

Osteosarcoma

Anatomic and Histologic Variants

Michael J. Klein, MD, and Gene P. Siegal, MD, PhD

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Abstract

Osteosarcoma is the most common primary tumor of bone, yet its absolute incidence among malignant tumors is low. Within its strict histologic definition, osteosarcoma comprises a family of lesions with considerable diversity in histologic features and grade. Its prognosis is dependent not only on these parameters but also on its anatomic site. It may occur inside the bones (in the intramedullary or intracortical compartment), on the surfaces of bones, and in extraosseous sites. Information of diagnostic or prognostic significance has not been elucidated from studies of its cytogenetics. This review summarizes the anatomic and histologic variations of osteosarcoma and offers a schema for its subclassification.

At an estimated incidence of 2 cases per million persons per year, osteosarcoma is the most common malignant primary bone tumor excluding hematopoietic intraosseous tumors. Although it occurs at any age, its peak incidence is in the second and third decades. Its statistical distribution roughly parallels skeletal growth; it is more frequent in tall people than in short people and in larger animals than in smaller animals.¹ Bones having the fastest rates of growth have the highest frequency of occurrence. When osteosarcoma appears earlier than the second decade or after the cessation of skeletal growth, there is often an association with another osseous abnormality. This may be a genetic predisposition such as the Li-Fraumeni or Beckman-Wiederman syndrome,^{2,3} an underlying abnormality such as Paget disease⁴ or fibrous dysplasia that has a predilection for the development of osteosarcoma,⁵ or previous radiation of the bone involved.

The definition of osteosarcoma is deceptively straightforward. It is a malignant tumor of connective tissue (mesodermal) origin within which the tumor cells produce bone or osteoid (often referred to as “tumor bone” or “tumor osteoid” in the vernacular). Although this makes it seem as though the cells giving rise to osteosarcoma must be of osteoblastic derivation, there is no evidence that osteoblasts, once they differentiate from osteoprogenitor cells, can actually revert to more primitive cells, let alone malignant ones. This implication is inherent in the more arcane term *osteogenic sarcoma*, which has fallen into disuse.

An additional feature often encountered in osteosarcomas is their propensity to produce variable amounts of cartilage matrix and fibrous tissue. In some cases, the cartilage matrix or fibrous tissue may so strikingly dominate the tumor tissue that the actual production of bone must be carefully sought to

make the correct diagnosis. Because osteosarcoma may differentiate along all or any of these pathways of matrix synthesis, it has more of a histologic similarity to fracture callus or fibrous dysplasia than it does to differentiated bone matrix-producing tumors such as osteoid osteoma or osteoblastoma. This has given rise to the 3 traditional subdivisions of osteoblastic, chondroblastic, and fibroblastic osteosarcoma. In actuality, most osteosarcomas demonstrate varying amounts of all 3 cell types and matrix. Consequently, division into any one of these types is arbitrary and capricious but generally is meant to signify greater than 50% predominance of any histologic type.

Although osteosarcoma usually arises in the medullary cavity of the metaphysis of a growing long tubular bone, it also may arise on the surface of a bone, it may be confined to the cortex, or it even may arise in an extraskeletal site. The osteosarcomas arising on the bone surfaces are about 20 times less frequent than their medullary counterparts. Interestingly, the majority of osteosarcomas of medullary origin are high-grade, whereas most arising on the surfaces of bones are of lower grade. Patients with surface osteosarcomas are often a decade or more older than typical patients with central osteosarcomas. Occasionally, high- and low-grade elements may be present in any given case of osteosarcoma. In these cases, the biologic behavior is usually that of the histologically highest grade area of the neoplasm.

Patients with osteosarcomas usually have nonspecific clinical symptoms, the most common of which is pain for several weeks or months. The pain often begins insidiously, but by the time patients come to medical attention, their pain is present at rest or even disturbs their sleep. The most common sign is a mass that is almost always firm and tender. There may be superficial erythema, venous distension, or other signs of hypervascularity. There may be a limp, loss of function, or even decreased range of motion. Any of these symptoms or signs is cause for further clinical investigation.

The imaging studies usually suggest a malignant tumor; at least half the time the specific diagnosis can be made from conventional radiographs. Especially characteristic is an ill-defined radiodensity occupying the metaphyseal region of a long bone. The intraosseous density often has a diffusely cloudy or fluffy appearance. Although there is seldom a fracture or cortical infraction in osteosarcoma, it is usual for the tumor to permeate the extant passages not only between osseous trabeculae but also of the Haversian systems and Volkmann canals. As the tumor reaches the outer cortical surface, the periosteum is dissected from the bone. The cambium layer of the inner periosteum reacts to separation from the cortex by producing new bone, which is sometimes visible as an incomplete bony shell that appears attached to the bone surface on only one end and is open or discontinuous in the middle, a

so-called Codman angle. Other kinds of periosteal reactions may cause so-called sunburst or hair-on-end radiographic densities **Image 1**.

Although periosteal new bone formation sometimes is associated with benign conditions, periosteal reactions associated with malignant tumors usually are discontinuous, implying that the tumor growth is too rapid for periosteal containment.⁶ In some cases, conventional radiographs may suggest a malignant tumor that is not osteosarcoma.⁷ This is especially true when a large proportion of the osteoid matrix in an osteosarcoma is not well mineralized. In rarer cases, the radiograph may not even appear to represent a malignant tumor.⁸ It must be kept in mind that although radiographs usually correlate well with histologic studies of bone tumors, radiographs merely reflect statistical odds ratios and, thus, the likelihood that a lesion is, first, a tumor, and second, malignant or benign. Like all statistics, there are some lesions of bone that are outliers and may not correlate well with the radiographic appearance; this is precisely the reason that even classically appearing bone lesions must be biopsied **Image 2**.

Historically, the malignant nature of osteosarcoma became obvious with the appearance of lung metastases, usually in about 18 months to 2 years after first diagnosis, and the

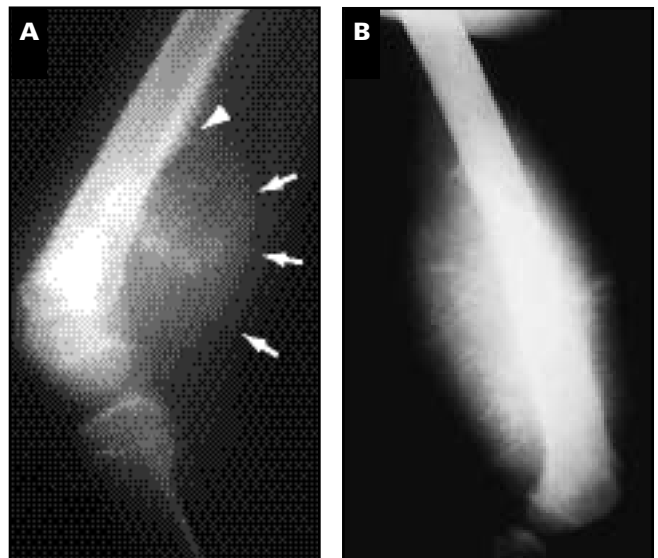


Image 1 **A**, Lateral radiograph of the distal femur demonstrates typical radiographic features of osteosarcoma. Radiodense, cloudy bone lies within an ill-defined radiolucency of the femoral metaphysis. The arrows delimit a very large soft tissue mass containing bone matrix. A Codman angle periosteal reaction is highlighted with an arrowhead. **B**, Lateral radiograph in a different case demonstrating a very large extraosseous, radiodense mass that contains extensively interrupted periosteal "streamers," forming a "sunburst" periosteal reaction.

5-year survival was on the order of 20%. Although its degree of malignancy has not changed, modern adjuvant chemotherapy has increased this survival more than 3-fold,⁹ and even people with metastatic disease sometimes can be saved.^{10,11}

Because osteosarcoma may produce various kinds of extracellular matrix and have different degrees of differentiation, its histologic pattern may vary significantly, not only from case to case but also from area to area in the same case. Its classification into various subtypes is not only by the predominant histologic pattern, but also by its anatomic location and sometimes by its histologic grade **Table 1** and **Table 2**.

The tendency to subclassify osteosarcomas in this way makes it seem that there are as many variations of this tumor as any tumor in the oncologic realm. The tendency to subdivide so rare a tumor into many such compartments also makes straightforward diagnosis more difficult for the general surgical pathologist. In a significant number of cases, however, the subclassification of osteosarcoma matters only if a given subtype behaves or responds to treatment in a consistently different way. The remainder of this review is dedicated to the comparison of these subtypes histologically, anatomically, and biologically.

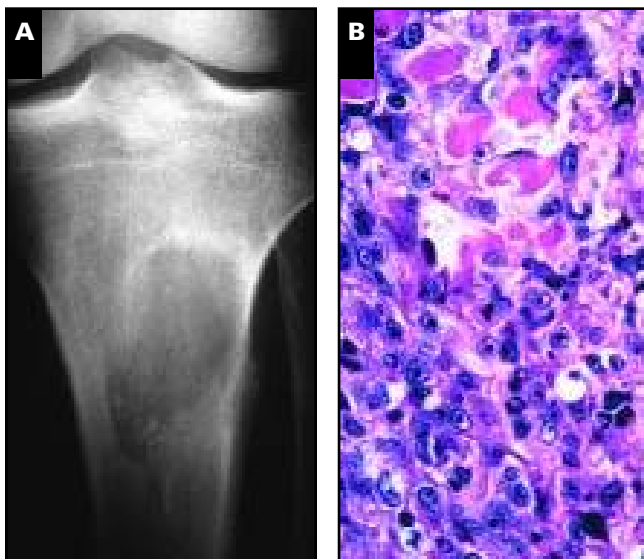


Image 2 **A**, An osteosarcoma that appears completely radiolucent and has a sclerotic, fairly circumscribed upper border, mimicking a benign lesion. Although the radiographs show little intraosseous radiodensity apart from a vague haziness near the sclerotic area, the lateral tibial border shows that the cortex is interrupted and there is a small interrupted periosteal reaction. **B**, Biopsy of the radiolucent mass demonstrates an osteosarcoma in which there is little bone/osteoid matrix (upper left) but obviously bizarre, pleomorphic malignant polyhedral tumor cells, apparent to the trained observer as malignant (H&E, $\times 400$).

Conventional Osteosarcoma

Osteosarcoma is diagnosed most easily when it appears in its classic, or conventional, form. The tumor cells vary from spindled to polyhedral; their nuclei are pleomorphic and hyperchromatic. Mitotic figures are easily demonstrable, and atypical mitotic figures also may be identified. The tumor cells are engaged in the production of extracellular matrix that may be osseous, cartilaginous, or fibrous in various proportions. The production of bone or osteoid directly by tumor cells at least somewhere in the tumor is the absolute requirement for diagnosis **Image 3**.

As noted previously, conventional osteosarcoma historically has been divided into osteoblastic, chondroblastic, and fibroblastic subtypes depending on the predominant type of extracellular matrix **Image 4**. This separation is largely artificial because there is no statistical difference in the survival of patients with high-grade tumors of these 3 histologic types and the treatment for all types is the same. Of some

Table 1
Osteosarcoma Types

Central
High-grade
Conventional
Telangiectatic
Small cell
Epithelioid
Osteoblastoma-like
Chondroblastoma-like
Fibrohistiocytic
Giant cell-rich
Low-grade
Low-grade central
Fibrous dysplasia-like
Desmoplastic fibroma-like
Surface
Low-grade
Parosteal
Intermediate-grade
Periosteal
High-grade
Dedifferentiated parosteal
High-grade surface
Intracortical
Gnathic
Extraskeletal
High-grade
Low-grade

Table 2
Osteosarcoma by Anatomic Site

Osseous
Central
Surface
Gnathic
Multifocal
Soft tissue
Intramuscular
Other

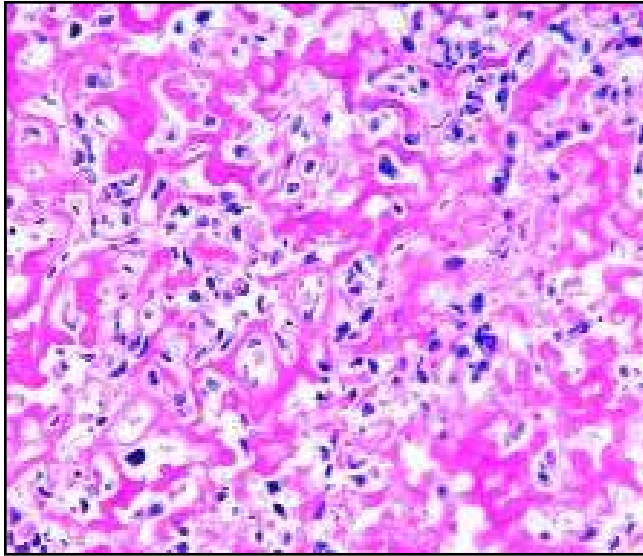


Image 3 Classic osteosarcoma in which there is abundant production of osteoid and bone matrix in a lacy pattern into which the malignant cells are incorporated. Because these sections usually are decalcified, the terms *osteoid* and *immature bone* are interchangeable, especially if the imaging studies do not reveal the precise biopsy site (H&E, $\times 250$).

diagnostic interest is that occasionally, purely sclerosing osteosarcoma is difficult to diagnose with a small biopsy specimen alone because of “normalization,” a phenomenon first described by Jaffe.¹² In this process, the production of osseous matrix is in excess to the proportion of tumor cells, which become incorporated into the bone matrix and resemble normal osteocytes. The production of bone matrix may be so excessive in sclerosing osteosarcoma that the cellular component of the tumor is difficult to identify; usually tumor cells are most obvious at the advancing edge of the tumor **Image 5**. Of additional importance is the knowledge that chemotherapy given after a biopsy and before definitive surgery, if successful, often causes a similar normalization effect along with necrosis. This phenomenon has been referred to as *maturation*, and the challenge becomes accurately quantifying the degree of tumor necrosis for prognostication and postsurgical therapeutic manipulation.¹³

Occasionally, the pattern of tumor advancement in sclerosing osteosarcoma is the deposition of bone matrix along the interseptal spaces between adipocytes in the marrow cavity. In this case, the surface tension of the fat globules in the marrow adipocytes forces the tumor cells and their matrix production to follow the path of least resistance between adipocytes. The low-power appearance of this type of tumor spread resembles adipose tissue but with thicker than normal septa **Image 6**. These thick septa actually are composed of delicate immature bone that surrounds the adipocytes; however, because sections usually are decalcified, the presence

of this bone (and the fact that the thick interlobular septa are, in fact, bone matrix) is obscured. The diagnosis becomes obvious if radiopathologic correlation is performed, because these tumors usually are radiodense and not circumscribed **Image 7**. In addition, this type of tumor may have soft tissue extension on the imaging studies that is not obvious in a small bone biopsy specimen.

Histologic grading in osteosarcomas is important in the oncologic staging of the tumor and for determining adjuvant treatment in addition to surgery. There are several grading systems for osteosarcoma, but there is a variable degree of subjectivity in each. The 4-tiered grading system popularized by the Mayo Clinic group is based on the original Broders grading of squamous cell carcinomas of the lip.¹⁴ In Broders’ schema, the numeric grade of the tumor from 1 to 4, was equated to the percentage of anaplasia in the tumor (from $\leq 25\%$ to 100%). Assuming that the most important factor in grading is the cytologic atypia of tumor cells,¹⁴ any significant focus of anaplasia in an osteosarcoma would itself represent grade 4 disease.

In practice, almost all conventional central osteosarcomas are assigned a grade of 3 or 4; ie, they are high grade. The osteosarcomas assigned a histologic grade of 1 are low-grade central osteosarcoma and the usual form of parosteal osteosarcoma. In the low-grade osteosarcomas, there not only is absence of anaplasia, but also on a cytologic basis alone, it is difficult to recognize these entities as neoplasms. Should a focus of anaplastic tumor be identified within what is otherwise a grade 1 tumor, the tumor is termed *dedifferentiated*, and it is assumed that its biologic behavior will follow a highly malignant course consistent with conventional osteosarcoma.¹⁵

In the bone and soft tissue staging schema outlined by the Society of Musculoskeletal Oncology, without demonstrable metastatic disease, the staging depends on whether the tumor is high or low grade.⁹ For the purposes of treatment with neoadjuvant chemotherapy (given before definitive resection), an orthopedic oncologist needs to know only whether the grade is sufficiently high to offer chemotherapy in the treatment regimen. Because almost all conventional osteosarcomas are high-grade tumors and almost all surface osteosarcomas are low-grade tumors, it may make more sense from a treatment standpoint to report osteosarcomas as high or low grade in a 2-tiered system. The reported exceptions to this are some gnathic osteosarcomas and periosteal osteosarcomas in which the degree of atypia is higher than that usually seen in grade 1 tumors but insufficient for the diagnosis of grade 2 or 3 tumors.¹⁴ These tumors would be called *intermediate grade* if they were inserted into a 2-tiered system, and the decision to add systemic therapy would be subject to the experience of the orthopedic oncologist.

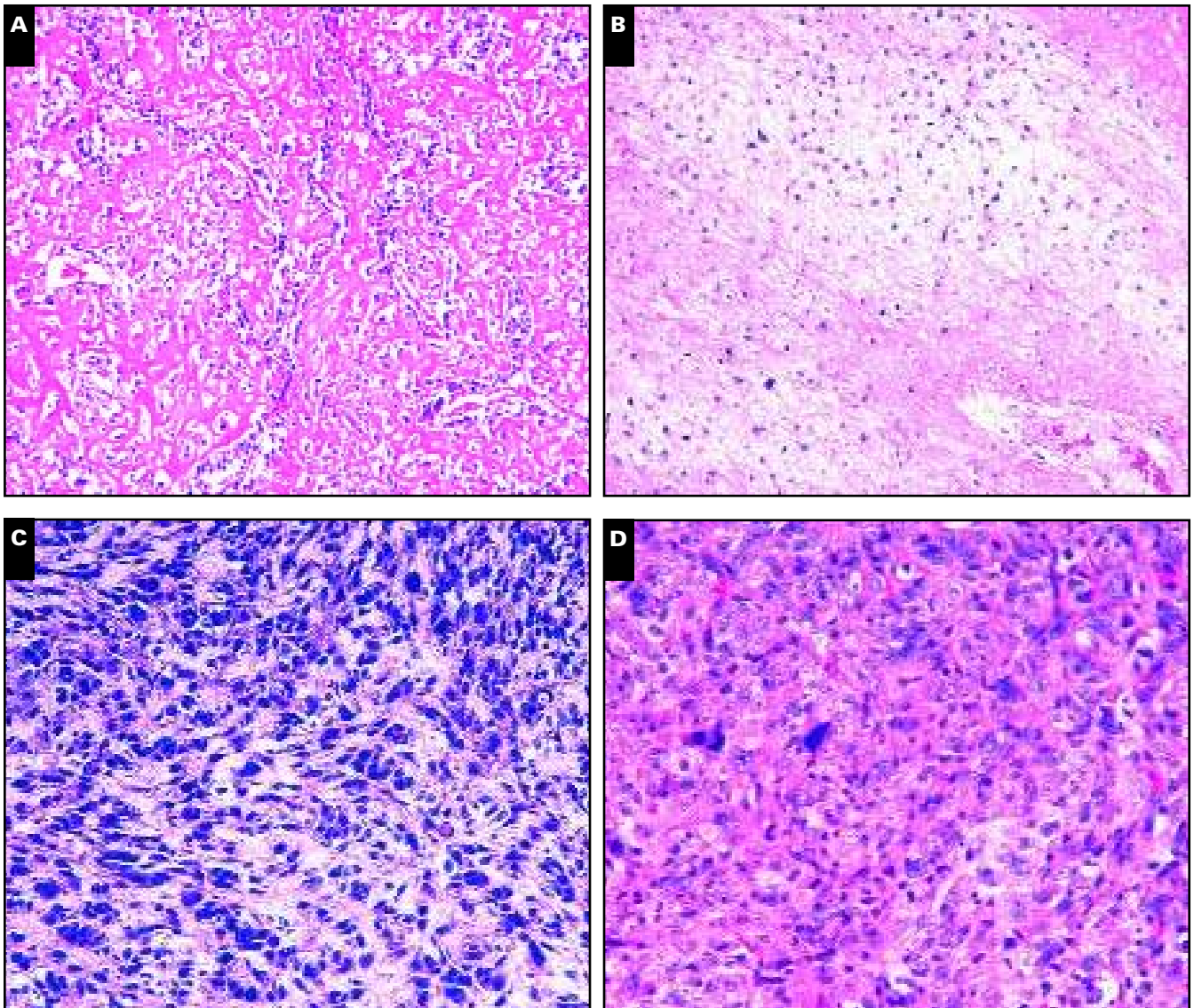


Image 4 Conventional osteosarcoma. **A**, So-called osteoblastic osteosarcoma is dominated by the production of extracellular bone matrix. This medium-power field demonstrates immature bone deposition in a pattern resembling lace into which tumor cells are incorporated (H&E, $\times 100$). The clinical radiograph (not shown) was radiodense in the area from which the biopsy was obtained. **B**, So-called chondroblastic osteosarcoma. This medium-power field is dominated by cellular hyaline cartilage but shows a few wisps of osteoid formation at the upper right (H&E, $\times 100$). The radiographic appearance depends on the predominant matrix type in the tumor; noncalcified cartilage portions are radiolucent. **C**, So-called fibroblastic osteosarcoma is dominated by spindle cells resembling atypical fibroblasts, usually contains little bone matrix (H&E, $\times 250$), and is radiolucent. **D**, Pleomorphic osteosarcoma might appear fibrohistiocytic or epithelioid and sometimes poses a difficult diagnostic problem because extracellular matrix is scant (H&E, $\times 250$) and the lesion is radiolucent. Pleomorphic bone sarcomas in children usually fall into this category.

Telangiectatic Osteosarcoma

Telangiectatic osteosarcoma is a type of osteosarcoma that resembles aneurysmal bone cyst radiographically and histologically.¹⁶ The lesion almost always produces radiolucent bone destruction, and there is often asymmetric expansion of

the bone involved. Unlike in aneurysmal bone cyst, a thin shell of periosteal neocortex may not be observed. There is sometimes an interrupted periosteal reaction, which is a clue to the correct diagnosis; however, because little bone is formed in this lesion, it is not unusual for new bone to be absent radiographically. On the other hand, the increased sensitivity of

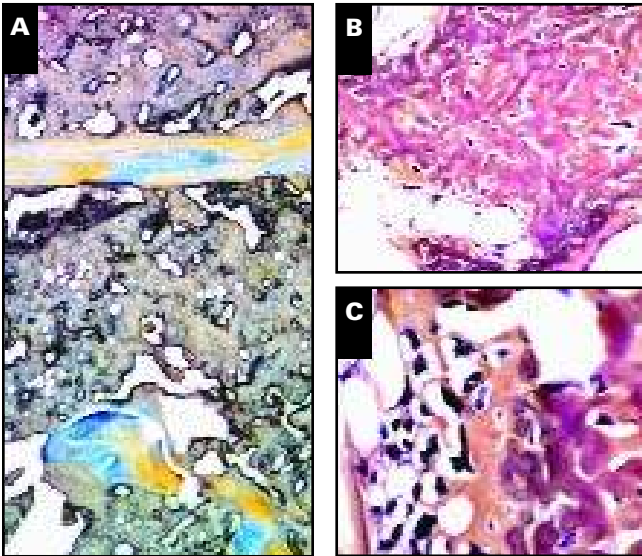


Image 5 “Normalization” of conventional osteosarcoma. **A**, Low-power view of cancellous bone spicules (blue and yellow) shows marrow replacement by osteosarcomatous bone matrix that appears compact (including Haversian systems) using partially polarized light with a first-order compensator (H&E, $\times 20$). **B**, Higher magnification of normalized area demonstrates somewhat immature bone matrix in which tumor cells seem to be compressed into the appearance of osteocytes (hematoxylin-phloxine-safranin [HPS], $\times 50$). If this field were taken out of context (ie, if it were not understood that this matrix was displacing normal marrow adipose tissue), malignancy of the lesion might not be detected. **C**, The advancing edge of the bone matrix demonstrates a greater number of pleomorphic enlarged tumor cell nuclei that do not appear to be osteocytes (HPS, $\times 250$).

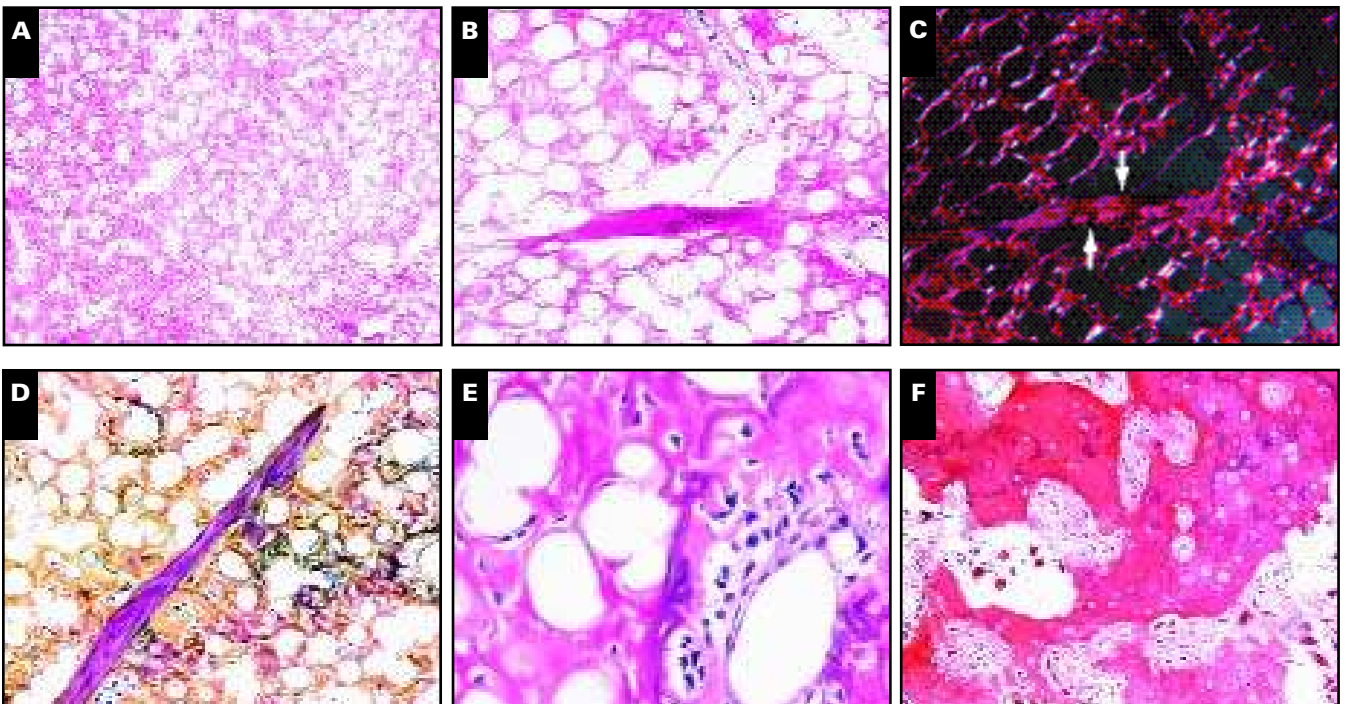


Image 6 Sclerosing osteosarcoma. **A**, Low-power magnification demonstrating subtle marrow septal permeation pattern. The adipocyte shapes are clearly visible, but the interadipocytic septa are thickened (H&E, $\times 25$). **B**, At higher magnification, the outlines of the fat vacuoles are preserved, but the septa are thick and eosinophilic. A small bone trabecula is present in the center (H&E, $\times 100$). **C**, The same photograph in polarized light reveals that the pink septa are composed of anisotropic immature collagen, which is bright in polarized light, whereas normal adipocyte septa are invisible. In the center of the field is a small preexistent bone trabecula that is lamellar (arrows) surrounded by the immature neoplastic bone (H&E, $\times 100$). **D**, Another field in the same tumor stained by the hematoxylin-phloxine-safranin (HPS) method demonstrates that the immature osteoid surrounding the adipocytes is safranophilic (yellow), whereas the preexistent mature bone trabecula is phloxiphilic (pink) and lamellar. At this magnification, normalizing tumor cells can just be discerned (HPS, $\times 100$). **E**, At higher magnification, normalizing tumor cells are discerned more easily (HPS, $\times 250$). **F**, Later in the process, the sclerotic bone matrix has overwhelmed the architecture of the adipose tissue and its normalization belies its malignant nature if taken out of context (H&E, $\times 100$).

computed tomography (CT) scanning has resulted in a detected incidence of some bone matrix in 85% of tumors, and magnetic resonance imaging (MRI) has detected fluid levels in 74% of tumors examined.¹⁷ The lesion usually is composed of multiple blood-filled sinusoids, and there is little solid tissue to evaluate. Consequently, at low power, telangiectatic osteosarcoma bears a striking resemblance to aneurysmal bone cyst. At higher power, the presence of nuclear pleomorphism and a high mitotic rate usually are obvious. In contrast, the sinusoidal lining cells are bland or even inapparent in aneurysmal bone cysts. In telangiectatic osteosarcoma, there usually is local destruction manifest by permeation of the process into adjacent marrow or cortical Haversian spaces. The replacement of normal anatomic spaces by a growing process is a usual histologic feature of malignancy **Image 8**. Although the production of bone or osteoid by the tumor cells helps considerably in formulating the diagnosis, extracellular matrix tends to be histologically sparse in telangiectatic osteosarcoma.

Giant cell-rich osteosarcoma (see later below) seems to be linked to telangiectatic osteosarcoma at a rate greater than chance. In addition, telangiectatic osteosarcoma, like aneurysmal bone cyst, often contains foci of such osteoclast-like giant cells. We speculate that an element in blood or a breakdown product may serve as a giant cell stimulus to the region in all 3 conditions.

Before the institution of neoadjuvant chemotherapy, the prognosis for telangiectatic osteosarcoma was statistically more dismal than that for conventional osteosarcoma.¹⁶ With the advent of chemotherapy, the prognosis for telangiectatic osteosarcoma has been reported as being as good as or even better than that associated with the conventional types of osteosarcoma.⁹ Although the reasons for this are unclear, most of the chemotherapy regimens for osteosarcoma are active during the proliferative (S) phase of the cell cycle; a histologic comparison of conventional and telangiectatic osteosarcoma often suggests fewer total tumor cells with a higher growth fraction in the latter.

Small Cell Osteosarcoma

Small cell osteosarcoma is a rare histologic variant of osteosarcoma with histologic features combining those of osteosarcoma and Ewing sarcoma.¹⁸ It constitutes between 1% and 2% of all osteosarcomas.¹⁹ The radiologic features are not consistently typical for osteosarcoma because there often is very little mineralized matrix produced. Histologically, it may be mistaken for Ewing sarcoma/primitive neuroectodermal tumor (PNET) because its cells are small and have round, hyperchromatic nuclei with very little of the nuclear pleomorphism characteristic of conventional



Image 7 Radiographic examples of sclerosing osteosarcoma. **A**, The lesion is cloudy, radiodense, and metaphyseal. The inferior border is not distinct, and there is lateral extension outside the bone. **B**, Diaphyseal lesion from which the sections in Image 6 are derived. Note the very radiodense lesion that not only has poorly defined osseous confines but also produces interrupted, bulky, cloudy, and trabeculated bone in the soft tissues.

high-grade osteosarcoma. Close observation sometimes reveals spindling of tumor cells. This finding is not characteristic of the Ewing/PNET group of tumors. In addition, the production of osteoid by tumor cells is not a characteristic feature of Ewing sarcoma, whereas it always is identified to confirm a diagnosis of osteosarcoma **Image 9**.

Several features reported in small cell osteosarcoma make it a controversial diagnosis. First, many, if not all, small cell osteosarcomas display a similar immunohistochemical profile to that of Ewing sarcoma/PNET. The most important of these is positive membrane staining for CD99, a marker of expression of the MIC-2 gene product. This marker is typical for tumors in the Ewing sarcoma/PNET group, mesenchymal chondrosarcoma, and some primitive hematopoietic tumors, but it is not found in other types of osteosarcoma. Furthermore, the reciprocal translocation between chromosomes 11 and 22, the most common one found in the Ewing sarcoma/PNET tumor family, occasionally has been reported in a small cell osteosarcoma, whereas it is not a feature of other subtypes of osteosarcoma. Some authors believe that tumors showing this translocation should be considered Ewing sarcoma/PNET regardless of whether they produce osteoid, implying that it is possible that some of the tumors classified as small cell osteosarcomas actually are Ewing sarcoma family tumors with divergent differentiation.⁹ The matter

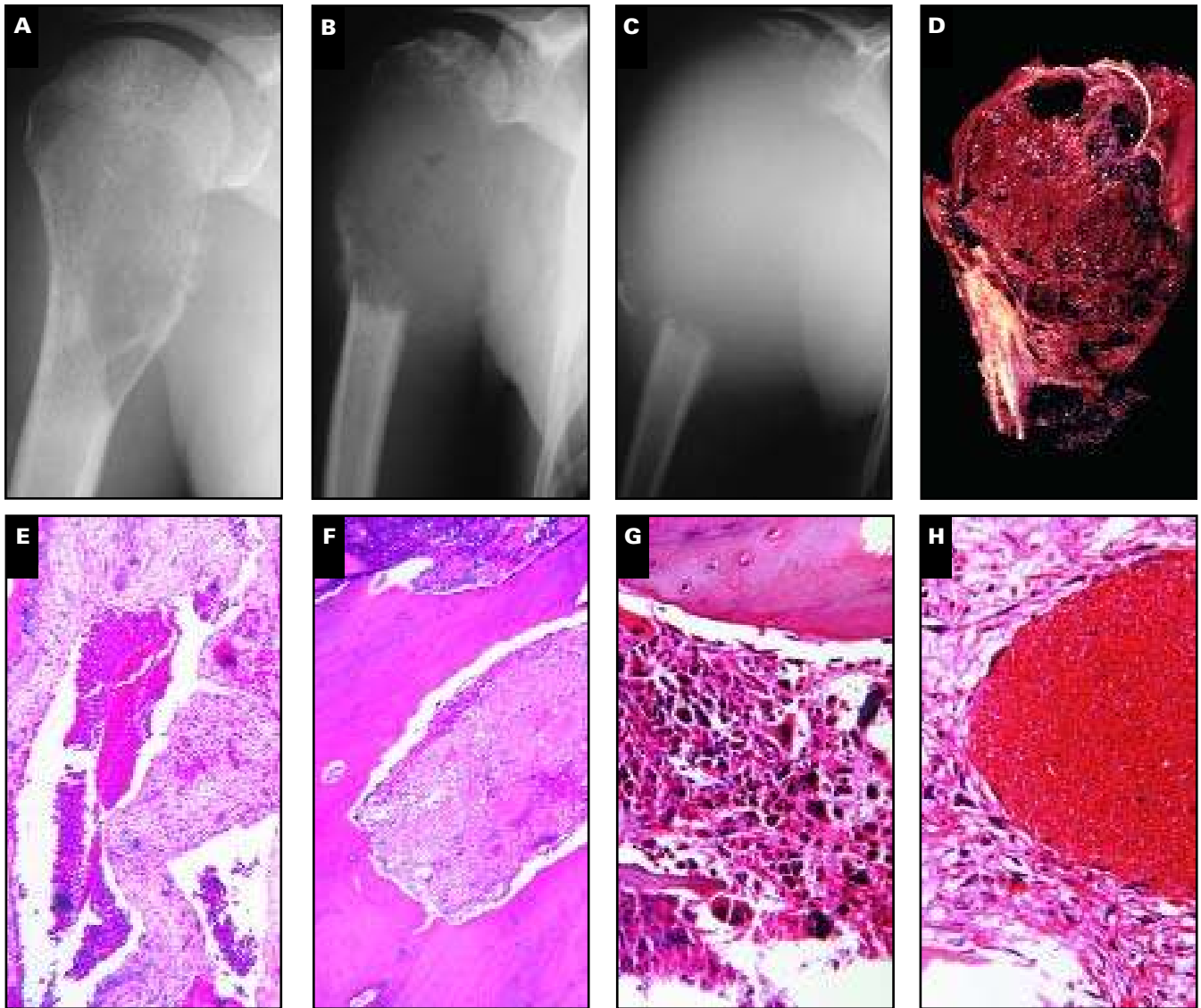


Image 8 Telangiectatic osteosarcoma. **A**, **B**, and **C**, A radiolucent destructive lesion originally thought to be an aneurysmal bone cyst because of the eccentric radiolucent expansion (**A**). Curettings were thought to represent aneurysmal bone cyst (**E**, H&E, $\times 50$). One month later, the patient returned with pain and increasing size of mass, and there was virtual destruction and expansion of the entire metaphyseal region of the right humerus. Retrospectively, the radiographs in **A** were noted to have a medial interrupted periosteal reaction. A portion of the cortex from the second procedure demonstrated permeation of Haversian canals by a vascular, osteoid-producing tumor (**F**, H&E, $\times 50$), and the diagnosis of telangiectatic osteosarcoma was made. The patient returned after 2 cycles of neoadjuvant chemotherapy. The mass had continued to grow and was excised owing to lack of clinical response (**C** and **D**). The radiograph demonstrates virtually no humeral structure proximal to the diaphysis (**C**). **D**, The gross specimen demonstrates a hemorrhagic, necrotic mass sparing only the medial articular cartilage. Although the histologic sections demonstrated significant necrosis after 2 cycles of chemotherapy, viable tumor with obvious pleomorphism was still demonstrable (**G**, H&E, $\times 250$), and the hypervascular and sinusoidal architecture responsible for its initial misdiagnosis were still present (**H**, H&E, $\times 250$).

is not entirely trivial because response to adjuvant chemotherapy for osteosarcoma has been variable and less successful in patients with small cell osteosarcoma.¹⁹ Moreover, Ewing sarcomas, which are exquisitely radiosensitive, may require radiation for local control, but osteosarcomas are almost always insensitive to that approach.

Epithelioid Osteosarcoma

Epithelioid osteosarcoma is an osteosarcoma in which the tumor cells are so poorly differentiated that it is difficult to determine histologically whether the tumor is a sarcoma or a carcinoma.¹⁴ If there are areas of histologically typical osteosarcoma

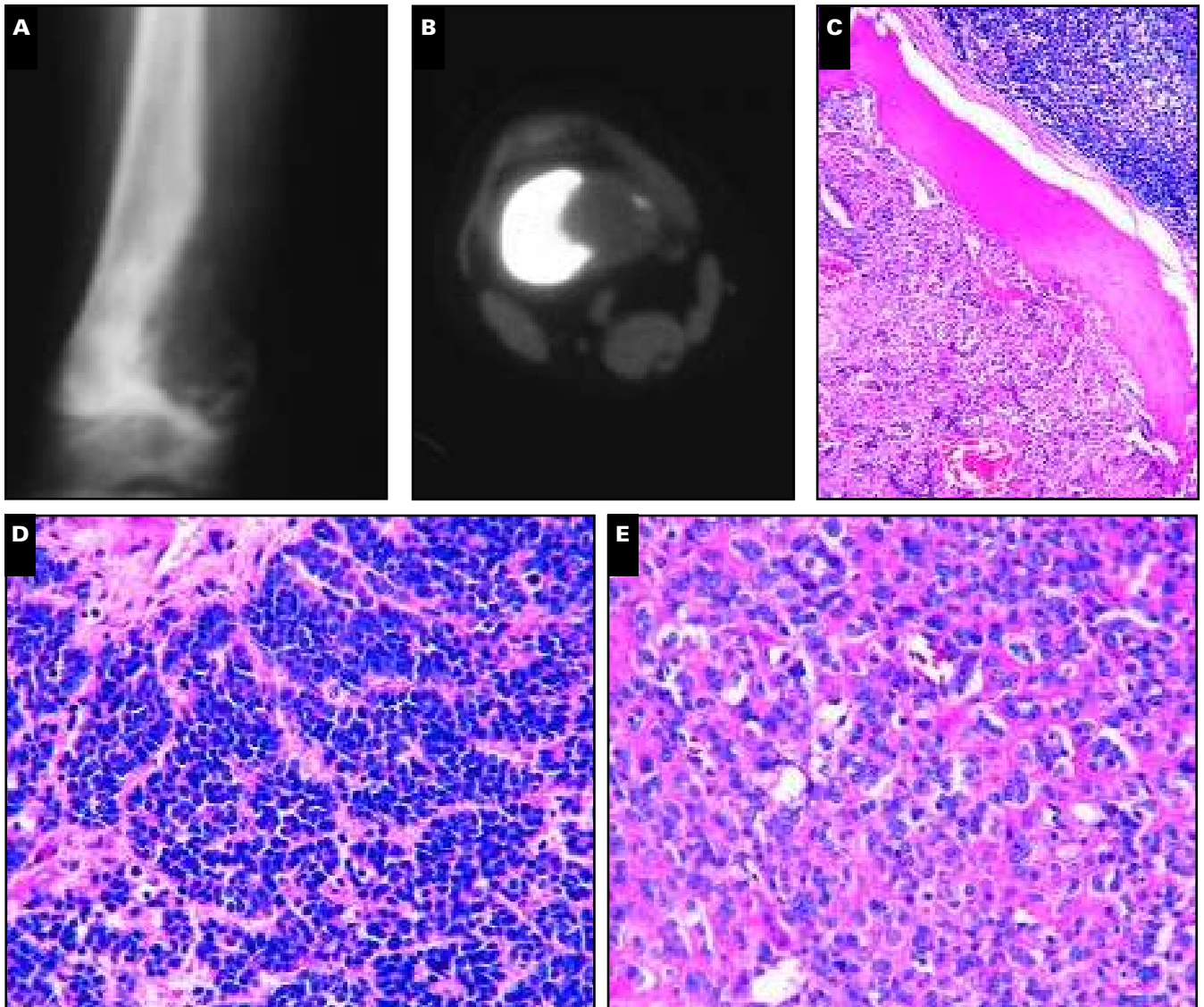


Image 9 Small cell osteosarcoma. The lesion is highly destructive and has no obvious radiodensity suggestive of osteosarcoma on routine radiograph (**A**) and computed tomography scan (**B**). **C**, The tumor above the bone trabecula appears to be composed of small cells dominated by round, blue nuclei suggestive of Ewing sarcoma/primitive neuroectodermal tumor. The tumor below the trabecula demonstrates that the tumor cells are separated by pink matrix (H&E, $\times 50$). **D**, At higher magnification, the tumor cells above the trabecula are indistinguishable from Ewing sarcoma (H&E, $\times 250$). **E**, At the same magnification, the tumor cells below the trabecula are clearly producing osteoid matrix (H&E, $\times 250$).

with obvious matrix formation elsewhere, the diagnosis is made easily. On the other hand, if the tumor cells resemble epithelial cells and there is little osteoid, the diagnosis becomes more complicated. The tumor cells often are round or polyhedral rather than spindle-shaped. Their round or ovoid enlarged nuclei may contain 1 or more prominent nucleoli, and the tumor cells may even appear as cohesive as in some poorly differentiated carcinomas. The cells may demonstrate gland-like structures¹⁴ or even contain cells arranged in papillary configurations. Although the association has yet to be validated scientifically, we have seen this pattern more often in postradiation osteosarcomas.

If tumors like these are observed in the bones of young patients, osteosarcoma should be considered strongly as the diagnosis. In older patients, the diagnosis of a poorly differentiated metastatic carcinoma is more likely.¹⁴ A diligent, careful search for osteoid matrix should be carried out, particularly in young patients, because immunohistochemical analysis may demonstrate keratins even in usual osteosarcomas. The effectiveness of this technique may be observing the tissue through crossed polarizers for woven bone after staining the sections with Sirius red or some other enhancer of collagen anisotropism **Image 10**.²⁰

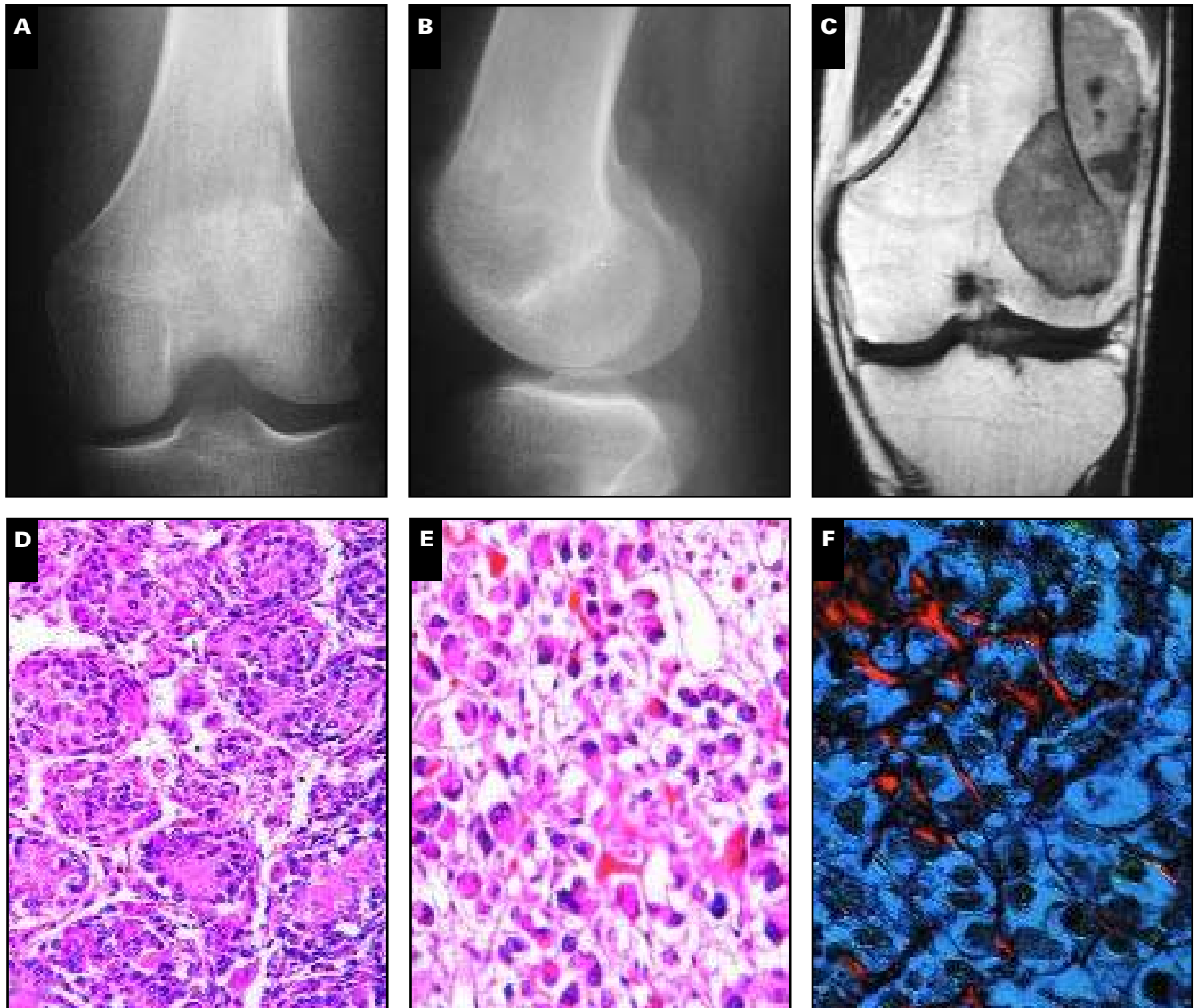


Image 10 Epithelioid osteosarcoma. The anteroposterior (**A**) and lateral (**B**) radiographs demonstrate an ill-defined process showing a few indistinct, cloudy densities and a small posterior soft tissue mass. **C**, The coronal T_1 -weighted magnetic resonance image demonstrates that the mass is in the lateral femoral condyle and extends into the overlying subperiosteal soft tissue. **D**, Histologic sections reveal clusters of polyhedral cells aggregated about central cores resembling papillary structures; some of these contain osteoid rather than vessels (H&E, $\times 150$). **E**, Higher magnification demonstrates epithelioid round cells loosely disposed among a few wisps of osteoid (H&E, $\times 250$). **F**, An area similar to that in **E** stained with Sirius red F3BA and photographed in polarized light ($\times 500$). This technique emphasizes the osteoid.

Osteoblastoma-like and Chondroblastoma-like Osteosarcoma

Osteosarcomas occasionally may be similar histologically to other types of benign matrix-producing tumors. Osteoblastoma-like osteosarcoma resembles osteoblastoma histologically in that it produces the same sort of microtrabecular bone lined by osteoblasts as does osteoblastoma. The radiographic appearance often suggests a malignant tumor²¹; however, this may not be completely helpful because there is

no constant radiographic pattern for osteoblastoma, which occasionally has the radiographic signs of malignancy.

To make matters more complicated, some osteoblastomas may contain atypical-appearing osteoblasts,²² and a spectrum of histologically overlapping lesions ranging from biologically quiescent to aggressive has been described.²³ The most important histologic parameters for malignancy include permeation of architecturally normal bone at its interface with tumor²⁴ and aneuploid mitotic activity **Image 11**, whereas benign osteoblastic tumors tend to show maturation

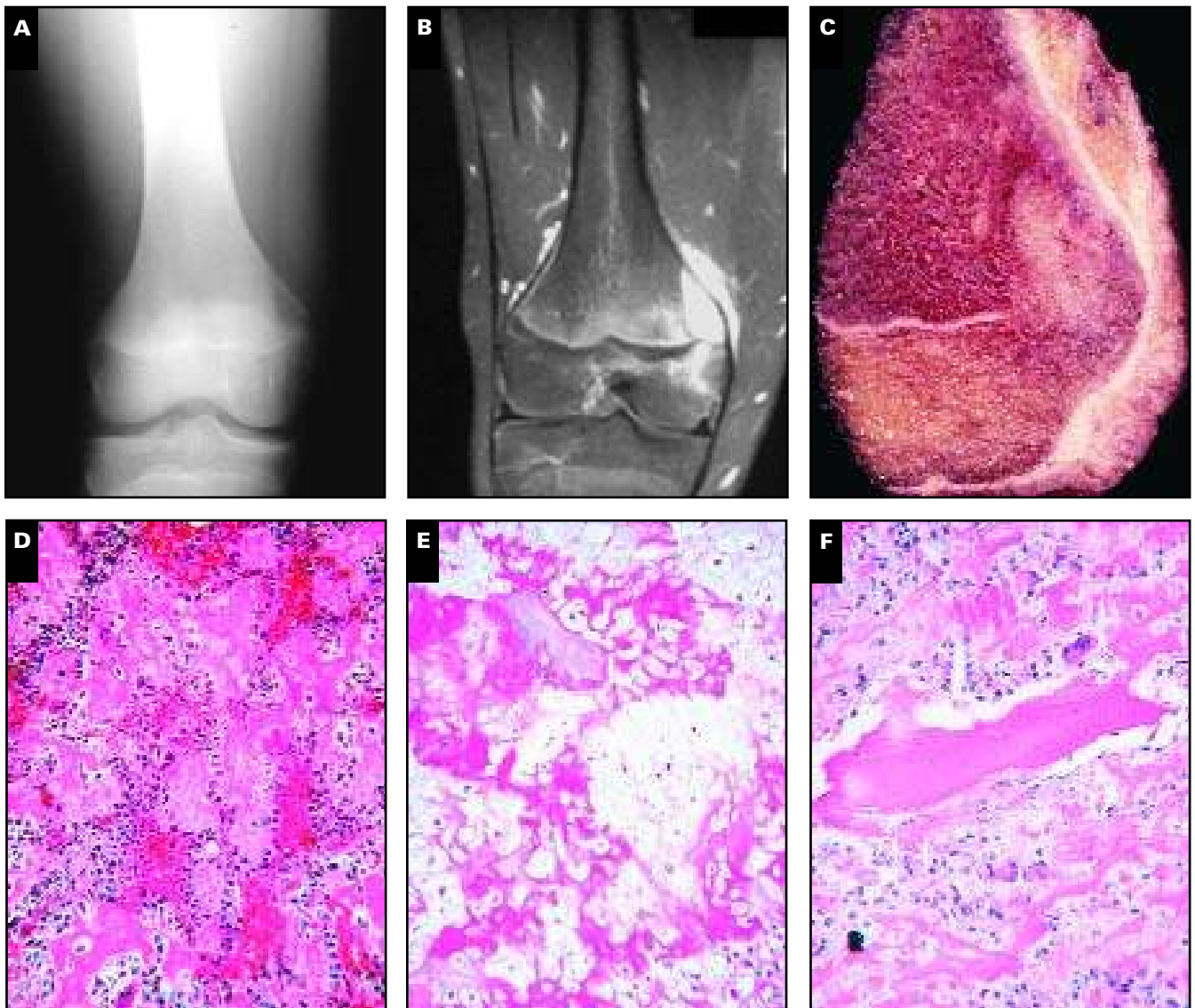


Image 11 Osteoblastoma-like osteosarcoma. **A**, The anteroposterior radiograph demonstrates a well-circumscribed tumor. **B**, The fat-suppressed T_2 coronal magnetic resonance image demonstrates that the tumor has a bright signal, focally involves the growth plate, and may involve the overlying soft tissues and cause edema. **C**, The resected specimen demonstrates obliteration of the growth plate medially and an organized periosteal reaction. Tumor external to the cortex is not present following neoadjuvant chemotherapy. **D**, **E**, and **F**, Representative histologic features before specimen resection. **D**, Microtrabecular osteoid lined by osteoblast-like cells as seen in osteoblastomas (H&E, $\times 100$). **E**, Foci of lace-like osteoid and hyaline cartilage in other microscopic fields from the same lesion (H&E, $\times 250$). **F**, Focal permeation of normal cancellous bone and marrow adjacent to the tumor mass (H&E, $\times 150$).

and circumscription at their edges.²¹ Because of this, differentiating this type of osteosarcoma from osteoblastoma may be extremely difficult, especially in small biopsy samples.²⁵

Rarely, osteosarcomas may appear histologically to be a chondroblastoma.²⁶ Chondroblastoma-like osteosarcoma may or may not be epiphyseal. When it is epiphyseal and well circumscribed, it is a very difficult diagnosis to make because radiologic studies specifically suggest a benign diagnosis. In these cases, the diagnosis must be made histologically in the face of conflicting radiographic data. Histologically,

its difference from chondroblastoma may be extremely subtle because despite its clinically benign behavior, chondroblastoma itself is a mitotically active, primitive tumor. This type of osteosarcoma is best distinguished by its osteoid or bone formation, atypical mitotic activity, and infiltration of adjacent intertrabecular spaces **Image 12**.

Both osteoblastoma-like and chondroblastoma-like osteosarcomas are extremely rare, but their accurate diagnosis is important because like their more common conventional counterparts, they may metastasize.

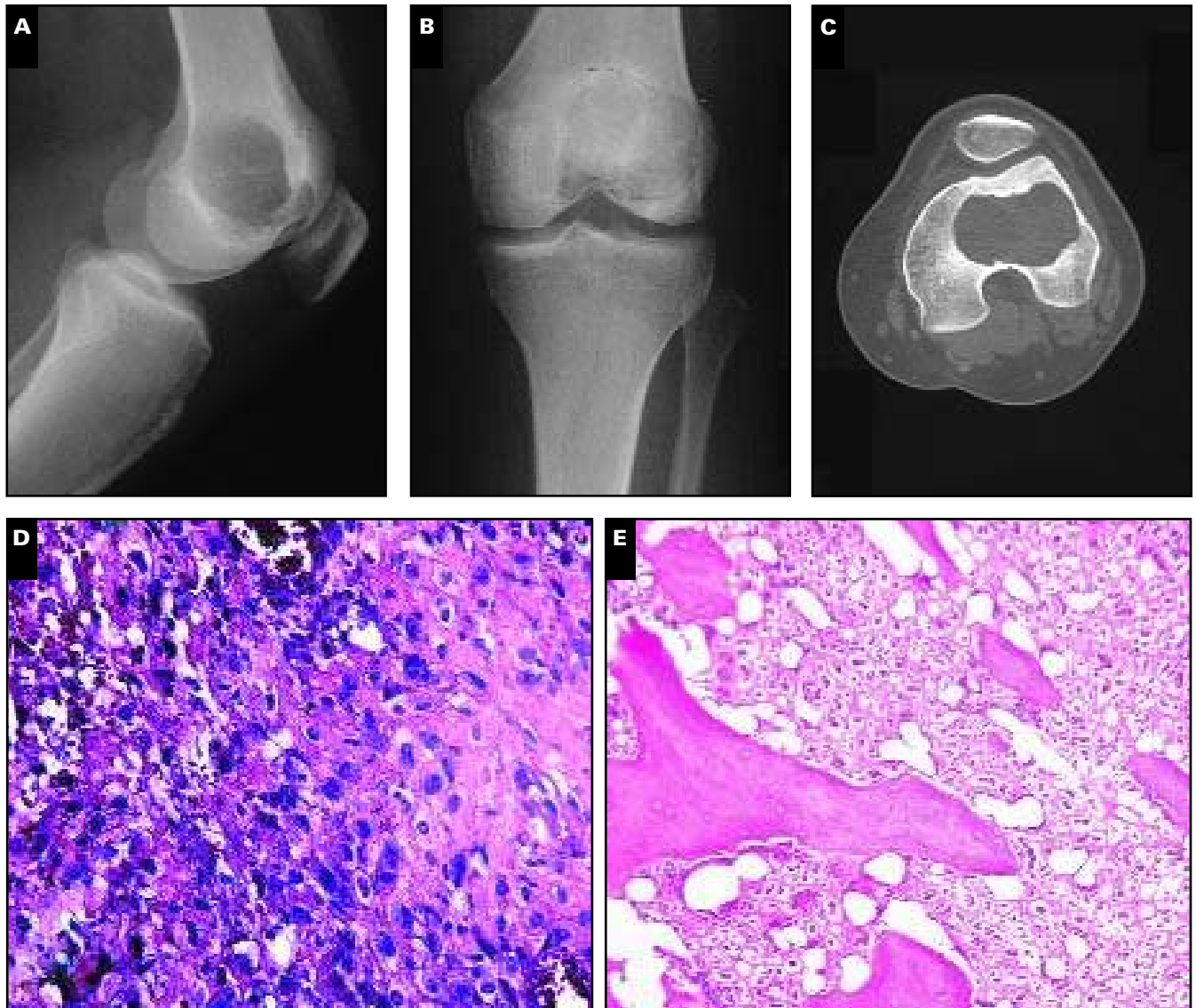


Image 12 Chondroblastoma-like osteosarcoma. The lateral (**A**) and anteroposterior (**B**) radiographs demonstrate a well-circumscribed radiolucency centered in the end of the bone. **C**, The computed tomography scan demonstrates that the borders are indeed well circumscribed and the lesion is confined to the bone. **D**, Most of the histologic features are that of a monotonous lesion composed of uniform cells with demarcated cytoplasmic borders and with bean-shaped, ovoid nuclei and rather fine, lattice-like calcifications in a chondroid background (H&E, $\times 400$). The overall initial biopsy impression was chondroblastoma; however, a few atypical mitoses raised suspicions of osteosarcoma. **E**, A more thorough sampling revealed foci of typical lace-like osteoid infiltrating cancellous bone at the periphery (H&E, $\times 150$), and the diagnosis of osteosarcoma was made.

Giant Cell-Rich Osteosarcoma

About 25% of osteosarcomas contain benign multinucleated giant cells resembling osteoclasts.¹⁴ Rarely, an osteosarcoma may contain so many benign giant cells that the malignant elements in the background are obscured; in these cases, the lesion may be mistaken histologically for a giant cell tumor.²⁶ This is more apt to occur in the sacrum, where giant cell tumor is much more common than osteosarcoma and the radiographic differences between giant cell tumor and

osteosarcoma are less apparent than in long bones, where the radiographic differences are more conventional and osteosarcomas are more common. As noted previously, multinucleated giant cells tend to be more numerous in telangiectatic osteosarcomas than in other types of osteosarcomas, but they are not distributed uniformly in any of the solid areas of tumor tissue. In addition, there usually is a great deal of nuclear pleomorphism evident in telangiectatic osteosarcomas **Image 13**.

By comparison, the usual giant cell tumor tends to arise in skeletally mature people and extends from the area that

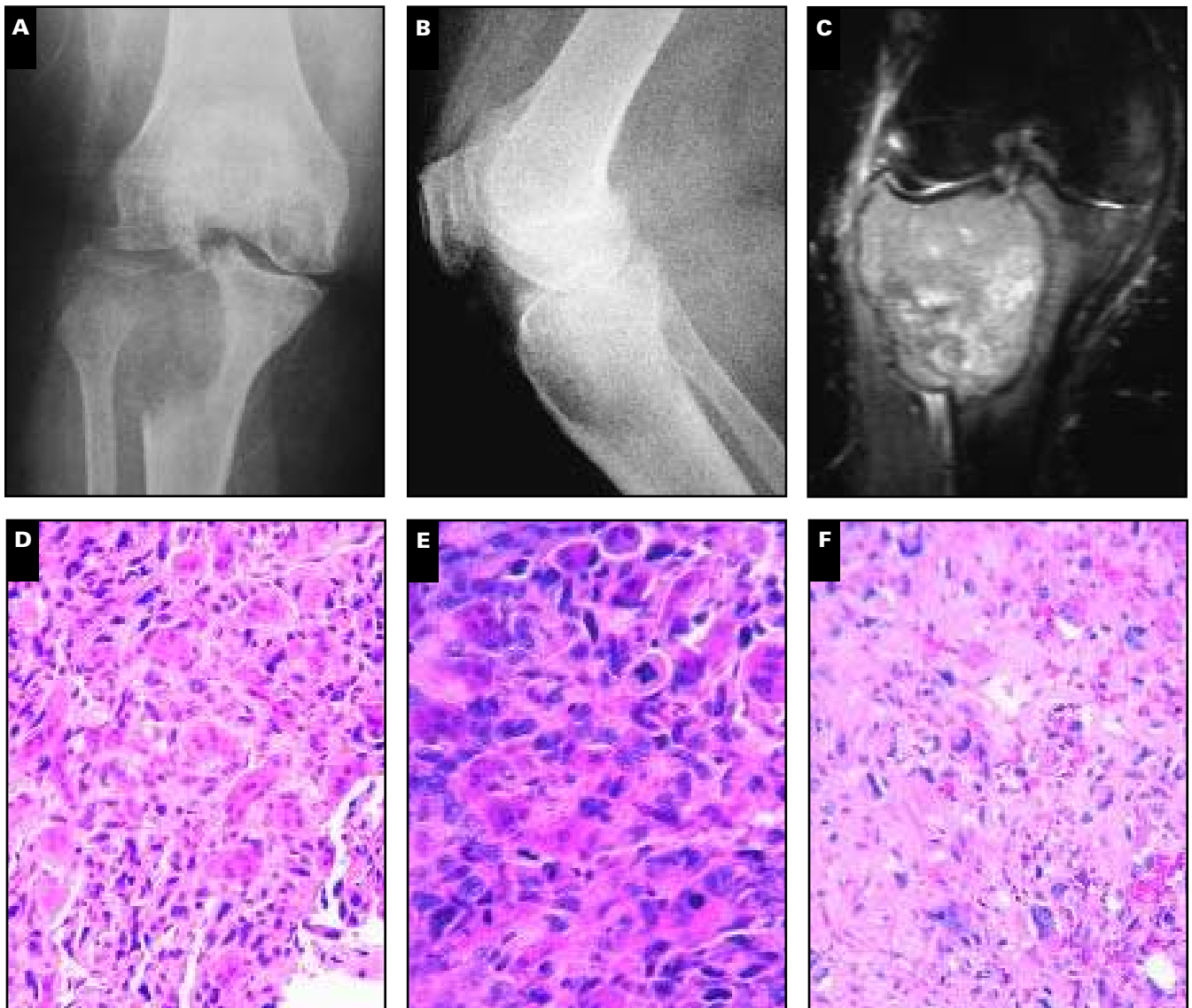


Image 13 Giant cell-rich osteosarcoma. The anteroposterior (**A**) and lateral (**B**) radiographs reveal a locally destructive tumor extending from the metaphysis to the articular end of the bone. There is internal circumscription and no discernible periosteal reaction. **C**, The coronal fat-suppressed magnetic resonance image demonstrates that the lesion has a heterogeneous isointense to hyperintense signal. The clinical diagnosis was giant cell tumor. **D** and **E**, Histologic sections demonstrate a giant cell rich lesion with mononuclear background; however, nuclear atypia and atypical mitotic activity are clearly shown (**D**, H&E, $\times 200$; **E**, H&E, $\times 400$). **F**, Individually malignant mononuclear cells and even polyploid giant cells within a collagenized matrix focally having the properties of osteoid (H&E, $\times 250$).

corresponds to the metaphyseal side of the growth plate to the ends of the long bones. In the absence of a fracture, a periosteal reaction also is uncommon in an uncomplicated giant cell tumor. A tumor that appears to be a giant cell tumor histologically but arises in a skeletally immature person, therefore, should be regarded with great suspicion and sampled widely to rule out osteosarcoma. This is particularly true if it is accompanied by a visible periosteal reaction.

True giant cell tumors also may develop malignant tumors within them. When a sarcoma is identified within the

tissue of an otherwise atypical giant cell tumor, the diagnosis often made to describe this event is a “primary malignant giant cell tumor.” A histologically typical giant cell tumor previously curetted that recurs and histologically shows sarcomatous tissue often is described as a “secondary malignant giant cell tumor.” Primary malignant giant cell tumor is clinically half as common as secondary malignant giant cell tumor. The type of sarcoma associated with both may be a spindle cell sarcoma with little or no extracellular matrix, but it may, in fact, contain osteoid matrix. If the malignant component replaces otherwise

typically conventional areas of giant cell tumor without replacing all of the giant cells, it would be easy to mistake the lesion for a giant cell tumor if there is little matrix present. It is possible that this also is a source of some of the giant cell–rich osteosarcomas reported in the literature.

Osteosarcomas that appear fibrohistiocytic resemble fibroblastic osteosarcoma histologically and, in addition, have a storiform arrangement and histiocytic giant cells **Image 14**. They contain smaller amounts of detectable bone matrix and tend to arise at a later age than conventional osteosarcomas.²⁷

Gnathic Osteosarcoma

Osteosarcomas of the mandible and maxilla usually manifest with swelling or pain. Radiographically, they often are radiolucent or a mixture of radiolucent and radiodense areas.²⁸ Anecdotally, we have seen several cases in which the conventional radiographs appear unremarkable, creating a dichotomy in clinical symptomatology, radiographic presentation, and histopathologic appearance. Gnathic osteosarcomas tend to be predominantly chondroblastic in matrix production **Image 15**, but osteoblastic, fibroblastic, and even small cell types

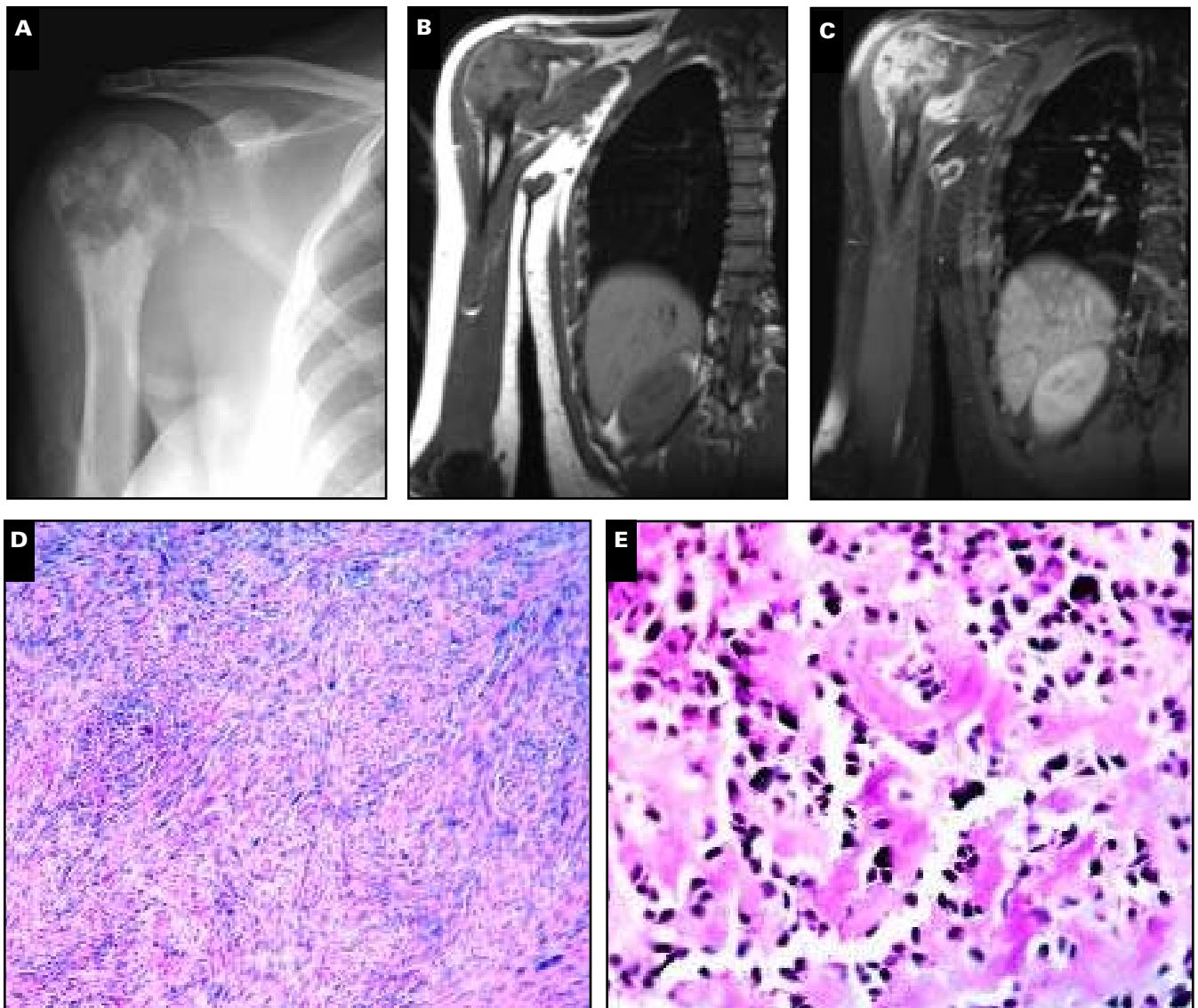


Image 14 Osteosarcoma, so-called fibrohistiocytic variant. **A**, The conventional radiograph demonstrates a destructive lesion of the proximal humerus extending to the articular end. There is some sclerosis in the humerus just distal to the humeral head. Coronal magnetic resonance imaging studies in T_1 (**B**) and T_2 (**C**) demonstrate hypointensity in T_1 and hyperintensity in T_2 . There is a soft tissue mass and periosteal reaction inferolaterally. **D**, Most of the lesion has a fibrohistiocytic pattern with a cellular stroma and storiform arrangement of tumor cells (H&E, $\times 150$). **E**, Areas of definite osteoid production are identified focally juxtaposed to the tumor cells (H&E, $\times 400$).

have been described.²⁹ Although they often are high-grade tumors histologically, they tend to give rise to uncontrolled local disease, with a small minority of patients developing distant metastatic disease. For this reason, and not on a histologic basis, they usually are thought of as pathologic entities different from conventional osteosarcoma.³⁰

Osteosarcomas arising in nongnathic craniofacial bones tend to arise in older patients, often are associated with an underlying predisposing condition such as Paget disease or previous radiation, and have a biologic potential more like that of conventional osteosarcoma.³¹

Low-Grade Central Osteosarcoma

This unusual variant of osteosarcoma constitutes a very small percentage of osteosarcomas. Its microtrabecular osseous matrix architecture in a bland fibrous stroma bears some resemblance to fibrous dysplasia and other benign lesions,^{32,33} but most often it resembles the histologic features of low-grade parosteal osteosarcoma. If bone formation is scant, there also is a histologic resemblance to desmoplastic fibroma,³⁴ and 2 reported cases were misdiagnosed initially as Paget disease.³⁵

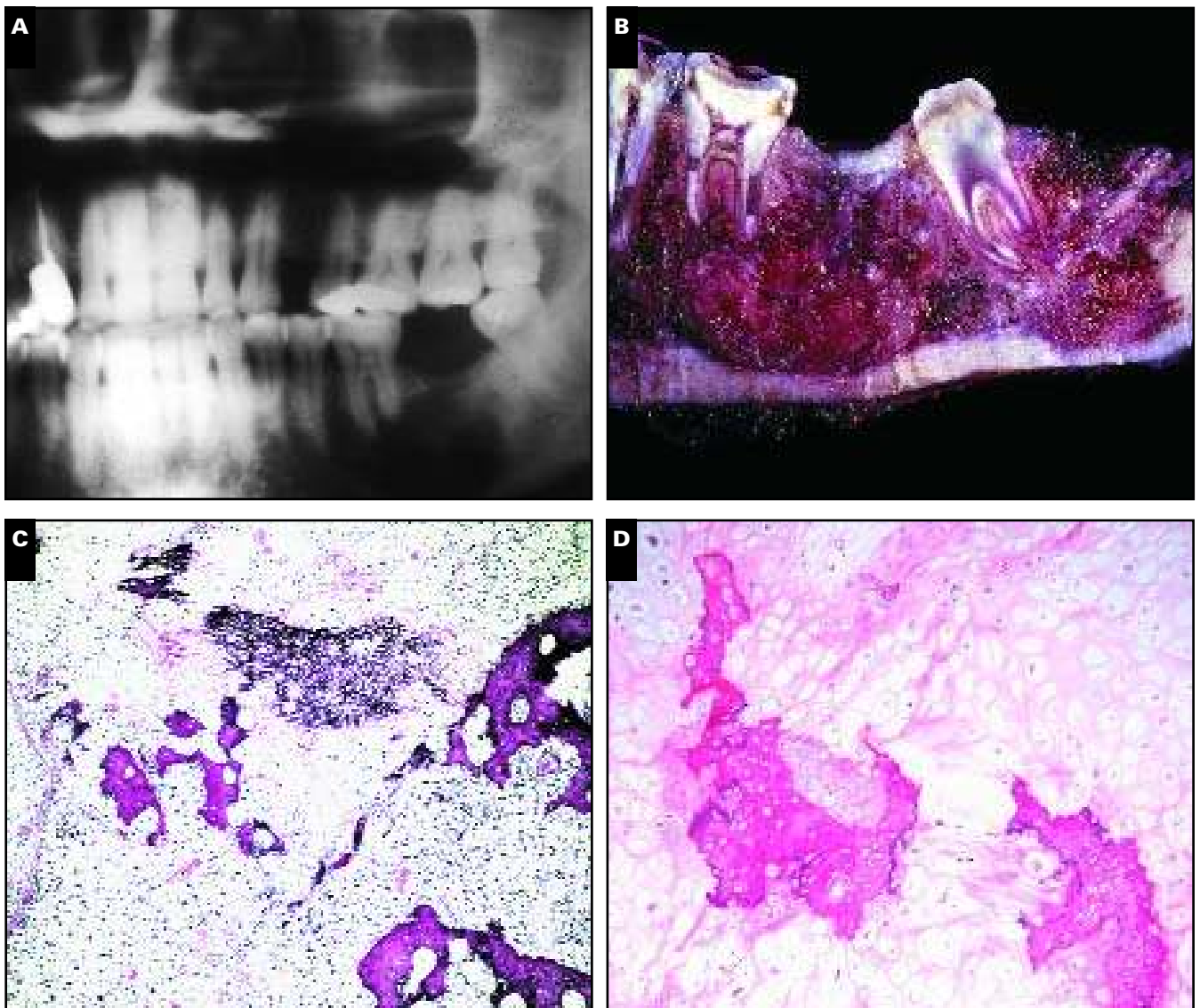


Image 15 Gnatheic osteosarcoma. **A**, The Panorex radiograph demonstrates a radiolucent space-occupying lesion under the area of the missing right lower second molar tooth. **B**, The gross specimen demonstrates rather soft tumor matrix filling the area under the missing molar and causing erosion of the underlying mandible. Histologic sections at medium (**C**, H&E, $\times 100$) and high (**D**, H&E, $\times 250$) magnifications demonstrate a mostly cartilaginous, highly cellular tumor that contains foci of immature osteoid production.

Accurate diagnosis is predicated on satisfactory correlation with clinical imaging studies and very careful evaluation of histologic findings **Image 16**. The imaging features are not invariably diagnostic, but they often suggest a lesion of greater local aggressiveness than fibrous dysplasia or other benign lesions.³⁶ These features may include indistinct circumscription, dense sclerosis, an interrupted periosteal reaction, or cortical infraction. Sections through the center of the lesion usually

demonstrate woven microtrabeculae of bone in a moderately cellular, fibrous stroma. If sections include the interface of the lesion with normal bone, fibrous tissue within Haversian canals or between mature cancellous trabeculae is a telltale sign of malignancy.³² In the absence of these findings, atypical mitotic activity may lead to the correct diagnosis. Although patients usually are treated with surgery alone and their prognosis is significantly better than in conventional

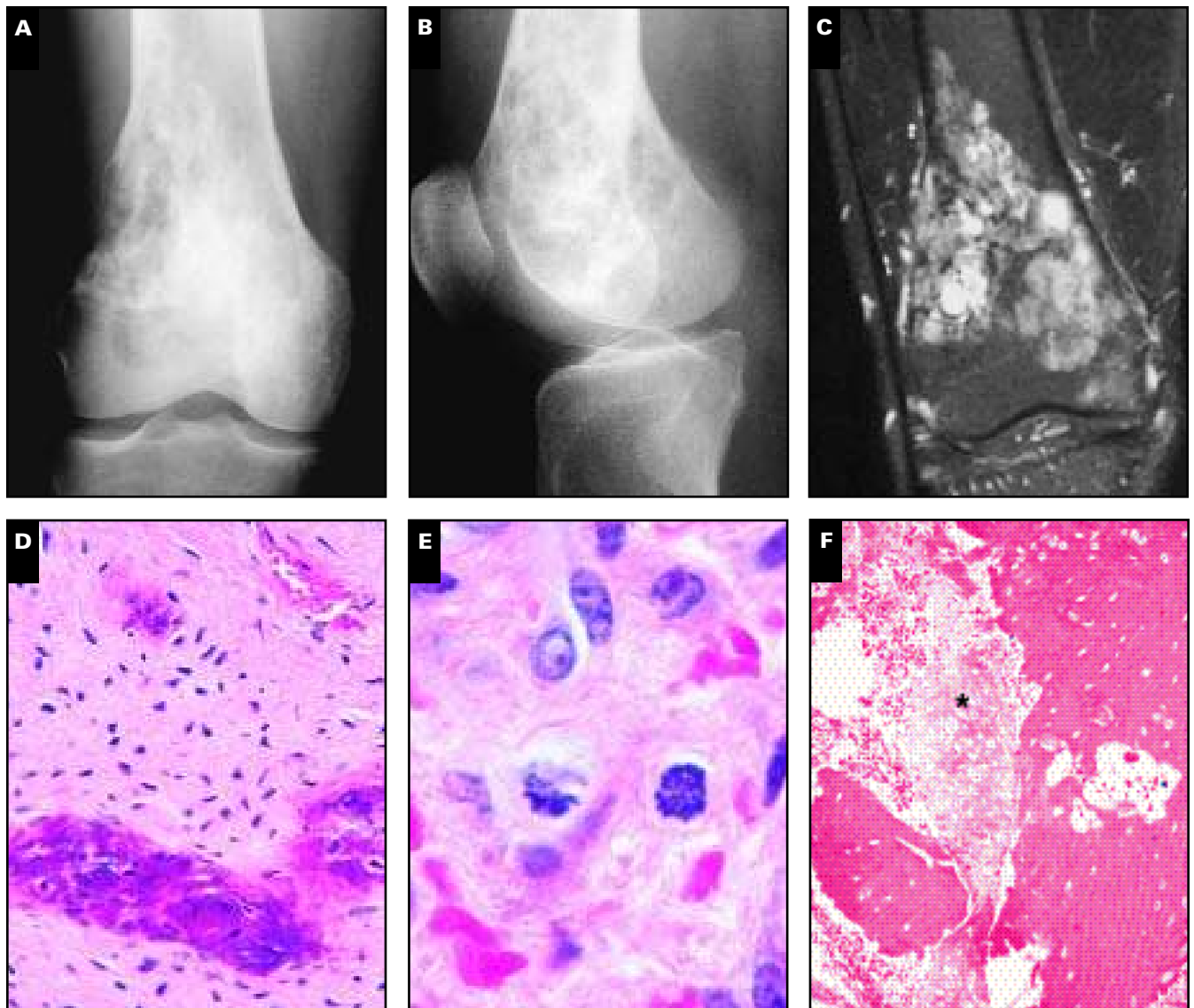


Image 16 Low-grade central osteosarcoma. The anteroposterior (**A**) and lateral (**B**) radiographs demonstrate a rather mottled, deceptively circumscribed lesion that resembles fibrous dysplasia except for the very focal area of cortical erosion of the lateral femoral metadiaphysis. **C**, The fat-suppressed magnetic resonance image in coronal view demonstrates actual extension of the hyperintense mass into the soft tissue. This finding is never seen in uncomplicated fibrous dysplasia. **D**, The majority of the histologic features are immature, poorly formed, woven trabeculae without appositional osteoblastic activity in a modestly cellular fibrous stroma (H&E, $\times 250$). This greatly imitates fibrous dysplasia except for the atypical features in the radiographs. **E**, A search of nuclei at higher magnification revealed not only mitotic activity but also atypical mitoses (H&E, $\times 787$). A diagnosis of low-grade central osteosarcoma prompted removal of the distal femur. **F**, A section through the cortex demonstrated permeation of the Haversian systems by tumor matrix (asterisk) (H&E, $\times 100$).

osteosarcoma,³⁷ a certain number of patients develop a secondary high-grade osteosarcoma (dedifferentiation) within the original low-grade tumor or at its previous anatomic site of origin in local recurrences.^{33,38,39} It is probable that some cases of fibrous dysplasia associated with secondary development of osteosarcomas are, in fact, low-grade osteosarcomas that later became higher grade.

Surface Osteosarcomas

Surface osteosarcomas are osteosarcomas whose epicenters are outside the cortex of the underlying bone. They usually arise in relation to the periosteum or the cortex of the bone with minimal or no involvement of the medullary cavity. Unlike conventional osteosarcomas, which are tumors of adolescents, these lesions usually arise in patients in the third and fourth decades.

There are several types of surface osteosarcomas, which have been characterized by exact anatomic location, by the predominant type of matrix, and by histologic grade. The majority of surface osteosarcomas are low-grade neoplasms with a propensity for local recurrence and a real but very limited capacity for distant metastasis. A relatively small number (approximately 10%) of surface osteosarcomas are high-grade tumors. The current classification system identifies indolent and high-grade tumors, so it is able to group the lesions needing specific kinds of therapy.⁴⁰

Parosteal Osteosarcoma

Geschicter and Copeland⁴¹ first described the most common form of surface osteosarcoma, parosteal osteosarcoma, although the term currently used for it was formulated by Dwinnell et al.⁴² This lesion often had been confused with osteochondroma and osteoma; however, its local recurrence rate when incompletely excised and its small but definite propensity for distant spread made it clear that it behaved clinically as a uniquely different entity. Parosteal osteosarcoma accounts for fewer than 1 in 20 osteosarcomas, and its average incidence is about a decade later than the usual type of central osteosarcoma. It has a unique presentation and anatomic distribution because 75% to 80% of cases arise as densely radiopaque masses attached to the distal posterior femur.

Although parosteal osteosarcoma may give rise to a sensation of fullness, prevent complete range of flexion, and even be perceived as a mass through the overlying soft tissues, it is unusual for the entity to be spontaneously painful. Its radiodensity often is not uniform, often being more radiodense centrally as it approaches the bone surface and less dense at its periphery. In contrast with osteochondroma, there is no usual continuity of the exterior of the mass with the adjacent cortex, and its inside is not in continuity with the underlying medullary cavity.

In localized heterotopic ossification (so-called myositis ossificans circumscripta) arising near the bone surface, the ossification pattern is exactly the opposite radiographically, with the densest bone being outside and the least dense being inside.

In parosteal osteosarcoma, there often is an incomplete radiolucent line separating most of the sclerotic mass from the underlying cortex **Image 17**. When a resected specimen is examined carefully, especially with specimen radiography, this radiolucent line corresponds to the underlying periosteum, to which the mass usually is fixed at one point on the outside. An underlying periosteal reaction is very unusual because to produce such a reaction, the tumor would have to lift the inner cambium layer of the periosteum away from the cortex. Parosteal osteosarcoma usually is not locally aggressive enough to do this.

Histologically, parosteal osteosarcomas consist of streamers of bone trabeculae that often show a high degree of parallel orientation similar to what might be observed in a periosteal new bone reaction **Image 18**. This concentration and arrangement of bone is what gives rise to the typically sclerotic trabecular architecture seen in radiographs, and the trabecular orientation may be discerned in a specimen radiograph of a thinly cut slice of the lesion. Mirra²⁶ has noted the histologic resemblance of this bone formation to “flowing steel wool.” When the bone spicules become thicker at the base of the lesion, there usually is very little actual maturation of the matrix into a lamellar architecture, and the lesion does not become enveloped within the cortex. There is a cellular cartilage cap external to the osseous portion of the lesion in about 25% to 30% of cases. This occurrence historically has resulted in the pathologic misdiagnosis of some parosteal osteosarcomas as osteochondromas, particularly if the radiographic findings showing a lack of cortical and medullary continuity are not correlated with the histologic features. There are even descriptions of so-called osteochondroma-like parosteal osteosarcomas that not only call attention to this phenomenon, but also propose that it be given a separate nomenclature.⁴³

The histologic key to the correct diagnosis is that a growing osteochondroma has the same internal development as a growing bone. There is a medullary cavity with fat or hematopoietic marrow in the intertrabecular spaces of normal bone and osteochondroma, whereas the intertrabecular spaces of parosteal osteosarcomas contain cellular fibrous tissue. This fibrous tissue is deceptively bland, and without radiographic correlation, it would be difficult to say that it represents a malignant condition. Occasionally, there is immature osteoid or osseous matrix found between the parallel bone spicules, and this helps in the definitive assessment of ordinary low-grade parosteal osteosarcoma.

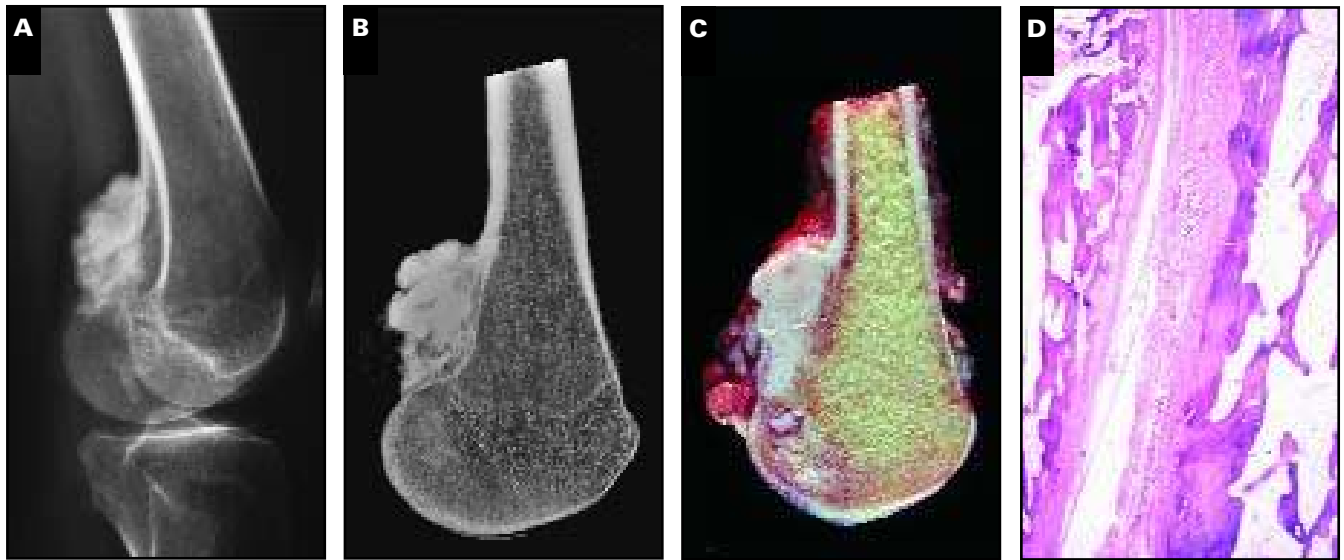


Image 17 Parosteal osteosarcoma. **A**, The lateral radiograph demonstrates a radiodense lesion attached to the posterior cortex of the femur; the density decreases peripherally, and there is a radiolucent line outside the cortex that corresponds to the periosteum. The specimen radiograph (**B**) and specimen (**C**) demonstrate that the radiodensity is due to rather compact bone. The radiolucent line corresponding to the periosteum can be seen between the dense overlying mass and the bone in the radiograph and corresponds to the dark linear area between the thin metaphyseal cortex and overlying mass in the specimen photograph. **D**, The diagonally oriented periosteum (lower left to upper right) interposed between the low-grade bone-producing tumor (left) and underlying bone (right) (H&E, $\times 250$).

The majority of parosteal osteosarcomas are associated with the outer fibrous layer of the periosteum, which does not produce typical periosteal reactions. Exceptions are rarely seen when an otherwise slowly growing tumor eventually penetrates the periosteum externally and gradually dissects apart the cortex and inner periosteum. Rarely, a typical low-grade parosteal osteosarcoma demonstrates invasion of the underlying bone **Image 19**. This event has been thought to have an adverse role in prognosis; however, so long as the tumor remains low grade, the outlook for this event probably is not significantly worse.

Periosteal Osteosarcoma

Unni and associates⁴⁴ first described this surface tumor, which is considerably less common than parosteal osteosarcoma and has a matrix component that is mainly cartilaginous. Although the lesion is associated with the bone surface, it tends to arise between the cortex and the cambium layer of the periosteum, so that there often is a periosteal reaction visible radiographically. There also often is underlying cortical thickening or erosion, and it usually occurs along the tibial or femoral diaphysis rather than posterior to the metaphysis of the distal femur.⁴⁵ Its histologic grade is intermediate between that of the usual grade 1 parosteal osteosarcoma and that of conventional grade 3 or 4 osteosarcoma **Image 20**. There rarely is extension into the underlying cortex, but there almost never is extension into the underlying endosteum.

Dedifferentiated Parosteal Osteosarcoma

Wold and associates⁴⁶ first described cases of histologically high-grade osteosarcoma arising in the clinical setting of recurrent parosteal osteosarcoma of the usual low-grade variety. In the first published series, the dedifferentiation took place over time in recurrences of well-documented tumors that previously were diagnosed as typical low-grade parosteal osteosarcomas.⁴⁷ With the discovery and description of more cases of this disease, it became clear that the dedifferentiation may, in fact, have been present at the time of first resection of the tumor. This event may be heralded by changing clinical signs and symptoms, such as a difference in the quality of pain or an area of radiolucency in an otherwise radiodense lesion. It may, on the other hand, be clinically unsuspected.

Grossly, the area of dedifferentiation often is discernible from the typically sclerotic areas of parosteal osteosarcoma. This may be because the higher-grade component is more cellular with respect to its matrix or because its bone matrix is less mineralized than in the lower grade areas. Less often, a higher grade area may result in cortical invasion and call attention to itself by its locally aggressive behavior. At least 1 study correlating CT and MRI with grade suggested that the presence of a soft tissue mass without osseous matrix is typical of dedifferentiation, particularly if it is of high signal intensity on T₂-weighted MR images.⁴⁷

Histologically, the tissue is composed of an admixture of typical appearing low-grade parosteal osteosarcoma and high-

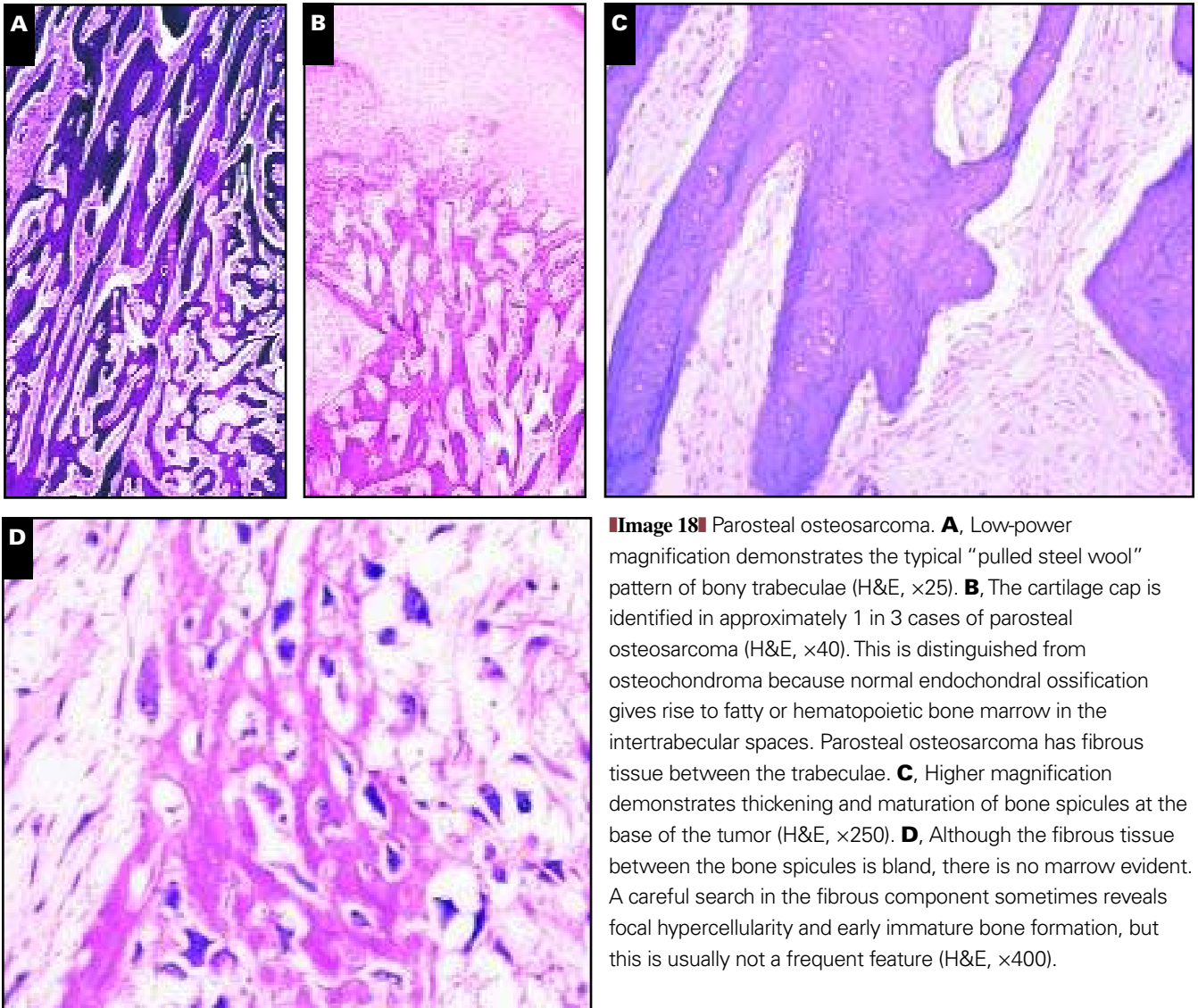


Image 18 Parosteal osteosarcoma. **A**, Low-power magnification demonstrates the typical “pulled steel wool” pattern of bony trabeculae (H&E, $\times 25$). **B**, The cartilage cap is identified in approximately 1 in 3 cases of parosteal osteosarcoma (H&E, $\times 40$). This is distinguished from osteochondroma because normal endochondral ossification gives rise to fatty or hematopoietic bone marrow in the intertrabecular spaces. Parosteal osteosarcoma has fibrous tissue between the trabeculae. **C**, Higher magnification demonstrates thickening and maturation of bone spicules at the base of the tumor (H&E, $\times 250$). **D**, Although the fibrous tissue between the bone spicules is bland, there is no marrow evident. A careful search in the fibrous component sometimes reveals focal hypercellularity and early immature bone formation, but this is usually not a frequent feature (H&E, $\times 400$).

grade conventional parosteal osteosarcoma **Image 21**. The dedifferentiated component has at least once been reported as being telangiectatic,⁴⁸ and it is possible that other varieties may be described as larger series are obtained. The prognosis is related to that of the least differentiated tumor component; it is worse than that of low-grade parosteal osteosarcoma but seems to be somewhat better than that of pure high-grade surface osteosarcomas.⁴⁹ At least 1 series suggests that patients with this disease derive benefit from adjuvant chemotherapy.⁵⁰ According to the recently published experience from the Rizzoli Institute, dedifferentiation occurs in approximately 1 in 4 low-grade parosteal osteosarcomas.⁴⁹

High-Grade Surface Osteosarcoma

This tumor, which manifests as a surface lesion of bone, is entirely high grade histologically.⁵¹ It may appear radiographically as an ordinary low-grade parosteal osteosarcoma

with dense sclerosis. Alternatively, it may have mixed sclerosis and radiolucency, or, occasionally, it may form a soft tissue mass with relatively little radiodensity. Because it is a higher grade lesion than ordinary parosteal osteosarcoma, its local growth and aggressiveness are more accelerated. Consequently, patients with this disease are more likely to have more distressing symptoms and signs than those with usually low-grade parosteal osteosarcomas.

Microscopically, the tumor is entirely high grade **Image 22**. It is possible that some high-grade surface osteosarcomas represent dedifferentiated parosteal osteosarcomas in which the high-grade component has replaced entirely the low-grade component. There usually is very little or no medullary invasion by the tumor in conventional radiography, although CT and MRI demonstrate occasional small foci of marrow involvement.⁵² If medullary invasion were a constant feature, it would be more difficult to make a case pathologically for the

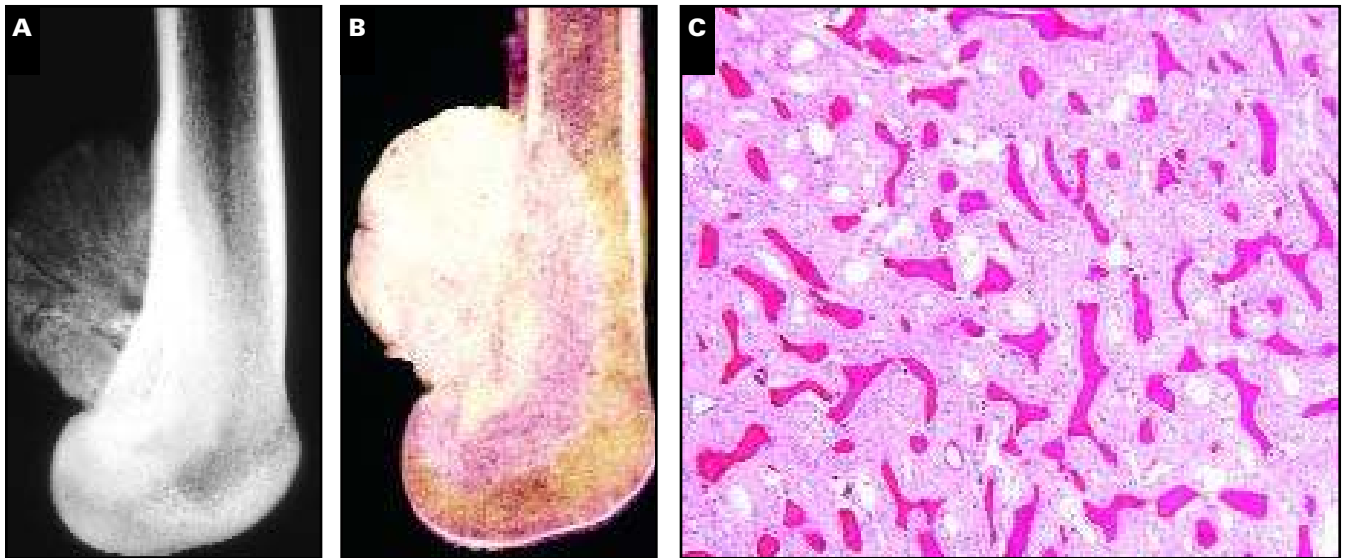


Image 19 Parosteal osteosarcoma, low grade, with intramedullary invasion. **A**, A specimen radiograph showing the typical striate radiodensity increased at the base of the lesion. Note that although there is no visible radiolucent line between the mass and the underlying bone, there is dense sclerosis adjacent to the surface mass that obliterates the trabecular architecture of the medullary cavity and obscures the cortex. **B**, The corresponding gross specimen. Although the intraosseous component is as large as the surface lesion, there is no periosteal reaction, strongly favoring a surface origin. **C**, Representative histologic features demonstrate that the lesion is entirely low grade and resembles fibrous dysplasia (H&E, $\times 40$).

lesion to have originated from the bony surface. On the other hand, because this tumor is considered to have the same malignant potential as conventional osteosarcoma, it is logical to occasionally have some degree of localized invasion of the cortex and endosteum. However, the radiographic epicenter and the great bulk of surface lesions must be external to the bone. In the case of high-grade surface osteosarcoma in particular, the lack of periosteal reaction to the tumor indicates that the neoplasm did not begin within the medullary cavity.

Intracortical Osteosarcoma

Jaffe¹² first described this very rare anatomic variant of osteosarcoma, a high-grade osteosarcoma entirely confined within the bony cortex. It usually manifests as an area of cortical radiolucency with perilesional sclerosis. Depending on its size, it may be confused with osteoid osteoma and osteoblastoma, but its cellular atypia and local aggressiveness distinguish it from those entities. Histologically, there usually is abundant osteoid or bone formation. Formation of cartilage is unusual but helps to distinguish the lesion from osteoblastoma and osteoid osteoma. Follow-up of the small number of cases thus reported reveals that although aggressively treated patients have favorable results, this lesion may give rise to systemic disease⁵³ and is best approached biologically like any conventional osteosarcoma **Image 23**.

Multifocal Osteosarcoma

This extremely unusual condition affects multiple osseous sites simultaneously at the time of presentation (synchronous form) or multiple skeletal sites at varying intervals (metachronous type) **Image 24**. The former variant tends to affect children and adolescents, whereas the latter type usually occurs in adults.⁹ The childhood form is radiodense, usually symmetric, and a high-grade sarcoma with a rapidly fatal course.⁹ In the adult metachronous form, after the appearance of the first osteosarcoma, there is a disease-free interval of several months to several years followed by the development of one or several skeletal osteosarcomas.²⁶ These lesions are not symmetric, they may have variable degrees of sclerosis, and their histologic features may vary from high to low grade. The patients have a longer survival interval than children with the synchronous form, and a few long-term survivors have been reported.²⁶ This could argue for their not being osseous metastases, but an independent test to separate multifocality from metastasis continues to remain out of reach.

Extraskelatal Osteosarcoma

Osteosarcoma in an extraskelatal site accounts for fewer than 2% of all soft tissue sarcomas. Unlike conventional osteosarcoma, it tends to occur in late adulthood, and most patients are in the fifth to seventh decades at the time of

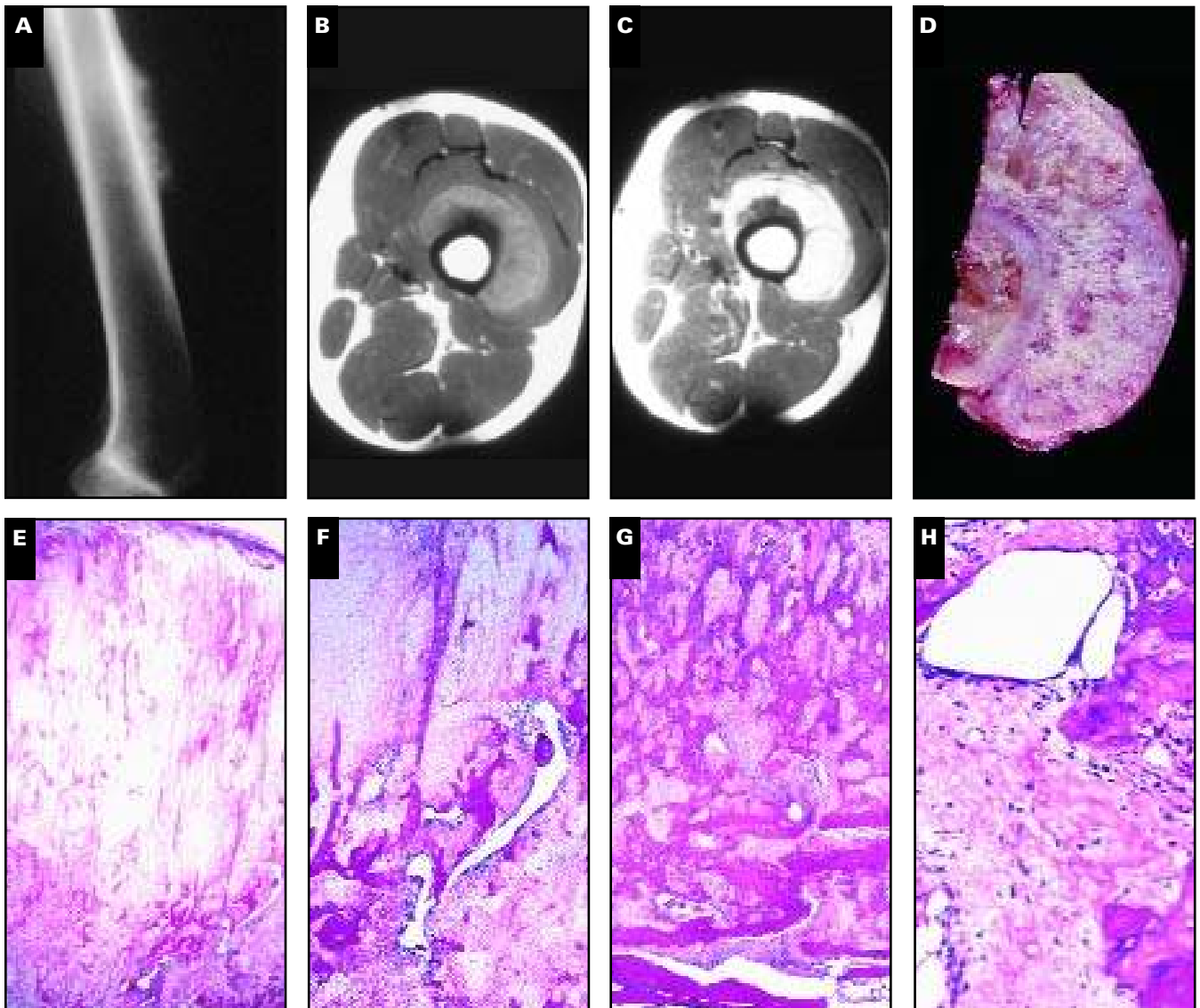


Image 20 Periosteal osteosarcoma. **A**, The lateral radiograph demonstrates a localized, interrupted, hair-on-end periosteal reaction without intramedullary abnormalities. The corresponding axial T_1 (**B**) and T_2 (**C**) magnetic resonance images demonstrate a partially circumferential hypointensity in T_1 and hyperintensity in T_2 ; this indicates a water-containing tissue consistent with cartilage. The base of the lesion is “signal void” in both studies, corresponding to the bony reaction in the plain radiograph. The marrow is bright in both sequences, indicating no tumor inside the medullary cavity. **D**, A partial diametric section reveals a circumferential mass confined to the space between the cortex and the periosteum. The color and partial translucency is consistent with calcifying cartilage. **E**, A scanning micrograph reveals the pink periosteal membrane overlying the bluish white cartilage matrix; at this power, pink streamers of periosteal new bone are seen within the cartilage (H&E, $\times 25$). **F**, A low-power micrograph from the base of the lesion demonstrates not only cartilage and periosteal bone streamers, but also bone formation (H&E, $\times 40$). **G** and **H**, Higher power magnifications from the base of the tumor show convincing bone formation in which tumor cells are entrapped (**G**, H&E, $\times 100$; **H**, H&E, $\times 250$).

diagnosis.⁵⁴ Most cases arise in the deep soft tissues with a predilection for the thigh followed by the buttocks, upper extremities, and the retroperitoneum.⁵⁵ Patients usually have an enlarging soft tissue mass, and the mass may be painful. Radiographs show a mass that may demonstrate mineralization, and CT scans increase the yield of cases that demonstrate mineralization.

Histologically, the tumors demonstrate all types of osteosarcoma seen in tumors that arise in bone **Image 25**. The most unusual histologic subtype is that of low-grade osteosarcoma. When the latter occurs, it has been described as the “soft tissue homologue of parosteal osteosarcoma,”¹⁵ although it could as easily have been described as the soft tissue

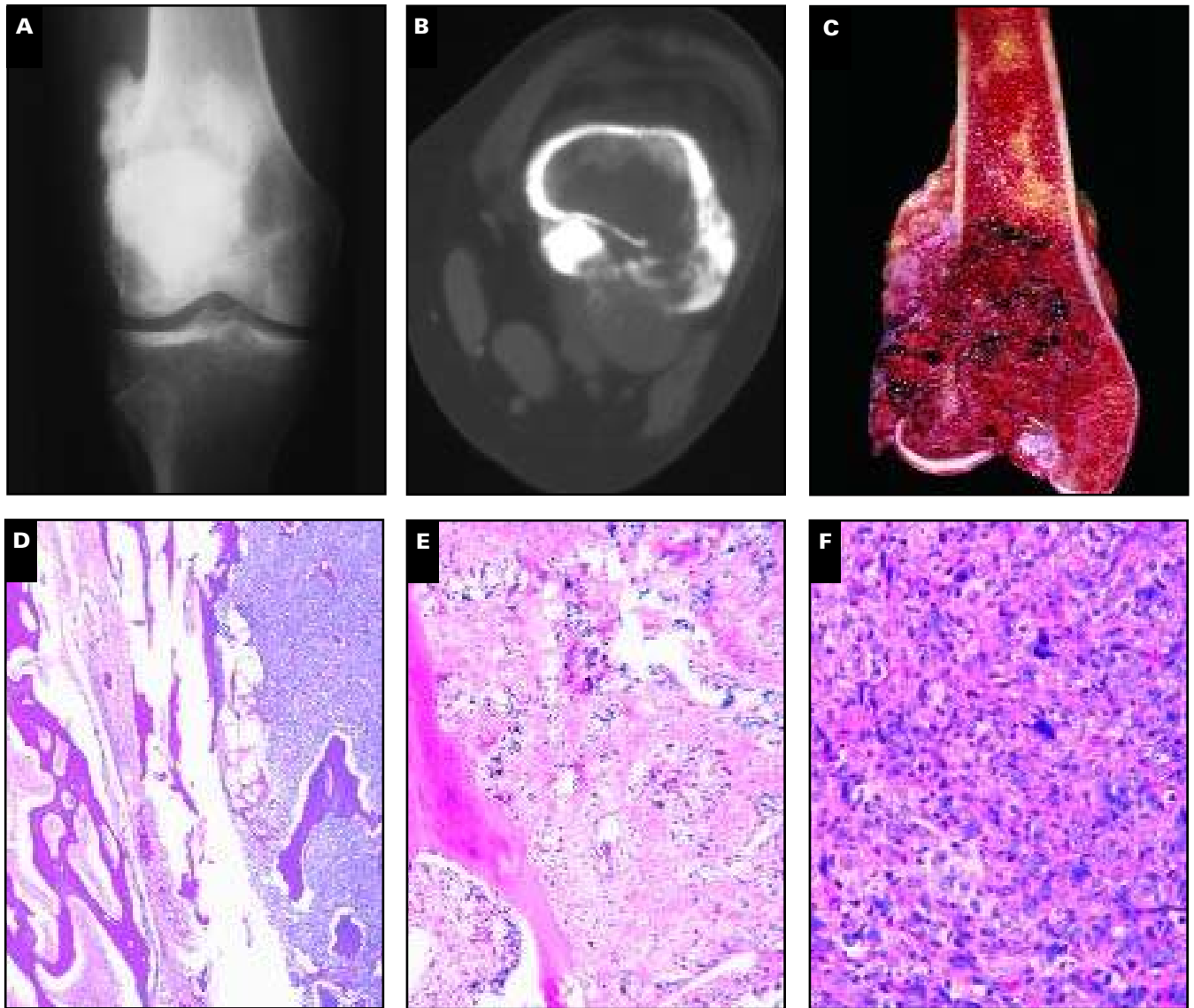


Image 21 Dedifferentiated parosteal osteosarcoma. **A**, The anteroposterior radiograph demonstrates cloudy, radiodense tumor matrix in the soft tissues. Note that the portion of lateral femoral condyle that does not overlap the patella and the upper medial metaphysis are markedly radiolucent compared with the bone of the metadiaphysis. **B**, The axial computed tomography scan demonstrates radiolucency and underlying cortical interruption at the base of the mass. The radiolucency also replaces the slightly denser cancellous bone. **C**, The gross specimen viewed coronally demonstrates that most of the surface tumor appears bony grossly and most of the tumor in the medullary cavity is hemorrhagic. There is no periosteal reaction, indicating that the mass began external to the bone and then invaded the bone. **D**, A low-power micrograph at the junction of external mass and invasive component demonstrates the typical trabecular pattern with intertrabecular fibrosis of low-grade parosteal osteosarcoma at the left and a more cellular, high-grade tumor within the underlying bone at the right (H&E, $\times 25$). There is no recognizable residual cortex in this photograph. **E** and **F**, Higher power photographs of the high-grade tumor components reveal sheet-like osteoid formation in an area of cortical disruption (**E**, H&E, $\times 50$) and an area of undifferentiated high-grade tumor without bone formation (**F**, H&E, $\times 250$).

homologue of low-grade central osteosarcoma. Recently, there was a reported case of high-grade dedifferentiation in a low-grade extraskeletal osteosarcoma analogous to that seen in parosteal and low-grade central osteosarcomas.⁵⁶

The prognosis is poor in soft tissue osteosarcoma of the high-grade type, with about 75% of patients dying of the tumor within 5 years of diagnosis.⁷ Anecdotally, patients with the low-grade variant seem to have a better

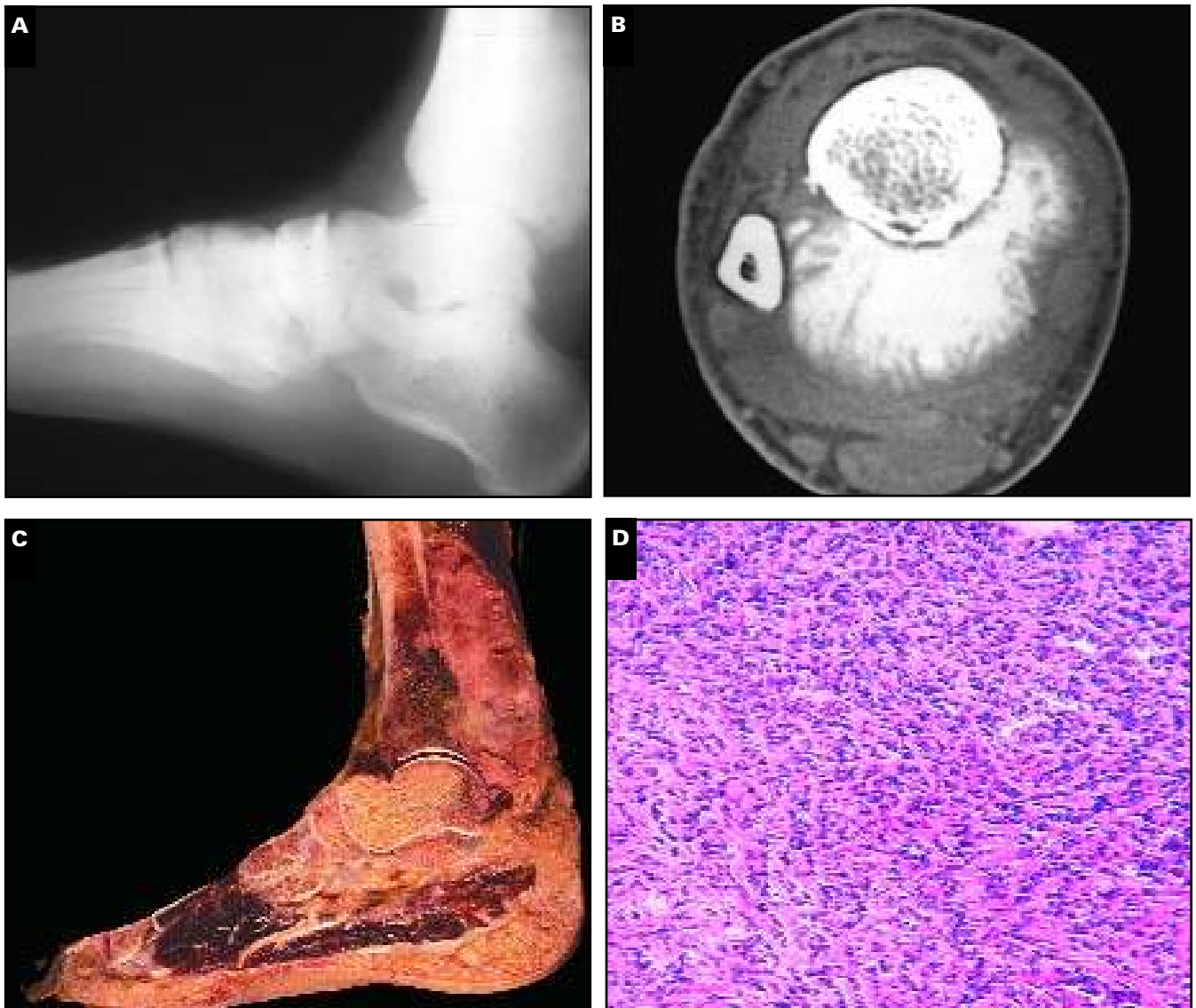


Image 22 High-grade surface osteosarcoma. **A**, A lateral radiograph demonstrates a radiodense tumor mass posterior to the tibia. **B**, A computed tomography scan demonstrates separation of the mass from the underlying bone by a dark periosteal line. The mass is progressively less radiodense away from the bone. **C**, The resected specimen demonstrates that the underlying tibia shows no gross invasion by the tumor. The patient died of metastatic disease less than a year after resection. **D**, The mass was biopsied at its periphery and found to be a high-grade neoplasm producing wispy osteoid (H&E, $\times 200$).

prognosis, although the total number of cases in the literature may still be too small to make accurate statistical analyses.^{56,57}

From the Departments of Pathology, Cell Biology, and Surgery, University of Alabama at Birmingham and the Birmingham Veterans Affairs Medical Center.

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Address reprint requests to Dr Klein: Section of Surgical Pathology, Department of Pathology, KB 506, University of Alabama at Birmingham, Birmingham, AL 35233.

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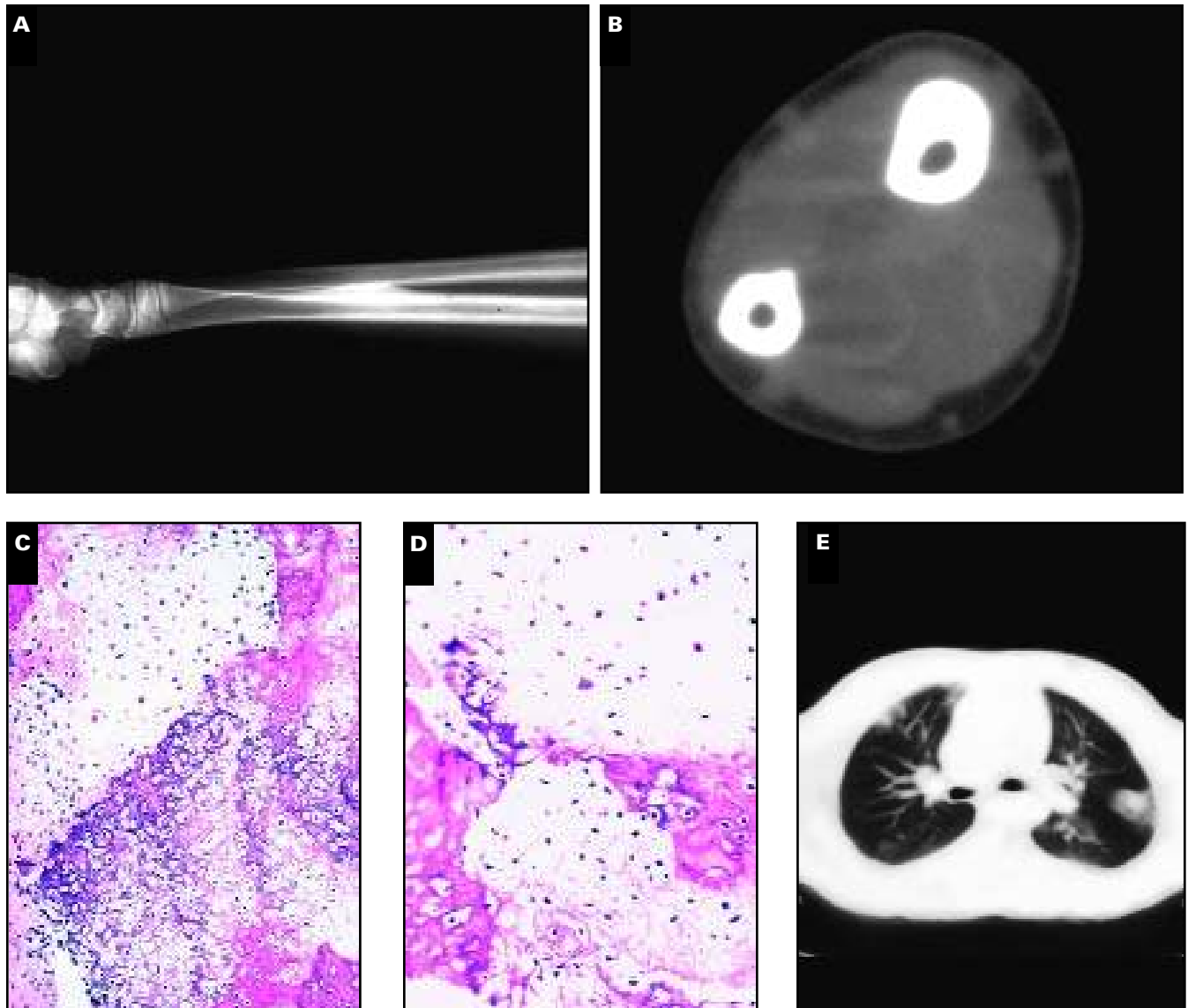


Image 23 Intracortical osteosarcoma. **A**, The lateral radiograph demonstrates a radiodense mass attached to the midshaft of the radius. The patient had a painless bump on the lateral arm. **B**, The computed tomography (CT) scan demonstrates eccentric thickening of the cortex. There was no history of trauma or radial deformity suggestive of a healed fracture. A biopsy specimen at medium (**C**, H&E, $\times 150$) and high (**D**, H&E, $\times 250$) power demonstrates highly cellular immature bone and cartilage formation. There is no appositional osteoblast activity and no maturation suggestive of a repair reaction. The process was considered an intermediate-grade osteosarcoma, and a CT scan performed at the same time (**E**) demonstrated multiple lung metastases.

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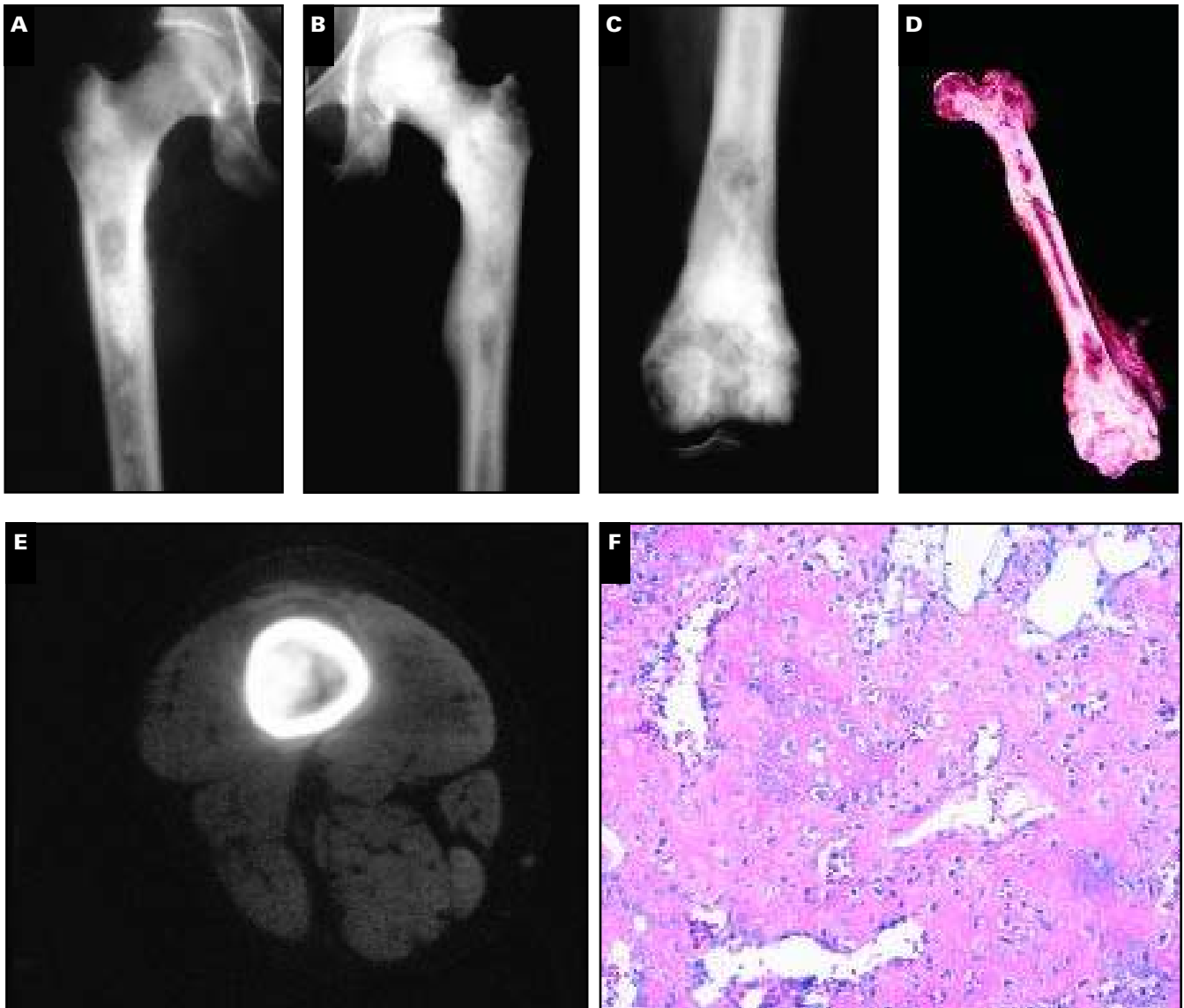


Image 24 Multifocal osteosarcoma. A 50-year-old woman had no history of radiation, Paget disease, or any other known familial condition that would predispose her to osteosarcoma. **B** and **C**, Pain in the left leg resulted in radiographs demonstrating multiple disparate osteosclerotic lesions of the femur. Because there were multiple lesions, she underwent a skeletal series that revealed multiple lesions of the medullary right femur shown in the anteroposterior radiograph (**A**) and the computed tomography scan (**D**). The right femur resection was performed because of intractable pain; there are at least 4 discrete lesions, 2 involving the cortex with remodeling changes. **E**, Midfemur scan demonstrating cloudy radiodensity of osteosarcoma matrix within the medullary cavity. **F**, The histologic features were those of a conventional osteosarcoma (H&E, $\times 250$). The diagnosis was presumed to be metachronous multifocal osteosarcoma. The patient was alive without lung metastases 4 years after the resection.

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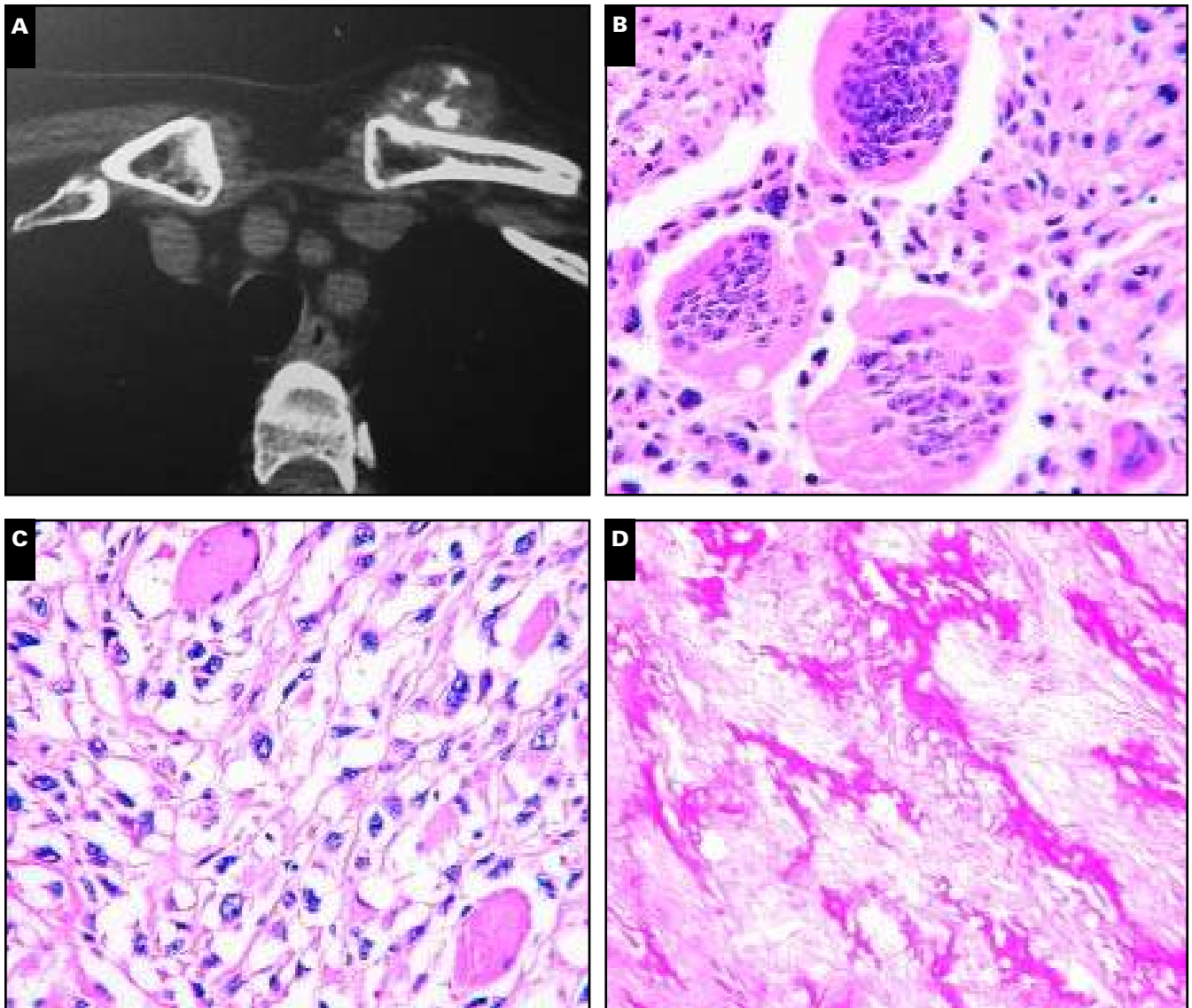


Image 25 Extraskelatal osteosarcoma. The patient had a 4-cm mass anterior to the left clavicle. The lesion was thought to be posttraumatic heterotopic ossification; however, the biopsy demonstrated pleomorphic cells producing the bone seen in the computed tomography scan (**A**). **B**, Pleomorphic mononuclear stroma with several osteoclast-like giant cells (H&E, $\times 250$). **C**, Infiltration of striated muscle by pleomorphic tumor cells producing osteoid (most apparent in the lower left) (H&E, $\times 400$). **D**, After chemotherapy, the resected lesion demonstrated extensive necrosis of the cellular stroma and tumor cells (H&E, $\times 250$).

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