Cancer precursor project - characteristics of premalignant precursors, part 4 (bone, joints and soft tissue malignancies)

26 May 2024

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MAY 26, 2024

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Our Cancer precursor project aims to better understand how cancer arises by compiling a regularly updated spreadsheet of all distinct human cancers (now 1,229) and their precursors (now 184).

In part 1, we discovered that the percentage of identified precursors varies widely by pathology subspecialty and we discussed precursors in subspecialties with epithelial sites (breast, head & neck, gyn, GI / liver, GU / adrenal and thoracic).

	Cancers	Precursors	%
Neuropathology	114	1	0.9%
Bone, joints and soft tissue	140	4	2.9%
Dermatopathology	79	6	7.6%
Hematopathology	207	19	9.2%
Breast	58	8	13.8%
Head & neck	128	19	14.8%
Gyn	96	20	20.8%
GI / liver	203	47	23.2%
GU / adrenal	141	34	24.1%
Thoracic	63	26	41.3%
Grand total	1229	184	15.0%

Figures as of 24 May 2024

Epithelial malignancies often have risk factors associated with chronic inflammation (due to microorganisms, parasites, autoantigens, trauma, excess weight, diet, aging), DNA changes (due to germline changes, carcinogen exposure, radiation, aging), constitutive hormone production (estrogens, androgens, insulin) or immune system dysfunction (Pernick 2021). These risk factors promote changes in molecular pathways that often produce precursor lesions (intraepithelial neoplasia or dysplasia), in situ carcinoma (malignancies confined to the original site) and ultimately invasive malignancies.

In part 2, we discussed neuropathology related malignancies and their lack of precursors and concluded that contrary to current thinking, most nonepithelial malignancies, including central nervous system tumors, lack precursors. These nonepithelial malignancies often have no known risk factors and appear to arise from random processes or “bad luck” (Pernick 2022).

In parts 3a and 3b, we discussed the six skin related malignancies with known precursors: cutaneous squamous cell carcinoma (which is epithelial) and 5 types of melanoma. Melanoma derives from melanocytes, which are not epithelial but reside in a network of epithelial keratinocytes that, we believe, constrains their malignant transformation in a similar manner as epithelial cells.

We speculated that within the skin, the cell - cell connections of squamous epithelial cells and keratinocytes may force some malignancies to go through a premalignant, intraepithelial neoplasia phase by making the traditional malignant process more difficult to achieve. In addition, the basement membrane limits invasion unless additional DNA changes are present.

We speculated that some nonmelanotic skin malignancies may have a molecular precursor with distinct molecular patterns but no morphologic changes, but this has not been proven. The remaining skin malignancies may be initiated by a defining mutation in a single stem or progenitor cell that multiplies and acquires additional mutations and malignant properties over time; however, there is no premalignant intraepithelial neoplasm or other morphologic precursor during this transformation.

In the bone, joints and soft tissue, of 140 distinct malignancies, we have identified premalignant precursors in only 4 bone malignancies (chondrosarcoma grade 1, chondrosarcoma grades 2 & 3, osteosarcoma, giant cell tumor of bone) and in no soft tissue tumors. In these 4 malignancies, premalignant precursors are rare except in syndromic or genetic disorders.

1. Atypical cartilaginous tumor / chondrosarcoma grade 1 rarely has enchondroma or osteochondroma as a precursor. Tumors are more common in patients with multiple enchondromas or osteochondromas.

2. Chondrosarcoma, grades 2 & 3 rarely has enchondroma or osteochondroma as a precursor. Grade 2 & 3 chondrosarcomas appear to be distinct from grade 1 tumors but grade 2 and grade 3 tumors appear to be variations on a theme and not distinct from each other.

3. Osteosarcoma, NOS / conventional osteosarcoma rarely has Paget disease of bone as a precursor. Tumors are more common in patients with multifocal disease.

4. Giant cell tumor of bone, malignant rarely has Paget disease of bone as a precursor.

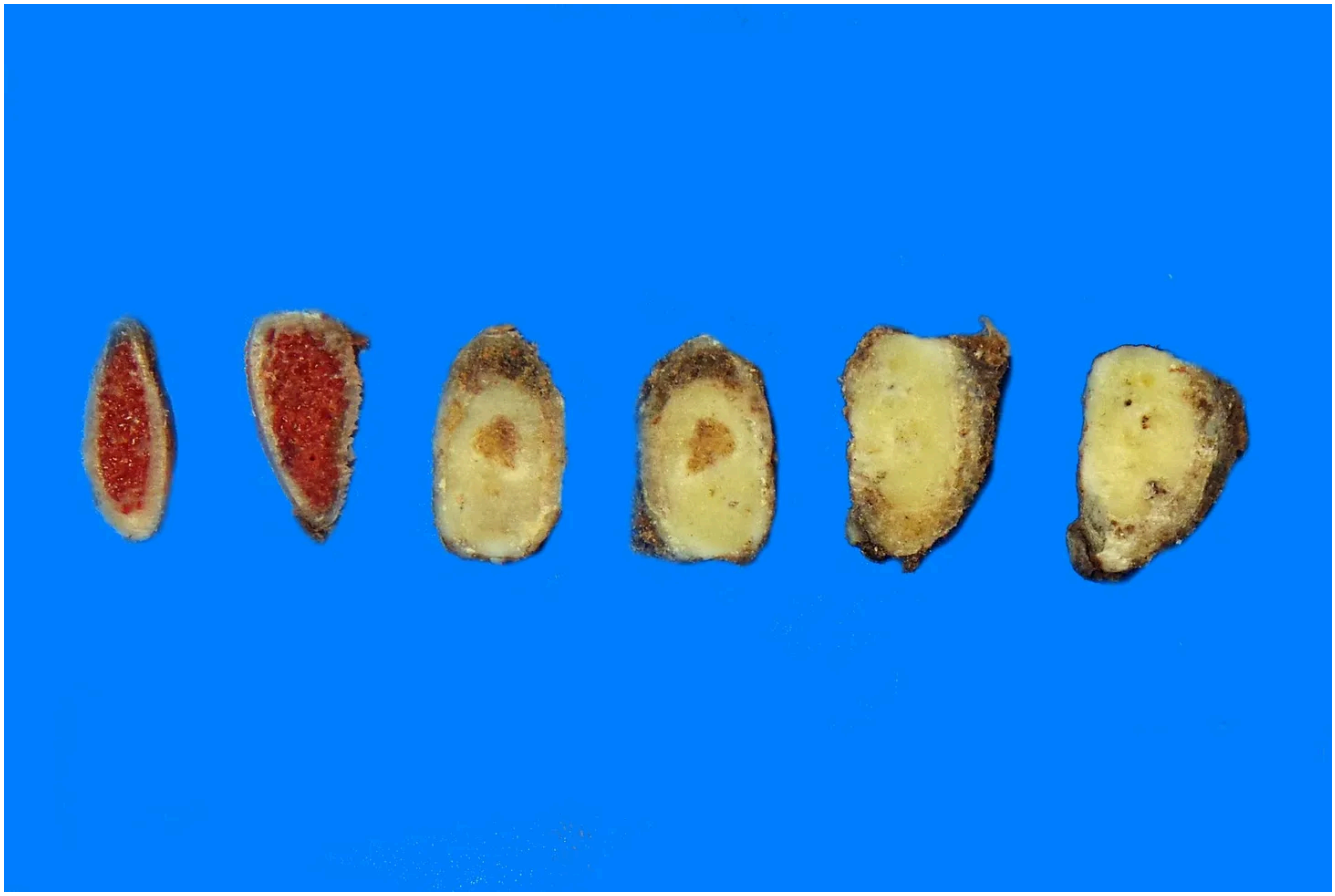
We now exclude known **malignant** precursors from our spreadsheet, such as low grade chondrosarcoma, a precursor of dedifferentiated chondrosarcoma and atypical lipomatous tumor / well differentiated liposarcoma, a precursor of dedifferentiated liposarcoma.

Enchondroma or osteochondroma as precursors of chondrosarcoma

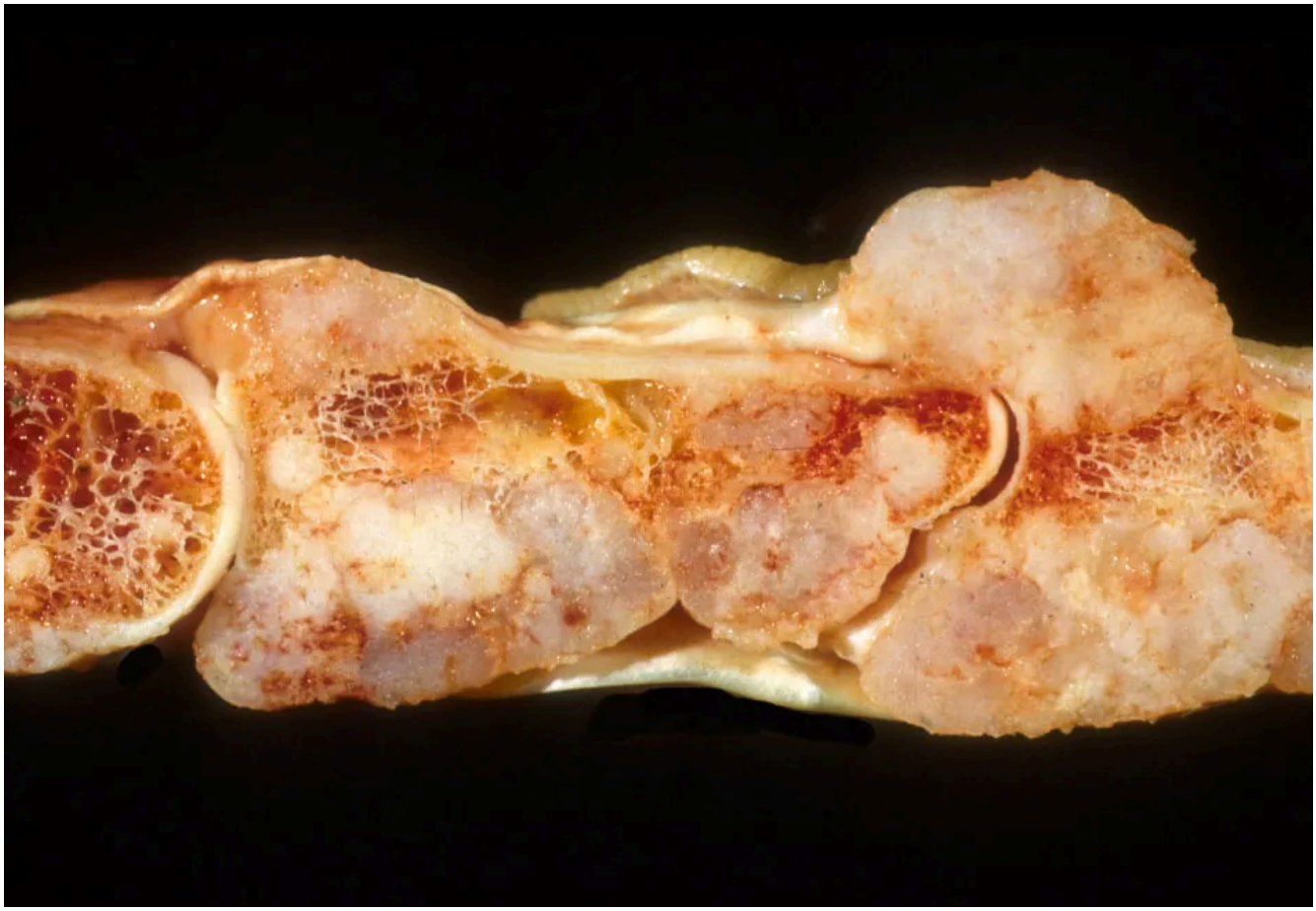
Enchondroma is a benign cartilaginous tumor that arises within the medullary cavity of bone. It has no malignant features (i.e., no cytological atypia, mitoses, cortical invasion or soft tissue extension). It usually occurs in a sporadic setting and malignant transformation is rare (< 1%). It may be caused by somatic mutations in the *IDH1* and *IDH2* genes, found in 40% of sporadic enchondromas and also found in gliomas (brain tumors). Mutant *IDH* enzymes produce 2HG, which results in widespread DNA hypermethylation and may produce the enchondroma.

Patients with Ollier disease and Maffucci syndrome have multiple enchondromas and *IDH1* or *IDH2* mutations in 80% of cases (Pansuriya 2011). Malignant transformation to chondrosarcoma occurs in up to 46% of patients with Ollier disease and 57% of patients with Maffucci syndrome (Herget 2014). Although traditionally considered nonhereditary diseases, a recent study found germline changes in the *HIF1A*, *VHL* and *IDH1* genes in some patients (Poll 2022), which we speculate might cause multiple enchondromas and malignant transformation.

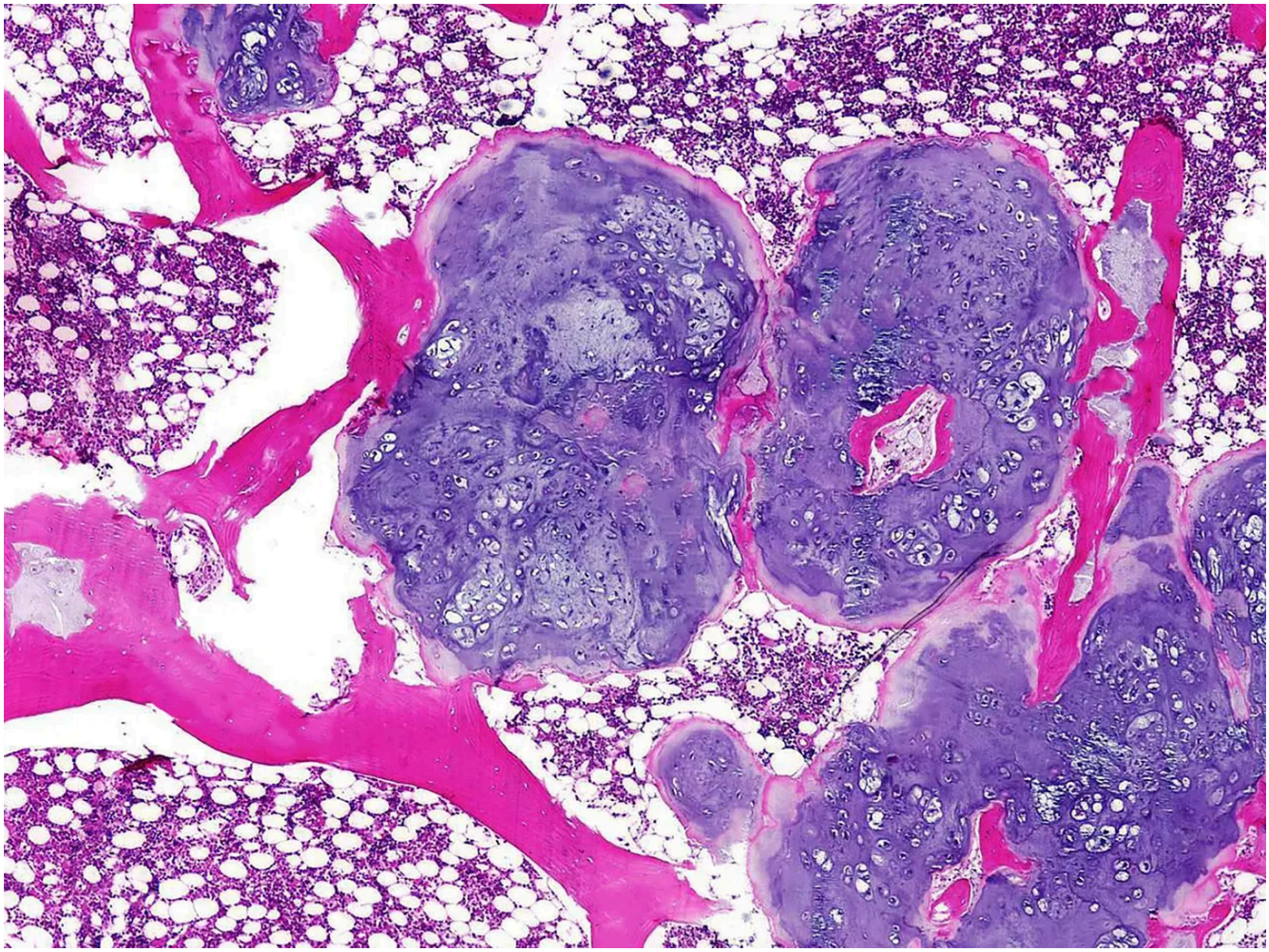
Endochondroma



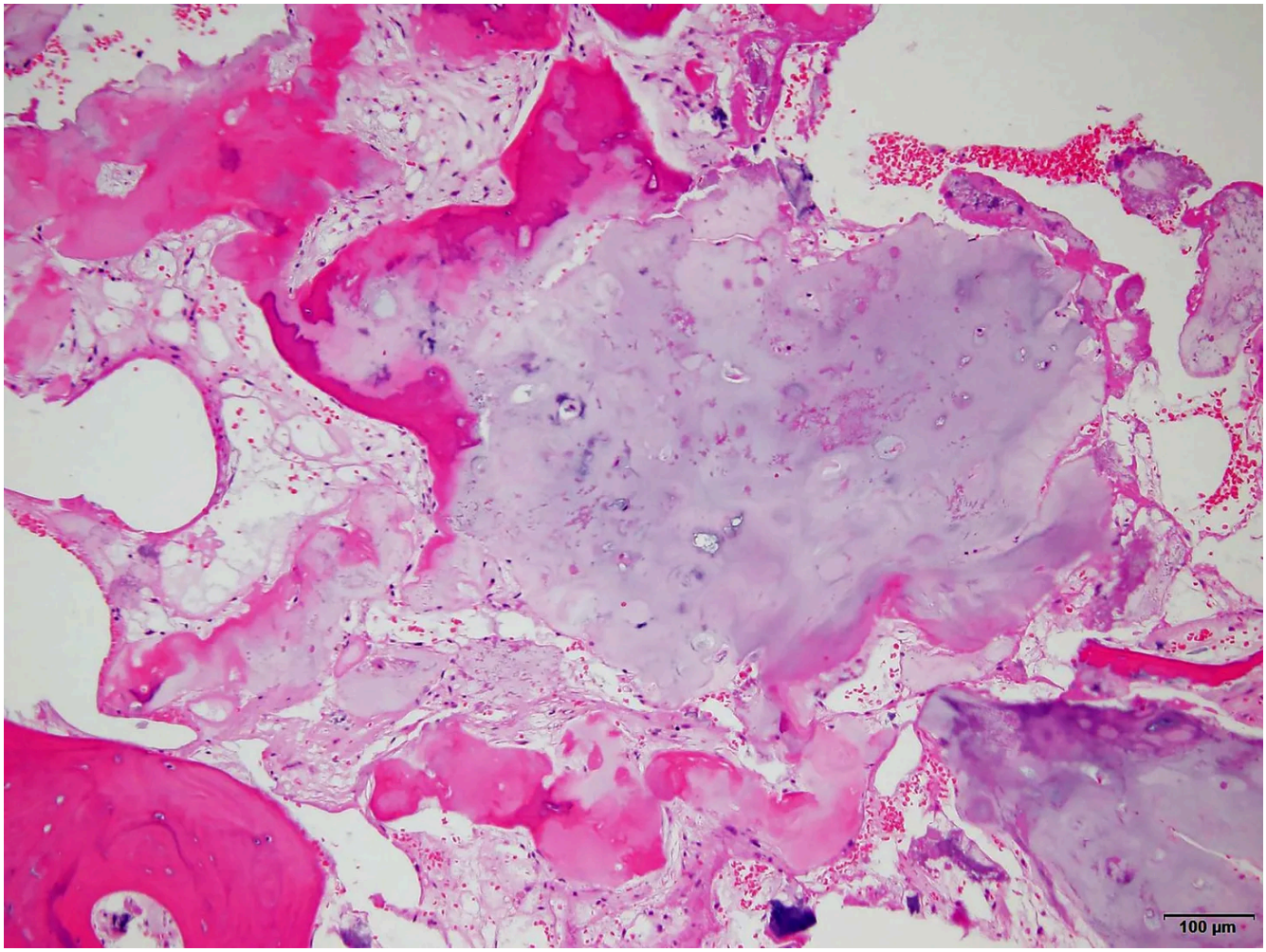
Enchondroma: Well marginated, whitish yellow tumor in the medullary cavity of the bone, with intact cortex (contributed by Borislav A. Alexiev, M.D.).



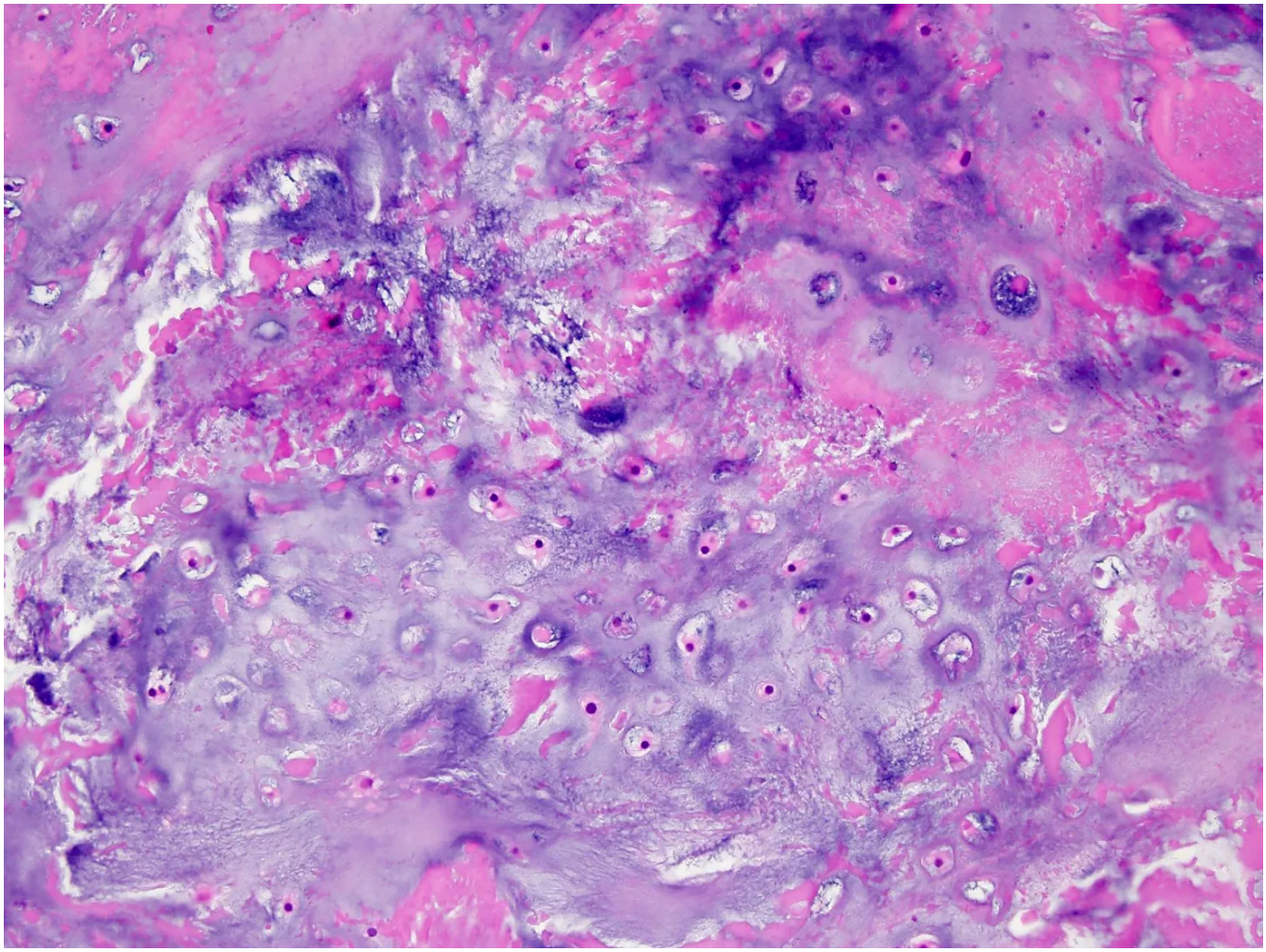
Multiple enchondromas present in an asymmetric distribution (contributed by Mark R. Wick, M.D.).



Enchondroma: Cartilaginous nodules surrounded by bone (contributed by Borislav A. Alexiev, M.D.).



Enchondroma: Hypocellular lesion with an abundance of hyaline cartilage matrix showing encasement (contributed by Borislav A. Alexiev, M.D.).



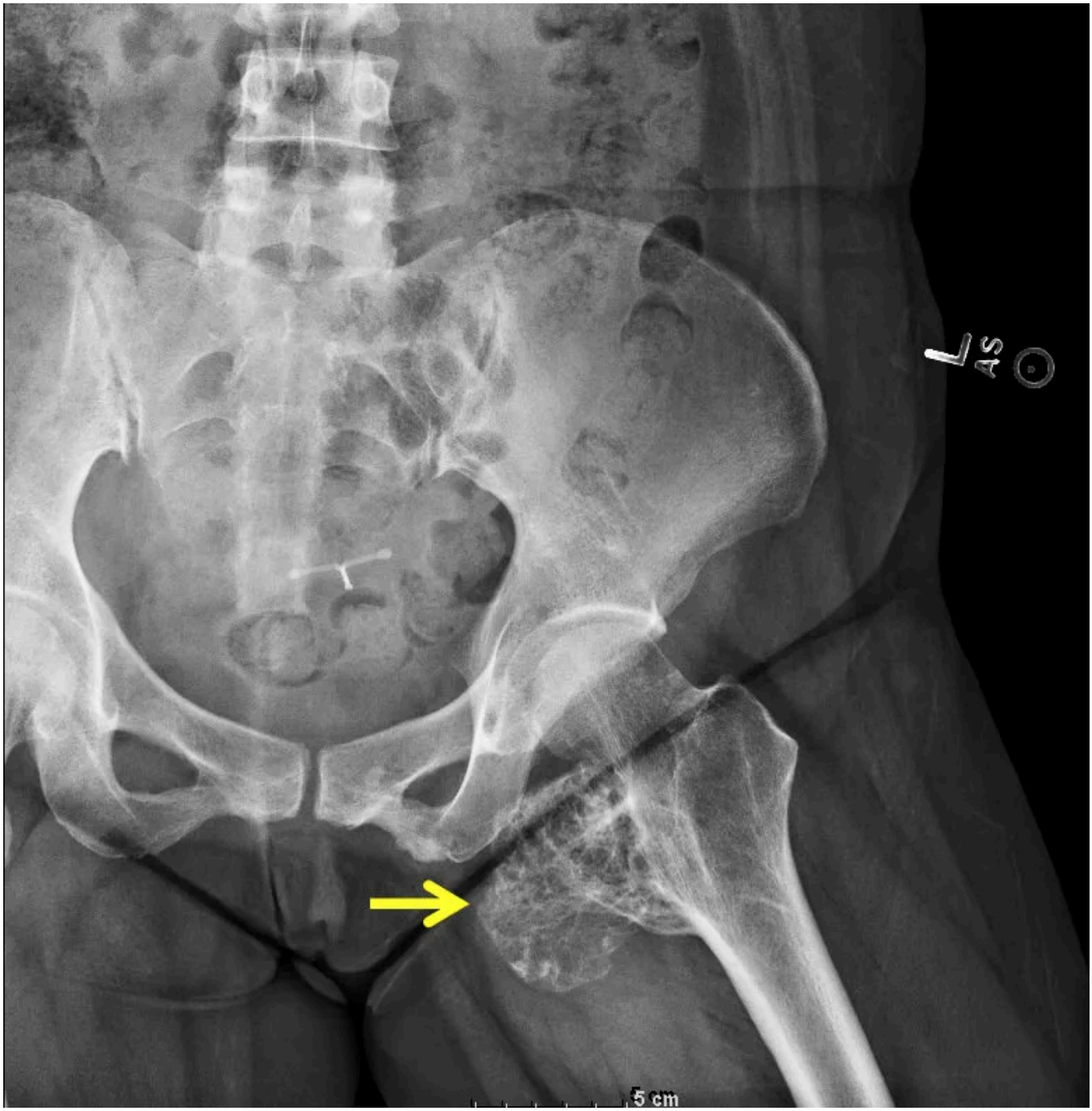
Enchondroma: Tumor cells are embedded within sharp edged lacunar spaces and are evenly distributed (contributed by Borislav A. Alexiev, M.D.).

Osteochondroma (exostosis) is a benign bone surface tumor composed of mature bone with a cartilage cap. It may be solitary or occur as multiple hereditary exostoses. It constitutes 10% of all bone tumors and 35% of benign bone tumors, is more common in men and typically occurs in children or teenagers.

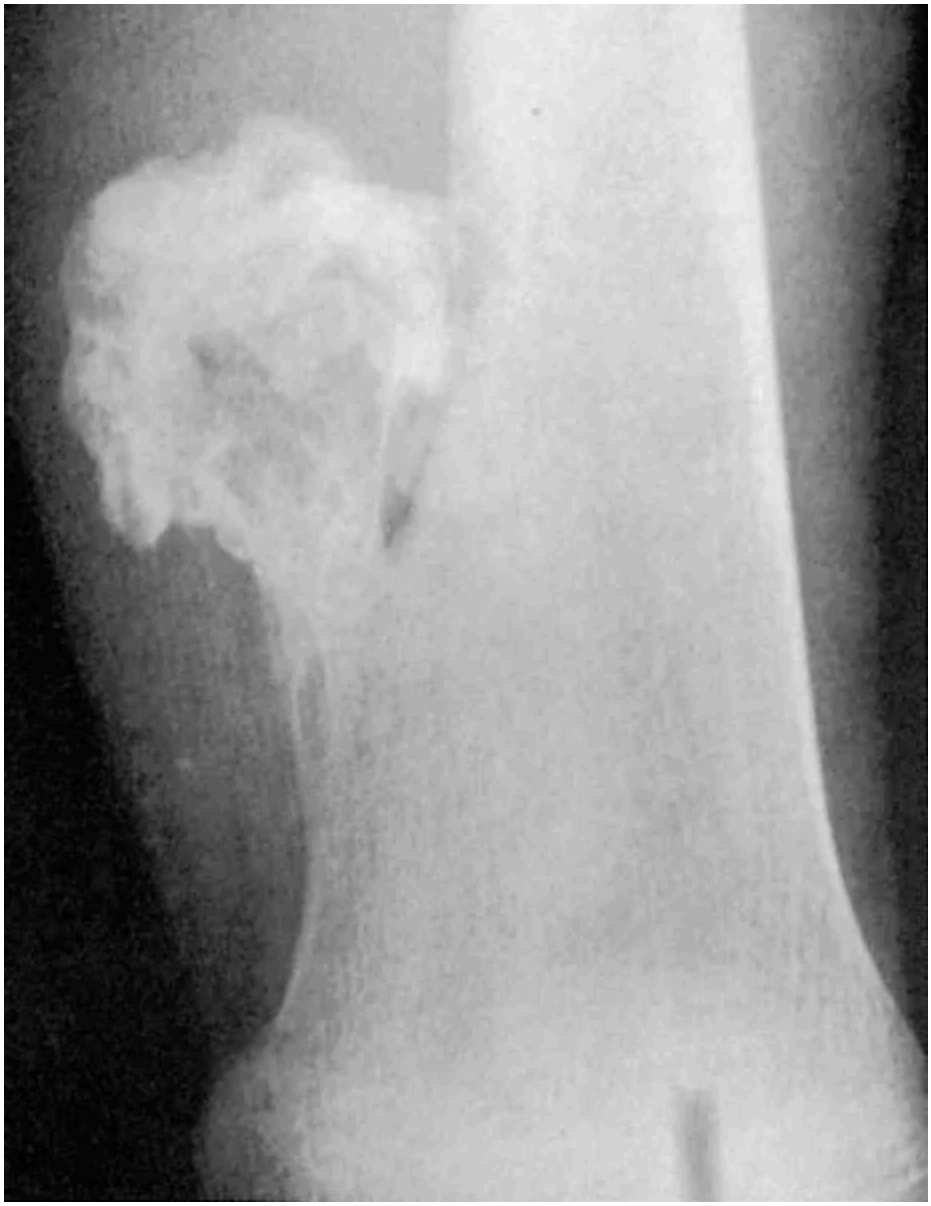
Osteochondromas, either solitary or as multiple hereditary exostoses, are associated with loss of function mutations in the *EXT1* and *EXT2* genes (Tanteles 2015). These genes produce proteins found in the Golgi apparatus that form a complex that modifies heparan sulfate, a protein similar to heparin, which regulates blood vessel formation and blood clotting and has a role in cancer metastases. Solitary tumors have somatic mutations (i.e., develop during life) with a 1 - 2% risk of malignant transformation.

Multiple hereditary exostoses have germline mutations (i.e., develop before birth) (Wutys 1998) with a 5 - 25% risk of malignant transformation.

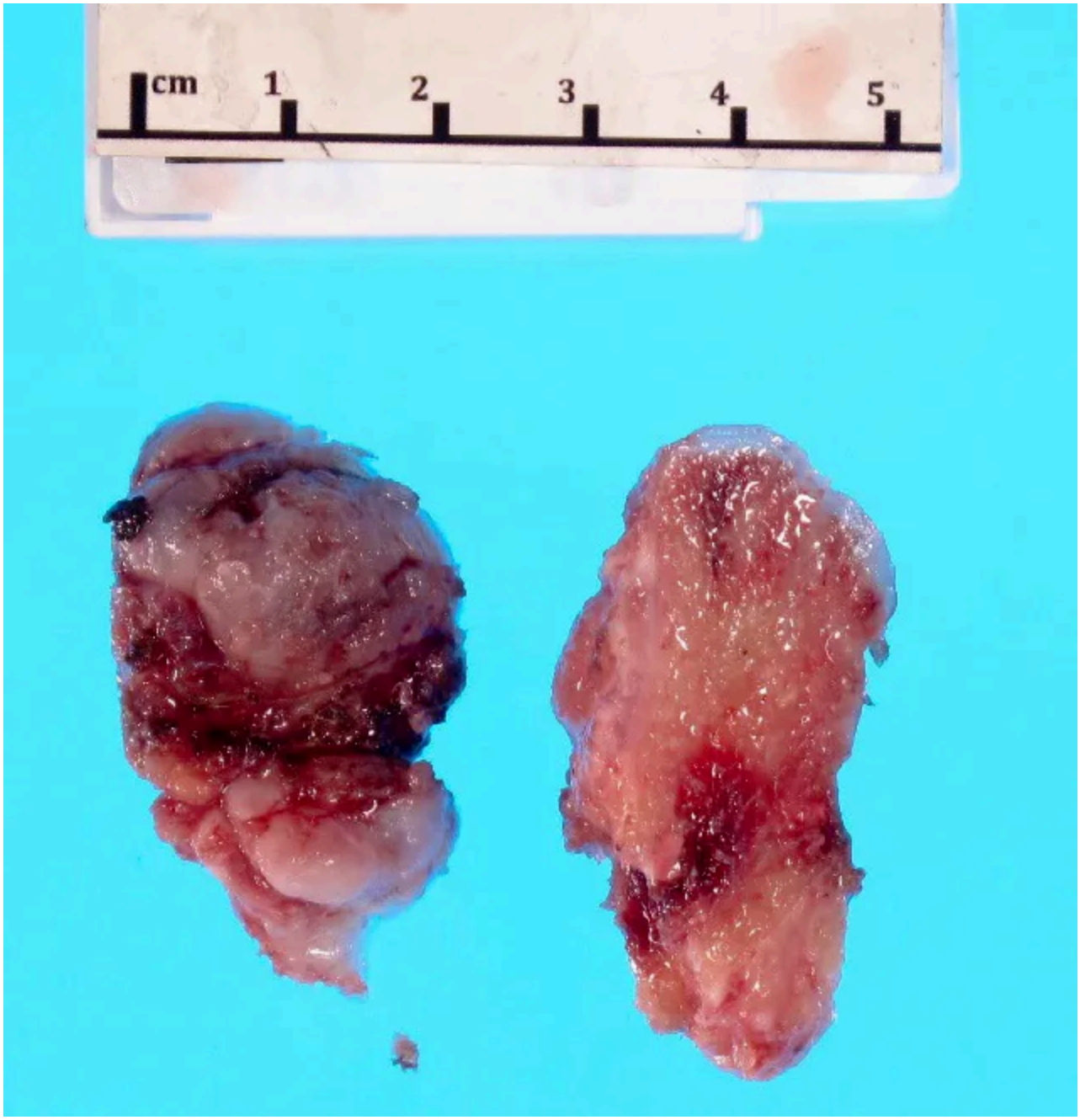
Osteochondroma



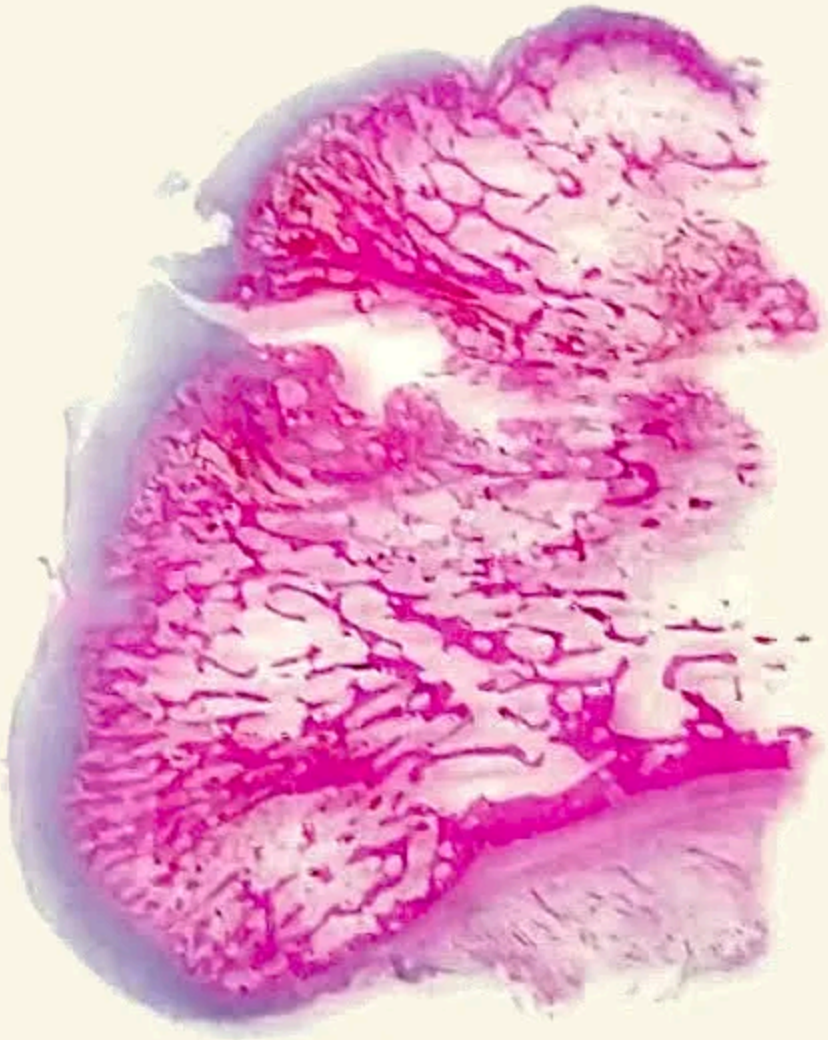
Xray of an osteochondroma arising in the proximal femur (contributed by Jose G. Mantilla, M.D.).



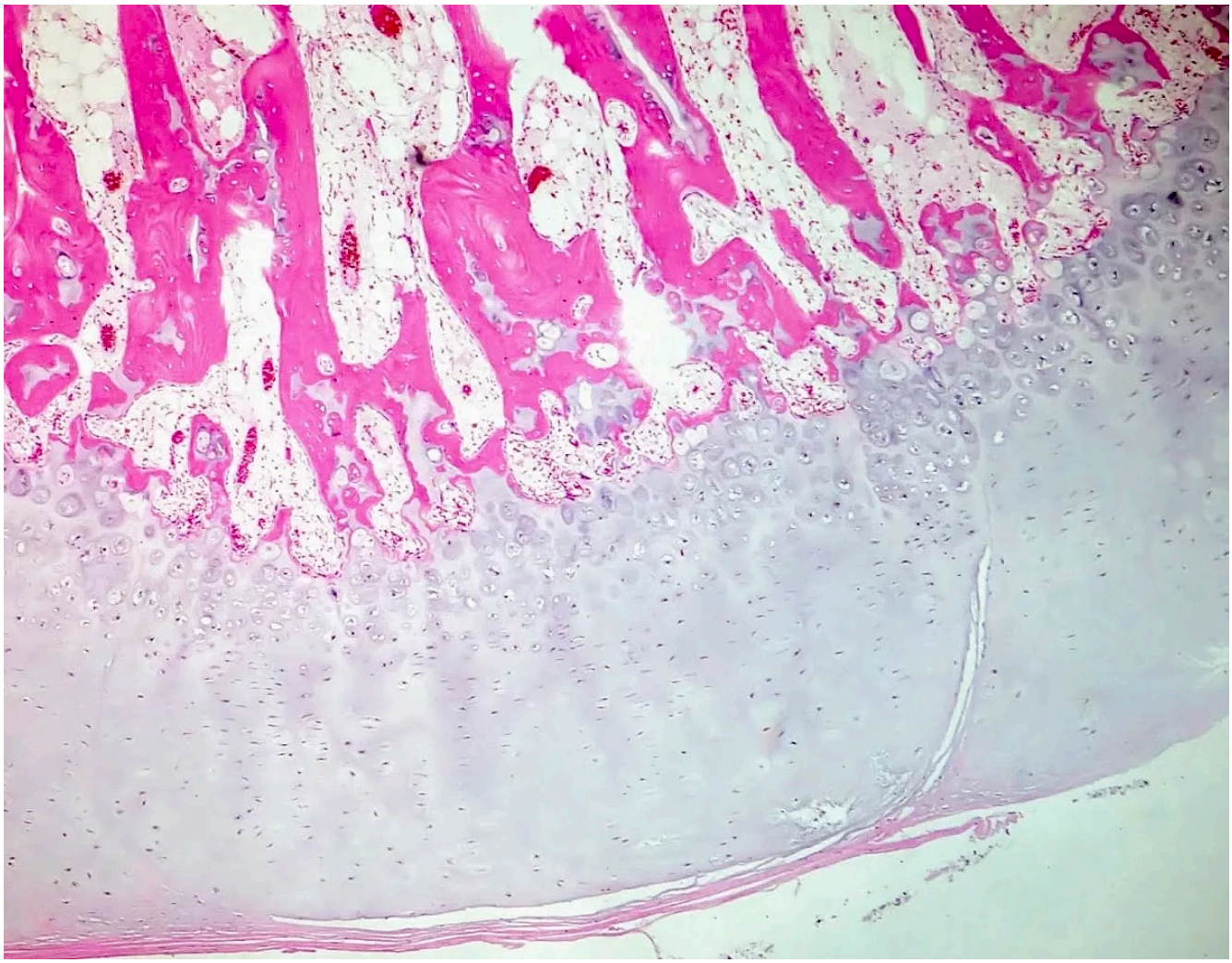
An osteochondroma involving the distal portion of the femur of a 13 year old boy has a well circumscribed, knobby surface. The lesion forms an acute angle with the cortex of the femur (contributed by the Armed Forces Institute of Pathology).



Osteochondroma has a hyaline cartilage cap overlying mature cancellous bone (contributed by Jose G. Mantilla, M.D.).



Osteochondroma has a hyaline cartilage cap overlying mature cancellous bone (contributed by Jose G. Mantilla, M.D.).

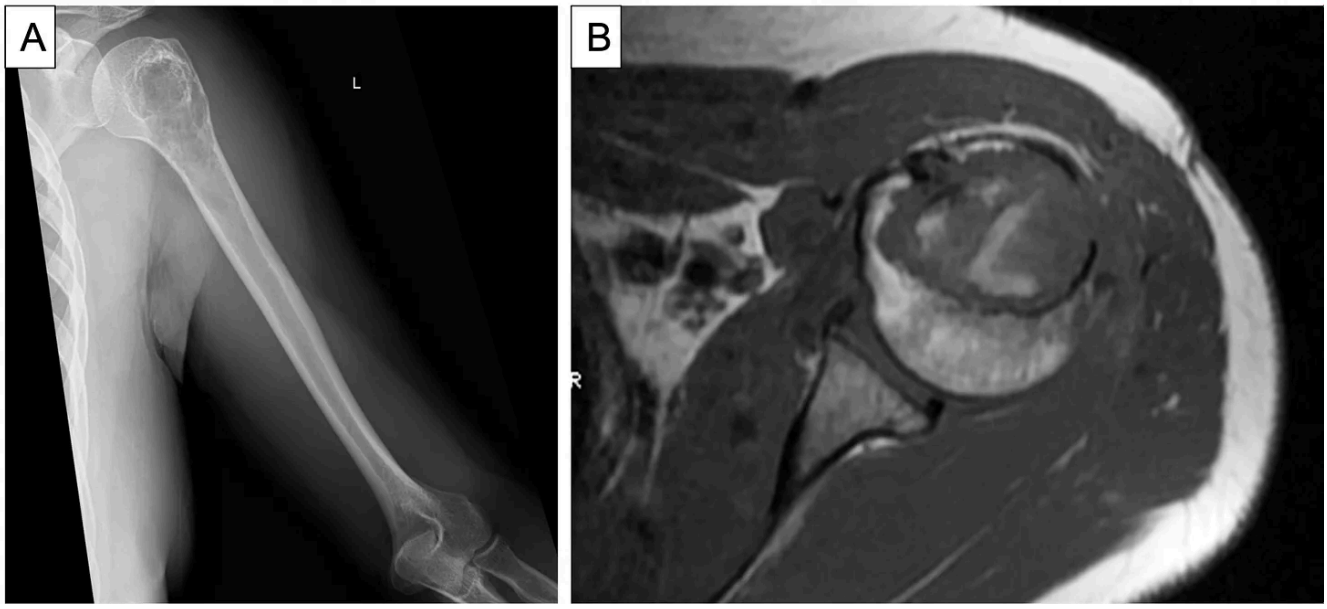


Osteochondroma has a cartilage cap lined by perichondrium, contiguous with mature bone (contributed by Jose G. Mantilla, M.D.).

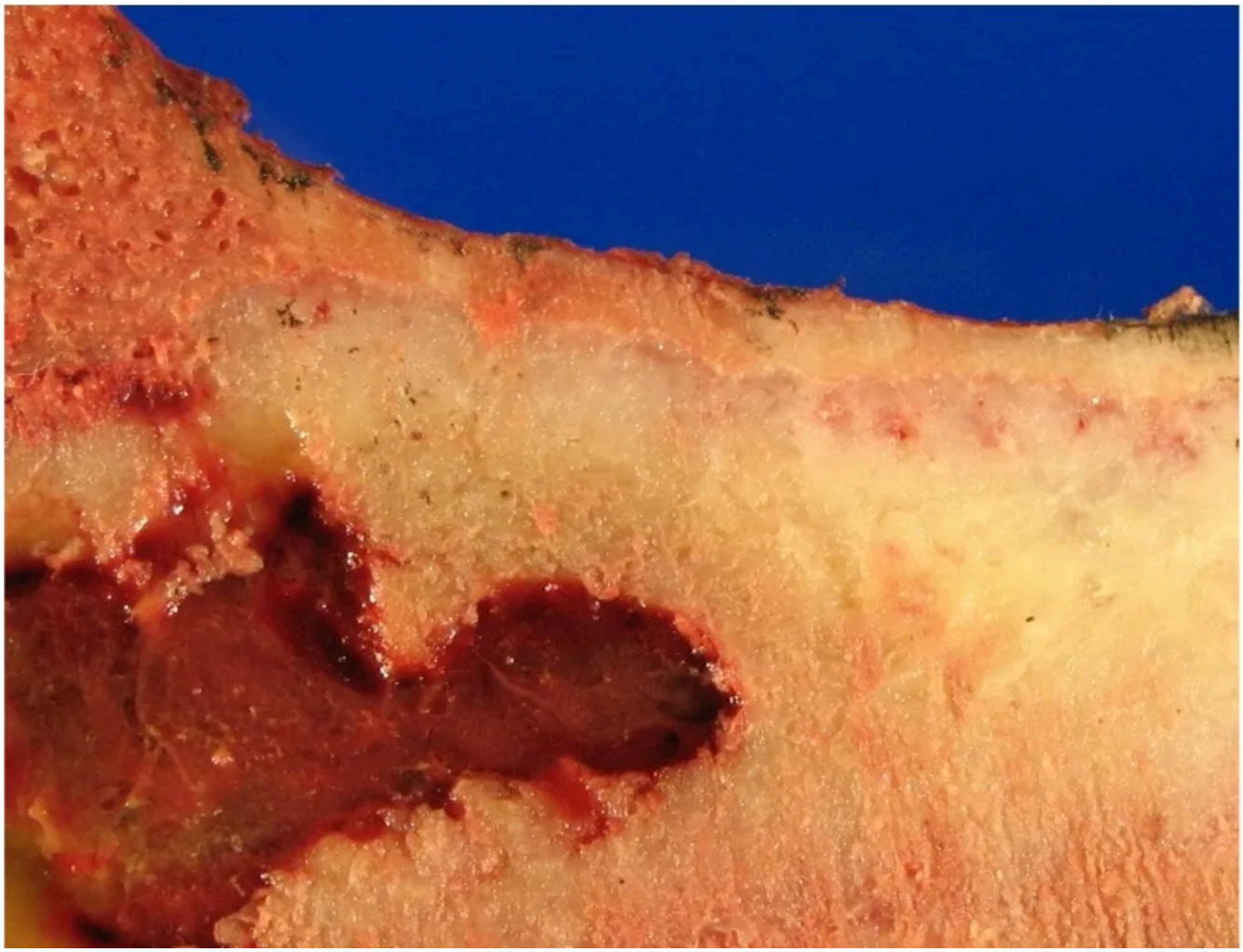
Atypical cartilaginous tumor / chondrosarcoma grade 1

Atypical cartilaginous tumor / chondrosarcoma grade 1 is a locally aggressive, hyaline cartilage producing neoplasm (abnormal growth of tissue, usually initiated by division of a single cell). Tumors in long and short tubular bones are termed atypical cartilaginous tumors but tumors in flat bones, including the pelvis, scapula and skull base are termed chondrosarcoma grade 1. These tumors have a good prognosis, with recurrence in only 10%, typically due to incomplete resection in difficult locations. They may recur as higher grade (more aggressive) chondrosarcomas. Xrays are essential for the diagnosis of this tumor because, microscopically, the tumors may appear benign.

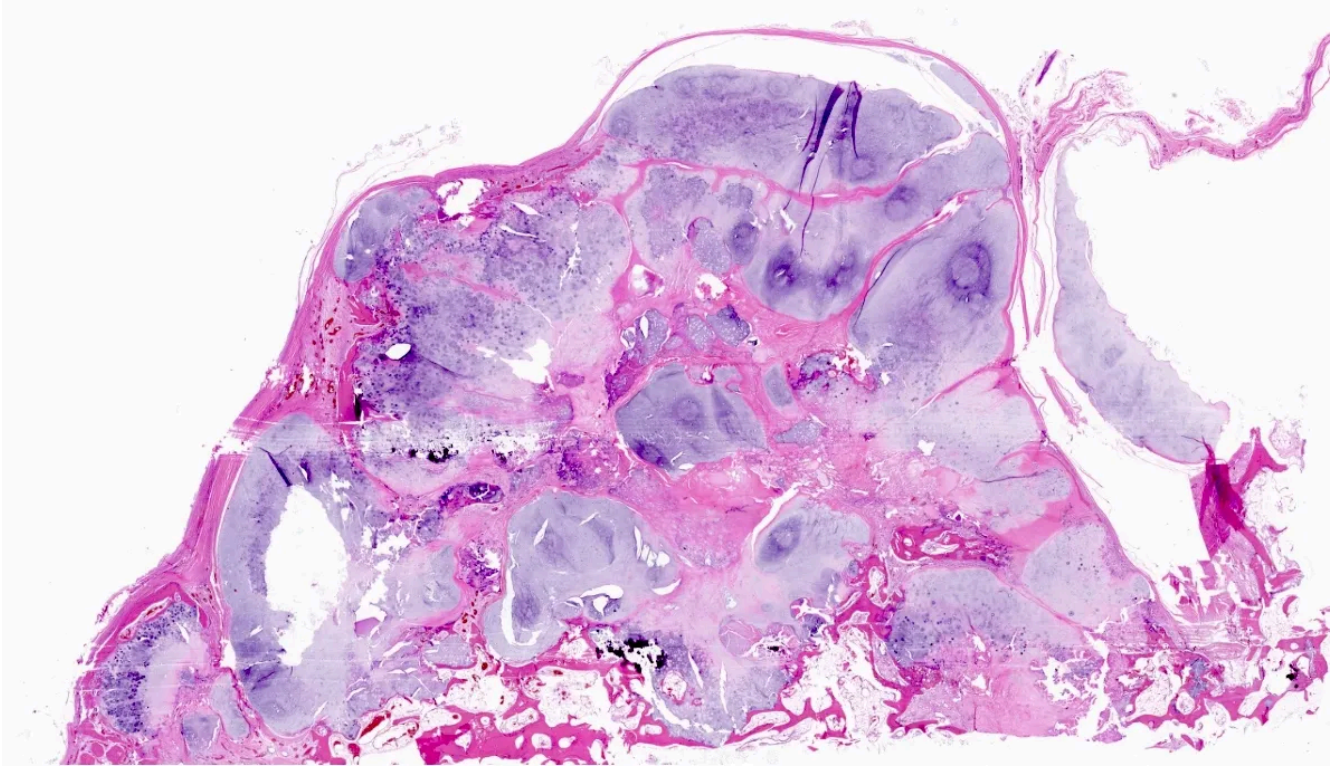
Atypical cartilaginous tumor / chondrosarcoma grade 1



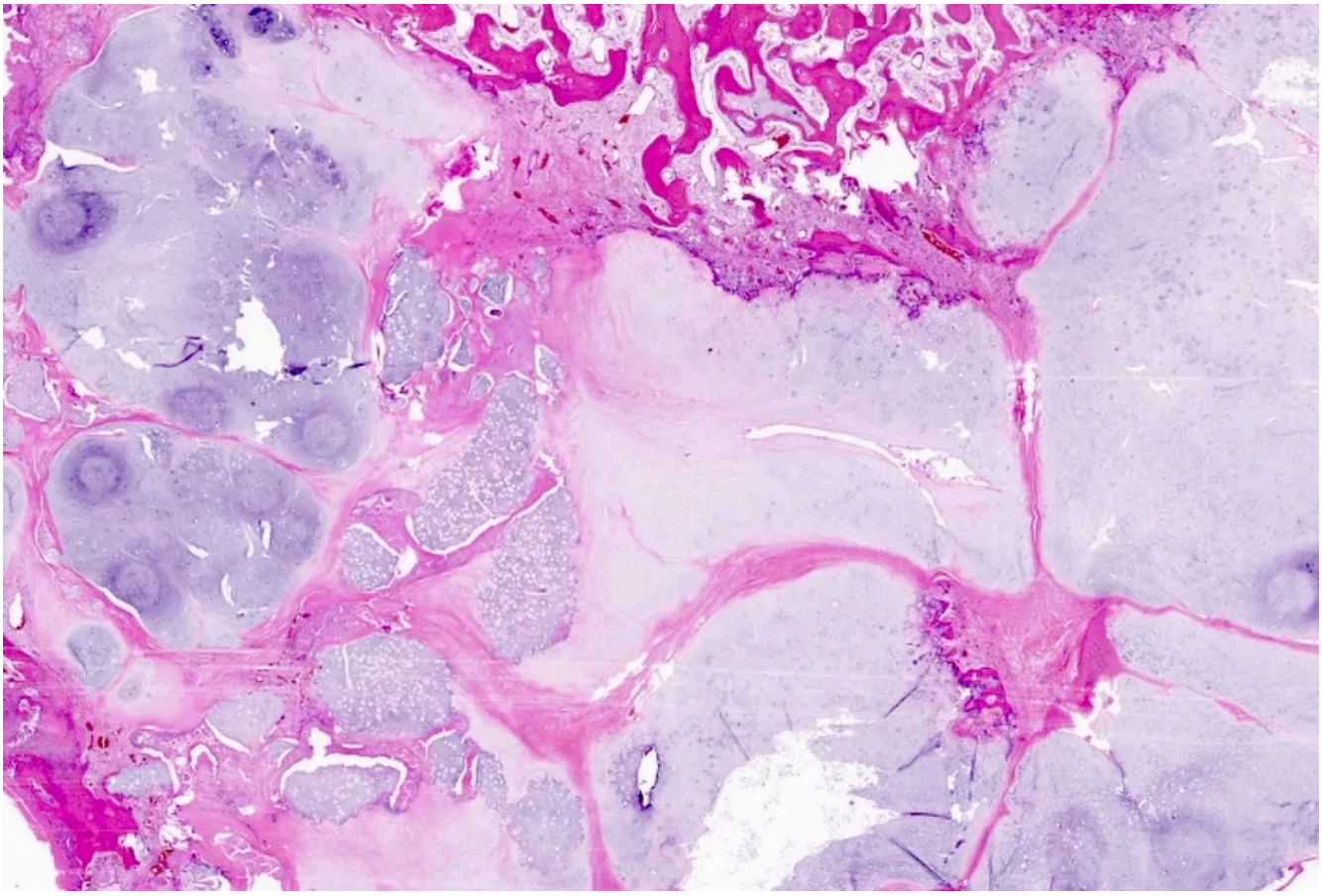
Atypical cartilaginous tumor: Xray (left) shows a lucent lesion involving the proximal left humerus (top left). The borders of the lesion are indistinct. There is endosteal scalloping and mild expansion laterally. MRI (right) shows an irregular, expansile, avidly enhancing mass (contributed by Serenella Serinelli, M.D., Ph.D. and Gustavo de la Roza, M.D.).



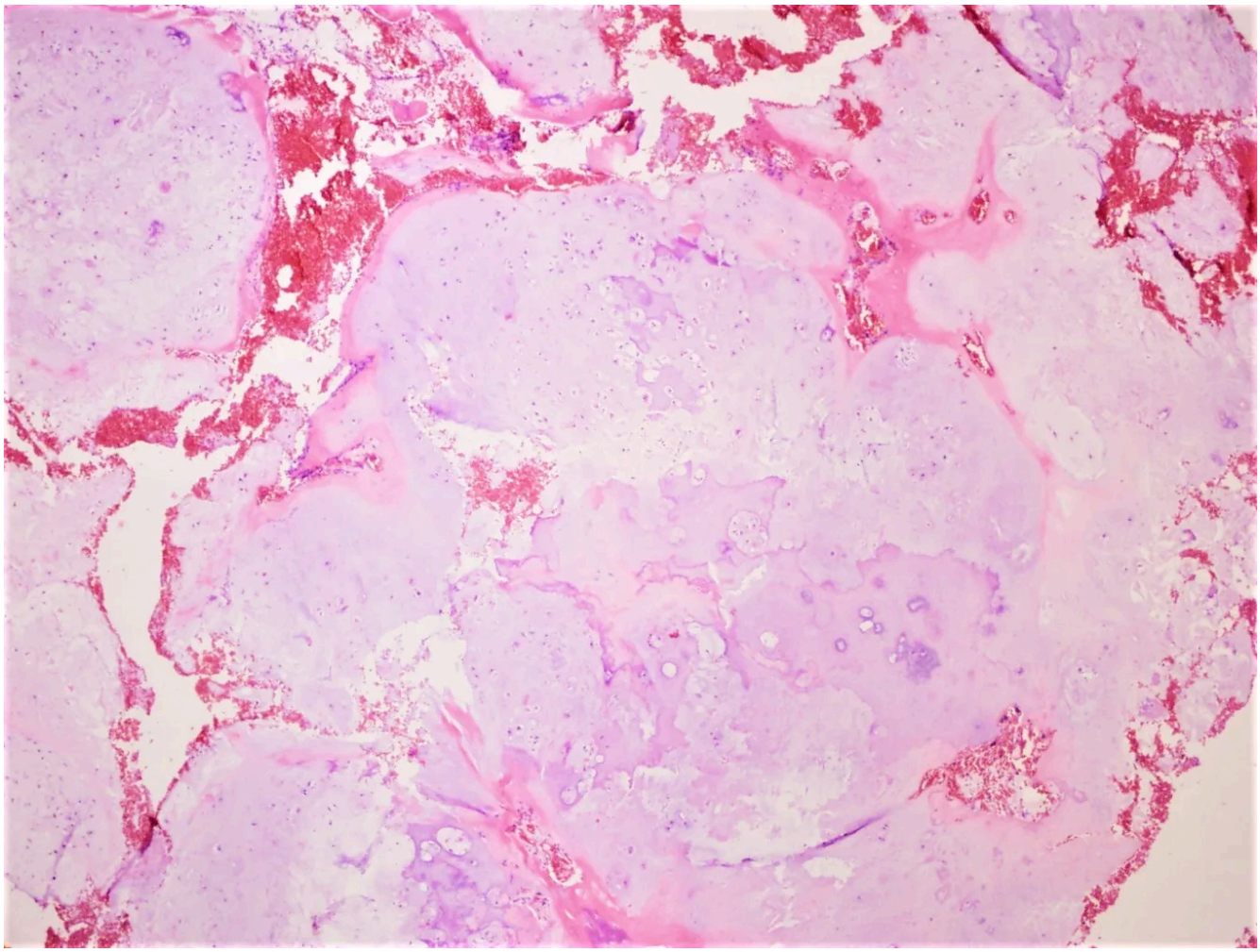
Atypical cartilaginous tumor: White-gray, cartilaginous lesion involving the metaphysis and diaphysis. The lesion appears to focally erode the cortical bone. There is a hemorrhagic and gelatinous soft area on the left (previous biopsy site) (contributed by Serenella Serinelli, M.D., Ph.D. and Gustavo de la Roza, M.D.).



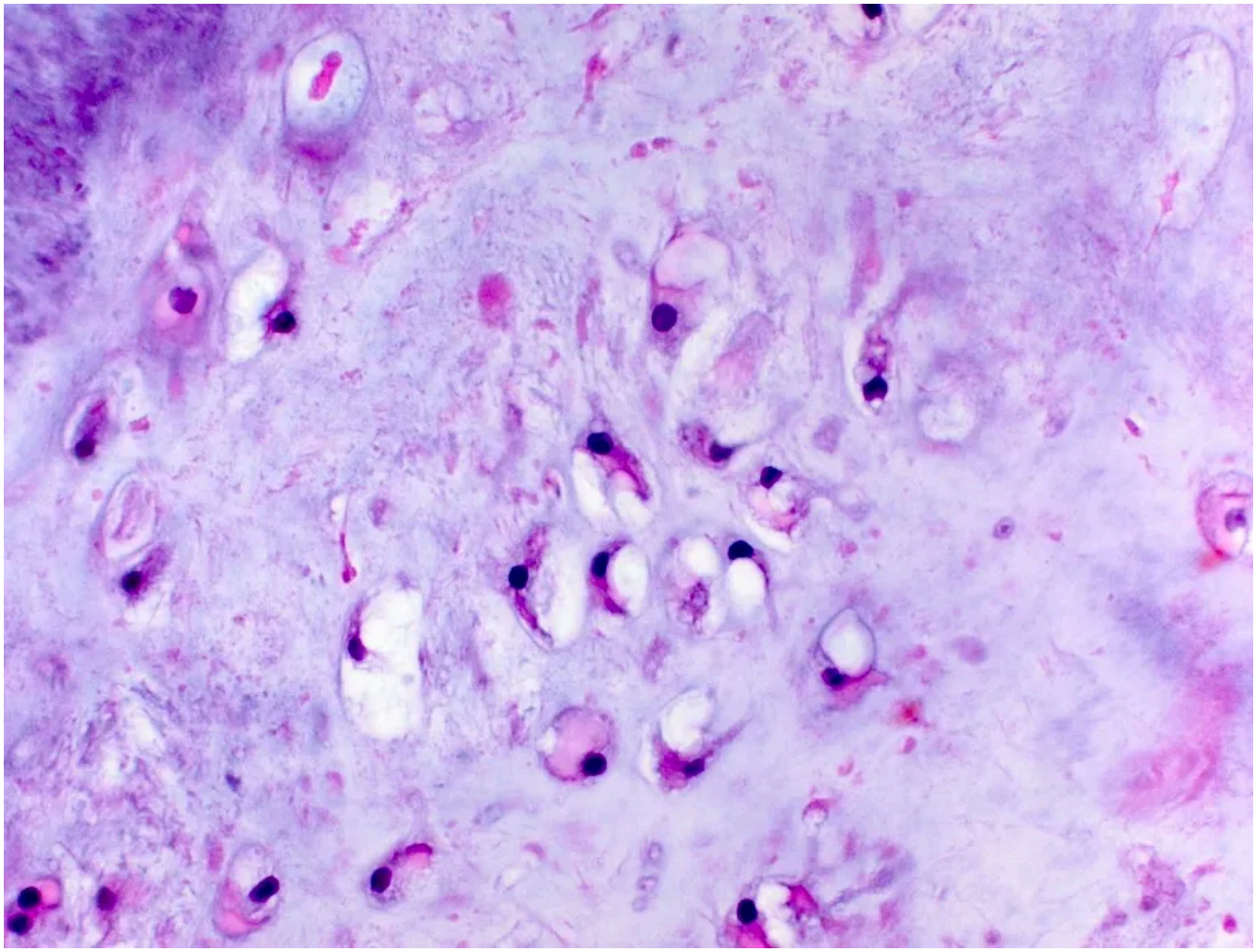
Thick, lobulated cartilaginous cap, involved by atypical cartilaginous tumor (contributed by Serenella Serinelli, M.D., Ph.D. and Gustavo de la Roza, M.D.).



Lobules have irregular shapes and sizes and are separated by fibrous bands (contributed by Serenella Serinelli, M.D., Ph.D. and Gustavo de la Roza, M.D.).



Grade 1 chondrosarcoma: This tumor often requires Xrays to determine if it is malignant or not. Note the tumor lobules on low power. Contrast to grades 2 and 3 chondrosarcoma images below (contributed by Shadi Qasem, M.D.).

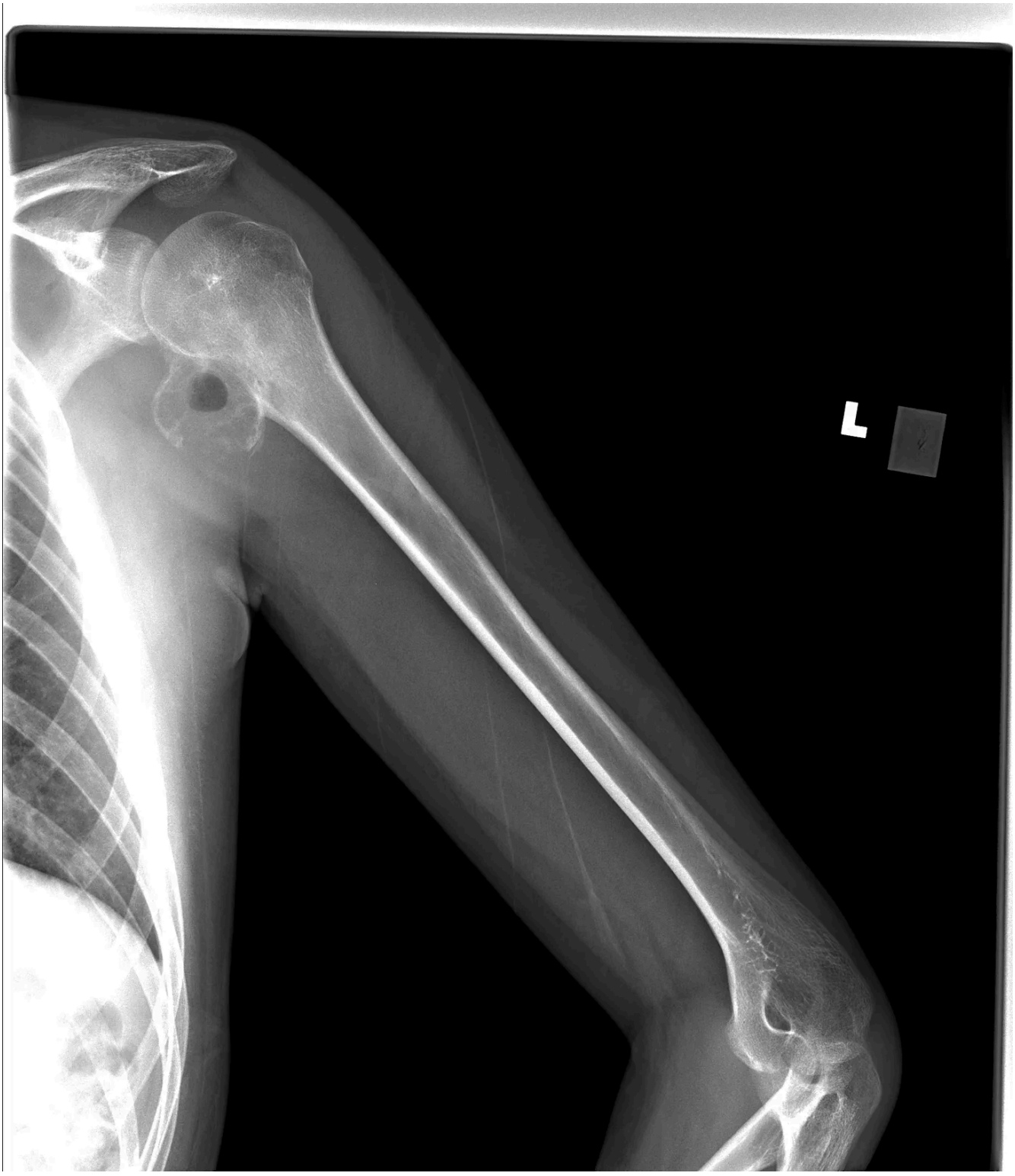


Cells show moderate eosinophilic to vacuolated cytoplasm. Nuclei are small and uniform, with condensed chromatin (lymphocyte-like). Binucleation can be observed (lower left corner). Mitoses and nuclear pleomorphism are absent (contributed by Serenella Serinelli, M.D., Ph.D. and Gustavo de la Roza, M.D.).

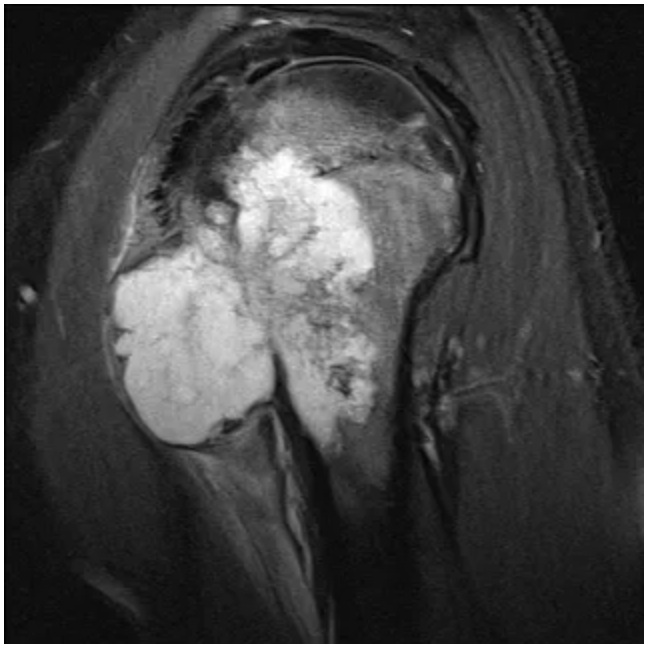
Chondrosarcoma grades 2 & 3

These chondrosarcomas are invasive malignancies characterized by the formation of a cartilaginous matrix. They may (secondary) or may not (primary) be associated with a preexisting enchondroma or osteochondroma. Their histologic grade (2 or 3), extracompartmental spread and local recurrence are important prognostic factors. They have a 5 year survival rate of only 50% in contrast to 85% survival for atypical cartilaginous tumor / grade 1 chondrosarcoma. Treatment is typically wide surgical resection with radiotherapy.

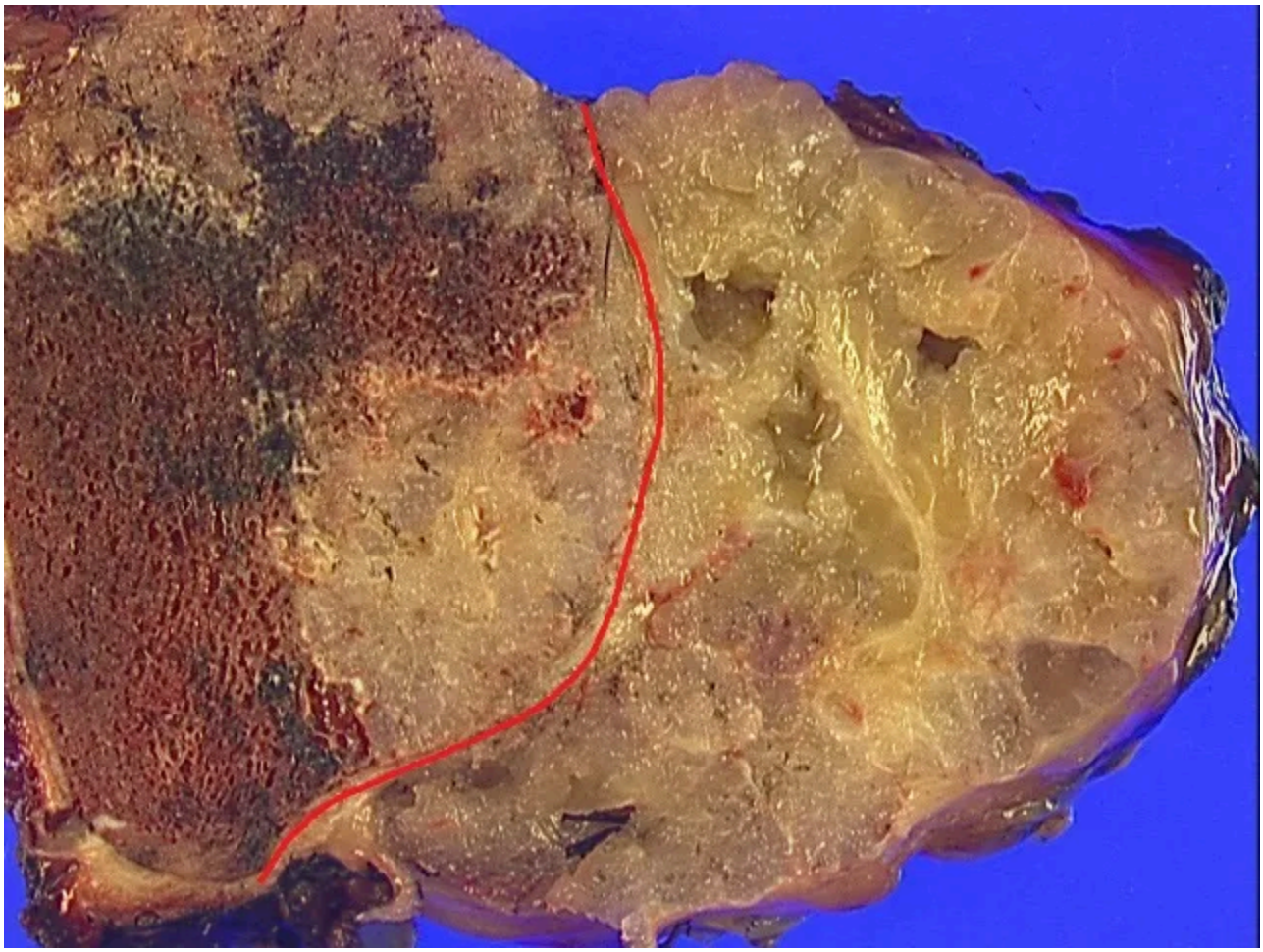
Chondrosarcoma grades 2 & 3



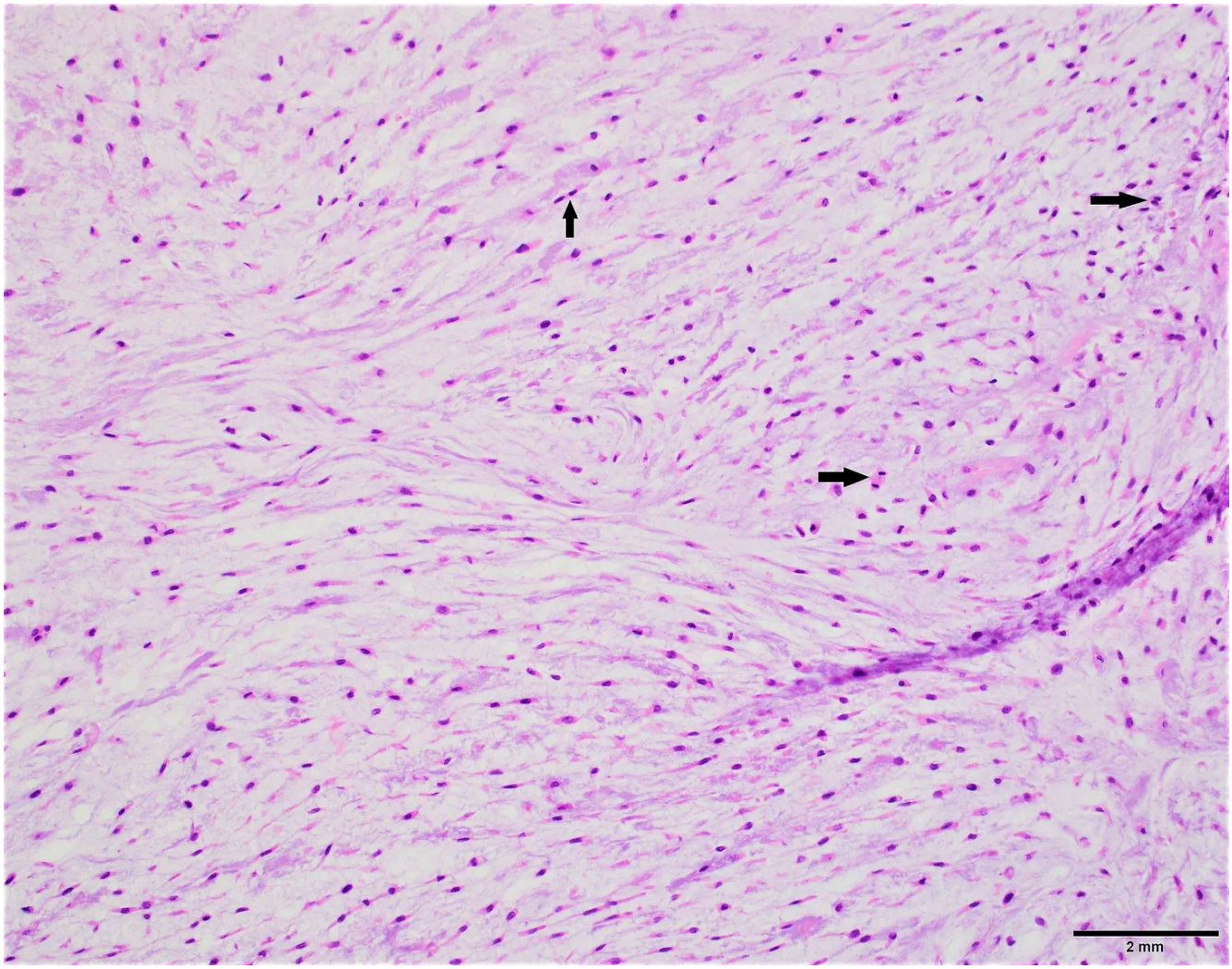
Chondrosarcoma, grade unspecified: An osteolytic tumor involving the proximal humerus (upper left) with extension into soft tissue (contributed by Shadi Qasem, M.D.).



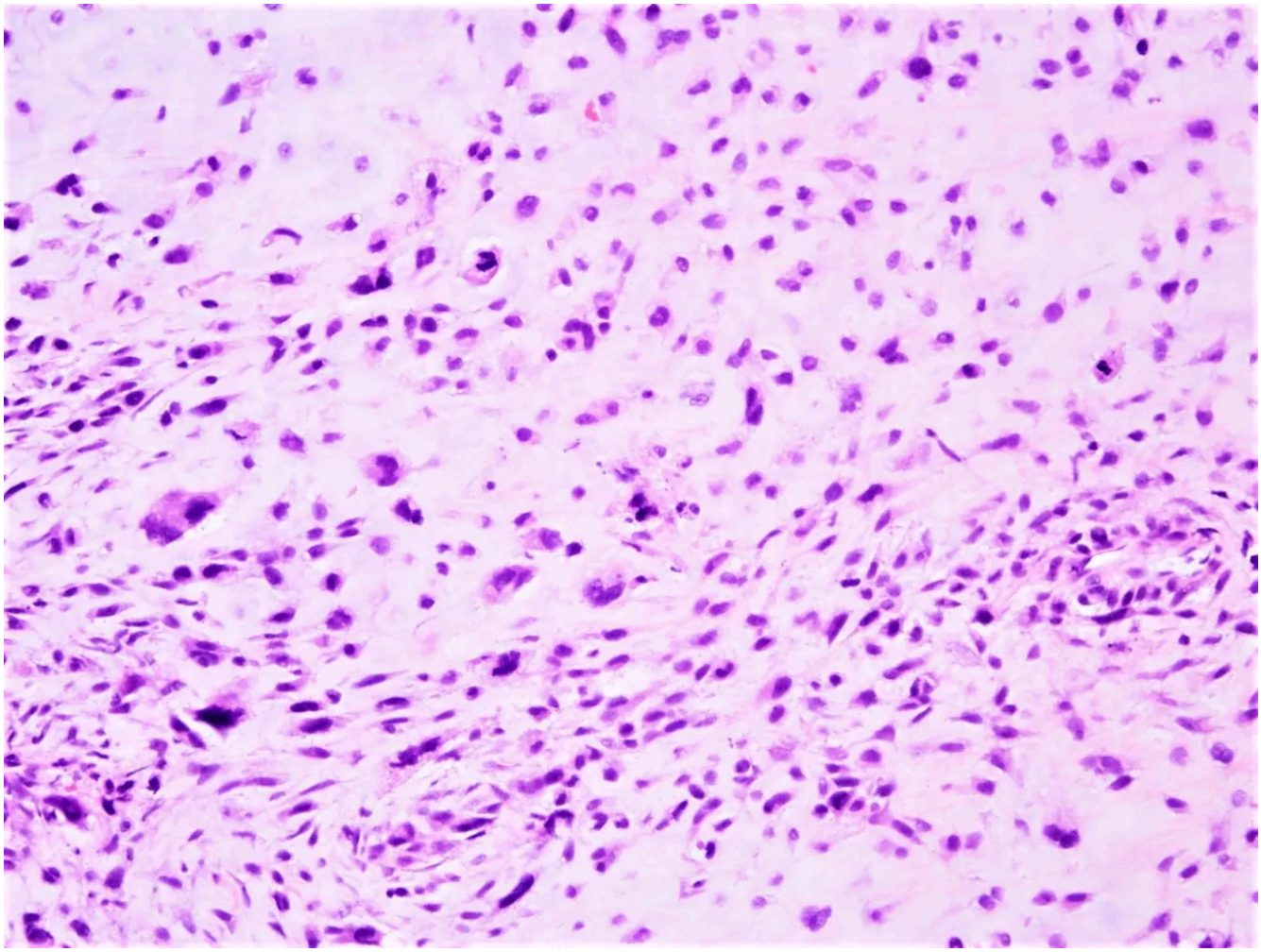
MRI shows the true extent of the tumor shown above. Notice the well defined borders of the tumor in soft tissue (contributed by Shadi Qasem, M.D.).



This chondrosarcoma (grade unspecified) is a large pelvic tumor arising in an existing osteochondroma. The red line separates the preexisting osteochondroma (left side) from the chondrosarcoma, which has cystic changes (right side) (contributed by Shadi Qasem, M.D.).



Grade 2 chondrosarcoma: There is increased cellularity and nuclear atypia. Note the binucleation (arrows) (contributed by Shadi Qasem, M.D.).



Grade 3 chondrosarcoma: There is obvious nuclear atypia and pleomorphism but the background is distinctly chondroid (contributed by Shadi Qasem, M.D.).

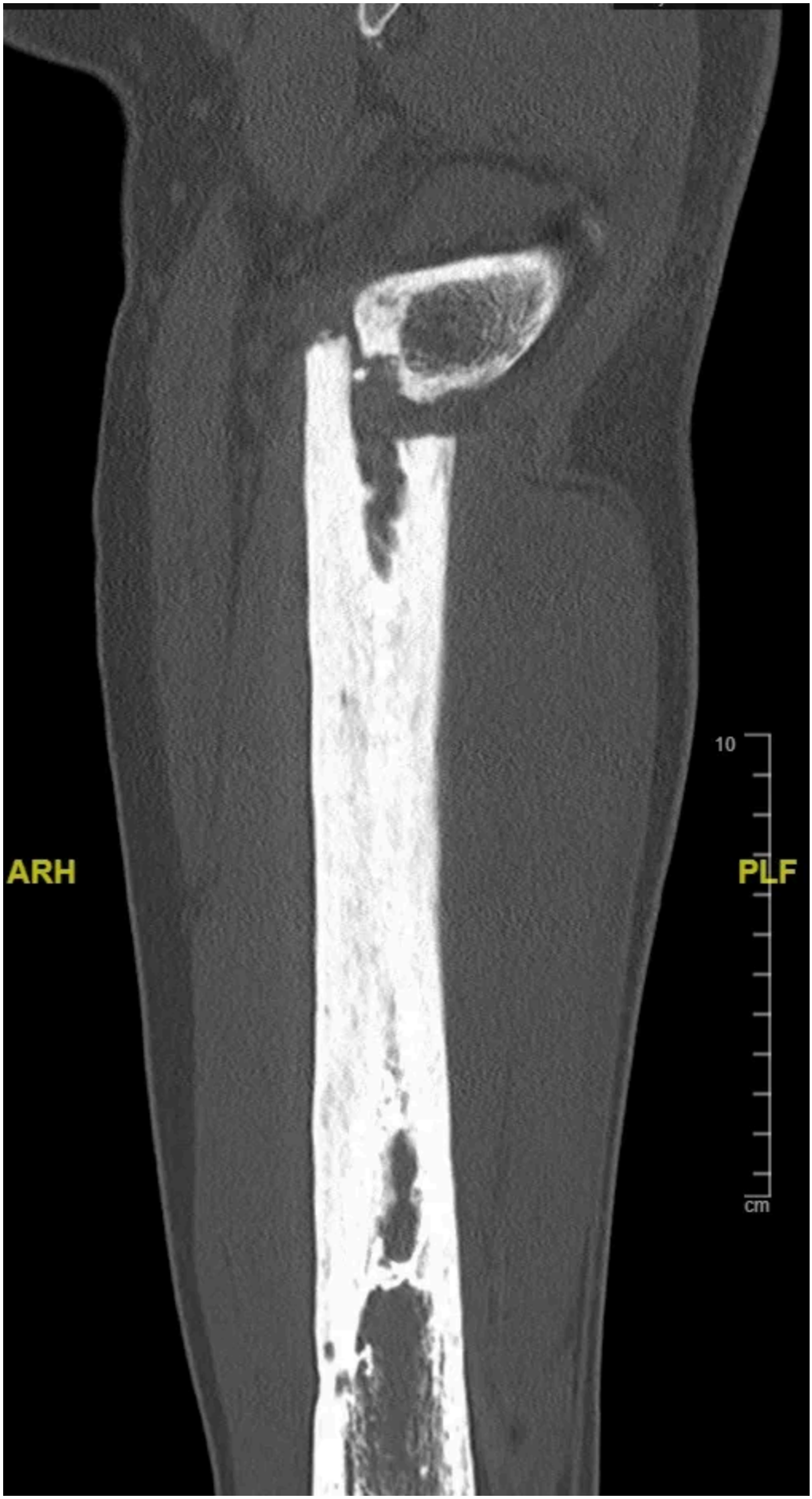
Paget disease of bone

Paget disease of bone, also called osteitis deformans, is a chronic disease of bone with accelerated bone turnover leading to disordered, poorly formed bone with increased density and an increased likelihood of fractures. It is not related to Paget disease of the breast or extramammary Paget disease, (all were discovered by Sir James Paget, a founder of pathology, Wikipedia, Al-Rashid 2015). Paget disease of bone occurs in 2% of older people and is more common in those with Western European ancestry but is rare in those with African, Scandinavian or Asian ancestry (Kravets 2018). It may be due to

genetic and environmental problems that disrupt osteoclasts, including mutations in the *SQSTM1* gene, which is involved in bone remodeling.

Patients with Paget disease of bone are generally asymptomatic or have mild symptoms. They often are diagnosed only after a fracture. Paget disease rarely progresses to osteosarcoma (Al-Rashid 2015) or malignant giant cell tumor of bone (Rendina 2015).

Paget disease of bone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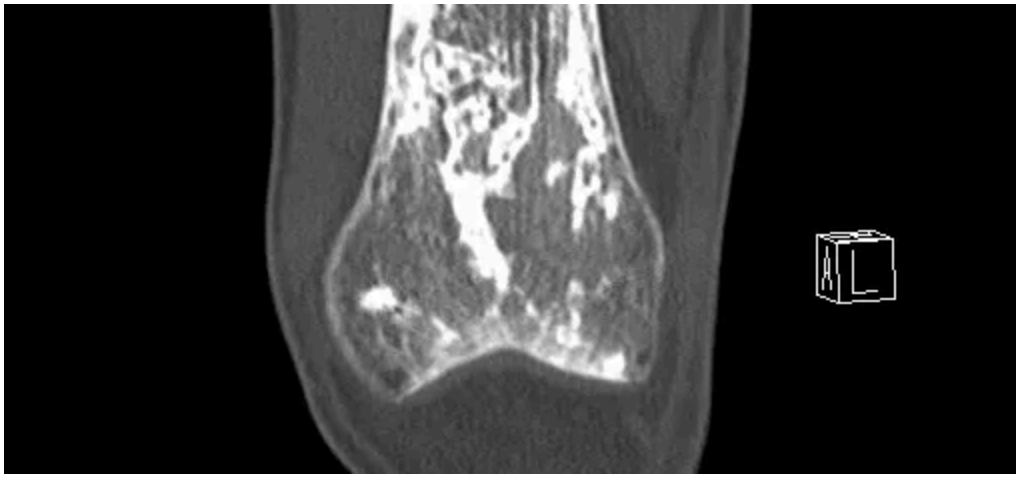
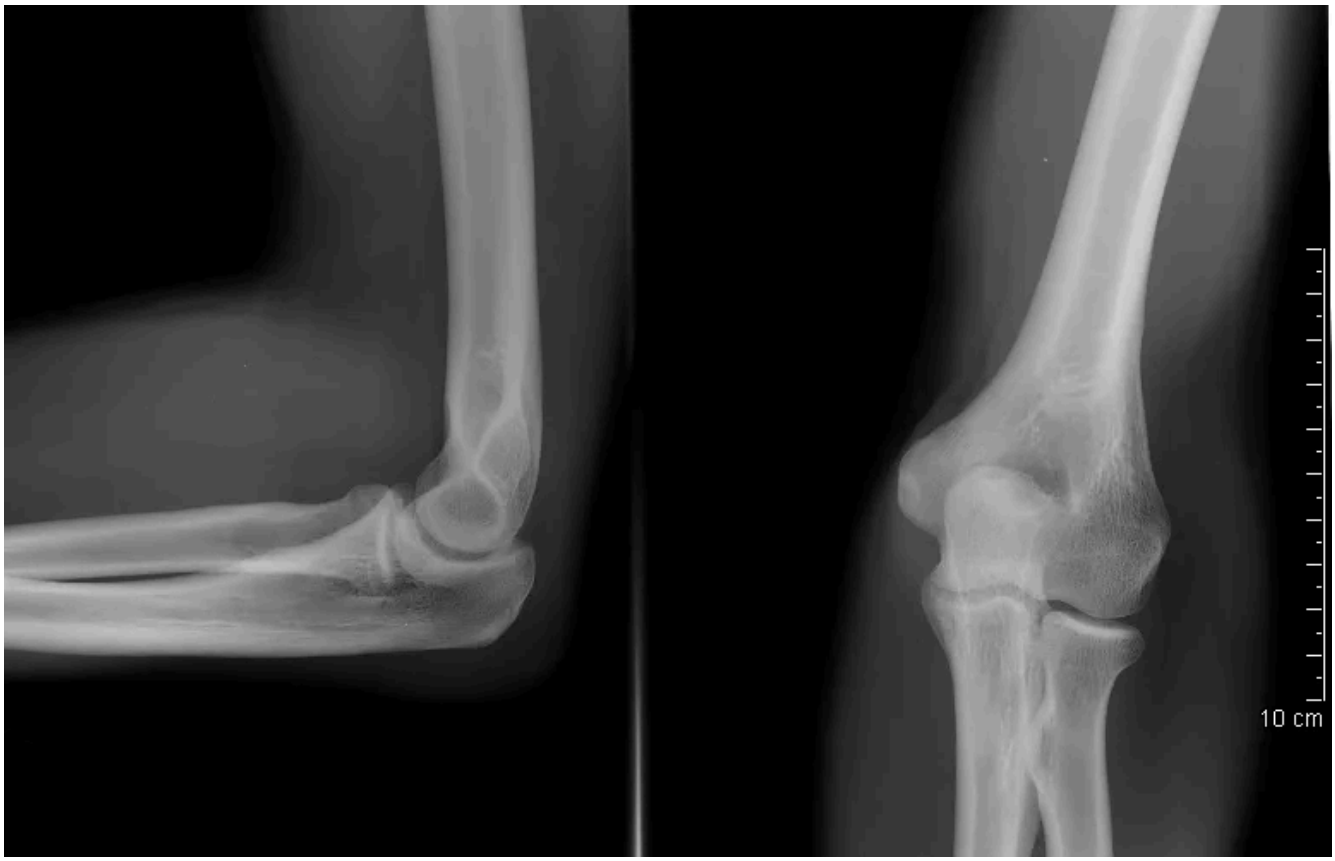
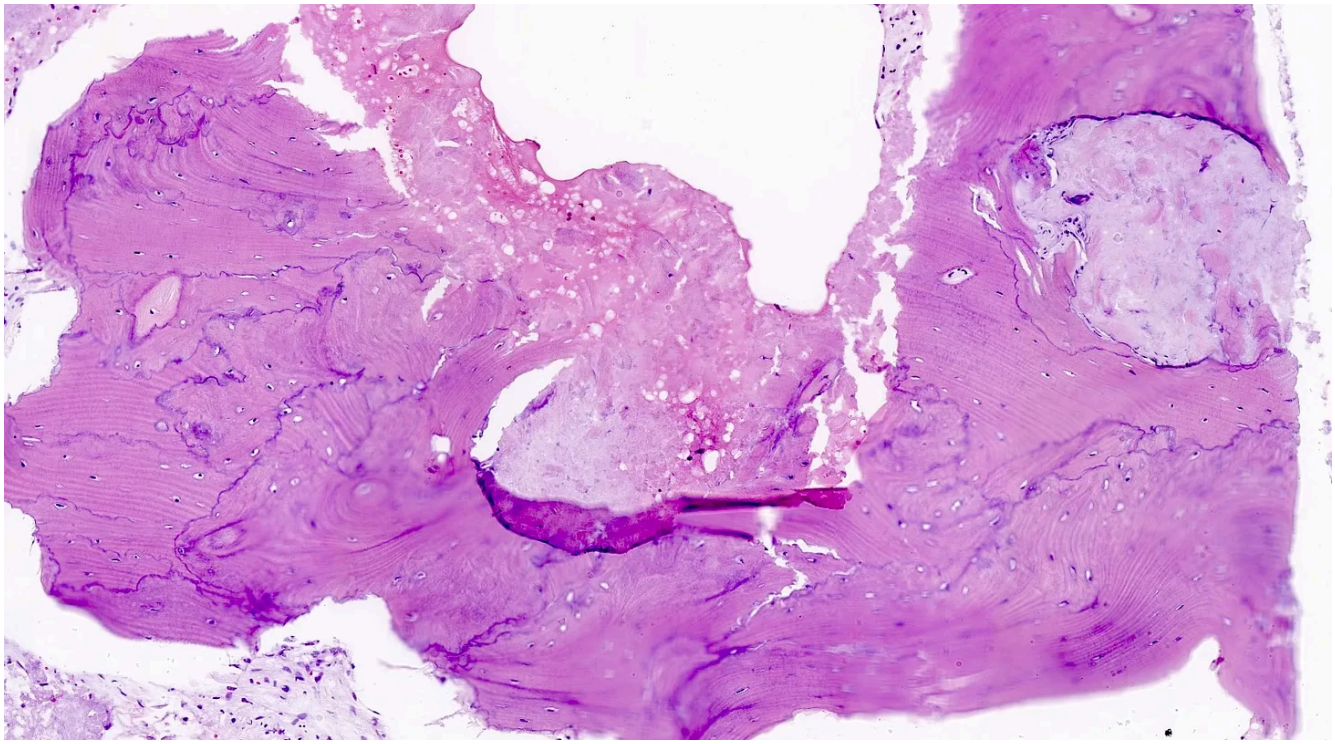


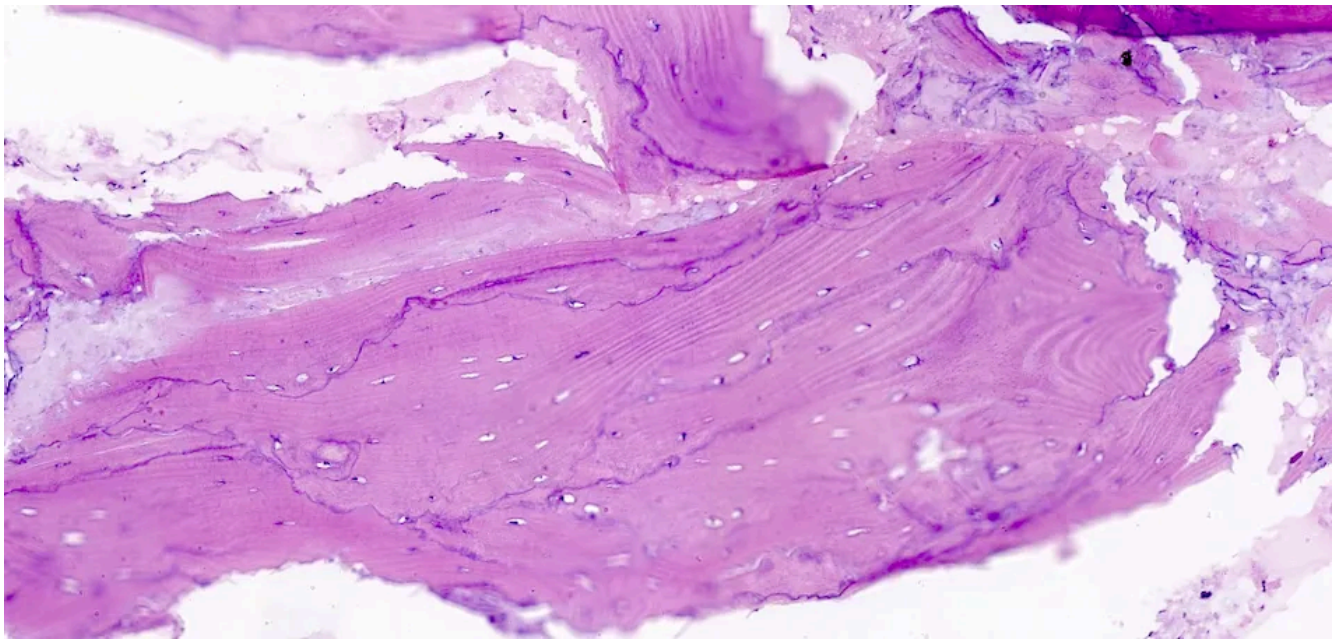
Plain coronal CT of Paget disease of the femur with a superimposed fracture at the top (contributed by Jose G. Mantilla, M.D.).



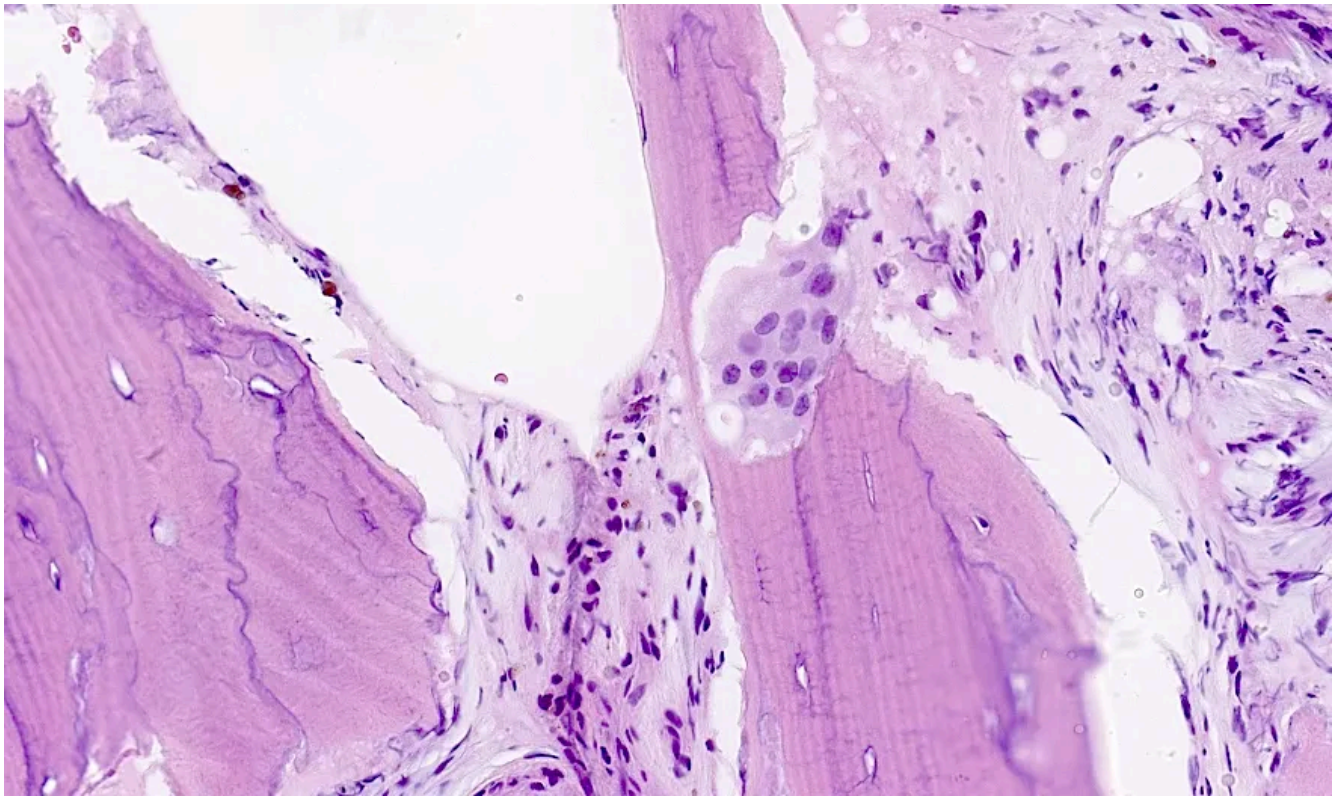
Normal bone at the elbow for comparison (Wikipedia).



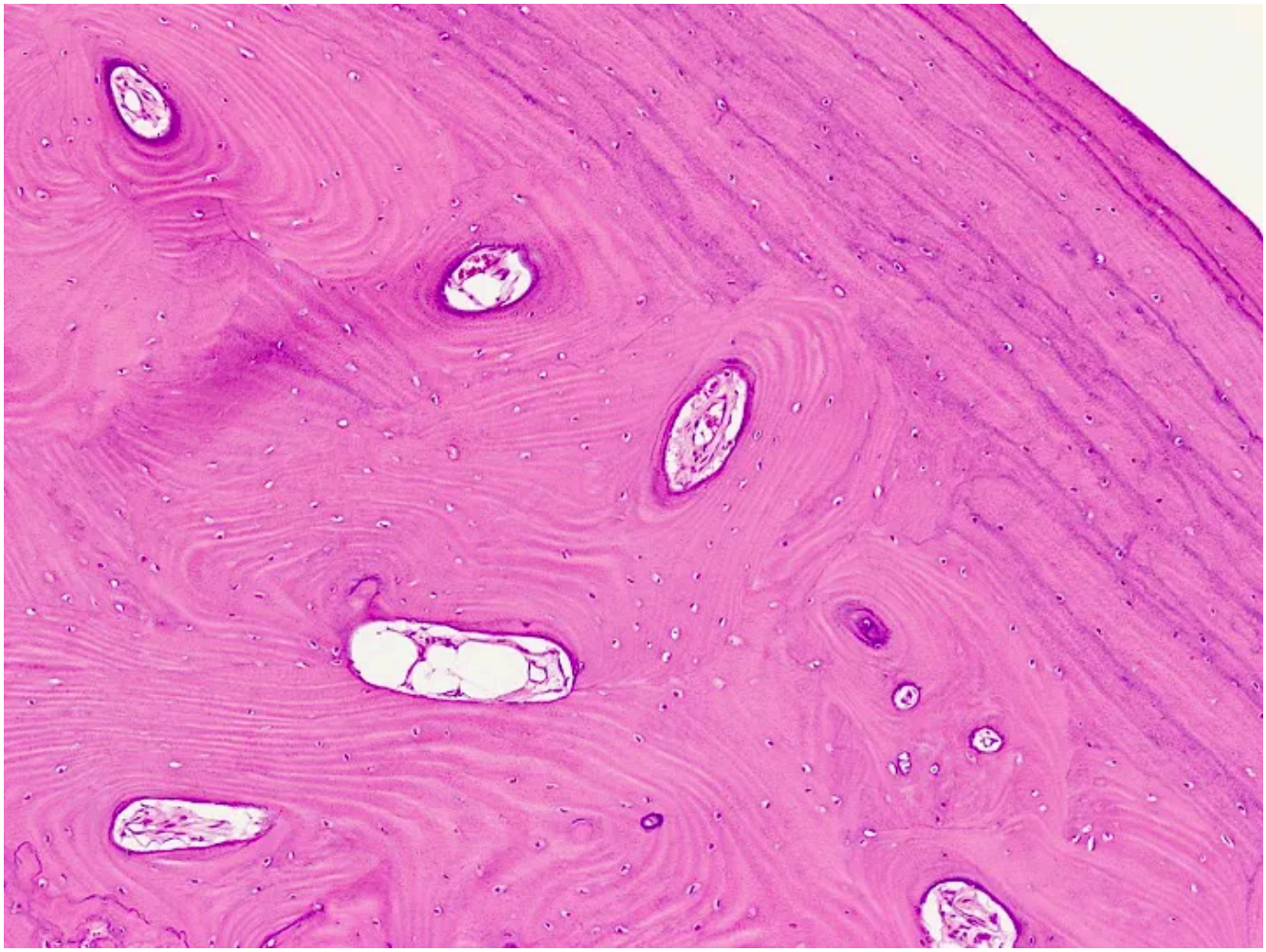
Paget disease of bone: Prominent, irregular cement lines of bone with characteristic mosaic pattern (contributed by Dana J. Hariri, M.D.).



Paget disease of bone: Haphazard cement lines of lamellar bone (contributed by Dana J. Hariri, M.D.).



Paget disease of bone: Osteoblast rimming bone with "bite marks" and remodeling on native bone (contributed by Dana J. Hariri, M.D.).



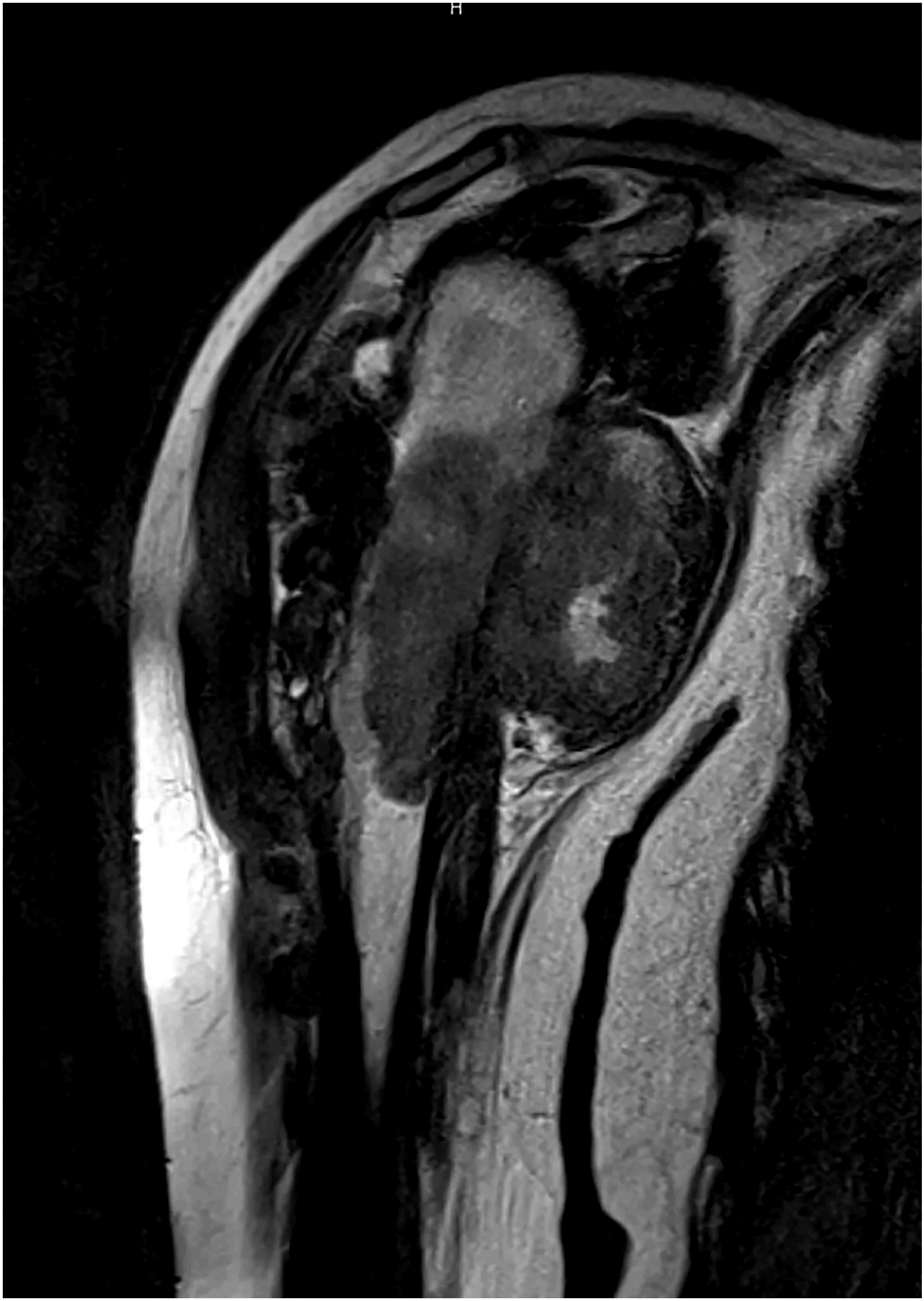
Normal bone for comparison: Plywood-like appearance with collagen bundles organized in parallel layers and concentric layers called lamellae (contributed by Nasir Ud Din, M.B.B.S.).

Osteosarcoma, NOS (conventional osteosarcoma) is a malignant tumor of connective tissue in which the tumor cells produce bone or osteoid. The tumor cells typically have a destructive growth pattern. There are many subtypes based on the location and microscopic features of the tumor.

Osteosarcoma develops in about 1% of patients with sporadic Paget disease but most cases (55 - 70%) arise in patients with polyostotic disease (i.e., occurring at multiple locations, Mangham 2009). The mechanism of malignant transformation is unknown. There are no special features of osteosarcoma associated with Paget disease. The images below are of osteosarcoma in general, not associated with Paget disease.

Osteosarcoma

High grade osteosarcoma involving the metadiaphyseal aspect of the proximal tibia (contributed by Jesse Hart, D.O.).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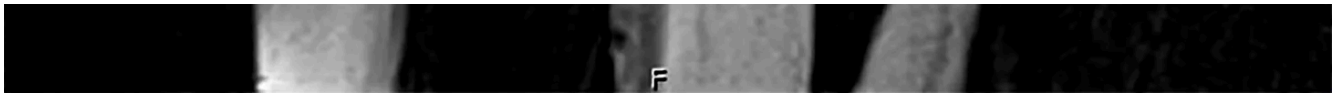
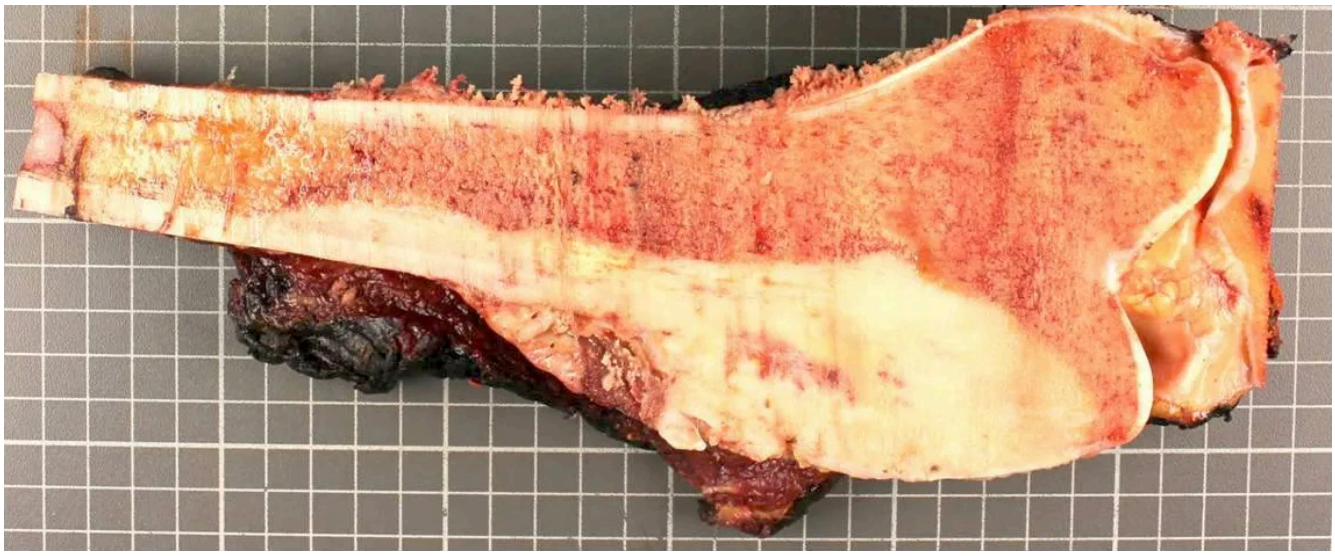
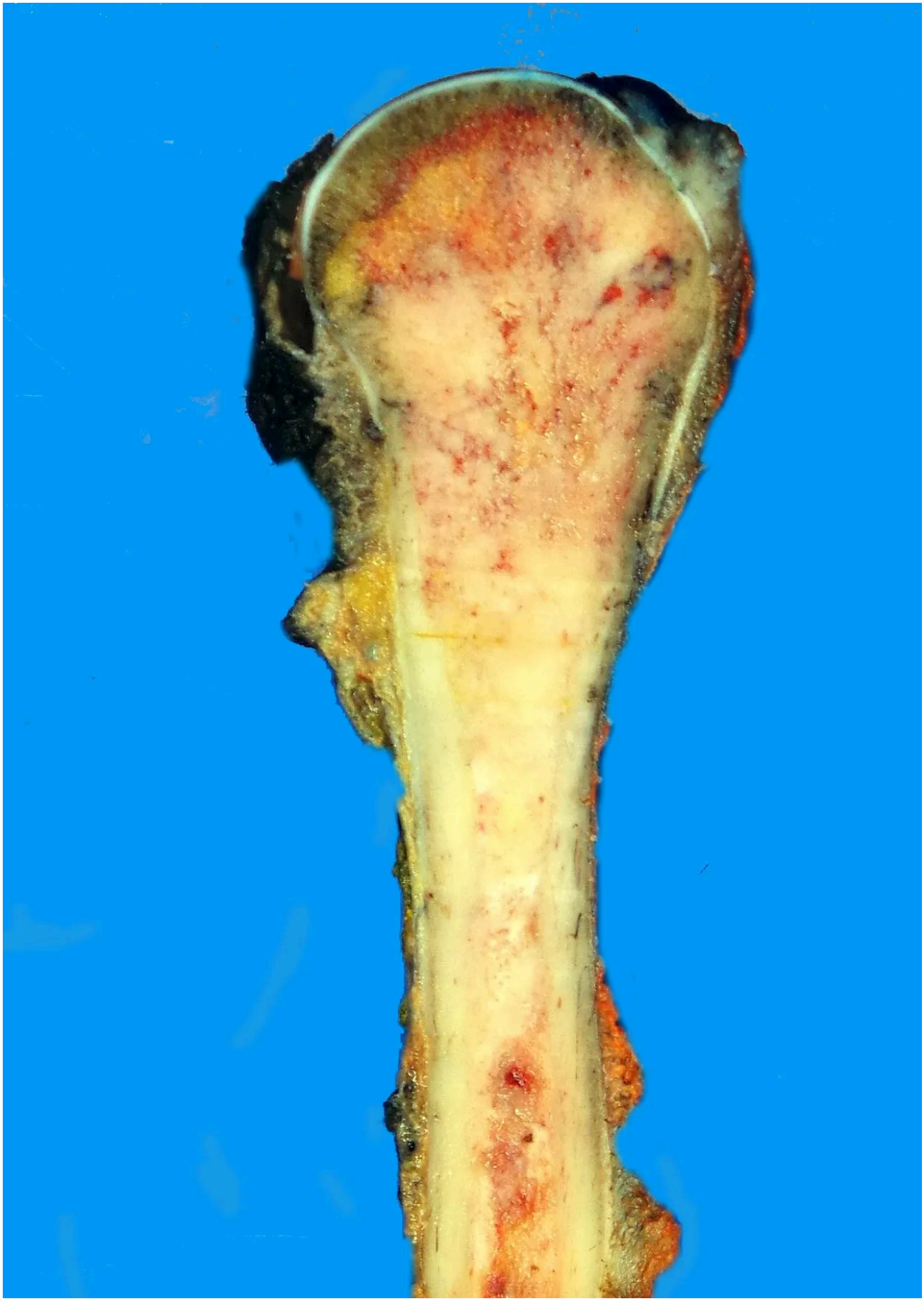


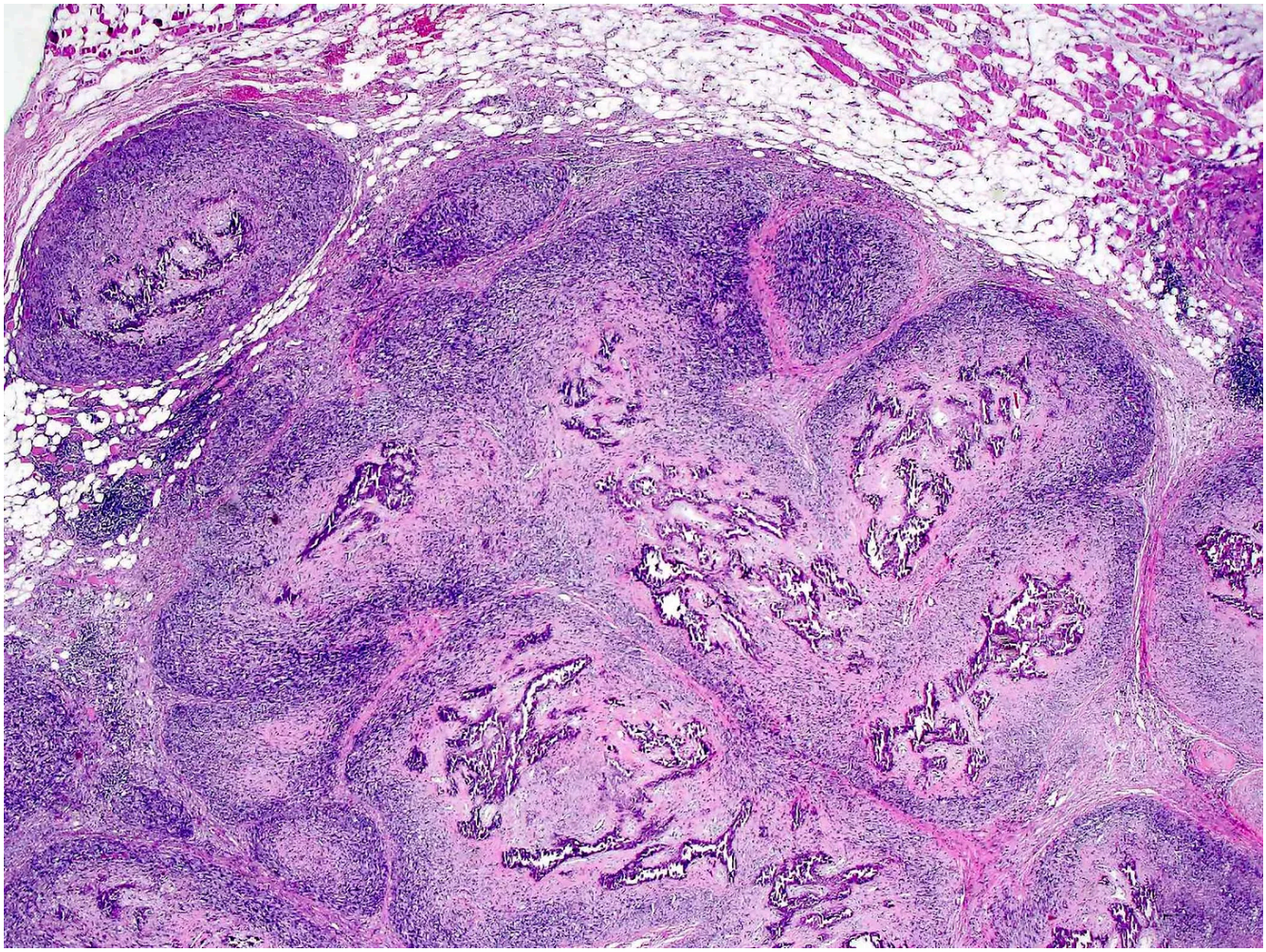
T2 coronal MRI: This central conventional osteosarcoma forms a large lytic mass in the proximal humerus with an extraosseous soft tissue component (contributed by Borislav A. Alexiev, M.D.).



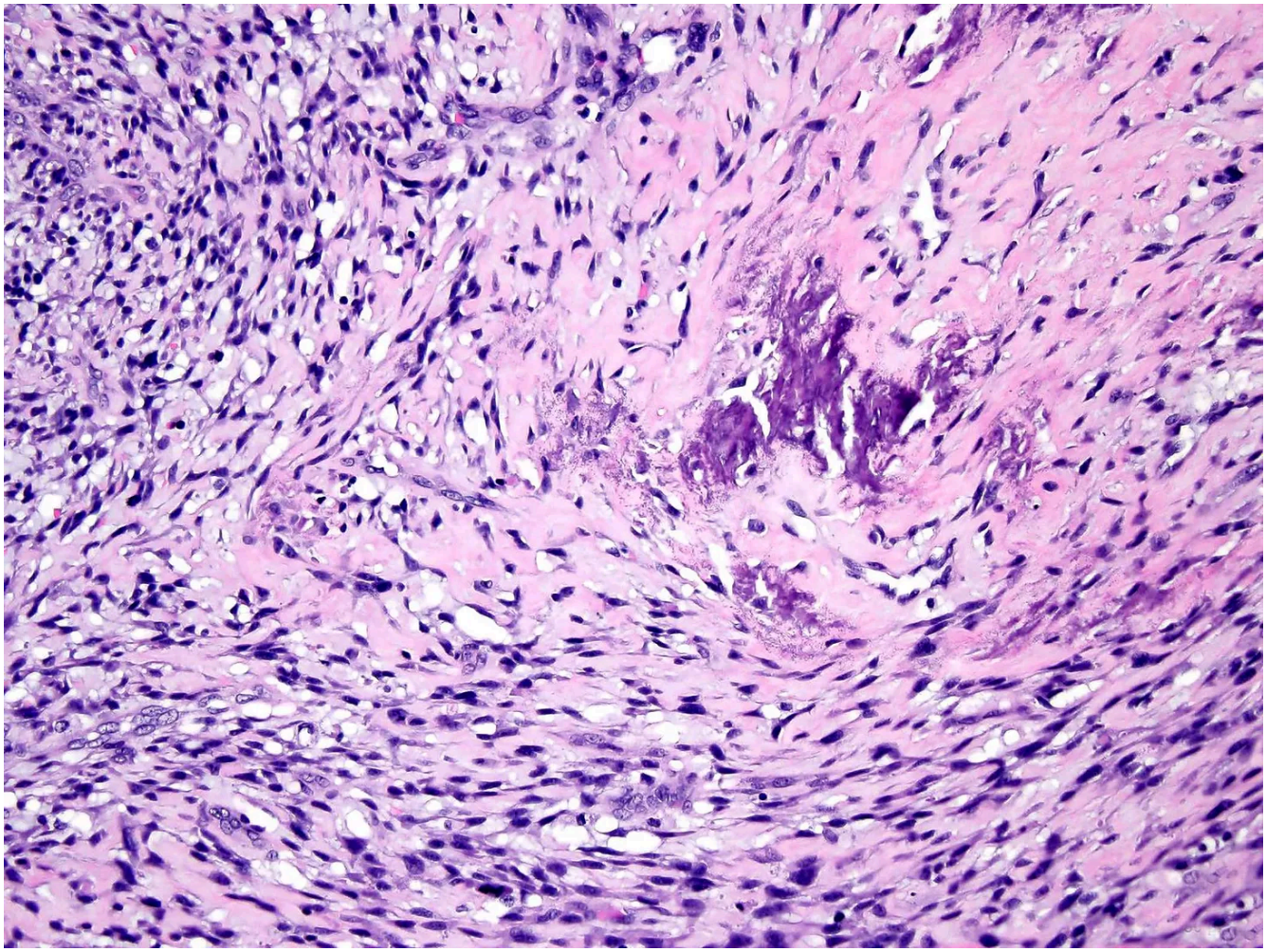
This low grade central osteosarcoma arose in the distal femoral metaphysis and invaded through the cortex and into the adjacent soft tissue (contributed by Jesse Hart, D.O.).



Central conventional osteosarcoma: Large, tan-white / yellow, densely solid, intramedullary mass centered in the metaphyseal region with extension into adjacent diaphysis and epiphysis (contributed by Borislav A. Alexiev, M.D.).



Conventional osteosarcoma: Note extraosseous soft tissue component (contributed by Borislav A. Alexiev, M.D.).

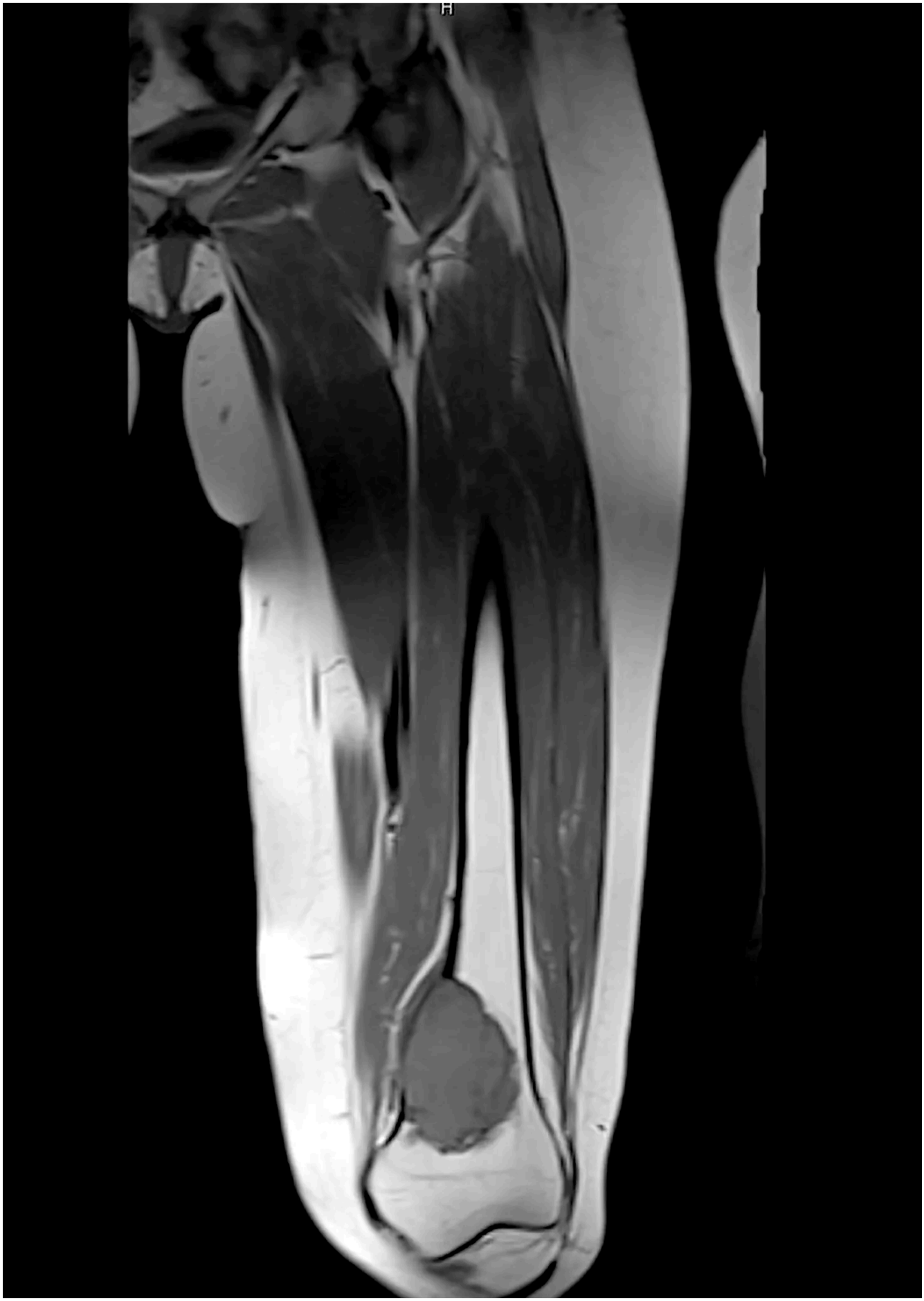


Conventional osteosarcoma: Highly atypical spindle cells produce immature and lace-like bone. Characteristically, the bone is intimately associated with the tumor cells (contributed by Borislav A. Alexiev, M.D.).

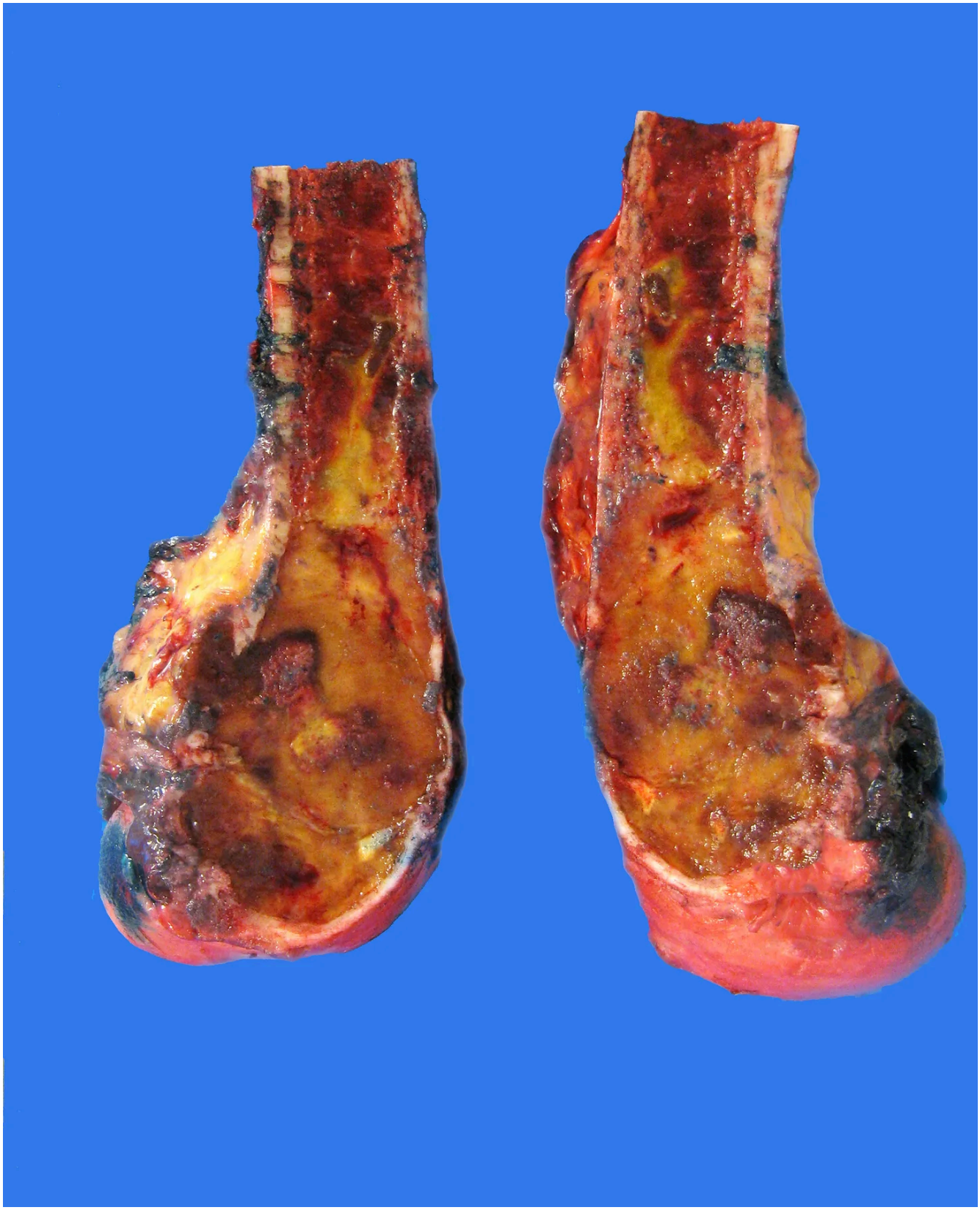
Giant cell tumor of bone is rarely associated with Paget disease of bone as a precursor. It is locally aggressive and rarely metastasizes. It is composed of neoplastic mononuclear stromal cells mixed with macrophages and osteoclast-like giant cells. Treatment is surgery or denosumab (Rutkowski 2015) with radiotherapy reserved for inoperable or refractory cases. Only rare cases are malignant, usually following radiation therapy (Palmerini 2019).

Due to the rarity of malignant giant cell tumor of bone, particularly of cases associated with Paget disease, most of the images below are of benign giant cell tumor of bone, not known to be associated with Paget disease.

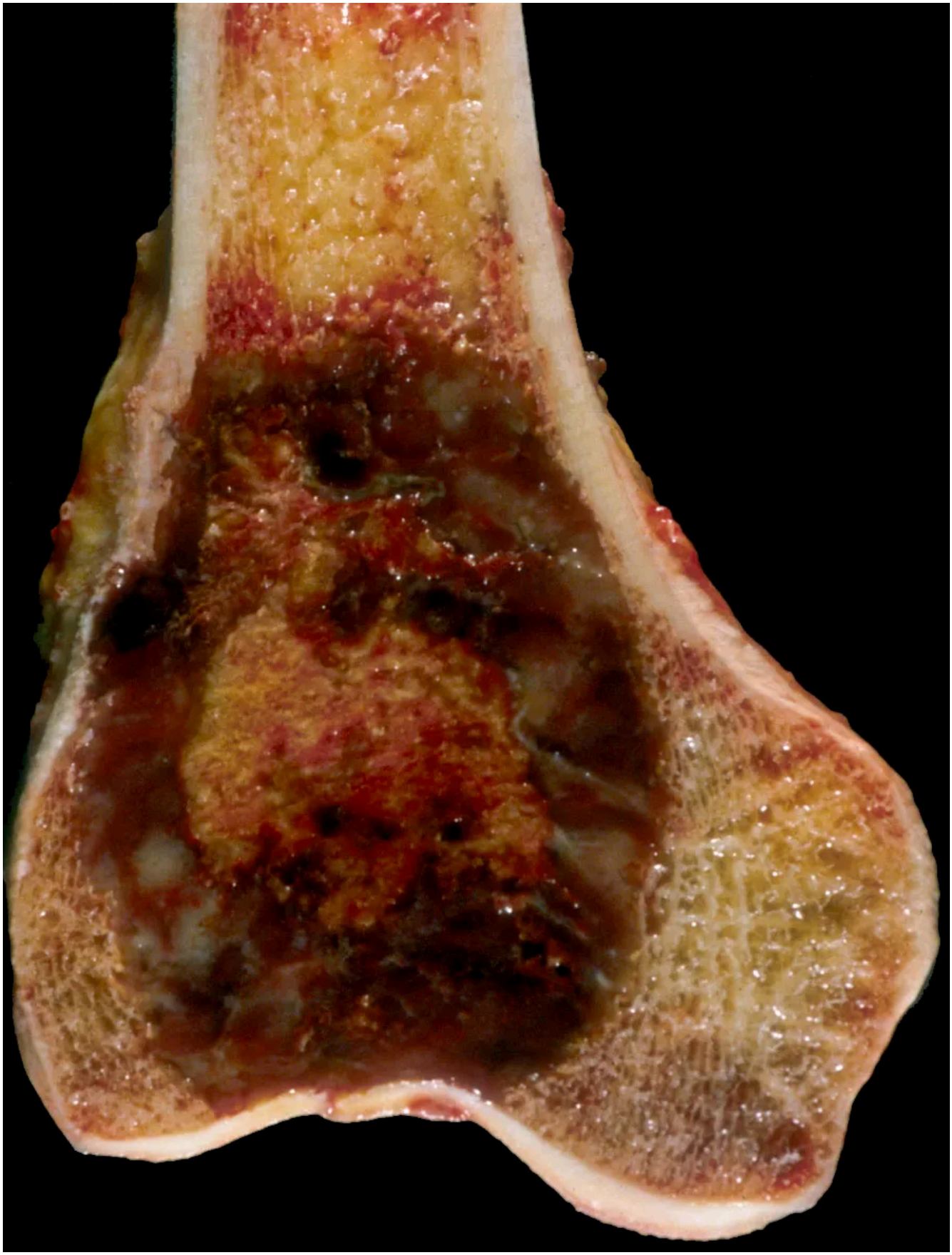
Giant cell tumor of bone


H

Benign giant cell tumor of bone: MRI demonstrates a left femur distal metadiaphyseal expansile, predominantly solid lesion. There is medial distal femur diffuse cortical thinning overlying the lesion and periosteal edema and enhancement (contributed by Borislav A. Alexiev, M.D.).

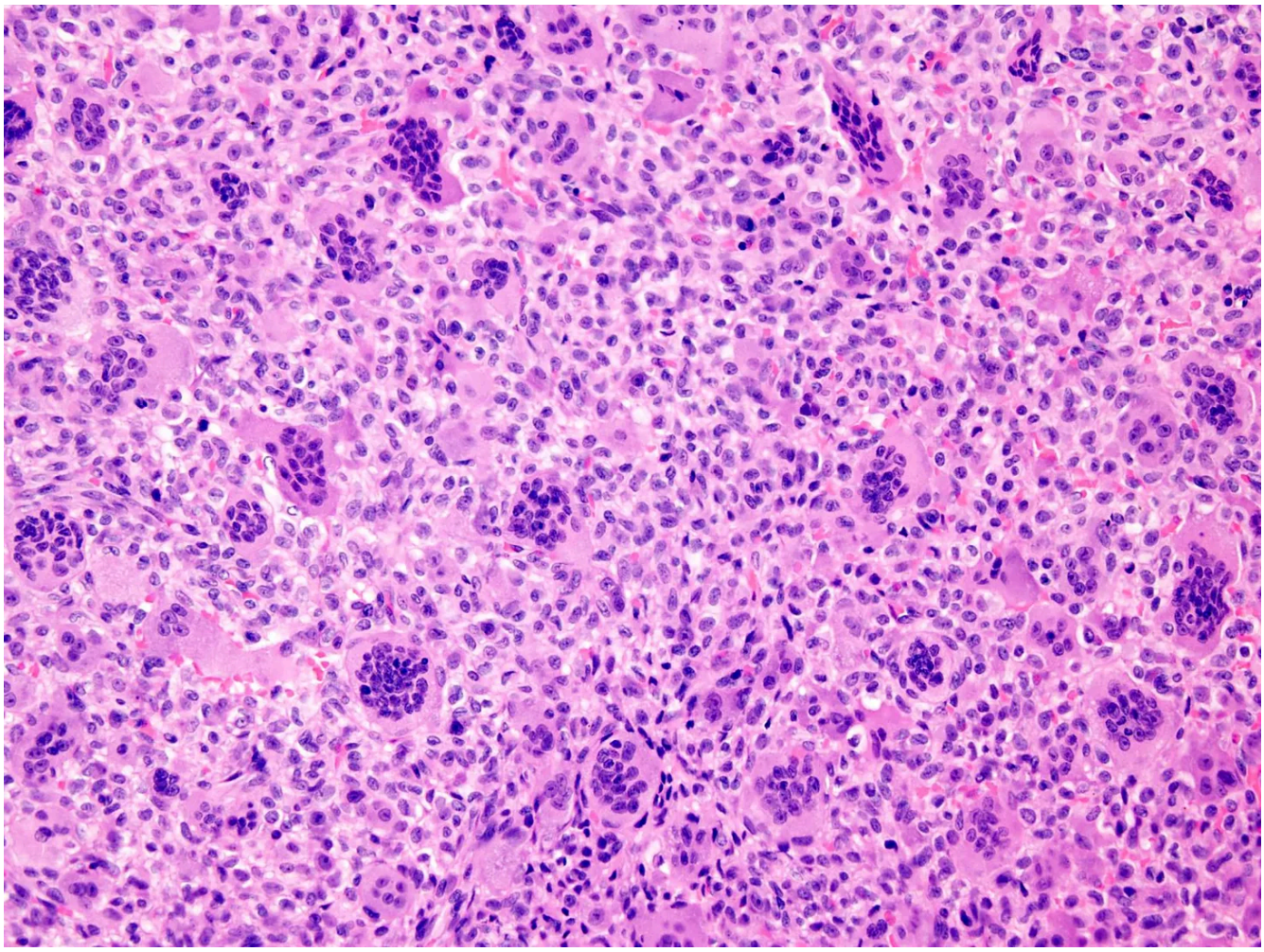


Benign giant cell tumor of bone: Solid, brownish to red, poorly defined tumor in the distal end of the femur. Note hemorrhages and yellow areas corresponding to xanthomatous change (contributed by Borislav A. Alexiev, M.D.).

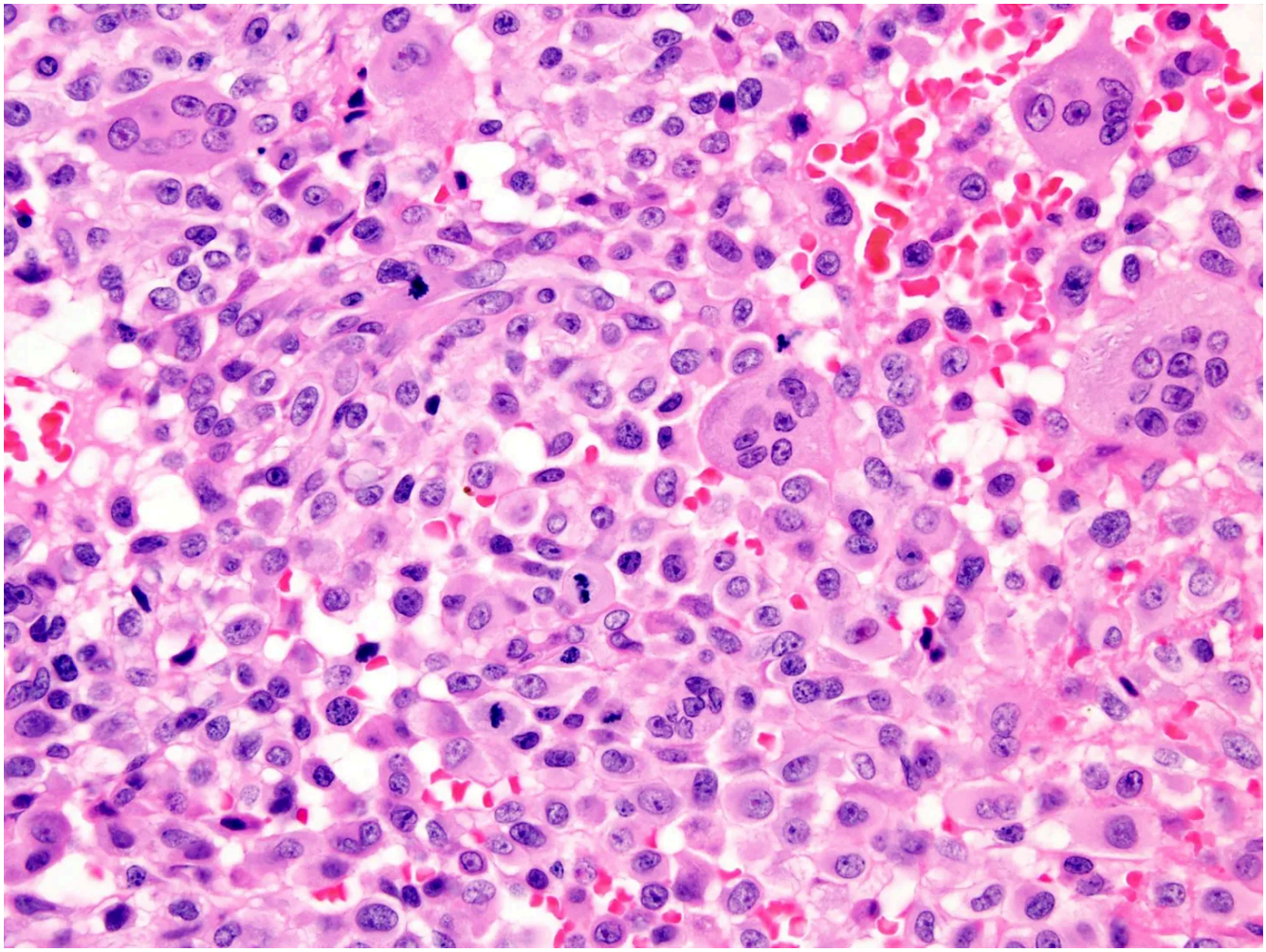


Benign giant cell tumor of bone: Well defined tumor with soft, red-tan and hemorrhagic appearance involving the epiphysis and metaphysis of a long

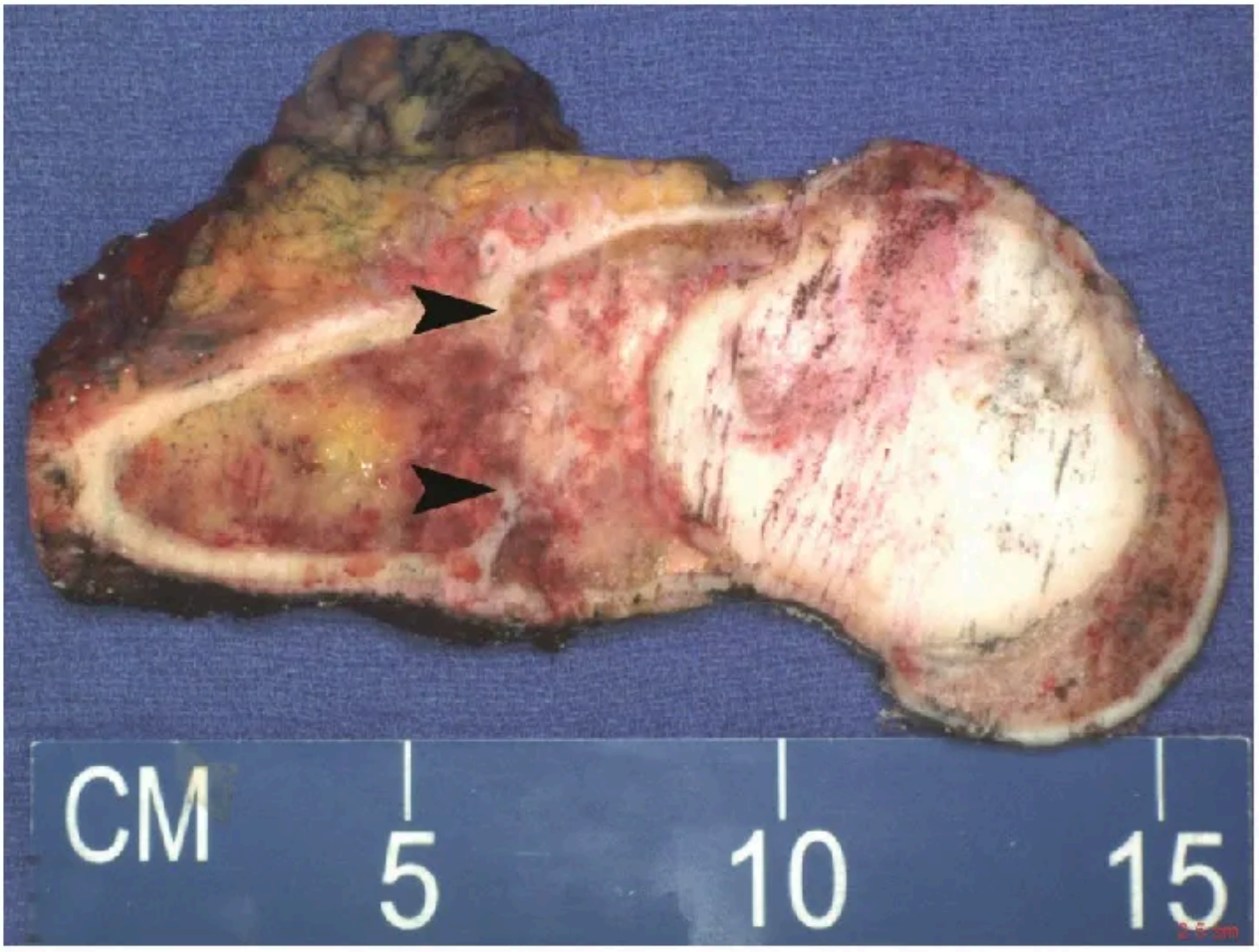
bone (contributed by Mark R. Wick, M.D.).



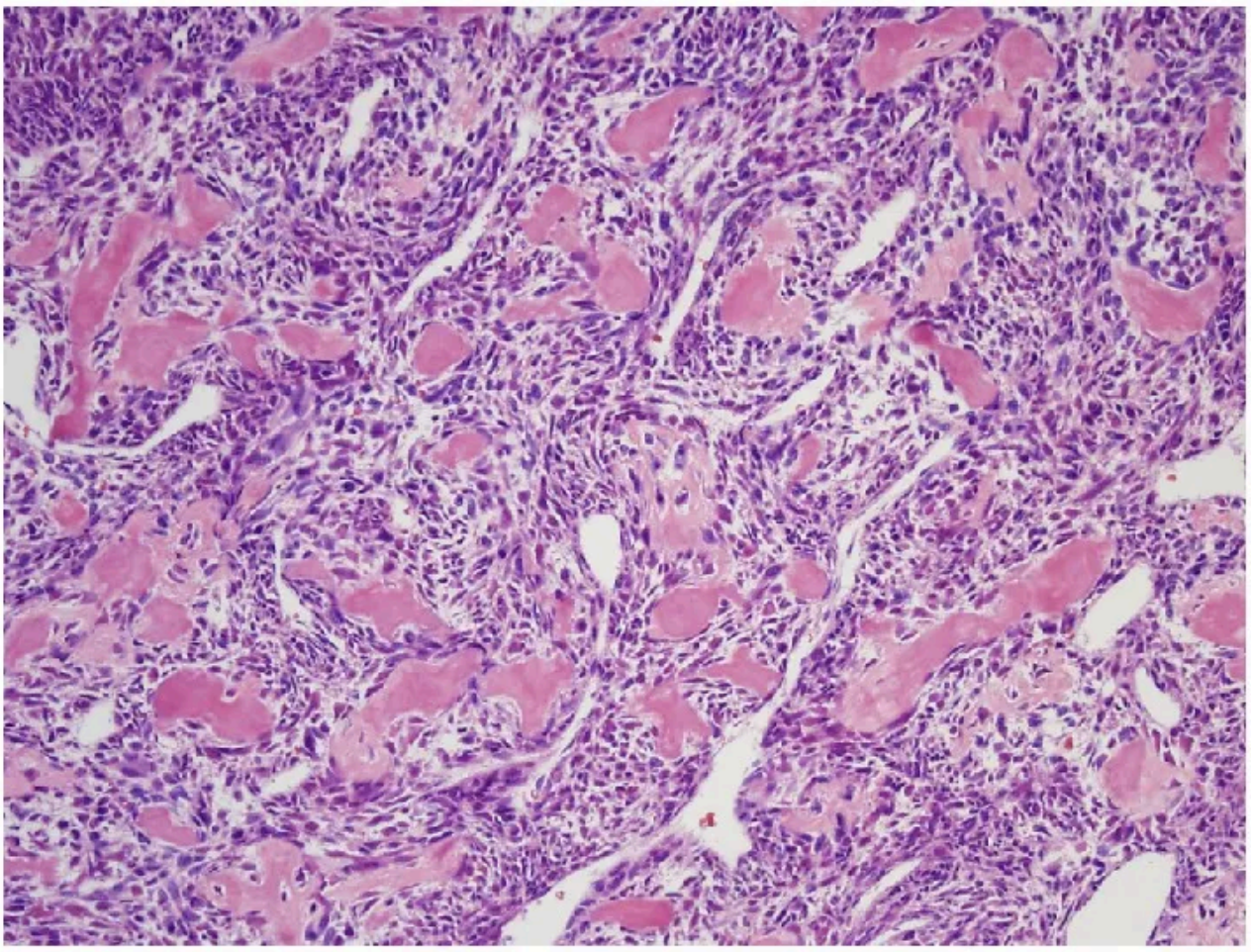
Benign giant cell tumor of bone: Numerous osteoclast-like giant cells, between which mononuclear neoplastic cells are embedded (contributed by Borislav A. Alexiev, M.D.).



Benign giant cell tumor of bone: Neoplastic mononuclear cells with eosinophilic cytoplasm and round to oval nuclei with dispersed chromatin and small nucleoli. Mitotic figures and scattered osteoclast-like giant cells are seen (contributed by Borislav A. Alexiev, M.D.).



Malignant giant cell tumor of bone: Distal femoral amputation shows an ill defined mass (arrows) proximal to a bone filler (all white, right side) (contributed by Broehm et al. 2015).



Histology of the above tumor shows malignant transformation to osteosarcoma with atypical, hyperchromatic spindle cells and osteoid formation (contributed by Broehm et al. 2015).

Part 5 will discuss precursors associated with hematological (bone marrow and lymphoid) malignancies.

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