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Primary Non-Hodgkin’s Lymphoma of Bone in Children

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Background: Primary non-Hodgkin’s lymphoma of bone, often more simply referred to as primary lymphoma of bone, is a rare subset of non-Hodgkin’s lymphoma in children. There are only a few small series of primary lymphoma of bone in children with long-term follow-up, and none have appeared in the orthopaedic literature.

Methods: A review of our institution's Pediatric Tumor Registry identified fifteen cases of primary lymphoma of bone among 306 cases of diagnosed non-Hodgkin’s lymphoma between 1970 and 2003. Retrospective evaluation included collection of demographic, clinical, radiographic, treatment, and follow-up data. A univariate analysis was used to assess the prognostic significance of risk factors with respect to survival of patients from this series and in a summary analysis of data collected from similar series in the literature.

Results: The patients included ten male and five female patients with a mean age of 11.6 years. Most patients had a presenting complaint of pain and had swelling and/or tenderness on physical examination. Eight children had a solitary bone lesion, and seven had multiple bone lesions. Overall, the mean number of bones involved was 3.1 per patient. The femur and the pelvis were the most frequently involved bones. The ten surviving patients were followed for a mean of 13.6 years. Five patients died: three of disease progression, one of treatment-related complications, and one of an unrelated cause. The mean time from diagnosis to death was 2.1 years. Nine patients received chemotherapy only, whereas six patients received a combination of chemotherapy and radiation therapy. In the present study, an age of nine years or less was predictive of poor survival (p < 0.05). In the summary analysis of cases collected from the literature, advanced stage, young age, non-large-cell histology, and multiple-bone involvement were predictive of poor survival (p < 0.05).

Conclusions: On the basis of the present series and a comprehensive review of similar series in the literature involving patients with primary lymphoma of bone, it appears that younger age, advanced-stage disease, multiple-bone involvement, and non-large-cell histology are associated with decreased survival as compared with older age, localized disease, single-bone involvement, and large-cell histology, respectively.

Level of Evidence: Prognostic Level IV. See Instructions to Authors for a complete description of levels of evidence.

Primary non-Hodgkin’s lymphoma of bone, often more simply referred to as primary lymphoma of bone, is a rare presentation of non-Hodgkin’s lymphoma in children. Initially described in adults in 1928 by Oberling, the first case series of adults with primary lymphoma of bone was presented in 1939 by Parker and Jackson. In adults and children, primary lymphoma of bone comprises between 2% to 3% of all primary bone tumors. Furthermore, it comprises <1% of all lymphomas and 5% of extranodal non-Hodgkin’s lymphomas. Primary lymphoma of bone is a rare entity, especially in children; most reports have described a median age of presentation for this disease in the fourth and fifth decades.

Reports of primary lymphoma of bone in children are often sparse and inconsistent regarding inclusion criteria, and there have been only a few small studies analyzing primary lymphoma of bone in children with long-term follow-up.

Although the orthopaedic presentation of primary lymphoma of bone has been examined in case series of adults, studies of children have concentrated on oncologic issues and no pediatric case series of primary lymphoma of bone have appeared in the orthopaedic literature, to our knowledge. Because the presentation of primary lymphoma of bone in children is rare, and few series have been published, we thought that a review of our clinical experience with this entity would make a meaningful contribution to the understanding of the presentation, current evaluation methods, treatment options, and expected outcomes for this disease in children.

Materials and Methods

After institutional review board approval had been obtained, a retrospective review of our institution’s Pediatric Tumor Registry from 1970 to 2003 was conducted to identify
children with non-Hodgkin’s lymphoma in bone. Over this period, 306 cases of non-Hodgkin’s lymphoma in children were identified. In eighteen of these cases, the primary site of involvement was bone.

The present study included patients with non-Hodgkin’s lymphoma that was limited to one or more osseous sites, including patients with bone-marrow involvement, provided that they had no evidence of other systemic involvement. Patients were excluded if they had a diagnosis other than non-Hodgkin’s lymphoma, if they had evidence of systemic involvement other than bone-marrow involvement, if they had non-Hodgkin’s lymphoma with secondary involvement of bone, and if they had less than two years of follow-up. Of the eighteen cases that were identified, fifteen were included in our review. Two patients were excluded because they were seen at our institution for a second opinion only and therefore had insufficient data. One patient was excluded because there had been less than two years of follow-up. The individual characteristics of the fifteen patients in the study group are presented in the Appendix. The study group included ten male and five female patients with a mean age of 11.6 years (median, 12.1 years; range, 1.2 to 19.1 years) at the time of presentation.

Clinical information was obtained from patient medical records. Retrospective evaluation included collection of demographic data, clinical and radiographic information, pathology reports, treatment information, and follow-up evaluations. All fifteen patients were included in the survival analysis. Ten patients survived, with a mean duration of follow-up of 13.6 years (median, 17.2 years; range, two to twenty-three years), and five patients died, with a mean interval from presentation to death of 2.1 years (median, 1.9 years; range, 0.4 to 4.9 years).

At the time of presentation, a complete evaluation was performed to rule out systemic lymphoma. The clinical staging methods differed among patients but variably included routine serum chemistry studies; a complete blood-cell count; urinalysis; lumbar puncture; posteroanterior and lateral chest radiographs; computed tomography of the chest, abdomen, and pelvis; an intravenous pyelogram; gallium scanning; abdominal and pelvic ultrasound; magnetic resonance imaging; and a technetium bone scan. All patients had plain radiographic imaging of the primary site. All patients had a bone-marrow examination (involving aspiration, biopsy, or both).

Considerable inconsistencies were found in the literature regarding the classification of primary lymphoma of bone in children. We therefore created a classification system in which patients were described as having localized disease (solitary-bone involvement, no marrow involvement), diffuse disease (multiple-bone involvement, no marrow involvement), or disseminated disease (bone and marrow involvement, no other systemic involvement).

Pathology slides of twelve of the fifteen cases were available for histologic review and were reexamined by a single hematopathologist (J.K.C.) at our institution. They were assigned revised World Health Organization classifications (see Appendix). Pathology reports, including the current World Health Organization classification, were available in the three cases in which tissue was not available for review. Lymphoblastic markers (TdT, MIC2, O13) were used to classify the subtypes. Staining for immunologic markers of B cells (CD20, CD79a, Pax-5) and T cells (CD3) were also used to further classify the tumor immunophenotypes by defining the types of malignant cells (B or T cells) that were present in the lesions.

A survival analysis for the patients in the present series was conducted to test the association between certain demographic, clinical, radiographic, and pathologic characteristics and survival. The primary end points for this analysis included relapse (defined as recurrent disease after treatment, either at the primary site or at a metastatic site) and death. The factors that were analyzed included gender, age, the type of bone involved (i.e., long bones, flat bones, vertebral bones), multiple-bone involvement, the presence of constitutional symptoms (including weight loss of 10% of baseline over six months, a fever of 38°C, and/or drenching night sweats), swelling or a mass on physical examination, tenderness to palpation, histologic subtype, a positive result on initial bone-marrow examination, a positive result on repeat bone-marrow examination, radiographic evidence of soft-tissue extension or pathologic fracture, anemia (defined as a hemoglobin level of <13 g/dL in male patients and <11.5 g/dL in female patients), elevated platelet count, elevated serum calcium (>10.2 mg/dL), elevated lactate dehydrogenase, elevated alkaline phosphatase, treatment regimen (chemotherapy or chemotherapy combined with radiation therapy), and treatment toxicity resulting in a change in regimen (defined as toxicity necessitating a reduction in the dose of chemotherapy or radiation, a change in agent, or discontinuance of the original regimen).

Using the same methodology that was applied to our patients, we considered prognostic factors in pooled data from all of the case series reported in the literature, including the present data, that have exclusively analyzed primary lymphoma of bone in children. We did not include patients who were found as part of a larger adult series. Although a total of 122 total patients were available when our patients were combined with those from the literature, the survival analysis did not include thirty-one children from one study of localized primary lymphoma of bone because accurate data for specific patients could not be determined from that report. A modified Murphy staging system was used to classify the patients in the literature as stage I (IE) (involvement of a single osseous site; i.e., localized disease), stage II (involvement of a single osseous site and regional lymph nodes; i.e., localized disease), stage III (involvement of multiple osseous sites without marrow or node involvement; i.e., diffuse disease), and stage IV (metastatic disease including bone-marrow involvement; i.e., disseminated disease). The factors that were analyzed for the ninety-one patients pooled from other studies in the literature with adequate data included age, gender, the type of bone involved (i.e., long bones, flat bones, vertebral bones), multiple-bone involvement, the degree of involvement (stage), and the type of treatment (chemotherapy alone or...
combination therapy). These factors were evaluated with respect to survival.

**Statistical Methods**

Statistical analysis was done with use of S-PLUS statistical software. A product-limit univariate analysis (Kaplan-Meier analysis) was performed to analyze the prognostic significance of various factors. Probability testing was conducted against the null hypothesis that there was no difference in survival between patients with a tested characteristic and those without it. A standard log-rank test was used to test for differences in the time to an event (death or relapse), and the level of significance was set at p < 0.05. Ninety-five percent confidence intervals were determined by a normal approximation using 1.96 times the standard deviation of each point estimate. Although the confidence intervals of the two data curves may have overlapped at individual data points, significance was determined with use of the log-rank test and the summation of the difference across the entire curve.

**Results**

**Clinical Presentation**

The clinical presentation of the individual patients is presented in a table in the Appendix. The most common presenting complaint was pain without antecedent trauma, which occurred in twelve of the fifteen patients. Other symptoms included swelling or mass (five patients), fever (four patients), weight loss (two patients), night pain (two patients), limp (three patients), and irritability (one patient). One patient presented with a pathologic fracture of the distal part of the femur after a fall. Another patient presented with neurologic symptoms consistent with a T9 sensory level, referable to a lesion in the T6-T9 vertebral bodies. Constitutional symptoms were present in four patients. Two patients had a generally “ill” appearance; one child appeared cachectic, and the other child presented with decreased responsiveness and hypotonia. The physical examination revealed swelling or a mass and tenderness to palpation in five patients, only swelling or a mass in three patients, and only tenderness to palpation in two patients. In five patients, neither tenderness nor a palpable mass was detectable on physical examination. There was no relevant family history in any of the patients studied.

The mean delay from the onset of symptoms until the final diagnosis was 6.2 months (range, 0 to 2.5 years). Twelve of the fifteen patients had a delay of more than one month and eight had a delay of more than three months. The causes of delay were multiple, and it is impossible to separate the individual contributors. Most often, this was due to a delay in the initial presentation, with patients describing a prolonged period of nonspecific pain and/or swelling before presenting to a physician. Occasionally, the physician attributed these nonspecific symptoms to other causes of musculoskeletal pain, such as muscle strain or synovitis. In several cases, the correct diagnosis was delayed because the histological findings were difficult to interpret. In five patients, the initial pathology report was not interpreted as demonstrating lymphoma and was misinterpreted in one patient each as Hodgkin’s disease or eosinophilic granuloma, osteosarcoma, histiocytosis X, chronic sterile osteomyelitis, and histiocytic proliferation versus osteomyelitis.

**Site of Involvement**

The distribution of the specific bones involved is illustrated in Figure 1. A total of forty-six osseous lesions were observed in the fifteen patients studied, and the most common sites of involvement were the pelvis (eleven), the femur (nine), and the spine (eight). Eight patients had single-bone involvement, and seven had multiple-bone involvement. Overall, the mean number of bones involved was 3.1 per patient (range, one to twelve bones per patient).

**Laboratory Values**

The laboratory studies that had been performed at the time of presentation were examined. Abnormal findings included anemia (eight patients), elevated erythrocyte sedimentation rate
(six patients), elevated platelet count (five patients), elevated lactate dehydrogenase (five patients), elevated serum calcium (three patients), and elevated alkaline phosphatase (three patients). None of the patients studied had an elevation of the white blood-cell count.

**Extent of Disease**

The extent of disease for individual patients is listed in the Appendix. Seven patients had localized disease, three had diffuse disease, and five had evidence of bone-marrow involvement (disseminated disease). Two of the latter five patients had an initially negative bone-marrow examination and then had a repeat bone-marrow biopsy that demonstrated tumor involvement. Four of the five patients with disseminated disease had pelvic bone involvement, and four of these patients had multiple-bone involvement. Of the seven patients with multiple-bone involvement, four patients had a positive bone-marrow examination, whereas only one of the eight patients with solitary-bone involvement had evidence of disseminated disease.

**Radiographic Imaging of the Primary Site**

All fifteen patients had a plain radiographic examination. Forty-six lesions were identified. Plain radiographs were available for twenty-three individual lesions, including all of the primary lesions as well as some of the secondary lesions. Plain radiographs of the remaining lesions were not available because these sites were studied only with other radiographic modalities. Two patients had radiographic findings that were interpreted as normal at the time of initial presentation. On plain radiographs, the majority of lesions demonstrated radiolucency (sixteen of twenty-three lesions) and/or sclerosis (ten of twenty-three lesions). Nine lesions demonstrated both radiolucency and sclerosis, seven lesions demonstrated only radiolucency, one lesion demonstrated only sclerosis, and six lesions demonstrated neither sclerosis nor radiolucency. The radiographs of these twenty-three lesions demonstrated evidence of pathologic fracture in association with four lesions, periosteal response in association with seven lesions, and soft-tissue mass association with three lesions.

Additional imaging studies of the primary lesion were variably obtained. Computed tomography of the primary lesion was performed for eight patients. Five of these patients had lesions that appeared radiolucent, permeative, or destructive, and two of these lesions also had evidence of sclerosis. Two lesions demonstrated abnormal marrow characteristics, and one lesion was characterized only by sclerosis. Three stud-
ies demonstrated evidence of a soft-tissue mass. Both patients who had negative plain radiographs had a positive computed tomographic scan. Magnetic resonance imaging was performed for six patients. Of these, four patients had had previous computed tomography whereas two had had only magnetic resonance imaging to further evaluate the lesion. Lesions were characterized by low signal intensity on T1-weighted images and high signal intensity on T2-weighted images (Figs. 2-A through 2-D). Magnetic resonance imaging demonstrated a soft-tissue mass in two patients in whom computed tomography had failed to demonstrate soft-tissue involvement. Overall, six of the fifteen patients had a soft-tissue mass on radiographic studies, with three soft-tissue masses demonstrated only with additional studies.

Histologic and Immunologic Features
The histologic subtypes of the individual patients are listed in the Appendix. According to the revised World Health Organization classifications, the majority of cases were classified as diffuse large-cell lymphoma (nine patients) or lymphoblastic lymphoma (four patients). One patient had Burkitt lymphoma. In one patient, the histologic diagnosis was unclear and the lesion was described as a CD30+ lymphoma. Although demonstrating some features consistent with Hodgkin’s disease, the specimen had characteristics of anaplastic large-cell lymphoma. Because of this finding, the patient was not excluded from the results. The immunophenotype (i.e., determination of the malignant cell of origin), available for thirteen patients, was classified as B cell in nine patients and pre-B cell in four.

Therapy
Two patients had a surgical procedure other than a biopsy. One patient had an emergent thoracic laminectomy because of spinal cord compression, and the other a multiple-rib resection with removal of associated soft tissues at the time of diagnosis prior to the initiation of chemotherapy. All fifteen patients received chemotherapy. Nine patients received chemotherapy alone, whereas six received a combination of chemotherapy and radiation therapy. The patients who received radiation therapy were diagnosed earlier in our study, when radiation was used more frequently as an adjunct to chemotherapy for lymphomas.

Thirteen patients had documented toxicity to the treatment and, as a result of this toxicity, seven patients required a change or discontinuance of the treatment regimen. Toxicity included neurologic abnormalities such as ptosis, tingling of
the peripheral extremities, obstipation, vocal cord paralysis, or foot drop (in patients managed with vincristine); hemorrhagic cystitis (in patients managed with cyclophosphamide); renal toxicity with a decrease in glomerular filtration rate; allergy; cholestatic jaundice (in patients managed with 6-mercaptopurine and methotrexate); and pancreatitis (in patients managed with L-asparaginase). There were no reported complications in the patients receiving radiation therapy.

**Long-Term Follow-up**

The outcomes for the fifteen patients for whom follow-up was available are presented in the Appendix. The mean duration of follow-up for the ten patients who survived was 13.6 years (median, 17.2 years; range, two to twenty-three years). All of these patients were free of disease at the time of the latest follow-up and were without any substantial long-term sequelae. Five patients had recurrent/metastatic disease, and the mean time to recurrence for these patients was 1.4 years (range, 0.3 to two years). The sites of recurrence included bone marrow in two patients and bone, mediastinum, and testes in one each. Four of the five patients who had a relapse died, and only the patient with a relapse in the testes survived. Overall, five patients in the current study died, with one patient each dying from disease progression with metastatic disease to the mediastinum, diffuse metastatic disease to liver and bone with sepsis, diffuse metastatic disease with bilateral pulmonary involvement, chemotherapy-induced acute myelogenous leukemia and sepsis, and reasons unrelated to the primary diagnosis. One patient who had development of recurrent disease was successfully treated and survived, whereas one patient in whom the disease was cured died of other reasons. The mean time from diagnosis to death for these five patients was 2.1 years (median, 1.9 years; range, 0.4 to 4.9 years).

Two of ten male patients and three of five female patients died. Four of the six patients nine years of age or less died, whereas one of the nine patients ten years of age or older died; the latter patient died from causes unrelated to the primary diagnosis. None of the eight patients with a delay in

### TABLE I Results of Univariate Analyses of Potential Prognostic Factors for Poor Survival in Current Study and Similar Case Series (including Patients from Current Study)

<table>
<thead>
<tr>
<th>Current Study (N = 15)</th>
<th>Similar Series* (N = 91)</th>
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<tr>
<td><strong>Prognostic factors for poor survival</strong></td>
<td>9 years of age or less (p &lt; 0.05)</td>
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<td></td>
<td>9 years of age or less (p &lt; 0.05)</td>
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<td>12 years of age or less (p &lt; 0.05)</td>
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<td></td>
<td>Multiple-bone involvement (p &lt; 0.05)</td>
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<td><strong>Trend for decreased survival</strong></td>
<td>Non-large-cell histology</td>
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<td>Positive bone-marrow examination</td>
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<td>Initial positive bone-marrow examination</td>
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<td></td>
<td>Elevated calcium</td>
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<td></td>
<td>6 years of age or less</td>
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<tr>
<td></td>
<td>Female gender</td>
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<tr>
<td><strong>No predictive value in terms of survival</strong></td>
<td>Type of treatment‡</td>
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<tr>
<td></td>
<td>Treatment toxicity requiring change in treatment</td>
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<td>Multiple bone involvement</td>
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<td>Type of bone involved§</td>
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<td>Elevated lactate dehydrogenase</td>
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<td>Radiographic evidence of soft-tissue extension</td>
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<td>Pathologic fracture</td>
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<td>Constitutional symptoms</td>
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<td>Tenderness on examination</td>
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<td>Swelling/mass on examination</td>
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*Including the fifteen patients from current study. †Significant differences in risk were observed when stage I was compared with stages II, III, and IV; when stages I and II were compared with stages III and IV; and when stages I, II, and III were compared with stage IV. ‡Chemotherapy plus radiation versus chemotherapy alone. §The analysis included spinal involvement, pelvic involvement, flat-bone involvement, long-bone involvement, and bone involvement other than long-bone involvement.
diagnosis of more than three months died, whereas all four patients who died of disease progression or a treatment-induced neoplasm had been diagnosed three months or less after the onset of symptoms.

Two of the nine patients with large-cell histology died, while three of the six patients with non-large-cell histology died. Three of the eight patients with solitary-bone involvement and two of the seven patients with multiple-bone disease died. Three of the four patients with radiographic evidence of a pathologic fracture died, whereas only three of the eleven patients without evidence of a pathologic fracture died. Two of three patients with elevated serum calcium died, whereas three of twelve patients without elevated calcium died of disease progression. Three of the nine patients who had been managed with chemotherapy alone died, whereas two of the six patients who had been managed with combined treatment died. Three of seven patients who had toxicity necessitating a change in treatment died, whereas two of eight patients who did not require a change in treatment secondary to treatment toxicity died.

**Univariate Analysis**

The association of various factors with the risk of death and relapse is presented in Tables I and II. The only factor with a negative prognostic value for survival in the analysis of the fifteen patients was an age of nine years or less (p < 0.05). Non-large-cell histology, positive bone-marrow examination, elevated serum calcium, an age of six years or less, an age of twelve years or less, and female gender were factors that had a trend toward decreased survival but were not significant risk factors. The type of treatment, the type of bone (i.e., long bones, flat bones, vertebral bones), multiple-bone involvement, radiographic evidence of a soft-tissue mass or pathologic fracture, and physical examination findings did not have any prognostic value in terms of survival.

**Summary Analysis**

The characteristics of patients from all existing similar case series of primary lymphoma of bone in children from the present study (fifteen patients) and the literature (107 patients) are reported in a table in the Appendix along with selected survivorship curves for specific factors as discussed below. Of these 122 patients, ninety-one had data that could be used for further analysis. These data were collected in order to compare our series with previously reported series. Of the ninety-one patients, forty-five were managed with chemotherapy alone, and forty-six were managed with a combination of chemotherapy and radiation. Forty-four patients had solitary-bone disease, and forty-seven had multiple-bone disease. The bones involved in these patients and in thirty-one additional patients from a study without specific treatment or follow-up data are summarized in Figure 3. According to a modified Murphy staging system, thirty-six patients were classified as having stage-I (IE) disease and nine were classified as having stage-II disease (yielding a total of forty-five patients who were classified as having localized disease), thirty-two patients were classified as having stage-III (diffuse) disease, and fourteen patients were classified as having stage-IV (disseminated) disease.

Twenty-seven of the ninety-one patients died. In this group, age (regardless of the cutoff) was a predictor of survival. Patients who were twelve years of age or less, nine years of age or less, and six years of age or less all had poor survival when compared with older patients (p < 0.05 for all three analyses). In addition, advanced stage, multiple-bone involvement, and non-large-cell histology were predictive of poor survival (p < 0.05). The type of bone involved, gender, and the type of treatment did not have prognostic value for survival.

Eighty-four of the ninety-one patients had a defined histologic subtype. Seventy-two of these eighty-four patients had either a large-cell or lymphoblastic subtype, and the remaining twelve had another histologic subtype. Among patients who were nine years of age or less, twenty-one of twenty-four patients had a lymphoblastic subtype whereas the other three had a large-cell subtype. In contrast, among patients who were ten years of age or older, thirty-four of forty-eight patients had a large-cell subtype and the other fourteen had the lymphoblastic subtype. The ratio of solitary to multiple-bone disease was similar across age-groups. Among patients who were nine years of age or less, seventeen patients had solitary disease and seven-
teen had multiple-bone disease. Among patients who were ten years of age or older, twenty-seven patients had solitary disease and thirty patients had multiple-bone disease. Among patients who were nine years of age or less, fifteen of thirty-four patients had localized (Murphy stage-I and II) disease whereas nineteen had disseminated or diffuse (Murphy stage-III and IV) disease. Among patients who were ten years of age and older, thirty of fifty-seven patients had localized disease whereas twenty-seven had disseminated or diffuse disease.

Discussion

Clinical Presentation

Primary lymphoma of bone in children is rare compared with other bone tumors. In a study of seven pediatric cases of primary lymphoma of bone that were treated over a twenty-five-year period, Howat et al. reported that eighty-eight cases of Ewing sarcoma were found over the same time-period. In the present study, primary lymphoma of bone was diagnosed in fifteen (4.9%) of 306 children who presented to this institution with non-Hodgkin's lymphoma over a thirty-three-year period. This finding is similar to other reports, in which 2% to 9% of cases of non-Hodgkin's lymphoma in children involve a bone as the primary site (see Appendix).

Primary lymphoma of bone affects children of all ages but most commonly is diagnosed in early adolescence. This was true in our study as well as in other similar series. Primary lymphoma of bone in children has a predominance in males.

Younger age was associated with an increased risk of death in our study and in the summary analysis. Any conclusion from such an analysis has limits, and it could be argued that the increased mortality in younger children is secondary to confounding factors. Although multiple-bone involvement was a predictor of poor survival, solitary disease was as prevalent as multiple-bone disease in this age-group. However, younger patients were more likely to present with non-large-cell histology and with disseminated disease, and both were found to be predictors of poor survival.

The femur, pelvis, and tibia are the bones that are most commonly affected by this disease. However, the type of bone involvement had no prognostic value in terms of survival or relapse. It appears that patients with primary lymphoma of bone are equally divided between those with solitary-bone involve-
ment and those with multiple-bone disease. Although it did not appear that patients with multiple-bone involvement had a poor prognosis in the current study, multiple-bone involvement was a significant predictor of poor survival in the summary study.

The orthopaedic surgeon is likely to be the first to see a child who has a primary lymphoma of bone because the clinical presentation often includes localized bone pain and occasionally includes a palpable mass. However, the clinical presentation is often nonspecific, and the clinical history may not be helpful for making an accurate diagnosis. While most patients in our series complained of pain and the physical examination often revealed localized swelling or tenderness, the examination revealed completely normal findings in three patients and there were no physical findings that had significant prognostic value. Occasionally, patients with primary lymphoma of bone may present with systemic symptoms such as weight loss, fever, anorexia, or malaise, which may indicate systemic spread.

Primary lymphoma of bone is a difficult diagnosis to make without a high level of suspicion. Therefore, the initial clinical impression is often different from the final diagnosis and there may be an extended period before the correct diagnosis is made. In a study of eleven patients by Furman et al., non-Hodgkin’s lymphoma was considered in only one patient. Patients may experience an extended period of symptoms before presenting to a physician. In the study by Furman et al., patients sought medical attention after having had symptoms for a mean of 4.5 months. Difficulty related to the histologic evaluation commonly delays an accurate diagnosis, and a second procedure may be needed if the first is nondiagnostic. This was true for three patients in our study, and, in a series by Coppes et al., nine of fourteen patients required a second procedure. Even if adequate pathologic material is obtained, the histologic diagnosis may be difficult to make, as exemplified by the inaccurate initial diagnosis made for five of our patients. Molecular methods may be used to confirm the diagnosis; in one of our patients, the diagnosis was based on molecular criteria alone. Another complicating factor in making an accurate diagnosis is that there is a gray and shifting line that separates non-Hodgkin’s lymphoma with marrow involvement from acute lymphoblastic leukemia with a bone lesion. The reason for the delay varies considerably among patients and is dependent on both patient and physician attitudes and actions. Separating these factors is nearly impossible and, although a delay in diagnosis is common, this delay does not appear to result in poor outcomes.

**Laboratory Abnormalities**

It has been reported that hypercalcemia is often associated with primary lymphoma of bone and that it may indicate a poor prognosis. In the study by Coppes et al., six of fourteen patients had hypercalcemia and five of them died. Although the mortality rate in the present study was higher among patients with elevated serum calcium than among patients with normal serum calcium, only three patients had hypercalcemia and this relationship was not found to be significant. Other laboratory abnormalities have not helped in determining the diagnosis or prognosis for children with primary lymphoma of bone.

**Staging**

Studies that have considered primary lymphoma of bone in children have differed with regard to the types of patients that they have included, and staging is ambiguous in patients with multifocal bone disease without bone-marrow involvement. Some studies have included patients with only localized disease, others have included patients with multiple-bone lesions but have excluded those with bone-marrow involvement, and others have included patients with a primary bone lesion with bone-marrow involvement. The inclusion criteria used in those studies are important because the reported prognosis depends on whether patients with disseminated disease are included, as such patients have worse outcomes.

With the technological advance of staging methods, it now seems acceptable to consider those with a primary bone lesion with bone-marrow involvement without other evidence of systemic spread to have disseminated primary lymphoma of bone. It becomes less clear, however, for patients who were staged in the past with use of inferior imaging methods. It is also difficult to determine the presence of disseminated disease when the bone-marrow biopsy site is at the site of disease. In four of the five patients with bone-marrow involvement in the present series, the ilium was a site of disease, and it is unclear whether the marrow involvement at this site truly represents disseminated disease.

**Imaging**

While several studies have concentrated on treatment and outcome, few reports have discussed the imaging of primary lymphoma of bone in children. Some investigators have claimed that imaging is most useful for documenting the extent of disease. Radiographic findings are generally nonspecific and can mimic the appearance of an aggressive lesion such as Ewing sarcoma or may appear to indicate a benign condition such as osteomyelitis or eosinophilic granuloma.

Plain radiographs often demonstrate osteolysis or osteosclerosis, but may fail to demonstrate a lesion at all. On computed tomography, the majority of lesions appear radiolucent, permeative, or destructive, with or without sclerosis. Computed tomography studies are more sensitive than plain radiographs; in the present study, all eight computed tomography studies were positive, including those for both patients for whom plain radiographs were negative. Also, in two patients, computed tomography demonstrated a soft-tissue mass that was not detected on plain radiographs. Magnetic resonance imaging of the primary lesion consistently demonstrated low signal intensity on T1-weighted images and a hyperintense appearance on T2-weighted images and was more sensitive than computed tomography for detecting a soft-tissue mass, indicating that magnetic resonance imaging should be routinely used in the orthopaedic workup of these lesions.
While it could be argued that radiographic characteristics such as a soft-tissue mass or pathologic fracture might indicate a more aggressive lesion, neither of these findings was a significant predictor of a poor prognosis in the present study.

**Histologic Analysis**

Histologic analysis is difficult, and the differential diagnosis of a malignant small round-cell infiltrate of bone in a child should include Ewing sarcoma, rhabdomyosarcoma, lymphoma, neuroblastoma, and primitive neuroectodermal tumor. Although Langerhans-cell histiocytosis and osteomyelitis may present similarly, cell-marker analysis will differentiate these entities. Diffuse large-cell or histiocytic lymphoma is the most common histologic subtype of primary lymphoma of bone, and lymphoblastic lymphoma is also frequently encountered. Proper histologic analysis is important as some studies have suggested that histologically driven treatment may result in better outcomes, and non-large-cell histology indicated a poor prognosis for survival in our summary analysis.

Studies of primary lymphoma of bone in children have included limited information on immunophenotype, although it has been suggested that this factor may have clinical importance. Hutchison et al. demonstrated that immunologic patterns are prognostic risk factors in children with non-Hodgkin lymphoma and that B-cell phenotype may be associated with a better prognosis. Although the current series offers the most extensive and complete immunophenotype analysis of primary lymphoma of bone in children to date, the prognostic significance of immunophenotype could not be assessed in the present study because all patients with large-cell lymphoma demonstrated a B cell type and all patients with lymphoblastic lymphoma demonstrated a precursor B subtype (Fig. 4).

**Treatment/Outcomes**

Non-Hodgkin’s lymphoma in children is a systemic disease; therefore, local therapy is not sufficient, even if the condition presents as localized disease. Treatment with combination chemotherapy regimens has improved the prognosis associated with non-Hodgkin’s lymphoma in this age-group, and the efficacy of chemotherapy for the treatment of primary lymphoma of bone in children is well established.

Serious therapy-related late effects are a problem in the treatment of children. Radiation therapy may lead to compromised musculoskeletal development and the appearance of secondary malignant disease. This risk is exemplified by the reported appearance of secondary bone tumors in two patients, five and 7.5 years after the use of radiation therapy for the treatment of primary lymphoma of bone. Both tumors occurred in the radiation field at the site of the original treatment. Similar findings were not reported in a study of thirty-one patients who were followed for six to twelve years after the remission of disease or in another series of thirty-one patients with long-term follow-up. In our experience, one patient had development of a chemotherapy-induced acute myelogenous leukemia.

Several series have demonstrated excellent survival in patients who have been managed either with chemotherapy alone or with chemotherapy combined with radiation therapy, suggesting that chemotherapy alone is likely adequate for this disease. In our series and in the summary analysis, patients who had been managed with chemotherapy alone had similar outcomes compared with those who had been managed with concurrent radiation therapy. Given the risk of growth disturbances, organ dysfunction, and secondary malignant disease after radiation therapy, it seems logical to avoid its use. It is important to realize that patients in the present study and in

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**Fig. 4**

A, Photomicrograph of a bone-marrow biopsy specimen, demonstrating diffuse large B-cell lymphoma. The large B-cell lymphoma cells are medium to large-sized cells with round to irregular nuclei, dispersed chromatin, indistinct to multiple nucleoli, and moderate cytoplasm. Among the tumor cells are small mature lymphocytes with more condensed chromatin that are consistent with reactive T cells. B, Photomicrograph of a bone-marrow biopsy specimen, demonstrating precursor B lymphoblastic lymphoma/leukemia. The lymphoblasts are small to medium in size with round to irregular nuclei, slightly condensed chromatin, indistinct nucleoli, and scant cytoplasm (hematoxylin and eosin, ×1000). Black bar = 10 µm.
similar studies were managed differently over time, which makes interpretation of the data difficult.

The mean duration of follow-up for the ten surviving patients in the present study was 13.6 years (range, two to twenty-three years). This represents a longer follow-up period than has been reported for any previous series. As increasing numbers of survivors of childhood cancer live into adulthood, the prevalence of long-term complications is expected to increase, and it is therefore important to document long-term follow-up.

The mortality rate that is reported depends on what types of patients are included. Studies that include patients with only localized disease demonstrate a better survival. In a study of thirty-one patients, the overall product-limit-estimated five-year event-free survival rate was 84%, with the event-free survival rate for seventeen patients with localized disease being 94% and the event-free survival rate for patients with more advanced disease being 70.7%. Overall, studies have demonstrated a survival rate of between 40% and 100% for children with primary lymphoma of bone with an event-free survival rate of 75% to 100% for those with localized disease and 25% to 71% for those with disseminated disease. In our summary analysis, patients with advanced-stage disease had a lower survival rate. The survival of patients in the present study is consistent with the relevant literature because although five of the fifteen patients died, the present study included patients with localized, diffuse, and disseminated disease.

Limitations

Studying primary lymphoma of bone in children is challenging because it is a rare disease and, in order to obtain a large case series, it is necessary to collect cases over several decades. In addition, the approaches to diagnosis, staging, and treatment vary over time. Advances in chemotherapy have substantially improved outcome in recent years, and including patients who were managed thirty years ago along with patients who were managed in the past five years may cloud conclusions about prognosis. Because of this variation, it could be postulated that patients who are managed with more modern therapeutic regimens are likely to have a better outcome; however, this is difficult to prove in a study of this size.

It should be noted that our univariate analysis of patients in this series had two limitations. First, the number of patients from our institution was small and may have failed to detect key trends. Second, although we tried to identify potential confounding factors, it was not possible to evaluate confounding factors in a univariate analysis involving a small number of patients. There are also inherent problems associated with combining data from the literature, and any conclusions about prognosis that are made on the basis of data obtained in this way are informational but certainly must be considered with great care.

It could be argued that the results of the present study are not much different from the natural history of this disease in adults. Although this may be true, pediatric patients have unique risks associated with treatment and disease that are not present for adults, and describing this population individually is important. In order for clinicians to better understand this entity, large series of patients with this condition who have been treated with current therapy and have had long-term follow-up are necessary.

Appendix

Kaplan-Meier curves as well as tables showing demographic and clinical features of the study patients and a summary of case series of primary lymphoma of bone in children as reported in the literature are available with the electronic versions of this article, on our web site at jbjs.org (go to the article citation and click on “Supplementary Material”) and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM).}

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