Tikrit University
College of Veterinary Medicine

NENPLESIA (CANCER)

Subject name: Pathology

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Lecturer name: Assist. Prof. Hassan Hadi Khorsheed

Academic Email:dr_patho80@tu.edu.iq

SCAN ME
Lecturers link

Neoplasia: is a very important topic in pathology because neoplasms are both common and serious diseases. A neoplasm literally means a new growth, and this term is used interchangeably with a tumor (swelling) because most tumors present as a mass. Oncology (Greek oncos = tumor) is the study of neoplasms.

A **neoplasm is defined as "an abnormal tissue proliferation**, which exceeds that of adjacent normal tissue. This proliferation continues even after removing the causative agent". The persistence of proliferation is the result of heritable genetic changes in the constituent cells; these provide the neoplastic cells with a growth advantage. In other words the neoplasm becomes autonomous i.e. independent of physiologic growth stimuli and inhibitors. The entire population of cells within any tumor originates from a single cell referred to as stem cell or tumor initiating cell (T-IC). This cell has sustained the initial genetic changes (mutations). A given tumor, therefore, consists of T-IC (the ancestor) and its progeny forming a clone of cells and hence tumors are said to be clonal.

Characteristic of cancer cell:

1- Proliferation without control

2- The tumor cell not resemble the original cell of body (the original tissue cell)

3- Not orderly structure

4- Not useful function (it harmful)

5- The cause anon (under stood)

6- Tolerate the pressure and squeeze themselves between cell

7- Compete for O2 and nutrition

8- Can destroy any adjacent thing

9- Can infiltrate during the BVs

10- Increase ratio of nucleus to cytoplasm

Cause of tumor

1- **Virus**. Female malignant lymphoma, female fibro sarcoma cause by c-type RNA virus.

2- **Hormones** ex. Massive doses of estrogen lead to mammary gland adenocarcenoma

3- **Parasite** ex. schistoma

4- **Chemical carcinogen** ex. Petrol ,hydrocarbon ,benzene ,aromatic amine

5- **Radiation** ex. UV, x-ray, uranium

6- Trauma

7- **Transplantation** ex. Transmissible venereal tumor cause by sex organ

8- **Congenital** ex. During gestation mysothelioma, embryo nephroma

9- Inheriditary, age, sex.

Metastasis (spread of tumor)

1- **Invasion** : tumor cell have ability to invade the surrounding tissue and form new mass of tissue ,this invasion called direct expansion

2- **Infiltration** : by BVs or lymphatic metastasis or spread through these BVs or lymphatic and reach to other organ, the tumor need O2 so spread from lymphatic to by which the tumor cell reach tothe lung

3- **Implantation** : by which the tumor cell reach or spread into adjacent cavity and implant.

Criteria for distinguish between benign and malignant tumor

	Benign tumor	Malignant tumor
Growth rate	Slow	Rapid
Growth	Limited	Unlimited
Made of growth	Expansion	Expansion and infiltration
Recurrence after removal	Rare	Frequent
Metastasis	None	Frequent

Tissue stricture	Nearly normal	Abnormal
stroma	Abundant	scanty
Mitotic figure	Few	Common
Vessels invasion	Rare	Frequent
Tissue distraction	Minimal	Frequent
Cell size	Uniform	Poly morphic
Nuclear chromatin	Normal amount	Hyper chromatic
Nucleoli	Normal	Many oval large

Important feature of cancer cell by which metastasis

1- Plasma membrane change: In which reduced the adhesiveness to one another, this due to decrease formation of spot desmosomes which are important point of adhesion between normal epithelial cell so decrease of adhesiveness may be important factor in the infiltration of surrounding tissue by the cells located at the periphery of a cancer and their penetration of BVs and lymphatic walls also some cancer impaired formation of gap junction.

2- Cancer cell increase negative surface charge: this negative surface charge in normal cell is attributable to the sialic acid residues of their surface glycol protein, cancer cell obscure some of sialic acid residues. This may have important effect on control of mitosis.

3- Anaerobic glycolysis: cancer cell rely more on anaerobic than aerobic glycolysis in normal cell as a some of energy this feature indicate the strong activity of cancer cell.

4- C.AMP level : decrease in cancer cell the level of C.AMP decrease in normal cell only during mitosis.

5- Lysosomal enzyme: collagenase, proteinase and lipase is a feature of cancer cell and in normal cell only during mitosis this enzyme responsible for damage of surrounding tissue for invasiveness of cancer cells.

NOMENCLATURE OF NEOPLASMS

In addition to the neoplastic (parenchymal) cells, all tumors have a second component called the stroma that is made up principally of connective tissue and blood vessels. The stroma is vital to the neoplastic cells; it provides them not only with adequate blood supply but also mechanical support (scaffolding). Additionally, there seems to be a cross talk between the stroma and the neoplastic cells that directly influence the growth of the neoplasm for e.g. neoplastic cells release substances that stimulate endothelial cells to form new vessels within the tumor (neovascularization) & endothelial cells release growth factors that encourage tumor cell growth. The relative proportions of the two components vary in different tumors. This variable contribution of the two determines the consistency of any given tumor. In some tumors, the stroma is scant i.e. the tumors consist predominantly of neoplastic cells; these neoplasms are soft and fleshy in consistency. Conversely, the neoplastic cells may stimulate the formation of abundant fibrotic stroma, referred to as desmoplasia. This desmoplasia imparts a hard (scirrhous) or even a stony hard consistency to the tumor. An example of the latter is carcinoma of the breast, which has been likened to unripe pear. However, it should be realized that despite the fact that both components (neoplastic cells & stroma) are complementary in their significance to the wellbeing of the tumor, the nomenclature of tumors is based on their neoplastic cells.

❖ Benign Tumors

In general, benign tumors are named by attaching the suffix **oma** to the cell of origin. Benign mesenchymal tumors generally follow this rule. For

example, a benign tumor of fibroblasts is called **fibroma**, a cartilaginous tumor is **chondroma,** and a tumor of osteoblasts is **osteoma**. The nomenclature of benign epithelial tumors is more complex in that they are variously classified according to their **A. Cells of origin B. Microscopic** &/**or macroscopic** (naked eye) appearance **Adenoma** is the term applied to a benign epithelial neoplasm that forms microscopically recognizable glandular structures e.g. thyroid follicular adenoma.

A **papilloma** is a benign epithelial neoplasm producing microscopically or macroscopically visible finger-like (warty) projections from epithelial surfaces e.g. squamous cell papilloma of the skin & larynx & transitional cell papilloma of the urinary bladder. A **cystadenoma** is an adenoma that form large cystic space (or spaces), e.g. ovarian cyst adenoma. A **papillary cystadenoma** is similar to cyst adenoma but has in addition papillary (warty) projections that protrude into the cystic spaces, e.g. ovarian papillary cystadenoma. A **polyp** is a benign neoplasm that forms a macroscopically visible projection above a mucosal surface (e.g. gastric, colonic, and laryngeal polyps) or skin. Malignant tumors may present as bulging masses with nodular surface (simulating multiple fused polyps); these are usually referred to as **polypoid cancers.**

❖ **Malignant Tumor:**

Cancer is a term applied for any malignant tumor. The nomenclature of malignant tumors follows essentially the same rules used for benign neoplasms but with certain additions.

Sarcomas are malignant tumors that arise from or differentiating towards mesenchymal cells**.** Generally, sarcomas have scant connective tissue stroma; they are fleshy in consistency (Greek sar = fleshy). Examples include **fibrosarcoma** (fibroblasts), **liposarcoma** (lipocytes),
leiomyosarcoma (smooth muscle cells), and **rhabdomyosarcoma** (striated muscle cells).

Carcinomas are malignant neoplasm that either arise from or differentiate towards epithelial cells derived from any one of the three germ layers**.** Thus, a cancer arising in or differentiating towards epidermal epithelial cells (ectoderm) is a carcinoma and a cancer derived from or differentiates towards renal tubules (mesoderm) is also carcinoma (renal cell carcinoma). Similarly malignant tumors originating from or differentiating towards the

endodermally derived epithelial cells that line the gastrointestinal or respiratory tracts are similarly called carcinomas. Carcinomas may be further qualified according to their pattern of arrangements. A carcinoma with a microscopic glandular growth pattern is termed adenocarcinoma**,** and one producing recognizable squamous cells arising in any epithelium of the body (e.g. skin, esophagus or cervix uteri) is termed a squamous cell carcinoma**.** Additionally, it is a common practice to specify, when possible, the organ of origin (e.g., colonic adenocarcinoma or bronchial squamous cell carcinoma).
Undifferentiated (anaplastic) malignant tumor refers to a cancer composed of undifferentiated (anaplastic) cells, which have no enough microscopic criteria to indicate their site of origin or differentiation.

BIOLOGY OF TUMOR GROWTH

Malignant tumors differ from benign ones by four features that in fact reflect their natural history (expected behavior); these are

I. Malignant transformation of the target cells
II. Growth rate of the transformed cells
III. Local invasion
IV. Distant metastases

Malignant transformation

Malignant transformation of target cells is associated with certain microscopic features that are usually used to differentiate benign from malignant neoplasms. These features are collectively come under the heading of differentiation and anaplasia.

Differentiation signifies "the extent to which neoplastic cells resemble comparable normal cells". The degree of tumor differentiation is represented by a spectrum according to which neoplasms are divided in to

Very well differentiate
Well differentiated
Moderately differentiated
Poorly differentiated
Undifferentiated (Anaplastic)

Very well differentiated neoplasm is the one in which the neoplastic cells are almost identical morphologically to the native normal cells. This is generally encountered with benign neoplasms. For example, the neoplastic cells in a leiomyoma of the uterus resemble very closely the normal native

myometrial cells. This resemblance is to such a degree that it may be impossible to differentiate microscopically neoplastic cells of a leiomyoma from native normal myometrial cells. It is only the gathering of these cells into a tumor mass that discloses the neoplastic nature of the lesion. What is just said about leiomyomas is also applicable to lipomas e.g. of the skin where the neoplastic lipocytes cannot be differentiated from those of the normal subcutaneous adipose tissue**.** Malignant neoplasms are generally divided into four categories depending on their degree of differentiation, these are

1. **Well-differentiated neoplasms** i.e. composed of cells resembling closely comparable normal cells of the tissue of origin. Certain well-differentiated thyroid follicular carcinomas (adenocarcinomas), for example, may form almost normal-appearing follicles, and the cells of some squamous cell carcinomas contain cells that do not differ significantly from normal squamous epithelial cells. Thus, the microscopic diagnosis of malignancy in well differentiated neoplasms can be quite difficult.
2. **Poorly differentiated neoplasms,** in contrast, are composed of cells that barely resemble the normal cells of origin. However, some resemblance occurs focally i.e. in some parts of the tumor, thus allowing the tumor to be assigned to a particular cell of origin or differentiation.
3. **Moderately differentiated neoplasms** occupy a morphological position that lies between welldifferentiated & poorly-differentiated tumors.
4. **Undifferentiated (anaplastic) neoplasms:** anaplasia signifies total lack of differentiation, and thus anaplastic cells have primitive appearance (unspecialized morphology) that cannot be assigned to any of the normal mature cells.

Morphologic features of undifferentiated (anaplastic) malignant cells include

1. Pleomorphism, i.e. variations in the size and shape of the neoplastic cells and their nuclei. Inanaplastic cancers, some cancerous cells are many times larger than their neighboring extremely small cancerous cells.

2. Abnormal nuclear morphology: characteristically the nuclei display

a. **Hyperchromatism,** which refers to a deep bluish staining of nuclei; this feature is due to their abnormally high content of DNA. In the routine

hematoxyline & eosin stain, the abundant DNA extracts more hematoxyline, and so the malignant nuclei appear deep blue in color.

b. **High nuclear-cytoplasmic ratio (high N/C);** in malignant neoplasms, the nuclei are disproportionately large for the cell size, and thus the nucleus-to-cytoplasm ratio may approach1:1 instead of the normal 1:4 or 1:6.

c. **Variations in nuclear shape and abnormal chromatin** clumping and distribution: the nuclear shape is very variable, and the chromatin is coarsely clumped and distributed along the nuclear membrane. Normal nuclei are vesicular i.e. have fine, evenly distributed chromatin granules.

d. **Large prominent nucleoli are sometimes seen** within malignant nuclei.

3. Frequent mitoses including abnormal ones: undifferentiated malignant cells usually possess large number of mitoses, reflecting their high proliferative activity. The presence of mitoses, however does not necessarily indicate that a tumor is malignant or that the tissue is neoplastic. Many normal tissues exhibit rapid cell turnover & hence their constituent cells show frequent mitoses e.g. the normal bone marrow cells. The adaptive hyperplastic tissue response also shows frequent mitotic figures. More important as a morphologic feature of malignancy is the presence of atypical mitotic figures, e.g. tripolar, quadripolar, or multipolar mitoses (instead of the normal bipolar spindles)

4. Loss of polarity: this means disturbed orientation of the cells. In malignancy, sheets of tumor cells grow in disorganized fashion. Normal epidermis shows normally oriented stratified constituent cells; from below up there are the basal cells followed by spinous cells then granular cells and finally the upper most layer of flattened, keratinized cells. Although differentiated squamous cells carcinoma tend to recapitulate to some extent this arrangement, it is totally lacking in poorly differentiated and undifferentiated examples i.e. there is no longer the orderly architectural stratification seen in the normal skin.

5. **Other changes**

a. Formation of tumor giant cells: some of these abnormally large cells possess only a single huge pleomorphic nucleus; others have two or more nuclei. These malignant giant cells are not to be confused with the inflammatory Langhan or foreign body giant cells; the latter are derived

from macrophages and contain many small, normal-appearing nuclei. In cancer giant cells, the nuclei show malignant features, for e.g. they are hyperchromatic and large in relation to the cell size.

b. Foci of ischemic necrosis: dividing and growing tumor cells require adequate blood supply for their survival. In many anaplastic tumors, because of the rapid proliferation of the constituent cells and/or scant stromal vascularity, the tumor may overrun the available blood supply. This leads to large areas of ischemic necrosis. The presence of necrotic areas within a malignant tumor is a poor prognostic sign, since it usually reflects an aggressive rapidly growing malignancy.

Local invasion

Benign tumors differ from malignant ones by their slow rate of growth growing and as cohesive masses, thus, benign tumors usually (not always) develop a rim of compressed connective tissue called fibrous capsule**,** which separates them from the native host tissue. An example is fibroadenoma of the breast. This tumor on clinical examination is well-defined and typically mobile mass. Benign tumors remain confined to the site of origin without having the ability to invade locally or metastasize to distant sites. In contrast, most malignant tumors are invasive and can be expected to penetrate and destroy the underlying tissues i.e. they are not surrounded by a capsule. Fixation of a breast mass on clinical examination makes it suspicious for malignancy. It is this invasiveness that makes surgical resection of cancers difficult. It is necessary during surgery to remove a margin of apparently normal tissues (margin of safety) adjacent to infiltrative cancer. One of the prime functions of the pathologist is to indicate, in his report of a surgically excised malignant tumor, of whether the tumor is totally removed (free excision margins) or incompletely excised (positive excision margins). In the latter instance recurrence of the tumor is a strong possibility. Some cancers progress from a preinvasive stage (carcinoma in situ); this commonly occurs in carcinomas of the skin, breast, and uterine cervix. In situ epithelial cancers display the cytologic features of malignancy but are devoid of invasion outside the encompassing basement membrane.