Prognostic impact of bone involvement in Hodgkin lymphoma

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The purpose of the study is to determine incidence and prognostic impact of osseous Hodgkin lymphoma (HL). Between 1997 and 2004, 198 patients with HL were treated at our institution. Advanced stages and nodular sclerosis histology prevailed. All patients were treated according to protocols of the German Hodgkin Study Group (GHSG). After minimum follow-up of 24 months, we retrospectively analyzed the incidence of osseous HL, treatment response and parameters of survival. We recorded 14 cases of osseous HL (7 %), always with concurrent nodal disease. Axial skeleton was most frequently involved. Eleven patients (78,5 %) achieved complete remission and three (21,5 %) progressed primarily. The patients with osseous HL had significantly lower 2-year freedom from treatment failure than the patients without bone involvement (71,4 and 92,7 %, respectively, p=0,004), with no significant difference in 2-year overall survival (85,7 and 95 %, respectively, p=0,14). On multivariate analysis, advanced stage was the only independent adverse prognostic factor. In conclusion, bone involvement is a relatively common finding in HL and is not an independent adverse prognostic factor.

Keywords: Hodgkin lymphoma – bone involvement – prognostic factors

Extranodal involvement is a prognostically unfavorable feature in Hodgkin lymphoma (HL). In the initial workup, bone marrow, liver and lungs are evaluated for possible involvement; bones are considered very rare extranodal site of Hodgkin lymphoma. Therefore, apart of clinical studies, routine bone scan is not recommended.

Primary osseous HL is extremely rare with about 25 patients reported in the literature [1]. Skeletal involvement with concurrent nodal HL is reported in 1-2 % of cases [2] and there is little data about its predictive and prognostic impact. The purpose of our study is to analyze this subgroup of patients in terms of demography, treatment response and parameters of survival.

Patients and Methods

In the period between January 1997 and July 2004, 198 patients with Hodgkin lymphoma were treated at our institution. There were 108 males and 90 females, median age 33,5 years (range 18 – 66). The majority of the patients had advanced stage disease and nodular sclerosis histology, see Tab.1 and 2.

Since our group is a member of the German Hodgkin Study Group (GHSG), all patients were staged and treated according to the protocols of the GHSG. For staging, chest X-ray, abdominal ultrasound, CT scan of neck, thorax and abdomen, bone marrow biopsy and bone scan were obligatory, MRI and PET were optional. For treatment, 3rd generation protocols were used between 1997 and 1998 (HD7, HD8, and HD9 for early, intermediate and advanced stages, respectively), 4th generation between 1999 and 2003 (HD10, HD11, HD12 and LPHD for early, intermediate, advanced, and lymphocyte predominant HL, respectively) and the currently running 5th generation since 2003. Details about the treatment strategy are beyond the scope of this publication and can be found elsewhere [3, 4]. The number of patients treated according to different protocols is summarized in Tab. 3.

All patients had follow-up at our institution. Three patients were lost to follow-up after 1, 18 and 22 months, respectively. Median follow-up was 24 months (range 1 – 84). Number of patients with bone involvement was evaluated and their basic characteristics: age, gender, stage, histology, sites of involvement, treatment response, 2-year freedom from treatment failure (FFTF) and 2-year overall survival (OS).

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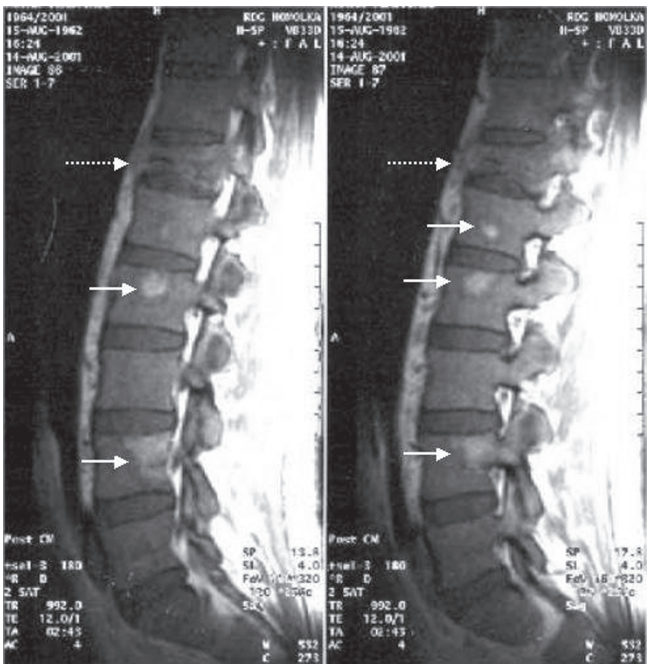

Figure 1. Patient Nr. 13. MRI, T2-weighted picture of osteolytic lesions in vertebral bodies of L1, L2 and L4 (arrows) and pathological compression of Th12 (dotted arrow)

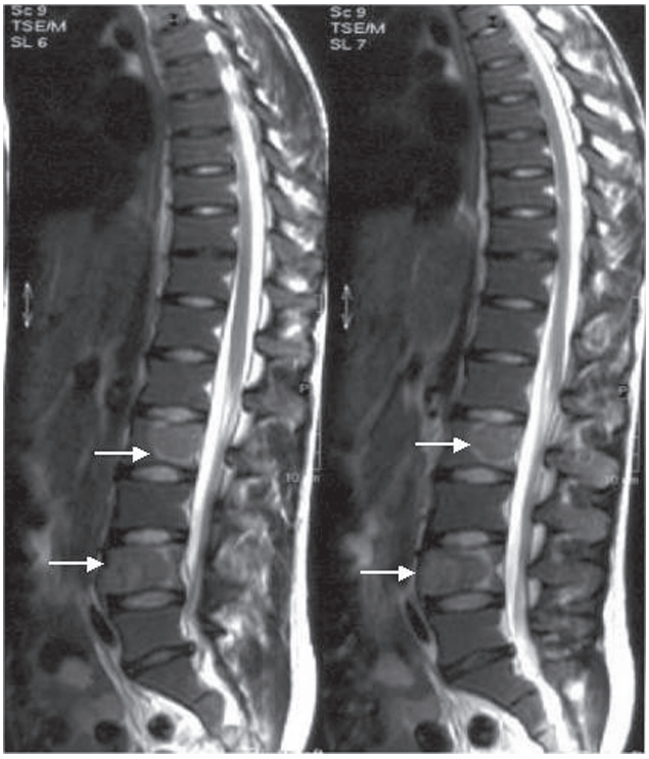

Figure 2. Patient Nr. 2. MRI, T2-weighted picture of osteolytic lesions in vertebral bodies of L2 and L4.

For statistical analysis, we used SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA) and Prism 4 for Windows (GraphPad Inc., San Diego, CA, USA). FFTF and OS values were estimated by Kaplan-Meier survival analysis, Cox proportional hazards model was used to estimate the hazard ratios for various baseline characteristics, such as gender, stage or histology.

Results

Of the 198 eligible patients, fourteen (7 %) had a primary bone involvement, always with concurrent nodal disease. There were eleven men and three women, median age 37,5 years. Advanced stages and nodular sclerosis histology prevailed among the subgroup; axial skeleton was the main site of involvement. Table 4 summarizes basic characteristics of patients with osseous involvement. Eight patients presented with pain of the involved area, the rest were asymptomatic. The involvement was most frequently found on CT scan and confirmed by bone scan, X-ray and/or PET scan. In case of doubt, MRI of the suspicious area was indicated (patients Nr. 2, 4, 13 and 14). In two patients (Nr. 9 and 11), CT scan was negative and the bone involvement was diagnosed exclusively by bone scan. Biopsy was only performed in one patient (Nr. 13) who was presented with pathological compressive fracture of Th12 of unknown etiology; complete staging was made after the histological examination. On figures 1 and 2, two cases of osseous Hodgkin lymphoma are shown.

Table 1. The stages (N=198)

Ann Arbor stage	Nr. of patients
I	12
II	86
III	43
IV	57

Table 2. Histological subtypes (N=198)

Subtype	Nr. of patients
Nodular lymphocyte predominant	8
Nodular sclerosis	124
Mixed cell	57
Lymphocyte rich classical HL	4
Not specified	5

Table 3. Treatment strategy – GHSG studies (N=198)

Protocols	Nr. of patients
3rd generation	53
4th generation	122
5th generation	21
LPHD	2

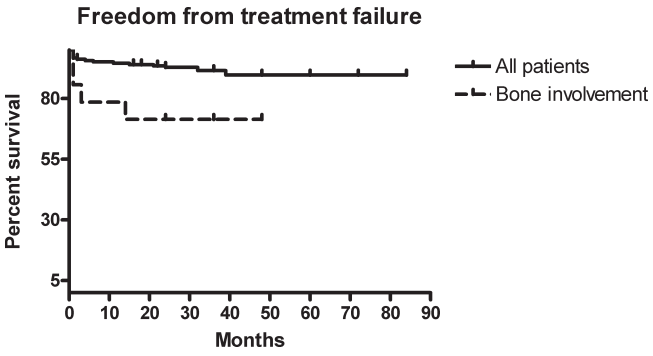

Figure 3. 2-year freedom from treatment failure

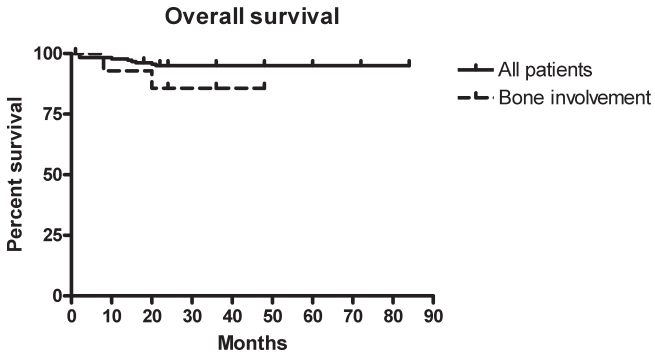

Figure 4. 2-year overall survival

All patients were treated by chemotherapy; seven of them were also irradiated because of intermediate stage (where radiotherapy is standard part of the curative treatment) or residual disease after chemotherapy in advanced stage of the disease. The involved sites of skeleton were a part of the radiotherapy target volume in four cases. After completion of the treatment we recorded eleven complete remissions (78,5 %), no partial remission, and three primary progressions (21,5 %) after 1, 1, and 3 months, respectively. These progression were nodal, no skeletal progression was recorded. At 2-years, overall survival (OS) and freedom from treatment failure (FFTF) were 85 % and 71 %, respectively.

The comparison of survival data in patients with and without bone involvement showed that patients with osseous disease have a significantly higher probability of relapse. The 2-year FFTF was 71,4 in patients with bone involvement and 92,7 % for patients without bone involvement (p=0,004, hazard ratio 4,39, 95% CI of ratio 2,430 to 117,6, see Fig. 3). Overall survival difference, however, was not statistically significant with 85,7 % in patients with bone involvement and 95 % in patients without bone involvement (p=0,14, hazard ratio 2,94, 95 % CI of ratio 0,5488 to 56,63, see Fig.4).

On multivariate analysis, however, only advanced stage was an independent predictor of relapse (p=0,003), see. Fig.5. Other variables such as bone involvement, histology, age or gender have not proven to be independent adverse prognostic factors.

Discussion

Extranodal involvement is a common feature of malignant lymphomas, especially non-Hodgkin lymphomas, where as much as 30 % of lymphomas have an extranodal origin [2]. In HL the incidence of extranodal disease is somewhat lower with spleen being most frequently involved (up to 25 % in mixed cellularity subtype [2]); the involvement of extralymphatic organs is far less common. Bone involvement is considered a rare way of extralymphatic spread; bone scan is therefore not rec-

Table 4. The overview of patients with osseous HL

Patient Nr.	Gender	Age	Stage	Histology	Diagnosis based on	Clinical symptoms	Involved site[s]	Biopsy response	Treatment	Current status
1	male	27	IV	NS	CT	none	sternum	no	CR	alive with NED (no evidence of disease)
2	female	23	IV	MC	CT + MRI	pain	lumbar vertebrae	no	CR	alive with NED
3	male	40	IV	HL, not specified	CT	pain	lumbar vertebra	no	CR	alive with NED
4	female	57	IV	NS	CT + X-ray	pain	lumbar vertebra	no	PD	death due to HL
5	male	43	I	NS	CT	none	sternum	no	CR	alive with NED
6	male	31	II	MC	CT	none	rib	no	CR	alive with NED
7	male	35	III	NS	CT	pain	rib	no	CR	alive with NED
8	female	26	IV	NS	CT	none	head of the humerus	no	CR	alive with NED
9	male	47	IV	NS	bone scan	pain	thoracic and lumbar vertebrae	no	CR	alive with NED
10	male	31	IV	NS	CT	pain	thoracic and lumbar vertebrae, pelvis	no	CR	relapse after 18 months alive with disease
11	male	47	II	NS	bone scan	pain	thoracic and lumbar vertebrae	no	CR	alive with NED
12	male	50	IV	LP	CT + PET	none	femoral head	no	PD	death due to HL
13	male	30	IV	NS	CT + MRI	pain	thoracic and lumbar vertebrae	yes	PD	alive with disease
14	male	45	IV	NS	CT + MRI	none	sacrum	no	CR	alive with NED

ommended as a standard staging procedure [5]. In our study, the contribution of bone scan to the staging is controversial. In vast majority of cases, diagnosis was made by CT scan and bone scan only confirmed the previously known findings. Two patients had a negative CT scan and subsequently a positive bone scan; however, both had positive history, i.e. pain, prior to the evaluation, so that bone scan would have been made anyway, even outside clinical trials. Since German Hodgkin Study Group includes bone scan as the obligatory staging evaluations, we'll be able to retrospectively evaluate the real impact of this staging procedure on a large group of patients in the future. The comparison of sensitivity and specificity of CT scan and bone scan will certainly be of great importance, the position of MRI in the staging of HL must be discussed as well [6].

The incidence of osseous Hodgkin lymphoma is quite high in our study. This is probably because our institutions serve as reference centers for HL so that selected patients with very advanced disease are referred here. In the literature, huge variation of incidence between 0,1 and 15 % is reported [7-11], our study standing somewhere in the middle.

Clinical picture of osseous HL is not specific; some patients have pain as the first symptom, others are asymptomatic and the diagnosis is coincidental. The lesions have no uniform appearance – they can be osteolytic as well as osteosclerotic or mixed [12, 13]. Differential diagnostically, osteomyelitis must be ruled out [14], especially when B-symptoms are present. Eosinophilic granuloma might also present similar bone lesions in young patients; the radiographic features, however, are different (sharply delineated osteolytic lesion [15, 16]). Histological diagnosis from the bone biopsy specimen is very difficult since necrosis and polymorphonuclear cell infiltration is often present. With the increasing use of PET-scan in the staging [17], this method might be capable to solve some differential-diagnostic problems. At present time, we diagnose osseous HL involvement in advanced stage patients with lesion(s) in the axial skeleton found on CT scan. In other patients we recommend further diagnostic procedures such as MRI or PET; we do not perform routine biopsy of the lesions.

Bone involvement has not proven to be an adverse prognostic factor on its own. Because of the frequent multiplicity of osseous lesion, there is a strong co-variation with advanced stage disease, which is an adverse prognostic factor [18]. The outcome of the patients with osseous HL is not worse than that of patients without bone involvement [19], this is true for our patients as well. At present time, therefore, there's no need for special treatment strategy for osseous HL. The response rate is somewhat lower in our patients with bone involvement (78,5 %) but the number of patients is very low and we are far from drawing any conclusion. The evaluation of the treatment response, however, is problematic. Bones regenerate very slowly and morphological changes in the bone structure often persist after the treatment. Sometimes it's impossible to discriminate between complete and partial remission. The sensitivity and specificity of functional imaging for bone involvement has not yet been established and there is a number of false positive results due to benign muscular hypermetabolism [20], false positivity was described in bone marrow as well [21]. If there's a place for additional prophylactic radiotherapy of the initially involved bony sites remains to be answered.

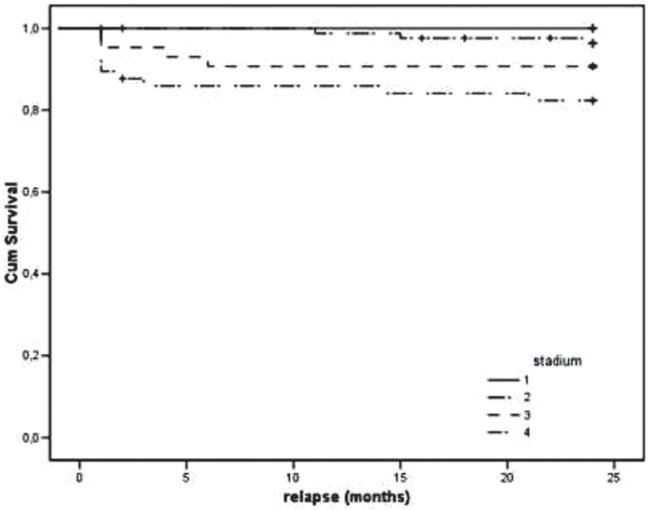

Figure 5. The influence of stage on FFTF

In conclusion, bones are relatively common extralymphatic site of HL. Diagnosis might be difficult and standard staging and re-staging procedures have not yet been determined. Treatment strategy and prognosis adhere to the stage of the disease and there's no need for additional treatment.

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