chondrosarcomas rarely metastasize, whereas 70% of grade 3 tumors spread hematogenously, especially to the lungs. The treatment of conventional chondrosarcoma is wide surgical excision. The mesenchymal and dedifferentiated tumors are also excised and additionally treated with chemotherapy because of their more aggressive clinical course.

Tumors of Unknown Origin

Ewing Sarcoma Family Tumors

Ewing sarcoma is a malignant bone tumor characterized by primitive round cells without obvious differentiation. Recently, Ewing sarcoma and **primitive neuroectodermal tumor** (PNET) have been unified into a single category: the **Ewing sarcoma family tumors** (ESFT) based on shared clinical, morphologic, biochemical and molecular features (discussed later). Although PNET demonstrates more neuroectodermal differentiation than Ewing sarcoma, the distinction is not clinically significant.

Ewing sarcoma family tumors account for approximately 6% to 10% of primary malignant bone tumors and follow osteosarcoma as the second most common group of bone sarcomas in children. Of all bone sarcomas, ESFT have the youngest average age at presentation, since approximately 80% are younger than 20 years. Boys are affected slightly more frequently than girls, and there is a striking predilection for whites; blacks and Asians are rarely afflicted. ESFT usually arise in the diaphysis of long tubular bones, especially the femur and the flat bones of the pelvis. They present as painful enlarging masses, and the affected site is frequently tender, warm, and swollen. Some affected individuals have systemic findings that mimic infection, including fever, elevated sedimentation rate, anemia, and leukocytosis. Plain radiographs show a destructive lytic tumor with permeative margins that extends into the surrounding soft tissues. The characteristic periosteal reaction produces layers of reactive bone deposited in an *onion-skin* fashion.

Pathogenesis. Most ESFT contain a (11;22) (q24;q12) translocation generating in-frame fusion of the *EWS* gene on chromosome 22 to the *FLI1* gene. Variant translocations fuse *EWS* to other members of the ETS transcription factor family. The exact fusion sites vary between tumors, leading to different downstream effects. How EWS fusion proteins contribute to transformation remains unsettled; effects on transcription, RNA splicing, and the cell cycle machinery have all been proposed. Similarly, the cell of origin still remains to be identified; the leading candidates are mesenchymal stem cells and primitive neurectodermal cells.

MORPHOLOGY

Arising in the medullary cavity, Ewing sarcoma usually invades the cortex, periosteum, and soft tissue. The tumor is soft, tan-white, and frequently contains areas of hemorrhage and necrosis. It is composed of sheets of uniform small, round cells that are slightly larger and more cohesive than lymphocytes (Fig. 26-31). They have scant cytoplasm, which may appear clear because it is rich in glycogen. The presence of Homer-Wright rosettes (round groupings of cells with a central fibrillary core) indicate a greater degree of neuroectodermal differentiation.

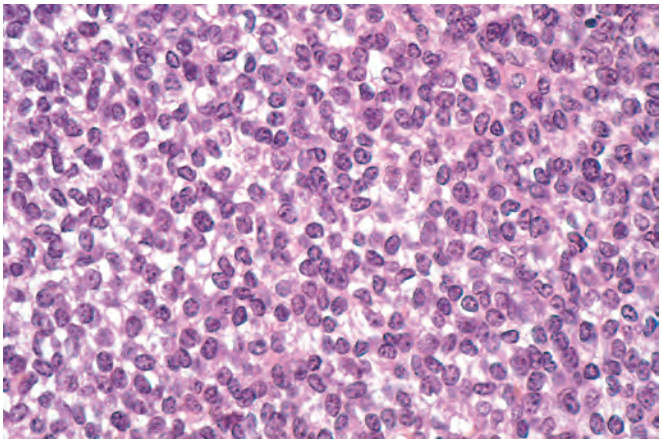

Figure 26-31 Ewing sarcoma composed of sheets of small round cells with small amounts of clear cytoplasm.

Although the tumor contains fibrous septae, there is generally little stroma. Geographic necrosis may be prominent, and there are relatively few mitotic figures in relation to the dense cellularity of the tumor.

Clinical Course. ESFT are aggressive malignancies treated with neoadjuvant chemotherapy followed by surgical excision with or without irradiation. The advent of effective chemotherapy has achieved 5-year survival of 75% and long-term cure in 50%. The amount of chemotherapy-induced necrosis is an important prognostic finding.

Giant Cell Tumor

Giant cell tumor is so named because the histology is dominated by multinucleated osteoclast-type giant cells, giving rise to the synonym **osteoclastoma**. It is a relatively uncommon benign, but locally aggressive, neoplasm. It usually arises in individuals in their 20s to 40s.

Pathogenesis. Current evidence suggests that the neoplastic cells of giant cell tumor are primitive osteoblast precursors but they represent only a minority of the tumor cells. The bulk of the tumor consists of non-neoplastic osteoclasts and their precursors. The neoplastic cells express high levels of RANKL, which promotes the proliferation of osteoclast precursors and their differentiation into mature osteoclasts via RANK expressed by these cells. However, the feedback between osteoblasts and osteoclasts that normally regulates this process during bone remodeling is absent. What results is a localized but highly destructive resorption of bone matrix by reactive osteoclasts.

Giant cell tumors arise in the epiphysis but may extend into the metaphysis. The majority arise around the knee (distal femur and proximal tibia), but virtually any bone can be involved. The typical location of these tumors near joints frequently causes arthritis-like symptoms. Occasionally, they present with pathologic fractures. Most are solitary; however, multicentric tumors do occur, especially in the distal extremities.

MORPHOLOGY

Giant cell tumors often destroy the overlying cortex, producing a bulging soft tissue mass delineated by a thin shell of reactive