Lecture 17 GENERAL PATHOLOGY

NEOPLASIA

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 and its progeny forming a clone of cells and hence tumors are said to be clonal.

Basic component of tumor

1- parenchyma :made up of neoplastic cells, largely determines its biologic behavior, and its from which the tumor derives its name
2-stroma (host derived non neoplastic) that is made up of connective tissue and blood vessels.
The stroma is vital to the neoplastic cells; it carries the blood supply and provides support for parenchymal cell. 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.

NOMENCLATURE OF NEOPLASMS

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. benign tumor of fibroblasts is called **fibroma**, cartilaginous tumor is **chondroma,** 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.
However, tumors derived from glandular tissues are also called adenomas even though they do not reproduce glandular structures e.g. some thyroid follicular adenomas are composed of packed trabeculae (bands) or cords of follicular epithelial cells.

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 Tumors

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), **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.. **adenocarcinoma:** A carcinoma with a microscopic glandular growth pattern
squamous cell carcinoma : carcinoma producing squamous cells arising in any epithelium of the body (e.g. skin, esophagus or cervix uteri)**.**

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.

Mixed tumors : the tumor cells undergo divergent differentiation, Mixed tumors are still of monoclonal origin, but the progenitor cell in such tumors has the capacity to differentiate down more than one lineage. The best example is mixed tumor of salivary gland. These tumors have obvious epithelial components dispersed throughout a fibromyxoid stroma, sometimes harboring islands of cartilage or bone . All of these diverse elements are thought to derive from a single transformed epithelial progenitor cell, and the preferred designation for these neoplasms is *pleomorphic adenoma.*

.**Lymphomas** and **leukemias** are malignancies derived from hematopoetic cells.

Teratoma is a special type of mixed tumor that contains recognizable mature or immature cells or tissues derived from more than one germ cell layer, and sometimes all three. Teratomas originate from totipotential germ cells such as those that normally reside in the ovary and testis

Germ cells have the capacity to differentiate into any of the cell types found in the adult body;
Teratomas are commonly seen in the ovary and since these ovarian tumors are commonly cystic they are designated as cystic teratomas**,** and because the skin (and its adnexae such as hair & sebaceous glands) is a major component of such tumors they are also have the alternative name of dermoid cysts.

some inappropriate designations that do not follow the above principles of nomenaclature

1-carcinomas of melanocytes have been called melanomas, although correctly they should be referred to as melanocarcinomas.
2-seminoma: a special type of testicular germ cell carcinoma
3-hepatoma :correctly a hepatocellular carcinoma

There also are other instances of confusing terminology Hamartoma is a mass of disorganized tissue indigenous to the particular site, such as the lung or the liver. While traditionally considered developmental malformations, many hamartomas have clonal chromosomal aberrations that are acquired through somatic mutations and on this basis are now considered to be neoplastic.

Choristoma is a congenital anomaly consisting of a heterotopic nest of cells. For example, a small nodule of well-developed and normally organized pancreatic tissue may be found in the submucosa of the stomach, duodenum, or small intestine.

CHARACTERISTICS OF BENIGN AND MALIGNANT NEOPLASMS

There are three fundamental features by which most benign and malignant tumors can be distinguished: differentiation and anaplasia, local invasion, and metastasis.

In general, rapid growth also signifies malignancy, but many malignant tumors grow slowly and as a result growth rate is not a reliable discriminator between good and bad actors

I-Differentiation and Anaplasia

Differentiation refers to the extent to which neoplasms resemble their parenchymal cells of origin, both morphologically and functionally; lack of differentiation is called *anaplasia*.

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. What is just said about leiomyomas is also applicable to lipomas 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.

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 well-differentiated & poorly-differentiated tumors.

4. Undifferentiated (anaplastic) neoplasms: anaplasia signifies total lack of differentiation, and thus anaplastic cells have primitive appearance (unspecialized morphology) that can not 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. In anaplastic 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 N/C ratio may approach 1:1 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.Abnormal mitoses: 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.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.