well-known tumor suppressors and oncogenes, including the following:

- *RB*, which you will recall is a critical negative regulator of the cell cycle. Patients with germline mutations in *RB* have a 1000-fold increased risk of osteosarcoma and *RB* mutations are present in up to 70% of sporadic osteosarcomas.
- *TP53*, a gene whose product functions as the guardian of genomic integrity by promoting DNA repair and apoptosis of irreversibly damaged cells (Chapter 7): Patients with Li-Fraumeni syndrome, who have germline *TP53* gene mutations, have greatly elevated incidence of this tumor, and abnormalities that interfere with p53 function are common in sporadic tumors.
- *INK4a* is inactivated in many osteosarcomas. You will recall that this gene encodes two tumor suppressors, p16 (a negative regulator of cyclin-dependent kinases) and p14 (which augments p53 function).
- *MDM2* and *CDK4*, which are cell cycle regulators that inhibit into p53 and RB function, respectively, are overexpressed in many low-grade osteosarcomas, often through chromosomal amplification of region 12q13-q15.

It is also noteworthy that osteosarcomas peak in incidence around the time of the adolescent growth spurt and occur most frequently in the region of the growth plate in bones with the fastest growth. The increased proliferation at these sites may predispose to mutations that drive osteosarcoma development.

MORPHOLOGY

Several subtypes of osteosarcoma are recognized and are grouped according to:

- Site of origin (intramedullary, intracortical, or surface)
- Histologic grade (low, high)
- Primary (underlying bone is unremarkable) or secondary to preexisting disorders (benign tumors, Paget disease, bone infarcts, previous radiation)
- Histologic features (osteoblastic, chondroblastic, fibroblastic, telangiectatic, small cell, and giant cell)

The most common subtype arises in the metaphysis of long bones and is primary, intramedullary, osteoblastic, and high grade.

Osteosarcomas are bulky tumors that are gritty, gray-white, and often contain areas of hemorrhage and cystic degeneration (Fig. 26-24). The tumors frequently destroy the surrounding cortices and produce soft tissue masses. They spread extensively in the medullary canal, infiltrating and replacing hematopoietic marrow. Infrequently, they penetrate the epiphyseal plate or enter the joint. When joint invasion occurs, the tumor grows into it along tendoligamentous structures or through the attachment site of the joint capsule.

The tumor cells vary in size and shape and frequently have large hyperchromatic nuclei. Bizarre tumor giant cells are common, as are mitoses, some of them abnormal (e.g. tripolar). Vascular invasion is usually conspicuous, and some tumors also exhibit extensive necrosis. **The formation of bone by the tumor cells is diagnostic** (Fig. 26-25). The neoplastic bone usually has a fine, lace-like architecture but also may be deposited in broad sheets or as primitive trabeculae. In addition to bone, tumor cells may produce cartilage or fibrous tissue, but these are not required for diagnosis. When malignant cartilage is abundant, the tumor is called **chondroblastic osteosarcoma**.

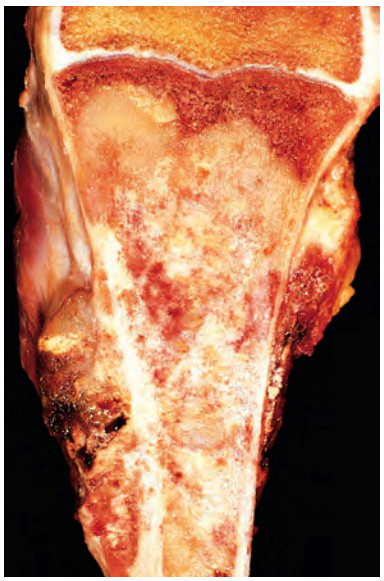

Figure 26-24 Osteosarcoma of the proximal tibia. The tan-white tumor fills most of the medullary cavity of the metaphysis and proximal diaphysis. It has infiltrated through the cortex, lifted the periosteum, and formed soft tissue masses on both sides of the bone.

Clinical Course. Osteosarcoma is treated with a multimodality approach that includes neoadjuvant chemotherapy, which is given under the assumption that all patients have occult metastases at the time of diagnosis, followed by surgery. The prognosis of osteosarcoma has improved substantially since the advent of chemotherapy, with 5-year survival rates reaching 60% to 70% in patients without overt metastases at initial diagnosis. These aggressive neoplasms spread hematogenously to the lungs. At the time of diagnosis, approximately 10% to 20% of affected individuals have demonstrable pulmonary metastases; of

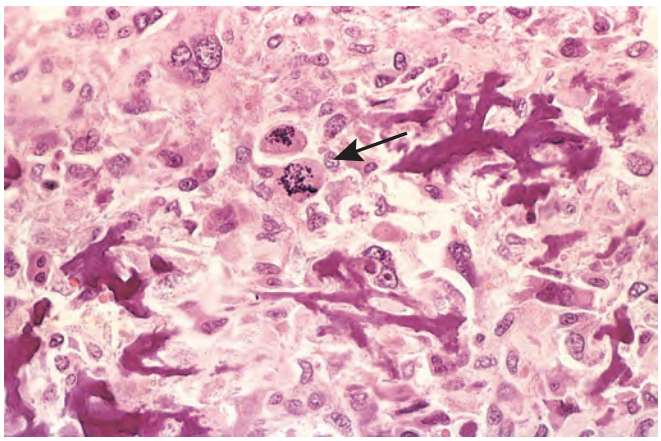

Figure 26-25 Fine, lacelike pattern of neoplastic bone produced by anaplastic malignant tumor cells in an osteosarcoma. Note the abnormal mitotic figures (arrow).