Lecture 19 GENERAL PATHOLOGY

NEOPLASIA

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

   NOTE; Are benign tumors precancerous? The answer is no, but there are exceptions, and perhaps it is better to say that each type of benign tumor is associated with a particular level of risk, ranging from high to virtually nonexistent.

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 (immuno-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, which 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 pan-hypopituitarism. Neoplasms in the GIT (both benign and malignant), may lead to obstructions as they enlarge.

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.

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.

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 basal 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.

6. Paraneoplastic syndromes

Symptom complexes that occur in patients with cancer that can't be explained by local or distant spread of the tumor or by the elaboration of hormones not indigenous to the tissue of origin of the tumor .there clinical recognition is important for several reasons

1. are frequent being encountered in 10% of patients with cancer
2. may be the earliest manifestations of as yet undiscovered (occult) malignancy
3. may be serious and sometimes fatal
4. may simulate clinically metastatic disease and as such confuse management

Some of the more common syndromes are:

I. Endocrinopathies: *These are frequently encountered paraneoplastic syndromes. Because the cancer cells are not of endocrine origin, this functional activity is referred to as* ***ectopic hormone production***.

II. The neuromyopathies *take diverse forms, such as peripheral neuropathies and a myasthenic syndrome similar to myasthenia gravis.*

III. Dermatopathies

IV. Hypertrophic osteoarthropathy& clubbing of the fingers *are encountered in up to 10% of patients with bronchial carcinomas.*

V. Vascular and Hematologic Changes

1-*Venous thrombosis*

2. Nonbacterial thrombotic endocarditis

VI. Others

Fever: this is likely to be due to pyrogen release (e.g. Hodgkin's lymphoma, renal cell carcinoma, osteosarcoma).

Nephrotic syndrome (proteinuria, hypoproteinemia and edema)**:** this is seen in various cancers.

Amyloidosis is sometimes associated with multiple myeloma and renal cell carcinoma.

GRADING AND STAGING OF CANCERS

To assess prognosis (the likely outcome of a disease) & effectiveness of various forms of treatment, malignant tumors should be studied to determine the degree of differentiation (**grade)** and extent of cancer spread**(stage), because both grade and stage** reflect the biological behavior and 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 well-differentiated; 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 and/or extent of local extension.

2. Its extent of spread to regional lymph nodes

3. The presence or absence of blood-borne metastases

Two major staging systems are currently in use, one developed by the International union against cancer (**UICC**- Union InternationaleContre Cancer) and the other by the American Joint Committee (**AJC**).

The UICC classification is referred to as the **TNM system— T** for primary tumor size, **N** for regional lymph node involvement, **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**.

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

surgical specimens delivered to the lab as far as tumor diagnosis is concerned should be be adequate, representative, and properly preserved.

Several sampling approaches are available

1. Incisional (only a portion of the lesion is sampled) or excisional biopsy (the entire lesion is removed) specimen for
   a. conventional histopathological diagnosis
   b. frozen section diagnosis intra-operative "*quick-frozen section*" diagnosis

2. Needle Biopsies
   a. Fine needle aspiration material (cytology)
   b. Needle-core biopsy material (histopathology)

3. Endoscopic biopsy material .During endoscopy, a thin, flexible tube with a light on the end (endoscope) is used to see structures inside the body**.**
   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

4. Laparoscopic, or thoracoscopic biopsies **:**Laparoscopy is similar to endoscopy but is used to look inside the abdominal cavity and remove tissue samples

5. Cytologic smears from the tumor in question .This approach is widely used to screen for carcinoma of the cervix

B. Histochemistry

sometimes, tissue morphology depending on H& E stained sections is not enough for establishing a final diagnosis. Several stains are available that react chemically with certain constituents of the neoplastic cells to give a colored reaction (e.g. presence of mucins in adenocarcinoma, These stains are called special stains

C.Immunohistochemistry

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. Biochemical Assays (serum 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.

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

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

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

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.

F. Molecular techniques

PCR

Real Time PCR