Neoplasm

Lecture 2

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Learning objectives

- ✓ The students must understanding Characteristics of Benign and Malignant Neoplasms.
- ✓ Routes of metastesis of malignant tumors .
- ✓ Difference between benign and malignant tumors.

Characteristics of Benign and Malignant Neoplasms

DIFFERENTIATION AND ANAPLASIA

Differentiation refers to the extent to which neoplastic parenchymal cells resemble the corresponding normal parenchymal cells, both morphologically and functionally. In general, **benign tumors** are well differentiated. In well-differentiated benign tumors, mitoses are extremely scant in number and are of normal configuration.

Malignant neoplasms are characterized by a wide range of parenchymal cell differentiation, from well differentiated to completely undifferentiated.

the morphologic diagnosis of malignancy in well-differentiated tumors may sometimes be quite difficult. In between the two extremes lie tumors that are loosely referred to as moderately differentiated.

Neoplasms that are composed of poorly differentiated cells are said to be **anaplastic**. Lack of differentiation, or anaplasia, is considered **a hallmark of malignancy**. In well-differentiated tumors, daughter cells derived from these "cancer stem cells" retain the capacity for differentiation, whereas in poorly differentiated tumors that capacity is lost.

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

- ❖ **Pleomorphism**. Both the cells and the nuclei characteristically display pleomorphism—variation in size and shape . Thus, cells within the same tumor are not uniform,
- ❖ **Abnormal nuclear morphology**. Characteristically the nuclei contain abundant chromatin and are dark staining (hyperchromatic). The nuclei are disproportionately large for the cell, and the nuclear-to-cytoplasm ratio 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. Large nucleoli are usually present in these nuclei.
- ❖ **Mitoses.** As compared with benign tumors and some well-differentiated malignant neoplasms, undifferentiated tumors usually possess large numbers of mitoses, reflecting the higher 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. Many normal tissues exhibiting rapid turnover, such as bone marrow, have numerous mitoses, and non-neoplastic proliferations such as hyperplasias contain many cells in mitosis. More important as a

morphologic feature of malignancy are atypical, bizarre mitotic figures, sometimes producing tripolar, quadripolar, or multipolar spindles.

- **Loss of polarity**. In addition to the cytologic abnormalities, the orientation of anaplastic cells is markedly disturbed (i.e., they lose normal polarity). Sheets or large masses of tumor cells grow in an anarchic, disorganized fashion.

. Another feature of anaplasia is the formation of tumor giant cells, some possessing only a single huge polymorphic nucleus and others having two or more large, hyperchromatic nuclei. 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. Although growing tumor cells obviously require a blood supply, often the vascular stroma is scant, and in many anaplastic tumors, large central areas undergo ischemic necrosis.

- . **Metaplasia** is defined as the replacement of one type of cell with another type. Metaplasia is nearly always found in association with tissue damage, repair, and regeneration. Often the replacing cell type is more suited to a change in environment. For example, gastroesophageal reflux damages the squamous epithelium of the esophagus, leading to its replacement by glandular (gastric or intestinal) epithelium, more suited to the acidic environment.
- **Dysplasia** is a term that literally means disordered growth. Dysplasia often occurs in metaplastic epithelium, but not all metaplastic epithelium is also dysplastic. Dysplasia is encountered principally in epithelia, and it is characterized by a constellation of changes that include a loss in the uniformity of the individual cells as well as a loss in their architectural orientation. Dysplastic cells exhibit considerable pleomorphism and often contain large hyperchromatic nuclei with a high nuclear to-cytoplasmic ratio. The architecture of the tissue may be disorderly.

  Mitotic figures are more abundant than usual, although almost invariably they have a normal configuration. Frequently, the mitoses appear in abnormal locations within the epithelium. For example, in dysplastic stratified squamous epithelium, mitoses are not confined to the basal layers but instead may appear at all levels, including surface cells.

  When dysplastic changes are marked and involve the entire thickness of the epithelium but the lesion remains confined by the basement membrane, it is considered a preinvasive neoplasm and is referred to as carcinoma in situ. Once the tumor cells breach the basement membrane, the tumor is said to be invasive. Dysplastic changes are often found adjacent to foci of invasive carcinoma, and in some situations, such as in long-term cigarette smokers and persons with Barrett esophagus, severe epithelial dysplasia frequently antedates the appearance of cancer.
  - ✓ However, dysplasia does not necessarily progress to cancer.

  Mild to moderate changes that do not involve the entire thickness of epithelium may be reversible, and with removal of the inciting causes the epithelium may revert to normal.
  - ✓ **Even carcinoma in situ may take years to become invasive.**

RATES OF GROWTH

The rate of growth of a tumor is determined by three main factors:

- **the doubling time of tumor cells.**
- **the fraction of tumor cells that are in the replicative pool.**
- **the rate at which cells are shed or die.**

The proportion of cells within the tumor population that are in the proliferative pool is referred to as the growth fraction. during the early, submicroscopic phase of tumor growth, the vast majority of transformed cells are in the proliferative pool . As tumors continue to grow, cells leave the proliferative pool in ever-increasing numbers as a result of shedding, lack of nutrients, necrosis, apoptosis, differentiation, and reversion to the non proliferative phase of the cell cycle (G0). Thus, by the time a tumor is clinically detectable, most cells are not in the replicative pool. Even in some rapidly growing tumors, the growth fraction is only about 20% or less.

Ultimately the progressive growth of tumors and the rate at which they grow are determined by an excess of cell production over cell loss. In some tumors, especially those with a relatively high growth fraction, the imbalance is large, resulting in more rapid growth than in those in which cell production exceeds cell loss by only a small margin. Some leukemias and lymphomas and certain lung cancers (i.e., small-cell carcinoma) have a relatively high growth fraction, and their clinical course is rapid

By comparison, many common tumors, such as cancers of the colon and breast, have low growth fractions, and cell production exceeds cell loss by only about 10%; they tend to grow at a much slower pace.

Several important conceptual and practical lessons can be learned from studies of tumor cell kinetics:

Fast-growing tumors may have a high cell turnover, implying that rates of both proliferation and apoptosis are high. Obviously if the tumor is to grow, the rate of proliferation must exceed that of cell death.

The growth fraction of tumor cells has a profound effect on their susceptibility to cancer chemotherapy. Because most anticancer agents act on cells that are in cycle, it is not difficult to imagine that a tumor that contains 5% of all cells in the replicative pool will be slow growing but relatively refractory to treatment with drugs that kill dividing cells. One strategy used in the treatment of tumors with low growth fraction (e.g., cancer of colon and breast) is first to shift tumor cells from G0 into the cell cycle. This can be accomplished by debulking the tumor with surgery or radiation. The surviving tumor cells tend to enter the cell cycle and thus become susceptible to drug therapy. Such considerations form the basis of combined-modality treatment. Some aggressive tumors (such as certain lymphomas and leukemias) that contain a large pool of dividing cells literally melt away with chemotherapy and may even be cured.

In general, the growth rate of tumors correlates with their level of differentiation, and thus most malignant tumors grow more rapidly than do benign lesions. There are, however, many exceptions to such an oversimplification. Some benign tumors have a higher growth rate than malignant tumors. Moreover, the rate of growth of benign as well as malignant neoplasms may not be constant over time. Factors such as hormonal stimulation, adequacy of blood supply, and unknown influences may affect their growth.

LOCAL INVASION

Nearly all benign tumors grow as cohesive expansile masses that remain localized to their site of origin and do not have the capacity to infiltrate, invade, or metastasize to distant sites, as do malignant tumors. Because they grow and expand slowly, they usually develop a rim of compressed connective tissue, sometimes called a fibrous capsule, which separates them from the host tissue. This capsule is derived largely from the extracellular matrix of the native tissue due to atrophy of normal parenchymal cells under the pressure of an expanding tumor. Such encapsulation does not prevent tumor growth, but it keeps the benign neoplasm as a discrete, readily palpable, and easily movable mass that can be surgically enucleated.

The growth of cancers is accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue. In general, malignant tumors are poorly demarcated from the surrounding normal tissue, and a well-defined cleavage plane is lacking. Slowly expanding malignant tumors, however, may develop an apparently enclosing fibrous capsule and may push along a broad front into adjacent normal structures. Histologic examination of such pseudo-encapsulated masses almost always shows rows of cells penetrating the margin and infiltrating the adjacent structures, a crablike pattern of growth that constitutes the popular image of cancer.

In situ epithelial cancers display the cytologic features of malignancy without invasion of the basement membrane. with time, most penetrate the basement membrane and invade the subepithelial stroma.

METASTASIS

Metastases are tumor implants discontinuous with the primary tumor. Metastasis unequivocally marks a tumor as malignant because benign neoplasms do not metastasize. The invasiveness of cancers permits them to penetrate into blood vessels, lymphatics, and body cavities, providing the opportunity for spread. With few exceptions, all malignant tumors can metastasize. The major exceptions are most malignant neoplasms of the glial cells in the central nervous system, called gliomas, and basal cell carcinomas of the skin. Both are locally invasive forms of cancer, but they rarely metastasize. It is evident then that the properties of invasion and metastasis are separable.

In general, the more aggressive, the more rapidly growing, and the larger the primary neoplasm, the greater the likelihood that it will metastasize or already has metastasized. There are innumerable exceptions, however. Small, well-differentiated, slowly growing lesions sometimes metastasize widely; conversely, some rapidly growing, large lesions remain localized for years. Many factors relating to both invader and host are involved.

Approximately 30% of newly diagnosed individuals with solid tumors present with metastases. Metastatic spread strongly reduces the possibility of cure.

Pathways of Spread

Dissemination of cancers may occur through one of three pathways:

(**1) direct seeding of body cavities or surfaces**,

(**2) lymphatic spread**

(3) hematogenous spread.

Seeding of Body Cavities and Surfaces.

Seeding of body cavities and surfaces may occur whenever a malignant neoplasm penetrates into a natural “open field.” Most often involved is the peritoneal cavity , but any other cavity—pleural, pericardial, subarachnoid, and joint space—may be affected. Such seeding is particularly characteristic of carcinomas arising in the ovaries, when, not infrequently, all peritoneal surfaces become coated with a heavy layer of cancerous glaze.. Sometimes mucus-secreting appendiceal carcinomas fill the peritoneal cavity with a gelatinous neoplastic mass referred to as pseudomyxoma peritonei.

Lymphatic Spread.

Transport through lymphatics is the most common pathway for the initial dissemination of carcinomas, and sarcomas may also use this route.

In breast cancer, determining the involvement of axillary lymph nodes is very important for assessing the future course of the disease and for selecting suitable therapeutic strategies. To avoid the considerable surgical morbidity associated with a full axillary lymph node dissection, biopsy of sentinel nodes is often used to assess the presence or absence of metastatic lesions in the lymph nodes. A sentinel lymph node is defined as “the first node in a regional lymphatic basin that receives lymph flow from the primary tumor.”Sentinel node mapping can be done by injection of radiolabeled tracers and blue dyes, and the use of frozen section upon the sentinel lymph node at the time of surgery can guide the surgeon to the appropriate therapy. Sentinel node biopsy has also been used for detecting the spread of melanomas, colon cancers, and other tumors.

Drainage of tumor cell debris or tumor antigens, or both, also induces reactive changes within nodes. Thus, enlargement of nodes may be caused by

(1) the spread and growth of cancer cells or

(2) reactive hyperplasia .

Therefore, nodal enlargement in proximity to a cancer, while it must arouse suspicion, does not necessarily mean dissemination of the primary

Hematogenous Spread.

Hematogenous spread is typical of sarcomas but is also seen with carcinomas. Arteries, with their thicker walls, are less readily penetrated than are veins..

In such vascular spread, several factors influence the patterns of distribution of the metastases. With venous invasion the blood-borne cells follow the venous flow draining the site of the neoplasm, and the tumor cells often come to rest in the first capillary bed they encounter. Understandably the liver and lungs are most frequently involved in such hematogenous dissemination .because all portal area drainage flows to the liver and all caval blood flows to the lungs.

Cancers arising in close proximity to the vertebral column often embolize through the paravertebral plexus, and this pathway is involved in the frequent vertebral metastases of carcinomas of the thyroid and prostate.

Certain cancers have a propensity for invasion of veins. Renal cell carcinoma often invades the branches of the renal vein and then the renal vein itself to grow in a snakelike fashion up the inferior vena cava, sometimes reaching the right side of the heart. Hepatocellular carcinomas often penetrate portal and hepatic radicles to grow within them into the main venous channels. Many observations suggest that mere anatomic localization of the neoplasm and natural pathways of venous drainage do not wholly explain the systemic distributions of metastases. For example, breast carcinoma preferentially spreads to bone, bronchogenic carcinomas tend to involve the adrenals and the brain, and neuroblastomas spread to the liver and bones. Conversely, skeletal muscles and the spleen, despite the large percentage of blood flow they receive and the enormous vascular beds present, are rarely the site of secondary deposits.