

Bone Tumors

Tutorial for Residents

UMDNJ-NJMS, Dept of Pathology

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Authors:

Violetta Barbashina, MD¹, Joseph Benevenia, MD², and Meera Hameed, MD¹

Contributors:

Anthony Grygotis, MD¹

Seena C. Aisner, MD¹

Stanley Cohen, MD, Chair¹

Marcia Blacksin, MD³

¹ Dept of Pathology

² Dept of Orthopaedic Surgery

³ Dept of Radiology

Webmaster:

Vladimir Makarov, MS, MLS

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Introductory Course

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Welcome to our Bone Tumor Pathology site

Bone tumors represent a unique group of pathologic conditions for which little time is assigned during the training period in most Pathology residency programs.

This website is created to introduce trainees in Pathology to the basic concepts in diagnosis of bone tumors. It is structured to walk you through this difficult field in a stepwise manner by which you will familiarize yourself with the various common skeletal tumors and tumor-like conditions.

At this site you will find:

- Overview of clinical, radiological and pathologic findings, characteristic of common bone tumors
- Case studies with relevant radiological and pathologic images
- Learn the importance and application of a combined clinico-radiologic-pathologic approach to Bone Tumor diagnosis.

Due to the limitations posed by the format of an online tutorial, the lesions discussed here are only those that are most common, and those that may present serious diagnostic difficulties. Obviously, the site is not meant to be all-inclusive and only serves a simple

purpose of getting you started. **For detailed information we would refer you to the following texts, which were used as sources for this website:**

1. Dorfman HD, Czerniak B: *Bone Tumors*. Mosby, Inc.1998
2. Helliwell TR: *Pathology of Bone and Joint Neoplasms*. Philadelphia, WB Saunders Co.1999
3. Mirra JM: *Bone Tumors: Clinical, Radiologic and Pathologic Correlations*. Philadelphia, Lea & Febiger 1989
4. Fechner RE, Mills SE: *Tumors of the Bones and Joints*. Washington, DC: Armed Forces Institute of Pathology; 1993. *Atlas of Tumor Pathology*; 3rd series, No.8
5. McCarthy EF, Frassica FJ: *Pathology of Bone and Joint Diseases*. Philadelphia, WB Saunders Co. 1998
6. Unni KK(ed): *Dahlin's Bone Tumors*, 5th ed. Philadelphia, Lippincott-Raven 1996

Please read through the Introductory Course before moving on to the Case Studies section. Unknown Slides section (quiz) is available if you wish to test your knowledge. There is also a Search option, if you need to look up a specific entity.

We are glad to have you here, and we would appreciate your comments and suggestions. Good luck!

Approach to Bone Tumor Diagnosis

General Considerations:

Bone Tumors can be divided into primary and secondary. Secondary tumors can be further subdivided into

- Metastatic tumors
- Tumors resulting from contiguous spread of adjacent soft tissue neoplasms
- Tumors representing malignant transformation of the pre-existing benign lesions.

Metastatic cancers are the most frequent malignant tumors found in bone. They are by far more common than primary bone tumors and are characterized by the following:

- Predominant occurrence in two age groups: adults over 40 years of age and children in the first decade of life.
- Multifocality and predilection for the hematopoietic marrow sites in the axial skeleton (vertebrae, pelvis, ribs and cranium) and proximal long bones. Metastases to long bones distal to the elbows and knees are unusual. Metastases to the small bones of the hands and feet are even rarer. Occasionally, metastases may appear as

solitary lesions (particularly true for the lung, kidney and thyroid cancer).

<i>Most common malignancies producing skeletal metastases:</i>	
<i>Adults</i>	More than 75% of skeletal metastases originate from carcinomas of the prostate, breast, kidney, and lung. Also common are metastases from thyroid and colon cancers. And do not forget melanoma.
<i>Children</i>	Neuroblastoma, rhabdomyosarcoma, and retinoblastoma

Radiographic appearance of the metastatic tumors can be

- Purely lytic (kidney, lung, colon, and melanoma)
- Purely blastic (prostate and breast carcinoma)
- Mixed lytic and blastic (most common appearance)

Primary bone tumors are characterized by the following:

- Predominant occurrence in the first 3 decades of life, during the ages of the greatest skeletal growth activity. The commonest sites for many primary tumors, both benign and malignant, are in the distal femur and proximal tibia, the bones with the highest growth rate.
- Relatively specific radiographic presentations. In some cases, the diagnosis can be confidently made based on the radiographic features alone.
- Benign tumors are by far more common than malignant ones. Some of them are not true neoplasms, but rather represent hamartomas (eg., osteochondroma). The most common benign tumors are osteochondroma, non-ossifying fibroma, and enchondroma.
- Some primary bone tumors are difficult to classify as benign or malignant. For example, giant cell tumor of bone is very aggressive locally but only rarely metastasizes.
- Among primary malignant neoplasms, osteosarcoma and multiple myeloma have the highest incidence, followed by chondrosarcoma and Ewing's sarcoma.

Two important features of bone tumors:

- The ability of some to dedifferentiate (eg., enchondroma or a low-grade chondrosarcoma transforming into a high-grade sarcoma)
- Tendency of high-grade sarcomas to arise in damaged bone, at the sites of bone

infarcts, radiation osteitis and Paget's disease.

Relevant clinical information

AGE (probably the most important clinical clue).

<i>Age group</i>	<i>Most common benign lesions</i>	<i>Most common malignant tumors</i>
0 - 10	simple bone cyst eosinophilic granuloma	Ewing's sarcoma leukemic involvement metastatic neuroblastoma
10 - 20	non-ossifying fibroma fibrous dysplasia simple bone cyst aneurysmal bone cyst osteochondroma (exostosis) osteoid osteoma osteoblastoma chondroblastoma chondromyxoid fibroma	osteosarcoma, Ewing's sarcoma, adamantinoma
20 - 40	enchondroma giant cell tumor	chondrosarcoma
40 & above	osteoma	metastatic tumors myeloma leukemic involvement chondrosarcoma osteosarcoma (Paget's associated) MFH chordoma

Summary: Primary osteosarcoma and Ewing's sarcoma are tumors of children and young adults. Occurrence of chondrosarcomas in children or Ewing's sarcoma in middle-aged patients is extremely unusual. In individuals older than 40 years, the commonest form of skeletal malignancy is metastatic cancer. Of the primary bone tumors in this age group, multiple myeloma and chondrosarcoma are most commonly encountered. Osteosarcomas in this age group are often secondary malignancies, which develop at the sites of bone damage. Giant cell tumor, a locally aggressive lesion, almost exclusively occurs in skeletally mature patients, 20 to 50 years of age, with closed epiphyses. It is practically never seen in children or patients older than 60 years.

PAIN (although a non-specific symptom, it may help in differential diagnosis).
Generally, benign non-growing lesions tend to be asymptomatic and represent incidental findings. Pain may be a symptom of:

- Growing lesions. This category includes locally aggressive lesions (eg., aggressive osteoblastoma and GCT), and malignant tumors
- Pathologic fracture complicating either benign or malignant tumor
- Significant local tissue reaction to the tumor.

The following clinical symptoms are worth remembering since they may help in the differential diagnosis:

- **Osteoid osteoma** - small lesion, but highly irritative to adjacent tissues and typically causes intense night pain relieved by non-steroidal anti-inflammatory drugs. Osteoid osteomas may also occur close to the articular surface of a joint, causing severe inflammatory synovitis, which often obscures the presence of the tumor.
- **Enchondroma vs. chondrosarcoma, grade 1** - histologically, the distinction between a grade 1 chondrosarcoma and an enchondroma is extremely difficult, as histologic features overlap considerably. The distinction is based on the behavior of the lesion. One of the clues to clinical behavior is the presence of pain. Low-grade chondrosarcoma is a growing tumor and, therefore, presents with pain. Enchondromas tend to be asymptomatic, unless associated with a pathologic fracture.

MULTIPLE LESIONS Although both benign and malignant tumors may be multifocal, benign lesions tend to show symmetrical distribution.

Radiological Correlation

The following imaging studies are commonly used in evaluation of bone tumors:

PLAIN RADIOGRAPH is usually the first imaging technique for a suspected bone lesion since it is inexpensive and easily obtainable. It is also the best for assessment of general radiological features of the tumor.

COMPUTER TOMOGRAPHY is a method of choice when plain film assessment is difficult owing to the nature of the lesion (eg., permeative pattern of destruction) or anatomic site (eg., sacrum). In addition, CT is the best technique in assessment of matrix mineralization, cortical detail, and detection of the cystic and fatty lesions.

MRI is a method of choice for local staging. It is superior to CT in the definition of medullary and extracortical spread and of the relationship of the tumor to critical neurovascular structures. However, remember that the MRI appearances of the majority of bone tumors are totally non-specific. You need to examine plain films or CT films to define a neoplasm.

BONE SCINTIGRAPHY is a highly sensitive but relatively non-specific technique. Its main role is in detection of suspected metastases in the whole skeleton. It may also be helpful in the detection of osteoid osteomas ("double density sign" is present in about 50% of cases and is highly suggestive of this tumor).

Radiographic examination should answer the following questions:

- What is the precise location of the lesion (type of bone and, if the long bone is affected, where exactly the lesion is centered - cortex or medulla; epiphysis, metaphysis or diaphysis)? Some tumors almost exclusively occur at specific sites; many others favor certain locations.
- Is there any evidence of underlying bone abnormality (eg., bone infarct, Paget's disease)? High-grade sarcomas tend to arise in damaged bone.
- Is the lesion multifocal?
- Does the tumor have a well-defined margin? Is there a rim of sclerotic bone? The presence of a well-defined margin and a sclerotic rim strongly suggests a benign non-growing lesion.
- Is there evidence of significant cortical expansion or destruction? These findings are seen with locally aggressive or malignant tumors.
- Is there an associated periosteal reaction and, if so, of what type? See discussion below.
- Does the lesion produce mineralized matrix (osteoid or cartilage)?
- Is there a soft tissue mass?

In many cases, the radiographic appearance of the lesion provides clues to its clinical behavior. It allows estimation of tumor growth rate and discloses expansive or infiltrative

growth patterns characteristic of locally aggressive and malignant tumors.

SKELETAL LOCATION (while many lesions favor certain bones, some tumors almost exclusively occur at specific sites)

<i>Lesions</i>	<i>Most common skeletal sites</i>
Ewing's sarcoma Multiple myeloma Leukemia/lymphoma Metastatic cancers	Hematopoietic marrow sites in the axial skeleton (vertebrae, ribs, sternum, pelvis, cranium) and proximal long bones (femur, humerus)
Non-ossifying fibroma	Metadiaphyseal regions of the tibia and distal femur (80%) Does not occur in the flat bones, craniofacial bones, the spine, or the small bones of the hands/feet.
Simple bone cyst	The vast majority of SBCs is found in the proximal humerus (55%) and proximal femur (20%).
Chordoma	Base of the skull or sacrum (90%)
Adamantinoma	Mid-shaft of tibia (90%), jaw bones
Chondroblastoma	Long bones (knee area, proximal humerus)- 70%
Giant cell tumor	Knee area, distal radius (65%)
Enchondroma	Small bones of the hands and feet (60%). This is in fact the commonest tumor at these sites.
Chondrosarcoma (primary, and to the less extent secondary)	Tends to develop in the axial skeleton with 25% to 30% occurring in the pelvic bones

Fibrous dysplasia	Femur, tibia, skull and ribs
Osteochondroma	Knee area, proximal humerus, pelvis
Osteoblastoma	Spine (30%) , mandible, long bones
Aneurysmal bone cyst	Any bone; common in the spine
Chondromyxoid fibroma	Knee area (30%), pelvis, small bones of the feet
Hemangioma	Spine , craniofacial bones

SITE OF LONG BONE INVOLVEMENT

(most primary bone tumors have favored sites within long bones; this may provide a clue to diagnosis).

The diagram illustrates the distribution of primary bone tumors in a long bone. The bone is divided into four regions: Diaphysis (shaft), Metaphysis (transition zones), Physis (growth plate), and Epiphysis (ends). A red tumor labeled 'Ch' (Chondroblastoma) is located in the epiphysis. A large blue tumor labeled 'GCT' (Giant Cell Tumor) is located in the metaphysis, extending into the epiphysis. Other tumors are shown in the diaphysis and metaphysis: a black tumor, a grey tumor, an orange tumor, and a pink tumor.

Epiphyseal lesions:
Chondroblastoma (Ch) and Giant Cell Tumor (GCT) are almost invariably centered in the epiphysis. Chondroblastoma is a rare tumor seen in children and adolescents with open growth plates. GCT is the most common tumor of epiphyses in skeletally mature individuals with closed growth plates. GCT often shows metaphyseal extension.

Metaphyseal intramedullary lesions:
Osteosarcoma is usually centered in the metaphysis. Chondrosarcoma and fibrosarcoma often present as metaphyseal lesions. Osteoblastoma, enchondroma, fibrous dysplasia, simple bone cyst, and aneurysmal bone cyst are common in this location.

Metaphyseal lesions centered in the cortex:
Classic location for a non-ossifying fibroma (NOF). Also, a common site for osteoid osteoma.

Metaphyseal exostosis:
Osteochondroma

Diaphyseal intramedullary lesions:

Favored location for Ewing's sarcoma, lymphoma, myeloma. Common for fibrous dysplasia and enchondroma.

Diaphyseal lesions centered in the cortex:

Adamantinoma, osteoid osteoma

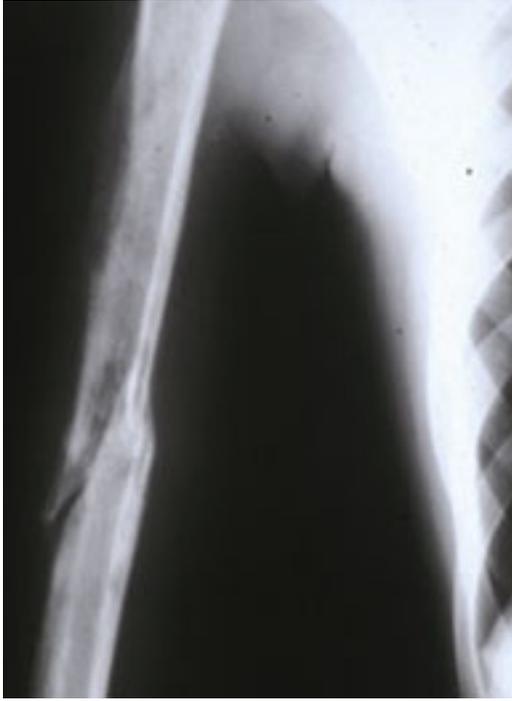
PATTERNS OF GROWTH and BONE DESTRUCTION



- Benign and non-growing (or extremely slowly growing) lesions are well circumscribed and show **geographic pattern** of bone destruction with a **sclerotic rim**. Geographic pattern refers to a well-defined area of lysis. The sclerotic rim is more commonly seen in the weight-bearing bones and represents bone reaction to the lesion. Its presence means that the bone has been given sufficient time to react. Some authors say that the sclerotic rim signifies benignancy to about 95%.



- If the lesion is growing more rapidly, it may still show a well-demarcated zone of bone destruction (geographic pattern), but it will lack a sclerotic rim. With continued growth, such lesions may show **cortical expansion**. Expansile growth pattern is defined as visible widening of the affected portion of bone. In many cases, an interrupted periosteal rim will surround the expanded portion of bone. This pattern may be seen in locally aggressive tumors and in low-grade malignancies.



- Rapidly growing lesions are poorly defined and may show aggressive, infiltrative patterns of bone destruction (**permeative or "moth-eaten"**). **"Moth-eaten" pattern** is defined as an ill-defined zone of multiple small radiolucencies that may coalesce.



- **Permeative pattern** is characterized by numerous tiny radiolucencies in between the residual bone trabeculae. Due to the minute size of radiolucencies the lesion may be difficult to see and to delineate on the plain film. Generally, the more rapidly growing a lesion, the more difficult it is to see on plain film. "Moth-eaten" and permeative patterns are indicative of destruction involving both medullary and cortical bone. They are seen in **high-grade malignant neoplasms and in osteomyelitis**.

TYPES OF PERIOSTEAL REACTION

The periosteum responds to traumatic stimuli or pressure from an underlying **growing** tumor by depositing new bone. The radiographic appearances of this response reflect the degree of aggressiveness of the tumor.



- Slow-growing tumors provoke **focal cortical thickening** (solid periosteal reaction, or "buttress")



- Rapidly growing lesions penetrate through the cortex causing separation of the periosteum and formation of lamellated new bone. If the periosteum elevates to a significant degree, it can break forming an acute angle (**Codman's triangle**). This is seen in malignant bone tumors and in some other rapidly growing lesions such as aneurysmal bone cyst, or in reactive processes (osteomyelitis, and subperiosteal hematoma). Codman's triangle is usually free of tumor unless infiltrated through its open end or by transcortical growth.



- Other types of periosteal reaction in response to a rapidly growing lesion include "onion-skinning" and **spiculated "hair-on-end"** types.

Note that bone metastases usually do not provoke a periosteal reaction.

PATTERNS OF MATRIX MINERALIZATION

Mineralization patterns (calcification or ossification) are helpful in identification of bone-producing and cartilage producing tumors.



- **Osteoid.** Malignant osteoid can be recognized radiologically as cloud-like or ill-defined amorphous densities with haphazard mineralization. This pattern is seen in osteosarcoma. Mature osteoid, or organized bone, shows more orderly, trabecular pattern of ossification. This is characteristic of the benign bone-forming lesions such as osteblastoma.



- **Chondroid.** Radiologically, it is usually easier to recognize cartilage as opposed to osteoid by the presence of focal stippled or flocculent densities, or in lobulated areas as rings or arcs of calcifications. They are best demonstrated by CT. Whatever the pattern, it only suggests the histologic nature of the tissue (cartilage) but does not reliably differentiate between benign and malignant processes.

General Histologic Assessment of the Lesion

The following are the most important histologic features to consider:

- Pattern of growth (eg., sheets of cells vs. lobular architecture)
- Cytologic characteristics of the cells
- Presence of necrosis and/or hemorrhage and/or cystic change
- Matrix production
- Relationship between the lesional tissue and the surrounding bone (eg., sharp border vs. infiltrative growth)

You should never try to make a diagnosis of bone tumor without integrating clinical, radiological, and histologic appearances. Biologically different types of tumors may have overlapping histologic features. Always obtain a list of differential diagnoses from a radiologist, make a habit of reviewing the films, and develop a good working relationship with an orthopedic surgeon. You are a part of a team.

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In this section, we encourage you to use *TABLES* accessible through the links in the drop-down menu called "*INTRODUCTORY*".

Case #1

Typical Clinical Presentation

A 17-year-old male presented with increasing pain in the left upper arm of approximately 3 months' duration and a recent onset of low-grade fever. On physical examination, there was some local tenderness and soft tissue swelling over the proximal and mid thirds of the left humerus.

- Most important here is the patient's age and short duration of symptoms. Note that clinical picture overlaps significantly with that of osteomyelitis.

Characteristic Radiological Findings



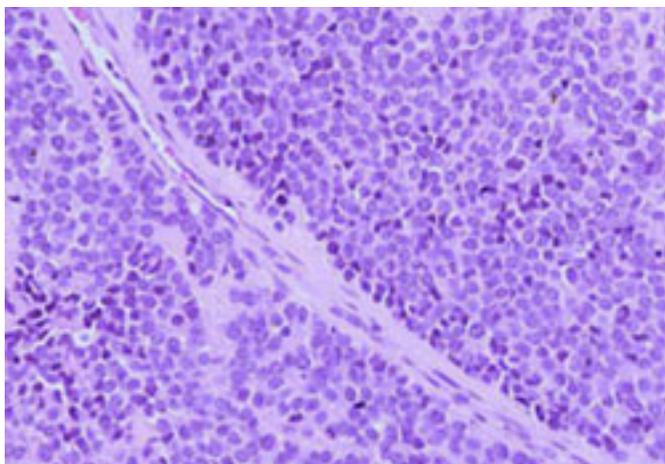
- Plain radiograph shows a large ill-defined, destructive, **diaphyseal intramedullary lesion** with **permeative pattern** of bone destruction and periosteal reaction of a "hair-on-end" type. The lesion is associated with a soft tissue mass.



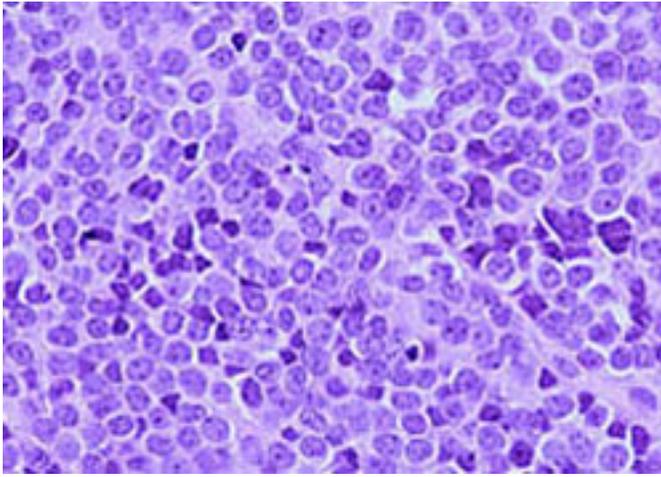
- MRI is superior to the plain film in demonstration of cortical disruption and soft tissue involvement.

The major clue here is the **intramedullary, diaphyseal location of the tumor**. Although the radiological features listed here (poor margination, permeative bone destruction, periosteal "hair-on-end" reaction and soft tissue involvement) are very common in this entity, they are not entirely specific, and just indicate the presence of a rapidly growing, most likely malignant, destructive tumor.

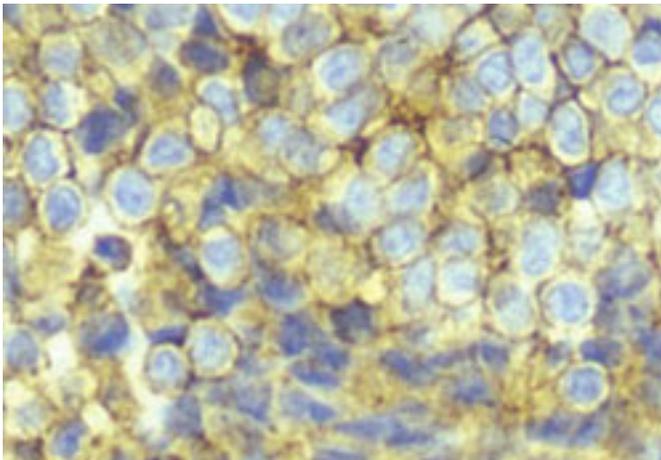
Pathological Findings



- Biopsy material showed a highly cellular, infiltrative neoplasm consisting of sheets of tightly packed, round cells with very scant cytoplasm ("round blue cell tumor"). Occasional Homer-Wright rosettes were identified. Other fields showed extensive necrosis.



- The cell population consisted of two distinct cell types: the larger round cells with a high N/C ratio, fine chromatin pattern and occasional small, inconspicuous nucleoli, and the smaller and darker cells with eosinophilic cytoplasm and hyperchromatic, "shrunken" nuclei (degenerated cells, a typical finding in this entity). Mitotic rate averaged 2 per 10 hpf.



- Tumor cells showed strong immunoreactivity with CD99/013. Neural markers (S-100; chromogranin and synaptophysin) were uniformly negative.

The clue here is in the cytological appearance and pattern consisting of *sheets of primitive cells with little histologic evidence of differentiation.*

Diagnosis of PNET as opposed to ES requires demonstration of neural differentiation, which is evidenced histologically by formation of Homer-Wright rosettes (more than 20%) and immunohistochemically by the expression of neural markers.

Diagnosis: Ewing's Sarcoma (ES)

Salient Points (Ewing's sarcoma and PNET)

- ES and PNET are "small round blue cell" tumors of children and young adults occurring in 80% of cases between the ages of 5 and 20 years. They are extremely rare in patients older than 30 years. The difference between the two is in the degree of neural differentiation. Some authors consider ES a tumor of undifferentiated neural cell, which is of more primitive origin than cells of PNET or neuroblastoma.
- Most common skeletal sites include diaphyses of femur, tibia and humerus, and also pelvis and ribs (Askin tumor of the chest). Associated soft tissue mass is a common finding.
- **The following studies are required to support the diagnosis of ES and PNET:**
 - Demonstration of t(11;22) or EWS-FLI-1 fusion transcript*(present in both ES and PNET)
 - Immunostains*(both ES and PNET are positive for CD99/O13. In addition, PNET shows positive staining with neural markers)
 - EM*(ES cells are undifferentiated and show prominent glycogen deposits; PNET shows neural differentiation)
- Aside from PNET, ES must be differentiated from other "small round blue cell" tumors:

<u>Tumor</u>	<u>Positive immunostaining</u>
ES	CD99/O13; may show positivity with NSE
PNET	CD99/O13 neurofilament; S-100; NSE; synaptophysin; chromogranin
Neuroblastoma	neurofilament; NSE; synaptophysin; chromogranin; S-100
Rhabdomyosarcoma	actin; desmin; vimentin; MyoD1; myogenin
Non-Hodgkin's lymphoma	CD45 (LCA)

Small cell carcinoma	keratin; NSE; synaptophysin; chromogranin
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- Studies have shown that occasionally ES/PNET may show strong immunoreactivity with cytokeratin (AE1/AE3, Cam5.2) with either diffuse or focal staining pattern. Beware.
- Prognostic factors. **Disease stage at diagnosis (including the tumor volume) is the main prognostic factor for patients with ES/PNET**; metastases are detected in about 15-20% of patients and portend a poor prognosis. **Response to pre-operative chemotherapy, as assessed by the degree of histologic tumor necrosis is a major independent prognostic factor**. Histologic response to chemotherapy can be graded as follows: Grade I - tumor necrosis of less than 50%, Grade II - tumor necrosis of 51%-90, Grade III - 91%-99% tumor necrosis, and Grade IV - absence of viable tumor cells (see reference below).
- **Experimental data:** Molecular prognostic factors for ES/PNET are being described. The most common and characteristic primary cytogenetic alteration seen in 95% of ES/PNET is t(11;22), which results in formation of the chimeric gene/protein EWS-FLI-1, an abnormal transcription factor. About 5% of ES/PNET show t(21;22) with formation of analogous EWS-ERG fusion gene/protein. These EWS fusions are presumed to be the initiating oncogenic events in ES/PNET. The structure of fusion may have an independent prognostic significance. Recent studies have shown that a specific type of EWS-FLI-1 (type 1) is associated with better prognosis. Studies have also shown that during tumor progression, secondary molecular alterations may occur, which often involve genes regulating cell cycle. Recent papers suggest that INK4A deletion (INK4A gene encodes a tumor suppressor p16^{INK4A}) is a frequent secondary molecular alteration in ES/PNET which may be prognostically significant. Aberrant p53 expression has been found in a small subset of patients with ES/PNET with a markedly poor clinical outcome.

Available publications for the topic: [Ewing's Sarcoma](#)

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6. Gu M, Antonescu CR, Guiter G, Huvos AG, Ladanyi M, Zakowski, MF: Cytokeratin immunoreactivity in Ewing's sarcoma: Prevalence in 50 cases confirmed by molecular diagnostic studies. *Am J Surg Path* 24(3):410-416, 2000

Case #2

Typical Clinical Presentation:

A 20-year-old male presented with a painless, hard subcutaneous mass in the popliteal fossa. He stated that the mass had been present for several years and did not change in size.

- Two words, "painless" and "non-growing" (or very slow growing), suggest that the lesion described here is probably benign.

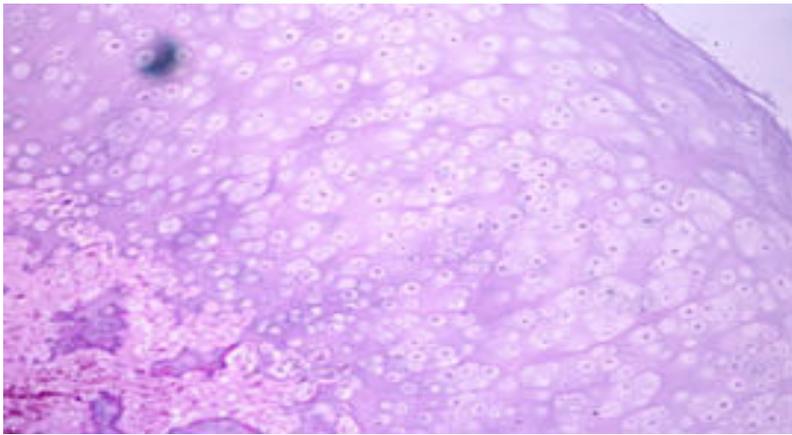
Characteristic Radiological Findings:



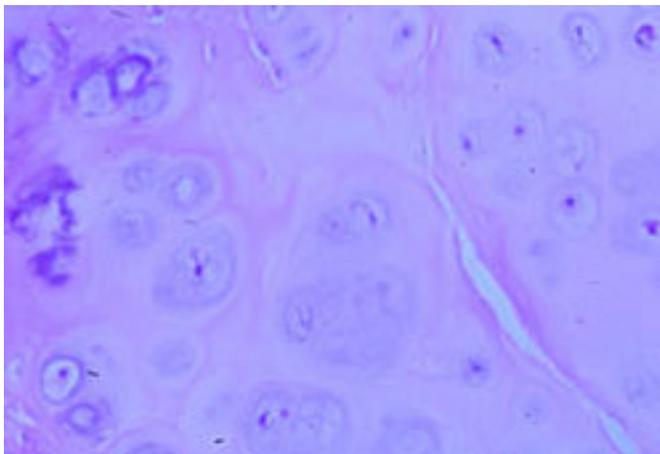
- Plain radiograph demonstrated a **pedunculated bony outgrowth** at the proximal tibial metaphysis. The lesion had a uniform, cartilagenous cap with stippled calcifications. The tibial cortex and medulla were continuous with those of the lesion.

Pathological Findings:

The specimen consisted of a pedunculated lesion, 3 x 3 x 2cm, with a lobulated cartilage cap measuring up to 0.9cm in thickness.



- Cross section through the lesion demonstrated mature trabecular and cortical bone with a uniform cartilage cap, less than 1cm in thickness. Few small islands of similarly appearing cartilage were present in the stalk and **at the resection margin.**



- Higher magnification of a cartilage cap shows mature, focally calcified hyaline cartilage.

Diagnosis: Osteochondroma

Salient Points:

- Most common skeletal sites include metadiaphyses of the femur and tibia at the knee (35%), proximal femur and humerus, pelvis and scapula. **This tumor does not occur in bones with membranous type of ossification.**
- Solitary osteochondromas may be either primary due to a developmental anomaly of bone, or secondary following trauma. Unlike primary osteochondromas, secondary lesions are often seen in the phalanges of the hands and feet and have their peak incidence in the 3rd and 4th decades of life. Multiple osteochondromas represent an autosomal dominant hereditary disorder and are associated with bone deformities.
- Clinical behavior. Osteochondromas are benign lesions with self-limited growth and are treated by simple excision. **Recurrence may develop when a portion of cartilage cap is left behind.** That is why assessment of surgical margins is important. Malignant transformation is more often seen in multiple hereditary osteochondromas. Most common secondary malignancy is chondrosarcoma. **The earliest pathologic sign of malignant transformation to a low-grade chondrosarcoma is increased thickness of the cartilage cap.** The cap thickness will exceed 2cm and will show increased cellularity with mild to moderate cellular atypia.
- **Experimental data:** There are many theories of osteochondroma pathogenesis. The older school of thought considers it a hamartoma arising from a portion of growth plate cartilage entrapped beneath the periosteum during skeletal growth. It is thought that the entrapped pieces continue to grow and ossify at the same rate as the adjacent bone. When skeletal maturity is reached, osteochondromas usually stop growing. Continued growth in skeletally mature individuals may signify malignant transformation. Molecular studies, however, suggest a neoplastic process for development and progression of osteochondroma. Clonal origin of both sporadic and hereditary osteochondromas is supported by the discovery of the clonal cytogenetic abnormalities. These include deletions of regions q24 of chromosome 8 (EXT1 locus) and p11-12 of chromosome 11 (EXT2 locus) that lead to inactivation of EXT1 and EXT2 genes. Although the precise role of EXT genes remains unknown, they are thought to act as tumor suppressors. It appears that the truly neoplastic part is the cartilagenous cap while the osseous part of the tumor is, probably, reactive. Bovee et al have shown loss of heterozygosity (LOH) and DNA aneuploidy in cells of the cartilagenous cap. It has been suggested that EXT inactivation is the initiating event in osteochondroma formation. Additional genetic alterations may be required for malignant transformation.

Available publications for the topic: [Osteochondroma](#)

Selected References::

1. Porter DE, Simpson AH. The neoplastic pathogenesis of solitary and multiple osteochondromas. *J Pathol* 1999;188:119-125
2. Bridge JA, Nelson M, Orndal C, Bhatia P, Neff JR. Clonal karyotypic abnormalities of the hereditary multiple exostoses at chromosomal loci 8q24.1 (EXT1) and 11p11-12 (EXT2) in patients with sporadic and hereditary osteochondromas. *Cancer* 1998;82:1657-1663
3. Bovee JVMG, Cleton-Jansen AM, Wuyts W, et al. EXT mutation analysis and loss of heterozygosity in sporadic and hereditary osteochondromas and secondary chondrosarcomas. *Am J Hum Genet* 1999;65:689-698

Case #3

Typical Clinical Presentation:

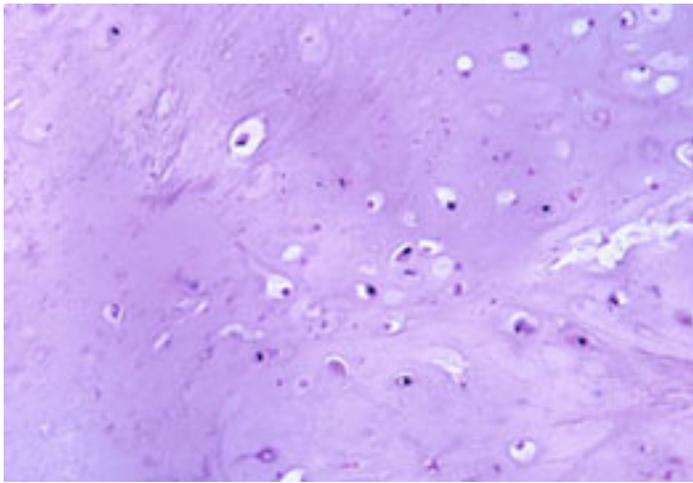
An incidental finding of a bone lesion in the distal femur of a 38-year old female. The lesion was completely asymptomatic.

Characteristic Radiological Findings:

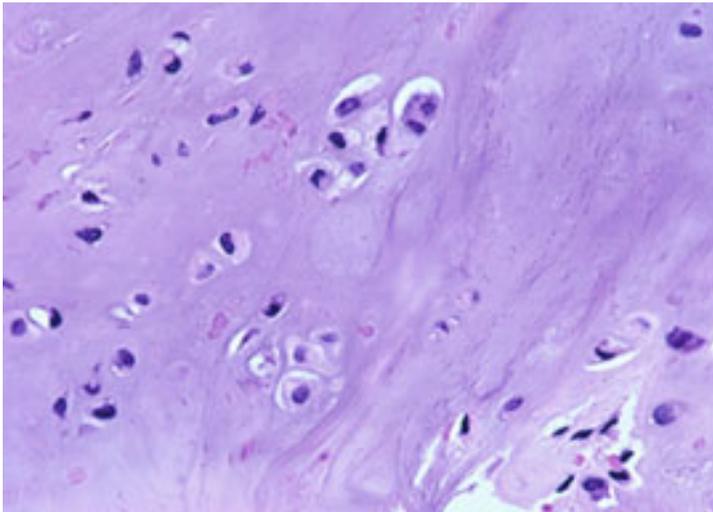


- Plain radiograph showed an intermedullary zone of **stippled and ring-shaped calcifications** in the distal femoral metaphysis. This mineralization pattern with radiodense stipples and rings is characteristic of mature hyaline cartilage.

Pathological Findings: :



- Low-power microscopic examination of the biopsy specimen shows **three characteristic features of this lesion**: a) vague lobularity; b) abundant cartilaginous matrix, which can be focally calcified; c) low cellularity.



- High-power view shows clustered and scattered chondrocytes with small, uniform, darkly stained nuclei. Occasional bi-nucleated chondrocytes are present. Importantly, there were no mitotic figures.

Diagnosis: Enchondroma

Salient Points:

- Enchondroma is a common, benign, intramedullary bone tumor composed of mature hyaline cartilage. It shows wide age distribution with peak incidence during the third and fourth decades of life. Characteristically, it has a limited growth potential and, therefore, many lesions remain small and asymptomatic. **Pain in enchondroma is a worrisome symptom, which indicates either a pathologic fracture or continued growth. It is one of the criteria used to distinguish this benign tumor from a low-grade (Grade 1) chondrosarcoma.**
- Location. In general, enchondromas are very rare in the sites most commonly affected by chondrosarcoma.

<u><i>Enchondroma</i></u>	Characteristically involves the acral skeleton (small bones of the hands and feet - 60%) and the long bones , such as femur, humerus, tibia, fibula, radius, and ulna). In the long bones, the tumor is found in the metaphyses and proximal/distal diaphyses. Mid-shaft involvement is rare. Enchondromas are very rare in the pelvis, ribs, scapula, and spine, and do not involve cranio-facial bones.
<u><i>Chondrosarcoma</i></u>	Common in the pelvis, ribs, and long bones. Not unusual in the scapula, spine, and cranio-facial bones.

- Differential Diagnosis. The difficult and important task is to distinguish an enchondroma from a low-grade (Grade 1) chondrosarcoma. Histological differences are very subtle, and special studies are of no help. Therefore, integration of clinical, radiological and pathologic findings is essential in making a diagnosis. The presence of pain, large size of the lesion > 5cm, certain skeletal locations (see above) and "aggressive" radiological features of the lesion favor the diagnosis of chondrosarcoma. Histologically, Grade 1 chondrosarcoma shows moderate cellularity, mild nuclear atypia, "open" chromatin, small nucleoli, frequent bi-

nucleated cells and rare mitotic figures. Infiltrative growth pattern is indicative of malignancy.

- **Clinical Behavior.** After the surgery, enchondromas typically heal. Recurrences are rare and should be carefully evaluated for malignancy. The incidence of malignant transformation in a solitary enchondroma is low.
- A rare, non-hereditary disorder characterized by multifocal proliferation of dysplastic cartilage is known as enchondromatosis, or **Ollier's disease**. It is usually diagnosed in children and adolescents between 10 and 20 years of age. The risk of malignant transformation, usually to chondrosarcoma, is very high (20% - 30%). For detailed discussion, see Dorfman HD, Czerniak B. Bone Tumors. 1998.

Available publications for the topic: [Enchondroma](#)

Case #4

Typical Clinical Presentation:

A 22-year-old male presented with intermittent dull pain at the ankle of approximately 6 months duration.

- Pain is the usual presenting symptom in this tumor.

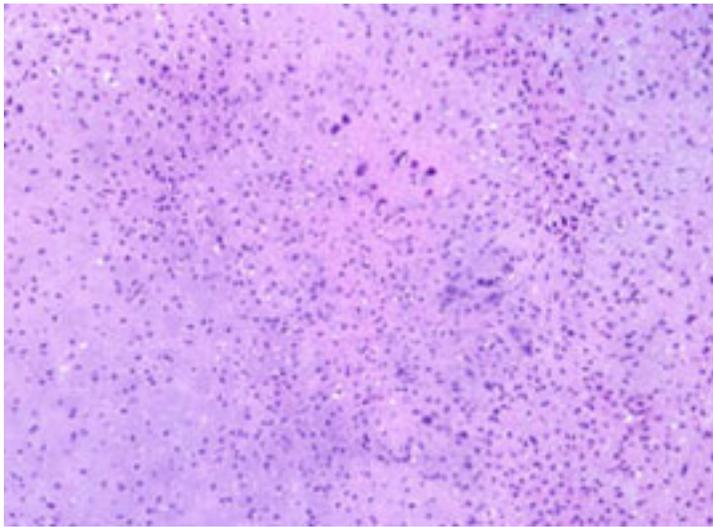
Characteristic Radiological Findings:



- Plain film shows a well-defined, expansile lytic lesion, which is centered at the distal fibular metaphysis and is bordered by a sclerotic rim.

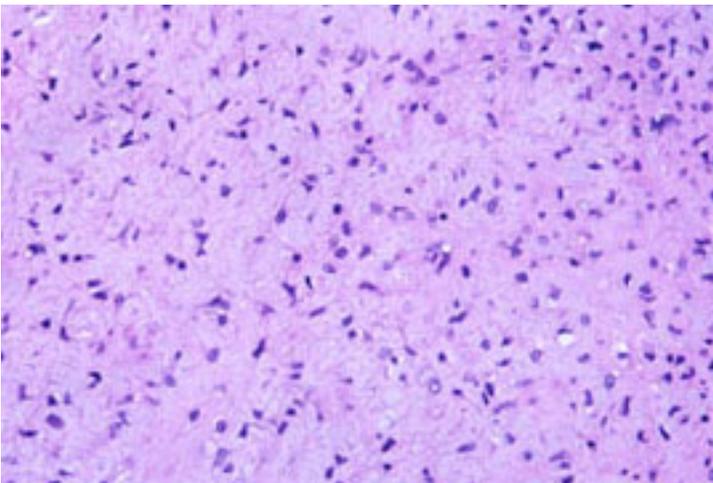
Benign nature of the lesion is suggested by its sharp demarcation from the surrounding bone, sclerotic rimming and lack of cortical disruption.

Pathological Findings: :



- Biopsy specimen consisted of fragments of white-gray rubbery tissue. Low power view shows a moderately cellular chondromyxoid tissue with the following **two characteristic features:**

- a. Vague lobularity caused by alternating highly cellular and less cellular areas;
- b. Increased cellularity at the periphery of the lobules.



- Higher magnification view of the lobule shows mildly pleomorphic, angular and stellate cells set in bluish-pink chondromyxoid stroma. Note that the **tumor lacks true hyaline cartilage matrix** seen in enchondromas and chondrosarcomas. Another important feature is **lack of mitotic activity**.

Diagnosis: Chondromyxoid Fibroma

Salient Points:

- Chondromyxoid fibroma (CMF) is a **rare benign tumor** with predominant occurrence in patients younger than 40 years. The peak incidence is between ages 10 and 20. It is one of two neoplasms of *incompletely differentiated cartilage*. The other neoplasm is chondroblastoma.
- Location. The most frequent skeletal sites are the knee area (30%), pelvis and the small bones of the feet. In the long bone, the tumor characteristically involves the metaphysis or metadiaphysis and is often seen in an eccentric position.
- Secondary cystic change in the form of aneurysmal bone cyst is not unusual.
- Differential Diagnosis of CMF includes chondroblastoma and, more importantly, chondrosarcoma. Distinguishing features of chondroblastoma are epiphyseal location and "chicken-wire" calcifications. The diagnostic criteria for chondrosarcoma include hyaline cartilage matrix, tumor permeation of the surrounding bone and mitotic activity. **Keep in mind that CMFs, even those showing marked cellular pleomorphism, have extremely low number of mitoses never exceeding 1 per 50 hpf.**
- Clinical Behavior. Recurrence rate averages 15%-20%. Large or recurrent lesions may be locally aggressive.

Available publications for the topic: [Chondromyxoid Fibroma](#)

Case #5

Typical Clinical Presentation:

A 39-year-old female gave a 2-month history of increasing pain in her knee. There was no evidence of joint effusion. Laboratory work-up showed normal serum levels of calcium, phosphate and alkaline phosphatase.

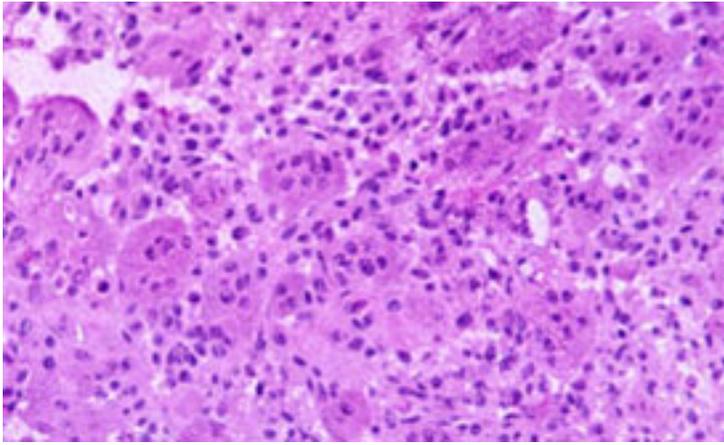
Characteristic Radiological Findings:



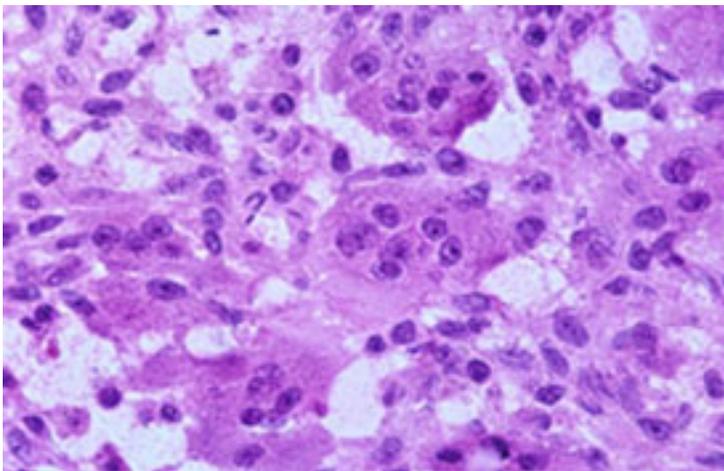
- Plain radiograph demonstrated a well defined, lytic lesion eccentrically located in the distal femoral epiphysis with subchondral and metaphyseal extension. There was associated focal thinning of the cortex.

This is a very common radiological presentation of this tumor. Note the features of a slowly growing/locally aggressive lesion: a geographic pattern of bone destruction with focal cortical erosion, and lack of a sclerotic rim. Eccentric location in the epiphysis (with or without subchondral and metaphyseal extension) is another important diagnostic clue.

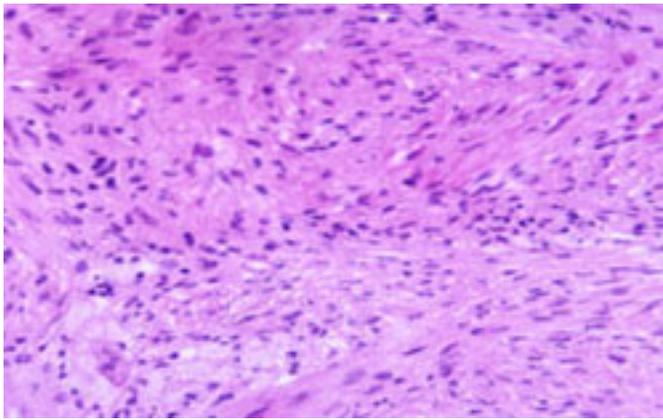
Pathological Findings: :



- Curettage specimen consisted of fragments of soft, hemorrhagic, tan-brown tissue with some firm areas and yellowish speckles. Microscopic examination showed a cellular lesion composed of numerous multinucleated giant cells in a background of small, ovoid, mononuclear stromal cells.



- **Stromal cells had poorly defined cytoplasmic borders and bland nuclei resembling those of giant cells.** Mitoses were easily found averaging 4 per 10 hpf. However, no atypical mitoses were identified. Multinucleated giant cells resembled osteoclasts by their centrally placed bland nuclei.



- Some areas showed prominent fibrohistiocytic changes with storiform arrangement of stromal cells and clusters of foamy histiocytes (xanthoma cells).

Diagnosis: Giant Cell Tumor of Bone (GCT)

Salient Points:

- Conventional GCT of bone is a **relatively common, locally aggressive neoplasm** accounting for approximately 4% of all primary bone tumors. It affects skeletally mature individuals, F > M, 20 to 50 years of age. It is extremely rare in children and patient older than 60 years. Histogenesis remains unclear. The cells of GCT have phenotypic features of both macrophage-like (CD68 positive) and osteoclastic cells (immunoreactive with tartrate-resistant acid phosphatase (TRAP), calcitonin and parathormone).
- Location. Most GCTs affect the long bones with the highest incidence (65%) in the distal femur, proximal tibia and distal radius. **In the long bones, the tumor is invariably centered in the epiphysis.** It can also be found in any other long bone, pelvis and sacrum, and spine (3%). GCTs of the hands and feet are very rare.
- Tumors that have radiological and morphologic features of GCT but are multifocal and/or located in the diaphyses are unlikely to be conventional GCTs. Most often they are "**brown tumors of hyperparathyroidism**" found in patients with abnormal serum levels of calcium and phosphate.
- Certain histological features are inconsistent with the diagnosis of conventional GCT. These include marked nuclear atypia and atypical mitoses in the stromal and multinucleated giant cells, as well as the presence of neoplastic cartilage or malignant osteoid.
- Note that in approximately 30% of cases, intravascular invasion is present. This incidental finding does not appear to correlate with

local aggressiveness or the development of pulmonary implants (see Dorfman HD, Czerniak B. Bone tumors. 1998). In a small number of patients, GCTs produce "benign", self-limited, non-invasive, pulmonary implants, which are successfully treated by surgical excision.

- Common secondary changes in GCT are hemorrhage and necrosis, fibrohistiocytic (xanthomatous) change, and aneurysmal bone cyst formation. Complications include pathologic fractures and malignant transformation (dedifferentiation).
- Clinical behavior. Conventional GCT is a locally aggressive neoplasm, which may produce bone destruction and soft tissue invasion. Local recurrences are common (25% - 30%) and may involve bone and/or soft tissue. **The risk of local recurrence is related to radiologic stage rather than particular histologic characteristics.** Secondary malignant transformation, a rare complication seen mostly in patients with prior irradiation, may be in the form of MFH, osteosarcoma or fibrosarcoma. **Primary de-novo malignant GCT is extremely rare** and is characterized by marked nuclear atypia of stromal cells and atypical mitoses.

Available publications for the topic: [Giant Cell Tumor of Bone](#)

Selected References::

1. O'Donnell RJ, Springfield DS, Motwani HK, et al: Recurrence of giant cell tumors of the long bones after curettage and packing with cement. J Bone Joint Surg 76A:1827, 1994
2. Kay RM, Seeger LL, et al: Pulmonary metastases of benign giant cell tumor of bone. Six histologically confirmed cases, including one with spontaneous regression. Clin Orthop Rel Res 302:219, 1994
3. Fornasier VL, Protsner K, Zhang I, Mason L: The prognostic significance of histomorphometry and immunohistochemistry in giant cell tumors of bone. Hum Pathol 27:754, 1996
4. Sanjay BKS, Sim FH, Unni KK, et al: Giant cell tumours of the spine. J Bone Joint Surg 75B:148, 1993

Case #6

Typical Clinical Presentation:

A 14-year-old female was seen in consultation for an increasingly painful left humeral lesion associated with mild joint effusion.

- Pay attention to the patient's age, skeletal location, and the presence of joint effusion, which may complicate epiphyseal lesions.

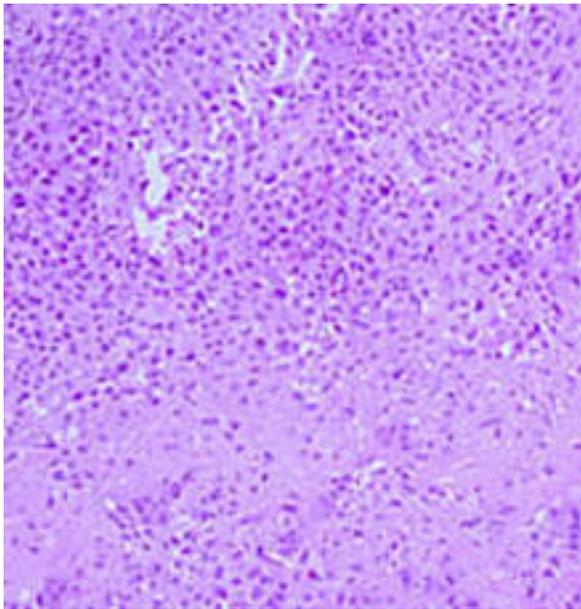
Characteristic Radiological Findings:



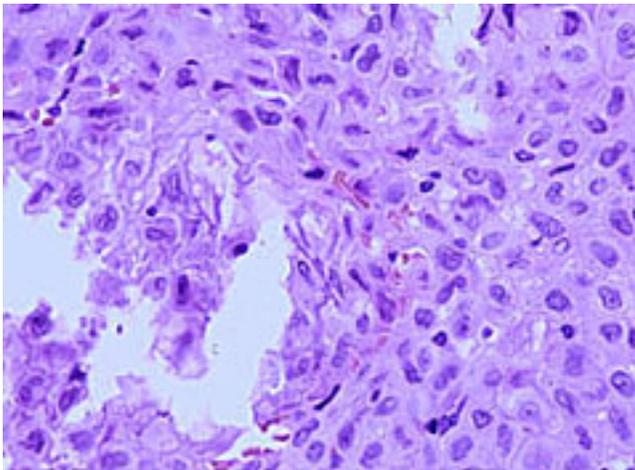
- Plain radiograph showed an irregular, but circumscribed, lytic epiphyseal lesion surrounded by reactive bone sclerosis. There was no evidence of bone expansion, and the cortex was intact. The growth plates were open.

The clue here is **the epiphyseal location** of the tumor above the open growth plate, and "benign" radiological features (good demarcation and a sclerotic rim).

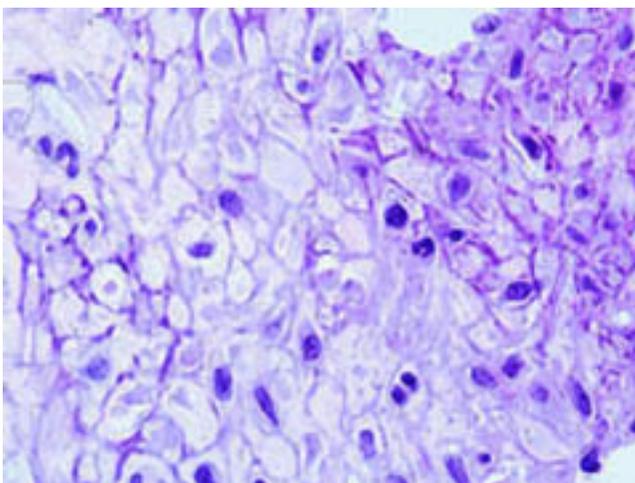
Pathological Findings: :



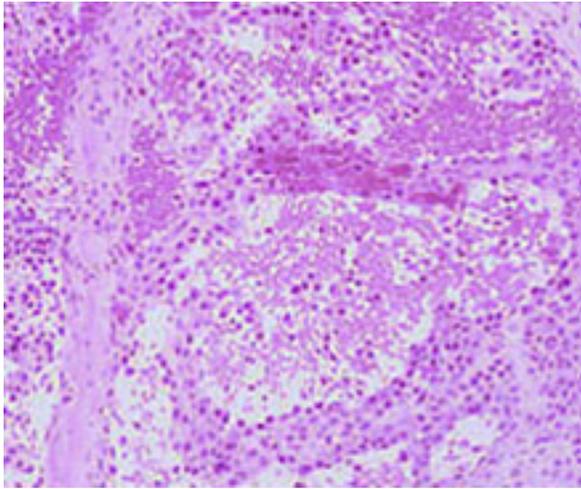
- Curettage material showed a **highly cellular tumor consisting of sheets of round to polygonal cells**. Multiple small foci of immature bluish-pink chondroid were present giving a vaguely lobular appearance to the tumor. Many multinucleated giant cells were scattered throughout the lesion.



- The cells were of intermediate size with folded, or clefted, nuclei, fine chromatin pattern and occasional inconspicuous nucleoli. Mitotic activity was low.



- The cytoplasmic borders were very distinct with multiple foci of "**chicken-wire**" **calcification** (calcified reticulin network around individual tumor cells).



- Few areas showed secondary cystic change.

Diagnosis: Chondroblastoma

Salient Points::

- Chondroblastoma is a **rare benign neoplasm** occurring in 75% of cases in the second decade of life, when the growth plates are still open. This is one of two neoplasms of *incompletely differentiated cartilage*. The other neoplasm is chondromyxoid fibroma.
- Most common locations are the long bones (70% arise in the proximal humerus and at the knee), and flat bones, including pelvis. In the long bones, the tumor almost invariably occurs in the epiphysis.
- **The neoplastic round and polygonal cells are chondroblasts positive for S-100. Multinucleated giant cells are of different cell line and stain positive for histiocytic markers (CD68). "Chicken-wire" calcification is virtually pathognomonic of chondroblastoma.**
- Secondary cystic change in the form of aneurysmal bone cyst is very common (20% - 30% of cases). This is most often seen in tarsal bones. Other types of cystic change include formation unilocular or multilocular cystic spaces filled with serous fluid.
- Differential Diagnosis. Unlike chondroblastoma, Giant Cell Tumor (GCT) occurs in skeletally mature individuals, lacks chondroid matrix, and shows negative staining with S-100. Chondromyxoid fibroma is centered in the metaphysis and lacks calcification. Clear cell chondrosarcoma, epiphyseally located malignant neoplasm, occurs in patients older than 40 years and shows clearly malignant chondrocytes and the characteristic large cells with clear cytoplasm.
- Clinical behavior. Chondroblastoma is a benign neoplasm, which can be successfully treated with curettage. Recurrence rate is about

10% within the bone or in the adjacent soft tissue. **Similar to GCT, chondroblastoma can occasionally produce "benign", clinically non-progressive lung implants** . They can be successfully managed with surgery. The term "aggressive chondroblastoma" is applied to large, locally destructive lesions, which may erode through the cortex and invade the soft tissue. This behavior is relatively more common in pelvic lesions.

Available publications for the topic: [Chondroblastoma](#)

Case #7

Typical Clinical Picture:

A 22-year-old female was seen in consultation for a lesion in the proximal femur. She complained of chronic mild to moderate pain in her right hip and was walking with a noticeable limp. Physical examination revealed hip deformity and minimal limb length discrepancy. There were no other abnormal findings.

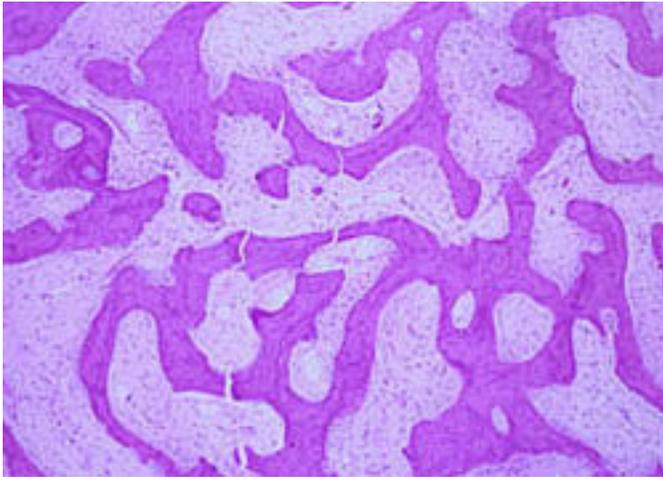
Characteristic Radiological Findings:



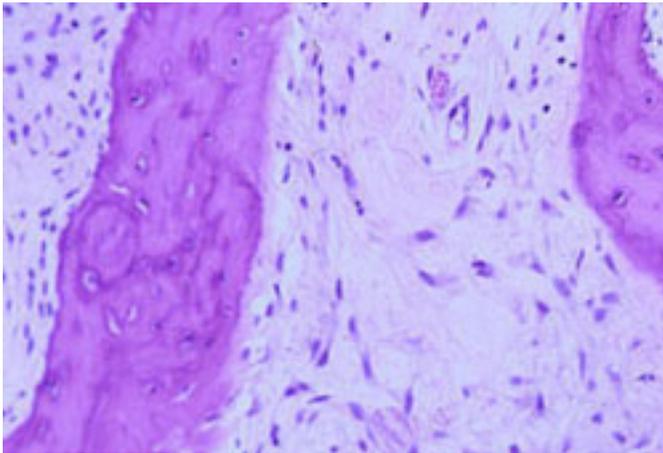
- Plain film shows a large, elongated, well-defined intramedullary lesion of the proximal femur with "shepherd's crook" deformity (lateral bowing) due to a healed pathologic fracture. The lesion is partially surrounded by a sclerotic rim and has a complex appearance with lytic areas, multiple foci of "ground glass" density, and radiopaque areas.

Note the intramedullary location of the lesion and its overall "benign" appearance evidenced by good demarcation, geographic pattern of bone destruction and partial sclerotic rim. A very characteristic feature is "*ground glass*" (*homogenous*) density. **Remember that when this disorder involves the long bone, it commonly produces what is called "long lesion in the long bone" with three key features: lucency, sclerotic rim and cortical expansion.**

Pathological Findings: :



- Curettage specimen consisted of pieces of firm, white-gray, gritty tissue. Microscopic examination showed moderately cellular fibrous tissue with a whorled arrangement of bland spindle cells and interspersed, slender, curved trabeculae of focally calcified woven bone ("chinese characters").



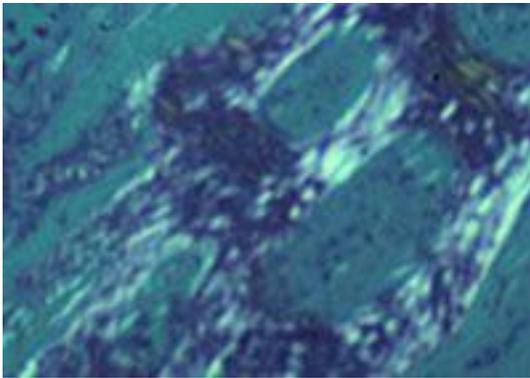
- The majority of the trabeculae did not show an osteoblastic rimming or osteoclastic activity.

Remember **three characteristic histologic features of this entity: a) thin, wavy spicules of woven bone ("chinese characters"); b) lack of osteoblastic rimming or osteoclastic activity; c) moderately cellular bland fibrous background.** In children, stromal mitoses may be frequent, 1 to 5 per hpf. In adults, mitotic figures are very rare to absent.

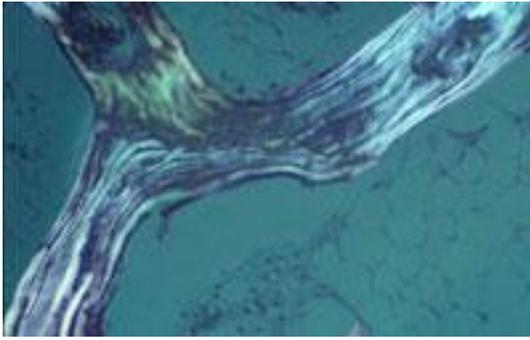
Diagnosis: Fibrous Dysplasia

Salient Points:

- Fibrous dysplasia is a **common benign fibro-osseous lesion**, which occurs sporadically during the period of skeletal growth (ages 10 to 25). It is a hamartoma and is characterized by the intramedullary location. There are two forms of the disease: monostotic (80% of cases) and polyostotic. Polyostotic involvement may be a part of McCune-Albright syndrome (fibrous dysplasia, patchy cutaneous pigmentation, and precocious puberty), or Mazabraud's syndrome (fibrous dysplastic lesions in close proximity to soft tissue myxomas).
- Most common locations include the long bones (femur, tibia and humerus), the ribs, cranio-facial bones and pelvis. In the long bones, the lesion is found in the metaphysis or diaphysis.
- **The hallmark of fibrous dysplasia is inability of tissue at the affected site to produce mature lamellar bone.** The maturation is arrested at the level of woven bone. The difference between the two types of bone is best appreciated by using polarizing light.



- **Woven bone (immature bone)** is characterized by random arrangement of the collagen fibers. **In adults, this type of bone is only seen in pathologic conditions such as fracture repair or bone-forming tumors.** Keep in mind that in benign conditions the bone trabeculae are surrounded by a fibrovascular stroma. In malignant tumors, those spaces are often occupied by malignant cells.



- In **lamellar (mature) bone**, the collagen fibers are orderly arranged forming layers, known as *lamellae*.

- Clinical behavior. Pathologic fractures and bone deformities are common complications. Occasionally, lesions may show rapid enlargement due to secondary cystic changes including aneurysmal cyst formation. Malignant transformation is a rare complication (less than 1%), more common with polyostotic disease. Secondary malignancies are high-grade sarcomas (MFH, osteosarcoma, chondrosarcoma).
- Differential diagnosis. Two important differential diagnoses include well-differentiated intramedullary osteosarcoma and, in the tibia, osteofibrous dysplasia. Low-grade osteosarcoma is characterized by infiltrative growth pattern and mild cellular atypia. Bone spicules are often rimmed by mildly atypical osteoblasts. Osteofibrous dysplasia can be ruled out based on the intracortical location and orderly osteoblastic rimming of bone spicules.

Available publications for the topic: [Fibrous Dysplasia of Bone](#)

Case #8

Typical Clinical Presentation:

An incidental finding of a bone lesion in the distal tibial meta-diaphysis of an 13-year-old male. The lesion was totally asymptomatic.

- As always, pay attention to the patient's age. The fact that the lesion did not produce symptoms and was found incidentally suggests benignancy.

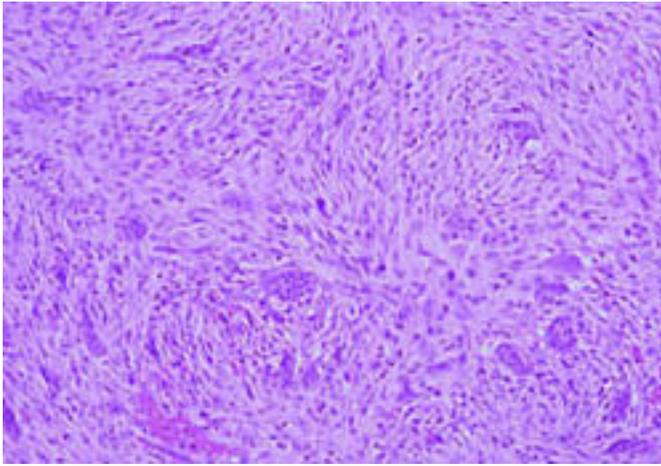
Characteristic Radiological Findings:



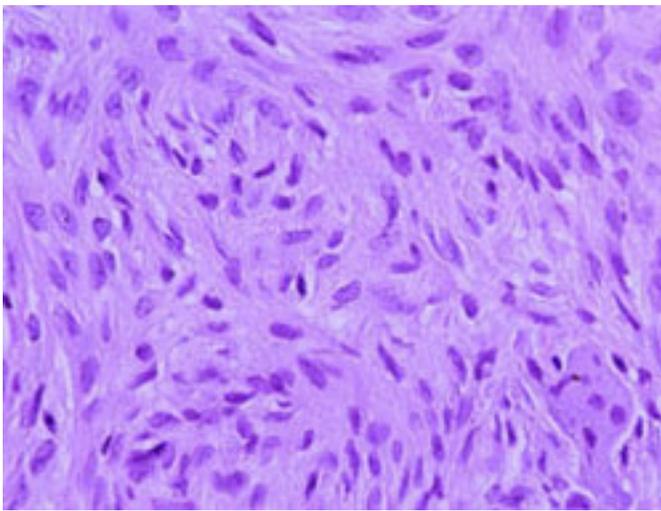
- Plain radiograph shows a sharply demarcated, lucent, loculated, **meta-diaphyseal lesion** surrounded by a rim of sclerotic bone. The lesion predominantly involves the lateral portion of the bone and produces mild cortical expansion.

Radiological findings are so typical that the diagnosis can be made with certainty by X-ray alone provided the lesion is in the typical skeletal site and appropriate age group. **Note the eccentric location along the long axis of the bone.** Large lesions can involve the entire diameter of the bone expanding the cortex. However, they are always sharply demarcated and rimmed by sclerotic bone.

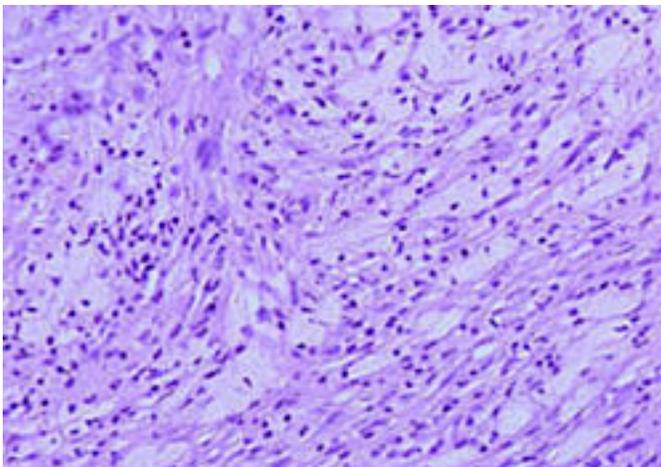
Pathological Findings:



- Curettage specimen consisted of firm red-tan tissue with few small yellowish areas. Low power view showed a moderately cellular lesion composed of **uniform spindle cells in a storiform pattern and scattered giant cells**; .



- **Spindle cells had bland appearance.** Mitotic figures were easily found averaging 4 per 10 hpf. However, no atypical mitoses were identified.



- Multiple collections of **foamy histiocytes (xanthoma cells)** were seen throughout the lesion. Other fields showed hemosiderin-laden macrophages.

Diagnosis: Non-Ossifying Fibroma (NOF)

(fibrous cortical defect, or metaphyseal cortical defect)

Salient Points:

- NOF is a **common, non-neoplastic, self-healing lesion occurring in skeletally immature individuals**, usually between the ages of 5 and 20 years. Small lesions are usually incidental radiological findings. The larger lesions occupying more than a half of the bone diameter may present with a pathologic fracture.
- Location. In most cases, NOF presents as a solitary lesion in the **metaphysis or meta-diaphysis of the long bone** at the knee (distal femur, proximal tibia or fibula), distal tibia and proximal humerus. A syndrome of multiple non-ossifying fibromas and cutaneous cafe au lait spots is known as Jaffe-Campanacci syndrome.
- For lesions that have the histologic features of NOF but occur in unusual locations such as pelvis, ribs or vertebrae, some authors use the term "benign fibrous histiocytoma". However, the designation remains controversial and is not generally accepted.
- GCT may enter your differential diagnosis. Remember, however, that it is characterized by the epiphyseal location and occurrence in adults.

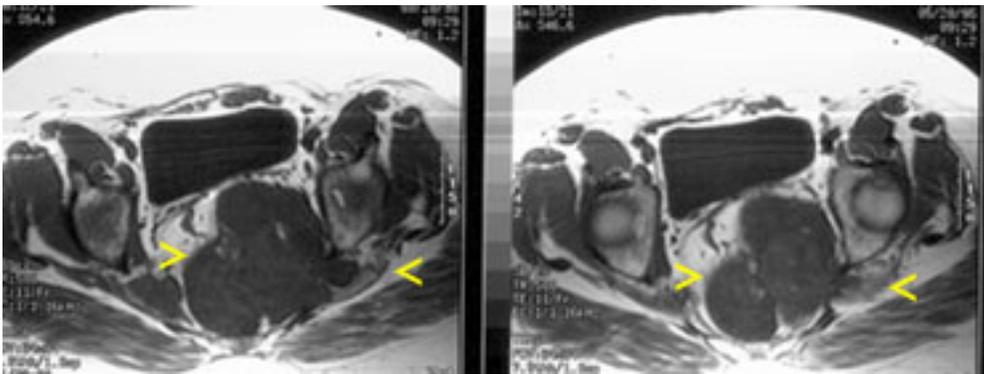
Available publications for the topic: [Non-Ossifying Fibroma](#)

Case #9

Typical Clinical Presentation:

A 52-year-old female presented with an 8-month history of dull low back pain, mostly over the sacrum, and recent onset of rectal pain and constipation. Her past medical history was non-contributory.

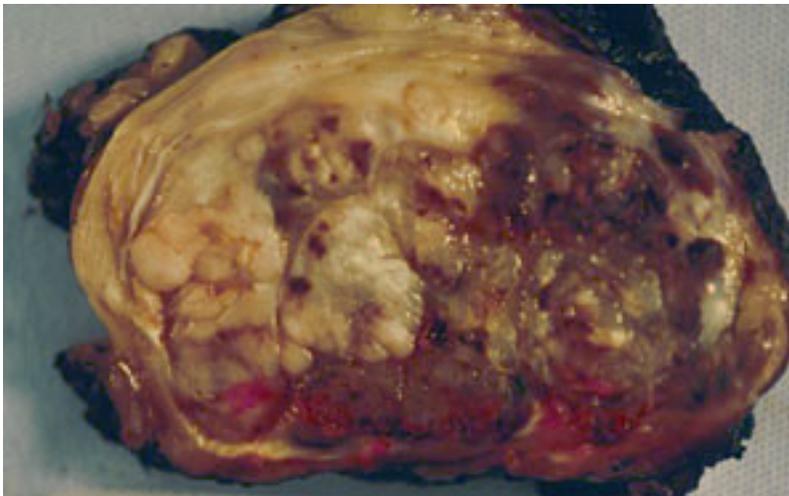
Characteristic Radiological Findings:



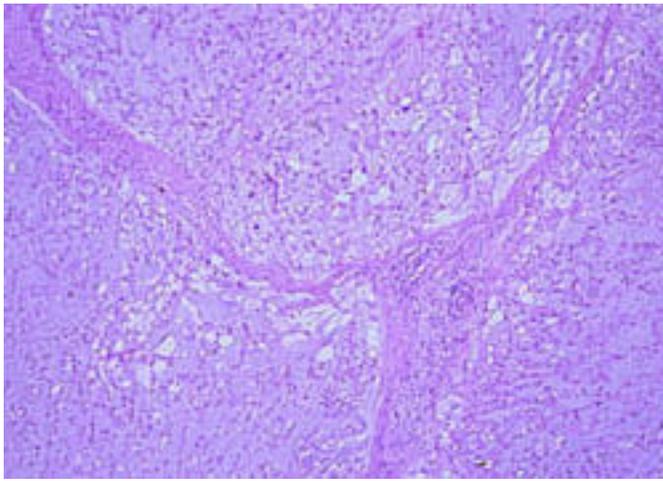
- MRI film shows a large, destructive, sacral mass with lobulated margins and antero-lateral soft tissue extension. The tumor appears to be centered in the midline.

The diagnostic clue here is the midline, axial location of the tumor. Also note "malignant" radiological features of the tumor evidenced by cortical destruction and a soft tissue mass.

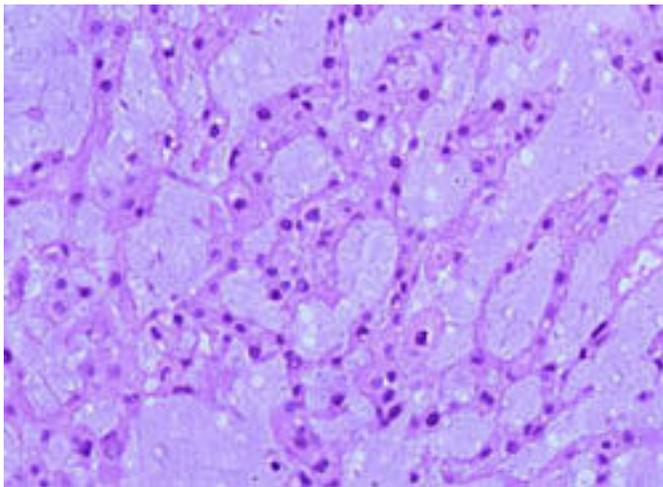
Pathological Findings: :



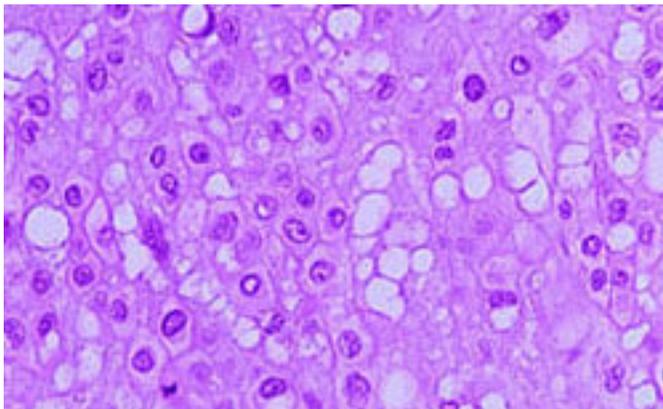
- Grossly, the tumor was **multilobulated with glistening cut surfaces and soft to gelatinous consistency**. Extensive hemorrhages and necrotic areas were present.



- Low-power view shows characteristic lobular architecture.



- The tumor shows cord-like arrangement of cells and abundant myxoid extracellular matrix.



- Two types of cells can be appreciated: smaller ovoid cells and the larger cells with numerous cytoplasmic vacuoles. The latter are the hallmark of this tumor and are called "**physaliphorous cells**". Occasional mitotic figures were identified. However, no atypical mitoses were found. These tumors often demonstrate

significant cellular pleomorphism that is, probably, of no prognostic significance.

Diagnosis: Chordoma

Salient Points::

- Chordoma is **an uncommon, slow-growing malignant bone tumor**, which is thought to arise from the notochord remnants. Peak age incidence is between 55 and 65 years.
- In 85% of cases, the tumor arises at either end of the notochord: in the sacrococcygeal(50%) or sphenoccipital(35%) regions. The remaining 15% involve the mobile spine.
- Immunohistochemistry is a very helpful tool in the differential diagnosis of this tumor. **Characteristically, chordoma shows positive staining with S-100 and epithelial markers (cytokeratin and EMA).**
- Two histologic variants are recognized: **chondroid chordoma** and **dedifferentiated chordoma**. Chondroid chordoma is a tumor containing a mixture of chondroid and cartilagenous elements. It seems to be associated with better prognosis. Dedifferentiated chordoma is a highly malignant biphasic neoplasm composed of typical chordoma and high-grade sarcoma. Use of immunostains usually helps to resolve diagnostic difficulties.
- Distinguishing a chordoma from a large notochordal rest (benign remnant of notochord tissue) may be difficult. "These lesions are histologically and immunohistochemically identical. In this situation, only evidence of destructive growth can identify a chordoma" (McCarthy EF, Frassica FJ. Pathology of Bone and Joint Disorders. 1998).
- Clinical Behavior. Chordomas are typically locally aggressive neoplasms, which because of their location may affect vital structures. With advanced tumors complete excision is difficult to achieve, and multiple local recurrences are typical. Distant metastases occur late in the course of disease and usually involve lungs, lymph nodes and skin.
- **Experimental data:** There seem to be no correlation between the morphologic appearance of a tumor and the clinical course. As reported by Bergh et al, the only two histological features that may have prognostic significance are microscopic tumor necrosis and Ki-67 labeling index >5%. Cytogenetic analysis of chordomas shows no specific or characteristic chromosomal anomaly. Telomere elongation, microsatellite instability and loss of heterozygosity (LOH) have been reported in small series of cases.

Available publications for the topic: [Chordoma](#)

Selected References:

1. Rosenberg AE, Brown GA, Bhan AK, et al: Chondroid chordoma - a variant of chordoma: A morphologic and immunohistochemical study. *Am J Clin Pathol* 101:36, 1994
2. Wojno KJ, Hruban RH, Garin-Chesa P, et al: Chondroid chordomas and low-grade chondrosarcomas of the craniospinal axis. *Am J Surg Pathol* 16:1144, 1992
3. Bergh P, Kindblom LG, Guntenberg B, Remotti F, Ryd W, Meis-Kindblom JM. Prognostic factors in chordoma of the sacrum and mobile spine: a study of 39 patients. *Cancer* 2000;88(9):2122-2133
4. Klingler L, Shooks J, Fiedler PN, Marney A, et al. Microsatellite instability in sacral chordoma. *J Surg Oncol* 2000;73:100-103

Case #10

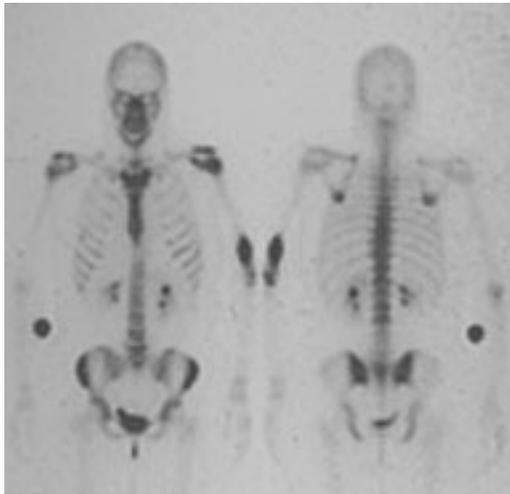
Typical Clinical Presentation:

A 14-year-old female presented with a 3 months history of increasing pain in her elbow.

Characteristic Radiological Findings:



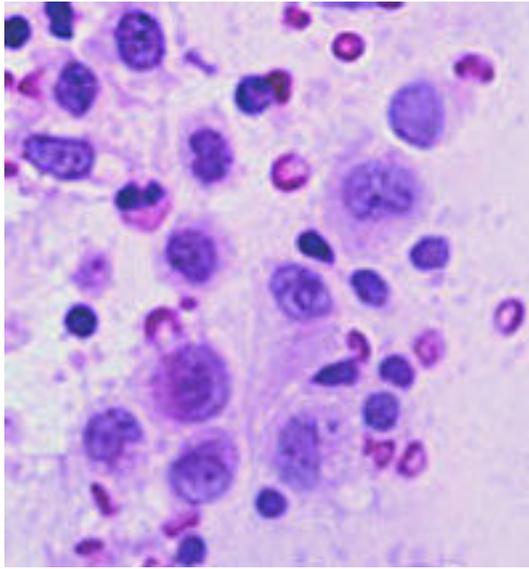
- Plain film showed a well circumscribed, "punched-out" lytic, intramedullary lesion in the distal humeral shaft. There was no sclerotic rim and no periosteal reaction.



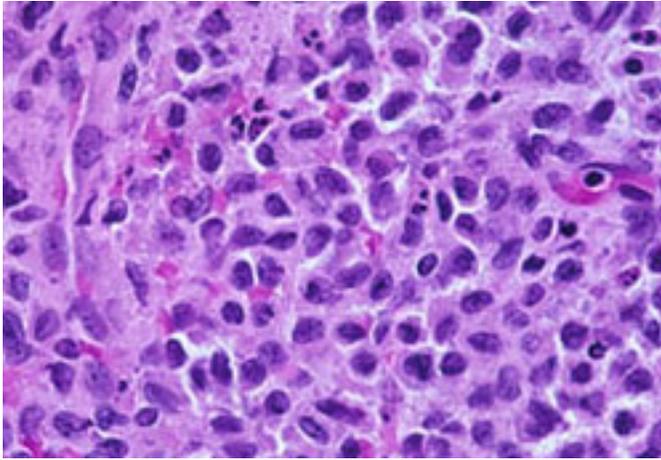
- Full skeletal survey showed no other lesions.

A well defined, "punched-out" appearance, intramedullary location and lack of periosteal reaction are very common in this lesion.

Pathological Findings: :



- Microscopically, the lesion was composed of several cell types. The predominant cell population was that of mononuclear, histiocyte-like cells with **indented or grooved nuclei** and distinct cytoplasmic borders (Langerhans cells). No mitoses were seen.



- The lesion also contained multiple eosinophils, mononuclear inflammatory cells and occasional osteoclast-like, multinucleated giant cells.

Diagnosis: Eosinophilic Granuloma (EG)

Salient Points:

- Classification of the lesions of **Langerhans Cell Histiocytosis** is based on the extent of disease and includes the following three forms:
 - a. **eosinophilic granuloma** (localized form of disease at single skeletal sites)
 - b. **Hand-Schuller-Christian disease** (extensive, multifocal, symptomatic disease with predominantly skeletal involvement)
 - c. **Letterer-Siwe disease** (aggressive systemic form of disease that involves multiple organs and systems and leads to functional impairment of the affected sites).
- EG commonly occurs in individuals younger than 30 years and has the highest incidence in the first decade of life.
- Location. Skeletal sites include craniofacial bones, ribs, vertebrae, pelvis, and major long bones such as femur and humerus. Small bones of the hands and feet are not affected. Extraskeletal lesions most commonly arise in the lungs and lymph nodes.
- The **Langerhans cells** are pathognomonic and clonal. They are characterized by histiocyte-like appearance and indented or grooved nuclei. Unlike histiocytes, these cells show strong positivity for **S-100** and **CD1a**, and contain **Birbeck granules** (rod-shaped and tennis racquet-shaped cytoplasmic inclusions), which can be demonstrated by electron microscopy.
- Differential diagnoses include osteomyelitis, granulomatous inflammation, Hodgkin's and non-Hodgkin's lymphoma. Identification of morphologic features of Langerhans cells and the use of appropriate markers and/or EM help to resolve diagnostic problems.
- Clinical behavior. EG is a benign, self-limited disorder. Progression to systemic disease occurs exclusively in the first two years of life.

Available publications for the topic: [Eosinophilic Granuloma](#)

Case #11

Typical Clinical Presentation:

A 12-year-old boy presented with a short history of pain in his thigh.

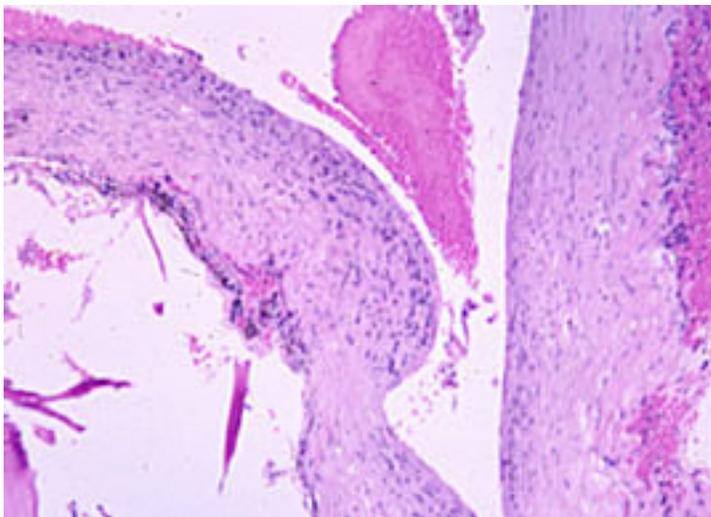
Characteristic Radiological Findings:



- Plain radiograph demonstrates a well-defined, symmetric, expansile, intramedullary lytic lesion of the proximal femur.

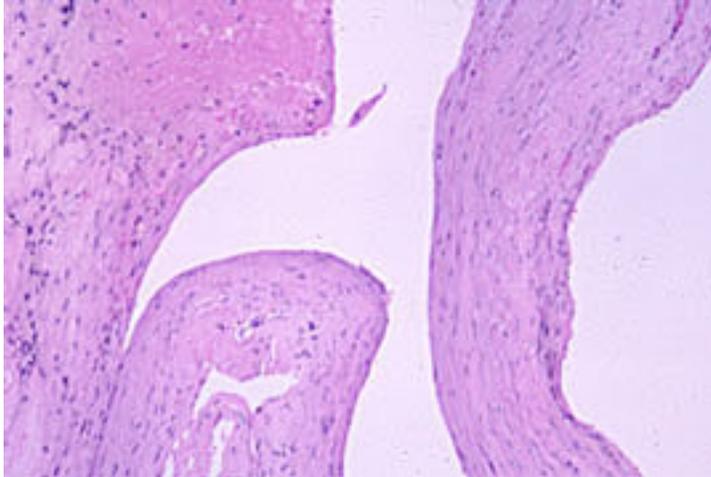
Above findings are common with benign, slowly growing lesions. In this case, the location and symmetric, expansile growth pattern are very important diagnostic clues. Note that there is no cortical disruption.

Pathological Findings: :

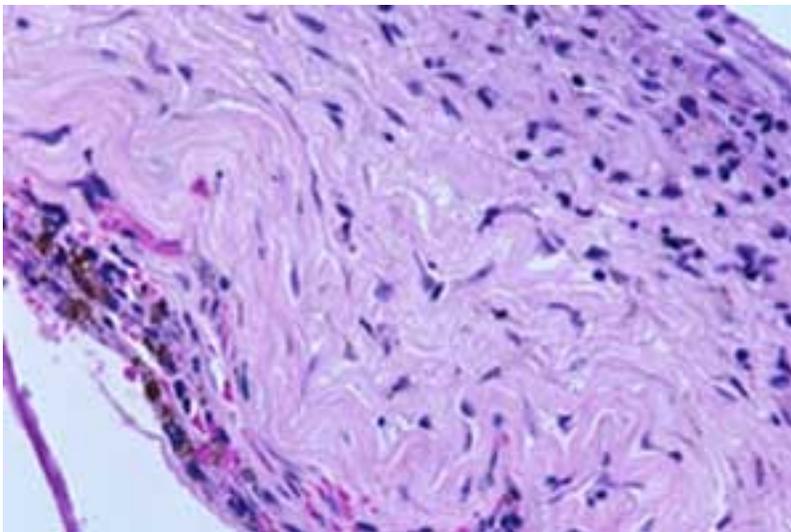


- The specimen was labeled "cyst wall" and consisted of **scant** fragments of rubbery white-gray tissue. Microscopic examination showed bland fibrous tissue with sparse inflammatory

infiltrate,
hemosiderin-
laden
macrophages, and
occasional
osteoclast-like
multinucleated
giant cells.



- Low magnification, additional



- High magnification

Diagnosis: Solitary Bone Cyst (SBC)

Salient Points:

- Solitary bone cyst is relatively common, non-neoplastic lesion, which typically occurs in the skeletally immature patients, in the first and second decades of life (80% of cases). It is usually a unicameral cyst, which does not have an epithelial lining (hence not a true cyst) and is filled with serous fluid.
- Location. About 80% of cases are diagnosed in two locations: humerus and proximal femur. In the long bone, SBC characteristically involves the metaphysis and diaphysis. Other possible skeletal sites are the ilium, talus, and calcaneus.
- Differential Diagnosis. **You should be aware of the cystic nature of the lesion (ask the surgeon!** - to his eye, the lesion is a cavity filled with clear fluid) This will help you to avoid misdiagnosis of SBC as a solid lesion.
- Clinical Behavior. SBC is a benign, slowly growing lesion with recurrence rate of approximately 15%. Pathologic fracture is a common complication. Rare cases of secondary malignancy (chondrosarcoma) have been reported

Available publications for the topic: [Solitary Bone Cyst](#)

Case #12

Typical Clinical Presentation:

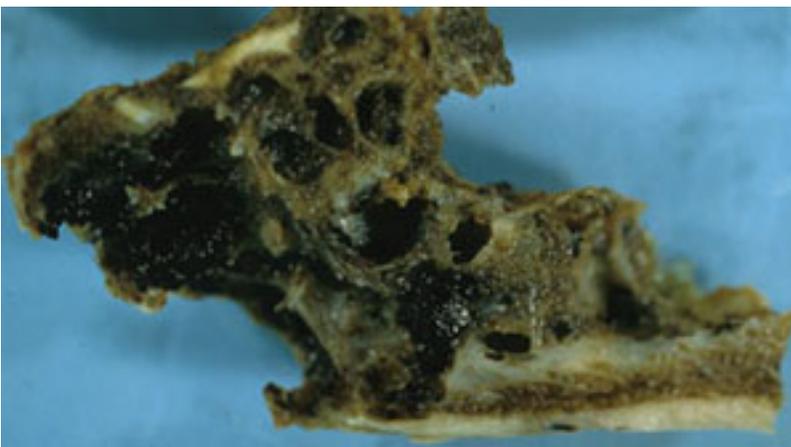
A 17-year-old male presented with a slowly enlarging, painful lesion of the right clavicle.

Characteristic Radiological Findings:

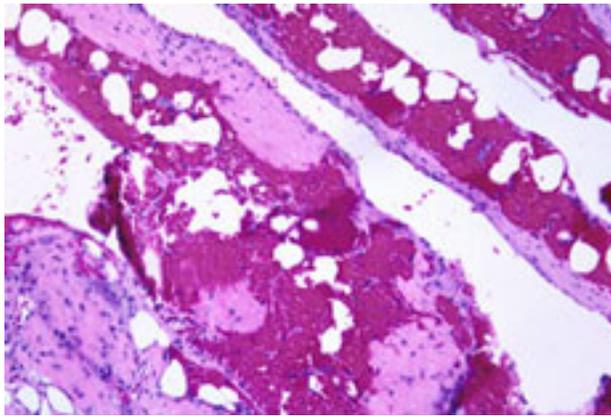


- Plain radiograph reveals a circumscribed, loculated, radiolucent lesion producing **blowout expansion** of the bone.

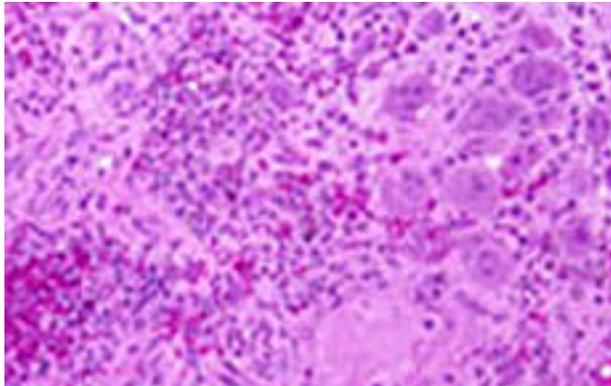
Pathological Findings: :



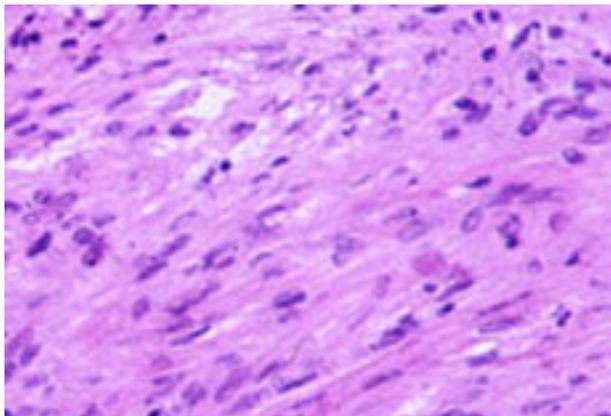
- Gross photograph shows a spongy, expansile lesion containing multiple, blood-filled cavities of varying sizes.



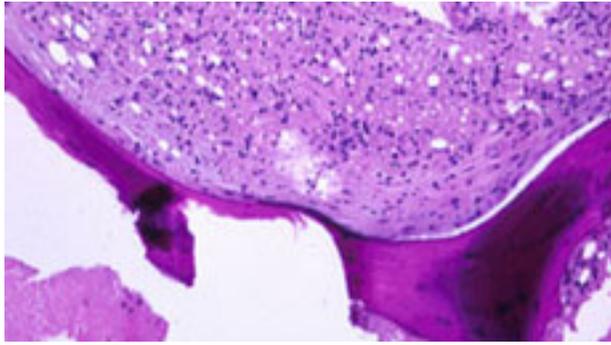
- Low-power view demonstrates blood-filled cystic spaces **without** recognizable epithelial lining.



- The septa are composed of vascular fibrous tissue containing multiple osteoclast-like giant cells, inflammatory cells and extravasated RBCs.



- High-power view shows uniform, but mitotically active stromal cells. However, no atypical mitoses were identified.



- The periphery of the lesion shows "pushed down", curved trabeculae of pre-existing lamellar bone.

Diagnosis: Aneurysmal Bone Cyst (ABC)

Salient Points:

- Aneurysmal Bone Cyst (ABC) is a rapidly growing, locally aggressive, intramedullary, vascular lesion, which characteristically produces blowout expansion of the affected portion of the bone. ABC can be primary (de novo) or secondary. **Secondary ABC may develop in a pre-existing benign lesion such as chondroblastoma, chondromyxoid fibroma, giant cell tumor, and fibrous dysplasia, or be superimposed on a malignant tumor (osteosarcoma).**
- Although ABC can occur at any age, the majority of patients are younger than 25 years.
- ABCs are unique among bone tumors in their almost uniform skeletal distribution and ability to spread to the adjacent bones and across the joint spaces (Dorfman HD, Czerniak B. Bone Tumors, 1998). Remember that it is a common lesion in the spine. In a long bone, ABC is usually centered in the metaphysis.
- Differential Diagnosis. **In diagnosis of ABC, correlation with clinical and radiological data is essential. Remember that secondary ABCs are common.** Therefore, you should examine the entire curettage specimen to search for evidence of a pre-existing lesion. The nature of that lesion, not the secondary cystic change, determines the clinical behavior. Underlying giant-cell tumor is suggested by the epiphyseal location in the knee area of a skeletally mature individual. The epiphyseal ABC in a teenager or a tarsal bone ABC suggests a chondroblastoma as an underlying lesion. Teleangiectatic variant of osteosarcoma may be extremely difficult to differentiate from an ABC, especially if the latter has "aggressive" radiological features. However, keep in mind that teleangiectatic osteosarcoma is a high-grade malignancy, and should have foci of sarcomatous stroma with markedly atypical cells, numerous mitoses and atypical mitoses. The presence of "malignant osteoid" is another feature distinguishing osteosarcoma from a benign lesion.

Available publications for the topic: [Aneurysmal Bone Cyst](#)

Selected References:

1. Martinez V, Sissons HA: Aneurysmal bone cyst. A review of 123 cases including primary lesions and those secondary to other bone pathology. *Cancer* 61:2291, 1988
2. Bertoni F, Bacchini MD, Capanna R, et al: Solid variant of aneurysmal bone cyst. *Cancer* 71: 729, 1993

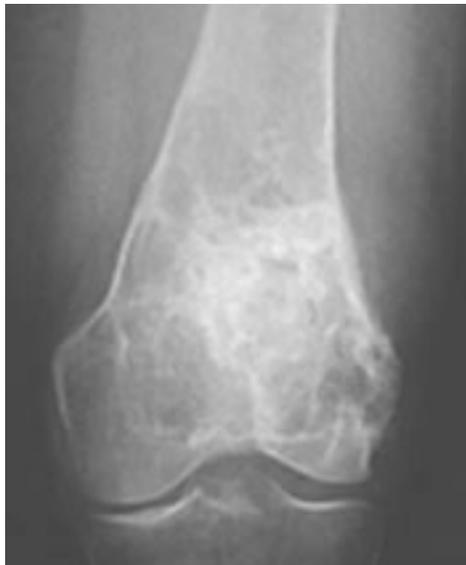
Case #13

Typical Clinical Presentation:

A 45-year old female presented with increasing pain and swelling around the knee. She mentioned that the symptoms had progressed over a 4-month period.

- Age of the patient is an important diagnostic clue. If a pathologic fracture is excluded, pain and swelling imply active growth of the lesion.

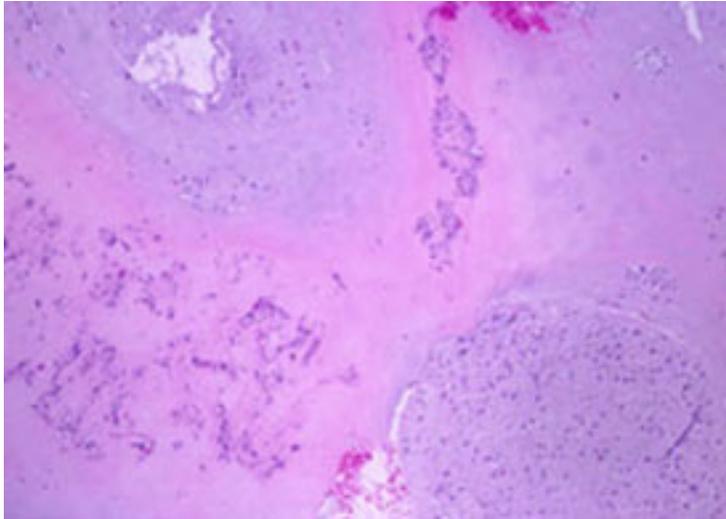
Characteristic Radiological Findings:



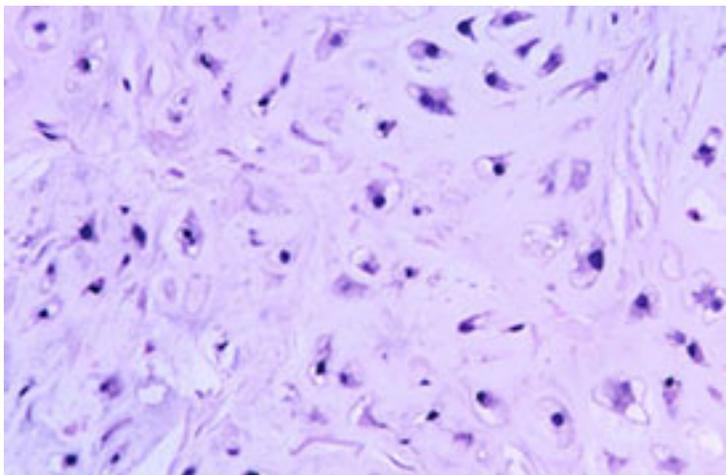
- Plain film demonstrates a **large**, lobulated, **ill-defined** lesion centered in the distal femoral metaphysis. There is **endosteal scalloping and periosteal thickening**. Central stippled and "ring and arc" calcifications are apparent and are typical of cartilaginous matrix. Small radiolucent areas are seen at the periphery of the lesion.

These are the features of a locally aggressive, cartilage-producing tumor. The size of the lesion and the presence of radiolucent foci are very suggestive of malignancy.

Pathological Findings: :



- Low magnification shows a moderately cellular, lobulated cartilaginous tumor.

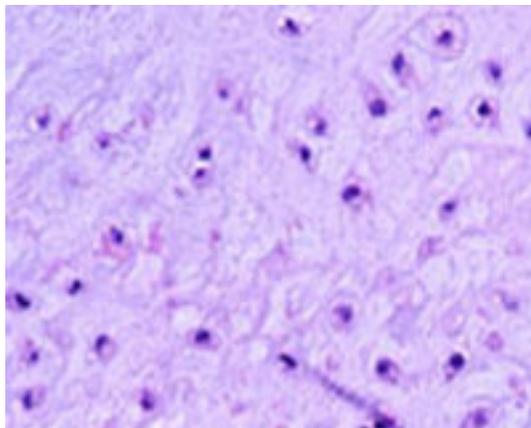


- High-power view shows scattered plump, moderately pleomorphic chondrocytes. Binucleated cells are present. Mitotic rate averaged 1 per 10 hpf.

Diagnosis: Chondrosarcoma, low-grade (Grade 2)

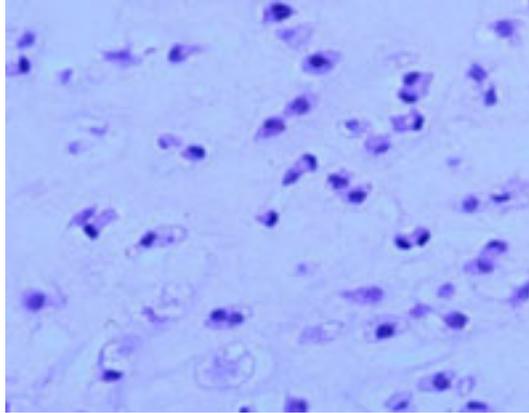
Salient Points::

- **Chondrosarcoma is a malignant, cartilage-producing tumor, which unlike most other primary bone tumors, tends to occur in the older age group (30-50 years) and is extremely rare in children. When it does occur in children, it is almost always of a high grade (Grade 3). The majority of chondroid tumors in children and adolescents are chondroblastic osteosarcomas, not chondrosarcomas.**
- Chondrosarcoma is the second most common primary malignant bone tumor after osteosarcoma.
- There are several variants of chondrosarcoma which differ by their location and histologic subtype. Sometimes, chondrosarcomas are subdivided into primary and secondary to indicate whether they have arisen in a pre-existing benign lesion. Secondary chondrosarcoma may develop at the sites of radiation osteitis and Paget's disease. Some benign bone lesions (osteochondroma, enchondroma, fibrous dysplasia) may undergo malignant transformation to a chondrosarcoma.
- Location. Unlike benign cartilaginous lesions, chondrosarcoma has predilection for the trunk bones including the pelvis (particularly, ilium), the ribs, and scapula. It is also common in the long bones such as the femur and humerus.
- **The aggressiveness of chondrosarcomas can be predicted by their histologic grade.** Grading system is based on three parameters: cellularity, degree of nuclear atypia and mitotic activity.



- **Grade 1 (low-grade)**
Very similar to enchondroma. However, the cellularity is higher, and there is mild cellular pleomorphism. The nuclei are small but often show open chromatin pattern and small nucleoli. Binucleated cells are frequent. Mitoses are very rare. Grade 1 chondrosarcomas are locally aggressive

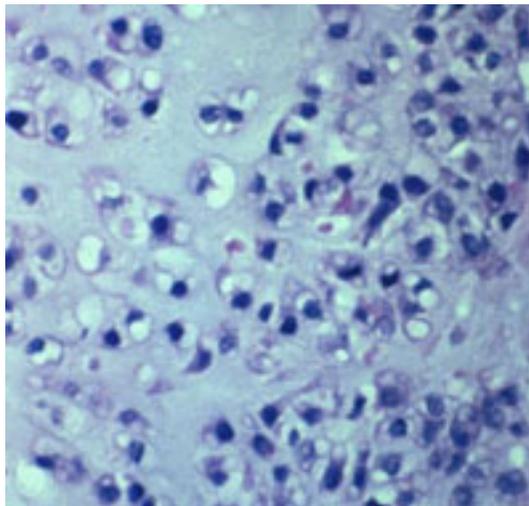
and prone to recurrences, but usually do not metastasize.



- **Grade 2 (low-grade)**

The cellularity is higher than in Grade 1 tumors.

Characteristic findings are moderate cellular pleomorphism, plump nuclei, frequent bi-nucleated cells, and occasional bizarre cells. Mitoses are rare. Foci of myxoid change may be seen. Unlike Grade 1 tumors, about 10% to 15% of Grade 2 chondrosarcomas produce metastases.

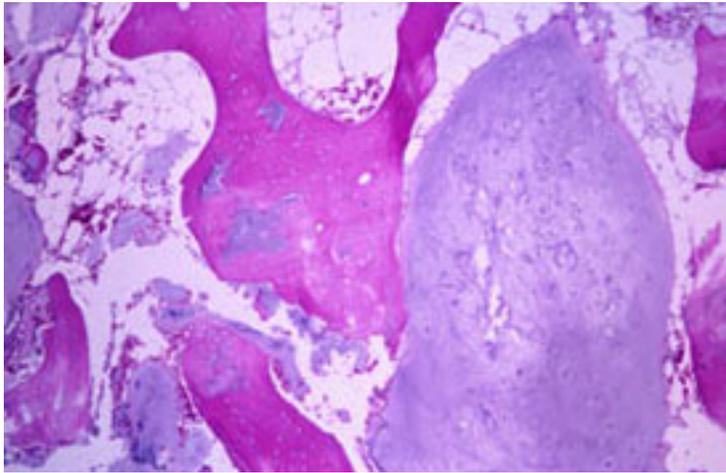


- **Grade 3 (high-grade)**

Characteristic findings are high cellularity, marked cellular pleomorphism, high N/C ratio, many bizarre cells and frequent mitoses (more than 1 per hpf). These are high grade tumors with significant metastatic

potential.

- One of the most important diagnostic features of malignancy is **infiltrative growth pattern**. Enchondromas usually have well defined borders with no evidence of invasion. Quite often you will see nodules of enchondroma surrounded by the bone marrow and reactive bone trabeculae. That should not be mistaken for invasion.



- On the contrary, **malignant nodules of chondrosarcoma infiltrate between the lamellar bone obliterating the marrow**. Separation of the nodules by fibrous bands would be another feature highly suggestive of malignancy.

- Prognosis. Survival is related to the histologic grade, location and stage of the tumor. Low-grade (Grades 1 and 2) tumors are locally aggressive and prone to recurrences, but their metastatic potential is low. Recurrent tumors may show an increase in grade. High-grade (Grade 3) tumors metastasize to the lungs, skin, and soft tissues.
- **Experimental data:** Studies have shown that p53 overexpression and high Ki-67 proliferation index correlate with clinically aggressive behavior in chondrosarcomas. Recent data suggest that these immunohistochemical stains may be particularly useful for determining the prognosis of patients with Grade 2 chondrosarcomas.

Available publications for the topic: [Chondrosarcoma, low-grade](#)

Selected References:

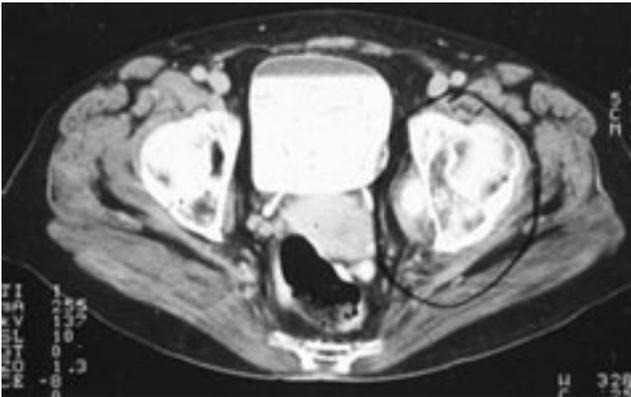
1. Hasegawa T, Seki K, Yang P, et al: Differentiation and proliferative activity in benign and malignant cartilage tumors of bone. *Hum Pathol* 26:838, 1995
2. Oshiro Y, Chaturvedi V, Hayden D, Nazeer T, Johnson M, Johnston DA, Ordonez NG, Ayala AG, Czerniak B. Altered p53 is associated with aggressive behavior of chondrosarcoma: a long-term follow-up study. *Cancer* 1998;83(11):2324-2334
3. Nawa G, Ueda T, Mori S, et al: Prognostic significance of Ki-67 (Mib1) proliferation index and P53 over-expression in chondrosarcomas. *Int J Cancer* 69:86, 1996

Case #14

Typical Clinical Presentation:

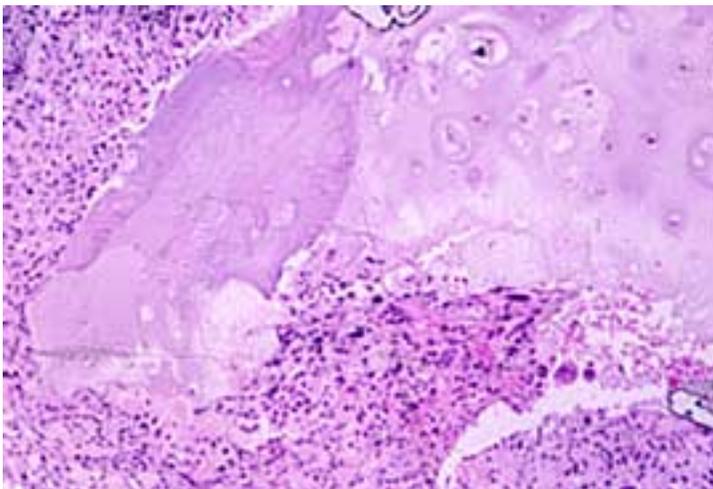
A 56-year-old female presented with a rapidly growing, large, destructive lesion in the pelvic bones.

Characteristic Radiological Findings:

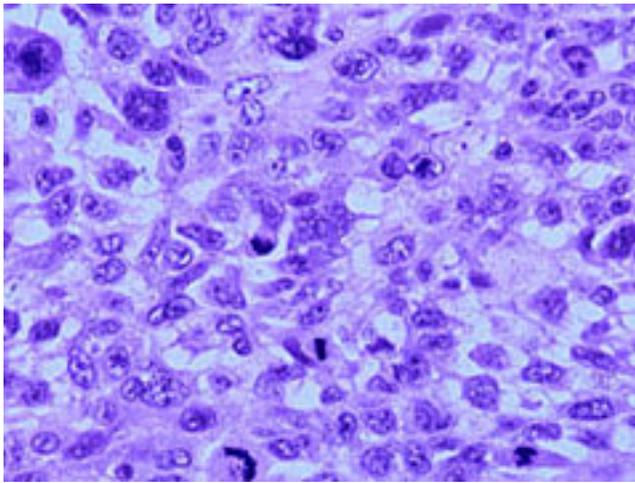


- CT scan of the pelvis shows a destructive bone lesion, which extends through the cortex into the soft tissues.

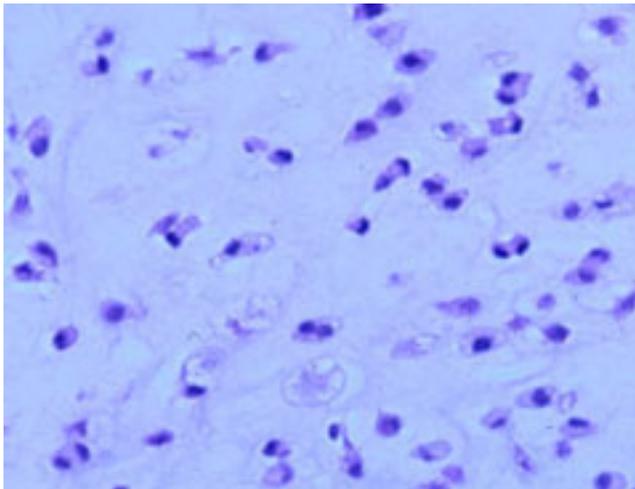
Pathological Findings: :



- Microscopic examination reveals a distinguishing feature of this entity. That is the presence of two distinct components: a low-grade cartilaginous neoplasm and a high-grade sarcoma.



- High-grade component has the morphology of MFH. Numerous mitoses including atypical mitoses are present.



- The cartilaginous component is a low-grade chondrosarcoma (Grades 1 to 2).

Diagnosis: Dedifferentiated Chondrosarcoma

Salient Points:

- Dedifferentiation means transformation of a low-grade (grades 1 or 2) chondrosarcoma into a high-grade sarcoma, most often with features of MFH or osteosarcoma. By definition, **the hallmark of dedifferentiated neoplasm is the co-existence of two components, a low-grade lesion and a high-grade sarcoma, with abrupt demarcation between them. This feature distinguishes dedifferentiation from a gradual increase in grade.** Clinically, dedifferentiation is heralded by a sudden increase in aggressiveness (eg., development of a rapidly growing soft tissue mass).
- Most patients are older than 50 years.
- Prognosis. This variant of chondrosarcoma is associated with a very low survival rate. The response to treatment is poor and widespread

metastases are the rule.

- **Experimental data:** Controversy remains as to whether both components of dedifferentiated chondrosarcoma are derived from a common precursor cell or they represent two separate lineages (collision tumor). The current hypothesis is that "high-grade components represent a failure of differentiation, rather than de-differentiation of mature chondroid cells". In a recent study by Bovee et al, molecular genetic characterization of both components of a dedifferentiated chondrosarcoma has provided evidence for a monoclonal origin and has suggested that the separation may be an early event in the histogenesis of this tumor.

Available publications for the topic: [Dedifferentiated Chondrosarcoma](#)

Selected References:

1. Bovee JVMG, Cleton-Jansen AM, Rosenberg C, Taminiau AHM, et al. Molecular genetic characterization of both components of a dedifferentated chondrosarcoma, with implications for its histogenesis. *J Pathol* 1999;189:454-462

Case #15

Typical Clinical Presentation:

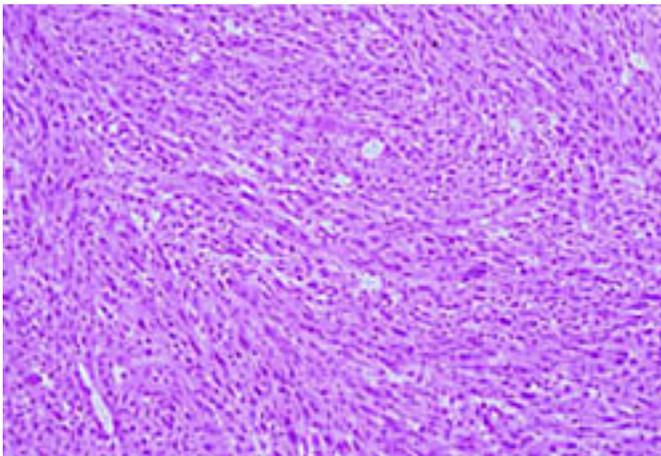
A 65-year-old female, who had been previously diagnosed with Paget's disease, presented with increasing pain and soft tissue swelling in the right upper arm.

Characteristic Radiological Findings:

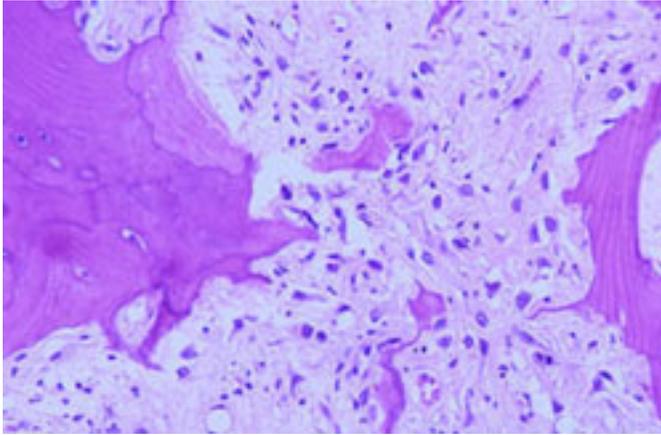


- Plain radiograph shows a diaphyseal, ill defined, destructive, radiolucent lesion with permeative margins. The lesion shows multifocal cortical disruption.

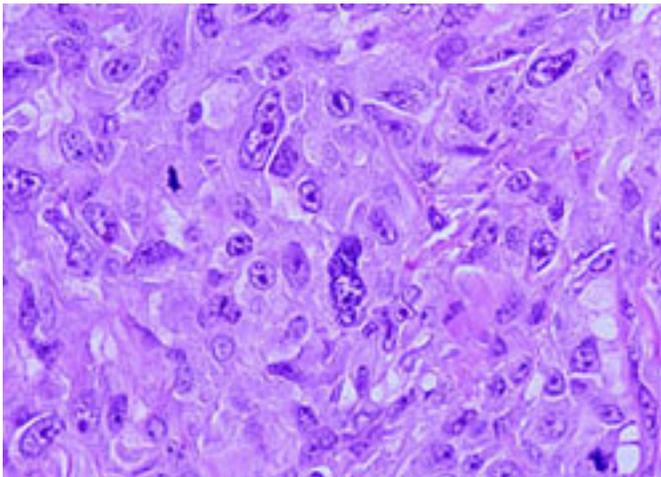
Pathological Findings: :



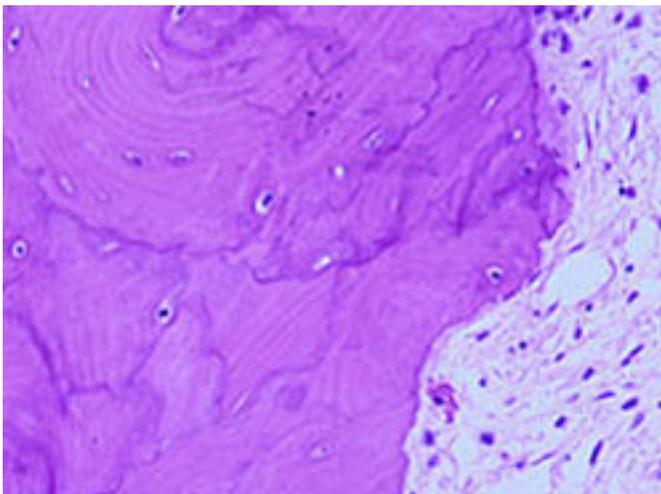
- Low power view shows a **highly cellular spindle cell neoplasm with focal storiform cellular arrangement and lack of identifiable matrix (osteoid or chondroid).**



- Some areas were less cellular but had many bizarre cells.



- On multiple sections, mitoses were frequent and included atypical forms. Special stains revealed strong immunoreactivity with vimentin and faint, focal immunostaining with cytokeratins AE1/AE3, Cam5.2.



- Pre-existent bone shows **features of Paget's disease** - thickened bone trabeculae with irregular, scalloped edges and mosaic lines of mineralization. Focal osteoclastic and osteoblastic activity was present.

Diagnosis: Paget's Sarcoma, Malignant Fibrous Histiocytoma type

Salient Points:

- **Paget's Sarcoma.** High-grade sarcoma is a relatively rare complication of Paget's disease occurring in 1% to 10% of cases. The incidence depends on the extent and severity of Paget's changes (Dorfman HD, Czerniak B. Bone Tumors. 1998). Most patients are between 55 and 75 years of age. Osteosarcoma is the most common type of Paget's sarcoma followed by malignant fibrous histiocytoma (MFH), fibrosarcoma, chondrosarcoma, and giant-cell sarcoma. Skeletal distribution of these tumors mirrors that of Paget's disease - axial skeleton, cranio-facial bones, and the major long bones (femur, tibia, and humerus). Prognosis is generally poor due to the high grade of the tumors, difficulties at their surgical removal, and the old age of patients.
- **MFH of bone** can be generally subdivided into primary or secondary. Studies show that approximately 28% of MFH are secondary lesions arising in a background of Paget's disease, radiation osteitis or bone infarcts (McCarthy EF, Frassica FJ. Pathology of Bone and Joint Disorders. 1998). This type of sarcoma is also found in dedifferentiated areas of low-grade neoplasms. High incidence of secondary MFH mandates a careful search for a pre-existing osseous lesion.
- MFH has a wide age distribution (ages 15 to 85) with a peak incidence in patients older than 40 years. Although any bone may be involved, the tumor is most commonly found in the knee area (30% of cases), proximal femur, humerus and pelvis.
- The histologic hallmark of MFH is the mixture of spindle cells in storiform arrangement and pleomorphic cellular areas. However, a variety of histologic patterns may be encountered. Those include myxoid, organoid, and hemangiopericytoma-like patterns to name just a few. Mitoses are usually numerous, and atypical forms are easily found. Eosinophilic, collagenous extracellular matrix may be present and may be confused with osteoid. However, remember that the only absolute diagnostic feature of osteoid is mineralization. Special studies are of little use in the diagnosis of MFH. Immunostains are used mainly to rule out other types of high-grade sarcomas.
- **Clinical Behavior.** MFH is a very aggressive sarcoma with a high rate of metastases, usually to the lungs. Studies show that secondary MFH behave in a more aggressive manner than primary MFH (Dorfman HD, Czerniak B. Bone Tumors. 1998).

Available publications for the topic: [Paget's disease of bone, malignant](#)

[transformation](#)

Available publications for the topic: [MFH of bone](#)

Selected References:

1. Wick MR, Siegal GP, Unni KK, et al: Sarcomas of bone complicating osteitis deformans (Paget's disease): Fifty years of experience. *Am J Surg Pathol* 5:47, 1981
2. Haibach H, Farrell C, Dittrich FJ: Neoplasms arising in Paget's disease of bone: A study of 82 cases. *Am J Clin Pathol* 83:594, 1985

Case #16

Typical Clinical Presentation:

A 32-year-old male presented with increasing pain in the knee area. There were no other physical complaints. His past medical history was non-contributory and negative for surgery or malignancy.

- The history of increasing pain is always alarming and suggestive of an aggressive lesion.

Characteristic Radiological Findings:

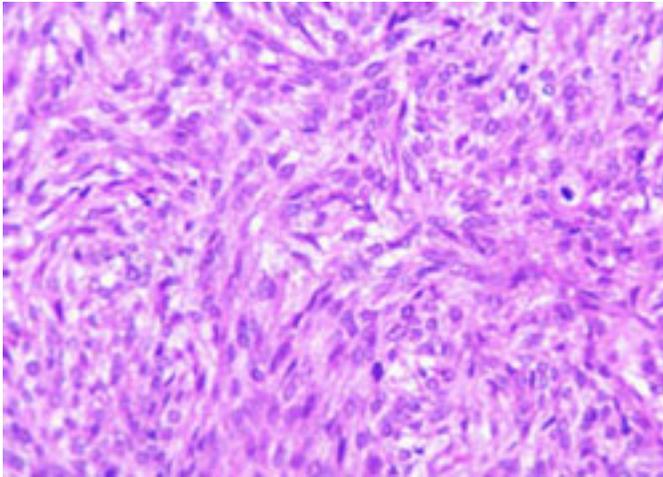


- Plain film shows an ill-defined, radiolucent lesion with permeative margins and focal cortical disruption. The lesion is centered in the distal femoral meta-epiphysis.

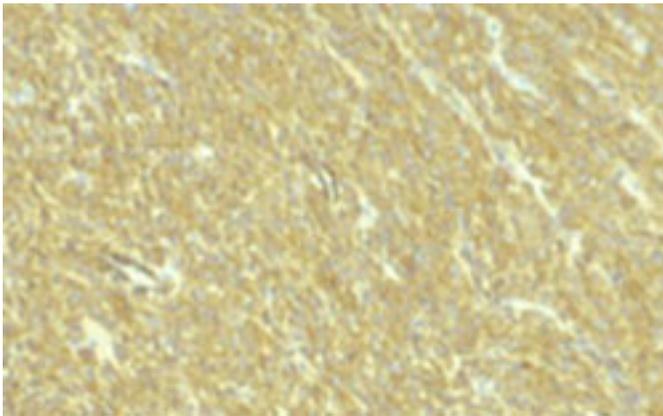


- MRI is superior to the plain radiograph in delineating the lesion.

Pathological Findings: :



- Microscopically, the lesion was composed of interlacing fascicles of mildly pleomorphic, spindle cells with blunt-ended nuclei and eosinophilic cytoplasm. Average mitotic rate was 3 per 10 hpf. Geographic areas of necrosis were present.



- The cells were strongly immunoreactive with SMA (smooth muscle actin) and focally positive for desmin.

Diagnosis: Leiomyosarcoma

Salient Points::

- Primary leiomyosarcoma of bone is extremely rare with approximately 50 cases reported in the literature. Our experience includes two cases. Benign leiomyoma of bone probably does not exist (Helliwell TR. Pathology of Bone and Joint Neoplasms. 1999).
- Before the diagnosis of a primary tumor can be made, a metastatic lesion must be ruled out. Common primary sites for leiomyosarcoma include the uterus, gastro-intestinal tract and soft tissues.
- Differential Diagnosis is usually not extensive and includes fibrosarcoma, MFH, and metastatic spindle-cell carcinoma. Leiomyosarcoma lacks herringbone or storiform patterns of fibrosarcoma and MFH, stains negative with cytokeratin, and exhibits **strong immunoreactivity with smooth muscle actin and muscle specific actin (HHF-35)**. Desmin positivity is seen in only about 50% of cases (see Helliwell TR: Pathology of Bone and Joint Neoplasms. WB Saunders Co, 1999)

Available publications for the topic: [Leiomyosarcoma of bone](#)

Case #17

Typical Clinical Presentation:

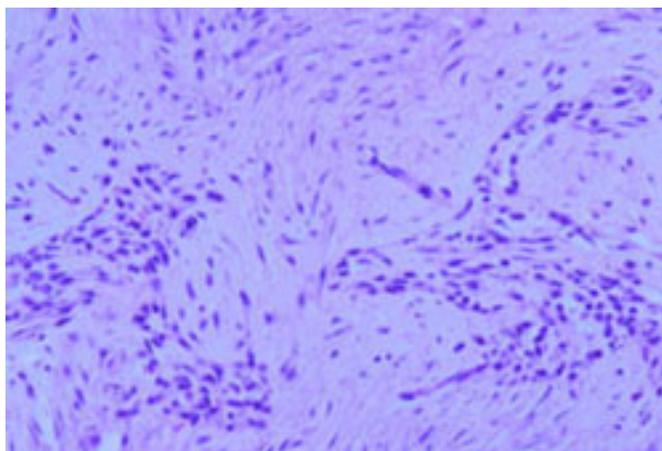
A 27-year-old male presented with chronic, dull pain and some soft tissue swelling along the antero-lateral surface of the left lower leg.

Characteristic Radiological Findings:

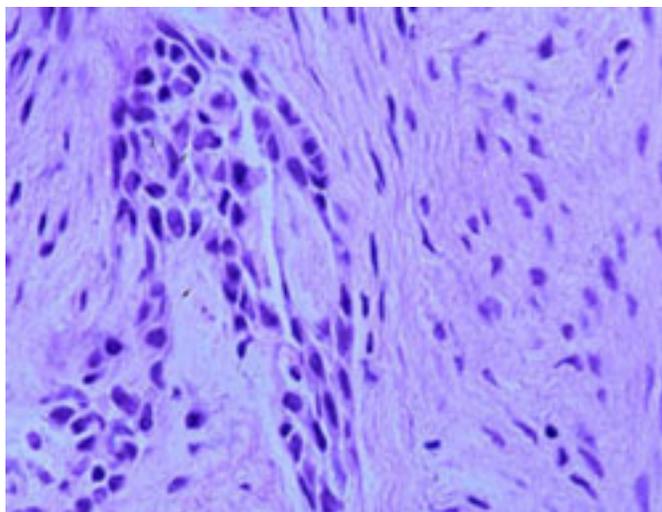


- Plain film shows a large, cortically based, radiolucent lesion partially surrounded by a rim of sclerotic bone, and two smaller lesions of similar appearance. The location in the cortex of the tibial shaft is a major diagnostic clue (about 90% of these tumors are centered in the antero-lateral cortex of the tibial shaft).

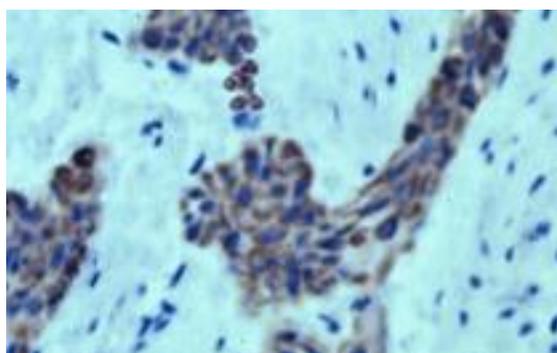
Pathological Findings: :



- Biopsy material shows a moderately cellular fibrous stroma containing nests and strands of darkly stained basaloid cells. Some nests demonstrated peripheral palisading reminiscent of basal cell carcinoma.



- Both stromal cells and epithelioid cells are cytologically bland. There were no mitotic figures.



- Epithelial cells stain positive with cytokeratin AE1/AE3.

Diagnosis: Adamantinoma

Salient Points:

- Adamantinoma is a rare, low-grade malignant neoplasm, which occurs almost exclusively in two skeletal locations: the bones of the lower leg and the jaw. Tumors of the jaw are also known as "ameloblastomas". Here, we will only discuss adamantinoma of long bones. Most patients are young adults, 20 to 30 years old.
- Radiological appearance is very typical. **In about 70% of cases the tumor involves the midshaft of the tibia** (Dorfman HD, Czerniak B. Bone Tumors. 1998). In the remaining cases, it is found at the ends of the tibia, and in the fibula. **Early lesions are characteristically centered in the anterolateral cortex.** Advanced tumors may involve the medullary cavity and the soft tissues.
- Histologically, the tumor consists of strands, nests, or large masses of epithelial cells embedded in a fibrous stroma. The appearance of the epithelial cells and the cellular arrangement determine a histologic subtype: basaloid (shown above), spindle, tubular, squamoid, and osteofibrous dysplasia-like.
- Differential Diagnosis. Adamantinoma should be differentiated from metastatic carcinoma. The location and radiological features help to separate the two. **Characteristically, epithelial cells of adamantinoma and stromal cells are bland with virtually absent (or very low) mitotic activity. By immunohistochemistry, epithelial cells of adamantinoma are strongly positive for cytokeratin.** Cytogenetic studies usually reveal complex chromosomal abnormalities involving multiple translocations and extra chromosomes.
- Clinical Behavior. **Despite its sometimes "benign" clinico-radiological appearance, adamantinoma behaves as a low-grade malignant neoplasm characterized by local aggressiveness, high recurrence rate, and ability to produce metastases.** Metastases usually develop late in the course of the disease, in up to 25% of patients (McCarthy EF, Frassica FJ. Pathology of Bone and Joint Disorders. 1998). The lungs are the most common site of metastatic spread.

Available publications for the topic: [Adamantinoma](#)

Case #18

Typical Clinical Presentation:

A 16-year-old boy was seen in consultation for increasing pain in the mid upper arm. Characteristically, the pain intensified at night and subsided with aspirin.

- The effect of aspirin is an important diagnostic clue here.

Characteristic Radiological Findings:

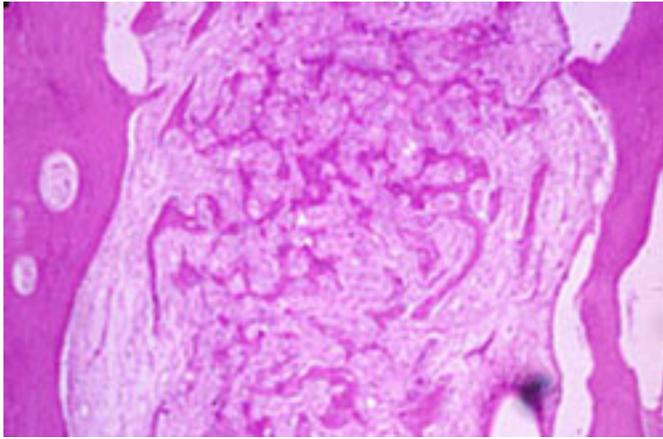


- Plain film shows a small, intracortical, radiolucent focus (nidus), surrounded by dense reactive periosteal bone. The lesion is located in the mid portion of the humeral shaft.

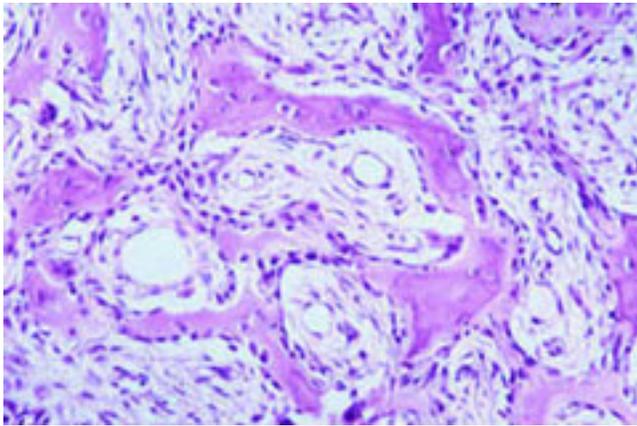
Pathological Findings: :



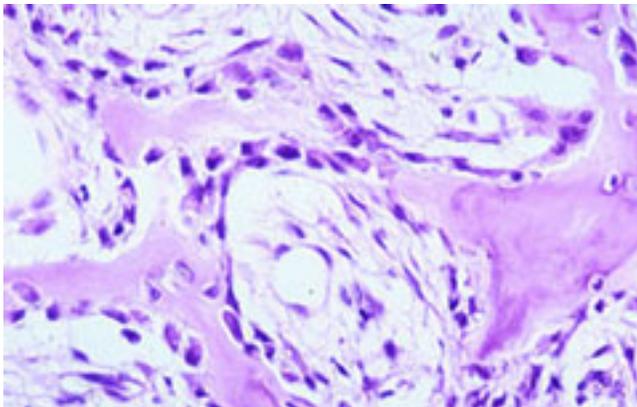
- If the nidus is removed intact, it appears as a circumscribed portion of red, trabecular bone, usually less than 1cm in size.



- Low-power view shows the lesional tissue ("nidus"), well demarcated from the surrounding sclerotic bone.



- The lesion is composed of thin, often interconnected spicules of osteoid and woven bone rimmed by osteoblasts. Osteoclast-like giant cells can be seen. Intervening fibrous stroma shows prominent vascularity.

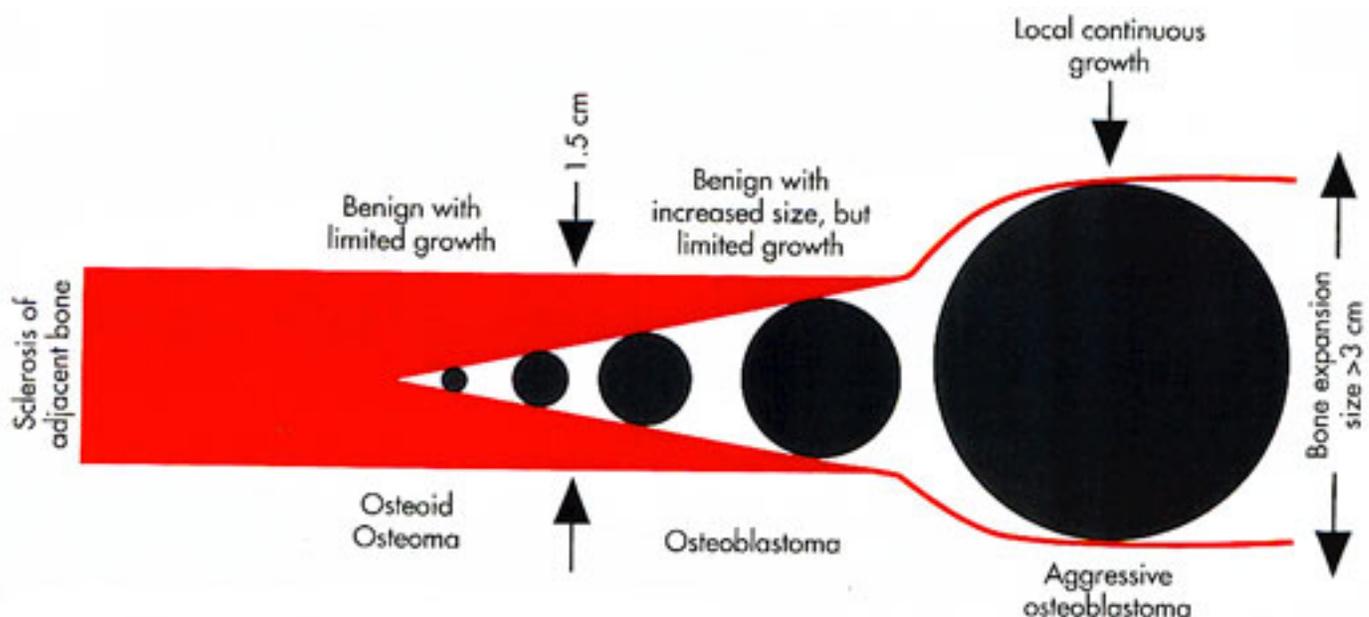


- Both osteoblasts and stromal cells are without significant nuclear atypia.

Diagnosis: Osteoid Osteoma

Salient Points:

- Osteoid osteoma is a common, benign, bone-producing neoplasm characterized by a small size, limited growth potential, and a tendency to cause extensive reactive changes in surrounding tissues. The lesional tissue, called a "nidus", usually appears as a small radiolucent focus, less than 1cm in size, either within the cortex or adjacent to it. The lesion is thought to produce prostoglandin/prostocyclin-mediated effects on the surrounding tissues inducing exuberant, reactive, periosteal sclerosis, soft tissue edema and pain. Aspirin, which acts through inhibition of prostaglandin/prostacyclin, has dramatic pain-relieving effect in patients with osteoid osteomas.
- Predominant occurrence is in males between the ages of 10 and 25 years.
- Location. Most frequently (50% of cases), osteoid osteomas arise in the femur and tibia. The femoral neck is one of the most common anatomic sites. Other skeletal locations include the humerus, the small bones of the hands and feet, and the spine. In a long bone, the tumor is usually found in the metaphyses or diaphyses. If the lesion occurs in a close proximity to the articular surface of the joint, it causes severe reactive synovitis.
- Precise localization of the lesion at surgery is difficult due to its small size and extensive reactive bone sclerosis. **Once the tissue has been removed, the pathologist should X-ray and thinly section the specimen to identify the nidus (lesional tissue). Make sure the nidus is present.** If not, contact the surgeon.
- Differential Diagnosis. Osteoblastoma is a benign bone-forming neoplasm, which is closely related to osteoid osteoma. Histological findings may be identical. However, remember that osteoblastoma is characterized by a larger size (more than 1.5 cm) and absence of diagnostic clinico-radiological findings of osteoid osteoma. Other important entity in the differential diagnosis is intracortical osteosarcoma. Look for the presence of significant nuclear atypia and invasive growth pattern indicative of malignancy.



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Available publications for the topic: [Osteoid Osteoma](#)

Case # 19

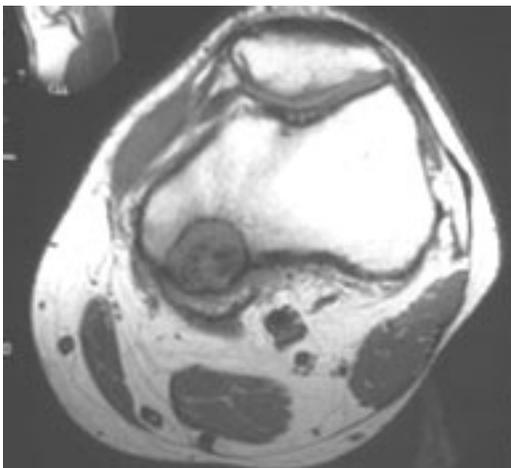
Typical Clinical Presentation:

A 21-year-old male with a 6-month history of dull pain in the knee that was not relieved by aspirin.

Characteristic Radiological Findings:

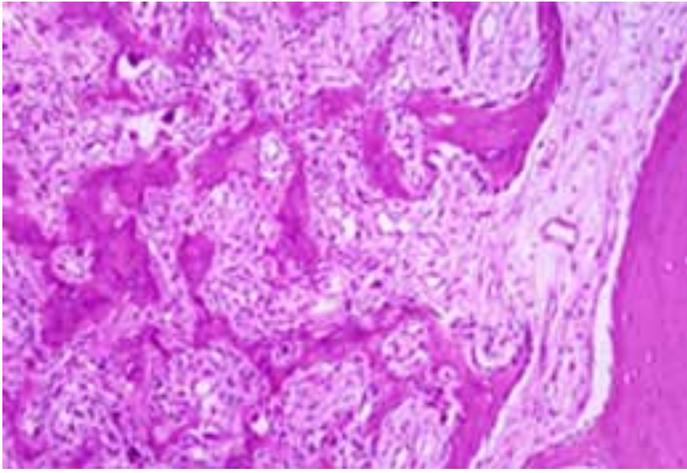


- Plain radiograph shows a well circumscribed, low metaphyseal, radiolucent lesion containing matrix-type radiodensities. Note the absence of a sclerotic rim.

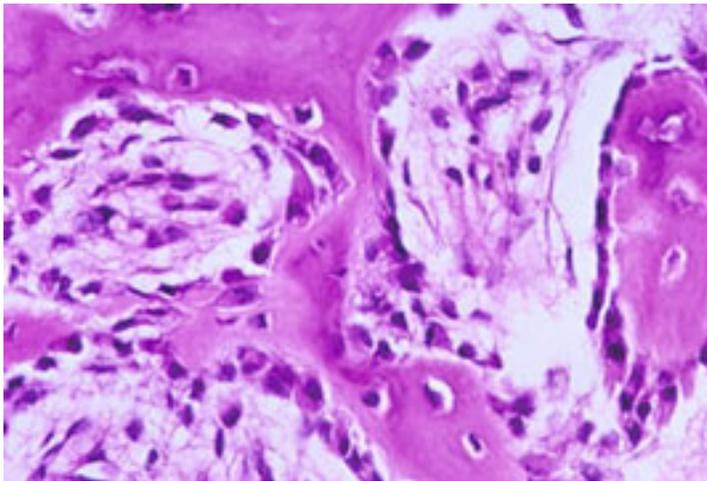


- MRI film demonstrates eccentric location and cortical expansion.

Pathological Findings: :



- The microscopic features resemble those of osteoid osteoma. Osteoblasts and osteoclast-like giant cells rim interconnected spicules of osteoid and woven bone. The intervening fibrous stroma shows prominent vascularity.



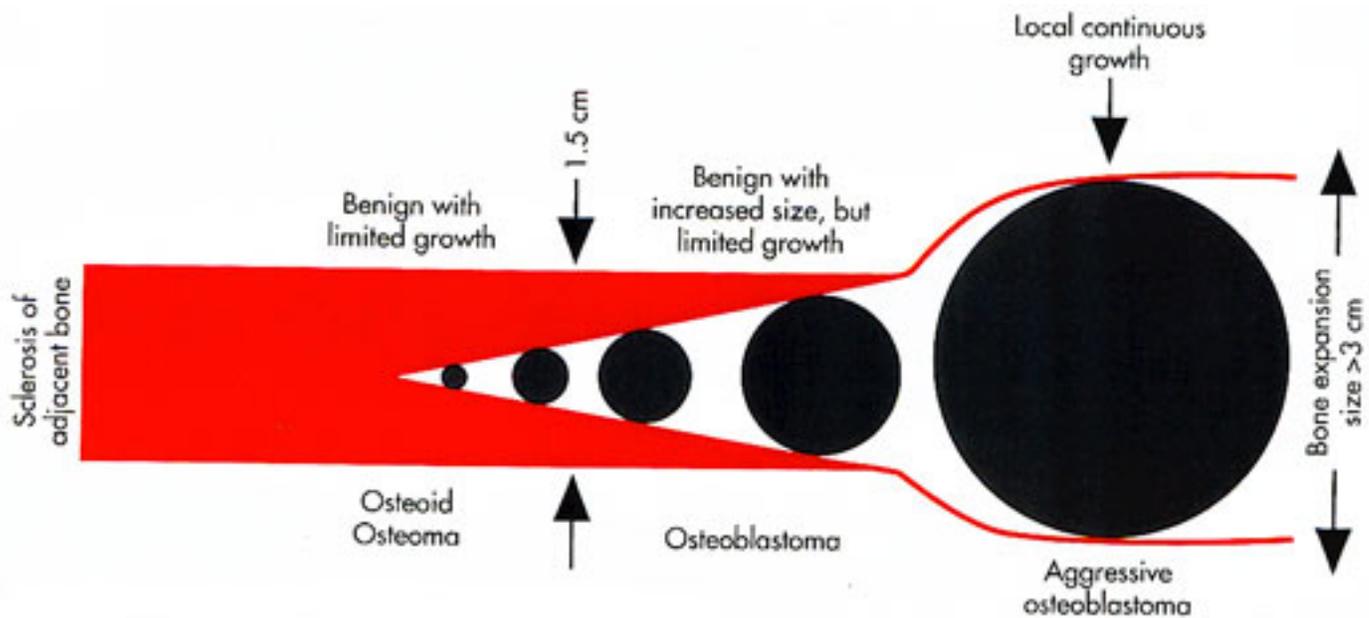
- There is no significant cellular atypia.

Diagnosis: Osteoblastoma

Salient Points (Benign Osteoblastoma and Aggressive Osteoblastoma)::

- **Osteoblastoma is a rare bone-producing neoplasm that closely resembles osteoid osteoma on microscopic examination.** However, there are significant differences between the two. By definition, all osteoblastomas are larger than 1.5cm. They are slowly and progressively growing neoplasms. Although any bone may be involved, osteoblastomas tend to arise in the axial skeleton, involving the spine and the sacrum in about 40% of cases. The second most frequent site is the mandible, followed by other craniofacial bones (Dorfman HD, Czerniak B. Bone Tumors. 1998). Unlike osteoid osteomas, osteoblastomas do not produce prostaglandin/prostocyclin-mediated tissue reaction.
- Peak incidence is in the second and third decades of life.
- The term "**aggressive osteoblastoma**" is applied to large, locally destructive lesions that mimic a low-grade osteosarcoma on microscopic examination.

- Characteristically, aggressive osteblastomas have atypical and mitotically active, **epithelioid osteoblasts**. But in contrast to osteosarcoma, the tumor shows no atypical mitoses and no evidence of infiltrative growth, or sarcomatous stromal changes.
- Clinical Behavior. Osteblastomas may grow to a considerable size and produce bone expansion and cortical destruction. Recurrences are common and occur in about 20% of cases. Metastases are not a feature of osteblastomas.



Reprinted with permission from Dorfman HD, Czerniak B: *Bone Tumors*. Mosby, Inc, 1998

Available publications for the topic: [Osteoblastoma](#)

Selected References:

1. Dorfman HD, Weiss SW: Borderline osteoblastic tumors: Problems in the differential diagnosis of aggressive osteoblastoma and low-grade osteosarcoma. *Semin Diagn Pathol* 1:215, 1984
2. Bertoni F, Unni KK, McLeod RA, et al: Osteosarcoma resembling osteoblastoma. *Cancer* 55:416, 1985

Case # 20

An 11-year-old male was seen in consultation for an increasingly painful distal femoral lesion associated with a soft tissue mass.

Characteristic Radiological Findings

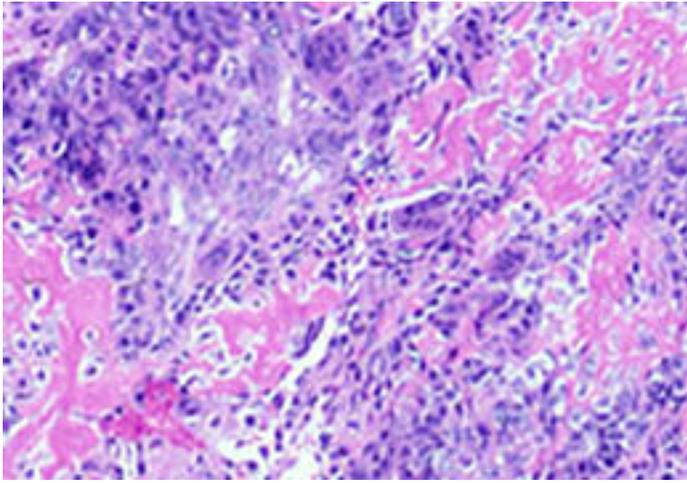


- Plain radiograph shows an ill-defined destructive tumor in the distal femur. Fluffy radiodense infiltrates represent malignant tumor osteoid.

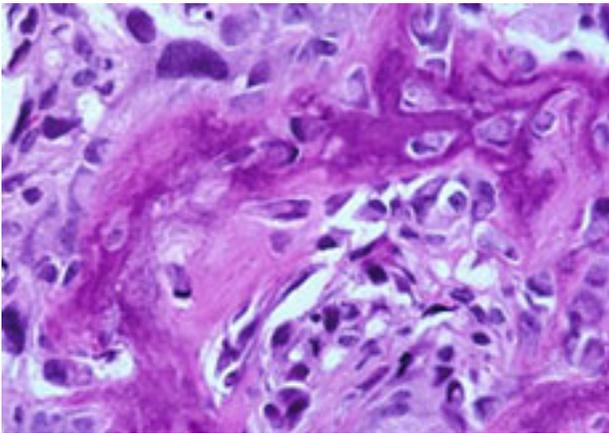


- MRI film delineates zones of bone destruction and soft tissue extension of the tumor.

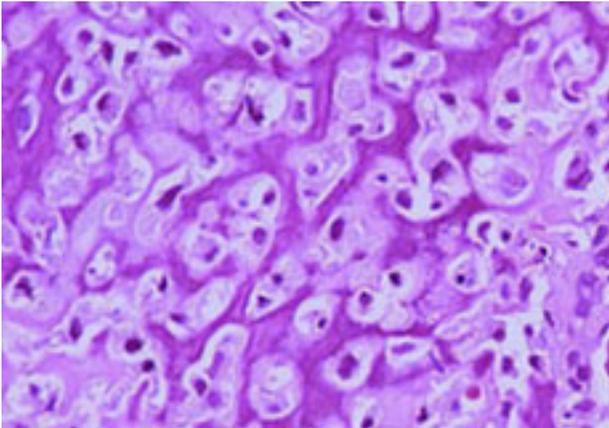
Pathological Findings:



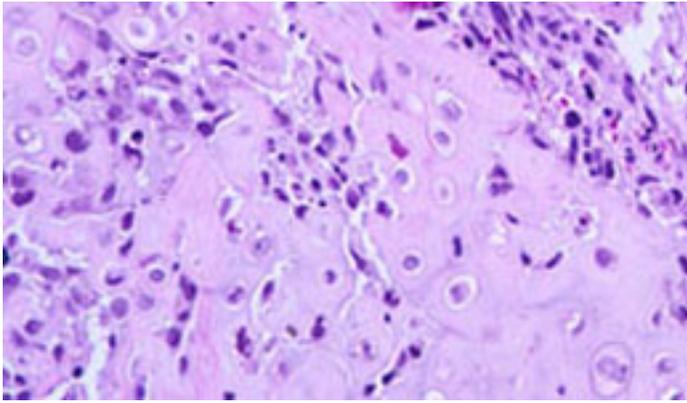
- Biopsy material shows two major components of this neoplasm: **highly pleomorphic cells and haphazard deposits of osteoid**. Note that the malignant cells fill the spaces between osteoid deposits.



- High magnification demonstrates anaplastic cellular features and mitotic activity.



- **Lace-like** osteoid deposition is very characteristic of this neoplasm.



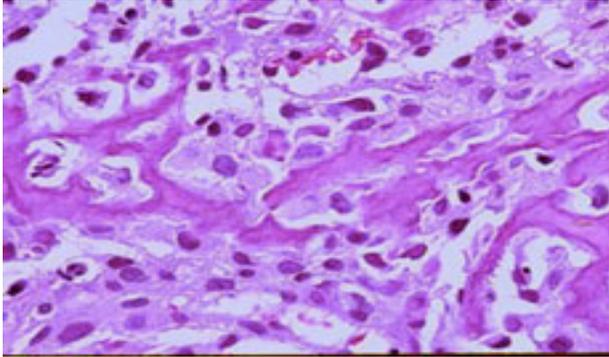
- Few foci of neoplastic cartilage were present.

Diagnosis: Osteosarcoma, high grade

Salient Points:

- Osteosarcoma is the most common primary sarcoma of bone. The peak incidence is in the second decade of life during the period of the most active skeletal growth. Fewer than 5% of osteosarcomas occur in children younger than 10 years (Dorfman HD, Czerniak B. Bone Tumors. 1998). In elderly, osteosarcoma is usually seen in association with a pre-existing bone disease, such as Paget's, radiation osteitis, or bone infarct. **By the time of presentation, all osteosarcomas are larger than 2 cm.**
- Location. In adolescents and young adults, osteosarcoma preferentially affects the most rapidly growing parts of the skeleton: the distal femur and proximal tibia (50% of cases), and the proximal humerus. Within the long bone, the metaphysis is the most common site. In elderly, osteosarcoma tends to involve the axial skeleton and the flat bones.
- Subtypes of osteosarcoma. Based on the location within the bone, osteosarcomas are subdivided into intramedullary, intracortical and surface osteosarcomas. Intramedullary, or central, tumors comprise the largest group and include conventional high-grade osteosarcoma, which accounts for about 90% of all osteosarcomas, and less common types such as well-differentiated (or low-grade) osteosarcoma, chondroblastic, small cell, and teleangiectatic osteosarcoma. Based on the degree of differentiation, osteosarcomas are subclassified into high-grade and low-grade.
- Pathologic diagnosis. Osteosarcoma is defined as a malignant tumor composed of neoplastic mesenchymal cells synthesizing osteoid or immature bone. However, the histologic findings can be extremely

variable. For example, the tumor may appear identical to the MFH showing minimal osteoid production, or it may contain masses of malignant cartilage, or numerous giant cells. Remember that **the presence of malignant osteoid distinguishes an osteosarcoma from other sarcomas**. Mineralization distinguishes osteoid from collagen deposits.



- **Malignant osteoid** is deposited either in a lace-like pattern or in the form of haphazardly arranged trabeculae of woven bone. Characteristically, the neoplastic cells fill the spaces between the osteoid deposits and often become entrapped in osteoid. This is very different from the reactive bone pattern, where the bone trabeculae are separated by a fibrovascular stroma.

- In cases of osteosarcoma, special techniques have been of little diagnostic help and used mainly to exclude other types of sarcoma.
- **Differential Diagnosis.** In general, low-grade osteosarcoma should be differentiated from benign bone-producing tumors (osteoblastoma), whereas a high-grade osteosarcoma must be differentiated from other sarcomas. When you choose between benign and malignant, look for the permeative growth pattern, cellular atypia, and mitotic activity. Also, examine the spaces between the bone trabeculae. In benign tumors they are occupied by a fibrovascular stroma. In osteosarcoma, they are filled with the aggregates of malignant mesenchymal cells. The pattern of osteoid deposition is orderly in benign tumors and haphazard or lace-like in osteosarcoma. When you choose between an osteosarcoma and other types of sarcoma, look for malignant osteoid produced directly by mesenchymal cells.
- **Clinical Behavior.** Conventional osteosarcoma is one of the most aggressive and highly lethal tumors. **Prognosis depends on the**

skeletal site of involvement, surgical stage and tumor response to pre-operative chemotherapy. The most powerful predictor of outcome is the histologic response of the tumor to pre-operative chemotherapy. Tumor necrosis can be graded according to the following system (Rosen G, Caparros B, Huvos AG, et al. Preoperative chemotherapy for osteogenic sarcoma. *Cancer* 1982;49:1221-1230). Grade 1 - 0% to 50% necrosis; Grade 2 - 51% to 90%, Grade 3 - 91% to 99%, and Grade 4 - 100% necrosis. Data from MD Anderson Cancer Center shows that 90% and more of tumor necrosis is associated with nearly 90% 5-year disease-free survival, comparing to only 14% 5-year disease-free survival in patients with less than 90% of tumor necrosis (Dorfman HD, Czerniak B. *Bone Tumors*. 1998). Metastases, usually to the lungs, bones, and liver, are extremely common. Surgical resection of solitary metastases may improve the patient's survival (similar as for Ewing's sarcoma).

- **Experimental data:** Abnormalities of the cell cycle regulating genes/proteins have been reported in different types of cancer. Inactivation of RB, p53, INK4A (encodes tumor suppressor p16), and increased expression of CDK4 (cyclin-dependent kinase) and MDM2 have been reported in osteosarcoma. Recent studies have shown frequent over-expression of Her2/neu by osteosarcoma and its correlation with a significantly worse histologic response to pre-operative chemotherapy and shorter event-free survival. Further studies are being conducted. Recent studies have revealed the presence of SV40 (simian virus 40) genome in human malignancies (mesothelioma, osteosarcoma). It appears that SV40 integrates in human osteosarcoma DNA. Its role in the pathogenesis of osteosarcoma remains unclear

Available publications for the topic: [Osteosarcoma, high grade](#)

Selected References:

1. Gorlick R, Huvos AG, Heller G, Aledo A, et al. Expression of Her2/erbB-2 correlates with survival in osteosarcoma. *J clin Oncol* 1999;17(9):2781-2788
2. Yamamoto H, Nakayama T, Murakami H, et al. High incidence of SV40-like sequences detection in tumour and peripheral blood of Japanese osteosarcoma patients. *Br J Cancer* 2000;82(10):1677-1681
3. Onda M, Matsuda S, Higaki S, et al: ErbB-2 expression is correlated with poor prognosis for patients with osteosarcoma. *Cancer* 77:71, 1996

Gross Appearances of Bone Tumors



- Osteosarcoma (conventional - intramedullary, high grade) with extension into the soft tissues



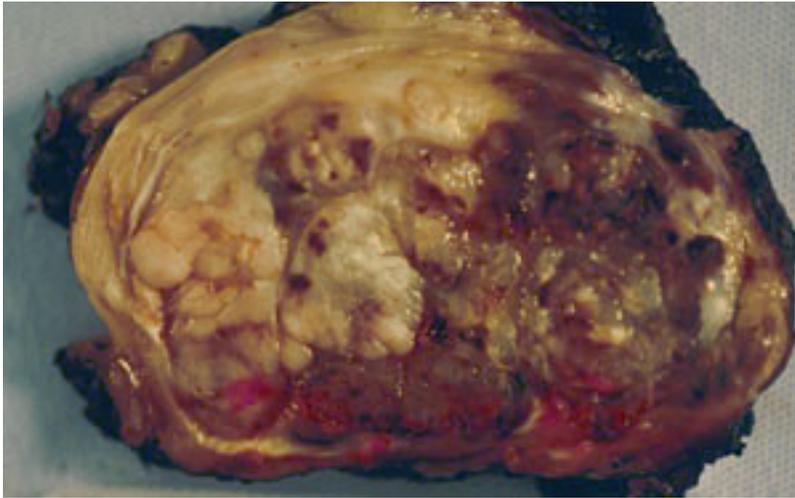
- Chondrosarcoma of scapula



- Ewing's Sarcoma of fibula



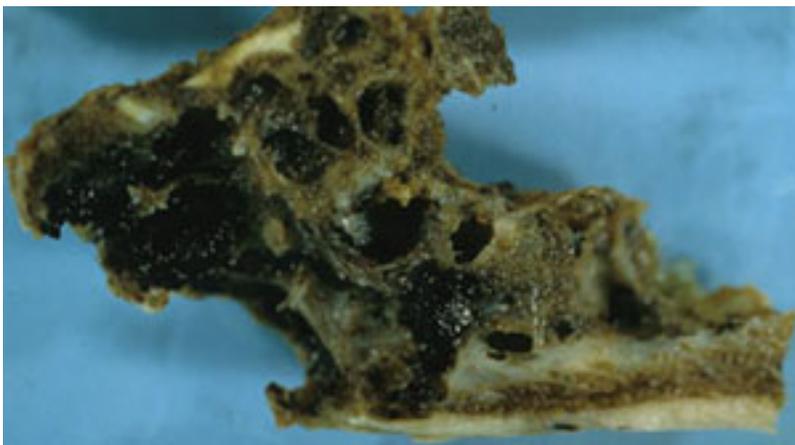
- Paget's Sarcoma, MFH type



- Chordoma, sacral



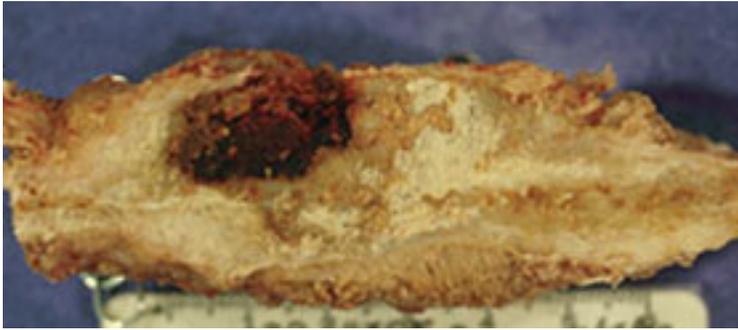
- Adamantinoma of tibia



- Aneurysmal Bone Cyst of Clavicle



- Osteoid Osteoma - nidus



- Osteoblastoma, 2.2cm in greatest dimension

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