Primary Lymphoma of Bone

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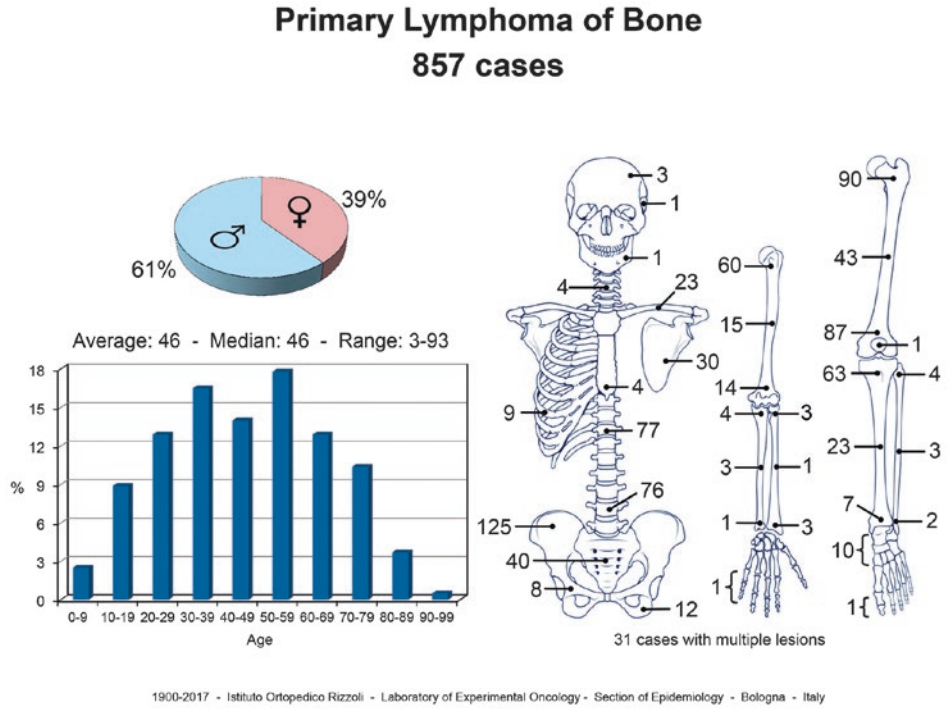
Definition: Intramedullary malignant lymphoma without lymph node involvement or other extranodal site.

Epidemiology: Primary bone lymphomas (PBL) are rare, representing 7% of all malignant bone tumors and 5% of all extranodal lymphomas. Secondary involvement of bone following primary node lymphomas is the more frequent situation. Males outnumber females. Typically the tumor affects adults with a mean age at diagnosis of 45 years.



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Localization: Most cases of PBL involve the axial skeleton including the pelvis and vertebrae. Other frequently affected sites are the long bones such as humerus and femur; lesions are usually located in the meta-diaphyseal region of bone. Multifocal bone lesions may be observed often involving multiple bones.

Clinical: Clinical presentation is variable and dependent on the localization of the disease. It may include pain, swelling, pathological fracture, and neurological deficits in case of vertebral involvement. Symptoms are mild and of long duration. Systemic symptoms referred to as "B-symptoms" (fever, night sweats, and weight loss) may also be present.

Imaging: On X-ray, small diffuse ill-defined lytic lesions featuring a permeative pattern are the most frequent appearance of PBL. Often a moth-eaten radiographic pattern is also observed in PBL. The cortex may be broken or destroyed with extension in the surrounding soft tissue, mimicking a bone sarcoma. Sometimes, the cortex can be thickened mimicking osteomyelitis. Usually, a periosteal reaction is absent but in rare cases a spicular or lamellar reaction may be observed mimicking radiologic features of osteosarcoma and Ewing sarcoma. At times, PBL is represented by an eccentric aggressive lytic lesion mimicking metastatic carcinoma. More rarely, non-Hodgkin lymphoma can have a sclerotic appearance on X-ray, a feature that is more commonly encountered in Hodgkin lymphoma. Pathological fractures are a common finding in PBL. CT scan shows the typical permeative or moth-eaten radiographic features of PBL. The mottled appearance on CT scan due to reactive hyperostosis is very useful to evaluate the relationship with the neurovascular bundles, the involvement of the joint and for the staging of the disease. MRI is not as useful in PBL affecting long bones as for PBL involving the spine, where MRI imaging can highlight possible spinal cord compression. Finally, bone scans may be useful to better define the lesions.

Histopathology: Diffuse large B-cell lymphoma (DLBCL) is by far the most common histotype of newly diagnosed PBL. The remaining minority of PBL includes other histotypes such as follicular B-cell lymphoma, marginal B-cell lymphoma, Hodgkin lymphoma, and anaplastic large T-cell lymphoma. On histology, PBL shows the same morphologic features encountered in nodal lymphomas. In addition, non-neoplastic inflammatory cells are frequently spread in and around the tumor, possibly obscuring the malignant cell population. Most PBLs are composed of sheets of neoplastic cells with a striking permeative growth pattern infiltrating in between bone trabeculae and medullary fat. The most common histotype, DLBCL, shows a diffuse proliferation of medium to large lymphoid cells that rarely have a pleomorphic appearance, with prominent fibrosis and presence of reactive osteoid. Mitoses are usually frequent and sometimes atypical. Additionally, DLBCL can be subdivided immunohistochemically in germinal center B-cell type and non-germinal center using BCL2, BCL6, CD10, and MUM1 (see table "immunohistochemical panel"). Anaplastic large T-cell lymphoma arising in bone is extremely rare, but the most common among T-cell lymphomas. Classical Hodgkin lymphoma primarily arising in bone is also extremely rare. Reticulin fibers surround small groups of cells forming thick fibrous bands. Immunostains for B- and T-cell markers and common leukocyte antigens can aid in the classification of PBL as well as in differential diagnosis. Additionally, useful tools to rule out double-hit large B-cell lymphoma include molecular analysis to investigate *BCL2*, *BCL6,* and *MYC* gene status.

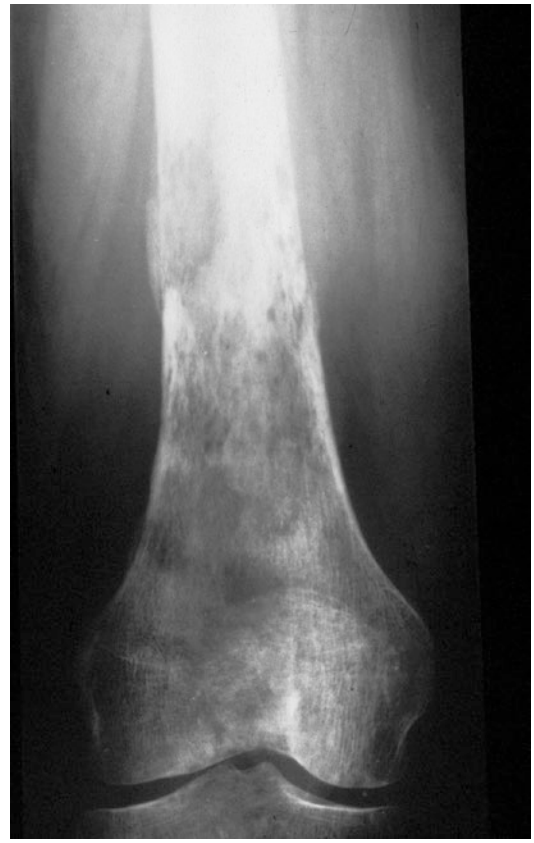
Course and Staging: When primary lymphoma of bone is diagnosed, it is necessary to stage the disease. It is important to evaluate the presence of multiple bone lesions and possible nodal and extraskeletal involvement.

Treatment and Prognosis: Combined chemo-radiotherapy is the standard treatment for PBL; however, there is no accepted consensus on therapy regimen for the localized form. Surgery may be indicated in spine localizations to decompress marrow and spinal roots or to prevent pathologic fractures in the long bones. Surgery is always combined with radio- and chemotherapy. The 5- and 10-year survival rates for PBL patients are about 65% and 53%, respectively, whereas

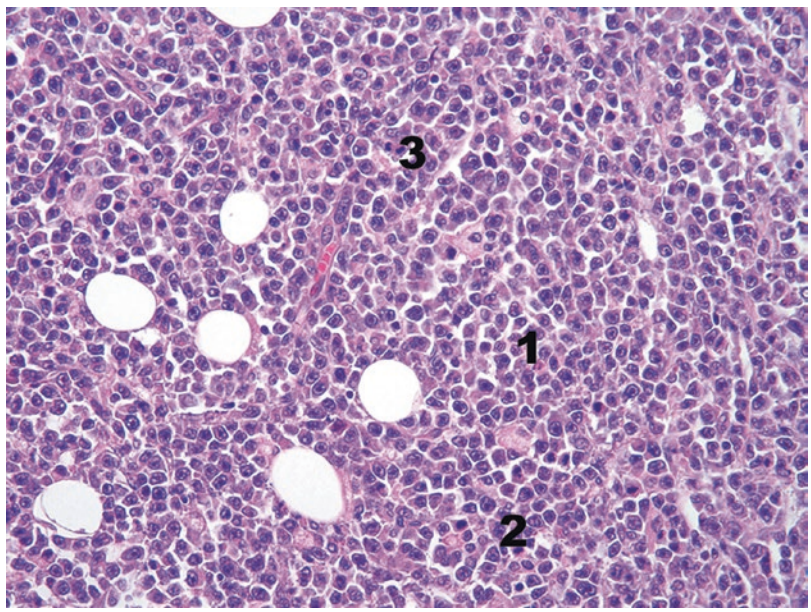
the survival rates in systemic lymphomas with bone lesion are 53% and 43%, respectively. Age less than 60 years is a favorable prognostic factor. Bulky disease, extraskeletal dissemination, and polyostotic involvement are considered unfavorable prognostic factors.

Key points	
• Clinical	Adults, pain and swelling, possible pathologic fracture
• Radiological	Large lytic destructive lesion, bone margins often moth-eaten or permeative, rare periosteal reaction
• Histological	Pleomorphic blue round cells
• Differential diagnosis	Osteomyelitis, osteosarcoma, Ewing sarcoma, langerhans cell histiocytosis, metastatic carcinoma

Immunohistochemical panel	
• DLBCL – Germinal center – Non-germinal center	CD45+; CD20+; CD79a+; PAX5+ CD10+; BCL6+ or MUM1− CD10−; BCL6− or MUM1+
• Anaplastic T-cell lymphoma	(CD3 CD2 CD4 CD5) ≥1 positive pan T-cell marker CD30+; ALK +/−
• Hodgkin lymphoma Reed–Sternberg cells	CD30+; CD15+; CD20−



Radiograph. Mixed lytic and sclerotic femoral lesion, with limited cortical destruction, and moth-eaten pattern



Primary lymphoma of bone: In this example of DLBCL, the tumor is composed of sheet of large atypical B cells, showing irregular and cleaved nuclei with prominent nucleoli (1). Nuclei are generally larger than those observed in Ewing sarcoma (2). Mitotic figures are frequent (3)

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