NENPLESIA (CANCER)

Metastasis

By definition metastases are "tumor implants discontinuous with the primary tumor". Metastasis is the only definitive criterion of malignancy because benign neoplasms do not metastasize. Almost all cancers can metastasize. The major exceptions are

1. Most malignant gliomas of CNS (gliomas are tumors derived from glial cells).
2. Most Basal cell carcinomas of the skin. Rodent ulcer is a clinical descriptive term used for basal cell carcinoma because of their destructive invasiveness. Yet, they do not, as a rule, metastasize. In general, cancers more likely to metastasize are

1. The more aggressive and more rapidly growing
2. Those of large size Metastatic spread strongly reduces the possibility of cure.

Pathways of Spread

Dissemination of cancers may occur through one of three pathways:

A. Direct seeding of body cavities or surfaces

B. Lymphatic spread

C. Hematogenous spread

A. Direct seeding of body cavities or surfaces

This may occur whenever a cancer, as a result of progressive invasion, 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. Peritoneal seeding is particularly characteristic of ovarian carcinomas. Sometimes mucus-secreting adenocarcinomas of the appendix fill the peritoneal cavity with a gelatinous (myxoid) neoplastic mass. This finding is referred to as pseudomyxoma peritonei**.** Lung and breast carcinomas as well as many other cancers may involve pleural cavity. Involvement of serous membranes by metastases is associated with pouring of exudates in to these cavities (malignant peritoneal, pleural or pericardial effusion).

B.Lymphatic Spread

This is the most common pathway for the initial dissemination of carcinomas, but some sarcomas may also use this route. The pattern of lymph node involvement follows the natural routes of lymphatic drainage. Because carcinomas of the breast usually arise in the upper outer quadrants, they generally disseminate first to ipsilateral axillary lymph nodes. Cancers of the inner quadrants may drain to the nodes along the internal mammary arteries. Thereafter the infraclavicular and supraclavicular nodes may become involved. Carcinomas of the lung arising in major respiratory passages metastasize first to the hilar-tracheobronchial and mediastinal nodes. 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. Usually, lymphatic spread of breast cancers is assessed by performing a full removal of axillary lymph nodes. Because this procedure is associated with considerable surgical morbidity, a biopsy of sentinel node is often used. A **sentinel lymph node** is defined as "the first node in a regional lymphatic basin that receives lymph flow from the primary tumor." This node is therefore a representative of the regional lymph nodes status. Assessment of sentinel node has

also been used for detecting lymphatic spread of melanomas, colon cancers, and other tumors. Drainage of tumor cell antigens without cancerous cells may induce reactive changes (reactive lymphoid hyperplasia) within the regional nodes causing their enlargement. Therefore, **nodal enlargement near a cancer does not necessarily mean dissemination of the primary tumor.** Differentiation between the two is only possible through microscopic examination of sections from the excised nodes.

C.Hematogenous Spread

Hematogenous spread is typical of sarcomas but is also seen with carcinomas. Veins, because of their thinner wall, are more readily penetrated than arteries. With venous invasion, the blood borne cells follow the venous flow draining the site of the neoplasm**.** The liver and lungs are most frequently involved by metastases. This is because all portal area drainage flows to the liver, and all vena cava blood flows to the lungs. Cancers arising in close proximity to the vertebral column often metastasize through the paravertebral plexus of veins, and this pathway is probably the cause of frequent vertebral (bone) metastases of carcinomas of the thyroid and prostate. Certain cancers have a remarkable tendency for invasion of veins. Renal cell carcinomaoften 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 venous radicles to grow within them into the main venous channels. Histologic evidence of penetration of small vessels within a primary neoplasm is obviously an ominous feature.

PRECANCEROUS CONDITIONS

Certain conditions are known to have an increased risk of association with cancer; these have been designated as precancerous conditions. They are divided into two groups

A. Non-neoplastic conditions; examples include

1. Chronic ulcerative colitis
2. Chronic atrophic gastritis
3. Chronic viral B & C hepatitis
4. Cutaneous actinic keratosis
5. Leukoplakia of oral cavity, vulva, and penis

B. Benign neoplasms; examples include

1. Villous adenoma of the colon
2. Familial adenomatous polyposis of the colon.

HOST DEFENSES AGAINST CANCERS—TUMOR IMMUNITY

A normal function of the immune system is to inspect the body for emerging malignant cells and destroy them, this is referred to as immune surveillance.

Immune Surveillance

The strongest evidence for the existence of immune surveillance is the increased frequency of cancers in immuno-deficient (immune compromised) hosts, whether this is congenital or acquired.

1. Congenital immunodeficiencies

About 5% of such individuals develop cancers, and this is about 200 times the prevalence in normal (immunocomponent) individuals.

2. Acquired immunodeficiencies Examples include immunosuppressed transplant recipients and patients with AIDS. Affected individuals have an increased incidence of malignancies. Most (but not all) of these neoplasms are malignant lymphomas. Most cancers, however, occur in persons who do not show any evidence of immunodeficiency. There must be then mechanisms developed by tumor cells to escape or evade the immune system in the immunocompetent hosts. These mechanisms include

1. Selective outgrowth of antigen-negative tumor cells: during tumor progression, strongly immunogenic subclones may be eliminated by the immune system leaving antigen-negative ones. These, understandably, cannot be detected by the immune system.
2. Loss or reduced expression of MHC molecules: tumor cells may fail to express normal levels of HLA class I molecules (which are required for activation of cytotoxic T cells) thereby escaping attack by cytotoxic T cells.
3. Lack of co-stimulation: T-cells requires two signals to be sensitized against cancer cells, one is offered by MHC class I antigenic molecules and the other by co-stimulatory molecules. Failure to express the latter by the tumor cells not only prevents sensitization but also may cause T-cells to undergo apoptosis.
4. Immunosuppression: tumor growth factor- β (TGF-β), secreted by many tumors, is a potent immunosuppressant.
5. Antigen masking: cell-surface antigens of tumors may be hidden, or masked, from the immune system.
6. Killing of cytotoxic T cells: some carcinomas (e.g. melanomas and hepatocellular carcinomas), as a defensive mechanism, kill tumor-specific T lymphocytes that encounter them.

EFFECTS OF TUMORS ON THE HOST

Cancers are more aggressive than benign tumors. Nonetheless, both types of neoplasia may cause problems through

1. Local progression

Some tumors have critical locations e.g. pituitary adenoma. Although the tumor is benign, its enlargement and expansion can destroy the remaining normal pituitary and thus lead to panhypopituitarism.

Neoplasms in the GIT (both benign and malignant), may lead to obstructions as they enlarge. The following are examples of tumors can cause outlet obstruction of their respective organs as they enlarge

1. Carcinoma of esophagus
2. Carcinoma of gastric pyloric antrum
3. Carcinoma of small & large intestines
4. Carcinoma of the head of pancreas, common bile duct, or duodenum leading to obstructive jaundice.
5. Sometimes, peristaltic movement telescopes the neoplasm and its affected segment into the distal adjacent segment, producing intussusception of the small intestine.

2. Functional hormonal activity

Neoplasms arising in endocrine glands may produce manifestations by synthesizing hormones. Such functional activity is more common with benign tumors than with cancers. The latter may be poorly differentiated or undifferentiated to the extent of losing their functional activity i.e.

hormone synthesis. A benign β-cell adenoma of the pancreatic islets may produce excessive insulin to cause fatal hypoglycemia. In addition, some nonendocrine tumors may produce hormones or hormone-like substances and give rise to paraneoplastic syndromes (to be described later).

3. Bleeding and secondary infections

The destructive growth of cancers or the expansile pressure of a benign tumor on any natural surface, such as the skin, mucosa of the GIT, urinary or respiratory passages, may cause ulcerations, that lead to melena, hematuria, and hemoptysis respectively. Additionally, destruction of these mechanical barriers predisposes to secondary microbial infections.

4. Acute presentation

May occur in association with tumors; these are caused by for e.g. perforation of the stomach, small or large intestine and spontaneous rupture or infarction of the tumor itself. The latter is exemplified by torsion of ovarian tumors. Additionally, malignant tumors may be associated with two additional complications

5. Cancer cachexia

This refers to a syndrome of progressive loss of weight accompanied by weakness, anorexia, and anemia that occur frequently in patients with cancer. It may be due to anorexia, tumor parasitism, and the action of soluble factors such as tumor necrosis factor (TNF) produced by the tumor as well as by the host in response to the tumor. In patients with cancer, basal metabolic rate is paradoxically increased despite reduced food intake. This is in contrast to starvation, where there is an adaptational lowering of metabolic rate. Furthermore, in cancer cachexia, there is equal loss of fat and muscle, whereas in starvation the muscle mass is relatively preserved at the expense of fat stores.

GRADING AND STAGING OF CANCERS

To assess prognosis (the likely outcome of a disease) & effectiveness of various forms of treatment, malignant tumors should be separated into different groups; each of which includes members that simulate each other in respect to certain microscopic & biologic properties. To achieve this, systems have been developed to express the degree of differentiation (**grade)** and extent of cancer spread **(stage).** Both grade and stage reflect the level of aggressiveness of various neoplasms.

Grading

Microscopic features that seem to influence the expected behavior of cancers are the grade, number of mitoses, and presence or absence of foci of necrosis; these features are inter-related. Cancers are classified into four grades (1 to 4) with increasing anaplasia i.e. G1 for welldifferentiated; G2 for moderately-differentiated, G3 for poorly-differentiated and G4 for undifferentiated cancers. Studies have shown that grading of cancers is of less clinical value than staging

Staging

The staging of cancers is based on

1. The size of the primary cancer
2. Its extent of spread to regional lymph nodes, and
3. The presence or absence of blood-borne metastases

Two major staging systems are currently in use, one developed by the Union Internationale Contre Cancer (**UICC**) (International union against cancer) and the other by the American Joint Committee (**AJC**). The UICC classification is referred to as the **TNM system**—**T** for primary tumor, **N** for regional lymph node involvement, and **M** for metastases. This TNM staging varies for each specific form of cancer, but there are general principles: with increasing size, the primary cancer is described as **T1 to T4**. Sometimes the T refers to the depth of invasion (not the size) as in GIT carcinomas. **TIS** indicates an in situ cancer.

N0 would mean no nodal involvement, whereas **N1 to N3** would indicate involvement of an increasing number and range of lymph nodes. **M0** signifies no distant metastases, whereas **M1 (or sometimes M2)** indicates the presence of blood-borne metastases. Example: breast carcinoma, 3 cm in maximal dimension, with axillary lymph node metastases on the same side of the cancer, but with no distant metastases would be T2 N1 M0.

Staging of neoplastic diseases is of great importance in predicting prognosis and in the selection of the best form of therapy for the patient and has proved to be of greater clinical value than grading. However, the two are generally correlated in that tumors of high grade present at high stage, while tumors of low grade present at low stage.

LABORATORY DIAGNOSIS OF CANCER

There are several approaches to the correct pathological diagnosis of cancer and sometimes more than one approach is employed.

A. Histologic and Cytologic Methods Separating benign from malignant neoplasms is usually not difficult by these two methods. However, care should be taken in diagnosing a group of tumors that lay in the middle of the spectrum i.e. in the gray zone; these are designated as borderline tumors. Cooperation between the clinician and the pathologist facilitates greatly the achievement of the correct diagnosis. Clinical data and surgical findings during the operation are helpful for optimal pathologic diagnosis. Surgical specimens delivered to the lab as far as tumor diagnosis is concerned should be

1. Adequate
2. Representative of the lesion
3. Properly preserved in a fixative; routinely formalin

Samples delivered for pathological evaluation may represent:

1. Incisional or excisional biopsy specimen for
a. conventional histopathological diagnosis
b. frozen section diagnosis
2. Needle Biopsies
a. Fine needle aspiration material (cytology)
b. Needle-core biopsy material (histopathology)
3. Endoscopic biopsy material
4. Laparoscopic, or thoracoscopic biopsies
5. Cytologic smears from the tumor in question

1. Incisional biopsy means that only a portion of the lesion is sampled, and therefore the procedure is strictly of a diagnostic nature. In **excisional biopsies**, the entire lesion is removed, usually with a rim of normal tissue, and therefore the procedure serves both a diagnostic and a therapeutic function. When excision of the whole lesion is not possible, incisional biopsy is performed, however, selection of an appropriate site for a biopsy of a large mass by the surgeon

requires awareness that the margins of the lesion may not be representative and its center may be largely necrotic. Requesting an intra-operative "**quick-frozen section**" diagnosis is sometimes desirable, for example, in determining the nature of a mass lesion or in evaluating the margins of an excised cancer to ascertain that the entire neoplasm has been removed. This method permits histologic evaluation within minutes, while the patient is still under anesthesia. The results in such cases will modify the course of the surgical operation.

2. Needle biopsies

Fine-needle aspiration of tumors During fine-needle aspiration, a long, thin needle is inserted into the suspicious area. A syringe is used to draw out fluid and cells for analysis. The material is then spread on a slide, stained and then examined for the evaluation of the mass.

Core needle biopsy A wide-bore needle with a cutting tip is used to draw a thin core of tissue (the size of a match stick) out of a suspicious area. The tissue obtained is processed to obtain histological sections for evaluation. Image-guided biopsy combines an imaging procedure, such as X-ray, computerized tomography (CT) or ultrasound, with a needle biopsy. Image-guided biopsy allows access to suspicious areas that cannot be felt through the skin, such as a suspicious lesion of the liver or prostate. Through the use of images, it possible to be sure that the biopsy needle reaches the correct spot.

3. Endoscopic biopsies

During endoscopy, a thin, flexible tube with a light on the end (endoscope) is used to see structures inside the body. Special tools are passed through the tube to take small samples of tissue for pathological analysis. Tubes used in an endoscopic biopsy can be inserted through the mouth, rectum, urethra (transurethral), etc. Examples of endoscopic biopsy procedures include

- Cytoscopy to collect biopsies from inside the urinary bladder,
- Bronchoscopy to get tissue from bronchial/lung structures and
- Gastroscopy or colonoscopy to collect tissues from the stomach or colon respectively

4. **Laparoscopy, Thoracoscopy, and Mediastinoscopy**

Laparoscopy is similar to endoscopy but is used to look inside the abdominal cavity and remove tissue samples. A small incision is made in the abdomen then the laparoscope is passed through this opening to see the inside. Similar procedures to look inside the chest are called thoracoscopy and mediastinoscopy.

5. Cytology

Diagnosing diseases based on looking at single cells and small clusters of cells is called cytology or cytopathology. It has become more important in cancer diagnosis over the past few decades.

Sometimes, as in some fine needle aspiration (FNA) samples, only one drop of blood or tissue fluid (containing tiny fragments of the tumor) is taken. On the other hand, some pleural fluid or peritoneal fluid cytology samples may include large amount of fluid. In the latter case, a sample (e.g. 5 ml) is taken and centrifuged. The deposit is taken and spread on a glass slide and then stained and screened under the microscope for malignant cells. Diagnostic cytology, when performed by well-trained, experienced individuals, offers an extremely high degree of reliability.

B. Histochemistry

The basis of surgical pathology is the examination of the specimens following fixation in formalin, processing in graded alcohols and xylene, embedding in paraffin, cutting of sections

with a microtome, and staining with hematoxylin-eosin (H&E). This technique gives a lot of information quickly with a little cost. That is why it is the standard method in all histopathology labs. In the H&E technique, hematoxylin staining of nuclei is followed by counterstaining of cytoplasms and various extracellular materials by eosin. However, sometimes, H& E staining of sections is not enough for establishing a final decisive diagnosis. Several stains are available that react chemically with certain constituents of the neoplastic cells to give a colored reaction that highlights a specific feature that would otherwise unclear with the H& E stain. (e.g., presence of mucins in adenocarcinoma, melanin in amelanotic melanoma, striations in rhabdomyosarcoma, glial fibers in gliomas, etc.). These stains are called special stains (because they are employed under special circumstances). Currently, a small minority of these special stains are of real diagnostic utility. This is especially true since the advent of immunohistochemistry, which renders many of these special stains out of date.

C. Immunohistochemistry (IHC)

This is the application of immunologic principles & techniques to the study of cells & tissues. The availability of specific **monoclonal antibodies** has greatly facilitated the identification of cell products or cell surface markers. In several situations, the differentiation between neoplasms may be very difficult for e.g. with the anaplastic large cell malignancies; even the most experienced pathologists cannot tell whether the submitted tumor is a squamous cell carcinoma, adenocarcinoma, lymphoma or a sarcoma. Differentiation between these is of prognostic & therapeutic implications. It is through the application of a panel of specific monoclonal antibodies, which disclose the presence or absence of certain products or cell markers in these cells, so that the more specific, final diagnosis can be reached. Examples of the utility of immunohistochemistry in the diagnosis or management of malignant neoplasms include

1. Categorization of undifferentiated malignant tumors
2. Categorization of leukemias and lymphomas
3. Determination the site of origin of metastatic tumors
4. Detection of molecules that have prognostic or therapeutic significance

D. Tumor Markers

Tumor markers are either substances released by cancer cells into the blood (or urine) or substances created by the body in response to cancer cells. They include cell-surface antigens, cytoplasmic proteins, enzymes, and hormones. In clinical practice, a tumor marker usually refers to a molecule specific to a particular neoplasm that can be detected in the plasma or other body fluids. Their main utility is a laboratory test to support the diagnosis of cancer to determine the response to therapy to indicate recurrence during the follow-up period. Some of these tumor markers can also be detected imunohistochemically in tissue sections. A host of tumor markers has been described, and new ones are identified every year. Examples include:

Carcinoembryonic antigen (CEA) is a complex glycoprotein that is elaborated by many different neoplasms. Its serum levels are reported to be positive in colorectal, pancreatic, gastric and breast carcinomas. In patients with CEA-positive colon carcinomas, the persistence of elevated CEA levels 6 weeks after surgical removal indicates a residual (left behind) tumor tissues, whereas a rising CEA levels indicates recurrence.

α-fetoprotein (AFP) is another well-established tumor marker. AFP levels have proved to be a useful indicator of hepatocellular carcinomas and germ cell tumors of the testis or ovary. AFP

levels decline rapidly after surgical resection of liver cell cancer or treatment of germ cell tumors of the testis. Serial post-therapy measurements of AFP levels in patients with germ cell tumors of the testis provide a sensitive index of response to therapy and recurrence.

Prostate-specific antigen (PSA) An elevated PSA level in the blood may indicate prostate cancer, but other conditions such as benign prostatic hyperplasia (BPH) and even prostatitis can also raise PSA levels. PSA levels are used also to evaluate how a patient has responded to treatment and to check for tumor recurrence. The development of tests to detect cancer markers in blood and body fluids is an active area of research.

Ca-125 is a glycoprotein expressed by coelomic epithelium during fetal development. Increased serum levels can be present in patients with ovarian cancer. Other malignancies such as pancreatic carcinoma may also have increased levels. Non malignant causes of high serum Ca125 include pregnancy, endometriosis and liver failure.

D. Electron microscopy:

The main use of diagnostic electron microscopy is involved not with the question of whether a tumor is malignant or not, but with the issue of tumor classification. Cytoplasmic organelles such as melanosomes are indicative of melanocytic lesions such as malignant melanoma, the presence of desmosomes points to an epithelial tumor (carcinoma), and structures such as myosin and actin filaments arranged in "Z" bands are indicative of skeletal muscle differentiation and hence if found in a tumor would suggest a rhabdomyosarcoma. Neurosecretory dense core granules are found in tumors with neuroendocrine differentiation. Several other relatively recent & sophisticated techniques are employed in both the diagnosis of & researches on neoplasia. These are beyond the scope of this lecture; the interested student can look them up in the specialized text books, examples of these include

E. Flow Cytometry is a technique used to measure individual cell characteristics such as membrane antigens and DNA content of tumor cells. The classification of leukemias and lymphomas is based on cell surface antigens which can be easily identified by flow cytometry. DNA ploidy appears to correlate with prognosis in a variety of tumors. In general, aneuploidy seems to be associated with a poorer prognosis in early-stage breast cancer, bladder, lung, colorectal and prostate cancer.