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Primary lymphoma of bone in the pediatric and young adult population ☆

Karen M. Chisholm MD, PhD [a,1], Robert S. Ohgami MD, PhD [b], Brent Tan MD, PhD [b], Robert P. Hasserjian MD [c], Olga K. Weinberg MD [a,d,*]

[a] *Department of Pathology, Boston Children's Hospital, Boston, MA 02115, USA*
[b] *Department of Pathology, Stanford University School of Medicine, Stanford, CA 94305, USA*
[c] *Department of Pathology, Massachusetts General Hospital, Boston, MA 02114, USA*
[d] *Department of Pathology, Brigham & Women's Hospital, Boston, MA 02115, USA*

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Summary Primary lymphoma of bone (PLB) accounts for 3% to 7% of primary neoplasms of bone and must be distinguished from more common bone tumors in the pediatric population such as osteosarcoma, Ewing sarcoma, and other small round blue cell tumors. In this study, pathology databases from 4 institutions were queried for PLB in individuals 1 to 21 years old. A total of 54 cases of PLB were identified, including 41 diffuse large B-cell lymphomas (DLBCL, 76%), 8 B-lymphoblastic lymphomas (BLL, 15%), 3 anaplastic large cell lymphomas (ALCL, 6%), and 2 low-grade follicular lymphomas (4%). The male/female ratio was 1.8:1 and median age was 16 years (range, 2-21). Patients with DLBCL were significantly older ($P < .001$), and patients with ALCL and BLL were significantly younger ($P = .050$ and $P = .008$, respectively) when compared with the other patients. Due to necrosis, crush artifact, and/or insufficient material, 30% of cases required multiple biopsies for diagnosis. The femur, tibia, pelvic bones, humerus, and vertebrae were most commonly involved. DLBCL patients had significantly more solitary bone involvement ($P = .001$), whereas BLL had significantly more polyostotic involvement ($P < .001$). Of the 37 patients with outcome data, all had no evidence of disease on last follow-up. This largest pediatric series of PLB identifies DLBCL as the most frequent subtype and documents rarer occurrences of BLL, ALCL, and follicular lymphomas. The differential diagnosis of bone neoplasms in pediatric patients, including those with necrosis, should include PLB.

1. Introduction

Primary non-Hodgkin lymphoma of the bone (PLB) was initially described in 1928 by Oberling [1], with the first case series later published as 17 cases of "primary reticulum-cell sarcoma of bone" from the National Tumor Registry in 1939 [2]. PLB is now a well-established entity, described in the *World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone* [3] as a malignant

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* Corresponding author at: Department of Pathology, Boston Children's Hospital, 300 Longwood Ave, Bader 126.2, Boston, MA 02115.
E-mail address: olga.weinberg@childrens.harvard.edu (O. K. Weinberg).
[1] Present address: Department of Laboratories, Seattle Children's Hospital, Seattle, WA, USA.

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lymphoid neoplasm producing at least 1 mass within bone, without involvement of supraregional lymph nodes or other extranodal sites. This definition was later interpreted by Messina et al [4] to represent (*a*) a single bony lesion with or without involvement of regional lymph nodes or (*b*) multiple bony lesions but without lymph node or visceral disease. The definition of PLB excludes lymphomas that have disseminated from lymph nodes or extranodal sites and represent secondary skeletal involvement. Overall, PLB accounts for approximately 3% to 7% of bone malignancies, 1% or less of all non-Hodgkin lymphomas, and approximately 5% of extranodal non-Hodgkin lymphomas [3,5-7]. On average, patients present in their mid-40s to early 50s (mean, 46.1 years; male/female ratio, 1.6:1) with localized pain sometimes associated with a soft tissue mass or swelling [8]. Although diffuse large B-cell lymphoma (DLBCL) accounts for the 70% to 80% of PLB, other lymphomas including follicular lymphoma (FL), marginal zone lymphoma, peripheral T-cell lymphoma, small lymphocytic lymphoma, Burkitt lymphoma, lymphoblastic lymphoma, and anaplastic large cell lymphoma (ALCL) have also been identified as PLB [3,9].

PLB accounts for a higher proportion of non-Hodgkin lymphomas in children, comprising 2% to 9% of cases [9-15]. In a series of 15 patients and review of 91 additional cases from the literature, Glotzbecker et al [9] identified childhood PLB to represent 3.3% of non-Hodgkin lymphoma cases, with a male/female ratio of 1.65:1 and a mean age of 11.3 years. The most common PLB subtype was DLBCL (50%), followed by lymphoblastic lymphoma (37%), and 13% other subtypes (not reported) [9].

The diagnosis of PLB is challenging as there are diverse clinical and radiologic presentations, and a wide spectrum of histologic features. In addition, biopsies are often small and may have suboptimal histology due to decalcification and crush artifact. This diagnosis must be distinguished from more common pediatric bone tumors such as osteosarcoma, Ewing sarcoma, and other small round blue cell tumors, which can resemble lymphoma clinically, radiographically, and even initially histologically. The goal of this present study is to characterize the pathologic and clinical features of PLB in a large cohort of pediatric patients.

2. Materials and methods

2.1. Case selection

With institutional review board approval, pathology databases across the 4 participating institutions were queried using the phrases "bone" and "lymphoma," with age range limited to individuals 21 years and younger. The databases were searched within the period of January 1975 through January 2015. Clinical records from the identified cases were researched to confirm a diagnosis of PLB. The clinical records were also reviewed to determine presenting symptoms, length of time of symptoms before diagnosis, radiologic appearance of the bone lesion(s), clinical differential diagnosis, number of biopsies required for diagnosis, all sites of lymphoma involvement, clinical stage, treatment modality, length of follow-up, and any recurrence of disease. Clinical staging was according to the Murphy staging [16]. Pathology reports and histology slides of initial and follow-up specimens, including staging iliac crest bone marrow biopsies, were reviewed for morphologic, flow cytometric, and immunohistochemical features of the lymphomas. The lymphomas were classified using 2008 WHO criteria [17]. Cases with a pathologic diagnosis of lymphoblastic lymphoma/leukemia lacking clinical records to determine if there was blood or bone marrow involvement defining acute lymphoblastic leukemia (circulating leukemia cells and/or >25% involvement of the bone marrow) were excluded from the study.

2.2. Immunohistochemical staining

Many of the cases diagnosed before 1997 were diagnosed only as malignant lymphoma by morphology; in these cases, immunohistochemical stains were performed to confirm the diagnosis and subtype of lymphoma. For B-cell lymphomas, these stains included CD20, CD10, TdT, BCL2, BCL6, and CD30. For each of these cases, 4 μm sections were cut from the formalin-fixed paraffin-embedded tissue block. Immunohistochemistry was performed using the anti-CD20 antibody (mouse clone L26) and anti-CD30 (mouse clone Ber-H2) from Ventana (Tucson, AZ), both at predilute ready-to-use dilutions. Automated staining was performed using the Ventana Benchmark XT with the Cell Conditioning solution Tris-based buffer. Stains for BCL2 (mouse clone bcl-2/100/D5), BCL6 (mouse clone LN22), and CD10 (mouse clone 56C6), all manufactured by Leica (Buffalo Grove, IL), were stained using the Leica Bond III autostainer at ready-to-use dilutions, with an EDTA (pH 9.0)–based retrieval system, and the Bond Polymer Refine Detection system. Immunohistochemistry for TdT (Leica's mouse clone SEN28) was stained also using the Leica Bond III autostainer at a ready-to-use dilution, but with a citrate buffer (pH 6.0) retrieval system with the Bond Polymer Refine Detection system. ALCL was similarly confirmed by performing CD30, ALK, CD43, CD4, and granzyme immunohistochemical stains using the same Ventana and Leica machines. All stains were visualized using diaminobenzidine as the chromogen. Additional immunostains were not performed in cases in which sufficient immunohistochemical staining had already been performed to confirm the diagnosis as part of the original workup.

2.3. Statistics

Students *t* test was used to analyze the data.