

Figure 7-8 Anaplastic tumor showing cellular and nuclear variation in size and shape. The prominent cell in the center field has an abnormal tripolar spindle.

differentiation” of mature normal cells or instead from incomplete differentiation of less mature cells is an important fundamental issue that is discussed later.

Lack of differentiation, or anaplasia, is often associated with many other morphologic changes.

- **Pleomorphism.** Cancer cells often display pleomorphism—variation in size and shape (Fig. 7-9). Thus, cells within the same tumor are not uniform, but range from small cells with an undifferentiated appearance, to *tumor giant cells* many times larger than their neighbors. Some tumor giant cells possess only a single huge polymorphic nucleus, while others may have two or more large, hyperchromatic nuclei (Fig. 7-9). These giant cells are not to be confused with inflammatory Langhans or foreign body giant cells, which are derived from macrophages and contain many small, normal-appearing nuclei.
- **Abnormal nuclear morphology.** Characteristically, the nuclei are disproportionately large for the cell, with

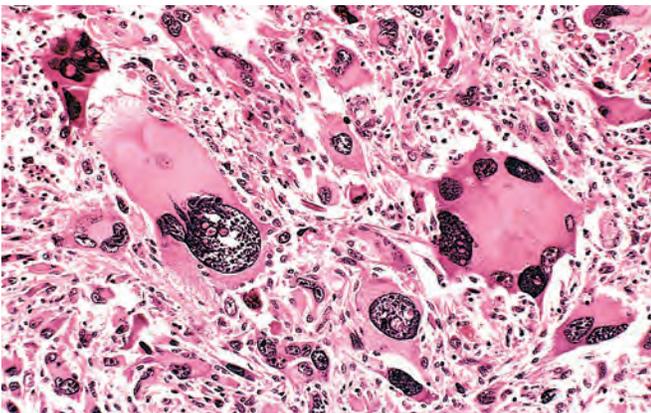


Figure 7-9 Pleomorphic tumor of the skeletal muscle (rhabdomyosarcoma). Note the marked cellular and nuclear pleomorphism, hyperchromatic nuclei, and tumor giant cells. (Courtesy Dr. Trace Worrell, University of Texas Southwestern Medical School, Dallas, Texas.)

a nuclear-to-cytoplasm ratio that may approach 1:1 instead of the normal 1:4 or 1:6. The nuclear shape is variable and often irregular, and the chromatin is often coarsely clumped and distributed along the nuclear membrane, or more darkly stained than normal (*hyperchromatic*). Abnormally large nucleoli are also commonly seen.

- **Mitoses.** Unlike in benign tumors and some well-differentiated malignant neoplasms, in undifferentiated tumors, many cells are in mitosis, reflecting the high proliferative activity of the parenchymal cells. The presence of mitoses, however, does not necessarily indicate that a tumor is malignant or that the tissue is neoplastic. Mitoses are indicative of rapid cell growth. Hence, cells in mitosis are often seen in normal tissues exhibiting rapid turnover, such as the epithelial lining of the gut and nonneoplastic proliferations such as hyperplasias. More important as a morphologic feature of malignancy are *atypical, bizarre mitotic figures*, sometimes with tripolar, quadripolar, or multipolar spindles (Fig. 7-8).
- **Loss of polarity.** In addition to the cytologic abnormalities, the orientation of anaplastic cells is markedly disturbed. Sheets or large masses of tumor cells grow in an anarchic, disorganized fashion.
- **Other changes.** Growing tumor cells obviously require a blood supply, but often the vascular stroma is insufficient, and as a result in many rapidly growing malignant tumors develop large central areas of ischemic necrosis.

As one might surmise, the better the differentiation of the transformed cell, the more completely it retains the functional capabilities of its normal counterpart. Thus, benign neoplasms and well-differentiated carcinomas of endocrine glands frequently secrete hormones characteristic of their origin. Increased levels of these hormones in the blood are used clinically to detect and follow such tumors. Well-differentiated squamous cell carcinomas of the epidermis synthesize keratin, and well-differentiated hepatocellular carcinomas elaborate bile. Highly anaplastic undifferentiated cells, whatever their tissue of origin, lose their resemblance to the normal cells from which they have arisen. In some instances, new and unanticipated functions emerge. Thus, some tumors express fetal proteins that are not produced by comparable cells in the adult, while others express proteins that are normally only found in other types of adult cells. For example, bronchogenic carcinomas may produce corticotropin, parathyroid-like hormone, insulin, glucagon, and other hormones, giving rise to paraneoplastic syndromes (described later). Despite such exceptions, rapidly growing anaplastic tumors are less likely to have specialized functional activity. The cells in benign tumors are almost always well differentiated and resemble their normal cells of origin; the cells in cancer are more or less differentiated, but some derangement of differentiation is always present.

Metaplasia and Dysplasia. *Metaplasia* is defined as the replacement of one type of cell with another type (Chapter 2). Metaplasia is nearly always found in association with tissue damage, repair, and regeneration. Often the replacing cell type is better suited to some alteration in