass)			
Diagnosis method			
Plain radiography		19	63.4
Computed tomography		18	59.9
Bone scintigraphy		12	39.9
Magnetic Resonance		4	13.0
PET CT		1	3.3
Involvement			
Single bone		24	80.0
Multiple bones		6	20.0
Bony sites			
Skull		12	40.0
Spine		5	16.7
Lower extremity		8	26.7
Pelvis		2	6.7
Thoracic bones		4	13.3
Mandibula-maxilla		3	10.0
Pathology method			
Excisional biopsy		19	63.3
Needle biopsy		7	23.3
BOS Cytology		1	3.3
Treatment method			
Surgery		1	3.3
Surgery + RT		15	50.0
RT		12	40.0
RT + CHT		1	3.3
Steroids		1	3.3
RT details			
Dose	1200 cGy (1000-3600)		
Fractionation	200 cGy (150-400)		
Disease control			
Complete remission		21	70.0
Partial remission		4	13.3
Stable		2	6.7
Progression		2	6.7
Palliation of symptoms			
Yes		27	90.0
No		2	6.7
Unknown		1	3.3

Table II. — Details of patients with recurrence

Patients	Disease site	Treatment	RT site	Recurrence site	Treatment at Recurrence	Status at last follow-up
1	Single	RT (10 Gy)	Involved bone	Different	Observation	Alive with disease
2	Single	RT (24 Gy)	Involved bone	In-field	Surgery + RT	Living without disease
3	Single	RT (30 Gy) + CHT	Involved bone	Different	?	Died
4	Multiple	Steroids	-	Different bones	RT	Alive with disease
5	Multiple	Surgery + RT (12.6 Gy)	Involved bone	Different bones	Observation	Alive with disease
6	Multiple	RT (10 Gy)	Single bone	Multiple + in-field	RT	Alive with disease
7	Multiple	RT (10 Gy)	Single bone	In-field	RT	Alive with disease
8	Multiple	RT (10 Gy)	Involved bones	Different bones	CHT	Died
9	Multiple	RT (10.8 Gy)	Involved bones	In-field	Surgery	Alive with diseas

that adult patients have better survival rates than the paediatric group, and systemic involvement was not frequent in adults.

The recurrence rate in adult patients was found to be higher than in the pediatric group in another study (*11*). In a study with pediatric patients, a biopsy and observation alone was considered adequate treatment in the majority of patients. More aggressive surgical treatment like curettage and grafting was advised in adults. Likewise, in our current analysis, the group with surgically resected tumours recurred less frequently than the RT alone group.

The role of RT for treatment of LCH has been derived from retrospective studies. RT indications, as well as fractionation, total dose and integration into the whole treatment process are still a question of debate.The Pediatric Oncology Group (POG) study 8047 examined 23 pediatric patients with single-system, unifocal or bifocal bone disease diagnosed by biopsy (*1*). Good local control is reported with curettage and excision. RT was used for recurrent lesions to a total dose of 3 to 6 Gy. Optimal RT dose was not determined in this study. Selch and colleagues reported 22 patients treated with RT, of which 16 were adults (*13*). Their median dose for bone lesions was 900 cGy and for soft tissue 1500 cGy. Local control was achieved in 46 of 56 sites (82%). Control rates for bone and soft tissue lesions were 88% and 69%, respectively. Recurrences were in-field and noted only in adults with involvement of multiple soft tissues plus bones. Additional therapy was not reported. Similarly, in our study, 4 recurrences were in-field.

Olschewski *et al* conducted a review to define the role of RT for treatment of osseous manifestations of adult LCH (*9*). They analysed 18 studies with RT and examined the patients in two major groups ; patients with osseous single system disease and patients with uni- or multifocal bony involvement in multi system disease. Twelve of 18 studies had operation as additional therapy. According to this data, local control rates were over 90% in both groups with RT with or without additional therapies. Prognostic factors for local control were not evaluated.

In 2006, the same authors performed a patterns-of-care study to define clinical practice with adult LCH in Germany (*10*). Ninety eight patients were evaluated, 38 patients were treated with only RT and 60 patients had other types of treatments prior to RT. Local control rate was 91% and complete remission rate was 77.5%, similar to our study. This study has evaluated the same group of patients as our own study, but unfortunately the authors did not report prognostic factors for recurrence. In our study, we showed that multiple site involvement was a worse prognostic factor for recurrence. Among our patients, only 6 patients had multiple bones involvement at diagnosis and all of these 6 patients recurred after treatment. Survival was also found to be better in patients treated with surgery + RT, which was also not studied before.

The literature does not clearly define the best dose and fractionation regimen for treating adult LCH with radiotherapy ; we also failed to define an optimal RT dose range for this treating disease. However, as suggested by Olschewski *et al*, we support the use of doses between 6-20 Gy in adult patients with LCH (*9*).

Results of this study should be viewed with caution due to the small number of patients but it gives additional knowledge for the treatment of a rare group of patients with adult LCH of bones which should be kept in mind. In order to define definitive treatment guidelines additional studies are needed. However, due to the rarity and clinical variability of adult LCH, it does not seem possible to establish prospective randomized studies for the role of RT for this tumour other than multicentric and multinational trials. Our current and previous knowledge still depends on retrospective collective data.

CONCLUSIONS

Radiotherapy as a single treatment modality in adult Langerhans Cell Histiocytosis of bones would appear insufficient for disease control, at least within the dose range examined in the current study, and surgery should be the primary choice for treatment., Radiotherapy should be reserved for :

- inoperable lesions involving bones where resection would significantly compromise anatomic function,
- recurrent lesions
- adjuvant treatment following marginal resection
- painful lesions not appropriate for surgery.

Multiple bone involvement is an unfavourable finding and should be treated with combined treatment modalities.

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