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Pathological Case of the Month

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A 10-YEAR-OLD Hispanic boy fell from a swing, had medial joint pain of the lower left extremity, and was unable to fully extend the knee. Plain radiography of the left lower extremity showed no evidence of fracture or dislocation. Arthroscopy revealed an old anterior cruciate ligament tear and exuberant synovium; biopsy findings showed fibrosis. Persistent inability to fully extend the knee and proximal tibial tenderness prompted repeated radiographic evaluation. Anterior, posterior, and lateral plain radiographs of the left tibia (**Figure 1**) revealed an ill-defined lytic lesion in the proximal tibial epiphysis. Soft tissue swelling was appreciated at the joint space on lateral view. On a T1-weighted magnetic resonance image, the lesion was crossing the growth plate and extended into the metaphysis. It was centrally located but extended laterally and medially to the epiphyseal and metaphyseal margins (**Figure 2**). The patient underwent left tibial biopsy (**Figure 3**).

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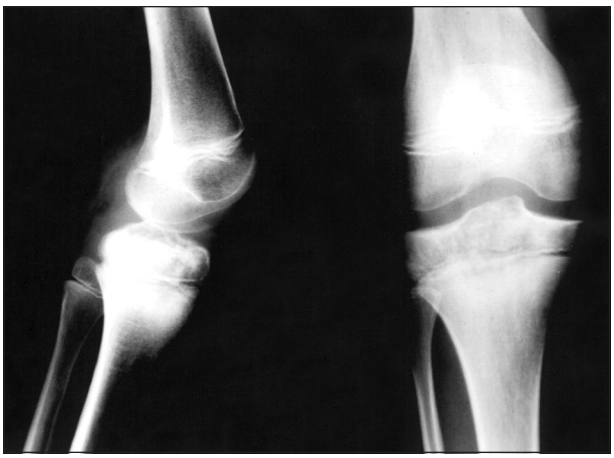

Figure 1.

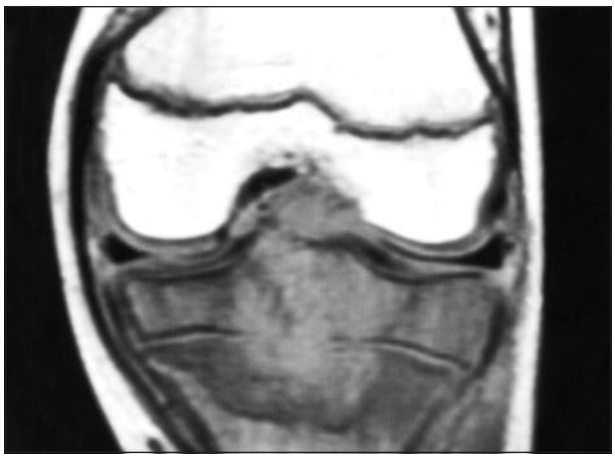

Figure 2.

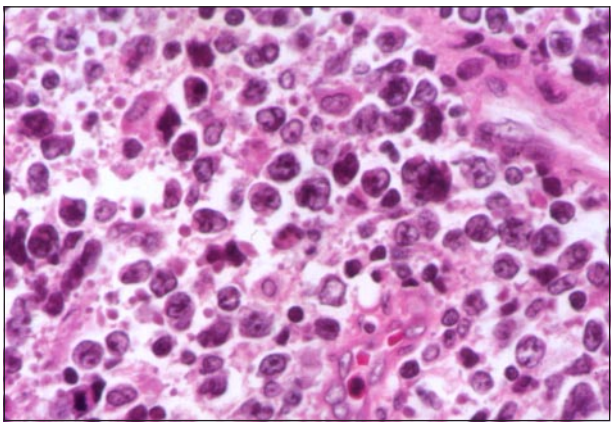

Figure 3.

Diagnosis and Discussion

Primary Bone Lymphoma: Diffuse Large B-cell Type

Figure 1. *Radiographic examination shows a destructive lesion involving proximal left tibial epiphysis.*

Figure 2. *A T1-weighted magnetic resonance image reveals the lesion in the proximal tibial epiphysis crossing the growth plate and extending into the metaphysis.*

Figure 3. *Results of left tibial biopsy show substantial crush artefact and a blue cell tumor characterized by large, sometimes polylobate, cells with irregular nuclei and scant cytoplasm.*

Pathological examination of the left tibial biopsy revealed morphologic appearance of a blue cell tumor, and led to the following special immunohistochemical studies:

Immunohistochemistry (Paraffin)		Immunohistochemistry (Frozen)	
CD20/L26	Positive	CD20/L26	Positive (weak)
CD45RA/4KB5	Positive	CD37/6A4	Positive
CD43/L60	Positive (weak)	μ	Positive
CD30/BerH$_2$	Negative	κ	Equivocal
p30/32^{MIC2}*	Positive	λ	Negative
		CD5/L1	Negative
		CD8/L2	Negative
		CD4/L3	Negative
		Ki-67	Positive (>95%)

*12E7 or HBA71

Immunohistochemical analysis provided support for a B-cell phenotype. The high fraction of malignant cells expressing proliferation marker Ki-67 was consistent with a high-grade lymphoma.

The diagnosis of diffuse large B-cell lymphoma (Revised European-American Lymphoma classification), or malignant lymphoma, intermediate grade, diffuse, large cell type (working formulation), was rendered. The patient was staged as stage IE: lymphoma isolated to a single osseous site. This is a B-lineage large cell lymphoma often characterized by large multilobated or cleaved cells.[1] Treatment included 3 cycles of induction chemotherapy (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone) followed by 6 months of maintenance therapy without radiation therapy. The patient remains in clinical remission with a full range of motion and 5/5 strength in the left lower extremity 7 years following completion of treatment. Plain radiographs reveal a stable postsurgical sclerotic lesion with closure of physis; magnetic resonance imaging reveals fatty marrow infiltration at the site of the original lesion.

This case highlights the important differential diagnosis of primary lymphoma of bone when presented with a blue cell tumor from a destructive lesion in a long bone. Initial diagnoses are incorrect in a significant proportion of cases; the mean time to correct diagnosis is 8 months in one large registry.[2] The importance of a positive Ewing sarcoma cell surface antigen p30/32^{MIC2} must be interpreted with caution. Evidence of p30/32^{MIC2} expression in some normal lymph node tissues[3] and a portion of non-Hodgkin lymphoma cases has been described.[4] Immunohistochemical findings of p30/32^{MIC2} antigen expression (also known as 12E7, or HBA-71) can lead to an erroneous diagnosis of Ewing sarcoma or primitive neuroectodermal tumor if additional immunohistochemical markers or cytogenetic and molecular genetic techniques are not also performed. The utility of immunohistochemical markers (CD45 and CD20) in the differential diagnosis of this primary bone malignancy, particularly in the pediatric setting, is highlighted by this case.

This case is representative of the uncommon stage IE lymphoma. In the pediatric setting, approximately 2.8% of patients with non-Hodgkin lymphoma present with a primary bone lymphoma according to the St Jude's experience.[5] All of these patients had high-grade lymphomas.[5] Patient age range for primary bone lymphoma is wide, and includes the pediatric age group. The most common clinical presentation for primary lymphoma of bone is pain, followed by a lump, or both pain and a lump, followed by fracture.[2] Presentation in a long tubular bone with variable radiographic manifestations, diffuse large cell histopathologic findings, associated fibrosis, B-cell origin, and generally favorable clinical outcome are all characteristic features of this entity. Magnetic resonance imaging is the method of choice for serial examinations of the lesions of primary bone lymphoma to assess therapeutic response.[6] Production of tumor cell tunnels through the cortex may be attributable to cytokine production by malignant cells, as evidenced by positive tumor cell immunoreactivity reported for interleukin-1-β, interleukin-6, and tumor necrosis factor α.[7]

Optimal treatment for stage IE primary non-Hodgkin lymphoma has not been determined. Retrospective analyses of various treatments for these patients have failed to conclusively demonstrate superior outcomes associated with a particular treatment regimen, such as radiation therapy in addition to chemotherapy vs chemotherapy or radiation therapy alone.[8,9] Consensus regarding the best treatment option awaits a prospective, randomized controlled trial.

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