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CASE REPORT

Pediatric primary lymphoma of bone in epiphysis case report

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Abstract
Primary lymphoma of the bone (PLB) is a rare entity, with a majority of pediatric cases presenting in the metaphysis of long bones. There have been only seven reported cases to date of pediatric lymphoma of the bone arising from the epiphysis, of which only two have been described in the proximal tibia. We report a pediatric case of PLB in the tibial epiphysis which presented initially with knee pain. Imaging was performed with X-ray, MRI, CT, and PET-CT with bone biopsies revealing diffuse large B-cell lymphoma. This patient also showed a second, synchronous lesion in the left iliac bone, which was also biopsy proven to diffuse large B-cell lymphoma. Lymphoma in the epiphysis for children is rare and often confused with infectious etiologies or other types of tumors. Misdiagnosis may result in inappropriate treatment and possible progression of the disease, thus making early identification important to initiate therapy.

Keywords Primary lymphoma of bone · Epiphyseal lesions · Pediatric osseous tumors

Introduction

Primary lymphoma of the bones (PLB) was first described in adults by Oberling et al in 1928 [1] and is a rare malignancy, accounting for only about 3–7% of all primary bone malignancies and less than 1% of non-Hodgkin lymphoma [2]. In the pediatric population, PLB accounts for a slightly higher proportion of non-Hodgkin lymphoma, reflecting 2–9% of cases [3]. PLB was previously defined by WHO 2013 classification as a soft tissue or bone tumor arising from lymphoid cells with at least one osseous lesion and no evidence of supraregional lymph node or extranodal involvement [4]. There is a male/female ratio of approximately 1.5–2:1 and mean age of presentation in the early second decade of life [5, 6]. Approximately 100 pediatric PLB cases have been reported, the majority of which involve metaphysis [5]. However, there have only been seven reported cases of lesions involving the epiphysis with or without metaphyseal extension, dating back to 1992 [6–11]. Only two of these cases involved the tibia, making this the third such case described in the literature. Presented here is a pediatric case of primary epiphyseal PLB and first reported synchronous PLB in two sites. Understanding PLB as a potential diagnosis for epiphyseal lesions in pediatrics can help clinicians better treat and manage these cases without delaying appropriate care.

Case report

A 14-year-old male presented with a 5-month history of pain and swelling in the right knee which initially began after a basketball injury. Initial urgent care X-ray was read as negative and the patient was discharged but continued to have intermittent pain and swelling. A few weeks later, the patient presented to an outside hospital with an exam notable for mild right knee swelling and warmth but no tenderness, redness, or fluctuation. The patient denied fever, chills, weight loss, night sweats, or other constitutional symptoms. Blood

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work revealed an elevated CRP 50.9 mg/dL, ESR 92 mm/h, and microcytic anemia hemoglobin 11.7 g/dL / hematocrit 36.4% and MCV 66.2 fL with RDW 16.3%. Given concern for possible osteomyelitis an MRI was performed at the outside hospital. A bone biopsy was also performed and sent for culture prior to initiation of antibiotics, as was the clinical practice at the outside institution, and subsequently, empiric antibiotics were begun.

Anterior-posterior, lateral, and sunrise radiographic views of the right knee were essentially normal; a subtle lucency in the lateral tibial plateau may possibly be seen on a retrospective review (Fig. 1a–c). MRI of the right knee revealed a T1 hypointense, T2 hyperintense lesion centered in the proximal tibial epiphysis with heterogeneous enhancement, with a small focus extending across the physis into the metaphysis (Fig. 2a–g). This lesion was initially read as osteomyelitis

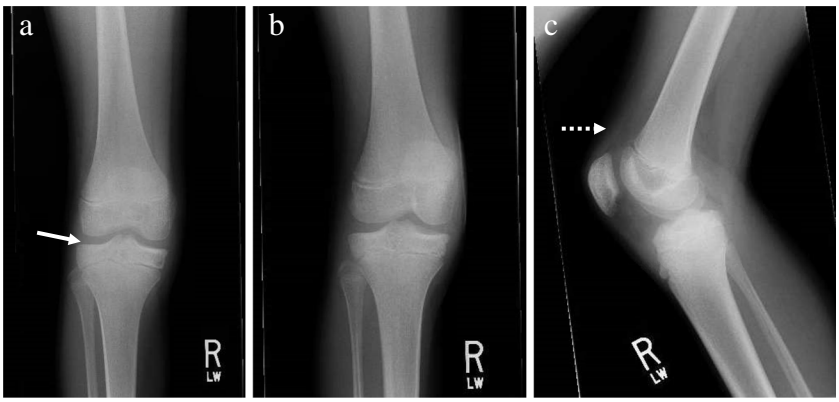

Fig. 1 Initial knee radiograph of a 14-year-old boy with chronic right knee pain. Anteroposterior (**a**), oblique (**b**), and lateral (**c**) views of the right knee demonstrate subtle, ill-defined lucency and permeative changes in the mid and lateral tibial epiphysis (solid arrow). No periosteal reaction is seen. A small joint effusion is present (dotted arrow)

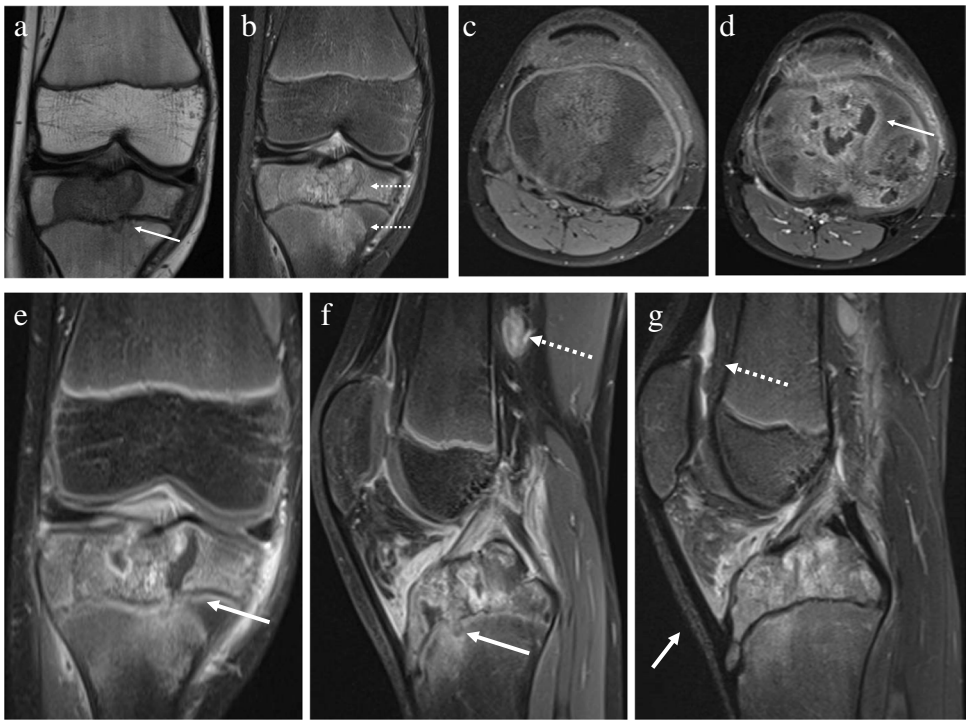

Fig. 2 MRI of the right knee for a 14-year-old boy presenting with knee pain for suspected infection or mass. Coronal proton density image (**a**) showing T1 hypointense lesion centered in the tibial epiphysis with focal extension across the physis into the metaphysis (solid white arrow). Coronal short inversion time inversion recovery image (**b**) showing T2 hyperintense bone marrow edema in both the tibial epiphysis and metaphysis (dotted white arrow). Pre-contrast axial T1 (**c**) and post-contrast axial T1 (**d**) images of the tibial epiphysis showing heterogeneous rim-enhancing lesions with central hypoattenuation (solid white arrow). Post-contrast coronal (**e**) and post-contrast sagittal images (**f**) redemonstrating heterogenous enhancement with the focal extension of the lesion into the metaphysis (solid white arrow). Partially visualized enlarged popliteal lymph node (dotted white arrow). (**g**) Sagittal STIR image shows a small joint effusion (dotted white arrow) and soft tissue edema (solid white arrow)

and less likely a primary bone tumor. A CT chest abdomen pelvis, which was subsequently performed after bone biopsy results, showed additional mixed lytic and sclerotic lesion in the left iliac bone with soft tissue extension into the adjacent left iliacus muscles (Fig. 3a–c). This lesion was presumed to be an additional site of disease and reflected either a metastasis, the primary lesion, or a synchronous PLB.

CT-guided biopsy of the right proximal tibia showed a diffuse infiltrate of lymphoid cells with irregular nuclei. Immunohistochemistry demonstrated CD20+, CD10+, and BCL6+, and MUM1- cells, diagnosis consistent with B-cell lymphoproliferative disorder with focal necrosis (the lesional tissue was not sufficient for definitive diagnosis). CT-guided biopsy of the left iliac bone lesion showed diffuse proliferation of large atypical lymphoid cells with irregular nuclear contour and prominent nucleoli. Immunohistochemical stains showed CD20+, PAX5+, and mild CD10+ consistent with diffuse large B-cell lymphoma. The biopsies of the right proximal tibia and the left iliac bone were similar enough in pathology to reflect the same entity or disease process.

PET-CT demonstrated abnormal FDG uptake in the proximal right tibia (SUV 11.5), left iliac crest (SUV 15.8), and mildly enlarged hypermetabolic locoregional nodes including right external iliac and right popliteal, which were read as possibly reactive versus lymphomatous involvement (Fig. 4a–d). The patient was considered to have stage III disease. Patient was started on systemic therapy per a Children's Oncology Group protocol, ANHL1131 (group B) with combination chemotherapy using cyclophosphamide, vincristine, prednisolone, doxorubicin, cytarabine, methotrexate and rituximab with intrathecal chemotherapy administration. The patient has completed all planned therapy with follow-up FDG PET/CT at 6 months showing no evidence of residual or new areas of disease (Fig. 5a–c).

Discussion

PLB is a rare entity in both the pediatric and adult population and comprises approximately 2-9% of non-Hodgkin's lymphoma cases. Cases generally involve the metaphysis or diaphysis of long bones, with the most common locations including the femur (50%), upper extremity (20%), and other locations such as flat bones (30%) [12]. Seven cases of PLB arising from the epiphysis have previously been described in literature (Table 1, 6–11). Four of seven involved the distal femur, two in the proximal tibia, and one in the proximal humerus. This is the third reported case to involve the tibial epiphysis. Six cases were in boys, with an average age of 9.7 years old. Almost all cases presented with localized pain, often with no history of trauma. Patients rarely displayed B-symptoms of fevers, night sweats, and weight loss and laboratory tests were usually positive for elevated inflammatory markers.

Initial radiographic imaging is often occult, or possibly present in retrospect as with some of the previously reported cases. Small joint effusions may also be detected due to the surrounding edema and inflammation. MRI often demonstrates a T1 hypointense and T2 hyperintense lesions with enhancement and with or without extension into the soft tissues or metaphysis. PET/CT has positive FDG uptake and is typically used for both initial staging and also response to chemotherapy to detect residual uptake. Repeat PET/CT is recommended 6-8 weeks after chemotherapy or 12 weeks after radiation therapy to detect response rates [13, 14].

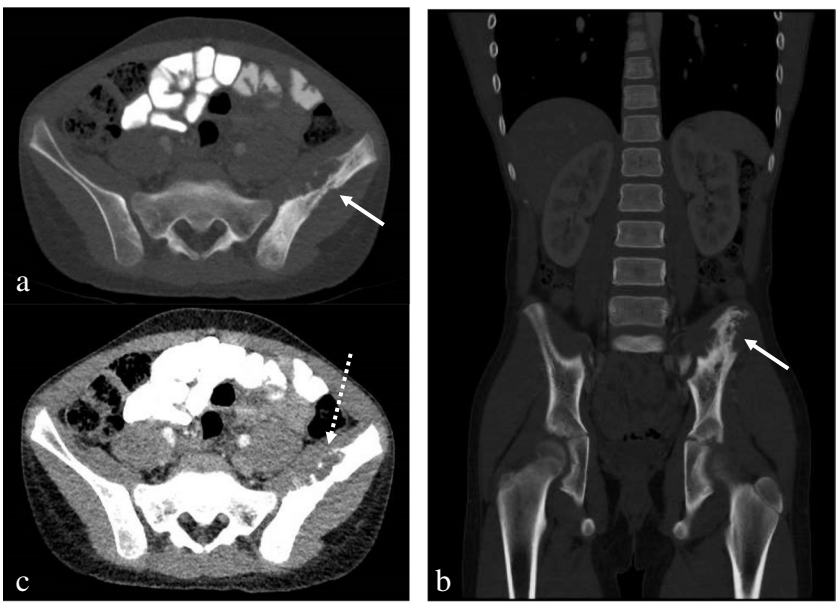

Fig. 3 Staging CT abdomen and pelvis for a 14-year-old boy after biopsy-proven primary lymphoma of the bone in the right proximal tibia. Axial CT image in the bone window (**a**) and coronal CT image in bone window (**b**) showing a permeative, mixed lytic and sclerotic lesion in the left iliac wing (solid white arrow). There is a thick periosteal reaction and cortical remodeling. Axial CT image in soft tissue window (**c**) showing extraosseous extension into the adjacent soft tissue (dotted white arrow)

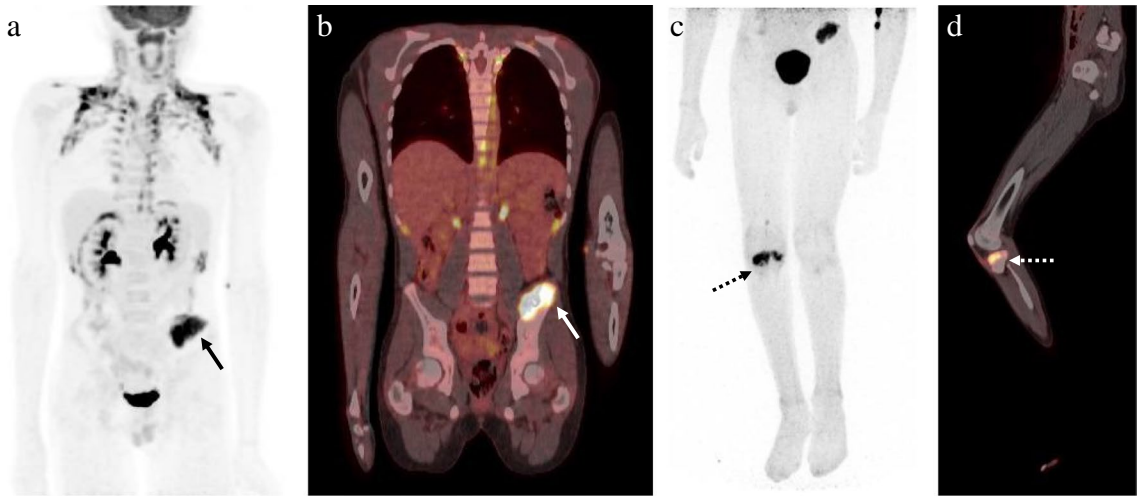

Fig. 4 Staging FDG PET/CT for a 14-year-old boy with newly diagnosed primary lymphoma of bone in the right proximal tibial epiphysis. Coronal MIP (**a**) and coronal CT fused (**b**) images showing FDG avidity in the left iliac wing (solid black and white arrows, respectively), corresponding to the indeterminate mixed lytic and sclerotic lesion seen on prior CT abdomen pelvis, possible metastasis or synchronous primary osseous neoplasm. Coronal MIP (**c**) and sagittal CT fused (**d**) of the right lower extremity show FDG avidity in the right proximal tibia (dotted black and white arrows, respectively) of biopsy-proven primary lymphoma of bone at the initial site of pain

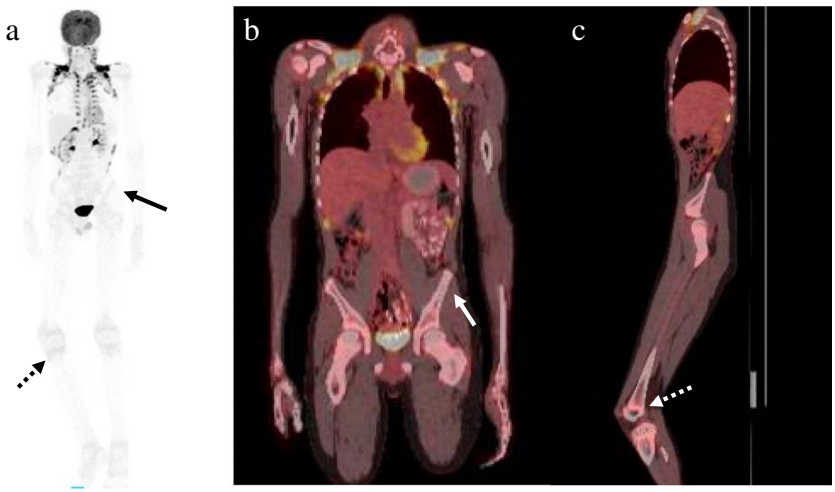

Fig. 5 Follow up post treatment 6-month FDG PET/CT for a 14-year-old boy with primary lymphoma of bone in the right proximal tibial epiphysis and left iliac wing. Coronal MIP (**a**), coronal CT fused (**b**), and sagittal CT fused (**c**) showing no suspicious osseous FDG uptake in treated right tibial (dotted black and white arrows) or left iliac (solid black and white arrows) tumors. No new FDG avid foci of concern

However, due to the possible mild background FDG uptake despite remission, bone scans have also been used as a supplementary tool for surveillance.

Pathology for prior epiphyseal PLB cases showed an even mix of diffuse large B-cell lymphoma (DLBCL) with nonspecific small round blue cells, with one case involving anaplastic large B-cell lymphoma. Literature has shown that DLBCL comprises about 70–80% of all cases of PLB and other types including follicular, marginal zone, peripheral T cell, anaplastic large cell lymphoma, Burkitt, and lymphoblastic comprise the remainder of cases [5, 15]. The histological appearance of pediatric DLBCL may be different than adult subtypes and generally do not have typical appearances of multilobulated nucleoli or centroblastic morphology [14]. Furthermore, the presence of CD10- cells does not always indicate a poor prognosis, as in the case of adult subtypes [14].

Primary ephiphyseal bone lesions are uncommon, with a differential that includes infection, inflammation, and neoplasm. Solitary epiphyseal lesions in the pediatric population are rare and the largest study to date from the Children's Hospital of Philadelphia showed that of 49 cases of epiphyseal lesions in pediatric patients, 92% were benign; the vast majority were chondroblastoma, followed by osteomyelitis [16]. Other less common lesions included aneurysmal bone cyst, enchondroma, and non-langerhans cell histiocytosis. Of this cohort, the majority were chondroblastoma followed by osteomyelitis. Only three cases (6%) were reported as

Table 1 Summary of previous case reports of epiphyseal location for primary lymphoma of bone in the pediatric population spanning from 1992 to 2018

Case	Age	Gender	Location	Clinical	Path	Treatment	Source
1	16	M	L proximal tibial epiphysis medial spine	Trauma 4 yrs prior, intermittent pain	DLBCL	No distant metastases, chemo; in remission	1992, Giudici [6]
2	10	M	L distal tibial epiphysis extend to metaphysis	6 weeks pain after fall	Small round cell blue tumor	No treatment reported	1992, Beatty [7]
3	8	M	Right upper extremity pain, thought elbow then saw humeral epiphysis	3 months atraumatic right upper extremity pain	Anaplastic large B-cell lymphoma	Currently on chemo	2006, Mounasamy [8]
4	15	F	L distal femoral lateral epiphysis and metaphysis	1 month atraumatic knee pain	DLBCL	No distant metastases; Chemo, in remission	2011, Garrett [9]
5	16	M	L distal femoral epiphysis extend to metaphysis	2 months atraumatic knee pain	Small round cell blue tumor	No distant metastases; Chemo, in remission	2015, Fox [10]
6	10	M	R distal femoral medial epiphysis extend adjacent soft tissue	4 months atraumatic knee pain	DLBCL	PET + LN pop, external iliac, abdomen; Chemo in remission	2015, Fox [10]
7	13	M	L distal femoral medial epiphysis no involvement of physis	6 months atraumatic knee pain	Small round cell blue tumor	No distant metastases; Chemo; in remission	2018, Kenan [11]

malignant, two of which were lymphoma (4%) and one chondrosarcoma. Lymphoma cases were reported as having more permeative or ill-defined margins with either lytic or sclerotic appearance; there was a significant overlap with features found in osteomyelitis [16].

Initially, PLB was treated with radiation therapy alone; however, recurrence rates were high and newer developments in combination chemotherapy regimens for lymphoma have become more widespread [17, 18]. The prognosis is favorable overall for PLB although data are limited due to the low number of cases. When the disease is localized, 5-year overall survival rates are reported around 70–90% and disease-free survival of 60–80% [5, 11, 12]. Age is an important prognostic factor where pediatric cases have overall survival rates of 80–90% compared to 62% in adults over age 60 [5]. Adjuvant chemoradiation therapy has been shown to improve overall survival and remission rates in adults with rates of 91% in combined therapy vs 68% with chemotherapy alone [19, 20]. Surgery is rare and usually only reserved for palliative care or pathologic fractures.

Primary epiphyseal lymphoma of the bone in children is a rare entity that has only been reported seven times prior dating back to 1992. Epiphyseal lesions in children are a relatively uncommon entity with the majority of cases being benign chondroblastoma or osteomyelitis. However, with the possibility of PLB as a differential diagnosis consideration, early detection is essential for initiating chemotherapy since the disease may have rapid progression if left untreated. With standard chemotherapy regimens, PLB has a good prognosis especially in the younger pediatric population compared to adult counterparts. Imaging features of PLB may be similar to those seen in osteomyelitis thus tissue sample is often relied upon for definitive diagnosis. Overall, though only a handful of cases have been reported to date for epiphyseal PLB in pediatric patients, it is an important differential to consider in reporting to avoid misdiagnosis, mistreatment, and delay of appropriate care.

Declarations

Consent Consent for the case report was obtained from the legal guardian of the patient verbally and documented in the clinical chart.

Conflict of interest The authors declare no competing interests.

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