Primary bone lymphoma: Clinical presentation and therapeutic considerations

Annika Müller, Martin Dreyling, Falk Roeder, Andrea Baur-Melnyk, Thomas Knösel, Alexander Klein, Christof Birkenmaier, Volkmar Jansson, Hans Roland Dürr

Abstract

Background: Primary lymphoma of bone (PBL) is a rare entity. Due to unspecific clinical signs and equivocal radiographs diagnosis may be delayed. This retrospective report of 109 PBL cases demonstrates typical aspects of the lesion. Treatment and prognostic factors are evaluated.

Methods: Retrospectively patient records were reviewed. All patients were followed for evidence of local or distant recurrence. Overall survival (OS) was used as clinical outcome.

Results: The median age of the 109 patients was 62.8 years. The most common symptoms were pain (76%), swelling (29%), neurologic symptoms and pathological fracture (16% each). Mean duration of symptoms was 8 months (0–197 months).

19% of patients had indolent NHL subtypes, 72% aggressive NHL subtypes and 7% cases Hodgkin disease. Cyclophosphamid, doxorubicin, vincristine and prednisone (CHOP) or CHOP plus rituximab (RCHOP) were given in 88 (81%) of patients. Radiotherapy was delivered in 67 (61%) of cases. 51 (47%) patients received both. Surgical interventions were restricted to cases with complications as fractures.

The 5-year OS was 66%. The 5-year OS was 66%. In the subgroup of 78 patients with aggressive NHL subtype there was a highly significant benefit for chemotherapy or chemotherapy and radiation in comparison to no treatment or radiation alone. Raised LDH, age, IPI and ECOG performance were prognostic factors. In multivariate analysis, age and raised LDH levels only kept significance.

Conclusions: In our series of primary bone lymphoma, chemotherapy resulted in a better outcome than Radiotherapy alone. Long-term survival is based on the stage of the disease, favoring younger (<60 years) patients with solitary bone lesions, low level of LDH and favourable ECOG performance status and IPI scores.

1. Background

Primary lymphoma of bone is a well-recognized but rather rare entity, accounting for about 5% of all patients with primary bone tumors [1,2]. It was initially described by Oberling in 1928 [3]. In 1939 this subtype of lymphoma was described as a distinct entity with infiltration of the bone or the adjacent soft tissues [4]. In advanced stages of the disease, it may be impossible to determine whether the lymphoma developed within the bone (primary) or invaded it (secondary) [5]. However, in general lymph node or visceral involvement is excluded by definition [6]. Whereas in some studies regional lymph node involvement is permitted [7,8]. According to the WHO classification (2013), PBL is defined as a neoplasm composed of malignant lymphoid cells, producing one or more masses within bone, without any...
supraregional lymph-node involvement or other extranodal lesions. In general it has a single skeletal lesion with or without regional lymph-node involvement and should be distinguished from secondary bone involvement in systemic lymphoma [9]. Affecting 1.7/1 Mio patients in the US [10] approximately 4% of all patients with NHL present with an obvious skeletal lesion [11], comprising 5% of all extranodal lymphomas [1]. In two series of NHL patients, routinely performed bone-marrow biopsies were positive in 18% and 23% of non-Hodgkin’s lymphomas [12,13]. In a group of 422 patients with primary or primary and secondary bone lymphomas at the Mayo Clinic, 38% showed extraskeletal involvement at the time of detection of bone involvement [14]. Continued observation for 3 to 6 months, to ensure that visceral sites are not identified, prior to classifying as PBL may be considered.

The occurrence of a primary Hodgkin’s lymphoma of bone is exceedingly rare. In many patients with localized primary lymphoma of the bone (PBL), diagnosis is delayed due to unspecific clinical signs and equivocal radiographs [15]. Magnetic resonance imaging (MRI) allows an early diagnosis, but due to the rareness of the lesion it is often not considered before biopsy [16,17]. Therapy is multimodal, mainly based on chemo- and radiotherapy. Surgery is only used in cases of skeletal complications [15]. The prognosis is superior to that of a localized Ewing’s sarcoma (which sometimes has been confused with this tumor entity) [18].

This retrospective report includes 109 primary lymphomas of bone, updating also 36 cases published in 2002 [15].

2. Patients and methods

A retrospective review was done of 109 patients with PBL treated in our institution between 1980 and 2015. Patient records of these 109 patients were reviewed including presenting symptoms, sites of involvement and imaging. Staging included the results of physical examination noted in the medical records, routine laboratory check-up and bone marrow biopsy. Depending on the location of the lesion and skeletal radiographs, computed tomography (CT) scans and magnetic resonance imaging (MRI) were analysed. This is a retrospective analysis going back to 1980. A standardized staging using advanced imaging methods as PET-CT scans has only been introduced in the last years.

2.1. Statistical analysis

All patients were followed for evidence of local or distant recurrence in general by regional MRI scans and CT scans of the thorax and abdomen. Overall survival (OS) was defined as the time from surgery to death from any cause and was calculated according to the Kaplan-Meier method. Significance analysis was performed using the Log-Rank, the Chi-Square test or the Cox proportional-hazards regression model. A p value of ≤0.05 was considered statistically significant.

3. Results

109 patients could be evaluated (61 males, 48 females). The median age was 62.8 years (mean 59.9, range 20–100). The most common location was the trunk in 61% of the cases, the most common symptoms were pain in 76% and a swelling distinct from lymph nodes as a soft-tissue tumor in 29% (Table2). Median duration of symptoms was 8 months, but a wide variation was observed (0–197 months), median 3.3 months.

Diagnosis was established by incisional biopsies in 54 cases and true-cut biopsies in 50 patients. Five patients had biopsies with first surgery. 72 patients got no surgical intervention, spinal surgery was performed in 14 patients, conservative therapy including orthoses in 12 patients and a spectrum of osteosynthesis and endoprosthetic reconstructions in the remaining patients.

Histologically 21 (19%) patients had an indolent NHL subtype, 78 (72%) patients had an aggressive NHL subtype and 7 (6%) cases showed Hodgkin’s lymphoma (Table 1). In 3 (3%) cases a subgroup analysis could not be established retrospectively.

The lactate dehydrogenase (LDH) level could be evaluated in 69 patients and was raised in 33 (48%). 49 (45%) of the patients showed an involvement of regional lymph nodes. In the subsequent clinical course involvement of liver (n = 8), bone marrow (n = 13), lung (n = 11), kidneys (n = 8) and spleen (n = 7) were observed.

The Eastern Cooperative Oncology Group (ECOG) performance status [19] was 0 (fully active) in 42 (38%), 1 (mild restriction) in 53 (49%), 2 (restricted but able for selfcare) in 11 (10%) and 3 (limited selfcare, 50% confined to bed or chair) 3 (3%).

The International Prognostic Index (IPI) (Age > 60 years, stage III or IV, elevated serum LDH, ECOG performance status > 1, more than 1 extranodal site) was found to be 0 in 9%, 1 in 24%, 2 in 27%, 3 in 27% and 4 in 13% of cases.

Non-surgical therapy consisted in the following forms of chemotherapy. CHOP scheme (4–6 cycles) alone or CHOP plus rituximab (RCHOP) was given in 88 (81%) of patients. Radiotherapy was delivered in a typically dose of 46 Gy in 67 (61%) of cases, 51 (47%) patients received both (CHOP + Radiotherapy). 4 patients got surgery alone and received neither CTX nor RTX.

At the time of latest follow-up 46 (42%) of the patients had deceased by death of any course. In the surviving 63 patients, the follow-up was 1–421 months (mean 102, median 64 months, 2 patients less than 12 months, 7 others 12–24 months). 56 (89%) of surviving patients were without evidence of disease. For all patients the 5-year OS as shown in Fig. 1 was 66% (mean OS 197, median OS 178 months. There was a trend for a worse survival in aggressive lymphomas, but without significance (Fig. 2). In the subgroup of 78 patients with an aggressive NHL subtype there was a highly significant benefit for those patients receiving chemotherapy (Fig. 3, p = 0.003). Also shown in this figure there was a trend for better overall survival in combined chemotherapy and radiation treatment but in a detailed analysis no significance for that. Rituximab was used in 49 patients. Interestingly, compared to 37 patients receiving CTX without rituximab no difference in overall survival was seen. Raised LDH (Hazard ratio 1.92, 95% CI 2.29–6.26, p = 0.01) or age below 60 years (Hazard ratio 0.51, 95% CI 0.28–0.93, p = 0.027) could be proven as prognostic factors. Accordingly, the International Prognostic Index (IPI) showed a significant better overall survival in patients with scores 0 or 1 (Hazard ratio 1.45, 95% CI 1.12–1.87, p = 0.005), with ECOG scale of performance status also a clear dependence was proven (p = 0.028). Regional lymph node involvement did not change the prognosis. Local relapse was observed in 11 (10%) patients. In the event of local relapse, overall survival was significantly reduced (p = 0.0478). Using Cox regression for multivariate analysis, age, raised LDH levels and the subtype only kept significance (Table 3).

### Table 1

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indolent</td>
<td>21 (19%)</td>
</tr>
<tr>
<td>CLL</td>
<td>3</td>
</tr>
<tr>
<td>Follicular</td>
<td>11</td>
</tr>
<tr>
<td>Marginal zone</td>
<td>1</td>
</tr>
<tr>
<td>Waldenström</td>
<td>6</td>
</tr>
<tr>
<td>Aggressive</td>
<td>78 (72%)</td>
</tr>
<tr>
<td>B-cell</td>
<td>76</td>
</tr>
<tr>
<td>T-cell</td>
<td>2</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>No subtype</td>
<td>3 (3%)</td>
</tr>
</tbody>
</table>

Distribution of histopathologic subtypes of indolent, aggressive lymphomas and Hodgkin's disease.
4. Discussion

This study represents a retrospective monocentric analysis in a large group of 109 patients with PBL and continues a study we published in 2002 [15].

The distribution of age and gender in the current study was similar to that in the literature as shown in a large population based study based on the SEER database [20]. Malignant bone lymphoma was seen in all decades of life with the majority of patients being between 50 and 70 years of age. PBL in children is rare, and differentiation, especially from Ewing’s sarcoma, is important [21]. The differential diagnosis is long and generally considers all small blue round-cell lesions of bone. In addition from imaging analysis metastases, as well as chronic osteomyelitis, primary bone sarcomas, Ewing sarcoma, rhabdomyosarcoma, neuroectodermal tumors as PNET, small cell lung carcinoma, small-cell osteosarcomas, but also leukemic infiltrates have to be considered.

Ostrowski et al. published a large study of 422 patients with malignant lymphoma of the bone seen at the Mayo Clinic from 1907 to 1982 [14]. Histological typing may be difficult especially in high-grade malignant lymphomas [22]. The initial histological diagnosis in some of our cases was primarily undifferentiated sarcoma. This was later revised after discussing the radiological aspects of the cases and

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Indolent</th>
<th>Aggressive</th>
<th>Hodgkin’s disease</th>
<th>No subtype</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>21 (19%)</td>
<td>78 (72%)</td>
<td>7 (6%)</td>
<td>3 (3%)</td>
<td>109 (100%)</td>
</tr>
<tr>
<td>Age (mean, years)</td>
<td>62.0</td>
<td>61.2</td>
<td>47.8</td>
<td>29.9</td>
<td>59.9</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trunk</td>
<td>13</td>
<td>46</td>
<td>6</td>
<td>2</td>
<td>67 (61%)</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>3</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>20 (18%)</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>6</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>20 (18%)</td>
</tr>
<tr>
<td>More than one</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture</td>
<td>5</td>
<td>11</td>
<td>0</td>
<td>1</td>
<td>17 (16%)</td>
</tr>
<tr>
<td>Pain</td>
<td>17</td>
<td>60</td>
<td>5</td>
<td>1</td>
<td>83 (76%)</td>
</tr>
<tr>
<td>Swelling</td>
<td>4</td>
<td>26</td>
<td>1</td>
<td>1</td>
<td>32 (29%)</td>
</tr>
<tr>
<td>Neurology</td>
<td>2</td>
<td>12</td>
<td>3</td>
<td>1</td>
<td>18 (17%)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>13</td>
<td>29</td>
<td>7</td>
<td>0</td>
<td>49 (45%)</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG (mean)</td>
<td>0.81</td>
<td>0.74</td>
<td>0.86</td>
<td>1.0</td>
<td>0.77</td>
</tr>
<tr>
<td>IPI (mean)</td>
<td>2.1</td>
<td>2.2</td>
<td>2.0</td>
<td>0.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Raised LDH*</td>
<td>4 (27%)</td>
<td>28 (55%)</td>
<td>1 (50%)</td>
<td>0 (0%)</td>
<td>33 (48%)</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>14</td>
<td>47</td>
<td>4</td>
<td>2</td>
<td>67 (62%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>13</td>
<td>70</td>
<td>5</td>
<td>1</td>
<td>89 (82%)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>9</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>49 (56%)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year OS (%)</td>
<td>81.9 ± 8.2</td>
<td>59.2 ± 6.0</td>
<td>68.6 ± 18.6</td>
<td>–</td>
<td>65.6 ± 4.8</td>
</tr>
</tbody>
</table>

Fig. 1. Overall survival in 109 patients with primary lymphoma of bone.
additional immunostaining resulting in the correct diagnosis.

In PBL all bones may be affected, but the axial skeleton is the main site of involvement. This reflects the distribution of red marrow. For the same reason the metaphyseal location is predominantly affected. The most common location in our series was the affection of the pelvis, the spine was the second most common location. The lesions are most commonly osteolytic. However they can also show an osteoblastic or mixed osteolytic/blastic bone change [23]. Pathologic fractures occurred in 16% of our patients. In the literature a pathological fracture was described as an independent adverse prognostic event [24]. In our group of patients this could only be proven as a trend but without significance.

In many cases in lymphoma only slight changes are seen in bone imaging despite a large soft tissue tumor in MRI. This is a major criteria for the diagnosis. This is due to the fact that the tumor sometimes shows such a rapid growth that it overruns the bony host response. Nuclear bone scans may produce false-negative results due to the predominantly osteolytic character of the lesions [25]. PET scans were first used in lymphomas in 1990 [26]. In a large number of studies PET-CT has been established as the most sensitive current imaging study not only for response assessment but also for staging of the disease [26–28].

**Fig. 2.** Overall survival in 106 patients with either indolent lymphoma (n = 21), aggressive lymphoma (n = 78) or Hodgkin’s disease (n = 7) n.s.

**Table 3**

Cox proportional-hazards regression for overall survival of raised LDH, age, IPI, ECOG, histopathologic subtypes (indolent, aggressive, Hodgkin’s disease), local relapse, chemotherapy (CTX) and radiotherapy (RTX), in 106 patients with PBL. 3 patients due to missing subtypes excluded.

<table>
<thead>
<tr>
<th>Factor</th>
<th>P</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised LDH</td>
<td>0.0232</td>
<td>4.6303</td>
<td>1.2327–17.3919</td>
</tr>
<tr>
<td>Age</td>
<td>0.0112</td>
<td>1.0426</td>
<td>1.0095–1.0767</td>
</tr>
<tr>
<td>IPI</td>
<td>0.1240</td>
<td>0.6658</td>
<td>0.3964–1.1181</td>
</tr>
<tr>
<td>ECOG</td>
<td>0.1642</td>
<td>0.5840</td>
<td>0.2737–1.2461</td>
</tr>
<tr>
<td>Histopathologic subtype</td>
<td>0.0349</td>
<td>3.2039</td>
<td>1.0858–9.4538</td>
</tr>
<tr>
<td>Local relapse</td>
<td>0.9267</td>
<td>1.0681</td>
<td>0.2627–4.3429</td>
</tr>
<tr>
<td>CTX</td>
<td>0.8924</td>
<td>1.0974</td>
<td>0.2855–4.2177</td>
</tr>
<tr>
<td>RTX</td>
<td>0.1859</td>
<td>0.5005</td>
<td>0.1794–1.3959</td>
</tr>
</tbody>
</table>

HR indicates hazards ratio; CI 95% confidence interval.

Soft-tissue involvement in PBL is common, affecting more than 70% of the patients [15]. Thus a large soft-tissue tumor extending concentrically around the bone with infiltration of the bone marrow in the typical age group of patients may be the major clue to the diagnosis. One could call it an ‘Ewinglike’ pattern in adults aged 50 years or older.

**Fig. 3.** Overall survival in 78 patients with primary lymphoma of bone (aggressive NHL subtype) in respect to no radiotherapy/chemotherapy (n = 2), radiotherapy only (n = 6), chemotherapy alone (n = 29) and combined modality treatment (n = 40); p = 0.0034. If compared patients with chemotherapy only (n = 29) and combined modality treatment (n = 41), there was just the shown trend but no significance.
Local pain and swelling, may be the only signs of the disease. The duration of these symptoms was in some cases long, more than one year, but many patients described also a rapid growth of the lesions. This is reflected by the difference between the mean of 8 months and the median of 3.3 months. B-symptoms including fever, sweating, or weight loss may occur as described by Govi et al. in 16%, but are missing in many cases [24]. So first suspect is often bone or soft tissue sarcoma in younger and metastatic disease in older patients.

Treatment is based on systemic therapy. Surgical intervention is restricted to cases with neurological complications, impeding fracture, or fractures [15]. At present, there are no general protocols for applying and timing chemotherapy or radiotherapy. The optimal timing of radiation and chemotherapy in PBL is also unknown. As proposed by Mendenhall et al., radiotherapy should be delayed in monostotic and polyostotic diseases until chemotherapy is completed, in order to reduce the amount of radiotherapy and include only those sites of original gross involvement [30]. In some institutions, local radiation alone was recommended [31]. Chemotherapy seems to produce a better outcome than Radiotherapy alone; that still remains the best treatment for local disease control. Radiation therapy alone should be reserved for mandibular tumors, which are usually very small and earlier diagnosed [32]. In the IE1SG-14 study, patients managed with primary chemotherapy, whether followed by radiation or not, had a better OS compared with patients treated with primary radiotherapy, whether followed by chemotherapy or not [33]. This was also described by Govi et al. [24] Chemotherapy may also reduce the incidence of local recurrence in PBL and improve the prognosis in children and adults with disseminated disease. Our own results may strengthen this by a trend to better survival in patients with combined modality treatment (Fig. 3).

Several prognostic factors in PBL have been established. Unifocal versus multifocal disease at presentation was a weak but significant result. In their large study of 422 patients, Ostrowski et al. were able to demonstrate [14] a 5-year survival rate of 58% in unifocal disease versus 42% in multifocal osseous disease. This was also seen by Wu et al. comparing 81 cases of unifocal PBL with 35 cases of multifocal disease [35]. In our patients we found a overall 5-year survival of 66%, there was no difference between multifocal or unilocular osseous disease. The correlation between the site of the primary lesion and the prognosis is controversial. Having found no correlation in one study [36], Ostrowski showed local recurrence was higher in malignant lymphoma of the jaw, and systemic recurrence had a higher incidence in pelvic and spinal lesions. The 5-year overall survival rate was also very low in this group (24%) as compared with the extremities, such as the femur (79%). In our study, a significant influence of trunk vs extremity lesions could not be shown. This might be contributed to advances obtained in radiotherapy of critical locations. Advanced age was significantly associated with a reduced overall survival, as found also by others [37]. ECOG status, age, LDH levels, IPI stage are known significantly associated with a reduced OS, maybe attributed to a smaller sample number [42].

5. Conclusion

In summary PBL is a rare clinical entity. Clinical symptoms are unspecific, and the delay between onset of symptoms and diagnosis may either be short or long. Roentgenmorphology is heterogenous, one of the typical radiologic signs is large soft-tissue involvement surrounding the bone with little or no bone changes on radiographs. Treatment is based on systemic chemotherapy. Surgical intervention is restricted to cases with complications as fractures. Chemotherapy seems to produce a better outcome than radiotherapy alone; that still remains the best treatment for local disease control in unifocal cases. Long-term survival is based on the stage of the disease, favoring younger (< 60 years) patients with solitary bone lesions, low level of LDH and favourable ECOG and IPI scores.

6. Declarations

All authors have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work. This study was not supported by any grants or external funding.

7. Ethics approval and consent to participate

This study was approved by the ethics committee of the Medical Faculty, University of Munich. Written consent was obtained from all surviving patients included in this study. For non-surviving patients data were irreversibly anonymized as recommended by the ethics committee.

8. Competing interests

The authors declare that they have no competing interests.

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10. Authors’ contributions

A.M. Student doing her thesis on PBL. She contacted the patients and acquired the data, involved in drafting and revising of the manuscript.

M.D. Oncologist. Responsible for the decision to treat and how to treat the patients, involved in drafting and revising of the manuscript.

F.R. Reviewing the radiotherapy and deciding which patient to treat or not to treat, involved in drafting and revising of the manuscript.

A.B. Reviewing the pathologic investigations, involved in drafting and revising of the manuscript.

T.K. Pathologist reviewing the pathologic investigations, involved in drafting and revising of the manuscript.

A.K. Surgeon on many of the cases, involved in drafting and revising of the manuscript.

C.B. Surgeon, involved in drafting and revising of the manuscript.

M.D. Oncologist. Responsible for the decision to treat and how to treat the patients, involved in drafting and revising of the manuscript.

C.F. Oncologist. Responsible for the decision to treat and how to treat the patients, involved in drafting and revising of the manuscript.

H.R. Oncologist. Responsible for the decision to treat and how to treat the patients, involved in drafting and revising of the manuscript.

A.R. Oncologist. Responsible for the decision to treat and how to treat the patients, involved in drafting and revising of the manuscript.

A.B. Radiologist reviewing the radiologic investigations, involved in drafting and revising of the manuscript.

T.K. Pathologist reviewing the pathologic investigations, involved in drafting and revising of the manuscript.

A.K. Surgeon on many of the cases, involved in drafting and revising of the manuscript.

V.J. Surgeon on many of the cases, reviewed the manuscript, involved in drafting and revising of the manuscript.

H.R.D. Corresponding author. Developed the study concept, did the final data analysis and provided the major clinical input in writing and revising of the manuscript.

Each author has contributed significantly to, and is willing to take public responsibility for this study: its design, data acquisition, and analysis and interpretation of data. All authors have been actively involved in the drafting and critical revision of the manuscript. All authors read and approved the final manuscript.

References

