Immunohistochemistry. The availability of specific antibodies has greatly facilitated the identification of cell products or surface markers. Examples of the utility of immunohistochemistry in the diagnosis or management of malignant neoplasms follow.

- **Categorization of undifferentiated malignant tumors.** In many cases malignant tumors of diverse origin resemble each other because of limited differentiation. These tumors are often quite difficult to distinguish on the basis of routine hematoxylin and eosin (H&E)-stained tissue sections. For example, certain anaplastic carcinomas, lymphomas, melanomas, and sarcomas may look quite similar, but they must be accurately identified because their treatment and prognosis are different. Antibodies specific to intermediate filaments have proved to be of particular value in such cases, because solid tumor cells often contain intermediate filaments characteristic of their cell of origin. For example, the presence of cytokeratins, detected by immunohistochemistry, points to an epithelial origin (carcinoma) (Fig. 7-49), whereas desmin is specific for neoplasms of muscle cell origin. Other useful immunohistochemical markers include lineage-specific membrane proteins (e.g., CD20, a marker of B-cell tumors) and transcription factors.
- **Determination of site of origin of metastatic tumors.** Many cancer patients present with metastases. In some the primary site is obvious or readily detected on the basis of clinical or radiologic features. In cases in which the origin of the tumor is obscure, immunohistochemical detection of tissue-specific or organ-specific antigens in a biopsy specimen of the metastatic deposit can lead to the identification of the tumor source. For example, prostate-specific antigen (PSA) and thyroglobulin are markers of carcinomas of the prostate and thyroid, respectively.
- **Detection of molecules that have prognostic or therapeutic significance.** Immunohistochemical detection of hormone (estrogen/progesterone) receptors in breast cancer cells is of prognostic and therapeutic value because these cancers are susceptible to antiestrogen therapy (Chapter 23). In general, receptor-positive breast cancers have a better prognosis than receptor negative tumors. Protein products of oncogenes such as *ERBB2* in breast cancers can also be detected by immunostaining. Breast cancers with strong immunohistochemical staining for the protein product of the *ERBB2* gene product, HER2, generally have a poor prognosis, but are amenable to treatment with antibodies that block the activity of the HER2 receptor. Because high-level expression of HER2 is caused by amplification of *ERBB2*, fluorescent in situ hybridization (FISH) to confirm *ERBB2* gene amplification is sometimes used as an adjunct to immunohistochemical studies. Similarly, immunohistochemical stains for ALK protein can be used to identify lung cancers and lymphomas expressing constitutively active ALK fusion proteins.

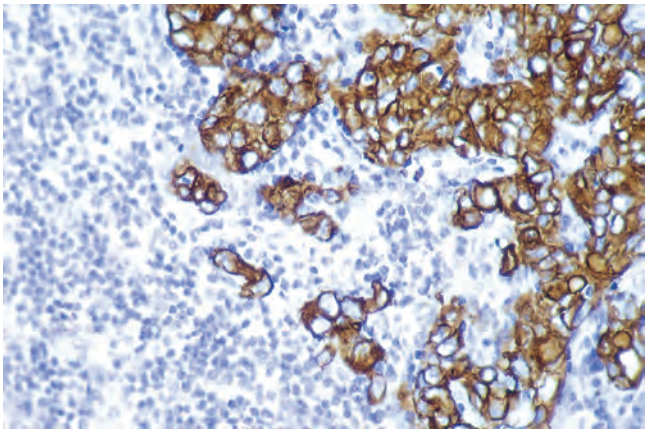

Figure 7-49 Anticytokeratin immunoperoxidase stain of a tumor of epithelial origin (carcinoma). (Courtesy Dr. Melissa Upton, University of Washington, Seattle, Wash.)

Flow Cytometry. Flow cytometry can rapidly and quantitatively measure several individual cell characteristics, but is mainly used to identify cellular antigens expressed by "liquid" tumors, those that arise from blood-forming tissues. These include B- and T-cell lymphomas and leukemias, as well as myeloid neoplasms. An advantage of flow cytometry over immunohistochemistry is that multiple antigens can be assessed simultaneously on individual cells using combinations of specific antibodies linked to different fluorescent dyes. Monoclonal antibodies directed against various lymphohematopoietic cells are listed in Chapter 13.

Circulating Tumor Cells. Instrumentation that permits detection, quantification, and characterization of rare solid tumors cells (e.g., carcinoma, melanoma) circulating in the blood is being explored as a diagnostic modality. Some of the latest devices rely on three-dimensional flow cells coated with antibodies specific for tumor cells of interest (e.g., carcinoma cells) that efficiently capture rare tumor cells present in the blood. Such methods currently fall in the realm of clinical research, but have the potential to permit earlier diagnosis, to gauge the risk of metastasis, and to provide a minimally invasive means of assessing the response of tumor cells to therapy.

Molecular and Cytogenetic Diagnostics. Several molecular or cytogenetic techniques—some established, others emerging—have been used for diagnosis and, in some cases, for predicting behavior of tumors.

- **Diagnosis of malignant neoplasms.** Although molecular methods are not the primary modality of cancer diagnosis, they are of considerable value in selected cases. T and B cell tumors are derived from single cells with unique antigen receptor gene rearrangements, whereas reactive lymphoid proliferations contain many different lymphocyte clones, each with a different set of rearrangements antigen receptor genes. For this reason, PCR-based evaluation of rearranged T-cell receptor or immunoglobulin genes allows distinction between monoclonal (neoplastic) and polyclonal (reactive) proliferations. Many hematopoietic neoplasms (leukemias and lymphomas) are associated with specific translocations that activate oncogenes. Detection of such translocations, usually by routine cytogenetic analysis or by FISH (Chapter 5), is often extremely helpful in diagnosis. Diagnosis of sarcomas (Chapter 26) with