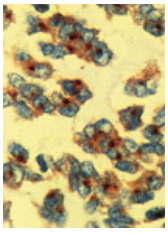

Pathology Update

PATHOLOGIC AND RADIOLOGIC FEATURES OF PRIMARY BONE TUMORS

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This regular feature presents special issues in oncologic pathology.

Introduction

Primary bone tumors are comparatively rare and, therefore, physicians rarely accumulate enough experience in the management of these neoplasias. Due to the complexity in radiologic and histopathologic appearances and the serious consequences of inappropriate surgical treatment, clinical management of bone tumors is best achieved through a multidisciplinary approach.

Accurate diagnosis of primary bone tumors requires evaluation of clinical, radiologic, and pathologic features.[1-9] Thus, communication among the orthopedic surgeon, the radiologist, and the pathologist is necessary to avoid serious diagnostic errors and subsequent therapeutic mismanagement.[1-9] The following clinical parameters provide essential diagnostic information and should be part of every diagnostic algorithm[1-9]:

• *Age* (if the patient's age is outside the typical range for a tumor, the diagnosis should be viewed with suspicion)

• *Family history* (eg, hereditary multiple osteochondromatosis, neurofibromatosis)

• *Past history* (eg, evaluation of metastatic disease)

• *History of presenting complaint* (characteristics of pain, swelling, etc)

• *Physical examination*

• *Laboratory data* (alkaline and acid phosphatases, prostate-specific antigen levels in serum, neutrophilia, immunoglobulin spikes, etc)

This information should be available prior to a radiologic evaluation since only a small number of bone tumors have radiographic features that are sufficiently characteristic to allow a radiologic diagnosis (eg, non-ossifying fibroma, simple cyst, hemangioma of vertebral body, osteochondroma and osteochondromatosis, phalangeal enchondromas, conventional osteosarcoma). Nevertheless, for most entities, a radiologic differential diagnosis can and should be provided to the pathologist. The pathologist should not attempt to issue a diagnosis without clinicoradiologic information. This multidisciplinary approach allows the distinction of "benign vs malignant" in approximately 98% of cases.[1,2,8,9]

Radiologic Features of Primary Bone Tumors

On the initial assessment of a radiograph, it is important to ascertain if a given lesion is located in the bone, the joint, or the soft tissues.[9] The differential diagnosis of a lesion that is located exclusively within a joint is relatively short and includes very few neoplastic processes and only rarely a malignancy. Soft-tissue tumors that are located behind a bone can appear on a radiograph as a malignant primary bone tumor with secondary soft-tissue extension. However, careful evaluation with computed tomography and/or magnetic resonance imaging studies will reveal if the lesion is a primary bone tumor extending to the soft tissues or a soft-tissue tumor adjacent to bone.

Once the decision has been made that the lesion is a primary bone tumor, attention should be paid to the particular bone involved, since certain bone tumors have a tendency to occur only in specific locations of the body.[1,3,4,9] Chordomas tend to occur centrally and commonly within the sacrum or the clivus. Malignant pelvic tumors are frequently chondrosarcomas or Ewing's sarcomas. Adamantimomas are most frequently anterior tibial lesions. Giant-cell tumors typically occur in the epiphysis of the radius. Cartilage lesions of the sternum are invariably chondrosarcomas, and tumors of the hands and feet are usually benign.[9]

Bone tumors also show a preferential location for certain areas of the bone (Tables 1-2). Thus, epiphyseal lesions are rarely neoplastic, and the differential diagnosis is reduced to giant-cell tumor, chondroblastoma, low-grade osteogenic osteosarcoma, and clear-cell chondrosarcoma (clear-cell chondrosarcomas are exclusively epiphyseal lesions and are common in the femoral head). A diaphyseal lesion is usually fibrous dysplasia, enchondroma, non-ossifying fibroma, chondrosarcoma, Ewing's sarcoma, or metastasis. The metaphysis is the most common location of skeletal neoplasms, and the differential diagnosis is extensive.[9]

Table 1. — Anatomic Division of Long Bones Pertinent to Tumor Diagnosis

Divisions:	Proximal
	Distal
Regions:	Epiphysis (articular surface to epiphyseal plate)
	Metaphysis (epiphyseal plate to diaphysis)

	Diaphysis (end of proximal metaphysis to beginning of distal metaphysis; further subdivided into proximal 1/3, middle 1/3, and distal 1/3)
	Meta-epiphysis (between center of epiphysis and center of metaphysis)
	Meta-diaphysis (between center of proximal or distal metaphysis and center of proximal or distal 1/3 of the diaphysis)
Anatomic Sites:	Medulla (approximately 50% marrow)
	Cortex (95% bone and 5% Haversian systems)
	Periosteum

Table 2. — Typical Anatomic Regional Location of Common Bone Tumors

Tumor	Epiphysis	Metaphysis	Diaphysis
Metastatic carcinoma	Rare	Common	Most common
Ewing's sarcoma	Rare	Common	Most common
Osteosarcoma, high grade	Rare	Most common	Uncommon
Osteosarcoma, low grade	Most common	Common	Uncommon
Osteosarcoma, telangiectatic	Rare	Common	Uncommon
Osteoblastoma	Rare	Most common	Uncommon
Osteoid osteoma	Uncommon	Common	Uncommon
Giant-cell tumor	Most common	Rare	Extremely rare
Chondroblastoma	Most common	Rare	Extremely rare
Chondromyxoid fibroma	Rare	Most common	Common
Enchondroma	Rare	Common	Common
Chondrosarcoma	Uncommon	Common	Most common
Osteochondroma	Extremely rare	Most common	Common
Non-ossifying fibroma	Extremely rare	Most common	Common
Aneurysmal bone cyst	Common	Common	Rare

Another important part of the radiologic analysis is the identification of tumors as intramedullary or juxtacortical. Common juxtacortical lesions are osteocartilaginous exostosis, parosteal and periosteal osteosarcomas, and myositis ossificans. In osteocartilaginous exostosis, the cortex is part of the lesion and contiguous with the cortex of the bone. In juxtacortical osteosarcomas, the lesion is attached to the cortex of the bone but is not part of the lesion. In pure myositis ossificans, the cortex of the bone is not involved at all.[1,9] Occasionally, however, myositis ossificans can be combined with periostitis ossificans if the injury not only involves the soft tissue, but also leads to subperiosteal hemorrhage.

The following are important parameters to consider in the evaluation of a primary bone tumor[1,9]:

Tumor Location

• Solitary vs multiple: malignant and multiple (eg, lymphoma, metastatic disease); benign and solitary (eg, osteoblastoma, chondroma, chondroblastoma, giant-cell tumor, aneurysmal bone cyst); benign and often multiple (eg, fibrous dysplasia, eosinophilic granuloma, and enchondromatosis).

• Location of the "epicenter" of the lesion within the bone.

• Radiologic site of presumed origin: intramedullary, cortical (no less than 90% of the tumor within the cortex), paracortical (no less than 90% of tumor within paracortical tissues), periosteal (tumor deriving from periosteum), parosteal or juxtacortical (tumor deriving from periosteum or other paracortical tissues such as fascia, ligaments or tendons.

Pattern of Bone Destruction

Typical histologic features and corresponding potential diagnoses are presented in Table 3.

Table 3. — Typical Histologic Features and Corresponding Potential Diagnoses

Features	Potential Diagnoses
Osteoblastic rimming	Benign bone-forming lesions (except fibrous dysplasia)
	Grade I intramedullary and parosteal osteosarcoma
Bone marrow permeation by bone-forming tumor with trapping of host lamellar bone spicules	Osteosarcoma
Bone marrow permeation by hyaline cartilage tumor with trapping of host lamellar bone spicules	Chondrosarcoma
Intramedullary islands of viable hyaline cartilage separated by normal bone and marrow and/or cartilage nodules surrounded by lamellar bone	Enchondroma

• Geographic: one or more cavities of more than 1 cm in diameter, with well-defined borders and visible transition from tumor to intact bone, indicating slow growth rate (non-ossifying fibroma, chondromyxoid fibroma, simple bone cyst, fibrous dysplasia, grade I chondrosarcoma, giant-cell tumor of the bone).

• Moth-eaten: multiple 2- to 5-mm cavities with a tendency to coalesce, indicating intermediate growth rate and/or cortical destruction (eosinophilic granuloma, lymphoma, myeloma, fibrosarcoma, chondrosarcoma).

• Permeative: lesions with ill-defined borders and multiple cavities, less than 1 mm in diameter, indicating enlarged Haversian systems and rapid growth rate (Ewing's sarcoma, osteosarcoma, leukemia, lymphoma, myeloma, metastases, and infections).

Bone Response to the Tumor

• Intramedullary: A complete rim of reactive bone sclerosis indicates benignity in more than 95% cases, but the lack of a rim does not necessarily imply malignancy. An incomplete rim, however, can be produced either by a benign lesion undergoing malignant transformation or by an old benign lesion undergoing regression such as in non-ossifying fibroma.

• Periosteal: A dense, thick, convex to elliptical periosteal response suggests a benign irritative lesion (eg, osteoid osteoma, infection, trauma). The triangular cuff, or "Codman's triangle," indicates rapid growth rate, and biopsy is mandatory. The "onion-skinning" (multiple parallel, thin submillimeter periosteal lines) often contains no tumor and may result from intermittent and sequential intramedullary tumor growth/infarction events and host responses. The "sunburst" (spiculated, wavy, perpendicular, Sharpey's fibers) results from rapid, continuous lifting and periosteal stretching.

• Bone deformation: The "bent" bone is typical of bone remodeling after fractures. The "expanded" bone reflects destruction of cortex followed by new cortex deposition by the periosteum, indicating slow growth rate and benignity in more than 80% of cases. The "bubbling out" (eccentric expansion) is a peripheral rim of periosteal bone indicating slow growth. A "finger-in-the-balloon" is a typical sign of an aneurysmal bone cyst.

Soft-Tissue Mass

A "naked" soft-tissue mass that lacks a rim of new periosteal bone indicates malignancy in more than 90% of cases. Exceptions are giant-cell tumor of the bone, aneurysmal bone cyst, and eosinophilic granuloma.

Intralesional Densities

Radiologic features and corresponding potential pathologic diagnoses are shown in Table 4.

Table 4. — Radiologic Features and Corresponding Potential Pathologic Diagnoses

Features	Potential Diagnoses
Complete sclerotic rim	Benign lesion (95% accuracy)
Epiphyseal, solitary, lytic lesion with sclerotic border	Chondroblastoma, enchondroma, GCT
Epiphyseal, solitary, lytic lesion without sclerotic border	GCT, chondrosarcoma
"Kissing" bones (lytic lesions in contiguous epiphyses)	GCT, angiosarcoma, pigmented villonodular synovitis, infections
Cumulus cloud	Osteosarcoma, stress fracture
Ground glass	Fibrous dysplasia, osteoblastoma, grade I osteosarcoma
Ring-like to popcorn density	Enchondroma and secondary chondrosarcoma
Poorly demarcated, expansile lesion with windblown calcifications	Chondrosarcoma
Expansile, trabeculated lesion	Grade I sarcoma, GCT, myeloma
Finger-in-the-balloon	ABC
Fallen fragment sign	Simple bone cyst
Codman's triangle	Osteosarcoma, osteomyelitis, ABC
Onion-skinning	Ewing's sarcoma, osteomyelitis, osteosarcoma, eosinophilic granuloma
Bone expansion	Benign tumor (90% cases), grade I sarcoma, myeloma, metastasis

GCT = giant-cell tumor
ABC = aneurysmal bone cyst

• Densifications are calcifications within cartilage, dystrophic calcium deposits in noncartilaginous tumors, tumoral bone, or reactive bone.

• "Cumulus cloud" is typical of osteosarcoma and is rarely seen in calluses, stress fractures, and giant bone islands.

• "Popcorn-like" densities are 1 to 5 mm in diameter with "ring-like" contours resulting from peripheral plates of reactive host lamellar bone around small cartilaginous lobules. They are typical of enchondroma and of foci of enchondroma within secondary chondrosarcoma.

• Spotty, round densities of 1 mm to 2 cm are found in hyaline cartilage tumors, indicating dystrophic calcification and/or enchondral ossification.

• A "windblown" sign indicates reactive woven bone and/or dystrophic calcification within or at the periphery of growing cartilaginous lobules.

• A "ground-glass" appearance consists of fine densities less than 0.5 mm that result from numerous trabeculae of woven bone. In more than 95% of cases, they will be due to fibrous dysplasia, and they are rarely seen in low-grade osteosarcoma and osteoblastoma.

General Histopathologic Features of Primary Bone Tumors

Characteristics of Tumor Matrix

Histologic features of reactive and tumoral matrices are shown in Table 5.

Table 5. — Histologic Features of Reactive and Tumoral Matrices	
Reactive Matrix of Periosteal Origin	Surrounded by benign, exuberant, fibroblasts
	Osteoblastic rimming (except low grade osteosarcoma)
	Outer surface of the bone
Tumoral Matrix	Continuity between tumor cells and matrix
	Tumor cells produce the matrix

• Osteoid is an unmineralized matrix that is laid down by osteoblasts (Fig 1). Osteoblasts release into the osteoid matrix microscopic fragments of cytoplasm ("initial calcification foci" or "matrix vesicles") containing ATPase and alkaline phosphatase. Hydroxyapatite is then deposited on the membranes of these vesicles, and bone formation proceeds as a cascade from the vesicles to the osteoid.[9]

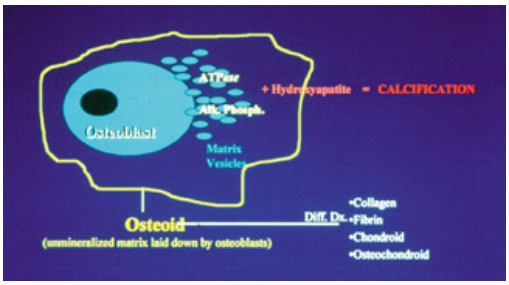

Fig 1. — Formation of osteoid and bone.

• Lamellar bone consists of parallel sheets of collagen fibers alternating with other collagen fibers at right angles that impart great structural strength. Osteosarcomas do not produce lamellar bone (only low-grade parosteal osteosarcomas may produce a primitive form of lamellar bone).

• Woven bone is composed of disoriented collagen fibers arranged in a "crisscross" pattern (primitive bone). It is seen in new bone formation and in states of high turnover. It may coexist with lamellar bone (eg, Paget's disease and fracture callus).

Substances Easily Confused With Osteoid

Collagen, fibrin, chondroid, and chondrosteoid can be easily confused with osteoid.[9]

• Collagen is a longitudinal structure easily seen under polarized light. Only the detection of matrix vesicles by electron microscopy distinguishes osteoid from collagen. Osteoid is pink and more amorphous (rich in proteoglycans and less fibrillary) than conventional collagen.

• Fibrin is an area of hemorrhage without collagen fibers under polarized light.

• Chondroid is tinctorially identical to osteoid (a bluish appearance suggests cartilage).

• Chondrosteoid is cartilage-osseous matrix in fracture callus and osteosarcomas.

Fracture Callus

The histopathologic appearance of a fracture callus may be strikingly similar to that of a neoplastic process.[1,2,8,9] Clinical and radiologic data are essential to the pathologist, particularly in the first three weeks of callus formation. The diagnostic features are described in Table 6.

Table 6. — Histologic Sequence of Callus Formation	
Week 1	**Tissue culture-like:** Hemorrhage, fibrin, variable necrosis, mesenchymal growth on both sides of the fractured bone, and cells migrating along the fibrin fibers.
	High mitotic activity, pleomorphism, high nuclear: cytoplasmic ratios, and infiltrative pattern.
Weeks 2 to 3	**Osteoid and primitive bone production (7-10 days):** Absence of osteoblastic rimming (similar to osteosarcoma) and early calcification mimicking primitive bone. Osteoblasts and stromal cells at similar maturation stages.
	Zonation phenomenon: Cells at the center of the lesion "younger" than at the periphery (the opposite in osteosarcoma).
	Osteoblastic rimming: Osteoblasts at the periphery of the osteoid of bone spiculae, at the same stage of maturation.
Weeks 3 to 4	Prominent rimming sign, intertrabecular vascularity ("injury vessels"), mature granulation tissue.
	Conversion of osteoid into trabeculae of woven bone, Roman aquaduct sign, hypocellular stroma.
	Osteoblasts are less pleomorphic.
Weeks 5 to 7	Lamellar bone and marrow fat production (primitive lipoblasts).
Week 8	Hematopoietic elements and mature adipose tissue in the bone marrow.

Pathologic and Radiologic Correlations of Selected Primary Bone Tumors

Radiologic features are usually sufficient to differentiate benign from malignant bone-forming tumors (Tables 7-8, Figs 2-3). However, histopathologic examination (Fig 4) may be necessary to distinguish conventional osteogenic osteosarcoma from Ewing's sarcoma, well-differentiated osteosarcoma from fibrous dysplasia, telangiectatic osteosarcoma from aneurysmal bone cyst, or giant-cell tumor from giant-cell-rich osteosarcoma.[10-21]

Table 7. — Common Bone-Forming Tumors and Corresponding Differential Diagnoses

Tumor	Differential Diagnoses
Osteoma	Senescent osteochondroma, parosteal osteosarcoma, periostitis ossificans
Solitary enostosis (bone island)	Osteosarcoma
Fibrous dysplasia	Low-grade intramedullary osteosarcoma fibrous dysplasia-like, parosteal osteosarcoma, osteofibrous dysplasia, Paget's disease, meningioma (skull)
Osteoid osteoma	Solitary enostosis, osteomyelitis, Brodie's abscess, osteoblastoma, osteosarcoma, eosinophilic granuloma
Intramedullary osteosarcoma	Fracture callus, osteoblastoma, aneurysmal bone cyst, chondroblastoma, giant-cell tumor, Ewing's sarcoma, chondrosarcoma, fibrosarcoma

Table 8. — Histologic Variants of Osteosarcoma

Primary, intramedullary, high grade	Sclerosing (bone rich)
	Cartilage rich or chondrosarcoma-like
	Spindle cell rich or fibrosarcoma-like
	Malignant histiocyte-rich of MFH-like
	Telangiectatic or ABC-like
	Small-cell type
	Epithelioid type
	Chondroblastoma-like
Solitary, low grade, intramedullary	Fibrous dysplasia-like
	Non-ossifying fibroma-like
	Osteoblastoma-like
	Chondromyxoid fibroma-like
Juxtacortical	Parosteal osteosarcoma
	Periosteal osteosarcoma
	High-grade surface osteosarcoma
Secondary osteosarcoma	Paget's disease
	Postradiation
	Associated with benign bone lesions
	Retinoblastoma and other childhood cancers
Multifocal	Type I — synchronous, young patients
	Type II — synchronous, adults
	Type III — metachronous

ABC = aneurysmal bone cyst
MFH = malignant fibrous histiocytoma

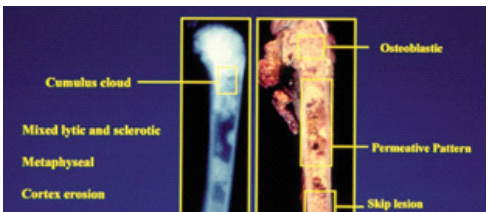

Fig 2. — Radiographic features of osteosarcoma.

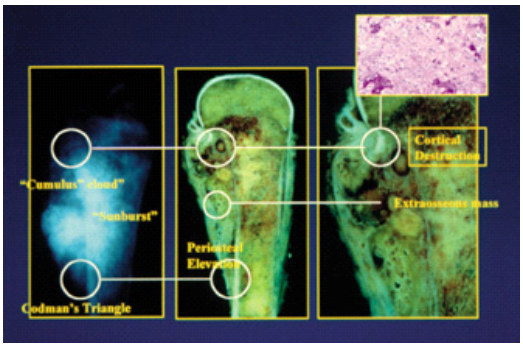

Fig 3. — Radiographic features of primary bone tumors.

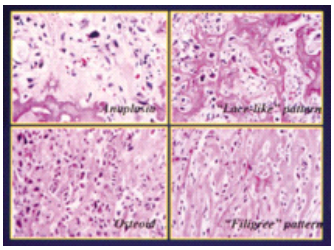

Fig 4. — Histopathologic examination of osteogenic osteosarcoma.

In the group of cartilage-bone tumors (Tables 9-12),[22-26] a particularly difficult differential diagnosis is between enchondroma (Fig 5) and low-grade chondrosarcoma (Figs 6-7). Both radiologic and histopathologic parameters are necessary for the diagnosis in this situation. An important study on this issue was recently conducted by Murphey et al[26] from the Armed Forces Institute of Pathology. In their analysis of multiple parameters in 92 enchondromas and 95 chondrosarcomas, they found that a chondrosarcoma can be diagnosed confidently in at least 90% of cases when the following findings are present: (1) pain related to the lesion, (2) deep endosteal scalloping affecting more than two thirds of the cortical thickness, (3) cortical destruction and soft-tissue mass (by computed tomography or magnetic resonance imaging), (4) periosteal reaction (by radiography), and (5) greater uptake of radionuclide in the lesion than in the iliac crest (by scintigraphy).

Table 9. — Common Cartilage- and Chondroid-Producing Tumors

	Benign	Malignant
Lesions producing "pure" hyalin cartilage:	Enchondroma	Chondrosarcoma
	Ollier's disease	
	Maffucci's syndrome	
	Parosteal chondroma	
	Tenosynovial chondroma	
Tumors producing "non-pure" cartilage and other cellular and matrix elements	Osteochondromatosis	Chondrosarcoma with fibrosarcomatous or osteosarcomatous transformation Mesenchymal chondrosarcoma, chordoma
	Chondrohoblastoma	
	Chondromyxoid fibroma	

Table 10. — Histologic Grading of Chondrosarcoma

	Clinical Behavior	Chondrocytes	Matrix
Grade I (30-35%)	Slow growing	Small, dark nuclei, scant cytoplasm Arranged in clones, occupy lacunae No mitoses	Low cellularity Abundant matrix Calcification
Grade II (40-50%)	Locally aggressive Metastasis in 20%	Larger and paler nuclei Mild pleomorphism More abundant cytoplasm Very rare mitoses	More cellular Focal myxoid change
Grade III (15-30%)	Metastasis in 70%	Large and vesicular nuclei Abundant cytoplasm Intense hypercellularity Mitoses: 2 or more per 10 HPF	Sparse matrix Little chondroid differentiation

HPF = high power fields

Table 11. — Chondroma vs Chondrosarcoma

Histopathologic Feature	Chondroma	Chondrosarcoma
Growth pattern	Expansive	Permeative
Cartilaginous nodules	Continuous with main mass	Separated from the main mass
Surrounding bony trabeculae	Intact	Entrapped
Cellularity	Hypocellular (long bones)	Depending on grade
Matrix	Solid chondroid	Myxoid
Mitoses	None	Very rare (less than 6%)
Cartilaginous cap	Suspicious if >1 cm	Suspicious if >3-4 cm
Columns of chondrocytes	Toward the base of the cap	Loss of arrangement

Table 12. — Histopathologic Patterns Associated to Enchondroma vs Grade I Chondrosarcoma

Enchondroma (% of cases)	Chondrosarcoma, Grade I (% of cases)
Islands of cartilage (90%)	Permeation pattern (80%)
Lamellar bone encasement (60%)	Haversian system permeation (33%)
	Soft-tissue mass (50-75%)
	Bands of fibrosis (81%)
	Marrow fat invasion (8%)

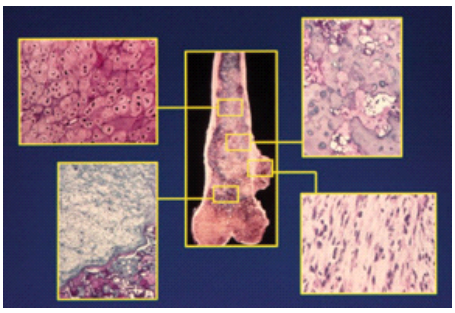

Fig 6. — Low-grade chondrosarcoma.

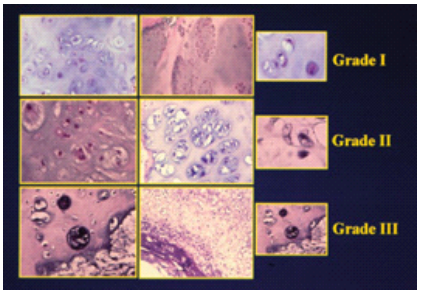

Fig 7. — Grade I, grade II, and grade III chondrosarcoma.

The issue is further complicated by the presence of multinucleated, osteoblast-like giant cells in many neoplastic and nonneoplastic conditions and also by the occurrence of secondary cystic change in noncystic lesions (Tables 13-15). Histopathology is also needed to distinguish fibrous dysplasia from osteofibrous dysplasia, to distinguish giant-cell tumors from brown tumors of hyperparathyroidism and giant-cell reparative granulomata, and to confidently diagnose hematopoietic diseases and metastases.[27-37]

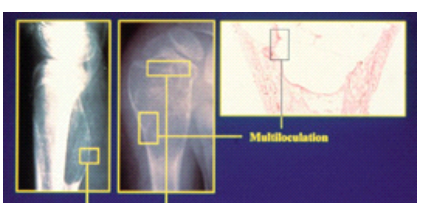

Fig 8. — Solitary bone cyst.

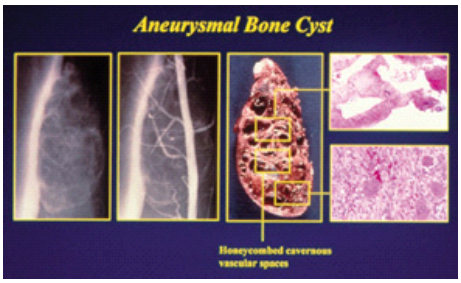

Fig 9. — Aneurysmal bone cyst.

Table 13.— Simple (Unicameral) Bone Cyst

Radiologic Findings	Histopathologic Features	Differential Diagnosis
Proximal humerus	Unicameral	Osteosarcoma
Femur	Single continuous membrane	Aneurysmal bone cyst
Metaphyseal, symmetric	Clear-yellow or serosanguineous fluid	Fibrous dysplasia (cystic)
Lytic, uniloculated	Thin fibrous-walled cyst	Osteoblastoma
Abut epiphyseal plate	Monotonous benign cellular layer lining	
"Fallen fragment" sign	Occasional cementum-like matrix	

Table 14. — Aneurysmal Bone Cyst

Radiologic Findings	Histopathologic Features	Differential Diagnosis
Metaphysis	***Conventional:***	Osteosarcoma, telangiectatic
Incipient phase:	Fibrous, multiloculated cyst-like walls	Giant-cell tumor
Diffuse permeating or circumscribed lytic	Variable cellularity	Osteoblastoma
Circumscribed lytic	Osteoid and woven bone production	Fibrous dysplasia
	Osteoblastic rimming, not prominent	Osteosarcoma
Midphase:	Osteoclast-like giant cells	
Eccentric expansion or "blowout"	"Lacy" chondroid (blue and reticulated)	
Codman's triangle		
Incipient rim of periosteal bone	***Variants:***	
"Finger in the ballon" sign	Pseudosarcomatous	
Late phase:	Solid	
Rounded contours with rim		

Table 15. — Giant-Cell Tumor

Radiologic Findings	Histopathologic Features	Differential Diagnosis
Epiphyseal, central	***Constant:***	Hyperparathyroidism
Lysis without trabeculation	Osteoclast-like giant cells	Paget's disease
Geographic destruction	Spindle stromal cells	Non-ossifying fibroma
Extension to articular surface	Spread to subchondral position	Chondroblastoma
Absence of sclerotic rim		Osteoblastoma
Absence of calcifications	***Variable:***	Giant cell-rich osteosarcoma
	Reactive osteoid and woven bone	Fibrosarcoma
	Storiform pattern, collagenization	Malignant fibrous
	Hemorrhage and necrosis, foam cells	Aneurysmal bone cyst
	Intravascular osteoclasts	
	Aneurysmal bone cyst component	

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